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Regulatory and Economic Aspects in Oncology

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Evelyn Walter
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Regulatory and Economic Aspects in Oncology

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Contents

About the Editor

Dr. Evelyn Walter has been the Head (and Co-founder) of the Institute of Pharmaeconomic Research (IPF) in Vienna since 2003. The IPF's main areas include health economic evaluation, modeling, and expert advice on reimbursement decisions, pharmaceutical pricing and distribution. She first studied Mathematics at Vienna University of Technology, before switching to the Vienna University of Economic Sciences, where she completed a master's and a doctorate in Economics. She has authored or co-authored some 60 publications, chiefly in refereed journals, and serves as a reviewer for several health economics journals. In Austria, she initiated the "Guidelines for Health Evaluation." She is a Member of the Scientific Advisory Board for the "System of Health Accounts" at Statistics Austria. As a Member of the International Society of Pharmacoeconomics and outcome Research (ISPOR), she co-chaired the 17th and 18th Annual European Congresses. She is a Lecturer at the University of Applied Sciences in Burgenland, where she teaches courses on Health Economics, Health Technology Assessment, and Pharma Management.

Introduction and Overview

Evelyn Walter

Abstract

The overall aim of this book is to set out the main changes needed in the field of economic and regulatory conditions as a consequence of these rapid developments in oncology. The traditional approaches of health economics, like health economic evaluation, health technology assessment (HTA), modeling methods, assessing value, pricing techniques, are bound to be altered in the contributions to this book. It is understandable that with the life-threatening diagnosis of cancer the new treatment options need to be accompanied by the best available health economic tools. This pertains to well-implemented decision rules concerning willingness to pay, incremental cost-effectiveness ratio thresholds, equity, patient access, end of life criteria, etc. Their application differs with regard to the usual health economic analyzes implemented in other treatment areas. Overstating a bit one could ask whether we need a strongly modified concept of oncology economics?

Keywords

Cancer incidence · Oncology cone · Prices of cancer medication

The emergence of disruptive innovations is always a challenge for the systems which are prone to be affected. Cancer therapies for decades experienced improvements, yet no breakthroughs. They had to rely on incremental discoveries. With the advent of advanced antibody constructs, cell therapies, nucleic acid therapies, cancer vaccines, immunotherapies, genomic and proteomic biomarkers and a further personalization of treatments the picture has changed. At this stage of substantial advances in cancer therapies, an assessment is mandatory to ascertain to what extent the present health system is compelled to adapt. In this vein, this book

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Recent Results in Cancer Research 213,
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provides insights authored by eminent specialists in the field. The perspective adopted is from economics of health.

The overall aim of this book is to set out the main changes needed in the field of economic and regulatory conditions as a consequence of these rapid developments in oncology. The traditional approaches of health economics, like health economic evaluation, health technology assessment (HTA), modeling methods, assessing value, pricing techniques, are bound to be altered in the contributions to this book. It is understandable that with the life-threatening diagnosis of cancer the new treatment options need to be accompanied by the best available health economic tools. This pertains to well-implemented decision rules concerning willingness to pay, incremental cost-effectiveness ratio thresholds, equity, patient access, end of life criteria, etc. Their application differs with regard to the usual health economic analyzes implemented in other treatment areas. Overstating a bit one could ask whether we need a strongly modified concept of oncology economics?

Cancer incidence is estimated to double by 2035. The greatest increase in cancer cases is expected in low-income and middle-income countries (LMICs) due to demographic changes, such as aging of the population, and increasing exposure to risk factors. While an estimated 60% of cancer cases occur in LMICs, only 5% of global spending on cancer is directed to these countries (Prager et al. 2017). Addressing the growing cancer burden as a public health priority is challenging, because it is not a single disease but rather a multitude of diseases. Many cancers are heterogeneous in their characteristics, with hundreds of histological and biological subtypes. It requires specific diagnostic and therapeutic strategies, as well as a qualified workforce to implement them, coupled with the imperative need of coordinated multidisciplinary patient care (Prager et al. 2017).

The dramatic advances in cancer care over the past few decades are obviously reflected in significant improvements in outcome. These technology advances create four primary opportunities to improving cancer care for patients: earlier detection, new treatment strategies, personalization, and improved monitoring (McKinsey & Company 2016). Concerning new treatments, 63 cancer drugs, each approved in one or more tumors, have impacted the treatment of 24 different cancer types over the past 5 years. The rise of immuno-oncology since the first launches in 2014 has been largely centered on the checkpoint inhibitors (PD-1 and PD-L1), which have broad efficacy across solid tumors and are used across 23 different tumor types (IQVIA Institute 2018). An optimal insight into the changing landscape of the EU pharmaceutical legislation concerning regulation and evidence requirements and how new treatments receive marketing authorization is described in the article by Francesco Pignatti and Elias Péan from the European Medicines Agency (EMA).

The prices of cancer medication have increased rapidly during the last years. Spanning over an observational period of 8 years, prices went up by an average of 6% or more per year, while the inflation rate was just under 1.1% (Reuters 2017). Spending on cancer medicines—both for therapeutic and supportive care use—rose from $96 billion in 2013 up to $133 billion globally in 2017 (IQVIA Institute 2018). In the United States alone the situation is even more dramatic, spending on cancer drugs has doubled since 2012 and reached almost $50 billion in 2017

(IQVIA Institute 2018). Two-thirds of the expenditure growth is due to the intensified use of drugs launched within the past 5 years. Outside the United States in 2017, oncology costs exceeded $60 billion, driven by new product launches and increased use of existing brands. The contribution of *Bengt Jönnson* analyzes the costs of cancer defined as full accounting of costs and not with the single focus on drugs only. This full accounting of the costs of cancer should include an estimate of the health burden of cancer.

With regard to list prices of new cancer drugs at launch, one observes a steady rise over the past decade. The median annual cost of a new cancer drug launched in 2017 exceeded $150,000, compared to $79,000 for the new cancer drugs launched in 2013. Attention has also to be given to the fact that most cancer drugs—including those with high annual costs—are used by relatively few patients—with about 87% of drugs being used by fewer than 10,000 patients in 2017 (IQVIA Institute 2018). Increasingly, new cancer medicines are destined for smaller patient populations, with 10 out of 14 therapies launched in 2017 targeting orphan indications (IQVIA Institute 2018). *Daria Korchagina* from Maison de Solenn provides a review of orphan legislations and health technology assessment frameworks. She analyzes the position of oncology drugs on the orphan drug market and discusses future perspectives.

Due to the waves of innovation in cancer care stakeholders increasingly consider whether the level of innovation is commensurate with the increases in costs. *Patricia M. Danzon* from the Wharton School University of Pennsylvania explains in her contribution the development of drug pricing and brings light into the extensive discussion on the main drivers of high prices for cancer drugs seen from the US perspective.

HTA is increasingly used to judge value for money, but countries differ substantially on the methods they use. In which ways and to what extent HTA is used in Europe is presented in the two contributions of *Clement Francois* and *Szymon Jarosławski* from the Aix-Marseille University. For example in the United Kingdom, NICE (the National Institute for Health and Care Excellence, previously the National Institute for Clinical Excellence) judges value against a £30,000 per quality-adjusted life year gained by the treatment (Kleinrock 2015). As a consequence in the United Kingdom, a cancer drugs fund was created to fund strongly desirable cancer drugs and ensure patient's access, even if NICE has determined them to be too expensive (Kleinrock 2015).

It is well accepted that economic models are adequate and essential tools for decision-making. Here again, oncology with its rapidly evolving technologies present new challenges that make assessing and demonstrating value—expressed as health outcomes achieved per monetary value—especially complex (Miller et al. 2014). Hence, there is wide latitude for improvement in oncology modeling methodologies and the presentation and interpretation of the model results. Indeed, this is the area of the contribution by *William Green* and *Matthew Taylor* from the University of York who highlight various more recent and sophisticated modeling approaches.

Economic models typically involve the evaluation of clinical, economic, and humanistic (i.e., quality of life) outcomes in one or more hypothetical patient cohorts defined by demographics, disease history, clinical characteristics or presentation, and other factors (Miller et al. 2014). Various value frameworks were established using scoring systems, methods of measuring efficacy and safety or include patient-centric metrics (i.e., quality of life). In addition, the issue has to take into account the diverging perspectives of payers and providers. It is widely believed that payers often care mainly about direct clinical and economic outcomes (e.g., cure rates, survival, costs of care), whereas providers may care about patient-oriented outcomes, such as the impact of treatment on patient functioning and on quality of life (Miller et al. 2014). Three articles focus on outcome measures. One authored by *Evelyn Walter* gives an overview of available value frameworks. Two deal with patient-reported outcomes (PROs): First, *Mondher Toumi* and colleagues from the Aix-Marseille University explain PRO instruments and how they are used in oncology. In particular, the authors highlight the increasing importance of PROs since 85% of oncology trials between 2006 and 2012 have incorporated PROs. Second, *Mandi Pratt-Chapman* from the George Washington University and *Afsan Bhadelia* from the Harvard T. H. Chan School of Public Health and Johns Hopkins School of Public Health add the aspects of using PRO data in assessing existing treatment options and in the use of reimbursement algorithms.

Restrained by budget considerations, however, decisions on spending and drug reimbursement inevitably affect the important issue of equity. Healthcare payers must make difficult choices regarding spending and the ethical distribution of funds. *Nikolaus Knoepffler* and colleagues from the Friedrich Schiller University deal with the question of scarcity while respecting fundamental principles of human dignity and human rights.

In conclusion, it is hoped that this book opens forays into what could be termed as "new approaches to the economics of oncology." Thus, it should incite further research. In this way, economics of health adhere to the Hippocratic Oath and help combat cancer.

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Cost of Cancer: Healthcare Expenditures and Economic Impact

Bengt Jönsson

Abstract

Healthcare expenditures for cancer account for a low share of total healthcare expenditures, compared to the relative burden of the disease. The share has also not changed very much over the last decades. Cost for cancer drugs has increased as a share of total expenditures, but this has been offset by a reduction of inpatient hospital care for cancer. Accounting for the cost of cancer should not be limited to healthcare expenditures. Resources are also used for public and private care of cancer patients outside the healthcare sector, for example for palliative care. Informal care by family and friends is an important complement to professional care, and estimates indicate that this amounts to between half and one-third of the costs of formal care. Indirect costs related to the loss of production for persons with cancer are estimated to be of the same magnitude as the direct healthcare expenditures. Indirect costs related to premature mortality dominate the estimate of indirect costs, but those costs have declined over time, despite increasing incomes, due to the reduction in mortality due to cancer in the economically active age groups. Estimates of indirect costs due to morbidity are uncertain and vary significantly between published studies. A full accounting of the costs of cancer should include an estimate of the health burden of cancer. Loss of quality-adjusted life expectancy (QALY) can be measured and valued based on the willingness to pay for a QALY. Such estimates are possible to derive from decisions about allocating resources for cancer. There are few estimates of these costs, but available studies indicate that the intangible costs of lost QALY are by far the dominating cost of cancer. The value for policy-making of costs of cancer estimates increases when results with consistent methods and data are available

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that allow comparisons between countries and over time. The evidence about the cost of cancer is still limited, but when current scientific progress produces an increasing number of new options for prevention, diagnosis and treatment, studies of the cost of cancer become increasingly important to inform decisions about resource allocation.

Keywords
Cancer · Direct costs · Costs for cancer drugs · Indirect costs · Informal care · Intangible costs · International comparison

1 Introduction

There are two concepts of costs in economics, opportunity costs and accounting costs. Opportunity cost is the value of the next best alternative that is forgone when another alternative is chosen. The opportunity cost includes both explicit and implicit costs. Explicit costs are costs that involve a direct monetary outlay, and implicit costs are costs that do not involve an outlay of money. They are usually forward-looking and may not be objectively verifiable. Accounting costs appear on accounting statements from private and public firms/bodies and are explicit costs that have occurred in the past. Since these costs are used to inform different stakeholders, the costs must be objectively verifiable.

Both opportunity costs and accounting costs are relevant for health policy decisions in cancer. Opportunity cost estimates are relevant when we make private or public decisions to allocate resources for investments in programs for prevention and treatment of cancer. Undertaking cost-effectiveness studies to inform such studies involves estimates of costs that ideally should include both explicit and implicit costs, regardless of problems involved in measurement and valuation. When the decision is made, the cost estimates are not relevant any more. However, it can still be interesting to review such estimates if they are published, being observant regarding the context and potential publication bias (Greenberg et al. 2010).

Accounting cost studies in cancer inform different policy questions. One question may be whether healthcare resources for cancer are allocated according to criteria for effectiveness and/or equity, and another how out-of-pocket payments influence access to specific cancer care services. Such studies may also provide information to understand how financial incentives for providers influence their clinical practice. There is also a general interest in understanding how spending for cancer varies between countries and over time, and how budgets are determined through political and administrative decision-making.

There is no systematic recording and reporting on accounting costs for cancer. The system of healthcare accounts developed by the WHO and the statistics on healthcare expenditures published by the OECD do not provide any direct estimates of the costs of cancer. However, these data can be used in combination with other data to undertake estimates of the costs of cancer. Recorded data on healthcare expenditures do not cover all relevant costs for cancer. Important costs outside the healthcare sector, relevant for important health policy questions, are not accounted for in the data on healthcare expenditures.

The purpose of this paper is to present estimates of the costs of cancer using a cost-of-illness framework described in the methods section and to discuss how the different estimates relate to specific policy issues in cancer.

2 Methods

The cost-of-illness (COI) framework is a method for assigning costs to a specific disease, in this case cancer, using an accounting method which relates to the economic concept of opportunity costs; all costs should be counted, but only once. An important difference from opportunity costs is that these accounting costs are for past periods of time, even if it is possible to make forecasts as well, for example based on predicted changes in incidence, prevalence and patterns of care.

There is much debate on the details of the COI methodology, which will be left out from the discussion in this paper, for example about different methods for assigning unit costs to specific units of resources used or lost as a consequence of the disease (Hodgson and Meiners 1982). The key concepts used are the distinction between direct and indirect costs, and the two important subgroups of these two cost items: direct costs within and outside the healthcare sector and indirect costs due to morbidity and mortality, respectively.

We will also explore the opportunities to provide estimates of a third COI category, the intangible costs in terms of loss of healthy life expectancy. Adding this component is important to meet the objective of including all costs, but may create problems in terms of potential double counting. There is also the additional complication that expected loss of utility as an implicit measure of cost may have shortcomings as a method when counting costs of cancer (Meropol and Schulman 2012).

3 Total Health Expenditures on Cancer

Estimates of the total expenditures for cancer are of interest to answer questions about variations in spending patterns between countries and over time and the relation to measures of burden of the disease.

Table 1 Total health expenditure and estimated direct cost of cancer in Europe (% and € per capita adjusted for PPP), 2014 and % 2009 by L-F (3)

	Total health expenditure per capita (€ PPP)	Health expenditure on cancer (%)	Direct cost of cancer per capita (€ PPP)	Health expenditure on cancer (%) 2009
Austria	3,917	6.8[a]	266	4
Belgium	3,635	6.2[a]	227	3
Bulgaria	976	6.8[a]	66	5
Croatia	1,176	6.9[a]	81	n.a.
Cyprus	1,666	6.3	105	4
Czech Republic	1,681	5.4	91	5
Denmark	3,633	4.5	163	2
Estonia	1,196	5.8	69	6
Finland	2,848	4.4	125	5
France	3,417	6.2	212	3
Germany	3,898	6.8	265	5
Greece	1,955	6.5	127	5
Hungary	1,497	7.0	105	5
Iceland	2,962	3.8	113	n.a.
Ireland	3,283	5.0[a]	164	4
Italy	2,400	6.7	161	5
Latvia	1,001	6.2[a]	62	5
Lithuania	1,285	6.2[a]	79	3
Luxembourg	5,181	6.2[a]	323	3
Malta	2,060	6.5[a]	134	4
Netherlands	4,626	5.7	264	3
Norway	4,681	3.4	159	n.a.
Poland	1,239	6.5	81	6
Portugal	2,078	3.9	81	3
Romania	812	6.8[a]	55	6
Slovakia	1,733	6.2[a]	107	5
Slovenia	2,070	6.7	139	4
Spain	2,220	5.8	129	4
Sweden	3,272	6.8	223	3
Switzerland	5,080	6.5[a]	330	n.a.
United Kingdom	2,726	5.0	136	3
Europe	2,899	6.1[b]	176	4

Notes GDP = gross domestic product, PPP = purchasing power parity

Total health expenditure in 2014 was calculated with GDP data from 2014 and the share of total health expenditure on GDP from 2013

Source Luengo-Fernandez et al. (2013), Jönsson et al. (2016a)

[a]Estimated share based on data from similar countries; see Appendix for methodology

[b]The estimate is calculated as total health expenditure on cancer of all countries (not adjusted for PPP) divided by total health expenditure (not adjusted for PPP)

Table 1 compares the result of two major studies of health care spending on cancer in countries in Europe. The main conclusion is that cancer accounts for a rather small share of the total healthcare costs (6%) compared to the burden of the disease in terms of mortality (25%) and disability-adjusted life years (DALY) lost (19%). A second conclusion is that variations in per capita spending on cancer are mainly related to the overall variation in healthcare spending; that is, the variation in per cent of total spending on cancer between countries is rather small, and there is no systematic difference related to GDP per capita. The share spent on cancer is lower (4%) in the study by Luengo-Fernandez et al. (2013). The main reason for this is the bottom-up method used in L-F to estimate the costs for five different cost categories (primary care, outpatient care, emergency care, hospital care, and drugs) as opposed to the top-down method used in the study by Jönsson et al. (2016a, b).

Inpatient care accounted for 56% and drug expenditures for 27% of total cancer-related expenditures (Luengo-Fernandez et al. 2013). The variations between countries are great, which probably reflect both systematic variations, for example higher share for drugs in countries with lower incomes, as well as variations in how healthcare systems are organized and financed, and as a consequence, how cost data are reported.

Figure 1 shows the development of the cost of cancer in Europe from 1995 to 2014 in current and constant prices. There is a continuous increase in both current and fixed prices, but the share of healthcare resources devoted to cancer has been more or less constant during the 20-year period. This may be surprising since the relative burden of cancer has increased over time, both as a consequence of an increasing incidence of cancer and as a result of the reduction in the burden of cardiovascular disease (CVD) during the period. In many countries in Europe, cancer has now surpassed CVD as the main disease burden.

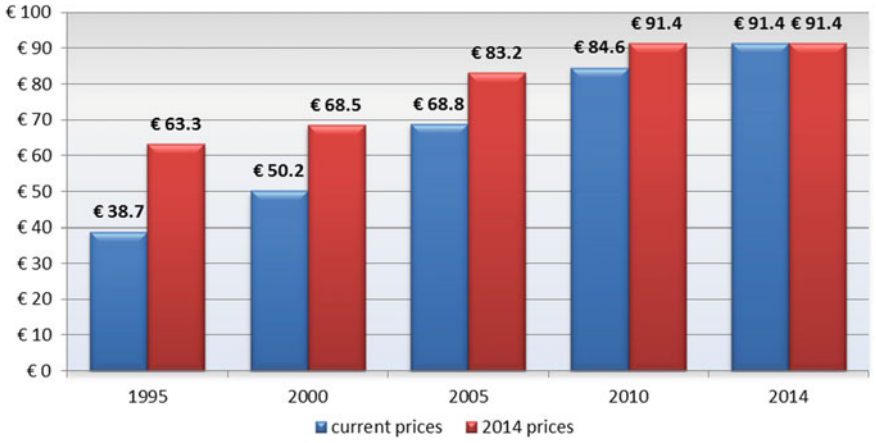

Fig. 1 Total health expenditure on cancer in Europe (in billion €), 1995–2014. *Source* Jönsson et al. (2016a)

4 Spending on Cancer Drugs

There have been a growing number of new cancer drugs coming to the market. As is seen from fig. 2 below, half of the drugs introduced during the last 20 years were introduced during the last five-year period. There is also a change in the type of new drug introductions with an increase in targeted therapies, often indicated for small patient populations. At the same time, prices for new drug introductions have increased and thus the cost per patient per treatment episode (Howard et al. 2015).

It is thus not surprising to see a continuous increase in cancer drug expenditures and also an increase in their share of total health expenditures on cancer. In the last ten years, the cost has more than doubled and the share of cancer drugs increased from 12 to 23% in Europe (Table 2).

Table 2 also shows the significant variation in per capita costs between countries, with significantly lower spending in countries with low income per capita, despite a high share of drugs in total health expenditures for cancer. This is mainly explained by the price differential between local healthcare resources, mainly salaries for healthcare workers, and prices for new cancer drugs on the international market. This may partly be a statistical phenomenon since different types of rebates and other market access agreements are not included in the published data. But data on volumes consumed support the conclusion that countries with low incomes have very limited access to and use of new cancer drugs.

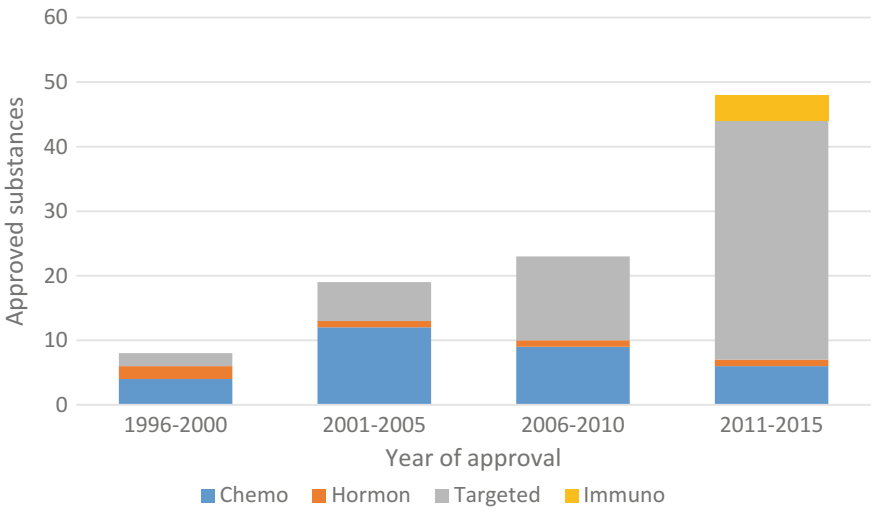

Fig. 2 Cancer drug introductions 1996–2015. *Source* Jönsson et al. (2016a)

Table 2 Expenditures on cancer drugs (unadjusted current prices), 2005–2014

	Total (million €)			Per capita (€)			Share of health expenditure on cancer		
Country	2005	2010	2014	2005	2010	2014	2005 (%)	2010 (%)	2014 (%)
Austria	183	374	510	22	45	60	11	17	21
Belgium	214	407	488	20	38	44	13	17	18
Bulgaria	28	49	128	4	7	18	25	27	61
Croatia	23	56	67	5	13	16	13	22	31
Czech Republic	100	198	162	10	19	15	26	33	28
Denmark	102	213	274	19	38	49	11	18	23
Estonia[b]	3	9	9	2	7	7	8	17	13
Finland	102	168	219	19	31	40	17	24	27
France	1,809	3,042	3,322	29	47	50	16	22	22
Germany	1,349	3,657	4,765	16	45	59	8	19	22
Greece[b]	89	128	45	8	11	4	7	9	4
Hungary	103	207	232	10	21	23	20	38	41
Ireland	88[a]	147	191	21[a]	32	41	14[a]	20	25
Italy	1,012	1,968	2,456	17	33	40	12	20	26
Latvia[b]	3	6	14	1	3	7	5	8	17
Lithuania	7	11	16	2	3	6	9	9	12
Luxembourg[b]	4	7	6	10	14	10	3	4	3
Netherlands	288	534	654	18	32	39	12	13	15
Poland	144	317	430	4	8	11	15	20	24
Portugal	221[a]	240	227	21[a]	23	22	35[a]	33	35
Romania	39	232	275	2	11	14	13	47	51
Slovakia	39	118	148	7	22	27	23	34	39
Slovenia	23	53	65	12	26	32	14	24	29
Spain	804	1,679	1,658	19	36	36	19	29	31
Sweden	165	273	338	18	29	35	9	12	12
United Kingdom	682	1,516	2,366	11	24	37	8	19	25
EU	7,626	15,608	19,062	15	31	38	12	20	23

Notes Cyprus and Malta are missing due to lack of data
Source Jönsson et al. (2016a)
[a]The value in 2005 for Ireland is the deflated value from 2006 and for Portugal from 2010
[b]Data for Estonia, Greece, Latvia and Luxembourg only comprise retail sales

There are also variations in spending per capita among the western European countries, but they are rather small, with the exception of the low spending per capita in Portugal that also may be explained by economic factors.

Another way of looking at the increased spending on cancer drugs is to separate the spending on new and older drugs. Figure 3 below shows the share of sales attributable to drugs launched within the last three years, between three and five

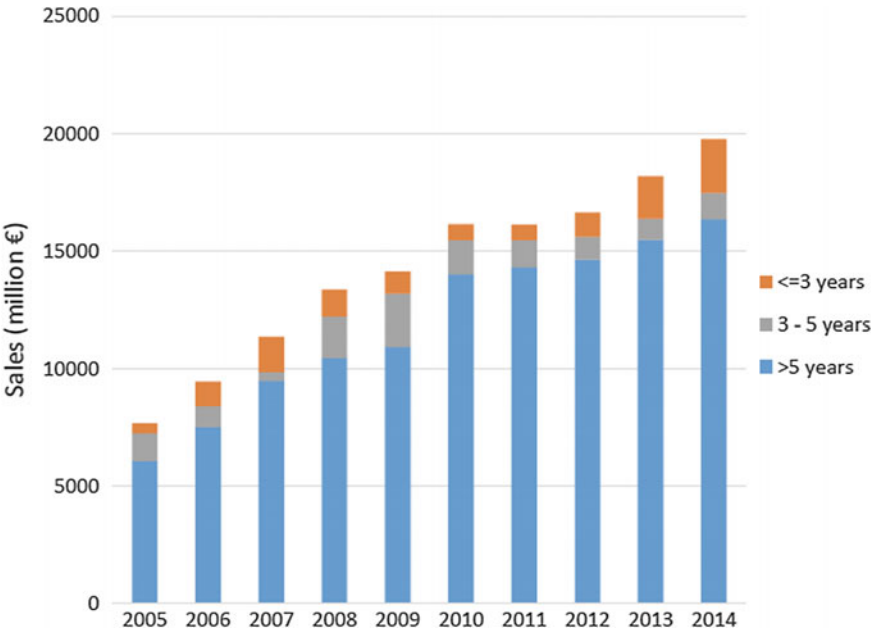

Fig. 3 Sales of cancer drugs 2005–2014 after year of introduction ("vintage"). *Source* Jönsson et al. (2016a)

Table 3 Top ten drugs by market share 1995–2014—all countries

1995		2000		2005		2014	
Molecule	Share of total sales (%)	Molecule	Share of total sales (%)	Molecule	Share of total sales (%)	Molecule	Share of total sales (%)
Goserelin	9.7	Paclitaxel	11.0	Imatinib	9.3	Trastuzumab	8.9
Leuprorelin	8.9	Leuprorelin	7.6	Rituximab	7.1	Rituximab	8.2[a]
Calcium folinate	8.4	Goserelin	7.5	Docetaxel	6.5	Bevacizumab	8.1
Tamoxifen	8.4	Docetaxel	5.3	Paclitaxel	5.7	Imatinib	5.9
Flutamide	6.1	Gemcitabine	4.9	Oxaliplatin	5.6	Lenalidomide	4.7
Interferon alfa-2a	5.9	Bicalutamide	4.4	Trastuzumab	5.4	Abiraterone acetate	4.4
Triptorelin	5.3	Triptorelin	4.3	Anastrozole	5.3	Pemetrexed	3.5
Carboplatin	4.7	Carboplatin	3.5	Bicalutamide	5.3	Bortezomib	3.3
Epirubicin	4.7	Irinotecan	3.5	Leuprorelin	4.5	Leuprorelin	2.6
Paclitaxel	4.4	Tamoxifen	3.4	Goserelin	4.2	Paclitaxel	2.5
Total	66.7	Total	55.4	Total	58.9	Total	52.0

Source Jönsson et al. (2016a)

[a]Also includes sales outside oncology, approximately 20% of value globally

years ago, and more than five years ago. Sales of drugs launched in the last three years were roughly 1.1 billion € per year; this number has been fairly stable over time with the exception of the last two years where the contribution to costs has been larger. As a proportion of sales, the newest drugs (launched within the last three years) have made up 8% of the total sales on average, varying between 4 and 11% per year. Drugs launched 3–5 years ago made up another 8% of the total sales on average.

While we can see a steady increase in costs, the drugs that make up the majority of these costs have changed very much over time as is shown in Table 3 below.

The ten most sold cancer drugs, of a total of over 100 different molecules, account for over half of the total sales. Paclitaxel is the only drug that is on the list all years; it was number 10 in 1995, number 1 in 2000, number 4 in 2005 and number 10 again in 2014.

5 Resource Use Outside the Healthcare Sector for Care of Cancer Patients

Healthcare expenditures are not the only resources used for care of patients with cancer. The definition of what is included or excluded in the accounting for health services may also vary between countries. Public and private nursing home and hospice care, and other services used for care of cancer patients at the end of life may only to a certain degree be included in healthcare expenditures for cancer. These services are often substitutes and complements to healthcare services, and a full understanding of variations in costs between countries and over time must include these services.

Caring for cancer patients by family members, relatives and friends, what often is referred to as informal care, should also be included in a comprehensive estimate of the costs of cancer. These resources are also complements and substitutes for other types of care, and part of the increase in costs over time may be due to a transfer of care from informal to formal care. While the magnitude of that care can be measured in number of hours, there are no accounts of the number of hours spent. There is also the additional problem that there are no payments and thus no opportunity to observe the cost per hour.

Finally, there are many studies pointing to the financial burden for patients with cancer (Ramsey et al. 2013). To some extent, these "out-of-pocket" costs are included in estimates of healthcare expenditures and other costs of formal and informal care, so careful assessment is needed to avoid double counting.

There are few attempts to conduct a systematic account of costs outside the healthcare sector. L-F (Luengo-Fernandez et al. 2013) estimated the total cost of informal care at 23 billion Euro, which can be compared with 51 billion for healthcare expenditures.

6 Resources Lost Due to Economic Impact on Persons with Cancer

Calculations of indirect costs due to lost production generally separate three types of sources for these costs: short-term absenteeism; long-term disability and premature mortality. The first two are related to morbidity, and the separation is generally explained by the fact that there are different sources of data for the two different reasons why a person with cancer stops working temporarily or permanently.

The three different reasons for lost production may also have different policy implications. Improvement in management of cancer, with fewer side effects of treatment and a shift from inpatient to ambulatory treatment, will make it easier for persons with cancer to continue working during treatment and thus reduce the number of days off work. Thus, we will expect this cost to decrease over time.

When survival improves, there are more persons living with a cancer that may increase long-term disability, and thus, the loss of production from this increased prevalence. But the improvement in management may also increase the ability to work, and this will reduce the number of persons with partial or full early retirement due to cancer.

Cancer is the most common cause of death among the working population. With improvements in prevention and treatment, the number of life years lost before retirement age will be reduced and thus also the costs due to premature mortality.

L-F (Luengo-Fernandez et al. 2013) reports estimates of indirect costs from cancer due to mortality and morbidity, without separating the cost of temporary and permanent absence from work. The method they use calculates costs up to 90 days of absence from work, a version of the friction cost method. For EU as a whole, morbidity costs are slightly less than a fourth of the mortality costs. The low share is partly explained by a difference in the method for calculating the two types of indirect costs. If morbidity costs had been calculated with the same method as mortality costs, the proportion would have been slightly over a third or that morbidity accounts for a quarter of the total costs of lost production. However, the estimates for different countries vary between 0.03 (Italy) and 0.58 (Belgium). The great variation in the magnitude of these estimates in the underlying data and methodology.

Comparing the results with other country estimates, a study for Spain using the human-capital method in the calculation of all three sources of productivity loss estimated that productivity loss due to premature mortality accounted for 61%, sickness absence for 7%, early retirement for 32% of the total indirect costs (Antoñanzas et al. 2006). A recent study for Sweden gives a ratio between morbidity and mortality costs of 0.34, which is much lower than the one from Spanish study, and the main reason is a much lower cost estimate for early retirement (Lundquist et al. 2016). However, a study from Norway gives an estimate more in line with the Spanish study (Oslo Economics 2016).

Table 4 Indirect costs of cancer 2009 and 2014 (in million €; unadjusted prices)

Year	2009 L-F et al. (2013)				2014 (Jönsson et al. 2016)			
Country	Health expenditure	Indirect costs			Health expenditure	Indirect costs		
		Mortality	Morbidity	Morbidity/mortality		Total	Male	Female
Austria	1,202	750	136	0.18	2,290	1,110	698	413
Belgium	1,308	1,047	604	0.58	2,722	1,437	875	563
Bulgaria	87	119	26	0.22	210	151	97	55
Croatia	124	n.a.	n.a.	n.a.	213	217	137	80
Cyprus	32	53	5	0.09	74	43	25	18
Czech Republic	271	446	166	0.35	577	487	332	155
Denmark	708	1,010	380	0.38	1,215	949	534	415
Estonia	23	61	34	0.56	65	63	41	21
Finland	482	464	77	0.17	808	560	320	240
France	10,300	4,990	2,299	0.46	15,005	7,509	4,996	2,513
Germany	15,356	11,607	2,213	0.19	21,737	11,607	7,271	4,336
Greece	927	917	86	0.09	1,144	699	487	212
Hungary	562	416	48	0.12	568	602	407	194
Iceland	n.a.	n.a.	n.a.	n.a.	42	37	n.a.	n.a.
Ireland	252	603	63	0.10	771	486	280	207
Italy	5,969	3,966	143	0.03	9,543	4,953	3,145	1,808
Latvia	28	88	20	0.23	85	80	52	29
Lithuania	29	100	40	0.40	138	100	61	39
Luxembourg	75	57	18	0.32	211	76	41	35
Malta	16	12	1	0.08	44	22	15	6
Netherlands	1,780	2,519	706	0.28	4,507	2,480	1,408	1,072
Norway	n.a.	n.a.	n.a.	n.a.	1,205	716	n.a.	n.a.

(continued)

Table 4 (continued)

Year	2009 L-F et al. (2013)				2014 (Jönsson et al. 2016)			
Country	Health expenditure	Indirect costs			Health expenditure	Indirect costs		
		Mortality	Morbidity	Morbidity/mortality		Total	Male	Female
Poland	787	1,306	386	0.30	1,757	1,627	1,045	581
Portugal	392	1,118	98	0.09	639	698	478	220
Romania	465	643	81	0.13	534	651	449	202
Slovakia	129	180	88	0.49	376	235	162	73
Slovenia	176	147	72	0.49	225	175	112	63
Spain	2,950	2,838	482	0.17	5,319	3,443	2,294	1,148
Sweden	1,369	923	478	0.52	2,746	861	442	419
Switzerland	n.a.	n.a.	n.a.	n.a.	3,570	1,404	n.a.	n.a.
United Kingdom	4,478	6,186	682	0.11	9,554	7,259	4,398	2,861
EU	50,524	42,565	9,431	0.22	87,895	50,737[a]	30,601[a]	17,979[a]

Notes Cancer is defined as ICD-10 C00-D48 for health expenditure and ICD-10 C00-97, B21 for production loss due to premature mortality from cancer during working age ("mortality loss")

[a]Excluding Iceland, Norway and Switzerland

Source Luengo-Fernandez et al. (2013), Jönsson et al. (2016a)

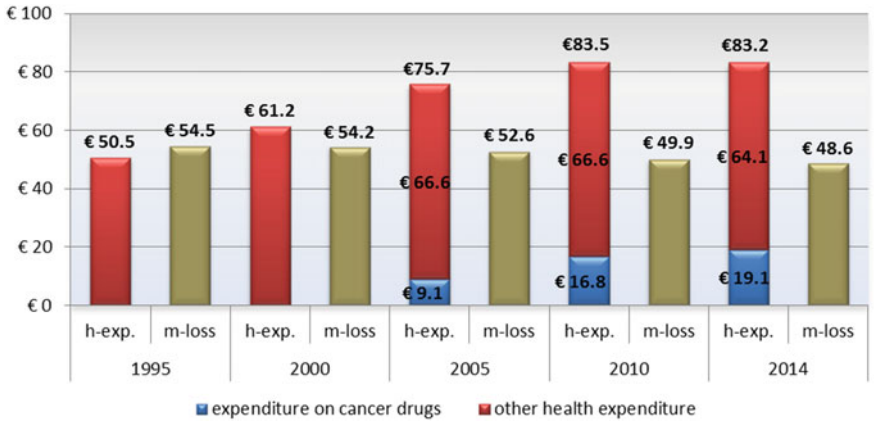

Fig. 4 Components of the total cost of cancer in the EU (in billion €; 2014 prices), 1995–2014. *Source* Jönsson et al. (2016a)

Estimates of indirect costs due to mortality are rather close in the two estimates reported in Table 4, taking into account the increase in prices (salaries) between 2009 and 2014. Looking at individual countries, the high estimate for Portugal by L-F et al. sticks out (Luengo-Fernandez et al. 2013). Comparing estimates of indirect and direct costs in the two studies, indirect costs due to mortality are 85 and 58% of direct costs, respectively, but this difference is explained by the lower estimate of direct costs by L-F et al. (Luengo-Fernandez et al. 2013). For Portugal and Croatia, estimates of indirect costs are higher than direct costs.

Over time, the indirect costs of mortality in constant prices have declined, while direct costs have increased (Fig. 4). The ratio between the two has been reduced from 108 to 58%. Explanations for this are the improvement in treatment and a shift in incidence towards older age groups.

7 Loss of Health in Economic Terms

Accounting for indirect costs includes loss of income due to mortality and morbidity. However, there is no account for the value of the loss of life years and quality of life that occur in all age groups. Estimates of disability-adjusted life years lost can be used as a complement to calculations of economic costs, but it does not give a monetary value that can be compared with the estimates of direct and indirect costs.

One method for calculation of the value of health years lost is to estimate the number of quality-adjusted life years lost and assign a value to a QALY lost. There are no systematic estimates of this opportunity cost of cancer. We will use an estimate for breast cancer in Sweden to get an idea of the magnitude of this (Lidgren et al. 2007) (Table 5).

Table 5 Cost of breast cancer in Sweden in 2002 and comparison with 2013

Cost item	Lidgren et al. (2007)	Share (%)	Lundquist et al. (2016)
Direct cost	**895**	**9**	**1,700**
Screening	200		439
Ambulatory care	287		428
Inpatient care	325		404
Drugs	83		458
Indirect cost	**2,105**	**22**	**2,240**
Morbidity	1,001		915
Mortality	1,104		1325
Intangible cost	**6,574**	**69**	n.a.
	276		
	6,298		

Million SEK in current prices
Source Lidgren et al. (2007) and Lundquist et al. (2016)

Intangible costs or the opportunity cost of lost health is by far the dominating cost item, and it is the part related to mortality that is totally dominating, as is also the case in the calculations of DALY lost.

Comparing with an estimate for 2013, we can see that the direct costs have nearly doubled, while the indirect costs have remained about the same, despite the increase in prices and salaries over time (Lundquist et al. 2016). The table also shows the changes in direct costs over time, where cost of screening and ambulatory care has doubled, and cost of drugs increased more than fivefold. The latter is a consequence of the introduction of Herceptin for HER2-positive breast cancer in 2000, and the extended use to adjuvant treatment from 2005 onwards. Cost of inpatient care, including palliative care (20% in 2013), has increased more modestly and in fact been reduced in constant prices.

8 Summary and Conclusions

There are many different approaches to the study of the economic costs of cancer depending on the specific issues and policy questions that the study aims to answer. Cancer is rapidly becoming the most significant health burden in many countries, and new medical methods are introduced to manage the disease and improve outcomes. Studies of the increasing medical expenditures for new diagnostic and therapeutic opportunities are important for a proper understanding of the impact and design of relevant policies. New technologies are often introduced for selected patient populations, but the healthcare system needs to manage all patients with cancer at all points of time. A comprehensive view of the healthcare expenditures for cancer is therefore needed.

Health accounts are not designed to attribute resource use and costs to a specific disease or a specific group of patients with the disease. Estimating costs of cancer make it necessary to attribute costs to cancer, which raises a number of methodological and data issues. It is thus not surprising that estimates of healthcare expenditures related to cancer vary between different studies. However, there is a consistent observation that the share of healthcare expenditures used for cancer is small, in the magnitude of 6%, compared to the burden of disease in terms of the share of total mortality and DALYs lost. There is also the consistent result that this share of total healthcare expenditures has not increased significantly over time. There is an increase in the costs for cancer drugs and ambulatory care, but this has been offset by reductions in costs for inpatient care, making costs for cancer grow in parallel with the overall growth of healthcare expenditures.

An important policy question is to what extent direct costs of caring for cancer patients outside the health care system has increased or decreased over time. Accounting for these costs is also important for the interpretation of variations in healthcare cost between countries. Some of the services needed and used by cancer patients can be provided in public or private institutions and by professions that are not included in the definition of health services. Without properly designed patient surveys, it is difficult to get an accurate estimate of magnitude of these costs. Studies in other diseases, for example diabetes and multiple sclerosis, have revealed that official health accounts underestimate the real use of services (Brundin et al. 2017).

Several studies have attempted to include estimates of the costs of informal care. These studies indicate that costs for informal care are between half and one-third compared to the estimated healthcare expenditures (Luengo-Fernandez et al. 2013; Lundquist et al. 2016). However, estimates vary considerably between studies, and there is a need for improvement in data and standardization of methodology in order to arrive at estimates that can be used to inform policy decisions.

With a growing incidence of cancer among the elderly population, it will be more difficult to separate the costs of cancer from the direct healthcare costs in patients with cancer. Both measures are relevant for policy decisions. It will also be increasingly important to include relevant costs of care outside the healthcare system.

Broadening the perspective to include indirect costs due to mortality and morbidity is an important contribution from an economic perspective on costing. Early studies showed that the indirect cost of cancer was significantly higher than the direct costs. A major reason for this is the dominance of cancer as a cause of death in the economically active age groups; 40% in the age group 50–64 years. Over time, we have seen a reduction in the indirect costs from mortality. While there are no age-specific costs for cancer reported, it is safe to assume that the reduction in indirect costs outweighs the increase in direct costs for this age group. The major increases in direct costs are seen in the higher age groups where all the increase in incidence over time occurs.

There are fewer and less reliable studies of the indirect costs due to morbidity for cancer. One may assume that the indirect morbidity costs should increase over time when cancer for many patients becomes a chronic rather than a fatal disease. However, a recent Swedish study reports indirect costs due to morbidity at about one-third of the mortality costs in 2013. Another remarkable aspect of that study is the very low costs due to permanent disability for cancer. A recent study for Norway reports significantly higher indirect costs than Sweden and morbidity costs that amount to three quarter of the cost of mortality. The main reason for the difference is in the cost for permanent disability. This may be due to different polices for granting disability benefits due to cancer in Sweden and Norway, but further studies are needed to fully understand the development and the impact of different policies.

Very few studies include calculations of the economic costs of lost health per se. However, this is an important part of the opportunity cost of cancer. Not spending money on interventions that reduce mortality and morbidity has an opportunity cost in terms of health loss. It is also increasingly common to relate spending on interventions to potential gains in life expectancy or quality-adjusted life years gained. When we make policy decisions involving a benchmark cost per life year or QALY gained, this can be interpreted as a value or price that will be paid. In a study of breast cancer, Lidgren et al. (2007) used the benchmark value 600,000 SEK (62.000 euro) per QALY to calculate the intangible cost of health losses due to cancer. Applying this value shows that it is the intangible costs that make up the largest amount of the economic costs of cancer.

While it is rather straightforward to calculate the number of life years and QALYs lost due to cancer, it is more controversial which unit costs or price should be applied. There are studies indicating the willingness to pay for a QALY from reimbursement agencies like NICE and TLV that can be used as guidance. Dakin et al. modelling the likelihood of NICE recommending for or against new technologies found that the odds of NICE recommending in favour of a new technology are 3.1 higher for cancer medicines (Dakin et al. 2015). There are also studies on the implicit price per LYG for new cancer drugs that could serve as a guide for costing. These studies show an increasing willingness to pay for a life year gained over time (Howard et al. 2015). In the same way as price changes affect the calculations of direct and indirect costs, changes in the willingness to pay for reducing the health burden of cancer impact economic estimates of accounting and opportunity costs.

There are a number of data and methodological problems involved in estimating the cost of cancer. There are also some unresolved issues related to how some cost items such as cost of informal care, indirect costs and intangible cost should be counted and valued. However, systematic studies of the costs of cancer, and how they differ between patients and jurisdictions, and how they change over time, are important for understanding decisions about allocating resources for cancer, and for informing rational policy decisions.

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Oncology from an HTA and Health Economic Perspective

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Abstract

In this chapter, we will present and discuss the challenges of assessing oncology products from a health economic perspective. We will provide a brief introduction on the need for economic evaluation in health care and focus on cost-effectiveness and comparative aspects of the evaluation of oncology products, which are of paramount interest to HTA decision-making bodies using economic evaluation in their decision-making framework. As the burden of oncology is well-documented, we do not discuss it in detail here. Before we address the specific issue of oncology, we will briefly define the critical aspects of HTA assessment and also define what a cost-effectiveness analysis is and why economic modelling is the most appropriate tool to assess the cost-effectiveness of oncology products. We will touch upon the prices of oncology drugs and the questions that high prices raise regarding funding and availability. We then present an overview of the general structure of an oncology cost-effectiveness model. Usually, this is quite simple, representing response, progression, advanced-stage disease and death. Despite the relative simplicity of these models, some issues may render the evaluation more complex; we will touch upon these in this chapter:

- Issue with clinical inputs due to the design of randomised clinical trials (e.g. cross-over designs involving a treatment switch)
- Need for survival extrapolation and limitations of current parametric models

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- Rare conditions with limited economic and comparative evidence available
- High pace of clinical development

Finally, we will conclude with a discussion of the uncertainty around the evaluation of oncology products and the major evolution expected in health economics in oncology.

Keywords
Health technology assessment · Cost-effectiveness · Oncology drugs · Decision-making

1 Introduction

As resources are scarce and economic growth is flattening, it is becoming unavoidable that funding of health care interventions is based on economic considerations as well as medical benefit. Cost-effectiveness analysis (CEA) has become increasingly popular for prioritising interventions for funding purposes, as it aims to ensure that health care is delivered as equitably and efficiently as possible. Almost all countries have installed formal processes to assess the costs of new health care interventions in the light of their expected benefits, before actually committing to funding them. Most of the new and promising interventions have a higher price than currently available alternatives and do not generate savings when total expenditure is considered. A minor change to an intervention strategy can lower the cost without a substantial loss of benefit, or increase the benefit without increasing the cost (Kumar 2013). CEA is the best tool to compare different strategies accurately. It allows quantifying benefits related to effectiveness (e.g. decreases in mortality and/or morbidity) and the economic costs of achieving these benefits.

CEA compares a new intervention with alternative health care interventions (standard of care or no intervention), taking future costs and benefits into account and estimating the cost per life-year gained with the different interventions (Gold et al. 1996). Cost-effectiveness is typically evaluated using an incremental cost-effectiveness ratio (ICER) comparing the new treatment with the reference comparator. Usually, ICER is expressed as an incremental cost per life-year gained. However, there are two significant limitations related to CEA. First, while CEA is useful for comparing different treatments for the same disease, it does not allow to compare treatments for different diseases that vary in outcome measures. Second, CEA cannot combine reductions in morbidity and reductions in mortality into a single index; thus, it does not allow direct comparisons between treatments that differ on these two dimensions. As a result, cost-utility analysis (CUA), which addresses some of these issues, has gained popularity among decision-makers.

Thanks to the development of "utility"-based outcome measures, like quality-adjusted-life-years (QALYs), CUA enables comparison between treatments for different diseases with varying treatment outcomes. Results of CUA are expressed as cost per QALY gained. The National Institute for Health and Care Excellence (NICE) defines a QALY as "A measure of the state of health of a person or group in which the benefits, regarding length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0–1 scale)." It is especially useful when decision-makers operate within a limited budget and need to choose between financing specific treatments and forgoing others. Thus, CUA enables to compare the value of cancer therapy to that of, for instance, an anti-hypertensive drug (Miller et al. 2014).

CUA is, ultimately, a CEA where the outcome is defined as QALY, and HTA agencies often do not distinguish CUA as a separate type of analysis, presenting it as part of CEA in their publications.

In the last decade, we have seen major advances in the management of cancers, and the progress seems to be accelerating. Survival rates have dramatically increased over the last five decades from an average of 24% the early 1970s to about 50% nowadays. The introduction of new drugs is what mainly drives this process. Therefore, the value of oncology drugs must be recognised, and premium prices can be seen as legitimate. In a growing number of countries, the amount of the premium is defined based on the threshold the country is willing to pay for an additional benefit (often the willingness to pay for one QALY). The threshold is estimated taking into account different factors—often the country's per capita gross domestic product (GDP) (e.g. the ICER threshold could be three times the GDP per capita) (Murray et al. 2000; Sarin 2008).

However, the spiralling increase in cancer drug prices has caused growing concerns. As early as 2013, a group of experts in chronic myeloid leukaemia expressed strong concerns regarding the unsustainable prices of cancer drugs. The expert group identified four critical issues with prices: 1—too high, 2—unsustainable, 3—may compromise access to highly effective therapy and 4—harmful to the sustainability of our national health care systems (Experts in Chronic Myeloid Leukemia 2013). It was indeed estimated that prices of many cancer drugs lead to ICERs far above the thresholds above; for instance, the price of cetuximab was $800,000 per year of increased survival (Fojo and Grady 2009). "Financial distress", linked to out-of-pocket payments of costly oncology drugs (OD), was the basis for the development of the new concept called "financial toxicity" (Zafar et al. 2013; de Souza et al. 2014).

As innovative, high-cost cancer therapies continue to come to market, economic modelling is needed to enable health care decision-makers to assess their value (Toumi 2017). In the next paragraphs, we describe briefly cost-effectiveness models in oncology and discuss specific issues applicable to the assessment of products in this therapy area.

2 Brief Overview of Cost-Effectiveness Models in Oncology

A cost-effectiveness model, or decision analysis model, allows simulating treatment received by patients and permits the assessment of complicated clinical issues that would require years to test through prospective studies. Such a model synthesises evidence on health consequences and costs consequences of introducing a new intervention from many different sources, including data from clinical trials, observational studies, insurance claim databases, case registries, public health statistics, and preference surveys (Weinstein et al. 2003).

Cost-effectiveness models in oncology are usually quite simple, utilising a Markov structure composed of four health states representing no progression/response, progression, advanced-stage disease and death (Fig. 1) (Marsh et al. 2014). Some of the models may not include a state representing advanced disease, being composed only of progression-free, post-progression and death states (Bai et al. 2017).

Markov models are useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once (Sonnenberg and Beck 1993). In a Markov model, the prognosis for long-term diseases is divided into several stages, and patients' progress through these stages is simulated over a specified period. These characteristics make Markov models suitable for oncology economic modelling.

Although some models include a subsequent treatment line and even extrapolate the results over a lifetime horizon, they remain quite simple from the structural perspective. Because of the relative simplicity of the structure and the clarity of the outcome in cancer (death), it is the quality of the inputs and the extrapolation that mostly drives the quality of the model in oncology. In the subsequent paragraphs, we discuss the specific issues associated with cost-effectiveness modelling in oncology.

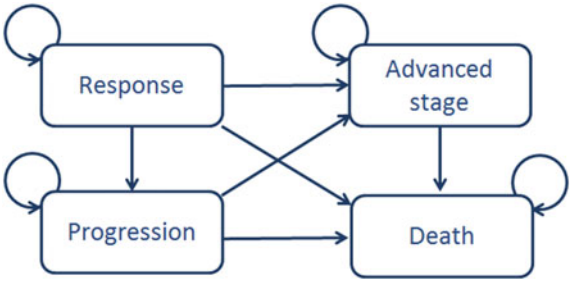

Fig. 1 General structure of a cost-effectiveness model in oncology

3 Issue with Clinical Inputs Due to Crossover (Switch) in Randomised Clinical Trials

Trials of new oncology treatments often involve crossover that allows patients receiving the control treatment to cross over to receive the experimental treatment at disease progression, or when sufficient evidence about the efficacy of the new treatment is achieved. The primary reason for this design is that it would be unethical to maintain patients under the reference therapy that appears less effective than the new therapy. It is also worth noting that some authors use the term "treatment switching" rather than "treatment crossover", since the latter term may be erroneously associated with cross-over trials, which are a different entity (Latimer and Abrams 2014).

Crossover is often a complex challenge to address in oncology HTA modelling. When an interim trial analysis shows a significant benefit on progression-free survival (PFS), it is common that all patients switch to the new and more effective treatment, as described above. Although this is ethically appropriate, it means the trial cannot reach unbiased estimates of key endpoints, such as overall survival (OS), as following the switch all patients receive the same treatment, regardless of initial randomisation.

Providing accurate estimates of an OS advantage may not be critical for obtaining approval, as long as the trials give evidence of a favourable benefit-risk ratio. However, HTA agencies almost always require precise estimates of the treatment effect on OS (Weinstein et al. 2003). To decide on price, premium payers need to accurately weigh the benefit of the new drug over current therapies against its additional cost. HTA agencies usually recommend that the model assesses the cost-effectiveness of treating an entire disease population with a novel treatment over a lifetime horizon, especially for interventions that increase survival (National Institute for Health and Care Excellence 2013). An economic model applying biased estimates of treatment effect on OS is likely to generate inaccurate cost-effectiveness results. If control group patients benefit from the experimental treatment, the increase in survival with the new therapy would be underestimated and, consequently, the ICER would likely be overestimated. This may, in turn, influence the HTA decision and lead to inefficient resource allocation. Therefore, it is necessary to provide adjusted estimates of the treatment benefit associated with the new treatment and to assess the sensitivity of cost-effectiveness results to these adjustments, as they are performed post hoc and not part of the statistical analysis plan of the original RCT. Several groups of researchers have reviewed the methods used to analyse trials with crossover (Weinstein et al. 2003; Jönsson et al. 2014; Watkins et al. 2013). Common methods are discussed in the following paragraphs.

Simple methods, which do not adjust for crossover, are commonly applied in RCTs with crossover. Intention-to-treat (ITT) analysis and per protocol (PP) analysis are two such simple methods. In ITT analysis, all randomised subjects are included in the analysis, and treatment groups for the analysis are based only on the initial, randomly assigned treatment, without taking subsequent treatments into

account. In PP analysis, patients that switch to the new and more effective treatment arm are excluded from the analysis or censored at the point of switch.

These simple methods are subject to substantial bias. ITT analysis may underestimate the treatment effect on OS, which is composed of PFS and post-progression survival (PPS). It can capture the difference between the two groups in PFS but not in PPS since control group patients are switched at progression to the experimental treatment. PP analysis excluding patients that switch is likely to be subject to selection bias and disrupt randomisation. PP analysis for OS by censoring patients that switch relies on an unlikely assumption that censoring is independent of the outcome, which is often biased. In this case, OS is likely to be artificially inflated in the control arm since patients who progress (and so may not live long) come off the curve, while those who respond well to control treatment remain on study.

Several complex methods are proposed to eliminate or reduce the bias due to crossover. Inverse Probability of Censoring Weights (IPCW) and Rank Preserving Structured Failure Time Model (RPSFTM) are two commonly used complex methods. The IPCW method censors patients at the time of switch and records remaining observations weighted by the inverse of the probability of being censored. The probability of being censored is predicted with each patient's baseline and time-dependent prognostic factors. The RPSFTM method compares the treatment arm survival time with the counterfactual survival time for control groups as if they did not switch. The counterfactual survival time is calculated with a treatment effect parameter which shrinks the survival time after crossover to remove the treatment effect on the survival time.

However, these methods are also associated with difficulties in adjusting for crossover. Besides being complicated to implement, they rely on certain assumptions which may not always be true. IPCW assumes no unmeasured confounders for estimating the probability of crossover, which is implausible. RPSFTM assumes a constant treatment effect for all patients at any treatment time. In this case, survival time in the treatment group is always assumed proportional to the counterfactual survival time in no treatment group regardless when the patient has a crossover to the treatment group. This restricts its use to cases where this kind of treatment effect is biologically plausible.

Although these methodologies have been developed to address the limitations of oncology trials, they are not widely accepted and remain somewhat controversial. Results obtained using the aforementioned complex adjustment methods are accepted by HTA organisations in the UK (NICE) (National Institute of Health and Care Excellence 2011) and Sweden (Dental and Pharmaceutical Benefits Agency) (Dentaland Pharmaceutical Benefits Agency 2012), but not in France (HAS) and Germany (GBA). A recent article has evaluated the impact of crossover on GBA assessment. The authors concluded that in GBA appraisals, oncology medicines with a crossover in their trials received better additional benefit ratings than that without crossover, but the evidence supporting them was considered of lower level. The authors also stressed that the way in which crossover is implemented might influence the assignment of evidence level by the GBA (Isbary et al. 2017).

4 Need for Survival Extrapolation and Limitations with Current Parametric Model

Health economics evaluation for pharmaceuticals has developed in response to most HTA agencies considering it mandatory for product assessment. The aim of economic evaluation within HTA is to assess all differences between considered treatments regarding costs and outcomes to inform rational decisions on resource allocation. The primary expected outcome of interventions used in oncology is the impact on patients' survival. Hence, from the perspective of economic evaluation, it is crucial to estimate the absolute gain in survival obtained due to the application of new treatment instead of comparative intervention.

It is a common belief that economic evaluations should not be limited to using only the comparative data available directly in clinical trials, especially for assessment of interventions affecting survival. To estimate an absolute gain in survival, consideration of a lifetime horizon in economic evaluations is usually deemed appropriate (Latimer 2011). However, most often survival data available in clinical trials are censored, and the presence of censoring makes in necessary to use data extrapolation for estimating total survival gain. Without extrapolating the outcomes, survival benefit evaluated within the economic analysis would be limited to the outcomes obtained during the follow-up of a particular clinical trial; therefore, it is likely to be underestimated. This underestimation can significantly influence the final results of the economic evaluation, including the conclusion on the cost-effectiveness of the assessed intervention.

The most straightforward and most frequently applied survival models in economic evaluation are so-called parametric models. The use of parametric models is associated with an assumption that survival data follow a particular probabilistic distribution, which can be described with a formula dependent on one to several parameters. Miscellaneous parametric models are available, e.g. exponential, Weibull, Gompertz or lognormal (Fig. 2). Each of these models is characterised by different features, in particular regarding the hazard pattern that can be described using them. Briefly speaking, the hazard is a conditional risk of death (or other events of interest) for patients alive at a certain point in time. The use of parametric models is adequate under the condition that hazard is constant over time or changes monotonically, i.e. only decrease or increases over time. Additionally, some parametric models apply to a situation where hazard initially increases up to a specific point in time and decreases afterwards (National Institute of Health and Care Excellence 2011). The main limitation of the standard parametric models is their lack of applicability to more complex hazards, which are often observed in oncology clinical trials.

Extrapolation of survival data with different models seems to be an unavoidable step of economic evaluation of oncology treatments. However, as with any forecast, there is some level of uncertainty connected with survival extrapolation. The uncertainty of survival extrapolation increases with the length of the extrapolated time horizon and reduced maturity of the data used for extrapolation. Furthermore,

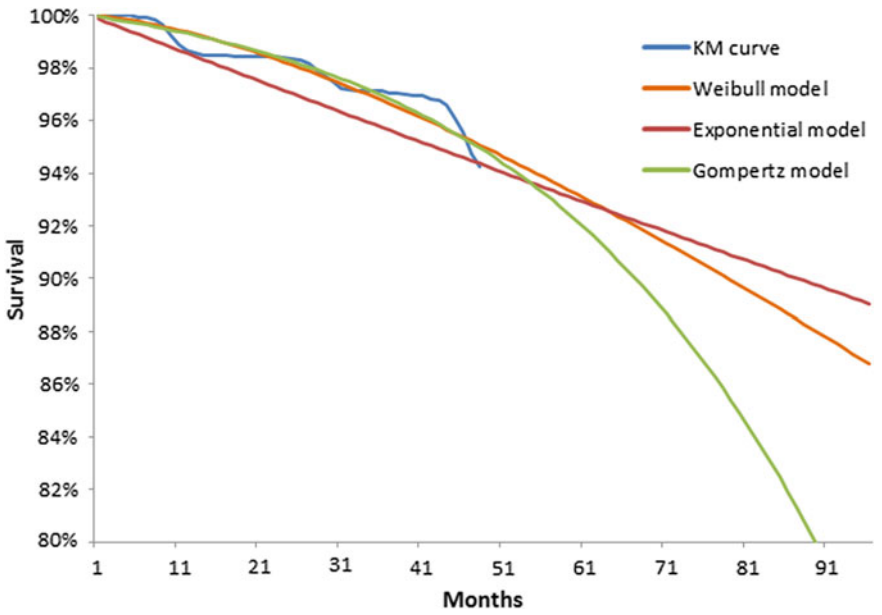

Fig. 2 Illustrative survival data from a hypothetical clinical trial fitted using different parametric models

many survival models can be considered for use in economic evaluation, taking into account the individual situation, different statistical measures as well as clinical plausibility. Economic evaluations applying different models for survival extrapolation can result in significantly different outcomes and even lead to contradictory conclusions on cost-effectiveness. Consequently, the choice of extrapolation methods may influence recommendations from health authorities, which adds another level of uncertainty connected with survival extrapolation, beyond the uncertain forecast itself.

In the face of the necessity for survival extrapolations within economic evaluation, the variety of possible methods and the impact that the choice of the method may have on the results, one would expect comprehensive guidelines to specify which model should be used in given circumstances. Nevertheless, to the best of our knowledge, such guidelines do not exist, and most probably will not be developed in the short to medium term, as it was deemed too complicated and even inappropriate to indicate specific methods (Watkins et al. 2013). Instead, a systematic process for survival model selection has been proposed. The proposed algorithm aims to improve transparency and consistency of economic evaluations so that they can be readily comprehended not only by HTA agencies but also by an oncologist and the public (Watkins et al. 2013). However, a systematic approach to choosing the survival model has rarely been used in historical economic evaluations (National Institute of Health and Care Excellence 2011).

Furthermore, parametric models are often insufficient to address all the methodological issues appearing within the economic evaluations of new oncology treatments, namely the immaturity of the clinical data, frequent lack of a control group and the availability of intermediate endpoints only. Therefore, there is a need to explore the validity of already available methods, as well as to develop new survival models with better flexibility, which would be more suitable for use in changing circumstances. Many innovative approaches have been proposed in recent years (Latimer 2013; Annemans n.d.), and, for some of them, it has been shown that their use in past economic evaluations would have resulted in more adequate estimates (Gibson et al. 2017).

Moreover, in a particular situation, it may be necessary to develop a novel survival model. This concerns mainly innovative treatments with novel mechanisms of action against cancer, for which features distinguishing them from current treatments can be noticed when analysing survival data. Recent examples of such innovative treatments with unique patterns of survival are immuno-oncology drugs. These agents stimulate the immune system of a patient against cancer. The response to the drug may be delayed, as obtaining effective immune response may take more time than the response to treatments acting directly on cancer cells. However, such a response can be durable in the subset of patients in whom it has been achieved. Delayed response is evident when looking at survival data. Initially, survival of patients using immunotherapy is similar to that with conventional treatments. At a certain point, a separation of the survival curves between these two kinds of therapies can be noticed, together with perceptible plateau achieved with immuno-oncology drugs. The plateau suggests a long-term survival benefit, which should be reflected in the extrapolation. Standard methods for survival modelling are not appropriate in such situations, as parametric models underestimate the long-term response to immunotherapy. Hence, established extrapolation methods prove inadequate for economic evaluation of immune-oncology drugs and new methods had to be developed (Dentaland Pharmaceutical Benefits Agency 2012; Isbary et al. 2017). However, some uncertainty regarding these methods remains from the perspective of the decision-makers (Ziomek et al. 2017). Nevertheless, it can be expected that more and more survival extrapolation methods will be developed in the future to meet new needs arising together with the emergence of new drugs.

5 Rare Indications with Limited Economic and Comparative Evidence Available

Economic models in oncology often need to be adapted to cope with data paucity. This is because clinical trial safety and efficacy outcomes for cancer treatments are collected over short periods and may omit information about resource utilisation, costs or patient preferences (Miller et al. 2014). Indeed, 75% of cancer trials have been shown to have 100 or fewer participants, with a median number of 43 patients (Califf et al. 2012). Small, early phase, non-randomised trials with only one study

arm are the most challenging from the economic evaluation perspective and lead to high uncertainty about the modelled clinical-economic outcomes. Better economic evidence from oncology drug trials is always in demand, as it can improve the validity of the models (Cressman et al. 2015).

Major challenges in oncology-related health economic modelling arise from the rarity of many indications, or from new potentially innovative therapies targeting the last line of treatment and, thus, lacking an effective comparator. However, the information on the cost of managing such rare or terminal conditions, and on associated utilities, is even scarcer, making the modelling exercise much more uncertain.

6 High Pace of Clinical Development

As someone has put it "patients are dying, and they are dying now", so regulators have set some new paths to achieve faster access to new therapies, such as breakthrough designation, conditional approval, adaptive approval, approval under exceptional circumstances and early entry (before marketing authorisation is granted). Therefore, innovative drugs—of which oncology products are the most numerous—enjoy faster regulatory approvals than other products (The Economist 2018). As regulatory approval times for cancer treatments have decreased, surrogate endpoints assessed over a short time frame are common in clinical trials of these drugs. Moreover, many products are approved with immature data, leading to substantial uncertainty when modelling the long-term benefit of such therapies.

Furthermore, as new products are being developed, clinical practice may change dramatically, making ongoing clinical trials invalid or useless. For example, while a product is being tested in a clinical trial in the second line, a new first-line drug emerges, making this trial uninformative.

Finally, HTA evaluation frameworks may change as new product classes emerge. NICE has developed a report on immunotherapy called chimeric antigen receptor (CAR) T-cell therapy, where they reviewed the applicability of NICE guidelines for (CAR) T and acknowledged the need to adapt their decision-making framework to such new emerging therapies (Crabb and Stevens 2016) This is even more true for gene therapies.

7 Further Issues with Health Economic Models in Oncology

7.1 Health-Related Quality of Life

Many cancer therapies extend survival only marginally or delay disease progression without extending survival. Therefore, given the high cost of these treatments, a QALY-based CUA is unlikely to reach value-for-money levels that would enable

recommendation for financing. Also, the practice of eliciting QALY weights based on valuations from the general population can be challenging, because cancer is dreaded by many people more than other life-threatening conditions (Neumann et al. 2012) Further, utilities are one of the most influential parameters in CUA for advanced tumours submitted to NICE (Oncology Health Economic Modeling Post-Progression Working Group 2017). Therefore, the utility and validity of QALY-based HTA remain an open debate, and some countries have created exceptional HTA pathways for oncology interventions or have eased access to cancer treatments. This was achieved either through modifiers allowing a higher ICER in specific situations (such as end-of-life or disease-severity creating inequity) or through exceptions within HTA policies. Such exceptional circumstances are often applied without being explicitly acknowledged. Indeed, the ICER under which oncology products were recommended by NICE was significantly higher than for non-oncology products (Collins and Latimer 2013). Some countries operate a specific fund for oncology products that are not cost-effective (i.e. Cancer Drugs Fund in the UK) (Prasad and Mailankody 2016), which allows non-cost-effective products to be used within the NHS. However, the Cancer Drugs Fund was heavily criticised for wasting resources without bringing any additional value (Cohen 2017). Following criticism, CDF underwent a substantial reform in 2016 and drugs are now re-assessed after two years.

8 Comparator and Off-Label

When comparing oncology products in health economic models, efficacy data for both treatments should come from head-to-head clinical trials comparing the two drugs. However, new drugs are often approved based on trials versus placebo, so that modelling has to rely on indirect comparisons. Further, 50–75% of cancer care is provided off-label ("Off-Label" Indications for Oncology Drug Use and Drug Compendia 2005) and, to reflect the real-life situation, models may need to compare treatments used in non-approved indications, for which clinical trial data is absent. The missing data can be obtained from other sources, e.g. patient registries, but this can lead to further uncertainty around modelling outcomes.

9 Cost-Effectiveness Vs Affordability

We believe it is essential to raise two points before we conclude this chapter. Firstly, cost-effectiveness does not address budget constraints of payers and may mislead decision-makers by considering that a cost-effectiveness treatment option is also affordable. Secondly, theoretical limitations of CUA are widely described in the literature, so that when assessing a CUA, the reviewer must exert extreme caution in evaluating the methods and assumptions employed in the model,

as subtle biases in the specification of the model can dramatically alter the results (Ryder et al. 2009). However, despite the limitations of CUA, no alternative methods have been proposed. Moving forward, integrating additional information into CUA may help to facilitate informed policymaking.

10 Conclusion

High uncertainty is the main challenge in CEA of newly approved oncology products. This uncertainty has increased dramatically over the recent years, with the emergence of new therapies that display efficacy, response features and survival shape distinct from all previously known products. These novel therapies are often associated with very high efficacy that cannot be easily quantified at time of launch due to immature data and come with a very high price tag. The development of gene and cell therapies targeting, often rare, cancers further increases the uncertainty in oncology health economics assessment. New methods for addressing this uncertainty have been developed but remain controversial, and have not yet been adopted by all experts or HTA agencies. In the coming years, we can expect health economics in oncology to evolve substantially, to address the challenges ahead.

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Heterogeneous Recommendations for Oncology Products Among Different HTA Systems: A Comparative Assessment

Szymon Jarosławski, Eve Hanna, Monique Dabbous, Lylia Chachoua and Mondher Toumi

Abstract

Rising budget constraints and demands for healthcare services create additional complexity within the decision process for resource allocation. Innovations and scientific progress have been shown to be key drivers of the increase in healthcare expenditures (1). In the context of rising medical care costs and limited resources, Health Technology Assessment (HTA) was developed as a tool to inform decision-making and to provide the rationalization behind these decisions driving resource allocation and spending for health technology products. Furthermore, HTA agencies make the decision-making process more transparent. The HTA approach involves evaluating multiple aspects of a new product's value in order to maximize health gain provided within the setting of limited resources.

Keywords

Health technology assessment · HAS · IQWiG/G-BA · NICE · Cost-effectiveness

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1 Introduction

Development of HTA among European countries, the USA, and Canada has been asynchronous and is still ongoing. However, it appears that the implementation of HTA methodologies for the evaluation of newly marketed healthcare interventions is widespread, and HTA is now a mandatory part of the market access (MA) process in Europe, Canada, and Australia. In the USA, HTA is driven by non-for-profit and scientific organisations and it is not required for MA by commercial or public payers.

Since healthcare resources are scarce and should be allocated with maximum efficiency, interventions awaiting reimbursement need to be prioritized. Resources may be allocated based on implicit or explicit prioritization. Whereas implicit prioritization of healthcare spending is a non-transparent process, explicit prioritization is based on a pre-defined and publicly available set of criteria that allow justifying a decision to provide or deny the financing of a given healthcare intervention. These criteria are based on evidence generated through the HTA process.

Best practice in the organization of the healthcare financing decision process involves separating the HTA, the pricing decision and the regulatory approval. This allows independent opinions to be collected at three different levels:

- Regulatory decision is driven by a benefit-risk assessment and relies largely on internal validity of clinical trials for a given intervention, excluding of any economic considerations. Regulatory decision results in a licence to commercialize the product (marketing authorization).
- HTA is driven by effectiveness as well as economic consideration and relies mainly on external validity of the clinical trial data and on modelling of the product's value for money, usually expressed as cost per quality-adjusted life year (QALY). However, some HTA agencies do not consider economic evidence in their decision process and focus more on real-life clinical aspects. Usually, the HTA results inform the reimbursement decision.
- Pricing decision is driven by the HTA outcome, including appraisal of the HTA evidence in various contexts, budget considerations and public health impact as well as priorities.

These three levels of activities within the healthcare financing decision process use distinct mechanisms and rely on different types of expertise and experience, so that they cannot readily be undertaken by a single committee.

Overall, HTA decision frameworks can be influenced to a varying degree by health economic assessment or clinical value of a healthcare intervention (Table 1). In the following section, we discuss the HTA decision-making framework in selected countries.

Table 1 Differential focus of HTA frameworks across countries

Health economics	Clinical value	Mixed
UK (NHS [payer] perspective), Sweden (societal perspective)	Germany, Italy,	France, Spain, Poland, Belgium, Turkey

2 Brief Overview of Selected HTA Agencies

2.1 France—HAS

In France, marketing authorization is usually provided by the European Union via the European Medicines Agency (EMA) or by the French National Agency for the Safety of Medicine and Health Products (ANSM). After receiving a marketing authorization, all products undergo HTA through the French National Authority for Health (HAS). HAS is composed of two committees that review the products filed to the agency; these committees are the Transparency Committee (CT) and the Economic and Public Health Assessment Committee (CEESP). The CT reviews the clinical evidence and provides two critical scores for each product. The first score, the Service Médical Rendu (SMR), represents the assessed absolute therapeutic value of the drug on a 5-level scale. The incremental or added value of the product (ASMR) is also rated on a 5-level scale. The SMR determines the reimbursement rate, while the ASMR drives the pricing of the product. If a product is considered innovative by the manufacturer and is projected to potentially reach €20,000,000 in sales, it has to undergo a health economics assessment performed by CEESP. If the product is to be available in retail pharmacies, the recommendations of the two HAS committees are then sent to the Economic Committee of Health Products (CEPS) for pricing negotiation. Hospital products are priced during the procurement process via negotiations between the CEPS and the hospital buyers. Dependent on the hospital buyer and their negotiation with CEPS, the price may vary; thus, hospital product prices may vary between hospitals.

2.2 Germany—IQWiG/G-BA

In Germany, the marketing authorization is provided at European level by the EMA. At the national level, it is ensured via Federal Institute for Drugs and Medical Devices (BfArM)/Paul-Ehrlich-Institut (PEI). In Germany, products with a marketing authorization are automatically reimbursed by the statutory health insurance, with the exception of lifestyle products. In Germany, hospital-only medicines are not subject to evaluation by HTA bodies. For drugs available in the retail sector, the manufacturer has to submit a dossier to initiate the AMNOG process (the German HTA process). This requires submitting evidence to the Federal Joint Committee (G-BA) to identify if the product is more effective than a relevant

established comparator. G-BA mandates an independent scientific institute, the Institute for Quality and Efficiency in Healthcare (IQWiG) to examine the Additional Benefit (AB) and harm of the drug and give its preliminary recommendations. The AB is rated on a 5-level scale (major, significant, small, unquantifiable and no added benefit). Evaluation of the additional benefit and harm is based on three patient-relevant outcomes of mortality, morbidity and HRQoL. Germany addresses the uncertainty surrounding the evidence provided for additional benefit assessment by classifying its strength; the evidence supplied may be classed as providing a proof, indication, or a hint of a given claim. In Germany, a product will be freely priced for the first year on the market. Special regulation exists for EU-designated orphan drugs with an annual out-of-hospital turnover less than €50,000,000 in any of the two years postlaunch or in previous 12 calendar months. For such drugs, if IQWIG confirms a potential turnover lower than the arbitrary value of €50,000,000, G-BA should acknowledge the AB automatically.

2.3 UK—England—NICE

The UK, health service is a devolved matter, i.e. remains a responsibility of the constituent countries. This paragraph focuses specifically on England, which has a long-standing history of performing HTA assessments. Marketing authorization in England may be granted at the cross-EU level by the EMA or, at the national level, by the Medicines and Healthcare Products Regulatory Agency (MHRA). Following marketing authorization, the National Institute for Health and Care Excellence (NICE) undertakes HTA on the product. NICE provides both single technology appraisals and multiple technology appraisals, by reviewing clinical and economic data. The assessment of products informs the National Health Service (NHS) where to best allocate their funds for reimbursable products. In the UK, pricing schemes have been set up by the UK Department of Health (DH). For hospital products, actual prices are negotiated between the hospital and manufacturer, or established via tenders. Retail pricing for branded drugs can follow two different schemes—the Pharmaceutical Price Regulation Scheme, which includes free pricing for new active substances and price negotiation for other products (constituting indirect profit control), or the Statutory Price Regulation Scheme, which involves statutory price limits on sales of prescription drugs. Generics in the UK are subject to free pricing, albeit their price is below that of the off-patent original product. NICE uses cost-effectiveness analysis (CEA) in its economic assessment with particular attention given to the incremental cost-effectiveness ratio (ICER) per QALY. The ICER is the key driver of determining CE for a product and its potential for reimbursement. A product is considered cost-effective if its ICER lies between £20,000 per QALY and £30,000 per QALY (products which lie below £20,000 per QALY are likely to have positive recommendations, while those that exceed £30,000 per QALY will mostly likely receive negative recommendations). However, other product characteristics and considerations (e.g. rarity of the condition) may result in an exception being made with regard to the ICER threshold. NICE

makes its overall decision based on comparators, clinical effectiveness and health-related factors, cost-effectiveness, and other non-health factors. The decisions NICE can make range from recommended, recommended with restrictions (often referred to as optimized), only in research, not recommended, and recommended for use in the Cancer Drugs Fund (CDF) (oncology appraisals only). CDF provides patients access to new treatments either via an MAA, while further evidence is collected to address clinical uncertainty or as interim funding for all newly recommended cancer drugs.

2.4 UK—Scotland—SMC

In Scotland, marketing authorization originates from the EMA, or from the MHRA, which powers extend across the UK. However, Scotland has its own HTA agency, the Scottish Medicines Consortium (SMC), which has been advising the Scottish NHS on newly licenced medicines, formulations and indications since 2002. The SMC uses a two-stage decision-making process. The New Drugs Committee (NDC) makes recommendations on the basis of clinical and economic evidence submitted by the manufacturer; this is followed by a deliberative process and a final advice by the SMC committee. During the assessment, the SMC does not directly refer to an ICER threshold and modifiers, such as orphan drug status, substantial clinical benefits or the absence of alternatives can allow the SMC to accept drugs with higher uncertainty about the ICER estimate. However, the SMC does refer to NICE's ICER per QALY thresholds during decision-making. Pricing in Scotland follows the schemes set up by the UK Department of Health, but the SMC advises the Scottish NHS on funding. The SMC delivers its final opinion as either recommended, recommended with restrictions or not recommended. This opinion is driven by clinical efficacy and safety, cost-effectiveness and budget impact.

2.5 Sweden

After getting a marketing authorization from the EMA or the Medical Products Agency Läkemedelsverket (MPA), the Dental and Pharmaceutical Benefits Agency (TLV) assesses both the additional therapeutic value of the health product and the efficiency it may generate (i.e. cost-effectiveness). TLV decision is driven by cost-effectiveness analysis, but the agency does not use a fixed ICER threshold. TLV issues the final decision on a product but the Country Councils Pharmaceuticals committees are responsible for its execution. TLV decides if the pharmaceutical is to be included in the pharmaceutical benefit scheme (which involves setting the product's price and level of reimbursement), and if any restrictions or conditions should be applied.

2.6 Australia

In Australia, marketing authorization is granted by the Australian Register of Therapeutic Goods (ARTG). The Australian government aids in the funding of products on the ARTG through various entities, such as the Pharmaceutical Benefits Scheme (PBS) and the Medicare Benefits Schedule (MBS). Funding for products in Australia can also come from the private health insurance. Distinct groups conduct health technology assessment (HTA) in Australia to ensure the Department of Health can make informed decisions in channelling public funds for new products; among these groups are the Therapeutic Goods Administration (TGA), the Medical Services Advisory Committee (MSAC), the Pharmaceutical Benefits Advisory Committee (PBAC) and the Prostheses List Advisory Committee (PLAC). The PBAC is independently commissioned by the Australian Government to recommend new products for listing; without a recommendation from the PBAC, a product cannot be listed. The PBAC takes into consideration clinical effectiveness, safety and cost-effectiveness as well as the medical conditions the product targets. The PBAC consists of two sub-committees—the Economics Sub-Committee (ESC), which reviews clinical and economic evidence of products, and the Drug Utilization Sub-Committee (DUSC), which reviews information surrounding the expected drug utilization before its listing on the PBS and monitors drug use after listing. The PBAC can ultimately make one of three types of recommendations: recommend to list the medicine on the PBS, recommend not to list the medicine on the PBS, or defer the recommendation decision until additional information is available. The various bodies involved in HTA within Australia are all dedicated to providing appraisals of both the safety and efficacy of health technologies for market regulation, and of their comparative safety, clinical and cost-effectiveness. These appraisals inform the decision-making on public funding, private health insurance reimbursement and post-market surveillance of products.

2.7 Canada

The Canadian Ministry of Health, Health Canada, grants marketing authorization for products entering Canada. The Canadian Agency for Drugs and Technologies in Health (CADTH) is an independent, not-for-profit agency, dedicated to providing evidence-based information about the effectiveness of drugs and other health technologies to Canadian healthcare decision makers. CADTH fulfils its mandate through a HTA programme, known as the Common Drug Review (CDR) process. Under CADTH's mandate, the CDR process accepts drug submissions from manufacturers, conducts systematic drug reviews and provides participating public drug plans (federal, territorial, and all Canadian provinces except Québec) with evidence-based clinical and economic information, and expert advice, to support their formulary listing decisions.

The pan-Canadian Oncology Drug Review Process (pCODR) is a cross-jurisdictional review process for all oncology drugs, based on Ontario's

pre-existing cancer drugs review. Quebec, predominately French speaking, does not, for the most part, participate in such pan-Canadian processes that serve the rest of the country (English speaking). For Quebec, the Conseil du médicament—Québec (CM-Q) is the provincial body that accepts drug submissions from manufacturers and makes recommendations concerning listing a drug on the provincial drug formulary (Liste de Medicaments). The final listing decision is made by Québec's Minister of Health.

3 Comparison of HTA Decision-Making Frameworks

3.1 HTA Outcomes

HTA outcomes are a collection of intervention characteristics that describe its clinical and/or economic value, as well as the economic impact of financing the intervention. Although similar product characteristics can be assessed by different national HTA agencies, they are not determined similarly and do not impact decisions in the same way. Furthermore, a number of different characteristics may be relevant to reimbursement and pricing decisions as discussed below.

Clinical considerations

Clinical evidence is the starting point of benefit assessments conducted by HTA organisations. In Germany, only clinical evidence is considered when assessing additional benefit. In France, clinical benefit remains the cornerstone to acknowledging the additional benefit of a new intervention. While the French HTA approach is focused on the absolute therapeutic benefit, the German one relies more on comparative difference. In Italy and Spain, although multiple criteria are considered, in practice the assessment remains driven by clinical evidence. Below, we describe the metrics used by various agencies.

- In France, the absolute therapeutic benefit, SMR, is assessed by the CT and determines the intrinsic value of the drug, irrespective of its comparators. The SMR informs whether the intervention should be reimbursed and what level of coverage should be provided by the statutory health insurance. Furthermore, the additional benefit over the reference comparator, the ASMR is used during the pricing negotiations between the Economic Committee for Medicinal Products (CEPS) and the manufacturer.
- In Spain, the General Directorate for Pharmacy and Medical Devices (Dirección General de Farmacia y Productos Sanitarios, DGFPS) considers the product's absolute therapeutic clinical benefit when developing the reimbursement recommendation.
- In Germany, the additional benefit, proposed by the IQWiG and determined by the G-BA, establishes whether the manufacturer can negotiate a reimbursed

price with the statutory health insurance and provides guidance on any potential price increase as compared to the existing products.
- In Sweden, the major HTA driver is cost-effectiveness. However, interventions with a marginal clinical benefit ("no other available medicines are significantly more suitable") can be reimbursed within the pharmaceutical benefits scheme. The higher the marginal benefit is, the higher price can be set.
- In Italy, the degree of innovation helps determine the inclusion of the product on the national reimbursement list and the reimbursement setting (both in-patient and out-patient, or in-patient only). The Pricing and Reimbursement Committee (CPR) then leads the pricing negotiations with the manufacturer and the Committee for Economic Planning (CIPE). Budget Impact

Budget impact of an intervention in the healthcare system is a widely assessed parameter. Although in the past it was rarely considered when making a recommendation, there is a trend for HTA agencies to increasingly request budget impact analysis (BIA). BIAs submitted by the manufacturers are usually first reviewed by HTA agencies and then referred to during the negotiation processes between manufacturers and decision-making bodies.

- In Spain, BIAs are considered in both the reimbursement and pricing recommendations.
- In France, BIA is now mandatory for an innovative product that has an expected drug budget impact equal to or higher than €50,000,000, while non-innovative products are expected to have a neutral effect on the budget.
- In Canada, although BIA is not assessed by the CADTH as part of the HTA process, it is regularly performed on request of the provinces. CADTH is primarily focussed on cost-effectiveness analysis.
- In England, in April 2017, the NHS England introduced a "budget impact test" where drugs that are likely to cost more than £20,000,000 in any one of their first three years will be subject to negotiations between the company and the NHS. This applies to therapies which are deemed cost-effective by NICE, but are expected to have high budget impact. As a result, companies can negotiate prices confidentially with NHS England, to speed up patient access to therapies recommended by NICE.

Cost-effectiveness

- In France, a CEA should be provided if the product is innovative (ASMR I to III) and anticipated to generate a yearly turnover of at least €20,000,000. In this case, the CEESP reviews the consistency of the methodology used in the manufacturer submission with the HAS guidelines and identifies the conditions for efficiency of the new technology. The definition of the conditions of efficiency remains unclear, but from experience it represents the positioning of the new intervention which provides the best ICER (Toumi 2017). In France, there is no official ICER threshold, but an analysis of CEESP opinions on pricing

decisions suggested that the ICER is around €50, 000 per QALY gained (Toumi et al. 2017). Further, this threshold proved to be variable, depending on the unmet need, burden, and rarity of the targeted condition (Toumi et al. 2017).

- NICE technology appraisals based on cost-effectiveness evaluation lead to the implementation of the recommended technologies within the NHS in England, and potentially also in Wales and Northern Ireland. Similarly, the SMC assesses for new products based on their cost-effectiveness and determines whether the technology will be recommended within NHS Scotland. For both jurisdictions, the ultimate decision-making is driven by the cost-effectiveness analysis.
- In Italy, cost-effectiveness data are considered for both pricing and reimbursement decisions, but their impact remains unclear and likely very limited. Similarly, in Spain, cost-effectiveness analyses are expected to substitute BIA in the DGFPS recommendation process, but—at present—it is still not a critical piece of information for final decision-making. A health economics committee was set up through a royal decree, but it has not been active for many years.
- In Canada and Australia, CEA is the driver of HTA decision-making. However, in Australia access to innovative products tends to be dramatically delayed in comparison to other developed countries, while Canada provides a reasonable time to access. In Canada, discounts from list prices may be negotiated by the provinces. The provinces may also join forces through common purchasing, which facilities the negotiation of such rebates.

3.2 HTA Aspects Specific to Oncology

The cost per QALY is an established outcome of cost-utility modelling, including cancer therapies. However, this metric is likely to fall well above societally acceptable thresholds for cancer therapies that are costly and only provide a small incremental improvement in survival or quality of life.

In addition, the practice of eliciting QALY weights based on valuations from the general population can be challenging because cancer is dreaded by many people more than other life-threatening conditions (Neumann et al. 2012). Therefore, the utility and validity of QALY-based HTA in oncology remains an open debate.

Furthermore, the choice of meaningful clinical trial outcomes to feed HTA models remains a challenge. Illustratively, progression-free survival (PFS) has become the most commonly used primary endpoint in oncology trials. PFS is related to clinical response and progression definitions that are standardized metrics used in phase II clinical trials, which describe how tumours are affected by the tested therapy (Therasse et al. 2000). However, PFS is often poorly correlated to overall survival (OS) (Buyse et al. 2010; Kim and Prasad 2015; Svensson et al. 2013). Nevertheless, an OS gain may not be necessary for a positive recommendation by HTA agencies and PFS is sufficient (Chabot and Rocchi 2014).

When appraising HTA evidence, healthcare payers are concerned with issues related to relevance, quality, and interpretability of patient-reported outcomes

(PROs), such as HRQL, and may dismiss PROs that do not independently predict improved outcomes (Zagadailov et al. 2013). Quality concerns can be related, for instance, to data from open-label trials or to missing trial data (Basch et al. 2015). Also, there is no consensus among different national payers on the relative value of objective clinical outcomes and HRQL and each payer may value these outcomes differently (Zagadailov et al. 2013).

Clinical survival endpoints are critically important measures for economic evaluation within HTA. However, survival modelling is not straightforward when data needs to be extrapolated into the future (N L, S R, A B 2017). Exceptional caution when choosing survival modelling techniques is necessary in case of immuno-oncology (I-O) products, which are often approved based on less mature data, frequently without a control group, and with intermediate endpoints only. Survival extrapolation for I-O drugs can be a more complex issue, which is caused by the presence of a delayed treatment effect, false progression, or the possibility of some patients achieving long-term survival (Othus et al. 2017). The traditional parametric methods often underestimate the clinical value of I-O therapies, giving rise to misleading estimates of cost-effectiveness. More flexible approaches are needed to capture the non-standard pattern of survival endpoint characteristic for I-O (Gibson et al. 2017). These methods, such as flexible parametric models, mixture cure models, or response-based models are currently being refined and appraised by researchers.

4 Evaluation Criteria and Processes in HTA

Although there is an overall trend to support a consistent general concept of good practice among HTA organizations (e.g. the European Network for Health Technology Assessment (EunetHTA) guidelines, http://www.eunethta.eu/hta-core-model), evaluation of the parameters of interest can differ across countries. The factors taken into account in each country are summarized in Table 2.

All new original drugs are assessed by HTA bodies in France, Germany, Italy, Spain and Sweden. In Germany, hospital-only medicines are not subject to evaluation by HTA bodies, as well as known substances that are already approved. Generics are assessed in Italy, Spain and Sweden; submission of health economics data is not required. In Italy and Spain, absolute and relative therapeutic value as well as budget impact is used as main decision criteria. TLV in Sweden uses both absolute and relative therapeutic value, but it is the product's cost-effectiveness that is ultimately the main decision driver.

In England, NICE assesses only new drugs identified through specific criteria, such as clinical benefit, public health interest, and potential budget impact to the NHS (excluding vaccines and HIV products). Its decision is based primarily on cost-effectiveness analysis.

Table 2 Comparison of HTA and reimbursement rules in selected European countries

		France	Germany	Sweden	England	Canada	Australia
Scope	All new original prescription drugs	✓	✓	✓	×	×	✓
	All generics	× (with exceptions)	×	✓	×	×	×
Key reimbursement criteria	Absolute therapeutic value[a]	✓✓✓	✓	✓✓✓	✓	✓✓	✓✓
	Relative therapeutic value[b]	✓	✓✓✓	✓✓✓	✓	✓✓	✓✓
	Budget impact	×	✓	×	×	×	×
	Cost-effectiveness	✓ (innovative products)	×	✓✓✓	✓✓✓	✓✓✓	✓✓✓

[a]Disease severity and burden, unmet needs, efficacy/safety of the product
[b]Incremental efficacy/safety versus available comparators
The number of ✓ indicates the extent to which a given criterion is considered in each country

In France, HTA decision criteria to assess the benefit over the next best alternative is primarily based on absolute therapeutic difference in efficacy or safety, and on cost-effectiveness for innovative products (less than 5% of products undergoing an HTA). In Germany, the decision is based on relative efficacy/safety. Relative efficacy is assessed through the 95% upper limit of the confidence interval of the relative risk/ratio.

The high heterogeneity in the decision analysis framework, the variability in risk aversion, and the differences in affordability, appreciation of unmet needs and public health impact between countries explain the large variability of HTA recommendations (Nicod 2014; Allen et al. 2017; Massetti et al. 2015; Pomedli 2010). A study comparing methods, procedures and contextual characteristics of HTA-based decision-making among Germany, UK, France and Sweden found considerably more differences than similarities of HTA features across agencies and countries (Schwarzer and Siebert 2009). Illustratively, there was a wide variation in the rate of positive recommendations for oncology products, ranging from 48% in England to 95% in Canada, and inter-agency decision agreement was low (Chabot and Rocchi 2014). A low decision agreement was also found among all HTA drug recommendations made by agencies in Canada, Australia, Sweden and Scotland (Lexchin and Mintzes 2008; Nicod and Kanavos 2012).

Further, the so-called Market Access Agreements (MAAs) which are negotiated between healthcare payers and manufacturers in certain countries can be influenced by HTA assessment (Jaroslawski and Toumi 2011a; b). MAAs typically aim at obscuring the real drug price agreed with the payer, in order to optimize international price setting through the external price referencing regulation. They have become increasingly common for oncology products that do not meet the cost-effectiveness criteria in the UK and Sweden and, in Italy, for products deemed to be too expensive. Reaching a rebate of 50–60% for oncology products is not rare, especially in the UK. Those rebates are confidential in all countries but Germany.

Moreover, the difference in affordability as expressed in Purchasing Power Parity (PPP) has shown to be a driver of recommendations between countries. The countries with a higher PPP happen to finance innovative drugs earlier and at a wider scale than those with a lower PPP. A recent study has shown that, when adjusted on affordability, the prices of orphan drugs may be up to nine times more expensive in the lowest-income EU countries versus the richest ones (Young et al. 2017). Consequently, these drugs often face negative financing decisions in the low-income countries, which also often receive lower rebates than the richest ones.

4.1 Cross-Country Comparison of HTA Recommendations in Oncology

The authors reviewed HTA recommendations for oncology products among national HTA organizations in a selection of countries: France, Germany, UK (England and Scotland), Sweden, Canada and Australia.

The authors selected oncology drugs, excluding generic, biosimilar and withdrawn or suspended products, authorized by the European Medicines Agency (EMA) from 1/1/2015 to 31/12/2017. Available HTA reports for each of the 44 retained products were downloaded from the official HTA websites in the seven countries: France—HAS: https://www.has-sante.fr/portail; England—NICE: https://www.nice.org.uk; Scotland—SMC: https://www.scottishmedicines.org.uk; Sweden—TLV: https://www.tlv.se/in-english.html; Australia—PBAC: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes; Canada CADTH: https://www.cadth.ca/fr; Germany—G-BA: http://www.english.g-ba.de and IQWIG: https://www.iqwig.de.

Not all products were identified in all countries because of the time lag in publication of HTA reports, the selective assessment by some agencies, or the strategic decisions of the manufacturers to delay filing of HTA evidence in some countries.

The authors have found that France was the only country that did not give a negative recommendation for any of the 16 products assessed, followed by Germany, which gave only one negative recommendation among 23 assessed products. Four products in France and 11 in Germany were recommended with restrictions.

On the other hand, Canada did not recommend any of the 12 assessed products without restrictions and Australia fully recommended only one of 14 products. Further, Australia gave eight (50%) negative or "unable to recommend" decisions, Sweden six (60%), Scotland six (32%), England five (26%) and Canada three (25%) (Fig. 1).

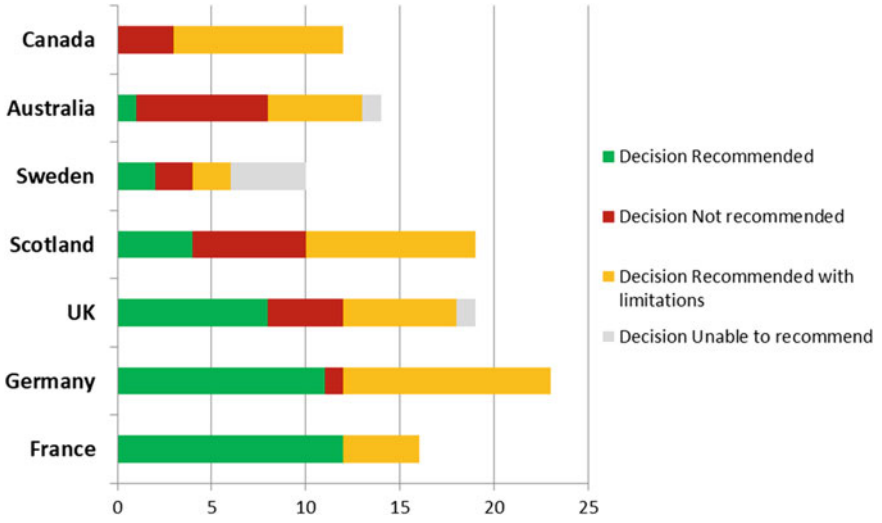

Fig. 1 Available HTA recommendations per country for 44 oncology products approved by the EMA

A closer analysis of the decisions issued by France and Germany revealed that the French CT gave substantial or important absolute therapeutic value rating (SMR) for 14 (88%) products and the German IQWIG and G-BA gave 13 (57%) proven or considerable additional benefit ratings (Fig. 2). However, the French additional benefit rating (ASMR), which is used for price negotiations, was merely IV or V (minor or no additional benefit) in 13 (81%) of the assessed products.

The large opening for reimbursement in France is associated with a low rating of additional therapeutic benefit, which—in theory—caps the price of the product in France. While this provides the pricing committee with an advantage in negotiating the price of such treatments, it may also suggest that the French HTA rating scale suffers from a floor effect which makes it insensitive to innovation. On the contrary, the German HTA assessment scale covers a broad range of scores suggesting that it is a better tool for assessing the additional benefit brought about by new medicines. However, as shown in Fig. 2, there is a discrepancy between the ratings of IQWIG, which performs data analysis, and the ratings of the G-BA, which is responsible for evidence appraisal. This proves that the separation of the two processes is indeed effective and that the G-BA plays a vital role in decision-making by putting the data analysed by IQWIG in a broader perspective.

It appears that countries such as France and Germany, which focus on clinical evidence in the HTA assessment, are less often critical of the comparator proposed by the manufacturer (50 and 39% of reports respectively) than countries where HTA is economically driven, where 60–70% of reports raised comparator-related objections (Fig. 3). The most commonly criticized aspects in France were limited efficacy data and the choice of the comparator, while in Germany—limited efficacy and safety data, in the UK—the choice of comparator, cost-effectiveness, limited

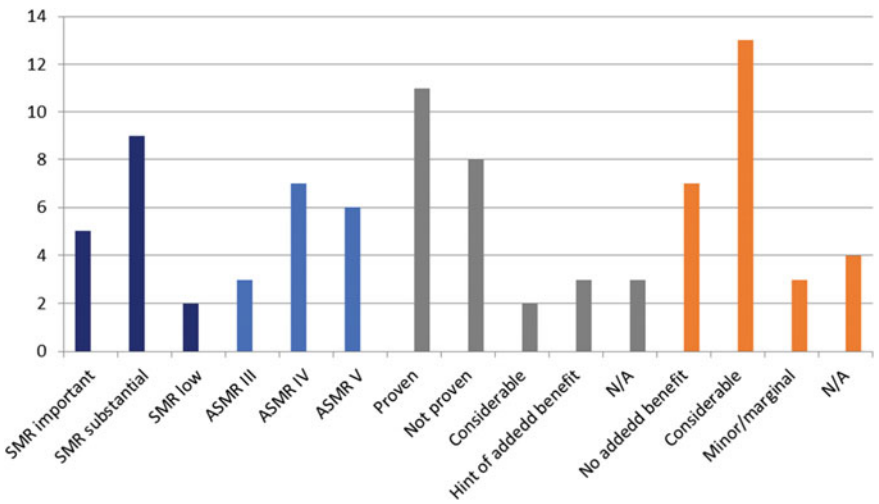

Fig. 2 Outcomes of HTA assessments carried out by the national agencies in France and Germany

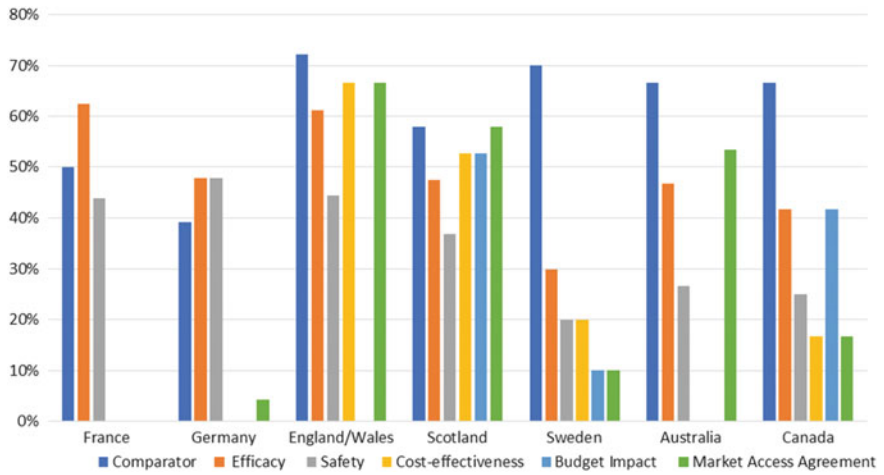

Fig. 3 Product characteristics raised critique from the national agencies when appraising HTA data

efficacy data, in Scotland—the choice of comparator, limited efficacy data, cost-effectiveness, in Sweden—the choice of comparator, in Australia—the choice of comparator, and in Canada—the choice of the comparator.

MAA was mentioned in HTA reports in England, Scotland and Australia. However, the lack of information in reports from other countries does not prove a lack of such agreements. They may not be reported in the HTA due to customary, procedural, or contractual reasons. In fact, in Germany, price discounts are routine for all new products. In France, price volume agreements and price discounts are frequent, and in Sweden, coverage with evidence development is often employed to address modelling uncertainty, which is common in oncology HTA.

5 Conclusion

Different HTA agencies have different decision analysis frameworks with different scopes; therefore, it is not surprising that the HTA decisions are just as heterogeneous. Oncology is a field where products are increasingly approved based on immature trial efficacy data, leading to high uncertainty of the value estimated through the HTA. This uncertainty contributes to the divergence in HTA decisions as aversion to risk varies dramatically between agencies. Recent research illustrates this divergence well and shows a high heterogeneity in access to innovative oncology therapies in various countries. Germany and France seem to offer the highest level of access, while Australia appears to provide the lowest. In Canada, access to innovative oncology drugs is reasonable, but restrictions on the target population are frequent.

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Patient-Reported Outcomes in Oncology, Beyond Randomized Controlled Trials

Mondher Toumi, Szymon Jarosławski, Christos Chouhaid, Bruno Fallissard and P. Auquier

Abstract

The goal of the treatment of a disease has moved from treating organs and diseases through symptoms, biological parameters and imaging towards treating a human being as a whole. The treatments should deliver benefits that patients can personally perceive. However, the patient's perspective does not always match the one of those surrounding them. Illustratively, patients' symptom assessments are more predictable for daily health status, whereas clinicians' symptom measurements are more related to clinical outcomes. The term, patient-reported outcomes (PROs), includes any data that are reported directly by the patient without an intermediary, such as a family member or a healthcare professional. The use of PROs in oncology trials is increasing and the U.S. Food and Drug Administration has published guidelines on the review and evaluation of PROs. However, while PROs are increasingly used in clinical trials, they are rarely used in daily clinical practice. Further, healthcare payers are concerned with issues related to relevance, quality, and interpretability of these outcomes.

Keywords

Patient-reported outcomes (PROs) · Health-related quality of life (HRQoL) Symptom assessment · Oncology Payers · Patient preference Clinical trials

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1 Introduction

According to the World Health Organization, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1946).

Over the years, the goal of treatment of a disease moved from treating organs and diseases through symptoms, biological parameters, and imaging towards treating a human being as a whole. Disease treatments should deliver benefits that patients can personally perceive as improvements in their "quality of life" and they should be able to assess as well as prevent serious events in future. For example, it only makes sense to treat hypertension if we reduce symptoms such as headaches or if we significantly reduce the risk of later occurrence of heart failure or haemorrhagic stroke. Reducing the blood pressure per se is not the ultimate objective. Because the "quality of life" can depend on factors other than health, health-related quality of life (HRQL) term was proposed for use in healthcare settings (ISPOR 2001).

2 Patient Perspective Differs from HealthCare Professional Perspective

Studies have shown that, for severe health conditions, practitioners rate the HRQL worse than patients, whereas for non-severe conditions the practitioners rate it better than the patients (Toumi 2016). However, this can be reversed when treatment-related side effects are assessed. For example, during head and neck cancer chemoradiotherapy practitioner-reported toxic effects are lower than patient self-reports (Falchook et al. 2016). Also, proxies (such as caregivers, family) can reliably report on the quality of services and on observable symptoms, but not for subjective aspects of the patient's experience, such as pain, anxiety and depression (McPherson and Addington-Hall 2003). Further, in a palliative care setting, whereas family caregivers tend to give more accurate ratings than healthcare practitioners, both proxies under-valuate the quality of life which may lead to overtreatment of symptoms (Dawber et al. 2016). This suggests that the patient's perspective does not always match the one of those surrounding them.

Further, the literature review found that patients' symptom assessments are more predictable for daily health status, whereas clinicians' symptom measurements are more related to clinical outcomes (Xiao et al. 2013). However, clinicians have the propensity to underestimate the incidence, severity or distress of symptoms experienced by cancer patients (Xiao et al. 2013). Further, a retrospective reliability analysis on cancer patients found that agreement between different clinicians when reporting adverse symptom events is moderate at best (Atkinson et al. 2012). There is also some evidence that patient-reported symptoms are more strongly correlated with clinical outcomes than practitioner-reported ones (Quinten et al. 2011).

3 Definition of PROs and Classification

The term patient-reported outcomes (PROs) includes any data that are reported directly by the patient without an intermediary, such as a family member or a healthcare professional and includes, but is not limited, to HRQL (Willke et al. 2004).

According to the US Food and Drug Administration (FDA), a PRO is "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else". It can be measured in absolute terms (e.g., severity of a sign, symptom or state of a disease) or as a change from a previous measure (US Food and Drug Administration Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims 2009). Similarly, the European Medicines Agency's (EMA) defines a PRO as "any outcome directly evaluated by the patient and based on patient's perception of a disease and its treatment(s)" (EMA 2005).

According to EMA, PRO encompasses both single and multidimension domains such as health status and satisfaction with treatment. HRQL is a specific type of a PRO, defined as a patient's subjective perception of the effects of the disease and treatment(s) on daily life; well-being; and psychological, physical and social functioning (Patrick et al. 2011).

A PRO instrument (i.e., a questionnaire plus the information and documentation that support its use) is a means to collect data about a PRO concept (Patrick et al. 2011).

4 PROs in Oncology Clinical Trials

The use of PROs in oncology trials is increasing. Eighty-five per cent of oncology trials registered at ClinicalTrials.gov between 2006 and 2012 incorporated a PRO that evaluated HRQL or symptom measures (Zagadailov et al. 2013). Further, the use of PRO in clinical trials translates into the use of PRO in FDA labels. Twenty-four per cent of product labels approved by the FDA between 2006 and 2010 contained PRO claims, and the largest percentage of product claims was in oncology (Gnanasakthy et al. 2012).

In 2009, the FDA published a formal guidance on the review and evaluation of patient-reported outcomes (PROs) related to claims included in medical product labelling (Zagadailov et al. 2013).

In general, PRO instruments used in oncology should include four key domains (Basch 2015):

1. Physical functioning
2. Disease-related symptoms
3. Symptomatic toxicities (treatment-related adverse events)
4. Global HRQL

In practice, PRO instruments often measure HRQL or specific symptoms, such as pain, fatigue, sexual functioning or treatment-related adverse events or a combination of the domains. In both cases, the instruments can be generic or disease-specific.

Many cancer-specific instruments exist that have been developed to measure HRQL or symptoms relevant in a given cancer. Table 1 presents examples of commonly used PRO instruments in oncology (Zagadailov et al. 2013; EHA 2011).

However, the use of PRO in clinical trials should be incorporated into the clinical development plan, and care should be taken that collected data is complete. In order to be valid, PRO instruments should be carefully selected and incorporated into trial protocols and transparently analysed and reported (Brundage et al. 2013).

Table 1 Examples PRO instruments used in oncology (Zagadailov et al. 2013; EHA 2011)

Type of tool	PRO instrument
Health-related quality of life	
Generic	• SF-36 (Short Form 36-Item) • PROMIS (Patient-Reported Outcomes Measurement Information System) • EQ-5D (EuroQoL-5 Dimensions Index) • WHOQOL-100 (World Health Organization Quality of Life-100) • PROMIS (Patient-Reported Outcomes Measurement Information System) • NHP (Nottingham Health Profile) • SIP (Sickness Impact Profile)
Cancer-specific	• FLIC (Functional Living Index-Cancer) • EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) • FACT-G (Functional Assessment of Cancer Therapy-General)
Cancer-site specific	• EORTC QLQ-BR23 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast) • EORTC QLQ-LMC21 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Colorectal Liver Metastases) • FACT-L (Functional Assessment of Cancer Therapy-Lung) • FACT-B (Functional Assessment of Cancer Therapy-Breast) • FACT-NCCN (Functional Assessment of Cancer Therapy—Lymphoma Symptom Index (FLymSI)—non-Hodgkin's lymphoma)
Symptoms and symptom burden	
Generic	• Visual analogue scale
Cancer-specific	• Symptom Distress Scale • Memorial Pain Assessment Card • Rotterdam Symptom Checklist • MDASI (Monroe Dunaway Anderson Symptom Assessment Inventory)
Cancer-site specific	• LCSS (Lung Cancer Symptom Scale)

5 Validity of PRO Instruments

PRO instruments are designed to capture concepts related to the health experiences of individuals. That is, how patients feel or function in relationship to their disease, condition or treatment (Patrick et al. 2011). Thus, the instruments must possess content validity that is evidence that the structure and content (items) capture the connection between the measurement concept intended by researchers and the way patients understand that concept (Patrick et al. 2011). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on PRO Content Validity Good Research Practices lists five steps to elicit concepts for new PRO instruments and document content validity (Patrick et al. 2011):

1. Determine the context of use (medical product labelling)
2. Develop the research protocol for qualitative concept elicitation and analysis
3. Conduct the concept elicitation interviews and focus groups
4. Analyse the qualitative data
5. Document concept development and elicitation methodology and results

Content validity must be based on direct input from an adequate, diverse sample of patients from the targeted clinical study population. The final PRO instrument should be insensitive to variations in demographic and clinical characteristics and experiences within the target population (Patrick et al. 2011).

6 Other Methods to Capture Patient's Perspectives

PRO methods are not the only way to capture the patient's perspective. Patient preference methods have been described as more grounded in economic theory and are more patient-centred than the HRQL methods used in outcomes research (Bridges et al. 2007). Whereas PRO methods are concerned with measuring the patient's status along several aggregate domains, patient preference methods measure the patient's value for a specific component, or attribute, either in absolute terms or in relation to another attribute. Thus, PROs capture patient reports of outcomes in individual domains without providing information about patient preferences across domains. The relative importance of these domains is quantified by patient preference methods (Bridges et al. 2007).

Examples of patient preference methods are (Bridges et al. 2007; Ryan and Farrar 2000):

- The contingent valuation or willingness to pay (WTP)
- Discrete choice experiments (conjoint analysis)
- Exit interview (qualitative interview by a psychologist at the end of a clinical trial)

7 Value of PRO in Oncology

PFS has become the most commonly used primary end point in all lines of treatment in oncology. Clinical response and progression definitions are standardised metrics used in phase II clinical trials that describe what happens to tumours during therapy (Therasse et al. 2000). PFS is believed to translate into clinical benefit and is used as a surrogate end point of treatment efficacy in oncology clinical trials. However, such surrogate end points may not necessarily infer a patient-relevant benefit (Buyse et al. 2010; Kim and Prasad 2015; Svensson et al. 2013). Therefore, they should be underpinned by additional end points that demonstrate patient benefit which support the primary PFS end point (Friedlander et al. 2016). Symptom improvement or delay in developing symptoms may be more important from the patient's perspective than a 2-month increase in PFS (Au et al. 2010).

Extending life may only be desirable while the treatment can at least maintain the patients HRQL or ideally improve it. Therefore, clinical trials should not be restricted to just showing overall survival or PFS benefit, but should also reflect the patients HRQL. This is crucial, especially for oncology therapies that often have serious adverse events. Improvements in HRQL have been shown in treatment with certain biological therapies for lung cancer (Blackhall et al. 2014), melanoma (Long et al. 2016) and renal cancer (Cella et al. 2016).

Further, PROs have been shown to correlate with survival in patients receiving cancer therapy. Changes in HRQL scores from baseline during treatment are significant prognostic factors for survival (Ediebah et al. 2014). Also, overall quality of life (QoL) measured at the time of lung cancer diagnosis was a significant and independent prognostic factor for survival in patients with lung cancer (Sloan et al. 2012); the physical component of HRQL was associated with overall and cancer-specific survivals in patients operated on for early-stage non-small-cell lung cancer (Pompili et al. 2013); pretreatment global QoL, but not comorbidity, had significant prognostic value for survival of elderly patients with advanced non-small-cell lung cancer who were treated with chemotherapy (Maione et al. 2005).

PROs are often better predictors of survival than performance status, but studies are needed to determine whether interventions that improve PROs also increase survival and to identify explanatory mechanisms through which PROs relate to survival (Gotay et al. 2008).

However, while PROs are increasingly used in clinical trials in oncology, they are rarely used on non-trial settings. This means that oncologists cannot track patients progress or satisfaction with treatment in the clinic where PRO tools are not available. Also, clinicians may not understand the trade-offs; the patients are willing to make between improvements in objective biological outcomes such as tumour shrinkage and possible worsening in other symptoms or HRQL (Zagadailov et al. 2013). Therefore, the potential of PRO use beyond clinical trials remains underutilized.

Further, healthcare payers are concerned with issues related to relevance, quality and interpretability of PROs and may dismiss PROs that do not independently predict improved outcomes (Zagadailov et al. 2013). Quality issues can be related, for example to PRO data from open-label trials or to missing trial data (Basch et al. 2015). Also, there is no consensus among payers on the relative value of objective clinical outcomes and PROs and each may attach different valuations to each of these outcomes (Zagadailov et al. 2013).

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Patient-Reported Outcomes in Health Economic Decision-Making: A Changing Landscape in Oncology

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Abstract

Cancer causes significant death and disability globally. However, costs of more personalized cancer care continue to climb, while access to basic cancer screening and treatment is not available to much of the world. This chapter provides an overview of the status of patient-reported outcomes (PROs) in cancer clinical care and research. PROs are valuable for health care and health economic decision-making at institutional, regional, national, and international levels. PRO data should be considered along with cost and survival data when approving new therapies. PRO data can also be helpful when assessing existing treatment options for patients, particularly for drugs with minor outcome and toxicity differences. Finally, PROs can be useful in reimbursement algorithms to ensure delivery of quality cancer care in value-based financing environments. The authors advocate for reframing the concept of health value, aligning PRO measures with societal values, and broadening the definition of society to extend beyond national boundaries.

Keywords

Patient-reported outcomes · PROs · Cost · Patient-centered care · Health economics · Cost · Value · Cancer

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1 Introduction

Cancer causes more death and disability globally than any other disease (World Health Organization 2015). Yet, access to high-quality cancer care remains a major problem in much of the world. Rising costs and inadequate healthcare infrastructure make quality care both unaffordable and inaccessible to many cancer patients worldwide. For those who are able to access timely, quality cancer care, significant long term and late effects of cancer and cancer treatment demand attention to patient values and preferences of care from the onset of treatment and throughout the care continuum. Given sustained health and healthcare access inequities and escalating costs, a reassessment of value in health economic decision-making is paramount.

Value of health care varies based on the perspective of the stakeholder, as well as based on whether it provides intrinsic or instrumental benefits to the individual, to society, or to the health system. Alleviation of suffering is of intrinsic value to the individual and society as it underlies the imperative of addressing basic needs and providing dignified care in life and death. Intrinsic value can be seen to serve a direct purpose, such as with providing pain relief for the sake of minimizing suffering of and harm to the patient. Instrumental value is that which has a duality of purpose, both an end in itself (of direct benefit) and as a means to an end (of indirect benefit) (Bhadelia et al. n.d.). From an economic perspective, health care is of instrumental value and is understood as quality—or positive health outcomes—divided by cost. Thus, rising costs and reduced quality both lead to poorer value.

Health economics is concerned with the efficient allocation of resources to maximize health benefits to society (Goeree and Diaby 2013). Health economic decision-making thus relies not only on costs of comparable therapies but on the impact of therapies on both duration and quality of life (QOL). Cost–utility contextualizes healthcare expenditures through quality-adjusted life years (QALYs) saved with a wide variation of what is an acceptable cost per year of a person's life [e.g., $50,000–300,000 based on willingness to pay (WTP)]. Costs of health interventions capture direct medical costs at minimum, but may include other costs. Health-related quality of life (HRQOL) encompasses physical, emotional, psychological, sexual, financial, social, functional, and other drivers of personal health. HRQOL is difficult to measure consistently due to bias, construct heterogeneity, and response shift. Further, interpretability of HRQOL data can be challenging. Thus, the various components of assessing cost–utility for a particular therapy are partly subjective and may shift over time.

This chapter provides an overview of patient-reported outcomes (PROs) in cancer care and research. PROs are self-reported patient satisfaction, experience, functionality, pain, distress, and other outcomes that are not interpreted by clinicians or any other proxy. The authors advocate for reframing health value and broadening the definition of society beyond national boundaries. Such a reframing requires a clearer understanding of what social values resonate among individuals and communities within and across nations. For example, respect, autonomy,

palliation, and longevity may all be important, but which, if any, of these should be considered when making health economic decisions? How do we balance individual preferences and health equity more broadly in economic evaluations of health care? Ongoing public discourse is critical to determine what constructs beyond length of life should be included in health economic decision-making and how and when is best to measure those constructs, including their weighting.

2 Global Oncology Snapshot

The World Health Organization (WHO) estimates that 57% of the 14 million annual cancer diagnoses globally and 65% of cancer deaths are from low- and middle-income countries (World Health Organization 2015). While the percentage of countries with cancer registries is increasing (World Health Organization 2015), the lack of adequate surveillance infrastructure in many countries suggests that the cancer burden is even greater than what is estimated in low- and middle-income countries.

Cancer care is more complex than ever before, but it is also more promising—for some. In the last 5 years, 70 new oncology drugs have come to market to treat more than 20 cancers (IMS Institute for Healthcare Informatics 2016). This growth in pharmacotherapies, in some cases, provides more therapeutic options from which clinicians and patients can choose. In the USA, 67% of cancer patients now survive at least 5 years, and more than 15.5 million cancer survivors are alive as a result of earlier screening and diagnosis and more personalized treatments (American Cancer Society 2016). The discovery of genetic markers, the development of targeted therapies, and use of the immune system to combat cancer have resulted in greater survival curves and fewer side effects.

However, gains have not been equal. Pharmacotherapy and radiotherapy are not available in many countries. While drug spending in the USA is higher than in any other country, reaching $107 billion in 2015, a recent study of 23 cancer drugs in six countries showed no correlation between cost of drug and affordability (Goldstein et al. 2016). Cancer treatment is available in 90% of higher-income countries where drugs are most costly as compared to only 30% in lower-income countries (World Health Organization 2015). Additionally, 25% of countries report having no radiotherapy available (World Health Organization 2015). Overall spending on cancer in the USA is projected to rise to $173 billion by the year 2020 (Mariotto et al. 2011). Cancer health disparities alone cost an estimated $193 billion in premature death (Institute of Medicine 2003), and cancer causes approximately $471.5 million in lost productivity in the USA each year (Alexander et al. 2014).

3 Reframing the Value Equation

With rising healthcare costs, a strained oncology workforce, a growing population of cancer survivors, and the demand for value from payers, several US organizations have issued position statements or frameworks for value-based health services delivery. In 2013, the National Academy of Sciences issued its report Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis (IOM 2013), recommending the following critical aspects of quality cancer care: engaged and informed patients, a trained workforce, evidence-based care, learning healthcare information technology, translation of evidence into clinical practice and accessible, affordable care. In 2015, the American Society of Clinical Oncology (ASCO) published a value framework for oncology care with an emphasis on clinical benefit, toxicity, and costs of therapy including financial toxicity to patients (Schnipper et al. 2015). The ASCO authors acknowledge the plethora of factors that inform a patient's perception of value, including efficacy of therapy, side effects, out-of-pocket expense, QOL, convenience, and indirect costs (Schnipper et al. 2015). Higher insurance premiums and higher patient cost-sharing strain patients and families and drag down the economy (Schnipper et al. 2015). Notably, however, patient-centeredness, timeliness of care, and health equity are not captured in the ASCO framework (Pratt-Chapman et al. 2015).

Lack of transparency among the various stakeholders profiting from the business of cancer in the USA and globally makes it difficult to create viable solutions to escalating costs draining our economies. The current system protects business interests over alleviation of suffering, health equity, or patient-centeredness. Lack of transparency ranges from acquisition costs of drug to reimbursement costs by payer. Costs of cancer therapy vary widely and largely depend on what the market can bear. Corporate decisions about where to invest in research, which populations to study, and how to price drugs are both financially and politically driven, making cutting-edge precision therapies available to some and basic screening, radiotherapy, and palliation inaccessible to many. Since most pharmaceutical profits are generated in the USA, other countries have less negotiating power even while their populations are least likely to benefit from drugs that have not been studied in their populations.

Existing algorithms for cost-effectiveness and cost–utility do not directly incorporate PROs or social values. In fact, the existing rhetoric around drug innovation for cures masks real patient experiences with cancer and its impacts. The move to value-based purchasing in the USA provides a window of opportunity, however, to align broader social values with PRO measures to ensure that health equity and HRQOL are incorporated into the value equation. A frank assessment of cost–utility must acknowledge wide disparities in basic access to health care. Indeed, the most cost-effective interventions are disseminating what is known to work rather than disproportionately investing in "me-too" drug therapies. The cost of the recently FDA-approved drug nivolumab, for example, is $141,000 in just the first twelve weeks and $256,000 for the first year (Loftus and Winslow 2015).

The push for cures, while laudable in theory, detracts from economic decision-making that could broaden both access and quality to underserved citizens globally. Aligning societal interests and values with core PRO measures to move closer to informed health economic decision-making is not simple work. Clarifying social values requires ongoing national and international dialogue; but the alternative is increasingly disparate healthcare access to unequal cancer care delivery systems.

4 Patient-Centered Care and Patient-Reported Outcomes

As survival rates in higher-income countries have increased, medical understanding of long-term sequelae of cancer and cancer treatment has led to an acknowledged need to engage patients in their care. The importance of the patient voice was institutionalized through the concept of patient-centered or person-centered care. This concept has evolved extensively since its introduction. Initially intended to provide normative guidelines for the interpersonal interaction between patient and provider as well as to take account of the unique experiences with illness of and broader circumstances faced by each patient when providing care (Balint 1968), patient-centered care has been extended to various dimensions of care. These can include not only respect for expressed patient values, preferences, and needs, but also coordination and integration of care, continuity in the provision of care with appropriate information and communication, assurance of physical comfort and emotional support, and engagement of family and friends (Beach et al. 2006).

The seminal publication by the National Academies of Science on Crossing the Quality Chasm used the term person-centered care as a directive to ensure that "patient values guide all clinical decisions" (IOM 2001, p. 14). A recent National Academies of Science report, Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis, puts the patient at the center of a high-quality cancer care delivery system, emphasizing the importance of patient engagement in care and public reporting of quality of care. Patient self-rated quality of health has been prioritized by federal agencies and national organizations in the USA since 2000 through the development of PRO measures (Rock et al. 2007) as well as the use of PROs as endpoints in clinical trials (U.S. Department of Health and Human Services 2009).

Lipscomb et al. state, "For diseases that are often chronic and sometimes incurable, with interventions that can have toxic and long-term consequences, it is especially important that decisions influencing patient outcomes reflect the patient's own perspective. Cancer provides a compelling case in point" (2007, p. 278). Novel cancer therapies often result in only marginal survival improvements and may come with significant adverse events and impacts. For diseases that are refractory to treatment and/or have short progression-free survival, PROs are especially important to differentiate therapeutic choices for patients and clinicians (Zagadailov et al. 2013). PROs can also be important when testing expensive immunotherapies that may be efficacious for some patients and not others.

PRO data can also guide treatment adjustments by informing clinicians of the impact of cancer therapies on patients' QOL and HRQOL. QOL is a broad concept that includes economic satisfaction, political freedom, safety, quality of relationships, education, and health care. HRQOL refers to aspects of QOL that involve a patient's health; however, this concept is still affected by a broad range of factors such as social determinants, financial impact of disease, mental health, available social supports, physical functionality, and personal resilience. Patients are best positioned to inform their healthcare providers about when and how cancer, cancer treatments, and supportive care impact their health and HRQOL. Indeed, patient preferences and many prevalent patient symptoms, such as pain and fatigue, can only be assessed by the patient. PROs provide critical information on patient functionality and adverse events (European Medicines Agency 2014). Incorporation of PROs into clinical assessments and monitoring can improve communication between patients and providers, improve shared decision-making and treatment planning, and target problems most important to patients to help them adhere to recommended treatment. Multimodal therapies make it increasingly important for physicians to monitor impacts on patients systematically.

Caregivers and families can also benefit from PROs by better understanding how to support patients and by encouraging dialogue across support givers. Further, PROs can help generate positive externalities and meaningful social impact on families and caregivers whose burden of care may be reduced as a result of more comprehensive care of the patient by the health system through the integration of PROs.

Some individuals and groups in the health systems community have sought to further the notion of placing the individual at the nexus of care by acknowledging that health systems are human systems, and hence, "live" with individuals that have varying roles in the health system and which provide its human character. Since health systems are social institutions, they function through networks of interactions between actors that include patients, providers, administrators, and researchers. Value must be derived for each of these individuals and human relationships to strengthen health systems (Sheikh et al. 2014). When focusing on the patient, this also translates to a systems-level responsibility for ensuring patient value in all interactions within the system, not just at the interpersonal patient–provider level. The people-centered health systems approach also provides an opportunity to address health disparities by striving for cultural competence in systems design. A culturally sensitive system design can adapt to the needs of underserved populations whose specific and unique patient concerns may otherwise be ignored (Beach et al. 2006).

5 Investments in PRO Measures

Several important investments have been made in recent years to advance PRO tools, data collection, and value assessment. The US National Cancer Institute invested in development of the Patient-Reported Outcomes Measurement

Information System (PROMIS®). PROMIS® measures assess physical, mental, and social health in children and adults and were developed to improve patient–provider communication in research and clinical settings. Major domains for adult health include physical function, pain intensity, pain interference, fatigue, sleep disturbance, depression, anxiety, and ability to participate in social roles and activities. Major pediatric domains include mobility, upper extremity function, pain intensity, pain interference, fatigue, depressive symptoms, anxiety, and peer relationships. Short forms and computer adaptive tests are also available for these measures. Measures are available in English and Spanish.

Another major investment—the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)—develops consensus reviews and recommendations to improve pain research. A major contribution of this initiative was the development of the Short-form McGill Pain Questionnaire 2 (SF-MPQ-2) which assesses quality and intensity of pain and related symptoms to guide research and clinical care (Dworkin et al. 2009).

The US National Cancer Institute and the Department of Veteran Affairs funded the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) from 2001 to 2014 to study outcomes of lung (n = 5,013) and colorectal (n = 4,223) cancer survivors across five geographic regions and two integrated healthcare delivery systems. Results of the study led to greater understanding of differential experiences of care based on race and language (Ayanian et al. 2010); determination of positive impact of survivorship care planning on lung and colorectal cancer survivors' follow-up care adherence and perception of health (Chrischilles et al. 2015) identification of overuse of palliative radiotherapy in patients with metastatic non-small-cell lung cancer (Chen et al. 2013); analysis of the intensity of medical interventions and use of hospice at end-of-life in metastatic lung and colorectal cancer patients (Brooks et al. 2016); improved understanding of the impact of physical and mental health symptoms on HRQOL of lung and colorectal cancer survivors (Kenzik et al. 2015); and identification of the correlation between greater depressive symptoms and lower social support with higher mortality of lung cancer patients (Sullivan et al. 2016). The study also contributed to knowledge of cancer caregiver experiences, including social stress (Litzelman et al. 2016).

Most recently, the National Patient Advocate Foundation released a tool called the Consumer-Based Cancer Care Value Index (CCCVI) that oncology programs can use to electronically survey their patients in order to aggregate patient-reported experiences post-treatment to identify potential quality improvements opportunities. Patient-reported experiences assessed include travel and transportation to oncology care, service and resource utilization, patient inclusion in decisions about cancer treatment, patient perceptions of their cancer care team, patient preferences in care, patient experiences of cancer impacts, overall health and well-being, and access and adherence to prescribed medications (Patient Advocate Foundation, n.d.).

A variety of existing measures assess patient satisfaction, experience with care, care climate, and other aspects of person-centered care. See Table 1 for a list of relevant tools which update and expand on instruments summarized by Morgan and Yoder (2012).

In addition to patient experience and satisfaction measures, many PROs are HRQOL measures which can be categorized as generic measures, general cancer measures, site-specific measures, and problem-specific measures (Lipscomb et al. 2007). One benefit of generic measures is the ability to compare HRQOL or other PROs across disease states which is helpful for cost–utility analyses. A commonly used generic measure is the Medical Outcomes Study Short Form (SF)-36 (Ware et al. 1999; Ware n.d.). General cancer measures such as the European Organization

Table 1 Sample instruments of patient/person-centered care

Instrument	Description
Person-centered climate questionnaire (PCQ)[1]	A 17-item instrument that measures degree to which climate (ambiance, culture, and safety) of inpatient care is person-centered
Individualized care scale (ICS)[2]	A 40-item instrument that assesses impact of nursing interventions in supporting a patient's individual characteristics, life situation, and control over decision-making during inpatient care
Patient-centered inpatient scale (P-CIS)[3]	A 20-item instrument that captures patient experience in terms of "personal identity threat" in healthcare delivery
Patient satisfaction with nursing care quality questionnaire (PSNCQQ)[4]	A 19-item instrument that assesses patient satisfaction with quality of nursing care
Functional independence measurement (FIM)[5]	A 10-item instrument that measures self-care management at admission and discharge
Patient assessment of chronic illness care (PACIC)[6]	A 20-item instrument that assesses degree to which patients with chronic conditions receive care aligned with Chronic Care Model; measures whether care is patient-centered, proactive, planned, and collaborative
Picker-commonwealth patient experience survey[7]	Survey that includes specific components on patient-centered care in various domains including information and education, coordination of care, emotional support, respect for patient preferences, and continuity and transition
Measuring patient-centered communication scale (MPCC)[8,9]	Assesses patient-centeredness across three domains: patient's illness experience, understanding of patient as a "whole person," and identifying common ground
Verona patient-centered communication evaluation scale (VR-COPE)[10,11]	Evaluates communication strategies to achieve patient-centered care across nine domains, including active listening, meeting patient's agenda, and identifying patient's expectations

(continued)

Table 1 (continued)

Instrument	Description
Patient-perceived involvement in care scale (PICS)[12]	A 13-item scale that measures the extent to which the physician facilitates patient engagement, patient demonstrates behaviors that are information-seeking and patient's initiative to partake in decisions
Patient-perceived patient-centeredness scale (PPPCS)[13]	A 14-item scale that measures degree to which physician elicits patient perspective in various areas such as symptoms, feelings and expectations, and physician encourages questions as well as seeks to identify common ground on the condition and treatment with the patient
Patient-centered score sheet[14]	A score card that rates "patient offers" or patient verbal communications in the categories of thoughts, feelings, prompts, and non-specific cues alongside rating of doctor's responses to these offers

[1]Edvardsson et al. (2009), [2]Suhonen et al. (2005), [3]Coyle and Williams (2001), [4]Laschinger et al. (2005), [5]Unsworth (2001), [6]Glasgow (2005), [7]Cleary et al. (1991), [8]Brown et al. (2001), [9]Stewart et al. (1995), [10]Epstein and Peters (2009), [11]del Piccolo et al. (2008), [12]Safran et al. (1998), [13]Ramsay et al. (2000), [14]Henbest and Stewart (1989)

for Research and Treatment of Cancer Core (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-General (FACT-G) and cancer-specific FACT measures—such as the FACT-L for lung cancer and the FACT-C for colorectal cancer—provide more accurate insights related to cancer impacts. Problem-based measures include the Brief Symptom Inventory (BSI-18) which measures elevated distress, including somatic symptoms, anxiety, and depression; the MD Anderson Symptom Inventory, a 13-item scale measuring severity of pain, fatigue, disturbed sleep, distress (emotional), shortness of breath, drowsy, dry mouth, sad, remembering, and numbness or tingling, nausea, vomiting, and lack of appetite (Cleeland et al. 2000); the Short-form McGill Pain Questionnaire 2 (SF-MPQ-2) which measures pain quality, intensity, and related symptoms; and the Edmonton Symptom Assessment System (ESAS) to determine palliation needs (Bruera et al. 1994).

6 Challenges and Potential Solutions

Despite widespread endorsement of PROs as important tools for patient-centered, quality cancer care, US oncology practices have been slow to embrace them. Most research on PROs has been conducted in Europe and Canada (Donaldson 2004). Multi-level challenges impede consistent use of PROs in clinical and research practice, including patient-, provider- and system-level factors as well challenges to consistent interpretation of PRO findings due to various kinds of bias and pressure to get drugs to market quickly.

Patient-level challenges include relevance of PRO measures to individuals, patient response burden, and response shift. Patient relevance is challenging given the need to balance consistent data collection for broad health services improvement with patient-specific needs that drive individual care decisions. Patients might also expect that their healthcare team is responsive to needs identified on PRO measures and become frustrated if the data is not used for clinical care improvements (Donaldson 2004). In addition, sometimes patients are unable or unwilling to consistently complete PRO instruments, leading to missing data. Unwillingness to complete PRO instruments may be due to repeatedly administering similar measures to the same person over time. Additionally, it may be difficult to interpret patient feedback through PROs. A recent analysis comparing the two most commonly used, validated, and reliable HRQOL instruments (the EORTC QLQ-C30 and the FACT-G) administered simultaneously in four groups of cancer patients (n = 418) showed lack of congruence in self-reported HRQOL constructs between the tools despite comparable scales, constructs, and domains (Holzner et al. 2001). In particular, emotional and role/functional domains were not well correlated and social measures were least congruent between the two instruments (Holzner et al. 2001). Furthermore, response shift is a demonstrated challenge in cancer clinical trials (Hamidou et al. 2011). Response shift happens when patient priorities change, recalibrating self-report of health status across time. Thus, PROs capture adjusted priorities rather than an actual health change within the patient. Finally, administration of PRO measures is challenging given the heterogeneity of patients and their needs.

Clinician challenges include relevance and heterogeneity of measures, impact on clinical workflow, and lack of reimbursement. Utility of measures for clinical action and systematized feedback loops to inform therapeutic management are critical if PRO data is to provide value to clinicians. Choice of PRO measures matter, along with how instruments are implemented. If multiple interventions exist, PRO measures need to be carefully tailored and may still not accurately assess the impact of the intended intervention (Rock et al. 2007). Type I (false positive) errors increase when a specific causal relationship cannot be determined. Clinicians may also worry about extending patient visits in a business that demands efficiency. Further, PROs might present legal liability for clinicians if they do not adequately address patient concerns (Donaldson 2004). This is especially worrying, since clinicians have no guidelines to determine when a change to a PRO is significant enough to warrant an adjustment in care or what that adjustment should look like.

Finally, system-level challenges include lack of resources for data collection and management as well as access to patient data by those not directly treating the patient. Information technology and workflow structures are critical to support routine use of PROs in clinical practice to ensure that patient, provider, and system concerns are addressed (Donaldson 2004). Data access beyond purposes for institution-specific clinical quality improvement raises privacy and patient consent considerations (Donaldson 2004).

The US Federal Drug Administration (FDA) has acknowledged the importance of PROs to assess health from the patient perspective. However, the FDA noted challenges to including PROs in the assessment of pharmaceutical labeling due to selection bias, reporting bias, missing data, and inconsistent results derived from heterogeneous HRQOL instruments (Rock et al. 2007). Oncology trials are more likely than other trials to be small, single-arm, open-label studies for pragmatic and ethical reasons (Gnanasakthy et al. 2016), and non-randomized control trials are more likely to have selection bias.

Other obstacles to use of PROs in research include pressure to expedite regulatory approvals, perception of subjectivity, and logistical challenges. Oncology trials are more likely to have short development and duration to expedite regulatory approval, making development and collection of PROs challenging (Gnanasakthy and DeMuro 2015). PROs are often perceived as "soft," subjective endpoints; thus, researchers may not invest in the substantial time needed to partner with colleagues with PRO expertise and select psychometrically sound measures and analyze them in context of "harder" endpoints. This may especially be true in industry-driven trials of anticancer agents that may have a high failure rate. Only 41% of phase 3 trials are successful in oncology compared to 65% for other diseases (Gnanasakthy and DeMuro 2015). Significant time is needed to invest in rigorous PRO data collection that may not feel worth the investment to pharmaceutical companies, since most compounds are not efficacious.

Meaningful use of PRO data in clinical care and research requires use of psychometrically valid and reliable measures responsive to health changes (Efficace et al. 2014) as well as sound data collection and statistical analysis (Lipscomb et al. 2007; Sloan et al. 2007). In 2009, the FDA issued Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. This report provides recommendations for content validity, reliability, ability to detect change, tailoring for special populations, design, and statistical analysis (U.S. Department of Health and Human Services 2009).

A recent international study revealed increasing interest in using PRO data in health economic decision-making among payers, although the use of PRO data registers at different levels based on the degree of healthcare system centralization (Brogan et al. 2017). PRO data may have a national impact in centralized systems like the UK, but only a local impact on physician behaviors in a decentralized system like the USA (Brogan et al. 2017). Payers emphasized the need for high-quality evidence captured through well-controlled trials, emphasizing that "the importance of PRO data in reimbursement decisions would increase in the next five years" (Brogan et al. 2017, p. 128). High-quality evidence requires methodological rigor in tailoring measures to the research questions being examined. However, it can be challenging to balance sufficient tailoring of measures with use of generic, validated instruments to allow for comparability across studies.

To track and improve the methodological rigor of research that includes PRO endpoints, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group launched the Patient-Reported Outcome

Measurements Over Time in Oncology (PROMOTION) Registry. The registry has catalogued study characteristics, methodology, and risk of bias in over 700 oncology randomized controlled trials with PRO endpoints since 2004 (Gimema QOL Working Party n.d.). Selected basic study characteristics catalogued include name of cooperative group, study location, industry support, primary endpoint(s), differential treatment protocols, trial sample size, PRO sample size, PRO instrument used, and summary of PRO results including statistical significance. In terms of methodology, the PRO hypothesis, PRO domain, mode of administration of PRO tool and data collection methods, rationale for choice of PRO instrument and documentation of psychometric characteristics, documentation of whether PRO is a primary or secondary outcome, summary of degree of missing data, statistical approaches for dealing with missing data, effect size, limitations of PRO components and PRO results are catalogued among other data elements. Finally, potential selection bias, random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, and reporting bias are assessed and noted (Efficace et al. 2014). This important initiative provides a database of methodological approaches to improve timing, selection, and administration of PRO data collection. Other PRO databases include the Patient-Reported Outcome and Quality of Life Instrument Database which includes over 1,300 PRO measures and the Grid-Enabled Measures Database (MAPI Research Trust, n.d.; National Institutes of Health, n.d.).

A national cancer data system that links cancer registry data with population-based PRO data from national surveys such as the National Health Interview Survey (NHIS), Medical Expenditures Panel Survey (MEPS), Medicare Health Outcomes Survey (HOS), and Behavioral Risk Factor Surveillance System (BRFSS) would increase the utility of PROs in research (Lipscomb et al. 2007). To optimize such a system, standardization of core measures with modular supplements would improve comparability of PRO data. The Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO) working group was developed specifically for this purpose and is currently working to advance PRO collection focused on fatigue, sleep, appetite, depression, cognition, and shortness of breath (Cleeland and Sloan 2010).

PROs are still relatively rare in oncology research, but are becoming more prevalent. From 2010 to 2014, only 7.5% of oncology drugs included PROs in labeling compared to 24% for all new molecular entities and biologics (Gnanasakthy et al. 2016). Across all studies registered on clinicaltrials.gov, however, 29% used at least one PRO measure (Vodicka et al. 2015)—up from 12% in 2007 (Gondek et al. 2007). Brogan et al.'s study (2017) concluded that PROs, and HRQOL data in particular, will be increasingly important for reimbursement decisions in years to come. Consistent use of validated, reliable PROs that can detect health change, are feasible, and have actionable guidelines for clinical practice is critical to advance cancer care and cancer research. Attention to calculating appropriate sample sizes to accurately capture PRO differences based on the length and complexity of the PRO tool is also critical.

7 Conclusion

In 2009, the FDA encouraged industry to include the target patient population in the prioritization of measures to be collected for drug trials, and recommended, at minimum, data collection of adverse events, physical function, and disease-related symptoms (Kluetz et al. 2016). Clearly defining PRO constructs relevant to the drug being studied, use of psychometrically sound PRO measures; rigorous design and sophisticated statistical plans; minimization of data loss through electronic data collection; and use of a fit-for-purpose measure to demonstrate large effects in open-label trials would improve use of PROs in industry (Gnanasakthy et al. 2016).

Given expanding prevalence of cancer and increasing complexity of therapies, PROs will become increasingly important in cancer clinical trials. PROs give patients a voice to evaluate impacts of cancer and particular treatments—providing clinicians, researchers, and payers information on positive and negative impacts of therapies from the patient's point of view—an invaluable perspective to include when financial stakes can be extraordinarily high for minimal survival gains. PRO data need not be limited to drug trials, however. PRO data can and should guide clinical care decisions and health economic decision-making more broadly.

PROs should be included in health economic decisions at institutional, regional, national, and international levels. When low-cost palliative care is inaccessible to many while high-cost drugs provide minimal survival advantage in other cases, an examination of shared societal values is imperative. Cost–utility analyses should include a transparent examination of costs by stakeholder group, including clarity regarding who benefits from existing healthcare economic decisions. If we are collectively willing, decision-making frameworks can be modified to align with societal values, such as alleviating suffering from cancer, as well as patient values, HRQOL, and preferences for care.

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Approaches to Capturing Value in Oncology

Evelyn Walter

Abstract

This article sets out to describe different value frameworks in the field of new developments in oncology. Since the costs of new oncological therapies follow a steep path, their implementation and financing demand a thorough assessment. This is an ambitious task due to the complex nature of oncological treatments within overall health policy. Five value frameworks were reviewed: European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale, American Society of Clinical Oncology (ASCO) Value Framework (version 2.0), National Comprehensive Cancer Network (NCCN) Evidence Blocks, Memorial Sloan Kettering Cancer Center DrugAbacus, and the Institute for Clinical and Economic Review Value Assessment Framework. They are all based on a large set of criteria. However, all these frameworks differ considerably in their outcomes. Among the main differences one has to cite are the inclusion of costs and the use of different outcomes, as well as the fact that they address different target stakeholders, etc. Despite these shortcomings, the value frameworks serve the necessity to introduce more rationality in health decision making seen from the perspective of physicians, patients, and financing bodies.

Keywords

Value framework · Quality-adjusted life year · Incremental cost-effectiveness ratio · Willingness-to-pay threshold

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1 Introduction

A cancer diagnosis is still devastating for patients and their families. Cancer-related deaths are the second leading cause of mortality with 8.8 million deaths worldwide in 2015 (WHO n.d.). Moreover, the number of new cancer cases is expected to rise in the future. The increasing number of cases, new innovative anticancer drugs, next-generation sequencing, and the extent of care have led to a dramatic growth in costs. It is estimated that cost increases from $104 billion in 2006 to over $173 billion in 2020 and beyond will take place (Smith and Hillner 2011). A closer look at drug costs shows that in the USA monthly costs of anticancer medication increased by 9% per year (from $7,103 in 2006 to $15,535 in 2015) while incremental costs rose by 21% per year (Reuters 2018). On the other hand, global life expectancy grew from 65.3 years (UI 65.0–65.6) in 1990 to 71.5 years (UI 71.0–71.9) in 2013. Cancer contributes to 0.4 years (GBD 2013 Mortality and Causes of Death Collaborators 2015).

No doubt, these figures are alarming. But they also raise the question—in a world of scarcity, where competition for public funding is fierce—what would be the optimum provision for new oncological therapies? It is hardly original to say that there is no simple rule for the provision and payment of oncological therapies. As in the textbook rule marginal benefits equal marginal costs, such therapies are a public or a merit good. In the absence of rules which the theory of pricing of public goods has so well developed but fails to be applicable in the complex environment of new oncological therapies, one resorts to the collection of criteria. This is what the "value frameworks" are about. Whether they help in achieving allocative and distributional efficiency under the boundary condition of limited public expenditures and clinical efficiency has to be evaluated. In any case, methods from the family of cost-benefit analysis have to be applied. But specifically, which metrics have to be applied in this context?

To assess the effect of cancer treatments on patients, the traditional end points of progression-free survival (PFS) and overall survival (OS), along with adverse events, are collected in clinical trials. These are sometimes supplemented with patient-reported outcomes and quality of life (QoL).

The preferred measurements among these values vary depending on the country, healthcare system, and patient population. The definition of value is generally accepted as a measure of outcomes achieved per monetary expenditure (Schnipper et al. 2015). The Institute of Medicine (IOM) has identified six elements of quality healthcare delivery: safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity (Schnipper et al. 2015). Based on the effort of diverse organizations, five major value frameworks (European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale, American Society of Clinical Oncology (ASCO) Value Framework (version 2.0), National Comprehensive Cancer Network (NCCN) Evidence Blocks, Memorial Sloan Kettering Cancer Center DrugAbacus, and the Institute for Clinical and Economic Review Value Assessment Framework) have emerged in recent years (Slomiany et al. 2017).

These frameworks enable a comparison of a new treatment regimen with the prevailing standard of care for a specific clinical cancer indication based on data derived from a prospective randomized clinical trial. Some frameworks calculate a net health benefit (NHB) score by awarding (or subtracting) points for clinical benefit and toxicity without taking costs into concern (ESMO), while others integrate costs (ASCO, NCCN, and DrugAbacus) or mainly focus on costs (Institute for Clinical and Economic Review).

These frameworks were used to provide cost-benefit results to enable conversation between patient and physician, or third-party payer, but none were developed as a mechanism to control cancer drug costs. Neither the ASCO nor ESMO models offer suggestions for how to calculate value-based pricing.

The approach is in marked contrast to how health insurance companies, employers, and regulators define value, which concerns longevity, quality of life (QOL), and cost. Cost is a key part in the value equation, regardless what part of the healthcare industry is involved. Why is defining value in cancer care more challenging than defining value in other areas of medicine (AVBCC 2013 Steering Committee 2012)?

2 Value—An Ambiguous Concept

The value of new innovative cancer drugs, whether individually or comparatively, and the definition of value itself have emerged as acute concerns in oncology, where the cost of cancer care has evoked issues of financial toxicity (Slomiany et al. 2017).

In economics, there exists a variety of value definitions; for example, the economist Ludwig von Mises interpreted "value" as exchange value, which was always the result of subjective value judgements. No price of an object could be determined without taking these judgements into account, as manifested by markets. Thus, it was incorrect to say that the economic value of a good was equal to what it costs to produce, or to its current replacement cost (Austrian Economics Analytics OG n.d.).

Value in the most basic sense can be referred to as "real value" or "actual value." This measure of value is based purely on the utility derived from the consumption of a product or a service. Utility-derived value allows products or services to be measured in terms of outcome, instead of demand or supply theories that have the inherent ability to be manipulated (Gatrell 2007). For example, the real value of a drug administered to a patient is zero because patients earn no additional income from being treated. However, treatment extends life expectancy and increases lifetime value earned by the patient. This is a value calculated by actual measurements of return of investment (ROI) instead of production input and/or demand versus supply. No single unit has a fixed value.

"Values" have been defined and categorized in various ways. Kenny and Joffres (Stafinski et al. 2014; Kenny and Joffres 2008) arrange them into terminal values (the goals that the decision is to achieve), procedural values (related to the decision-making process itself), and content values (the criteria and principles employed). Clark and Weale (Stafinski et al. 2014; Clark and Weale 2012) focus on process values (similar to procedural values above) and content values (which relate to factors considered in the decision-making process) (Stafinski et al. 2014). Merriam-Webster defines value as "a fair return or equivalent in goods, services, or money for something exchanged; the monetary worth of something; market price; or the relative worth, utility, or importance" (Feeley et al. 2010).

In Great Britain, where the National Health Service attempts to control costs, the National Institute for Clinical Excellence (NICE) has defined value of treatment as being based on scientific value judgments, including clinical and economic evaluations, and social value judgments, including considerations of efficiency and effectiveness (Feeley et al. 2010).

3 Quality-Adjusted Life Years (QALY) and ICERs Core Metrics

Before entering into a description of the "value frameworks," it is useful to assert in which context two crucial concepts of measuring value, QALY and ICERs (applied specifically by "the Institute for Clinical and Economic Review Value Assessment Framework," see below), are embedded. On a general and abstract level, the issues we are dealing with are well known in the ramification of applying welfare economics to the real world. The core point is the measurement of utility. In neoclassical and Austrian economics, utility is to be measured in an ordinal form only, due to its individualistic and non-comparability character. Happily enough, when theoretically constructing an ideal market price mechanism, the price relations reflect exactly a welfare optimum which is the bless point of efficiency. Sadly, real economies do not follow such an ideal world. Imperfection is at the root of the need for overall intervention in economic or health policy. Hence, subsidiary measures of utility have to be found. Neo-cardinalism would be the key word for it. In practice, operational concepts of utility have to be considered and expressed by different stakeholders.

In this understanding, this review article basically picks up crucial issues of the well-known debate in ordinal and neo-cardinal welfare theory (Olsen and Smith 2001; Brouwer et al. 2000; Edwards 2001; Barnett 2003) and looks into the ways these principles are applied in the field of outcome measurement in oncology. Not unexpectedly, the main issues emerge also in the context of oncological outcomes. How can one measure utilities, are there ways of comparing or even aggregating utilities of the different stakeholders in this field, i.e., patients, physicians (as gatekeepers or acting according to their own principles), and payers? Obviously, the perspective of and the weight given to different outcome measures have to be seen

in the respective structures of the health systems. These are always and necessarily so the result of a sort of bargaining process amongst the stakeholders under the auspices of social justice. In particular, to what extent are patients able to express their preferences, is responsibility partially transferred to the gatekeeping physicians, and are they implicitly or explicitly influenced by the threat of the boundary condition of savings or the instructions of the payers, etc.?

Beyond these general considerations and more concretely, a number of methodologies have been employed by health economists to assess the value of medical therapies in practice. Two commonly used metrics are quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs).

A QALY is a composite measure based on evidence of both health-related quality of life (HRQoL) and length of life. The first evidence for new cancer medicines originated from clinical trials. Trials typically run for 12–18 months, and measure, as their primary end point, clinical outcomes such as progression-free survival (PFS) (Devlin and Lorgelly 2017). This kind of outcome entails certain challenges for economic evaluation, as the estimation of QALYs relies on evidence of improvements in overall survival (OS), and trials are shorter to measure that (Devlin and Lorgelly 2017). Consequently, the use of clinical trial evidence in cost-effectiveness studies requires analysts to estimate OS curves on the basis of intermediate end points such as PFS, time to progression. A variety of methods are available for this, all of which rely on assumptions regarding the duration of treatment effects beyond the trial. After estimating survival, quality weights were used to calculate quality-adjusted life years. Based on PRO questionnaires, patients' self-reported health was captured to generate utility weights. Questionnaires encompass a series of dimensions, which can be scored and summarized in various ways to characterize or weight the patient's health (Devlin and Lorgelly 2017). An important issue with cancer is that often the side effects of treatment can be so detrimental that it reduces the patient's HRQoL during a treatment phase, with the future expectation that it will either improve their health in the long-term (Devlin and Lorgelly 2017) or reduce life expectancy due to necessary dose reduction.

To summarize the cost-effectiveness of a healthcare intervention, the ICER is calculated. It is defined by the difference in costs between two possible interventions, divided by the difference in their effect. The ICER can be used as a decision rule in resource allocation to establish a willingness-to-pay value for the outcome of interest. The ICER is then compared with a willingness-to-pay threshold which reflects the maximum cost per unit of outcome that a healthcare payer is willing to pay for a medicine. Different people or payers may be prepared to spend different amounts of money for the same level of benefit, depending on their own individual budgets and income. Hence, no single threshold exists for deciding whether or not a cost-effectiveness ratio is acceptable (Cohen and Reynolds 2008).

In the UK, the desired ICER for approval of treatments for cancer is typically less than £50,000 per QALY; drugs have been disapproved for not having an acceptable ICER per QALY. Normally, the English National Institute for Health and Care Excellence (NICE) recommends a new intervention if its ICER is below £20,000 per QALY gained. When the ratio increases from £20,000 to £30,000, it is

necessary that other factors supporting the intervention will be taken into account by the appraisal committee (Collins and Latimer 2013). The end-of-life criteria adopted by NICE allows interventions with an (unweighted) ICER over £30,000 to be recommended for patients with a short life expectancy. The rationality behind the criteria is that society values QALYs are obtained by patients at the end of life more highly than QALYs obtained by other patients. However, there is little evidence to support this assumption (Collins and Latimer 2013).

A similar threshold is also used in Canada. In the USA, the ICER is not considered for regulatory approval, but one commonly held ICER threshold is $50,000 to $100,000, a range chosen many decades ago based on the approximate yearly cost of dialysis (Siddiqui and Rajkumar 2012).

In Sweden and the Netherlands, relevant government authorities and important advisory bodies have recommended thresholds of 500,000 SEK (~€57,000) and €80,000 (Vallejo-Torres et al. 2016).

Recently, empirical studies have been performed in upper- and medium-income countries in Europe and Latin America which found that in order to reflect true opportunity costs the cost-effectiveness threshold should be set lower than 1 times the per capita national GDP (approximately $24,000–$40,000 per QALY by extrapolation for the USA) (Woods et al. 2016).

From the five value frameworks described below, only one—the Institute for Clinical and Economic Review—focusses on long-term value for money and recommends using ICER to value treatment. The threshold used is between $50,000 and $100,000.

4 The Five Value Frameworks

Several value frameworks have recently emerged to capture the diverse needs of healthcare stakeholders. In 2015, both the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) proposed frameworks to quantify the benefit of antineoplastic drugs in the face of rising costs (Becker et al. 2017). Each framework has overlapping similarities but differs with respect to purpose, focus, and means of assessment. Each framework has a unique set of strengths and weaknesses (Schnipper and Bastian 2016), and each was initially assessed for the presence of the following attributes: readiness to use now, transparency, target audience, scoring system, method of measuring efficacy and safety, and inclusion of patient-centric metrics (i.e., quality of life) (Wilson et al. 2017). Table 1 gives an overview of the properties of each.

4.1 The ESMO Magnitude of Clinical Benefit Scale

The European Society for Medical Oncology (ESMO) has developed the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) to evaluate clinical trial results

Table 1 Overview of the five value framers

Emphasis	ESMO	ASCO	NCCN	MSKCC	ICER
Application					
Target stakeholder	Payer Policymaker	Patient Physician	Patient Physician	Physician Policymaker	Payer Policymaker
Conditions addressed	Oncology: solid, blood, radiology, surgery	Oncology: solid, blood	Oncology: solid, blood, radiology, surgery	Oncology: solid, blood A	All conditions, focus on new drugs of high impact
Combination therapy evaluation	Yes	Yes	Yes	No	Yes
Clinical trial data					
Breadth of evidence	1 trial, RCT, comparative outcomes study, meta-analysis	1 trial, RCT	Published data, panel members' clinical experience, case reports	1 trial, registration trial of first indication (FDA label)	RCT meta-analysis and manufacturer-provided data
Trial sample size accounted	Indirectly, through lower bound of 95% CI	No	Yes	Yes	Yes
Allows for single-arm trials	No	Partially	Likely	Yes	Yes
Acknowledges trial contamination	Yes	No	Likely	No	Yes

(continued)

Table 1 (continued)

Emphasis	ESMO	ASCO	NCCN	MSKCC	ICER
Accounts for patient preference	No	No	Yes	Yes	No
Readout					
Outcomes	ESMO-MCBS	Net health benefit score	Evidence blocks scores	DrugAbacus price	Cost-effectiveness; budget impact
Measurement criteria	1. Survival outcomes 2. Toxicity 3. Quality of life	1. Survival outcomes 2. Toxicity 3. Additional benefits	1. Efficacy 2. Safety 3. Quality and quantity of evidence 4. Consistency of evidence 5. Affordability	1. Efficacy 2. Toxicity 3. Novelty multiplier 4. Cost of development 5. Rarity multiplier 6. Population burden of disease	1. Care value including quality-adjusted life years 2. Potential budget impact 3. Provisional value to the health system
Cost/price	Not specified, left to payers to evaluate	Price (WAC or ASP+) per month or course of therapy	Affordability scale	Abacus price per month or course of therapy	Cost per year

Source Table according to Table 1 in Slomiany et al. (2017) and Milken Institute and Avalere (2016)
ESMO European Society for Medical Oncology; *MCBS* Magnitude of Clinical Benefit Scale; *ASCO* American Society of Clinical Oncology; *ASP* average sales price; *CI* confidence interval; *FDA* US Food and Drug Administration; *ICER* Institute for Clinical and Economic Review; *MCBS* Magnitude of Clinical Benefit Scale; *MSKCC* Memorial Sloan Kettering Cancer Center; *NCCN* National Comprehensive Cancer Network; *RCT* randomized controlled trial; *WAC* wholesale acquisition cost

through a standardized approach. The ESMO-MCBS is a semiquantitative tool for clinical benefit, to prioritize therapies and enable a rapid access to all European citizens (Dafni et al. 2017), whereby the aspect of costs is not considered. Costs of procurement and out-of-pocket expenditures vary among European countries; the magnitude of clinical benefit, as derived from well-designed clinical trials, is relatively constant (Cherny et al. 2015). In the ESMO-MCBS v0.1, designed to evaluate comparative outcome studies in solid cancers, two separate forms for the curate and non-curative setting—form 1 and 2—were developed (Dafni et al. 2017). Thus, the clinical benefit of single-arm trials could not be evaluated.

A dual rule was implemented; first, the lower limit of the 95% confidence interval (CI) for the HR is compared with specified threshold values (absolute gains for survival, DFS and PFS); second, the observed absolute difference in treatment outcomes is compared with the minimum absolute gain considered as beneficial (Cherny et al. 2015; Dafni et al. 2017). For example, for a standard treatment median survival of 6 months, an absolute gain of 3 months corresponds to an HR = 0.67, while a gain of 1.5 months corresponds to an HR = 0.8 (Cherny et al. 2015). In a third step, the grade can be upgraded or downgraded to reflect the toxicity and quality of life (QoL) outcomes of the investigative treatment (Dafni et al. 2017).

Form 1 is used for adjuvant and neo-adjuvant therapies and for localized or metastatic diseases being treated with curative intent. This scale is graded A, B, or C. Grades A and B represent a high level of clinical benefit. The scale makes allowance for early data high DFS without mature survival data.

Form 2 (2a or 2b) is used to assess new agents without curate intent. This scale is graded 5, 4, 3, 2, 1, where grades 5 and 4 represent a high level of proven clinical benefit (Cherny et al. 2015). Form 2a is used for therapies evaluated using a primary outcome of OS and 2b when PFS or TTP is used as primary end point. The maximum preliminary grade is achieved in case of a true relative decrease in risk of at least 35% or more (or 30% or more, for OS with median control >12 months). A decrease of risk by at least 20% is necessary to satisfy the required minimum observed absolute benefit chosen by the ESMO-MCBS Working Group for achieving the maximal preliminary grade if median control for OS or PFS is $\leq$ 12 months (Dafni et al. 2017).

The ESMO-MCBS is an evolving tool with underlying rules that will be regularly improved and adapted according to the results of repeated rigorous testing and feedback from users and stakeholders (Dafni et al. 2017).

4.2 The American Society of Clinical Oncology (ASCO) Value Framework

The framework was developed by the ASCO Value in Cancer Care Task Force, which is an approach which provides a Net Health Benefit (NHB) score derived from efficacy, safety, and bonus points for secondary end points (Slomiany et al. 2017). The NHB is a combined and weighted measure of clinical benefit and side

effects. It represents the additional benefit of one drug compared with the prevailing standard as tested against each other in a randomized clinical trial. Maximum scoring for clinical benefit is 100 (more important weight on OS versus PFS or RR), while being 20 for toxicity. Bonus points are awarded for the tail of the survival curve (20 points); advance disease framework also includes palliation of symptoms (10 points) and/or treatment-free interval (20 points) and/or quality of life (QoL) (10 points). A low NHB means there is a little added benefit; a high NHB means there is a significant additional clinical benefit and/or less toxicity. An NHB of zero means that the two agents studied in a clinical trial are equivalent—not that the new agent does not work. In all cases, the framework is intended to help facilitate better-informed discussions between doctors and patients—and not to be used as a substitute for physician's clinical expertise or judgment. All clinical scenarios included in the framework are illustrative only (ASCO 2016).

The value framework also includes a comparison to direct treatment costs. Compared to Europe, drug costs are among patients' biggest concerns in the USA, because patients pay a significant share of these costs through co-payments. Many cancer care costs are not transparent and readily available nor are they easily quantified for any given group of patients (ASCO 2016).

ASCO updated its value framework with changes to the scoring methodology, providing additional secondary end points, such as improvement in quality of life and significant survival improvement in the tail of the curve for which bonus points could be earned (Slomiany et al. 2017).

4.3 National Comprehensive Cancer Network Evidence Blocks

The National Comprehensive Cancer Network (NCCN n.d.), a nonprofit alliance of 26 cancer centers throughout the USA, launched its evidence block framework in October 2015, with the goal to provide the healthcare provider and the patient with information to make informed choices when selecting systemic therapies based on measures related to treatment, supporting data, and cost (Slomiany et al. 2017; NCCN n.d.). The domains include effectiveness, safety, quality of evidence, consistency of evidence, and affordability. Guided by staff from the NCCN, in consultation with the group's members, this approach uses a standardized scale to provide consensus-based scoring of the efficacy, safety, and affordability of a drug or a regimen and the quality and consistency of the evidence associated with that drug or regimen (Slomiany et al. 2017; NCCN n.d.). Each of the 5 measures in the NCCN's approach is displayed as a solid block using a scale from 1 to 5, where 1 is considered least favorable and 5 is most favorable (Slomiany et al. 2017).

The evidence blocks lack specificity for defining each level of scoring. However, a panel of experts in each cancer area constitutes the guideline committee for a specific cancer type. Thus, one can assume that the final score for any domain represents a preponderance of opinions of the convened expert panel. The affordability domain includes drug cost (to whom is uncertain), supportive care,

administration costs, and monitoring and management of toxicity (Schnipper and Bastian 2016).

4.4 Memorial Sloan Kettering Cancer Center DrugAbacus

The DrugAbacus is the creation of a physician and policy expert at Memorial Sloan Kettering Cancer Center in New York and was launched in June 2015. The target stakeholders are physicians and policymakers, but not patients as in the case of ASCO and NCCN (MSKCC n.d.).

In contrast to the other value frameworks, the output of the DrugAbacus is not a value score, per se, but rather an "Abacus price" which represents the theoretical price the anticancer drug should be, according to the user. This theoretical price is juxtaposed onto the actual market price to contrast any price deficits or surplus for a given antineoplastic agent (Schnipper and Bastian 2016; MSKCC n.d.).

This system delivers a value-based price for a drug that graphically represents the user's weighted preferences and estimated monthly costs relative to 52 cancer drugs (Slomiany et al. 2017).

The Abacus price is calculated using a formula that consists of weighting factors used in other frameworks. Elements such as efficacy, toxicity, or population health burden are common to other value frameworks. However, the DrugAbacus also includes other factors such as research and development, rarity, and novelty, which are not commonly included in other assessment tools. The utility of these elements to individual patients or physicians may relate less to the day-to-day treatment decision process but may be more relevant for policymakers or from a societal perspective (Schnipper et al. 2016).

4.5 The Institute for Clinical and Economic Review Value Assessment Framework

The Institute for Clinical and Economic Review is an independent, nonprofit, research-based organization that produces independent reviews of the comparative clinical effectiveness and value of medical goods and services. The assessment program was launched in July 2015, with guidance from an advisory committee of payers, patient organizations, physician organizations, and the biopharmaceutical industry (Schnipper and Bastian 2016). Targeting payers and policymakers, the Institute for Clinical and Economic Review delivers a value-based price benchmark anchored in the real benefits that a specific drug brings to patients.

The framework is based on two primary directions: calculating the care value and the health-systems value. Care value is an estimate of the average per-patient costs, clinical outcomes, and broader health effects of two alternative interventions. The health-systems value supplements the aspect of affordability and calculates the degree to which the short-term budget impact of a new care option can be afforded by the healthcare system (Schnipper and Bastian 2016). Consequently, the goal

requires consideration of two general concepts: "long-term value for money" and "short-term affordability" (Institute for Clinical and Economic Review n.d.).

Within this framework, and in contrast to the others, the metric QALY is given particular importance.

Long-term value for money serves as the primary anchor of the Institute for Clinical and Economic Review Value Framework. The concept comprises the following multiple domains: (1) comparative clinical effectiveness; (2) incremental cost-effectiveness; (3) other benefits or disadvantages; and (4) contextual considerations (Institute for Clinical and Economic Review n.d.). An incremental cost-effectiveness ratio below $50,000 per QALY is defined as "high value," while a ratio above $150,000 would be deemed "low value." The commonly held threshold is between $50,000 and $100,000 (Institute for Clinical and Economic Review n.d.).

5 Are Frameworks a Boon or a Bane?

Due to the diversity of patterns within the frameworks, it is not possible to draw a common conclusion. The value of cancer drugs is multidimensional. However, it may be best that different stakeholders support the use of a few frameworks and methods since multiplicity and complexity may only complicate the assessment of therapeutic drugs and biologics and their companion diagnostics.

The following descriptions should outline some similarities, divergences, and further investigations needed to impact on the intended stakeholders' (i.e., patients, physicians, and/or payers) adoption of the frameworks.

5.1 Clinical Trial Data Versus Real-World Evidence

Randomized clinical trials (RCTs) are the gold standard for rational therapeutics in evidence-based medicine. RCTs, by the nature of their artificial design to minimize selection bias, are often not representative of the demographic distribution of the actual patient population (Slomiany et al. 2017). Less than 5% of adult patients with cancer participate in clinical trials and those who do are younger, healthier, and less diverse than their real-world counterparts (Gyawali et al. 2017). Thus, frameworks (e.g., NCCN's and ICER's frameworks) that rely on consensus or combined analysis of multiple clinical trials and a variety of clinical end points could provide a better indication of the therapeutic value and could more easily be extrapolated to the larger population (Slomiany et al. 2017).

Among the oncology value frameworks, there remains a lack of real-world evidence (RWE) and ready access to subpopulation analyses across patient types (Slomiany et al. 2017). Kiesewetter and colleagues have published real-life experience at the Medical University of Vienna and created MCBS field testing (Kiesewetter et al. 2016). However, RWE cannot definitively answer whether an

intervention is superior to a control, a question which is of prime importance in deciding whether to approve a new treatment indication. Thus, the utility of RWE may be limited when clinical trial rigor is vital to avoid harm or when a definitive answer is needed (Gyawali et al. 2017).

5.2 Method of Scoring

Slomiany and colleagues stated that, for example, in ASCO's framework the interchangeability of various primary end points, such as survival hazard ratio or overall survival with progression-free survival or recurrence rate, belies their subtle differences (Slomiany et al. 2017). The authors are in accordance with Schwartzberg and colleagues when noted that the interplay between shared decision making and the usability of information have asserted that the information should be accessible to patients, as well as understandable and usable (Slomiany et al. 2017; Schwartzberg et al. 2016).

Interviews with payers and secondary research exploring usability by Slomiany and colleagues have revealed that the framework and its outputs should at least be in a form that providers can easily relay to patients. Authors identified a dearth of investigation into patient and provider usability. Discussions with physicians and payers regarding the analysis of value confirm hesitancy in applying these frameworks in practice until they better understand how to apply and extract value from the frameworks' inputs. This caution was particularly expressed with regard to the ASCO and the NCCN frameworks (Slomiany et al. 2017).

5.3 Problems with QALYs

There is an ongoing animated academic discussion regarding QALYs. The criticisms of the use of QALYs can be addressed by good-quality economic modelling (Goldstein 2016). Only the Institute for Clinical and Economic Review Value Assessment Framework has incorporated a cost-effectiveness outcome. Apart from this framework, several countries in the EU, the USA, Canada, Australia, etc., use the cost-effectiveness ratio and/or cost-effectiveness thresholds for reimbursement decisions. That means that in addition to other value frameworks cost-effectiveness data has to be provided at a later step. In cases where the ESMO-MCBS or the ASCO-NBS guaranteed a high level of proven clinical benefit from a health economic perspective, oncologists required an average of six additional months of life for a cancer drug that costs $75,000, which implied an ICER of $100,000/QALY, and 7–8 months for a drug that costs $150,000, suggesting an ICER of $192,308/QALY (Carrera and IJzerman 2016).

It has been suggested that cost-effectiveness analyses are unable to account for differences in value perceptions among different people (Goldstein 2016). For example, one patient may be unwilling to tolerate grade 1 peripheral neuropathy secondary to oxaliplatin, despite the life-extending effect. Another patient may be

willing to tolerate even grade 3 peripheral neuropathy if he/she knew that their life was being extended (Goldstein 2016). Similarly, different people or payers may be prepared to spend different amounts of money for the same level of benefit, depending on their own individual budgets and income. This represents a reality that is sometimes rejected in behavioral economics. However, well-developed cost-effectiveness models are flexible and can produce results that account for variation in preferences and values (Goldstein 2016).

A series of authors address criticism regarding the QALY metric for having insufficient sensitivity to measure small but clinically meaningful changes in health status—or utility. The recognition of changes in health status is particularly important to certain patient subgroups, for example cancer patients where multiple studies have outlined a need for additional dimensions to be considered. For such patients with short life expectancies or reduced endurance limits, these standardized "trade-off" decisions may be invalid (Pettitt et al. 2016; Garau et al. 2011). This must, however, be balanced against the use of QALY measurements as decision-making tools applicable to whole economies rather than to just single patient levels (Pettitt et al. 2016).

ICER thresholds do not explicitly consider opportunity costs (i.e., the health benefits forgone by choosing not to spend finite resources on alternatives) as they consider interventions in isolation to other potential investments (Metcalfe and Grocott 2010; Simoens 2010). Therefore, some authors favor the replacement model as an alternative to the threshold ICER model (Simoens 2010). With this approach, the replacement model identifies an existing medicine B which would be cancelled for the new medicine A, which would generate at least enough resources to fund the incremental costs of medicine A. If the incremental outcomes associated with medicine A exceed the outcomes foregone from cancelling medicine B, then the healthcare payer can replace B with A, thereby increasing total health at the same or lower cost (Simoens 2010).

Doubts regarding QALYs enable the possibility to perform cost-effectiveness analyses without adjustment for quality of life. In that case, costs-per-life-year (LY) could be presented in addition. For example, bevacizumab in addition to chemotherapy in first-line metastatic colon cancer costs $571,240/QALY and $438,779/LY (Goldstein 2016). When using only dollars per LY as a cost-effectiveness result, the willingness-to-pay threshold has to be corrected. For example, if one considers an acceptable threshold to be $100,000/QALY and a treatment of advanced colon cancer costs $98,000/LY, it is not possible to declare that it is cost-effective. If not adjusting for quality of life, the threshold to be considered cost-effective would need to be higher (Goldstein 2016).

To summarize, challenges regarding the precise methodology used to understand quality of life are not a reason to discard the whole technique of cost-effectiveness evaluations (Goldstein 2016).

5.4 Perspective (Payer, Policymaker, Physician, Patient)

The recent development of frameworks to objectively assess the value of individual therapies and other healthcare services did not involve any significant input from patients or patient organizations to inform their models or definitions of value (Milken Institute and Avalere 2016). How these frameworks will be patient-tailored remains unclear because individual patient disease characteristics are not considered by the frameworks developed by ASCO, NCCN, or ESMO (Slomiany et al. 2017). The target stakeholder by ASCO and NCCN comprises patients and physicians, with the aim of helping physicians value new drug treatments as compared with one or several prevailing standards of care (Lemieux and Audet 2018). From the patient perspective on value, it would be essential to include an assessment of the clinical, functional, and quality-of-life benefits and any harmful side effects of a treatment that the patient would experience in the long term (Milken Institute and Avalere 2016). The ESMO-MCBS includes quality of life in a third step—to the extent that it can up- or downgrade the grade (Dafni et al. 2017). None of the current value frameworks consider short- or long-term value from the individual patient's perspective (Slomiany et al. 2017).

From the third-party payer or policymaker, perspective value frameworks are of utmost interest. Based on their assessments of the frameworks, organizations build on their value-based pricing and resource allocation decisions.

5.5 Including Costs

Reimbursement policies for anticancer drugs vary among countries even though they rely on the same clinical evidence of those drugs. Given the finite financial resources and rising costs of anticancer drugs, each country must be economical when deciding reimbursement policies for each anticancer drug (Lim et al. 2014). From the described frameworks, four include costs to a certain degree.

The aspect of costs is not considered in the ESMO Magnitude of Clinical Benefit Scale (Cherny et al. 2015). ASCO and MSKCC consider anticancer drugs costs, whereas other direct medical costs, such as reducing the need for surgery or hospitalization, laboratory costs, profiling, etc., were ignored (Slomiany et al. 2017). One argument by ASCO is that evidence shows that drug costs are the most rapidly rising component of cancer care (ASCO). Drug costs were assessed based on wholesale acquisition cost or the average sales price (Medicare reimbursement) plus patient out-of-pocket payments. Costs are not included in NHB. Other cost components are rarely available. The DrugAbacus by MSKCC estimates what a cancer drug should cost based on six criteria, and then compares the DrugAbacus price with the drug's actual price. The actual price is estimated by the amount that Medicare reimburses for the drug (Memorial Sloan Kettering Cancer Center n.d.).

The NCCN defines its affordability measure and includes the overall costs of an intervention, including the drug, infusions, supportive care, toxicity monitoring and

management, and the probability of care being delivered in the hospital (Slomiany et al. 2017).

Only the Institute for Clinical and Economic Review Value Assessment Framework considers the total cost per patient by evaluating the total aggregated cost (Slomiany et al. 2017).

In any discussion regarding the cost of health care, it is extremely important to define whose costs are being analyzed, whether that is costs to the healthcare provider, the patient, or society as a whole. In this context, we have to bear in mind that all cost descriptions by the frameworks track charges and not costs with the understanding that cost shifting is considerable (Feeley et al. 2010).

None of these frameworks, not even the patient-oriented ones, consider affordability at a patient-tailored level, such as, how can providers assess what is affordable, especially considering an individual patient's budget, impact and trade-offs, length of treatment, insurance coverage maximums, and co-payments (Slomiany et al. 2017).

6 MCBS Versus ICER

Previously, described differences in value assessment approaches would seem to indicate that there is no correlation between benefit score and costs or rather ICER. Becker and colleagues have analyzed 55 drug approvals regarding correlation between costs and benefit score (ASCO-NBS and ESMO-MCBS). No correlation between benefit score and cost (NHB, $r = 0.19$; ESMO, $r = -0.07$) was found by the authors (Becker et al. 2017).

Table 2 was developed based on the presentation of the ESMO-MCBS for advanced lung cancer by Kiesewetter et al. ESMO-MCBS and MCBS field testing data were used to compare benefit scores with ICER results from the published literature.

Data shows that the whole first-line-targeted treatment for stage IIIB/IV non-squamous EGFR-mutated or ALK-mutated metastatic lung cancer reached a high level of recommendation (ESMO-MCBS/MCBS-FT score 4) despite a lack of OS benefit in the majority of trials (Kiesewetter et al. 2016). ICER values for first-line-targeted treatments span for being dominant (treatment is cheaper compared with a higher benefit) in case of afatinib versus cisplatin plus pemetrexed and erlotinib versus platinum-based CT doublet to US$ 85,927.41 when erlotinib was compared to gemcitabine plus carboplatin. Depending on the countries' willingness-to-pay threshold, erlotinib compared to gemcitabine plus carboplatin would be classified as cost-effective or rejected. For both comparisons, the dominant OS data was collected and available.

Maintained treatment, after response to platinum doublet with erlotinib versus placebo, yields a MCBS field testing score of 1. An ICER was calculated for this comparison between €20,711 (UK) and €25,124. From a cost-effectiveness

Table 2 ESMO-MCBS (and field testing) versus ICER for the treatment of advanced lung cancer

Clinical trial	Analyzed treatment	Setting	Primary EP	PFS treatment	PFS control	HR	OS	OS control	HR	MCBS	MCBS-FT	ICER
OPTIMAL Zhou et al. (2011)	Erlotinib versus gemcitabine plus carboplatin	First-line IIIB or IV, non-squamous, EGFR-mutated	PFS	13.1 m	4.6 m	0.16 (0.10 to 0.26)	–	–	–	4		US$ 85,927.41 Wang et al. (2013)
EURTAC Rosell et al. (2012)	Erlotinib versus platinum-based CT doublet	First-line IIIB or IV, non-squamous, EGFR-mutated	PFS	9.7 m	5.2 m	0.37 (0.25–0.54)		19.5		4		Dominant to US $40,106/QALY Ting et al. (2015), Vergnenegre et al. (2016)
LUX-Lung 3 Sequist et al. (2013)	Afatinib versus cisplatin plus pemetrexed	First-line IIIB or IV, adenocarcinoma, EGFR-mutated (EGFR exon 19 deletion)	PFS (all) PFS (del 19)	11.1 m 13.6 m	6.9 m 6.9 m	0.58 (0.43–0.78) 0.47 (0.34–0.65)	33.3	28.2 m 21.1 m	0.54 (0.36–0.79)	N/A	4	Dominant Ting et al. (2015) £39,300 per QALY gained NICE[1]
IPASS Mok et al. Fukucka et al.	Gefitinib versus carboplatin plus paclitaxel	First-line IIIB or IV, non-squamous, (EGFR-mutated)	PFS (all) PFS (EGFR+)	NA 9.6 m	NA 6.3 m	0.74 (0.65–0.85) 0.48 (0.34–0.67)		–		N/A	4	£19,402 per QALY gained NICE[2]
Crizotinib versus CT Shaw et al. (2013)	Crizotinib versus pemetrexed or docetaxel	One prior platinum-based regimen IIIB or IV (ALK-mutated)	PFS	7.7 m	3.0 m	0.49 (0.37–0.64)				4		£71,400 and £137,883 per QALY gained[3]
Crizotinib versus cisplatin plus pemetrexed Solomon et al. (2014)	Crizotinib versus cisplatin plus pemetrexed	First-line IIIB or IV, non-squamous, (ALK-mutated)	PFS	10.	7.0 m	0.45 (0.35–0.60)				4		ICER of £47,291 per QALY gained[4]

(continued)

Table 2 (continued)

Clinical trial	Analyzed treatment	Setting	Primary EP	PFS treatment	PFS control	HR	OS	OS control	HR	MCBS	MCBS-FT	ICER
SATURN Capuzzo et al.	Erlotinib versus placebo	Maintenance after response to platinum doublet	PFS	12.3 w	11.1 w	0.71 (0.62–0.82)	12 m	11 m	0.81 (0.70–0.95)	1	NA	ICER between €20,711 (UK) and €25,124 (Germany) Walleser et al. (2012)
LUME-Lung1 Reck et al.	Docetaxel ± nintedanib	Second line (adenocarcinoma with PD 9 m after start 1st Line)	PFS (all) PFE (adeno.)	3.4 m 3.6 m	2.7 m 1.5 m	0.79 (0.68–0.92) 0.63 (0.48–0.83)	12.1 m 10.7 m	9.1 m 7.9 m	0.94 (0.83–1.05) 0.75 (0.6–0.92)	NA	4	ICER €66,985 per QALY gained[5]
Checkmate 057 Borghaei et al.	Nivolumab versus docetax	Second-line non-squamous cell lung cancer	OS		4.2 m		12.2 m	9.4 m	0.73 (0.59–0,89)	NA	4	NICE
Checkmate 017 Brahmer et al.	Nivolumab versus docetax	Second-line non-squamous cell lung cancer	OS	3.5 m	2.8 m	0.62 (0.47–0.81)	9.2 m	6.0 m	0.56 (0.44–0.79)	NA	5	ICER €136,215 per QALY gained[7]

Source Table according to Table 2 of Kiesewetter et al. (2016), ICER different sources

[1]NICE. https://www.nice.org.uk/guidance/ta310/chapter/3-the-manufacturers-submission

[2]NICE. https://www.nice.org.uk/guidance/ta192/documents/lung-cancer-nonsmallcell-first-line-gefitinib-final-appraisal-determination3

[3]NICE. https://www.nice.org.uk/guidance/ta296/documents/lung-cancer-nonsmallcell-anaplastic-lymphoma-kinase-fusion-gene-previously-treated-crizotinib-evidence-review-group-report3

[4]NICE. https://www.nice.org.uk/guidance/ta406/documents/final-appraisal-determination-document

[5]NCPE. http://www.ncpe.ie/wp-content/uploads/2015/02/Nintedanib-Vargatef-summary.pdf

[6]NCPE. http://www.ncpe.ie/wp-content/uploads/2016/04/Summary-Nivolumab-in-non-sq-NSCLC.pdf

[7]NCPE. http://www.ncpe.ie/wp-content/uploads/2016/03/Nivolumab-for-sq-NSCLC-summary.pdf

EP end point, *m* month, *w* week, *ICER* incremental cost-effectiveness ratio

perspective, the treatment would be classified as cost-effective. Hence, the results are controversial.

Generally, second-line-targeted treatments indicate higher ICER than first-line treatments. The second-line treatment of nivolumab versus docetaxel yields an ICER of about €200,000 for non-squamous cell lung cancer and a MCBS field testing score of 4.

Analysis of the literature data confirms that there is no correlation between benefit score and ICER.

7 Future Perspectives

The setup and the interpretation of value frameworks reviewed in this article are without doubt steps toward the need to assess more rationally the conundrum of value, costs, costs per QALY gained, etc., with respect to new advances in oncology.

Their main advantage therefore is the fact that they should enable more rationality in such processes and help to avoid excessive power struggles. However, more internationally harmonized priorities in the establishment and homogeneity in the approach of such value frameworks would be desirable. These are displayed in a study comparing the ASCO NHB score with the ESMO-MCBS, which found only a weak-to-moderate correlation (Lemieux and Audet 2018; Cheng et al. 2017). These findings were supported by the fact that FDA and EMA approvals are not based on the same criteria, apart from scoring methods. Another study observed a negative correlation between the ASCO NHB score and incremental cost (Lemieux and Audet 2018; Del Paggio et al. 2017).

For this purpose, "meta-criteria" would have to be developed by international health organizations to elucidate the strengths and weaknesses of these value frameworks. This, of course, cannot substitute national decision making since it is always affected by national peculiarities. Currently, the most commonly used "value" assessment for cross-discipline comparisons is the incremental cost-effectiveness ratio. Including cost aspects, not only anticancer drug costs but also total direct medical costs, would lead to a comprehensive application of the value frameworks since costs are the core issue after confirmation of the clinical benefit. Costs also comprise the crucial question of patient access to expensive treatments.

8 Conclusion

Great progress has been made in developing value frameworks with the aim of making informed decisions about the benefit of novel cancer therapies. Third-party payer or policymakers are able to decide on the societal benefit of funding those therapies.

The described tools have varying purposes. The ESMO framework is designed to provide data on the relative clinical impact of anticancer drugs to leave comparative effectiveness calculations to European health technology assessment committees. The ASCO tool has been developed to assess net health benefit and demonstrates costs of the anticancer drugs as these are discussed between oncologists and patients. Cost-effectiveness analyses, which include costs and QALYs, are the approach used by the Institute for Clinical and Economic Review Value Assessment Framework. The NCCN initiative is also designed as a tool to discuss the variety of regimens that can be offered to a patient, supplemented by an assessment of affordability.

The value-based frameworks are an important element for encouraging discussions around price and value. In this stage of development, results can support oncologists, healthcare decision-makers, or health technology assessment organizations to choose from treatment alternatives. As a next step, the aspect of total costs and QoL should be incorporated in a broader view. Which value framework becomes more established and widely accepted, and by what stakeholder, will influence how the pharmaceutical industry will shape the clinical and commercial development of its oncology drugs (Slomiany et al. 2017).

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Orphan Drugs in Oncology

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Abstract

Rare diseases represent a group of conditions affecting a very limited number of patients. Low profitability resulting from the small size of target population coupled with difficulties in conducting the research causes the lack of interest from the pharmaceutical industry. In order to promote research and development of medicines for rare diseases, a special 'orphan' legislation was introduced in a number of regions. These measures led to a significant increase in the number of approved orphan molecules. The high per patient cost of orphan drugs, as well the rapid growth of orphan drug sector, raised concerns regarding the sustainable funding of therapies for rare diseases. Rare cancers represent the majority of the current orphan drug market and are often associated with very high revenues. This chapter provides a review of orphan legislations and health technology assessment framework, analyses the position of oncology drugs on the orphan drug market and discusses future perspectives.

Keywords

Orphan drugs · Rare diseases · Health policy · Oncology · Health technology assessment · Equity · Patient access

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1 Introduction

Orphan medicinal products, or 'orphan drugs', constitute a class of drugs that have been developed specifically to treat a rare medical condition. The label 'homeless or orphan drugs' was first used by G. P. Provost in 1968 to qualify all categories of medications in which the pharmaceutical industry seemed to have very little interest (Provost 1968). As the name suggests, rare diseases occur in a very small population. The development of drugs for rare diseases is challenging due to very poor knowledge of the disease, its natural history and epidemiology. Difficulties in recruiting patients for clinical trials because of their small number hamper the demonstration of the comparative efficacy of the new drug. The complexity of the development coupled with the small size of the target population makes rare diseases unattractive for the pharmaceutical industry.

At the same time, rare diseases generally represent severe genetic conditions with poor survival and high unmet needs due to the lack of treatment options. In order to guarantee the access to appropriate therapies for patients with rare diseases, governments in some countries have introduced special orphan drug legislation and have provided a number of incentives to promote research and development in this field. As a result, the number of orphan drugs has dramatically increased and the total orphan drug worldwide sales reached $102 billion in 2015 with a projection of $178 billion in 2020 (EvaluatePharma 2013). Moreover, the orphan drug market continues to grow with a rate higher than the overall rate of growth of the total pharmaceutical market.

Because of the small number of potential patients, orphan drugs are typically associated with very high per patient costs. Although the budgetary impact of an orphan drug remains low, all together they may represent a significant burden to healthcare budgets, raising concerns regarding the affordability of such treatments (Schey et al. 2011; Kanters et al. 2014; EvaluatePharma 2013). Indeed, allocation of large resources for the treatment of a very limited population conflicts with the total utilitarianism concept which aims at maximising the total population's well-being (Davies et al. 2012). At the same time, it seems ethical to provide treatments for patients with high unmet needs suffering from severe life-threatening diseases. The idea of equity and equal rights for the access to treatment is supported by many authors (Schlander et al. 2014; Feltmate et al. 2015; Westermark and Llinares 2012; Davies et al. 2012; Hyry et al. 2015; Marshall 2005; Sheehan 2005; Clarke 2006; Hughes 2006).

Oncology drugs represent the largest orphan drug group. Almost 200 rare cancers have been identified, which all together represent 22% of all cancer cases diagnosed in the EU28 each year (Gatta et al. 2011). Except for 5 major tumour types including breast cancer in female, lung, colorectal, prostate and bladder cancers, all other cancers may be classified as rare (Macarthur 2008). Moreover, recent technical advances in genetic testing allowed further segmentation of cancer types into smaller subgroups.

2 Orphan Drugs: Regulatory Process

The USA was the first to establish a special orphan legislation by introducing the 'Orphan drug act' in 1983 (Orphan Drug Act 1983). This example was followed by Singapore in 1991, Japan in 1993, Australia in 1997, Taiwan in 2000 and South Korea in 2003 (Song et al. 2012). The EU was among the last to adopt such policies. The European regulation for orphan drugs was adopted by the European Parliament and European Council on 16 December 1999 (Regulation 141/2000/EC 1999). An orphan designation granted by the EMA is valid in all EU countries.

The definition of an orphan drug varies across jurisdictions. The main criterion to grant an orphan status is a limited patient population. The EMA defines the prevalence threshold for orphan drugs as 5 patients in 10,000 (European Medicines Agency n.d.-c). In the USA, Japan and South Korea, the threshold is given in absolute number of patients living on the territory of the country (200,000, 50,000 and 20,000 patients for the USA, Japan and South Korea, respectively) (US Food and Drug Administration 2017; Song et al. 2012). A systematic review on rare disease terminology found that the threshold for orphan designation varied from 5 to 76 patients per 100,000 people (Richter et al. 2015).

Granting an orphan designation allows the drug to benefit from a number of incentives established to facilitate return on investments (Gammie et al. 2015). Generally, the proposed incentives include financial assistance, a fast-track simplified approval procedure, protocol assistance and scientific advice, as well as market exclusivity (see Table 1). Financial assistance may involve a reduction in filling fees, which may depend on company size as in the EU, and special grants. In the USA, Orphan Products Grants Program (US Food and Drug Administration 2016) helps to fund the development of drugs for rare diseases. Special grants are also available in Japan and South Korea (Song et al. 2012). The EMA does not propose any direct financial help, but funding is available from the European Commission and other sources (European Medicines Agency n.d.-c). Tax credits or reductions may be applied for orphan drugs in the USA, Japan and South Korea.

In order to accelerate the access to orphan drugs, the approval process may be simplified. For instance, in the USA orphan drugs are eligible for a rolling review (US Food and Drug Administration 2014), where completed sections of the dossier can be submitted separately rather than waiting for the whole application to be

Table 1 Incentives for development of orphan drugs

Type of assistance	Example of incentives
Financial assistance	Fees reduction or withdrawing, tax credits or tax reduction, special grant programmes
Scientific advice	Protocol advice and consultations
MA procedure	Fast-track or accelerated procedure, priority review, rolling review
Market exclusivity	Market exclusivity period or extension of re-examination period

completed. In the EU, orphan drugs undergo a compulsory centralised approval procedure. Orphan drugs may be also granted a conditional marketing authorisation (MA) or an approval under exceptional circumstances on the basis of less complete data than required generally (European Medicines Agency, n.d.-a). However, these types of approvals are not specific to orphan medicines.

Additionally, a market exclusivity period of 7 and 10 years is established for orphan drugs in the USA and EU (CDER Small Business and Industry Assistance 2015; European Medicines Agency n.d.-b). This guarantees that no other treatment with a similar mechanism of action will be approved in the same indication except if it demonstrates higher efficacy. The market exclusivity period may be further extended by 6 months or 2 years in the USA and EU, respectively, in case of paediatric indication. Similar measures were introduced in Japan where a market exclusivity period is not available, but the re-examination period is extended up to 10 years (vs. standard 8 years) in the case of an orphan drug (Ministry of Health, Labour and Welfare, n.d.).

3 Orphan Drugs: Health Technology Assessment and Pricing

The appraisal of therapies for rare diseases represents an important challenge for health authorities. At the same time, fixing a fair price for orphan drugs is crucial to ensure access to the appropriate treatments for patients with rare diseases. There is no universal health technology assessment (HTA) decision framework for orphan drugs, and different jurisdictions focus on various HTA criteria, such as cost-effectiveness, budgetary impact, disease severity, therapeutic need, social benefits.

Unlike for the regulatory process, the progress in the development of a special HTA pathway for orphan drugs remains poor. Generally, the HTA process for orphan drugs follows the same steps as the one established for common diseases. However, standard HTA methods, such as cost-effectiveness analysis, demonstrated their insufficiency in case of rare diseases and were criticised by many authors (Winquist et al. 2012; Drummond et al. 2007; Hyry et al. 2015; Hughes et al. 2005; Sheehan 2005; Clarke 2006; Hyry et al. 2014; Simoens 2014; Gutierrez et al. 2015; Hughes-Wilson et al. 2012; Schlander et al. 2014).

First of all, a classic health economic approach may be impossible to apply to orphan drugs due to very limited clinical data. Calculating the incremental cost per quality-adjusted life year (QALY) gained suggests that survival and quality of life (QoL) data are available. However, in the case of a rare condition the difficulty in conducting clinical trials has several consequences for the quality of evidence, related to the clinical trial design (small number of patients, absence of a control arm due to ethical issues, lack of randomisation and blinding) and the use of surrogate endpoints, rather than patient-relevant endpoints (Emanuel and Miller 2001; Griggs et al. 2009; Augustine et al. 2013; Hall and Ludington 2013).

A review that looked at the clinical evidence of the pivotal studies of 64 orphan drugs approved by the EMA showed that the allocation was randomised in 64.8% of studies and a control arm was used in 68.5% (Picavet et al. 2013). Only half of the studies applied some type of blinding. A QoL-related endpoint was included in 26.9% of the studies. Low levels of clinical evidence are also prevalent in the field of orphan drugs in oncology. A systematic review of 60 randomised controlled trials and 21 cost-effectiveness analyses of 47 oncology orphan drugs showed that only 21 drugs (35%) had moderate- or high-quality clinical evidence, 11 had low- or very-low-quality clinical evidence, and 15 drugs could not be evaluated due to incomplete data (Cheng et al. 2012). Remarkably, there was a paucity of economic evaluations for these drugs.

Secondly, a comparative assessment may be complicated by the lack of data on the natural history of the disease and the absence of an established standard-of-care treatment with known efficacy.

Finally, even if an accurate cost-effectiveness evaluation is possible and a robust estimation of incremental cost-effectiveness ratio is obtained, it is generally never able to pass the cost-effectiveness threshold due to a very high per patient cost (Schuller et al. 2015). Indeed, the cost-effectiveness approach is associated with poor assessment outcomes when it concerns rare conditions (Kawalec et al. 2016; Cohen and Felix 2014; Mycka et al. 2015). As consequence, patients with rare diseases in countries that employ solely the cost-effectiveness approach may be deprived of access to orphan drugs.

Interestingly, France and Italy focus on criteria such as proven clinical value, evidence from cohort studies and the degree of innovation. In spite of the high price of orphan medicines, they are reimbursed in these countries because of their relatively low impact on budgets. For instance, only one orphan drug has been rejected for reimbursement in France. The French National Authority for Health (Haute Authorité de Santé—HAS) considered the benefit brought by mifamurtide in treatment of high-grade resectable non-metastatic osteosarcoma to be insufficient for reimbursement. The HAS was concerned about the quality of the submitted evidence and the statistical methods used and could not judge on the effect size of the therapy.

However, many countries have demonstrated a desire and made efforts to provide appropriate therapies to patients with rare diseases. Standard HTA approaches that require data from randomised controlled trials are often relaxed when applied to orphan drugs (Gibson and von Tigerstrom 2015). Payers are more tolerant in their acceptance of higher uncertainty in case of orphan drugs. For instance, lower significance levels for p values (e.g. 10% significance levels) for small sample sizes, as well as the evidence from surrogate endpoints rather than only 'hard' endpoints, are accepted in Germany (Tordrup et al. 2014).

Germany is also among a few countries that adopted a special framework for rare diseases after a failure to apply the standard HTA procedure to the first two assessed orphan drugs (Bouslouk 2016). The additional benefit of orphan drugs is now considered to be proven through the orphan designation, and only the extent of the additional benefit is assessed. Moreover, results of the studies for marketing

authorisation are accepted even if an appropriate comparator was not used. A complete benefit assessment vs. an appropriate comparator is required only if annual sales exceed €50 million per 12 months.

Another example of a special legal framework is highly specialised technology (HST) assessment which has been recently introduced for ultra-orphan (<1 in 50,000) drugs by the National Institute for Health and Care Excellence (NICE) in England and Wales (National Institute for Health and Care Excellence 2013). With the introduction of HST framework, NICE abandoned the classic cost-effectiveness approach in favour of a methodology which follows the principles of multi-criteria analysis. A number of criteria were introduced for HST assessment including the nature of the condition, the impact of the new technology, the cost for the national healthcare system (NHS), value for money and the impact of the technology beyond direct health benefits. No formal cost-effectiveness analysis had been required in the new HST framework (Brockis 2016). The Committee considered each of the criteria and reached a consensus regarding the recommendation for national commissioning. After several years of operating under the HST framework, the cost-effectiveness ratio was reintroduced into the assessment process. The NICE established a cost-effectiveness threshold of £100,000 per QALY and proposed QALY weighting to allow the threshold to be increased to £300,000 for drugs with a significant incremental QALY gain (National Institute for Health and Care Excellence 2017).

By mid-2015, only one drug has been assessed under the new framework. Eculizumab has been recommended for treating atypical haemolytic uraemic syndrome. A cost-consequence analysis was submitted by the manufacturer as a part of the dossier. Five other guidelines were in development (none of them in oncology).

For orphan drugs that were assessed by the NICE under the classic cost-effectiveness approach, higher incremental cost-effectiveness ratios (ICERs) could be potentially accepted under the condition that the drug met the end-of-life criteria (Collins and Latimer 2013). In other words, the drugs should be indicated for a disease associated with a survival of less than 24 months and should be able to extent survival by at least 3 months. Higher ICERs are also accepted for orphan drugs in Scotland or Sweden where the willingness-to-pay threshold is flexible to adjust for disease severity (Tordrup et al. 2014).

Even if significant progress has been made in providing patients with rare diseases with an effective treatment, many issues remain unresolved. High orphan drug costs often lead to a situation when a treatment for a rare condition is available but not accessible due to its high price (Cote and Keating 2012). Differences in the amount of financial resources, as well as in implemented HTA approaches, result in a significant heterogeneity in patient access across countries. A survey of the European Organisation for Rare Diseases (EURORDIS), which studied the availability of 60 orphan drugs in 10 European countries, found that proportion of patients with potential access varied from 34% in Greece to 98% in France (Le Cam 2010).

Moreover, uncertainty regarding the final number of patients may lead to significant concerns about affordability when dealing with very costly drugs. Orphan drugs are often seen as a highly lucrative opportunity for the industry (Cote and

Keating 2012; Murphy et al. 2012; Loughnot 2005). Indeed, the number of orphan drugs that became blockbusters with more than $1 billion annual sales demonstrates a high potential profitability of treatments for rare diseases. Potential extension of indication as well as off-label use may dramatically increase the number of concerned patients and boost the revenue.

4 Orphan Drugs in Oncology

4.1 Overview

Oncology is a fast-growing indication among orphan drugs. In 2016, there were 437 companies plus partners developing 617 orphan drugs in oncology (BioSeeker Group 2016). In a study that looked at orphan drugs approved in the USA from 1983 to 2014, 35% of orphan drugs were in oncology (Miller and Lanthier 2016).

Another study that focused on orphan drug approval in Europe found that 39% of all orphan drugs approved by the EMA through a centralised procedure were indicted to treat oncological diseases (Rodrigues et al. 2014). Furthermore, oncology seemed to be associated with a higher growth rate in terms of annual number of marketing authorisations, and the number of approved orphan drugs in oncology in 2012–2013 was as high as for all other categories taken together (see Fig. 1). In a report on the orphan drug market, among the 10 top indications in terms of total number of EMA orphan designations, 9 were cancers (including acute myeloid leukaemia, non-Hodgkin lymphoma, glioma, pancreatic cancer, ovarian

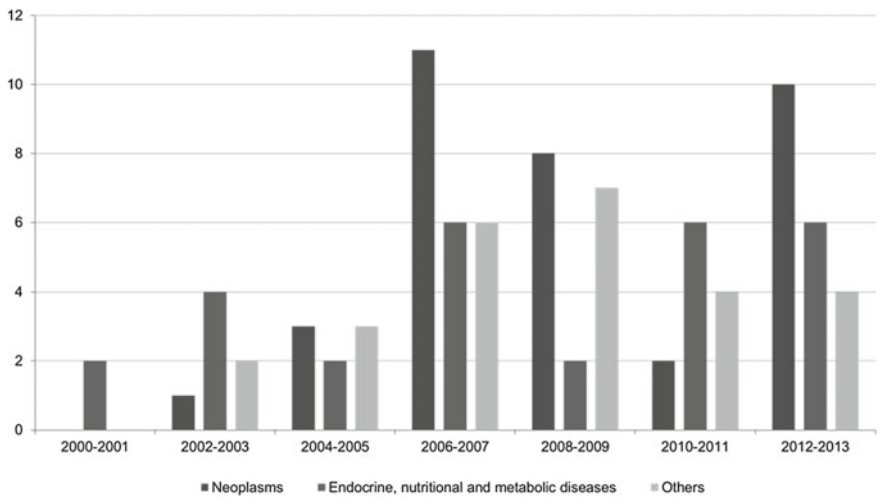

Fig. 1 Dynamic of orphan drug approvals in the EU by therapeutic area

cancer, multiple myeloma, renal cell carcinoma, hepatoma and liver cancer, and chronic lymphocytic leukaemia) (EvaluatePharma 2013).

Thus far, 49 orphan molecules have been granted MA in oncological diseases in Europe. The profiles of these drugs are summarised in Table 2. The selection included all oncology drugs which were approved by the EMA through a centralised procedure and held a valid orphan designation at the moment of approval.

There are four main reasons why oncology is an attractive field. Firstly, there are a great number of cancer types that are rare, especially in haematology oncology. Examples of solid tumours include renal cancer, carcinoma of the oesophagus, thyroid carcinoma, osteosarcoma, ovarian cancer, cholangiocarcinoma. Blood cancers include childhood acute myeloid leukaemia, chronic myelomonocytic leukaemia, hairy cell leukaemia.

Single-gene mutations are responsible for some rare, inherited types of cancer, e.g. the BRCA1/2 genes, which increase the risk of hereditary breast and ovarian cancers, and the FAP gene, which increases the risk of hereditary colon cancer.

Secondly, oncology is one of the areas where manufacturers may attempt to define patient subpopulations in a given cancer type (also known as 'salami slicing'), in order to decrease the number of eligible patients and make the medicine eligible for an orphan designation (Loughnot 2005; Cote and Keating 2012; Simoens 2011). To discourage manufacturers from using staging of a disease to create subpopulations small enough to qualify for an orphan designation, since 2013 the US Food and Drug Administration (FDA) no longer considers different disease stages as separate indications for the orphan designation. It has been suggested that the case of trastuzumab exemplifies why FDA decided to amend their orphan drug policy (Gibson and von Tigerstrom 2015). The drug was denied orphan status by FDA for HER2-positive metastatic breast cancer because the FDA considers Stage I breast cancer to be the same 'disease or condition' as Stage IV breast cancer when evaluating orphan drug designation requests for products that treat breast cancer.

Thirdly, the application of pharmacogenomics, where selected patients likely to respond to a drug can be identified through genetic testing, has enabled identification of new cancer types. For example, whereas non-small cell lung cancer (NSLC) is too prevalent to be considered a rare disease in the USA, crizotinib received an orphan designation from the FDA for the 'treatment of ALK-positive, MET-positive, or ROS-positive NSLC' and afatinib received an orphan designation for the 'treatment of epidermal growth factor receptor mutation-positive' subpopulation of patients with NSLC. Similarly, vemurafenib received an orphan designation for the subpopulation of melanoma patients with Stage IIb to Stage IV disease and positive for the BRAF (v600) mutation. Interestingly, none of these drugs have been granted an orphan designation in Europe, and the EMA's orphan approvals seem to focus on rare cancers rather than subpopulations.

Finally, after the drug has been developed for one type of cancer, the molecule may be tested for other cancer types where it can also achieve a significant efficacy. Targeting several cancer types gives an opportunity for an extension of indication and, thus, increases the number of potential patients and total sales volumes. This

Table 2 Overview of oncology orphan drug approval by the EMA

Medicine name	Active substance	MA holder	MA year	Condition	Orphan status	Condition approval	Exceptional circumstance
Adcetris	Brentuximab vedotin	Takeda Pharma A/S	2012	Hodgkin lymphoma	Valid	Yes	No
				Anaplastic large-cell lymphoma	Valid		
Afinitor	Everolimus	Novartis Europharm Limited	2009	Renal-cell carcinoma	Withdrawn	No	No
				Hormone-receptor-positive advanced breast cancer	No orphan designation		
				Neuroendocrine tumours of pancreatic origin			
				Neuroendocrine tumours of gastrointestinal or lung origin			
Arzerra	Ofatumumab	Novartis Europharm Ltd	2010	Chronic lymphocytic leukaemia	Valid	No	No
Atriance	Nelarabine	Novartis Europharm Limited	2007	T-cell acute lymphoblastic leukaemia T-cell lymphoblastic lymphoma	Valid	No	Yes
Blincyto	Blinatumomab	Amgen Europe B.V.	2015	B-precursor acute lymphoblastic leukaemia	Valid	Yes	No
Bosulif	Bosutinib	Pfizer Ltd	2013	Chronic myelogenous leukaemia	Valid	Yes	No
Busilvex	Busulfan	Pierre Fabre Médicament	2003	Hematopoietic stem cell transplantation	Expired	No	No
Ceplene	Histamine dihydrochloride	Meda AB	2008	Acute myeloid leukaemia	Valid	No	Yes
Cometriq	Cabozantinib	Ipsen Pharma	2014	Thyroid neoplasms	Valid	Yes	No

(continued)

Table 2 (continued)

Medicine name	Active substance	MA holder	MA year	Condition	Orphan status	Condition approval	Exceptional circumstance
Cyramza	Ramucirumab	Eli Lilly Nederland B.V.	2014	Advanced gastric cancer or gastro-oesophageal junction adenocarcinoma	Withdrawn	No	No
				Metastatic colorectal cancer	No orphan designation		
				Advanced or metastatic non-small cell lung cancer	No orphan designation		
Dacogen	Decitabine	Janssen-Cilag International N V	2012	Medullary thyroid carcinoma	Valid	No	No
Darzalex	Daratumumab	Janssen-Cilag International N V	2016	Multiple myeloma	Valid	Yes	No
Evoltra	Clofarabine	Genzyme Europe B.V.	2006	Acute lymphoblastic leukaemia	Expired	No	Yes
Farydak	Panobinostat lactate anhydrous	Novartis Europharm Ltd	2015	Multiple myeloma	Valid	No	No
Gazyvaro	Obinutuzumab	Roche Registration Ltd	2014	Chronic lymphocytic leukaemia	Valid	No	No
				Follicular lymphoma	Valid		
Gliolan	5-aminolevulinic acid hydrochloride	Medac GmbH	2007	Glioma	Valid	No	No
Glivec	Imatinib	Novartis Europharm Ltd	2001	Chronic myeloid leukaemia	Expired	No	No
				Gastrointestinal stromal tumour	Withdrawn		
				Myelodysplastic–myeloproliferative disease	Withdrawn		

(continued)

Table 2 (continued)

Medicine name	Active substance	MA holder	MA year	Condition	Orphan status	Condition approval	Exceptional circumstance
				Dermatofibrosarcoma protuberans	Withdrawn		
				Acute lymphoblastic leukaemia	Withdrawn		
				Hyper-eosinophilic syndrome/chronic eosinophilic leukaemia	Withdrawn		
Iclusig	Ponatinib	Ariad Pharma Ltd	2013	Chronic myeloid leukaemia	Valid	No	No
				Acute lymphoblastic leukaemia	Valid		
Imbruvica	Ibrutinib	Janssen-Cilag International NV	2014	Mantle cell lymphoma	Valid	No	No
				Chronic lymphocytic leukaemia	Valid		
				Waldenström's macroglobulinaemia	Valid		
Imnovid	Pomalidomide	Celgene Europe Ltd	2013	Multiple myeloma	Valid	No	No
Jakavi	Ruxolitinib	Novartis Europharm Ltd	2012	Chronic idiopathic myelofibrosis	Withdrawn	No	No
				Myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia	Withdrawn		
				Polycythaemia vera	Withdrawn		
Kyprolis	Carfilzomib	Amgen Europe B.V.	2015	Multiple myeloma	Valid	No	No
Lartruvo	Olaratumab	Eli Lilly Nederland B.V.	2016	Soft tissue sarcoma	Valid	Yes	No
Lenvima	Lenvatinib mesylate	Eisai Europe Ltd	2015	Differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma	Valid	No	No

(continued)

Table 2 (continued)

Medicine name	Active substance	MA holder	MA year	Condition	Orphan status	Condition approval	Exceptional circumstance
Litak	Cladribine	Lipomed GmbH	2004	Hairy cell leukaemia	Expired	No	No
Lynparza	Olaparib	AstraZeneca AB	2014	Epithelial ovarian, fallopian tube or primary peritoneal cancer	Valid	No	No
Lysodren	Mitotane	Laboratoire HRA Pharma	2004	Adrenal cortical carcinoma	Expired	No	No
Mepact	Mifamurtide	Takeda France SAS	2009	Osteosarcoma	Valid	No	No
Mozobil	Plerixafor	Genzyme Europe B.V.	2009	Multiple myeloma	Valid	No	No
				Lymphoma	Valid		
Nexavar	Sorafenib	Bayer Pharma AG	2006	Hepatocellular carcinoma	Valid	No	No
				Renal cell carcinoma	Valid		
				Differentiated thyroid carcinoma	Valid		
Ninlaro	Ixazomib citrate	Takeda Pharma A/S	2016	Multiple myeloma	Valid	Yes	No
Onivyde	Irinotecan hydrochloride trihydrate	Baxalta Innovations GmbH	2016	Pancreatic adenocarcinoma	Valid	No	No
Revlimid	Lenalidomide	Celgene Europe Ltd	2007	Multiple myeloma	Valid	No	No
				Myelodysplastic syndromes	Valid		
				Mantle cell lymphoma	Valid		
Sprycel	Dasatinib	Bristol-Myers Squibb Pharma EEIG	2006	Chronic myelogenous leukaemia	Valid	No	No
				Acute lymphoblastic leukaemia	Valid		

(continued)

Table 2 (continued)

Medicine name	Active substance	MA holder	MA year	Condition	Orphan status	Condition approval	Exceptional circumstance
Sutent	Sunitinib	Pfizer Limited	2006	Gastrointestinal stromal tumour	Withdrawn	No	No
				Renal cell carcinoma	Withdrawn		
				Pancreatic neuroendocrine tumour	No orphan designation		
Sylvant	Siltuximab	Janssen-Cilag International NV	2014	Castleman's disease	Valid	No	No
Tasigna	Nilotinib	Novartis Europharm Ltd	2007	Chronic myelogenous leukaemia	Valid	No	No
Tepadina	Thiotepa	Adienne S.r.l.	2010	Hematopoietic stem cell transplantation in haematological diseases and solid tumours	Valid	No	No
Thalidomide Celgene	Thalidomide	Celgene Europe Limited	2008	Multiple myeloma	Valid	No	No
Torisel	Temsirolimus	Pfizer Limited	2007	Renal cell carcinoma	Valid	No	No
				Mantle cell lymphoma	Valid		
Trisenox	Arsenic trioxide	Teva B.V.	2002	Acute promyelocytic leukaemia	Expired	No	No
Unituxin	Dinutuximab	United Therapeutics Europe Ltd	2015	Neuroblastoma	Valid	No	No
Venclyxto	Venetoclax	AbbVie Ltd	2016	Chronic lymphocytic leukaemia	Valid	Yes	No
Vidaza	Azacitidine	Celgene Europe Limited	2008	Myelodysplastic syndromes	Valid	No	No
				Chronic myelomonocytic leukaemia	No orphan designation		
				Acute myeloid leukaemia	Valid		

(continued)

Table 2 (continued)

Medicine name	Active substance	MA holder	MA year	Condition	Orphan status	Condition approval	Exceptional circumstance
Votubia	Everolimus	Novartis Europharm Ltd	2011	Renal angiomyolipoma associated with tuberous sclerosis complex	Valid	No	No
				Subependymal giant cell astrocytoma associated with tuberous sclerosis complex	Valid		
Xagrid	Anagrelide	Shire Pharmaceutical Contracts Limited	2004	Essential thrombocythaemia	Expired	No	Yes
Xaluprine	6-mercaptopurine monohydrate	Nova Laboratories Ltd	2012	Acute lymphoblastic leukaemia	Valid	No	No
Yondelis	Trabectedin	Pharma Mar S. A.	2007	Ovarian neoplasms	Valid	No	No
				Soft tissue sarcoma	Valid		
Zalmoxis	Allogeneic T cells genetically modified	MolMed SpA	2016	Hematopoietic stem cell transplantation in haematological malignancies	Valid	Yes	No

point can be clearly demonstrated by Table 1. Indeed, among 47 presented molecules, 15 were indicated in more than one condition. The absolute primacy belongs to imatinib. An anticancer drug with an exceptional efficacy and relatively good safety profile was first approved in chronic myeloid leukaemia. Imatinib was considered a highly innovative treatment and gave birth to a new class of drugs with a similar mechanism of action leading to substantial changes in the management of chronic myeloid leukaemia. Subsequently, imatinib obtained an approval from the EMA in five other conditions including gastrointestinal stromal tumour, myelodysplastic–myeloproliferative disease, dermatofibrosarcoma, acute lymphoblastic leukaemia and hyper-eosinophilic syndrome. The US FDA granted imatinib an authorisation in nine indications.

4.2 HTA Outcomes for Orphan Drugs in Oncology: Example of France, Germany and England

Table 3 summarises HTA outcomes for the oncology orphan drugs approved in Europe. The three countries were selected to represent the following cases: a country conducting HTA based on cost-effectiveness criteria (England), based on clinical value (France), and a country with a special HTA procedure for orphan drugs (Germany). The presented data were retrieved from the HTA reports and can be easily accessed through the official websites (Haute Authorité de Santé n.d.; Bundesanzeiger Verlag n.d.; National Institute for Health and Care Excellence n.d.).

France is frequently reported as one of the most favourable countries regarding orphan drugs coverage with a large access to therapies for rare diseases. Indeed, almost all oncology orphan drugs available in Europe have been assessed by the HAS and have obtained a positive recommendation for reimbursement. As described above, only one orphan drug (mifamurtide) was denied reimbursement, mainly due to the lack of evidence. The therapeutic effect of ramucirumab was also found to be too small for reimbursement in one of indications. However, a positive decision was reached for another indication. Only eight recently approved molecules (after 2014) have not yet been evaluated by the HAS.

The HTA process in France is based on the assessment of two criteria. The first one represents the actual benefit (AB) brought by the medicine and is the basis for reimbursement. A positive reimbursement decision is granted for medicines with substantial, moderate or low AB. AB is defined based on disease severity, its impact on public health, therapeutic need and efficacy/safety profile of the drug (Rémuzat et al. 2013). Given the high severity of rare oncological diseases, AB was judged to be substantial in most evaluations. Low AB was granted only to everolimus in breast cancer for which it does not have an orphan indication. Overall, low and moderate AB is rare for orphan drugs in France. Previous research, which studied HTA outcomes in France for drugs with an orphan designation, demonstrated that 88% of decisions were to grant a substantial AB (Korchagina et al. 2014). Low and moderate AB represented 3 and 8%, respectively. The remaining one drug (mifamurtide) was rejected.

Table 3 Overview of HTA outcomes for oncology orphan drugs in France, Germany and England

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
Adcetris	Hodgkin Lymphoma	Substantial/III	Not quantifiable	–	–
	Anaplastic large-cell lymphoma		Not quantifiable	–	–
Afinitor	Renal cell carcinoma	Substantial/IV	–	Rejected (£49.300–£51,700)	Met
	Hormone-receptor-positive advanced breast cancer	Low/V	–	Recommended with PAS after Cancer Drugs Fund review (£68,000)	Not met
	Neuroendocrine tumours of pancreatic origin	Substantial/IV	–	–	–
	Neuroendocrine tumours of gastrointestinal or lung origin	–	–	–	–
Arzerra	Chronic lymphocytic leukaemia	Refractory to fludarabine and alemtuzumab: moderate/V	–	Refractory to fludarabine and alemtuzumab: rejected (<£60,500–> £81,500)	Met
		Untreated and ineligible for fludarabine-based: substantial/V		Untreated and ineligible for fludarabine-based: restricted (£26,000)	–
Atriance	T-cell acute lymphoblastic leukaemia T-cell lymphoblastic lymphoma	Substantial/II	–	–	–
Blincyto	B-precursor acute lymphoblastic leukaemia	Substantial/III	Not quantifiable	–	–

(continued)

Table 3 (continued)

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
Bosulif	Chronic myelogenous leukaemia	Substantial/V	–	Recommended with PAS (chronic phase £40,000–£50,000, accelerated phase £58,000, blast phase £60,000)	Met
Busilvex	Hematopoietic stem cell transplantation	Adults: substantial/III Newborns, children and adolescents: substantial/II	–	–	–
Ceplene	Acute myeloid leukaemia	Moderate/V	–	–	–
Cometriq	Thyroid neoplasms	Substantial/IV	Minor	–	–
Cyramza	Advanced gastric cancer or gastro-oesophageal junction adenocarcinoma	In combination with paclitaxel: moderate/V In monotherapy: insufficient	Minor (in full assessment after losing orphan status: in combination with paclitaxel hint of minor additional benefit, in monotherapy no additional benefit proved)	Not recommended (when cytotoxic chemotherapy is not appropriate £188,100, when cytotoxic chemotherapy is appropriate £408,200)	Met
	Metastatic colorectal cancer	–	–	–	–
	Advanced or metastatic non-small cell lung cancer	–	No additional benefit proved	Not recommended (ramucirumab plus docetaxel compared with docetaxel alone £148,000, ramucirumab plus docetaxel compared with nintedanib plus docetaxel £1.1 million)	Met
Dacogen	Medullary thyroid carcinoma	Substantial/IV	Minor	–	–
Darzalex	Multiple myeloma	–	Not quantifiable	–	–
Evoltra	Acute lymphoblastic leukaemia	Substantial/II	–	–	–

(continued)

Table 3 (continued)

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
Farydak	Multiple myeloma	Moderate/V	Not quantifiable	Recommended with PAS (>£25,000)	–
Gazyvaro	Chronic lymphocytic leukaemia	Substantial/III	Not quantifiable	Restricted with PAS (people who cannot have bendamustine £20,000–£30,000, people who can have bendamustine >£30,000)	Not met
	Follicular lymphoma	–	–	–	–
Gliolan	Glioma	Moderate/IV	–	–	–
Glivec	Chronic myeloid leukaemia	Substantial/I	–	Recommended (vs. interferon alpha £19,000–£27,000, vs. hydroxycarbamide £87,000)	–
				Reassessment for 600 or 800 mg/day imatinib after disease progression on 400 mg/day: not recommended (dominated)	–
	Gastrointestinal stromal tumour	Non-resectable/metastatic: substantial/I	–	Non-resectable/metastatic recommended (2 years £59,00, 5 years £24,000, 10 years £14,000)	–
				Reassessment for 600 or 800 mg/day imatinib after disease progression on 400 mg/day: not recommended (> £30,000)	Not met
		At significant risk of relapse following resection: substantial/III		At significant risk of relapse following resection: recommended (1-year adjuvant imatinib vs. no adjuvant treatment £3,610–£12,100, 3-year adjuvant imatinib vs. 1-year adjuvant imatinib £16,700–£30,000)	–

(continued)

Table 3 (continued)

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
	Myelodysplastic–myeloproliferative disease	Substantial/III	–	–	–
	Dermatofibrosarcoma protuberans	Substantial/IV	–	–	–
	Acute lymphoblastic leukaemia	Newly diagnosed: substantial/I	–	–	–
		Newly diagnosed paediatric patients: substantial/I			
		Relapsed or refractory: substantial/II			
	Hyper-eosinophilic syndrome/chronic eosinophilic leukaemia	Substantial/III	–	–	–
Iclusig	Chronic myeloid leukaemia	T315I mutation: substantial/III	Not quantifiable	–	–
		No T315I mutation: substantial/V			
	Acute lymphoblastic leukaemia	T315I mutation: substantial/III No T315I mutation: substantial/IV	Not quantifiable	–	–
Imbruvica	Mantle cell lymphoma	Substantial/IV	Not quantifiable (full assessment: indication of major additional benefit if temsirolimus is indicated and no additional benefit proved if temsirolimus is not indicated)	–	–

(continued)

Table 3 (continued)

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
	Chronic lymphocytic leukaemia	Substantial/III	Not quantifiable (full assessment: not quantifiable in untreated and refractory if chemotherapy is not indicated, no additional benefit proved in refractory if chemotherapy is indicated)	–	–
	Waldenström's macroglobulinaemia	–	Full assessment: no additional benefit proved	–	–
Imnovid	Multiple myeloma	Substantial/III	Considerable	Not recommended (>£50,000–> £70,000)	Met
Jakavi	Chronic idiopathic myelofibrosis	Substantial/III	Minor (full assessment: indication of considerable benefit)	Recommended with PAS after revision (intermediate-2 risk myelofibrosis £26,000, high-risk myelofibrosis £38,000)	Met
	Myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia				
	Polycythaemia vera	Substantial/IV	Full assessment: indication of considerable benefit	–	–
Kyprolis	Multiple myeloma	–	Not quantifiable	–	–
Lartruvo	Soft tissue sarcoma	–	–	–	–
Lenvima	Differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma	Substantial/IV	Not quantifiable	–	–
Litak	Hairy cell leukaemia	Substantial/IV	–	–	–

(continued)

Table 3 (continued)

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
Lynparza	Epithelial ovarian, fallopian tube, or primary peritoneal cancer	Substantial/IV	Not quantifiable	Restricted with PAS (after 3 or more lines of platinum-based chemotherapy £46,600–£46,800)	Met in subgroup
Lysodren	Adrenal cortical carcinoma	Substantial/II	–	–	–
Mepact	Osteosarcoma	Insufficient	–	Recommended with PAS (£56,700–£60,200)	–
Mozobil	Multiple myeloma	Substantial/III	–	–	–
	Lymphoma		–	–	–
Nexavar	Hepatocellular carcinoma	Substantial/IV	–	Not recommended (>£52,600)	Met
	Renal cell carcinoma	Substantial/II	–	Not recommended (second line in patents in whom immunotherapy has failed £65,900, second line in patients unsuitable for immunotherapy £72,500–£74,900)	Met
	Differentiated thyroid carcinoma	Substantial/IV	–	–	–
Ninlaro	Multiple myeloma	–	–	–	–
Onivyde	Pancreatic adenocarcinoma	–	–	–	–
Revlimid	Multiple myeloma	Substantial/III	–	Restricted with PAS (two or more prior therapies £43,800, two or more prior therapies including thalidomide £41,300)	Met
	Myelodysplastic syndromes	Substantial/III	–	Recommended with PAS (£25,300)	–
	Mantle cell lymphoma	–	–	–	–

(continued)

Table 3 (continued)

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
Sprycel	Chronic myelogenous leukaemia	Chronic phase: substantial/II	–	Untreated: recommended with PAS after Cancer Drugs Fund review (vs. imatinib >£200,000, vs. nilotinib dominated)[a]	–
		Accelerated or blast phase: substantial/I		Imatinib-resistant: restricted with PAS after Cancer Drugs Fund review (> £30,000)	Not met
	Acute lymphoblastic leukaemia	Substantial/I	–	–	–
Sutent	Gastrointestinal stromal tumour	Substantial/II	–	Recommended with PAS (£31,800)	Met
	Renal cell carcinoma	Substantial/III	–	First line: restricted (< £50,000) Second line: rejected (£37,519)	Met
	Pancreatic neuroendocrine tumour	Moderate/V	–	–	–
Sylvant	Castleman's disease	Moderate/IV	Not quantifiable	–	–
Tasigna	Chronic myelogenous leukaemia	Chronic phase untreated: substantial/IV	–	Untreated: recommended with PAS (£26,000 – £36,000)[b]	–
		Chronic phase imatinib-resistant: substantial/II		Imatinib-resistant: restricted with PAS (>£22,800)	–
		Accelerated phase: substantial/I			

(continued)

Table 3 (continued)

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
Tepadina	Hematopoietic stem cell transplantation in haematological diseases and solid tumours	Substantial/IV	–	–	–
Thalidomide Celgene	Multiple myeloma	Reimbursed by derogation in 18 indications	–	Recommended (thalidomide, melphalan and prednisolone/prednisone vs. melphalan and prednisolone/prednisone £9,170, bortezomib, melphalan and prednisolone/prednisone vs. melphalan and prednisolone/prednisone £33,200)	–
Torisel	Renal cell carcinoma	Substantial/II	–	Not recommended (£102,000)	Met
	Mantle cell lymphoma	Substantial/IV	–	–	–
Trisenox	Acute promyelocytic leukaemia	Substantial/II	–	–	–
Unituxin	Neuroblastoma	–	–	–	–
Venclyxto	Chronic lymphocytic leukaemia	–	–	–	–
Vidaza	Myelodysplastic syndromes	Substantial/II	–	Recommended with PAS (£47,200)	Met
	Chronic myelomonocytic leukaemia		–		
	Acute myeloid leukaemia	>30% marrow blasts	–	>30% marrow blasts: not recommended (£240,000)	Not met

(continued)

Table 3 (continued)

Medicine name	Condition	HAS	G-BA	NICE	
		AB/IAB	Extent of additional benefit	Recommendation (ICER)*	End-of-life
Votubia	Renal angiomyolipoma associated with tuberous sclerosis complex	Substantial/III	–	–	–
	Subependymal giant cell astrocytoma associated with tuberous sclerosis complex	Substantial/II	–	–	–
Xagrid	Essential thrombocythaemia	Substantial/IV	–	–	–
Xaluprine	Acute lymphoblastic leukaemia	In children: substantial/IV	–	–	–
		In adults and adolescents: substantial/V			
Yondelis	Ovarian neoplasms	Substantial/V	–	Not recommended (£70,000)	Not met
	Soft tissue sarcoma	Substantial/V	–	Recommended with PAS (£34,500)	Met
Zalmoxis	Hematopoietic stem cell transplantation in haematological malignancies	–	–	–	–

*The extracted ICERs corresponded to the most plausible ICERs as judged by the NICE, if not available, manufacturer's base case ICER (or ICER range if the base case analysis was not specified) was extracted

[a]ICER does not include the revised PAS

[b]ICER calculated based on the model developed by the assessment group

Another criterion that is evaluated in France during the HTA process is the improvement in actual benefit (IAB). IAB represents the additional value of the new medicine as compared to existing treatments (Rémuzat et al. 2013). IAB has five levels from I (major improvement) to V (no improvement) and is the primary driver for the drug price. IAB I-III guaranties the access to a premium price reflecting the innovative character of the new therapy. Among oncological orphan drugs, the highest IAB level has been granted only to three molecules: imatinib, nilotinib and dasatinib, all three from the class of tyrosine-kinase inhibitors and approved in chronic myelogenous leukaemia. Among 40 molecules for which IAB was assessed, 22 (55%) obtained IAB I-III in at least one indication. This corresponds to the overall proportion of orphan drugs with IAB I-III in all therapeutic areas (Korchagina et al. 2014). For comparison, almost 85% of all drugs (orphan and non-orphan indications) assessed by the HAS in 2015 were granted the lowest IAB score corresponding to the absence of any therapeutic improvement (Haute Authorité de Santé 2015).

The Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) in Germany has been systematically evaluating new medicines since the introduction of the AMNOG law in 2011 (Leverkus and Chuang-Stein 2015). Drugs commercialised before this date were not assessed. In the general framework, the G-BA assesses the extent (major, considerable, minor, non-quantifiable, absent, less benefit than comparator) and the likelihood (proof, indication, hint) of additional benefit of the new treatment. Orphan drugs are exempt from the assessment of the likelihood of additional benefit since it is considered to be proved through the orphan designation, and only the extent of the benefit is evaluated. However, in most of cases G-BA judged that the submitted evidence did not allow the benefit to be quantified. Moreover, it seems that oncology is associated with a more frequent conclusion by the G-BA on non-quantifiable additional benefit among orphan drug evaluations. In a review of G-BA's assessments of orphan drugs during 2011–2015, from 12 assessments which concluded a non-quantifiable additional benefit, 8 concerned an oncological indication, although oncology orphan indications were as prevalent as non-oncology (Bouslouk 2016).

Indeed, the additional benefit in G-BA assessment was non-quantifiable for all oncology orphan molecules except for cabozantinib, decitabine (both indicated in thyroid neoplasms), ramucirumab (gastric cancer) and ruxolitinib (myelofibrosis) whose additional benefit was considered minor, and pomalidomide (multiple myeloma) whose additional benefit was estimated to be considerable. It worth nothing that pomalidomide was the only oncology orphan drug with considerable additional benefit as assessed by the G-BA. The only another orphan molecule that obtained 'considerable' score was ivacaftor for the treatment of cystic fibrosis. After the first evaluation, ruxolitinib was subsequently reassessed since its sales had exceeded €50 million in 12 months. Ruxolitinib was the first orphan drug which underwent a full assessment in Germany. The submitted evidence was convincing enough to allow G-BA to conclude a considerable additional benefit in all assessed indications.

More recently, ibrutinib also underwent a full assessment by the G-BA, but with much less success. Its additional benefit was judged to be major only in a subgroup of patients with mantle cell lymphoma in whom temsirolimus is considered an appropriate treatment. In all other indications, the additional benefit was either absent, or not quantifiable.

Overall, after a review of the G-BA's activity regarding orphan drugs, the adapted specific framework was judged to be efficient based on successful price negotiations and the absence of market exits (Bouslouk 2016).

In England, NICE applied the standard cost-effectiveness methodology in rare diseases before introducing a specific orphan drug framework for ultra-orphan drugs. However, orphan drugs were not analysed systematically as they generally have a small impact on NHS expenditure (Tordrup et al. 2014). The majority of NICE's recommendations concerns oncological orphan drugs, but even in this category only 18 molecules have been assessed. Predictably, positive decisions remain rare. Among 34 evaluations only 15 ended up with a positive recommendation, and in another 8 assessments the indication was restricted to a smaller population. Moreover, 3 decisions among the positive recommendations were issued only after a Cancer Drugs Fund review and another one after a revision. The ICERs for the assessed drugs were generally greater than the cost-effective level (£20,000–£30,000) and typically considered uncertain or too optimistic by the Committee. In some cases, the adjustment for end-of-life criteria allowed the drug to meet the cost-effectiveness criteria. Overall, in 16 assessments the end-of-life criteria were fulfilled. Patient access schemes were also proposed by manufacturers in most cases to allow the drug to be recommended. It should be noticed that for orphan drugs that were not recommended by the NICE, individual reimbursement is possible through an independent funding request (Tordrup et al. 2014).

4.3 High Costs of Oncology Orphan Drugs

Oncology is a clinical field where medicines are costly. Of the 12 anticancer drugs approved by the US FDA in 2012, nine were priced at more than $10,000 per month. Many targeted therapies have been priced between $70,000 and $115,000 per patient annually (Kantarjian et al. 2013).

In case of orphan drugs, there are specific conditions that contribute to further inflation of prices. Because there are few or no alternative treatments available to treat rare diseases, manufacturers of orphan drugs have market monopoly. Additionally, both FDA and EMA grant manufacturers of orphan drugs extended periods of marketing exclusivity. Further, the negotiating power of payers is limited, often as a result of political pressure to make new treatments available.

Moreover, orphan designation status in itself is associated with higher prices for drugs for rare diseases. A 2010 study that compared prices of 28 designated orphan drugs with prices of 16 comparable non-designated drugs for rare disease indications in Belgium found that orphan-designated drugs had a higher median price

(€138.56–IQR €483.06) than non-designated drugs (€16.55–IQR €28.67) for rare disease indications (Picavet et al. 2011).

Despite the small size of the initial target population, some orphan drugs appear to be highly profitable. By 2010, 43 orphan molecules reached blockbuster status with global annual sales over $1 billion (Murphy et al. 2012). Measures introduced to compensate for the complexity of drug development and low number of potential patients seem to be excessive for these drugs. Overall, the industry's expected return on orphan drugs was estimated at almost twice higher than on non-orphan drugs (10.3 times the investment (phase III cost) vs. 6.0 times the investment) (EvaluatePharma 2013). One of the reasons is the lower (or even absent) phase III trial costs due to smaller size of trial population. The number of patients recruited in phase III trials was found to be four times lower for orphan drugs, pulling down the cost of trial in same proportion ($5.5 billion vs. $21.8 billion).

The oncology indication on its own does not seem to be associated with higher treatment cost. In a study seeking to identify the determinants of orphan drug prices in France, annual per patient costs of oncological orphan drugs were significantly lower than those of orphan drugs for the treatment of metabolic, cardiovascular and hormonal disorders (Korchagina et al. 2016). Similarly, the oncology indication was not found to be associated with higher orphan drug costs compared to non-oncology indications in Belgium, Netherlands, Czech Republic, Italy and the UK (Picavet et al. 2014).

However, sales volumes may suggest the contrary. Rituximab (US FDA orphan designation), the first monoclonal antibody treatment for cancer, was the second top revenue-generating drug and the world's most sold cancer drug in 2012 (EvaluatePharma 2014; Thomson Reuters 2012). Its total worldwide sales were estimated at more than $7 billion in 2012 (EvaluatePharma 2014). Monoclonal antibody treatments and other cancer immunotherapies are known for being extremely costly and now are gaining their place among oncological orphan products. Rituximab, ofatumumab, alemtuzumab, trastuzumab, brentuximab, thalidomide and lenalidomide are only few examples of orphan immune therapies. The demonstrated efficacy of immunotherapies in combination with radiotherapy, chemotherapy or other immunotherapy agents will lead to further increase in treatment costs (Drake 2012; Overacre et al. 2015).

Overall, among 10 orphan molecules with highest projected sales in 2018, 8 are cancer treatments (EvaluatePharma 2013). One of the reasons for such high revenues is a large (for orphan-designated treatments) population. Indeed, multiple indications and extensions to other rare or non-rare types of cancer are very common for oncology orphan drugs. For instance, the above-mentioned rituximab was initially approved in B-cell non-Hodgkin's lymphoma and then also in other types of cancer and even rheumatoid arthritis. From other examples, lenalidomide was approved by the US FDA in six orphan indications between 2005 and 2015, and imatinib in nine orphan indications between 2001 and 2013. As a matter of fact, concerns regarding the extremely high costs of imatinib and other tyrosine-kinase inhibitors in the USA resulted in a collective letter signed by more than 100 experts

who argued for the need to lower cancer drug prices (Experts in Chronic Myeloid Leukemia 2013).

In general, many experts are concerned about cancer drug prices in the USA where they are associated with a significant financial toxicity for patients (Khera 2014; McDougall et al. 2014; Zafar 2016). The lack of price control and important out-of-pocket copayments often lead to debt and even personal bankruptcy of cancer patients. In a pilot study assessing out-of-pocket expenses in cancer patients, 42% of participants reported a significant or catastrophic subjective financial burden (Zafar et al. 2013). In order to decrease their expenses, patients may reduce spending on leisure activities, food and clothing, or even skip dosages, partially fill prescriptions, and postpone seeking psychological counselling or support (Zafar et al. 2013; Buzaglo et al. 2015).

In Europe, together with price control by member countries, the European Commission attempted to lower the economic impact of costly orphan drugs by reducing the period of marketing exclusivity if an orphan drug turns out to be 'sufficiently profitable' (Regulation 141/2000/EC 1999). It remains to be seen how this rule can be implemented.

4.4 Future Perspectives

Recent advances in genetic testing improved the understanding of the development mechanisms of oncological diseases. At the same time, it led to a hyper-segmentation of cancer subtypes. As a result, 'targeted' or 'personalised' therapies with higher efficacy were developed. Another consequence was a high proportion of cancer drugs among orphan designations and a significant impact of these drugs on the sustainability of national insurance systems. The number of oncological orphan indications is continuing to grow, and payers must be ready to deal with these costly medicines. There is a need to develop new public policies that will help payers and manufacturers align their perceptions of value of orphan treatments. On the one hand, these policies should allow the value of orphan therapies to be estimated, and innovation to be promoted. On the other, they should prevent excessive profitability and maintain the 'just price'. Multi-criteria decision analysis (MCDA) was proposed as a solution for the first point (Simoens 2014; Hughes-Wilson et al. 2012; Simoens et al. 2013; Gutierrez et al. 2015).

MCDA enables decision-makers to explicitly trade off various non-monetary factors against each other, alongside cost-effectiveness. To apply MDCA, the relative weight given to each factor in a society or decision-making setting needs to be assessed first.

A pilot study on the use of MCDA for orphan drugs proposed eight non-monetary criteria. Interestingly, the authors found that slightly higher weight was given by respondents to the nature of the disease being treated, rather than to the result of using the medicine to treat it. This means that the studied population would be willing to value treatments for rare diseases, even if the treatment outcomes were uncertain. The weights were assessed from two perspectives: experts

and patients, and contained some inconsistences, with higher weights attributed to social impact of the diseases and the treatment on patients and caregiver in the patients' focus group. Several other MCDA frameworks have been proposed (Sussex et al. 2013; Hughes-Wilson et al. 2012; Winquist et al. 2012; Kolasa et al. 2016; Paulden et al. 2015; Wagner et al. 2016).

One of the crucial steps in the development of an MCDA framework is the identification of the criteria (or elements of value). According to the ISPOR's good practice guidelines for MCDA (Marsh et al. 2016), the set of criteria should exhibit the following properties:

- Completeness: all relevant attributes are captured.
- Non-overlap: attributes measure separate objectives.
- Non-redundancy: no attributes that are judged unnecessary or not important.
- Preference independence: the importance of one attribute should be independent from others.

Regarding the reimbursement of orphan drugs, a scoping review identified 19 potential attributes which were cited in the literature (Paulden et al. 2015). The most common of them were disease prevalence and severity, availability of alternative treatments, treatment efficacy and effectiveness, social impact, cost of treatment, cost-effectiveness and budgetary impact, industrial and commercial policy considerations. The development of an efficient MCDA framework demands that the selected set of attributes as well as their weights reflect the preferences of society. However, studies on this subject remain very limited (Drummond and Towse 2014).

Together with the development of a tailored HTA method for orphan drugs, it is necessary to establish special measures to deal with uncertainty regarding the size of patient population resulting from multiple indications and potential off-label use. Both HTA and pricing methods should take into account that certain orphan drugs obtain multiple indications. In such cases, HTA and pricing processes need to be revised in this new indication and the price and/or reimbursement rate needs to be adjusted. However, it is unclear how to calculate such adjustments, and whether they should be applied to all indications or only on non-orphan ones. In Europe, a new EMA regulation has closed this gap by withdrawing orphan designation for a product that may be granted a common disease indication by EMA, even after it has obtained the orphan designation. However, the same product may continue to enjoy an orphan designation with indications in multiple rare diseases, thus expanding its market target population, sometimes significantly.

Another potential solution by analogy with conditional MA is a conditional pricing, and in some countries such schemes have already been adopted. For instance, the G-BA may in some cases grant a conditional resolution by putting a time limit for further adjusting their assessment, based on post-marketing data. Among 28 orphan drug evaluations conducted by the G-BA, a time-limited resolution was issued in 7 cases (Bouslouk 2016). This scheme is not limited to orphan drugs. By June 2014, the G-BA granted 23 conditional resolutions, most commonly

in cancer drugs (Assmann 2014). Another example of conditional decisions is the new Cancer Drugs Fund in the UK, which provides interim funding for certain cancer medicines until enough data have been collected to allow its cost-effectiveness to be assessed (NHS England Cancer Drugs Fund Team 2016).

Regardless of the methods adopted in the future, it is clear that the HTA assessment of orphan drugs cannot follow the same pathway as that of regular medicines. Otherwise, these drugs are unlikely to be recommended for reimbursement and patients will be deprived access to the necessary treatments. There is a clear need to reinvent the HTA and pricing process for orphan drugs.

5 Conclusion

Orphan drug policy incentives have stimulated the pharmaceutical industry to pursue R&D for diseases with significant unmet medical need. The revenue-generating potential of orphan drugs is similar to that of non-orphan drugs, even though patient populations for rare diseases are significantly smaller (Meekings et al. 2012). Oncology is the largest orphan therapeutic indication pursued by the industry, a trend that is expected to grow, given the rapid development of pharmacogenomics.

An increasing number of such therapies available at high prices may begin to have significant impact on payers' budgets. Moreover, current orphan drug policies are unlikely to be sustainable, because they have led to high prices of orphan drugs and limited coverage and restricted patient access when cost-effectiveness is the sole decision-making criterion. This calls for policy changes which are unavoidable in order to ensure the sustainability of our healthcare systems.

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Recent Developments in Health Economic Modelling of Cancer Therapies

William Green and Matthew Taylor

Abstract

Arguably, the most common structure currently adopted for oncology modelling is the three-state partitioned survival model with the following states: stable disease, post-progression and dead. This design can, therefore, be adopted to capture the progressive nature of cancer. This chapter outlines the three-state model approach as well as introducing several other key aspects of economic modelling in oncology.

Keywords

Health economic modelling · Survival model · Quality-adjusted life year · Utilities

1 Summary of the Standard Three-State Partitioned Survival Model

When adopting a partitioned survival model approach, patients enter the model in the stable disease state. Over time they can then transition into either the post-progression or dead state, and once a patient has transitioned they cannot return to the previous state. The model runs in cycles and for a specified time horizon, usually, until all patients have entered the dead state.

The proportion of patients in the three states at each time point is determined by survival curves, which map the number of pre-defined events that have occurred at various time points. For example, survival curves for progression-free survival

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(PFS) can be plotted, which show the proportion of people who remain in the stable disease state over time. Additionally, overall survival (OS) curves present the proportion of people who remain alive over time. Therefore, PFS and OS curves can be directly used to estimate the proportion of people in the stable disease and dead states at each cycle, with the difference between curves equating to the post-progression state (hence the term partitioned survival, as the OS curve is 'partitioned' into pre- and post-progression survival).

Partitioned survival models allow different treatments to be compared as, given a specified patient group (e.g. breast cancer patients), possible treatment options will be associated with different survival curves due to distinct levels of effectiveness. Therefore, the differences in PFS and OS between the treatment options can be specifically modelled based on available efficacy data (usually taken from relevant randomised controlled trials). For the purposes of health economic evaluations, the impact on costs and health-related quality of life (HRQoL) can also be quantified. This is achieved by, first of all, estimating the total cost of providing each treatment to patients, which will be dependent on the unit price and the length of treatment, along with any auxiliary costs (e.g. diagnostic tests to assess the impact of treatment). Other background costs and quality-adjusted life year (QALY) values can then be assigned to the model health states, and these costs and QALYs will accumulate over time, dependent on which state patients reside in and for how long. Cumulative values can then be estimated across the full time horizon resulting in total cost and QALY values for all treatments thus facilitating an assessment of cost-effectiveness.

There are a number of advantages with the adoption of partitioned survival models, namely that the simple structure allows for the approach to be easily understood, which is important for decision-makers who may be unfamiliar with the techniques applied in health economic evaluations. These models can also be developed using either summary data or individual patient-level data, which allows for flexibility. Altogether, this means that partitioned survival models are well recognised and widely accepted, particularly in terms of health technology assessments relating to advanced or metastatic cancer. The main limitation of the partitioned survival approach is the structural assumption that survival functions (i.e. PFS and OS) are independent. As there is no structural relationship, this can cause a number of issues, particularly when extrapolating survival from the within trial period as inaccurate predictions of PFS and OS can be made. For example, the parametric functions may predict a higher proportion of people being in stable disease stable than alive (i.e. the PFS curve lies above the OS curve), and this scenario is not feasible (Woods et al. 2017).

The above approaches may not be suitable for all cancer types, particularly early-stage tumours where resection and long-term remission are possible. In those cases, time dependency may become important (i.e. prognosis may depend on the time since an event, rather than time since the start of the model). In such cases, modelling using standard techniques becomes more complex, and it may be necessary to consider the use of other methods such as individual patient simulation models or discrete event simulations. Such models, by necessity, are often slower to run and more complex to populate with data, but can provide advantages in factoring in time dependency.

2 Survival Curve Analysis

As described previously, survival curves allow the impact of different treatments on patient outcomes (e.g. PFS and OS) to be quantified based on data that are available from relevant clinical studies. Observed data from clinical trials can be presented via Kaplan–Meier (KM) plots, which are nonparametric survival functions that show each event (i.e. progression or death) as a step down in the function. However, it is common that not all patients will experience the event of interest by the end of the observed trial period or patients may be lost to follow-up. This is known as censoring and it is problematic because, when it occurs, the sample mean from the clinical trial becomes a biased estimated of the true mean (Guyot et al. 2011). Survival analysis can overcome the problem of censoring via the use of statistical extrapolation to predict PFS and OS beyond the end of the trial period and until all patients have experienced the event of interest. However, survival analysis is only valid if the censoring is uninformative, which means that censoring does not provide prognostic information about the subsequent survival events (e.g. patients lost to follow-up, and hence censored, are just as likely to have the event compared with those remaining in the study) (Clark et al. 2003). There are a number of different approaches possible, often dependant on the level of censoring, and the choice of approach can have a significant impact on the predicted survival curves, so care must be taken in selecting the most appropriate methods.

When the extrapolation of survival curves is necessary then, if relevant individual patient data (IPD) are available for the treatment under evaluation, the most common method of extrapolation is through the use of parametric models that are fitted to the empirical data. There are six different parametric distributions that can be fitted: Weibull, exponential, Gompertz, lognormal, log-logistic and generalised gamma (Latimer 2013). The choice of model, from these six distributions, is important as it can have a significant impact on the estimated mean PFS and OS values due to sensitivity in the tails of the distribution (Guyot et al. 2017). Further, the sensitivity is expected to increase where the level of censoring is greater.

For the purposes of health economic evaluations, it will be necessary to compare the treatment under analysis with a relevant comparator(s), which facilitates the need to generate survival curves for this comparator. If IPD are unavailable for these comparators, then this is commonly achieved via the estimation of the hazard for the comparator. The hazard is the instantaneous rate of an event (e.g. progression or death) at a specific time point. Therefore, if the hazard function for both the treatment and comparator are known, then the hazard ratio between these options captures the difference in effectiveness (i.e. if the hazard of one treatment is lower than the rate of that event is also lower indicating it is more effect). A constant hazard ratio is often applied to the predicted treatment arm in order to generate a survival curve for the comparator in question. The use of a constant hazard ratio requires the assumption of proportional hazards between the treatment and comparator (i.e. the hazard functions of the two therapies share the same shape).

It should be noted that lognormal and log-logistic models do not produce a single hazard ratio, so the proportional hazards assumption need not hold for these models (Latimer 2013).

In order to generate the parametric models required for the extrapolation of survival curves, it is necessary to have the relevant IPD so that the coefficients for each distribution can be estimated. However, there may be scenarios in which survival curves need to be generated for a specific treatment when IPD data are unavailable, particularly for work being completed by independent researchers. Previously, survival curves have been fitted directly to KM curves to facilitate an extrapolation, and this was achieved using the least squares approach (i.e. minimising the sum of squares of differences between actual and expected survival probabilities) or undertaking regression analysis to predict the survival function (Hoyle and Henley 2011). However, Hoyle and Henley (2011) note that these traditional approaches have some important disadvantages, namely that the extrapolated curve will be influenced by all sections of the KM curve equally but due to the low number of patients at risk there are higher levels of uncertainty in the tail. Further, these methods do not capture the true level of uncertainty in survival. The authors, therefore, proposed an alternative method in which the IPD data are first estimated from published information on numbers at risk and the KM data, using freely available software, and the full survival curve is then estimated from this IPD data by the method of maximum likelihood. Similarly, Guyot et al. (2012) proposed a method in which an algorithm is used to reconstruct the IPD for a specific KM curve using the coordinates of the KM curve (obtained using digitalisation software), the numbers at risk and the total number of events. Parametric models can then be fitted to these reconstructed data, as described previously.

3 Newer Methods Such as Piecewise Curve Fitting and 'Mixed Cure' Models

The methods of fitting parametric survival curves, as just described, are not suitable for all scenarios. In particular, the six standard distributions have limited flexibility in relation to the hazard function. For example, the hazard must be constant for exponential, monotonic (i.e. increasing or decreasing at a constant rate) for Weibull and Gompertz and unimodal (i.e. only one peak or trough in the function) for lognormal and log-logistic (Bradbury et al. 2003; Latimer 2013). Therefore, alternative modelling approaches are required in scenarios in which variable hazards are observed over time. One such model type is the parametric piecewise model. In general, for piecewise models individual exponential models are fitted to different intervals across the full time horizon to account for the variable hazards. However, such an approach is limited for the extrapolated portion of the survival curve, as the hazards are unobserved, so an alternative parametric model (e.g. Weibull, Gompertz) may be fitted to the extrapolated section of the curve, particularly in scenarios were a constant hazard is inappropriate for the extrapolation (Latimer 2013).

Another alternative approach is mixture-cure models, in which a proportion of patients are deemed to be 'cured' due to a particular treatment. Patients are said to be cured if the hazard for the event (e.g. progression) matches the hazard for the general population. For the purposes of a health economic evaluation, two separate subgroups can be modelled: those who are cured and those who are not cured. For cured patients, the survival outcomes of patients would match those of the general population. Alternatively, for non-cured patients there is an excess risk of the event compared with the general population and, therefore, survival outcomes can be modelled using the survival analysis methods described previously, such as the use of parametric survival distributions.

A more recent model type with a similar approach is response-based survival analysis. For such an approach, again patients are separated into two groups: responders and non-responders. Responders are not strictly 'cured' so can still experience an event at greater rate than the general population. Nevertheless, they are sufficiently different from non-responders to justify the separation, which necessitates the plotting of separate parametric survival curves for the two groups. Such an approach is particularly relevant for immunotherapies, which when given to oncology patients may provide a strong and durable response in a subset of patients. Due to this response, the hazard rate is expected to change over time due to a delay from treatment initiation to response followed by a step decline in survival followed by a more gradual decline. If responders and non-responders were modelled as one, then standard parametric models may not be flexible enough to characterise the changes in hazard over time for responders, as the curve shape would largely be driven by the outcomes of non-responders who would follow standard distributions. Therefore, PFS and OS may be underestimated for responders.

Use of a response-based approach also requires landmark analysis to account for the risk of time immortal bias. Such a bias may exist because response to treatment does not occur instantaneously and can take a number of weeks or even months. Given that a patient has responded, this means they must have survived until the point of response (i.e. they are immortal during that period). Therefore, for the purposes of oncology modelling, by extrapolating PFS and OS from this period there is a likelihood that survival will be overestimated. During landmark analysis, all patients can be modelled together (i.e. not separated by response status) until the pre-defined landmark, likely to be related to the mean time to response, and then separate survival curves can be plotted for responders and non-responders.

4 How to Deal with Crossover or Single Arm Trials

It is increasingly commonplace in oncology modelling for comparisons to be made between treatments in which there is no head-to-head evidence directly comparing the efficacy of the treatments, commonly through randomised controlled trials. This issue can be overcome if each treatment was part of a comparative randomised trial

and the treatments shared common comparators (e.g. placebo) via the completion of a mixed treatment comparison (MTC). For example, if treatment A and treatment B need to be compared, and they were separately compared against treatment C, then the results of A versus C and B versus C can be used to infer the results of A versus B via an MTC (Ishak et al. 2015). However, within oncology there are scenarios in which only single-arm trials are completed for new therapies (i.e. there is no comparator arm in the trial), particularly for indications in which there is a small population group making patient enrolment a challenge. In these scenarios, there will be no common comparators that can be used to complete the MTC. As such, alternative approaches must be sought.

The simplest approach is to undertake a naïve comparison of the two treatments in question (e.g. directly compare the outcome measure reported from the clinical trial for each treatment). However, using this approach there is a substantial risk of bias due to confounding factors that may explain any differences in the outcomes, particularly those relating to patient characteristics (e.g. age, gender ratio and health at study baseline). The problem of confounding can be addressed using simulated treatment comparisons (STC) or matching-adjusted indirect comparisons (MAIC). These are very similar techniques in which comparisons of treatment effectiveness can be made by adjusting for differences in patient characteristics between compatible trials (Ishak et al. 2015).

In cases where patients are allowed to 'cross' between intervention arms in a trial (for ethical or other reasons), the analysis of data can be more problematic. Clearly, if patients in the control arm are to later receive the active treatment, then using the intention-to-treat analysis is likely to substantially overestimate the true survival of that group, since the active treatment would not be available in the counterfactual scenario of the economic evaluation (i.e. where the active therapy is not approved by the reimbursement body). A number of different approaches have been proposed in the literature but, in the absence of a gold standard or 'true' data with which to compare, all methods have potential limitations, and the potential biases are not fully understood. At the current time, rank preserving structural failure time models (RPSFTM) and iterative parameter estimation methods appear to provide the most accurate methods (Latimer et al. 2017) but, it should be noted, potential biases remain and many decision-making bodies treat such analyses with a large degree of caution.

5 Utilities—The Ways in Which Utilities Can Be Applied, Applying Utilities with Proximity to Death

The inclusion of utilities is important in oncology modelling in order to estimate the impact of therapies on patient health-related quality of life. This is commonly achieved by the application of state-specific utility values within the model. For example, in a three-state transition model utility values for the stable disease and post-progression states would be applied (within a utility of zero for all patients

who have died). These utility values would then combined with a measure of time to estimate the number quality-adjusted life years (QALYs) accumulated by a patient in that health state. This would be dependent on the number of cycles they remained in that state and the cycle length. For example, staying with the example of a partitioned survival model, if we assume patients in the SD state receive a utility score of 0.80 and remain in that state for 15 cycles with a cycle length of one month, then this equates to 1.2 QALYs ($0.8 \times 15/10$).

The utility values applied within specific health economic evaluations should be indication-specific, if possible. For example, if the evaluation is concerned with the impact of a new therapy on people with breast cancer, then utility values should relate specifically to the experiences of people with breast cancer as opposed to other oncology indications. Utility values can be estimated for specific indications via the administration of validated, preference-based questionnaires to relevant patients, and it is now commonplace for these instruments to be included within clinical trial protocols. A range of questionnaires are available to researchers, including disease-specific instruments; however, in the UK preference is often given the EQ-5D and this is specifically recommended by the National Institute for Health and Care Excellence (NICE) who is responsible for national decisions relating to the adoption of new health technologies in England and Wales (NICE 2013).

The previous methods just described assume that utility within a specific health state remains fixed for the duration of the analysis. However, as a patient's cancer progresses their HRQoL may also decline, particularly as they approach death. If a standard three-state model has been adopted, then this decline will be captured to a degree via the application of different utility values to the SD and PP states. However, this approach may not allow subtler variations in health to be captured, particularly in the PP state. This is particularly problematic if the utility values are based on survey instruments that were administered as a part of a trial protocol because if censoring has occurred, then the mean utility values for each health state may be more weighted to patients at the start of their time in the state. In this scenario, the utility values applied in the analysis would lead to an overestimation of the QALYs accumulated in that state. To overcome this issue, within each state separate utility values can be applied dependant on proximity to death. For example, if utility data have been collected from a clinical trial, then within individual health state values can be extracted based specific time from trial initiation groups (e.g. less than 30 days, 30–60 days, 60–90 days, more than 90 days). These values can then be applied within the economic model.

6 The Economic Implications of Increased Survival in Oncology

Because economic evaluations typically include all costs relevant to a disease, not only treatment-related costs, this can, ultimately, be prohibitive to an intervention's likelihood of being cost-effective since, as patients survive for longer with an active treatment, the increase in healthcare costs may outweigh the benefits accrued through that survival gain. It has been shown that, in some cases, even if a drug had zero price and was highly effective in increasing survival, it could be deemed not to cost-effective, since the associated costs with survival would be prohibitive (Davis 2014). This is more likely to affect those therapies that increase survival in the later stages of disease (i.e. where costs are high and quality of life is low). It could be argued that this may lead to disincentives fund to research for treatments in cancer areas that have a high 'background' costs. Conversely, it may incentivise research into preventative treatments or treatments that focus on improving quality of life. Investment in research in these areas may be better spent.

Decision-making bodies, such as NICE, must consider how treatments in these situations should be assessed. Some argue that certain medical treatments have 'value' that falls outside of the typical 'cost per QALY' metric, such as end of life care and dialysis. These are treatments that society has decided should be provided regardless of cost-effectiveness. Post-progression cancer survival care has similar 'value' such as palliative care and right to die with dignity. These 'values' could be seen as rights which must be provided regardless of cost-effectiveness. However, it can be questioned whether accepting a higher ICER should be considered in these areas given that the opportunity cost remains the same.

This is reflected in NICE's end of life criteria statement, where a re-weighting of the health benefits is allowed in certain conditions. NICE states that, if end of life criteria are met (i.e. if the natural prognosis of the disease is less than 2 years, if the therapy is likely to lead to at least three additional months of survival and if the potential population size is not too large), then the Appraisal Committee will consider 'the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases', and 'the magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the current threshold range' (NICE 2009).

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Drug Pricing and Value in Oncology

Patricia M. Danzon

Abstract

This paper first reviews the evidence on price levels, price growth, and value for cancer drugs. The available evidence suggests that prices for originator (brand-name) drugs are rising significantly more rapidly than general inflation, but the available data are inadequate for robust comparisons between cancer and other categories of specialty drugs. We then examine the factors contributing to high and rising prices for cancer drugs. This analysis focuses mainly on the USA, which accounts for 46% of global expenditures on cancer drugs. It is the country of first launch for most cancer and other specialty drugs and frequently has the highest prices for drugs.

Keywords

Cancer drugs · Pricing · Reimbursement · Affordability · R&D

1 Introduction

Concerns over pricing and value pervade healthcare systems, but are nowhere more acute than in the case of cancer drugs. For payers, the rapidly growing number and cost of cancer drugs challenge affordability, threatening to crowd out other valued services from limited healthcare budgets. Faced with high prices, payers routinely restrict access or, in some cases, simply refuse to provide coverage of high-priced drugs. High prices also raise questions of value-for-money, that is, whether the sometimes modest incremental survival and quality-of-life benefits delivered by

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these drugs justify their high prices. For patients, high prices can entail significant out-of-pocket costs in countries that lack comprehensive insurance coverage, including the USA and many middle- and low-income countries. Perhaps of greatest concern is that no end is in sight to the underlying factors that drive prices upward, with primary drivers in the USA and spillover effects to other countries.

This paper first reviews the evidence on price levels, price growth, and value for cancer drugs. The available evidence suggests that prices for originator (brand-name) drugs are rising significantly more rapidly than general inflation, but the available data are inadequate for robust comparisons between cancer and other categories of specialty drugs. We then examine the factors contributing to high and rising prices for cancer drugs. This analysis focuses mainly on the USA, which accounts for 46% of global expenditures on cancer drugs. It is the country of first launch for most cancer and other specialty drugs and frequently has the highest prices for drugs. Pricing strategies therefore tend to be developed with the US market in mind and then adapted to other countries. We argue that the design of public and private insurance coverage and reimbursement for cancer drugs in the USA is a major contributor to high and rising prices. This is illustrated by a review of the reimbursement rules of Medicare, the public insurance for all seniors over 65, which are similar to reimbursement rules for private insurance plans. Reimbursement rules are reviewed for both physician-dispensed drugs (which includes infused and injected drugs) and oral, pharmacy-dispensed medications. The basic approach relies on market forces to constrain prices. However, market forces work poorly for differentiated, highly priced drugs for which patients have insurance coverage with cost-sharing but protection through catastrophic caps, supplementary insurance, and other programs. The federal government is barred by statute from negotiating drug prices or using cost-effectiveness as the basis for coverage decisions. This reimbursement regime provides little if any constraint on the upward drift of prices.

High drug prices, including for cancer drugs, are sometimes attributed to high costs of research and development (R&D). Economic theory and evidence support the view that investors must anticipate a reasonable return on their investment (ROI), in order to continue investing. However, this does not imply that drug prices are based on the cost of R&D, which would be irrational. Producers in any profit-driven industry rationally set prices based on what customers are willing to pay. In the case of pharmaceuticals, this depends on the effectiveness, safety, and other characteristics of alternative treatments and, importantly, on payer reimbursement rules when drugs are largely covered by insurance. The evidence of strong investment flows into cancer compared to other therapeutic areas strongly suggests that cancer is perceived to offer relatively profitable investment opportunities, given current R&D costs and pricing environments.

In this paper, Sect. 1 reviews the evidence on rising prices, costs, and value for cancer drugs. Section 2 then reviews the main causes of rising prices and costs for cancer drugs. Section 3 briefly reviews the evidence on R&D costs and pricing. Section 4 discusses policy solutions.

2 Evidence on Expenditures and Price Growth for Cancer Drugs

2.1 Expenditures

Global expenditures on cancer drugs increased from $91b in 2012 to $113b in 2016 and are projected to grow to $150b by 2020 (QuintilesIMS Institute 2017). The USA accounts for 46% of global spending on cancer drugs, whereas the USA accounts for roughly 15% of global GDP, adjusted for purchasing power parities (PPPs).[1] The disproportionate US share of global drug spending, compared to its share of global GDP, applies to drugs in general and is not confined to cancer drugs. It reflects primarily that the USA has quicker and broader uptake of new drugs and higher prices, but not necessarily higher total volume of drug use (Danzon and Furukawa 2003, 2006). Illustrating the more rapid US uptake of new drugs in the case of cancer: Of the 42 cancer drugs launched globally between 2011 and 2015, the number available by 2016 was 37 in the USA, 35 in Germany, 33 in the UK, 25 in France, 22 in Japan, and 4 in India, China, and Indonesia (QuintilesIMS 2017).

Several recently published surveys provide overviews of the literature and accumulating evidence on trends in prices of cancer drugs (e.g., Prasad et al. 2017). Novel anticancer drugs routinely cost over $100,000 per year or course of treatment in the USA, less in other countries (Prasad et al. 2017; Vogler et al. 2016). However, when national cancer prices are compared to average per capita income (as a rough measure of affordability), prices are highest, relative to income, in emerging markets such as India (Goldstein et al. 2016). Simple theory and evidence from pharmaceutical markets more generally indicate that high prices, relative to average per capita income, contribute to the limited availability of the newest drugs in middle- and low-income countries (MLICs), as payers refuse to reimburse and/or patients cannot afford to pay out-of-pocket for these products (Danzon et al. 2013a).

Growth in the cost of cancer drugs reflects at least three factors: growth in launch prices of new drugs; price growth post-launch once drugs are on the market; and changing mix of drugs used, including increased use of drug combinations.

2.2 Launch Price Trends

Median launch prices for new cancer drugs increased between 1960 and 2016 from $100 to $10,000 per month of treatment (Bach 2009). In a study of trends in launch prices of orally administered cancer drugs, Dusetzina (2016) found that average cost per month increased from $1,869 in 2000 to $11,325 in 2014, after adjusting for inflation. Of course, this is not an apples-to-apples comparison, because the more recent drugs on average provide greater health benefits. However, when cost

[1] https://www.statista.com/statistics/270267/united-states-share-of-global-gross-domestic-product-gdp/.

is measured per unit of benefit gained, measured in terms of life-years saved, this standardized cost rose by an average of $8,500 per year since 1995 (Howard et al. 2015).

2.3 Price Growth Post-launch: Measurement Issues

Measuring post-launch trends in cancer drug prices poses several methodological challenges. Government statistical agencies in most countries report price indexes that measure the year-on-year price growth for defined baskets of major products, such as pharmaceuticals. For example, the US Bureau of Labor Statistics (BLS) publishes the pharmaceutical producer price index (PPI) that represents drugs in all therapeutic categories, weighted by use. The aggregate pharmaceutical PPI increased 83% (from 126.8 to 231.5) over the decade January 2007–December 2016, with the annual average growth rate increasing from 4.1% in 2007 to 8.8% in 2016,[2] which exceeds general inflation over the period. Unfortunately, a price index that specifically tracks cancer drug prices is not available from US government sources.

Although this aggregate US pharmaceutical PPI includes cancer and other specialty drugs, it is likely to understate price trends for such specialty drugs for several reasons. The PPI is a volume-weighted index, intended to represent drugs in proportion to their usage by patients in general and hence is more representative of widely used, primary care medications. Further, because it defines treatments by chemical name, it treats bioequivalent generic versions of chemical drugs as substitutable for the originator referent products. Thus when cheap generics enter and take a dominant market share after patent expiry for the originator, the volume-weighted average price, which includes both generic and originator prices weighted by market share, usually declines. Over the last 15 years, patent expiries and genericization of many major primary care drugs have significantly moderated the overall growth of drug prices as measured by the PPI, in which these chemical drugs carry a large weight. However, the aggregate PPI understates price growth of originator (brand-name) drugs and understates price growth for categories like cancer, with a relatively large share of biologics that are not subject to genericization comparable to chemical drugs.

To illustrate this price divergence for originator versus generic drugs, between 2008 and 2016, the Express Scripts Brand-Name Prescription Drug Price Index increased threefold, while their Generic Prescription Price Index fell over 50% (Commonwealth Fund 2017). Thus post-launch price growth has been significantly higher than general inflation for originator drugs in general in the USA, and this would include most cancer drugs.

The BLS has recently begun to produce disease-specific indexes for total cost of care (Bradley 2017) for certain diseases, including "Neoplasms" as a single disease category. For the period 2003–2013, the Neoplasm disease category is similar to other disease categories in overall expenditure growth and in each of the individual

[2] https://data.bls.gov/pdq/SurveyOutputServlet. Retrieved 8.29.17.

components of total cost growth that are identified, including overall inflation, real expenditures, population growth, prevalence growth, and per capita output growth.[3] However, drugs are not broken out separately, and price growth for drugs is not reported separately.

Measuring price change for cancer drugs is further complicated by variation across patients and over time in the definition of a dose. If price is defined as dollars per dose, e.g., price per 10 mg, and the normal dose per patient increases in terms of mg per kg body weight, then changes in dosing norms contribute to increases in cost per patient even with no change in price per mg. Studies in the literature of trends in cancer drug prices reach different conclusions, partly due to differences in data sources, products studied, dosing measure, health plan, and time period. In particular, studies that use the average price per prescription or per month of cancer therapy may confound changes in dosing and mix of drugs dispensed with change in price for a given drug mix and dosing. Of course, all three factors contribute to the rising cost of cancer care, but they suggest different causes and conclusions. Given these measurement challenges, there is no single, official, or gold standard measure of price growth for cancer drugs. The evidence summarized here reviews evidence from academic studies in the USA.

In the USA, pure post-launch price growth for cancer drugs typically exceeds general inflation with significant variation across individual drugs (e.g., Gordon et al. 2016). Prasad et al. (2016) studied both patented and off-patent drugs covered under Medicare Part B, which covers physician-administered drugs (see below). For the period 2010–2015, 64% of drugs increased in net price (net of all rebates), and 12.7% increased more than 100% over this 5-year period. Bennette et al. (2016) studied prices to commercially insured patients for 24 orally administered cancer drugs for the period 2007–13. They found that on average cancer drug prices increased 5% per year, after adjusting for general inflation. Prices rose an additional 10% with each FDA-approved indication and declined 2% with FDA approval of a competitor product. Post-launch price inflation also occurs for other on-patent specialty drugs in the USA, as noted earlier, and whether the experience is systematically different for cancer versus other therapeutic categories remains to be studied. Theory and existing evidence suggest that it would depend on the particular drugs and time period studied. However, it seems clear that on average price growth for cancer drugs in the USA exceeds general inflation. By contrast, because most other developed countries do not permit post-launch price growth, this positive post-launch US price growth contributes to divergence in prices between the USA and other countries.

[3] https://www.bls.gov/opub/btn/volume-6/pdf/cost-of-care.pdf.

3 Drivers of High Prices for Cancer Drugs: Reimbursement Rules Matter

In recent years, the majority of new drugs have been launched first in the USA, both because of the US FDA's relative speed in reviewing "novel" medicines and the US' lack of a formal price review as a condition of reimbursement, as required in other countries. Further, for strategic reasons, companies may prefer to launch first in the relatively unconstrained, high-priced US market, so that the US price becomes a benchmark from which discounts may be granted to other countries. Although the USA does not formally use external referencing to set drug prices, very large price differentials between the USA and other high-income countries can increase the political risk of calls for external referencing or drug importation in the USA. Thus, the US price plausibly influences prices in other countries indirectly, in addition to being directly referenced by a few other countries, including Canada and Japan. Thus, the factors contributing to high pricing in the USA are potentially important for pricing in other countries.

Within the pluralistic US system of public and private insurance plans, there is no overarching review process to set price and reimbursement limits for drugs, nor do individual public or private plans use formal processes to assess price relative to value created, comparable to the price and reimbursement processes used in many other countries, including individual EU countries, Canada, Japan. In the USA, the underlying presumption is that market forces should work to constrain prices, as manufacturers compete to get their drugs favorably placed on formularies and used by doctors and patients, and health plans compete for enrollees. In practice, this system does not work well to constrain prices for specialty drugs like oncologics, because of differentiation of the products, widespread insurance, and specific regulatory rules that undermine competition. The next section outlines the relevant features of this reimbursement system.

3.1 Reimbursement Rules and Pricing Incentives in the USA

Reimbursement rules for drugs in the USA depend on whether a drug is dispensed by a retail pharmacy; administered through a physician office or hospital outpatient department; or administered during an inpatient hospital episode. Although the detailed approaches in each of these contexts also differ across insurers, common features apply in each context. Retail pharmacy and physician outpatient locations are most important for cancer and are the focus here.[4]

Retail pharmacy-dispensed drugs. Drugs that a patient buys from a pharmacy for self-administration are covered by the pharmacy benefit of private insurance plans for the under-65 population and by Medicare Part D for seniors over 65. Pharmacy benefits are usually managed by specialized pharmacy benefit managers (PBMs) for private plans and by prescription drug plans (PDPs) for Medicare

[4]For more detail, see Danzon (2014).

Part D, which was modeled on and is implemented by private insurers, using very similar approaches. The basic strategy is to use a tiered formulary, offering a drug preferred tier placement in return for price rebates or discounts. Most formularies have at least four tiers: Tier 1 includes generics, with a $5–10 monthly co-pay; tier 2 includes "preferred" on-patent drugs with a modest co-pay (about $30 per script/month); tier 3 includes "non-preferred" on-patent brands, with significantly higher co-pay ($45–90 per script/month); and specialty drugs are put on tier 4 with coinsurance at 20–33% of the drug price, in addition to prior authorization (PA) and other requirements for access. PBMs/PDPs use tiered formularies with co-payment differentials and other access controls to steer patients to use preferred drugs. Because preferred formulary placement increases sales, manufacturers traditionally have been willing to grant price discounts in return for preferred tier placement.

This tiered formulary approach works reasonably well to generate manufacturer price discounts in therapeutic classes with multiple, close-substitute drugs, for which patients/physicians are willing to accept the PBM restrictions on prescribing freedom that are implied by tiered formularies. However, PBMs have less leverage to steer utilization through formulary design and hence to negotiate discounts in therapeutic classes such as cancer, where drugs are more differentiated and individual patients' conditions and preferences may influence appropriate choice of drugs. The growing number of drugs in many specialty classes has increased the drug choices and might be expected to enable PBMs/PDPs to negotiate discounts in return for preferred formulary placement. Such discounting in return for preferred placement occurred for the hepatitis C drugs, but these are similar in outcome and require relatively short treatment duration. In general, discounting in return for preferred formulary placement is not the norm for specialty drugs.

Most PDPs and PBMs place drugs costing over $600 a month on a fourth "specialty" tier with a 25–33% coinsurance rate,[5] rather than seeking discounts in return for preferred placement. This 25–33% coinsurance on such expensive drugs would be unaffordable for most patients, but few actually pay it, thanks to supplementary insurance, catastrophic caps, and/or coupons. Low-income seniors have cost-sharing assistance through Medicaid, and most higher income seniors have supplementary insurance. Moreover, under Medicare Part D, patient cost-sharing is capped at a "catastrophic threshold," above which the patient pays at most 5% (zero for low-income seniors), while the PDP pays 15% and taxpayers pick up the remaining 80%.[6] Under the Affordable Care Act, private insurance offered through exchanges must have an income-related catastrophic limit on patient cost-sharing, but health plans may no longer set annual or lifetime caps on their payments for covered benefits. For patients who do face high out-of-pocket costs, pharmaceutical companies offer patient assistance and coupon programs to cover cost-sharing.

[5]Medicare defines drugs costing at least $600 a month as "specialty drugs" and permits PDPs to place these drugs on a specialty tier with a coinsurance percentage up to 33%.

[6]In 2017, the catastrophic coverage threshold is $4,950 in True Out-of-pocket spending. http://www.kff.org/medicare/fact-sheet/the-medicare-prescription-drug-benefit-fact-sheet/.

The net effect and important implication of this patchwork of coverage for drug pricing strategy are that, because most patients have a cap on their cost-sharing and significant protection below the cap (through supplementary insurance, coupons, etc.), most patients are relatively insensitive to prices. In particular, at price levels that exceed the cost-sharing cap for most patients, price elasticity or sensitivity is likely to be minimal. Most novel cancer drugs are now priced in that range where increasing price is unlikely to significantly affect utilization.[7]

Physician-dispensed drugs: Drugs that require infusion or injection are dispensed in physicians' offices or hospital outpatient departments. These drugs are covered by a private insurer's medical benefit and by Medicare Part B for seniors (Kaiser Family Foundation 2017). Physicians buy these drugs from specialty pharmacies and are reimbursed by the health plan for the drug cost plus a modest dispensing fee—the "buy and bill model." Medicare Part B's reimbursement rules set the norm followed by many private payers. Since 2005, Medicare Part B reimburses the physician for the drug at its average selling price (ASP), calculated as the volume-weighted average manufacturer selling price, net of discounts and lagged two quarters, plus 6%. This ASP + 6% formula creates incentives for manufacturers to set a high rather than low ASP at launch, because a higher price offers a larger absolute margin to the dispensing physician and this may influence prescribing, other things equal. The ASP formula also discourages discounting by manufacturers to gain market share. Although a discount given to some customers in period T increases their margin in that period, the discount reduces the average selling price and therefore reduces the reimbursement paid to *all* customers in period T + 2. Many private payers follow Medicare's ASP-based reimbursement rule, with possible modifications such as using a different add-on percentage.

Thus this Medicare Part B reimbursement rule places no constraint on launch prices and has likely contributed to high prices for oncologics and other physician-dispensed drugs, by creating incentives for manufacturers to set high prices and avoid discounting. The 2-quarter lag structure may constrain rapid price increases, because reimbursement in quarter T is based on ASP in T-2, such that rapid price increases could result in physicians being reimbursed at less than their acquisition cost for drugs. Medicare patients face 20% cost-sharing with no catastrophic cap for Part B services, which might in theory create price sensitivity and provide a countervailing constraint on prices for Part B drugs. However, many Medicare patients have supplementary insurance—either private Medigap coverage or Medicaid—that covers their cost-sharing, making them less price sensitive. Those patients who do face the 20% coinsurance out-of-pocket may simply forego the drug, unless they are referred to a patient assistance program or a hospital outpatient department that may waive the co-payment.

Oncology drugs thus illustrate that the US' market-based approach to pharmaceuticals, which works reasonably well for many primary care drug classes with

[7]Specifically, for a Medicare patient using a fourth-tier drug with 25% coinsurance, they reach the cost-sharing cap and face incremental cost-sharing of at most 5% for any price beyond $20,000 per treatment.

moderately priced, closely substitutable, products, is poorly designed to deal with high-priced, differentiated products like the cancer drugs. The market approach presumes that price-sensitive consumers and their payers/PBMs choose between similar products on the basis of price. For cancer drugs, differentiation of drugs, patient conditions, and preferences mean that choice among drugs is heavily influenced by clinical factors, as patients and their physicians determine their preferred sequencing of drugs to manage the condition. Insurance coverage further drastically reduces price sensitivity, because many patients have cost-sharing covered through supplementary public and private insurance. Although the evidence shows some patients face "financially toxic" cost-sharing even in meeting these caps, in general the significant coinsurance provisions in US private and public insurances provide little if any constraint on manufacturer pricing because most patients have supplementary insurance, coupons or other cost-sharing assistance, while those who face the full out-of-pocket payment likely drop out of the market at quite low prices, leaving only the heavily insured patients who are price insensitive in the market. Further, for physician-dispensed drugs Medicare's ASP + 6% reimbursement creates incentives for manufacturers to set high launch prices for cancer and other physician-dispensed drugs, with no constraint except the nominal 20% patient coinsurance, which appears to be an ineffective constraint due to supplementary coverages.

The failure of reliance on patient cost-sharing to create price-sensitive markets is exacerbated by the requirement that all Medicare Part D PDP plans must cover all FDA-approved cancer drugs. Further, CMS is expressly barred by statute from negotiating prices with pharmaceutical companies or from using evidence on costs or effectiveness to make coverage decisions. CMS recently proposed some modest changes in its reimbursement for Part B drugs, but was forced to drop these initiatives under industry pressure. Although biosimilars are being developed as the earlier biologic drugs reach patent expiry, the US lags the EU in number of approved biosimilars. Further, because most biosimilars will not achieve the stringent standards for substitutability with originator products and reimbursement rules treat them as distinct products, incentives for competitive pricing by biosimilars are weak, at least under current rules.

In sum, the system is designed to rely on price-sensitive choice between similar products, but this cannot work well for costly, differentiated products like cancer drugs, where clinical distinctions matter and insurance considerations have appropriately led to catastrophic limits on cost-sharing in most public and private programs. If fully insured patients are the majority of customers, while those who face the large cost-sharing either forego their drugs or apply for patient assistance programs, the coinsurance has little constraining effect on manufacturer pricing. In this environment, if payers have no leverage to control prices, the manufacturer's rational pricing strategy may be to set a high price to the highly insured majority, while offering patient assistance or coupons to those who face significant out-of-pocket costs. This status-quo system is unsustainable because ultimately patients/enrollees/taxpayers must pay the insurance premiums and taxes to fund the private and public programs. Such willingness-to-pay is eroding as prices rise out of

line with perceived value of benefits delivered and opportunity cost of other goods foregone in order to purchase these products.

3.2 Pricing in Developed Countries Ex-USA

In contrast to the USA, all EU and other developed countries have national or social health insurance (NHI or SHI) systems that evaluate price and coverage criteria for drugs, as a condition of reimbursement. Countries differ in detail of these pharmaceutical price and reimbursement systems (see, e.g., Danzon 2012; Stargardt and Vandoros 2014). The payer typically evaluates the manufacturer's proposed price, relative to such factors as: evidence of clinical benefits and risks; prices of comparator drugs in the same country (internal referencing); and/or price of the same drug in other countries (external referencing). Reimbursement is contingent on the manufacturer and payer agreeing on a price, including any rebate or "access program" to reduces costs for the payer. Price increases are generally not permitted and payers may mandate price cuts or freezes to meet budgetary goals. Cancer drugs are subject to these general price/reimbursement constraints, but may sometimes receive special treatment on such grounds as: orphan status, which may justify a higher price; treatment of terminal conditions; and strong patient/physician advocacy of medical need.

The fact that ex-US payers operate within limited health budgets and can refuse to pay for treatments that are deemed poor value at the manufacturer's price gives payers some leverage to negotiate lower prices, but can also lead to less availability of new drugs and access for patients. Manufacturers may be reluctant to cut prices in one country if such cuts could spill over to other countries, through external referencing or parallel exports, which are common in the EU (see, e.g., Danzon et al. 2005; Kyle 2007). Spillovers may be avoided if price cuts take the form of rebates paid directly to payers, which must remain confidential to avoid spillover but hence lack transparency. The non-observability of discounts and rebates means that studies based on observable prices may underestimate the extent of cross-national price differences. But the fact that low-income countries have fewer of the novel, expensive drugs is consistent with the observed data, that prices vary across countries less than in proportion to per capita income and hence that drugs are least affordable, relative to per capita income, in low-income countries. However, the limited availability and relatively high prices (compared to per capita income) of drugs in low-income countries plausibly reflects a complex mix of factors besides limited ability to pay, including other medical priorities in these countries, lack of specialist physicians, and other complementary medical services needed to assure appropriate use of complex drugs, risks to intellectual property, and other factors.

4 R&D and Pricing

High prices for cancer and other drugs are sometimes attributed to high costs of R&D. Economic theory and evidence support the view that investors must be able to anticipate a positive return on their investment (ROI), in order to continue investing. However, it does not follow that prices are based on the cost of R&D, which would be an irrational pricing strategy. Producers in any profit-driven industry rationally set prices based on what customers are willing to pay. In the case of pharmaceuticals, this depends on the effectiveness, safety, and other characteristics of alternative treatments and, importantly, on payer reimbursement rules when drugs are largely covered by insurance.

Nevertheless, recognizing the need to maintain appropriate incentives for investment in R&D, some understanding of the structure and cost of R&D is important. As with pricing, the available data and studies have limitations, but are nevertheless useful. A recent study (DiMasi et al. 2016) estimated the average cost of bringing a new drug to market at $2.7b (2017 US dollars), including the cost of capital. This study used corporate data from the 10 largest companies for their self-generated drugs (discovered and developed in-house). This is a biased sample, because these self-generated drugs were a small and declining share of total drugs approved during the study period, when novel discovery R&D was shifting to smaller companies, including for cancer.

A more recent study (Prasad et al. 2017) focused at the other extreme, on 10 small cancer-focused companies that brought a single drug to market between 2006 and 2015. Their estimate of the median cost of bringing a new cancer drug to market was $757.4 m, including the cost of capital. Although both studies have limitations and the reported estimates have large ranges, the lower estimate from the Prasad et al. (2017) study is more consistent with other evidence of trends in cancer R&D. In particular, for phase III trials (which are usually the largest element of R&D cost) between 1997 and 2016 average trial duration declined from 2000 days to 1070 days, and average enrollment declined from 671 patients to 188 patients (QuintilesIMS Institute 2017). This reflects both the focusing on smaller niche conditions and streamlining of regulatory processes and trial design. Prasad et al. also report total revenue to date for the 10 drugs of $67b. Since this is at a median of 4 years since approval, it seriously understates their full lifetime expected revenues. This partial report of total revenue far exceeds the total $9.1b in R&D expense (including 7% opportunity cost of capital).

Further evidence that oncology is perceived to offer a relatively profitable R&D investment opportunity is provided by the 45% increase in the number of oncology drugs in clinical development over the past 10 years, with 631 late-stage drugs in development (QuintilesIMS Institute 2017). The incentive from generous pricing of cancer drugs reinforces other favorable factors, including the ease of stratifying cancers to target drugs for narrow conditions that qualify for orphan status, which brings benefits of R&D tax credits, 7-years market exclusivity, relatively small trial requirements and, if granted breakthrough status, favorable regulatory review

conditions. While the robust flow of investment into oncology R&D may bring new cancer treatments, it does raise the policy issue whether cancer is disproportionately favored, to the relative neglect of other therapeutic areas, on account of the high prices and relatively low R&D costs. Such concerns reinforce the case for a value-based approach to reimbursement for all drugs, including cancer drugs, in which pricing and reimbursement coverage are linked to evidence of value created across all therapeutic areas.

5 Value-Based Pricing: A Way Forward

The US lags many other countries in developing a consensus approach to measuring the value of drugs and using such data in reimbursement decisions. Frustration over high prices that appear unrelated to clinical value has recently prompted multiple initiatives to develop "value frameworks," including the value framework developed by the American Society of Clinical Oncology (Schnipper et al. 2015) and the drug Abacus developed by Peter Bach and colleagues at Memorial Sloan Kettering (https://drugpricinglab.org/tools/drug-abacus/). The ASCO approach is designed to assist physicians and patients make clinical choices. Outcomes include overall survival or progression-free survival, with an arbitrary weighting attached to risks, while costs include on the drug cost, either the full price or the patient's out-of-pocket cost, depending on perspective taken. The Abacus allows for more elements of "value," including not only expected survival and risk, but also the drug's R&D costs, treatment population size, price charged in one or more foreign countries, etc. The analyst must supply their preferred weights for each of these dimensions, and then the Abacus calculates a weighted aggregate "value," which can be compared to the drug's price, to determine whether or not the price is "fair." These approaches may provide useful aids to clinical decision-making, but they are not designed for use by payers to assure consistency in price and reimbursement decisions, which is essential to achieve the goal of maximizing health gain from a given health budget.

5.1 Value-Based Pricing

In fact, an extensive health economics literature addresses the issue of how to measure health outcomes and other dimensions of value with a view to maximizing health gain from a fixed health budget (see, e.g., Newman et al. 2017; Drummond et al. 2015; Sculpher et al. 2017). This literature recommends using a validated outcomes metric that captures at minimum both the quality and quantity of survival, as in the quality-adjusted life year (QALY). From a payer or societal perspective, costs should include the full price of the drug plus any additional costs or cost offsets, such as hospital days required or averted due to the treatment. Calculation of an incremental cost-effectiveness ratio (ICER) in terms of incremental cost,

relative to incremental QALYs gained for a new treatment, relative to customary treatment, provides a measure of incremental cost per unit of health gain. Assuming that the payer's objective is to maximize health gain, given its available budget, the payer should set a threshold willingness-to-pay (cost per QALY) and pay for those treatments that meet this threshold. Paying for treatments that are priced above the cost-per-QALY threshold while foregoing others that priced below the threshold implies that health gain would not be maximized for the budget.

With this approach, the payer need not directly regulate drug prices. By requiring that drugs meet a cost-per-QALY limit in order to be reimbursed, the payer creates incentives for manufacturers to price their drugs to meet this limit, in order to qualify for reimbursement. This implies that the products that yield significant incremental benefit, in QALYs gained or costs saved, can charge a significant premium over the comparator product and still meet the cost-effectiveness threshold. Conversely, a new drug that offers no incremental benefit must be priced at par with the comparator or risk exceeding the threshold and being denied reimbursement. Thus, use of a cost-per-QALY threshold as a condition of reimbursement creates incentives for manufacturers to charge prices commensurate with value created and creates incentives for R&D to focus on areas where significant value can be created (Danzon et al. 2013b) .

While the approach to value-based pricing described here is structurally similar to that used by the UK's National Institute for Care Excellence (NICE), important adjustments would be needed to adapt the approach to the pluralistic and more affluent US health system. In particular, different public and private health plans could choose different ICER thresholds and might also include different items in their measure of benefits, depending on their premium levels and implied budgets. In general, since ICER thresholds reflect taxpayers/enrollees' willingness-to-pay for health gain, such thresholds are expected to be higher in countries/health plans with high income and/or a high willingness-to-pay for health. Thus US health plans would surely adopt significantly higher ICER thresholds than those used in the UK.

More generally, this basic framework to induce value-based pricing could also be used to set drug price differentials across countries at different income levels. If each country unilaterally defined its approach to measuring value and sets its ICER threshold based on its willingness/ability to pay, this would create incentives for manufacturers to differentiate prices across countries such that prices would better align with affordability across countries. Of course, implementation of such a system presupposes an institutional framework that precludes either consumers or middlemen arbitraging price differences within and between countries. In fact, technological advances make it increasingly feasible to target price differentials through electronic rebates to specific payers, bypassing intermediaries. Such electronic rebates are widely used in the USA to maintain price differences across health plans and have also been used in other countries. Thus, the main obstacle to broader use of differential pricing is not technical feasibility but political acceptance of non-transparency, which could be addressed through audit mechanisms to prevent abuse.

6 Conclusion

In conclusion, a significant driver of high and rising prices for cancer drugs is the structure of reimbursement systems in US public and private insurances, which provide no constraint on the upward drift of prices. Constraining this upward drift while preserving appropriate incentives for R&D requires a mechanism that allows prices commensurate with value. Such value-based pricing can be achieved via the relatively simple, indirect approach of using an ICER threshold as a condition of reimbursement, which could differ across health plans and across disease or patient categories within a plan, e.g., higher willingness-to-pay for treatments of terminal conditions. This value-based pricing approach creates appropriate incentives for R&D and maximizes health gain for a given budget. It can be used with different ICER thresholds across countries, based on income, which would facilitate price differentials that are reasonably affordable relative to income, while incentives for R&D are maintained.

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Regulatory and Evidence Requirements and the Changing Landscape in Regulation for Marketing Authorisation

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Abstract

In this chapter, we describe the changing landscape of the EU pharmaceutical legislation concerning regulation and evidence requirements for marketing authorisation. First, we describe the legal requirements for marketing authorisation and the development of EU pharmaceutical legislation and the concept of risk-benefit balance. Second, we describe special types of authorisation, such as conditional approval and approval under exceptional circumstances, and special provisions such as incentives for orphan medicinal products and paediatric investigational plans. Lastly, we describe the available methodological guidelines focussing on choice of endpoints.

Keywords

EMA · Marketing authorisation · Anticancer drugs · Efficacy
Benefit-risk balance

1 Introduction

Much of the impetus behind the adoption of EU pharmaceutical legislation level stemmed from the determination to prevent a recurrence of the thalidomide disaster of the late 1950s early 1960s as a result of mothers taking thalidomide as a sedative during pregnancy. Since then, it has become clear that in order to protect public

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health, medicinal products can only be marketed with prior authorisation from the competent regulatory authority. Over the past 50 years, a large body of legislation has been developed around this principle, with the progressive harmonisation of requirements for the granting of marketing authorisations and post-marketing monitoring implemented across the entire EU. Special rules exist to address the specificities of certain types of medicinal products and promote research in specific areas including orphan medicinal products, medicinal products for children and advanced therapy medicinal products (Fig. 1).

The EU legal framework for medicinal products for human use is intended to ensure a high level of public health protection and to promote the good functioning of the internal market with measures which moreover encourage innovation (European Commission n.d.). In this chapter, we describe the changing landscape of the EU pharmaceutical legislation concerning regulation and evidence requirements for marketing authorisation. First, we describe the legal requirements for marketing authorisation and the development of EU pharmaceutical legislation and the concept of risk-benefit balance. Second, we describe special types of authorisation, such as conditional approval and approval under exceptional circumstances, and special provisions such as incentives for orphan medicinal products and paediatric investigational plans. Lastly, we describe the available methodological guidelines focussing on choice of endpoints.

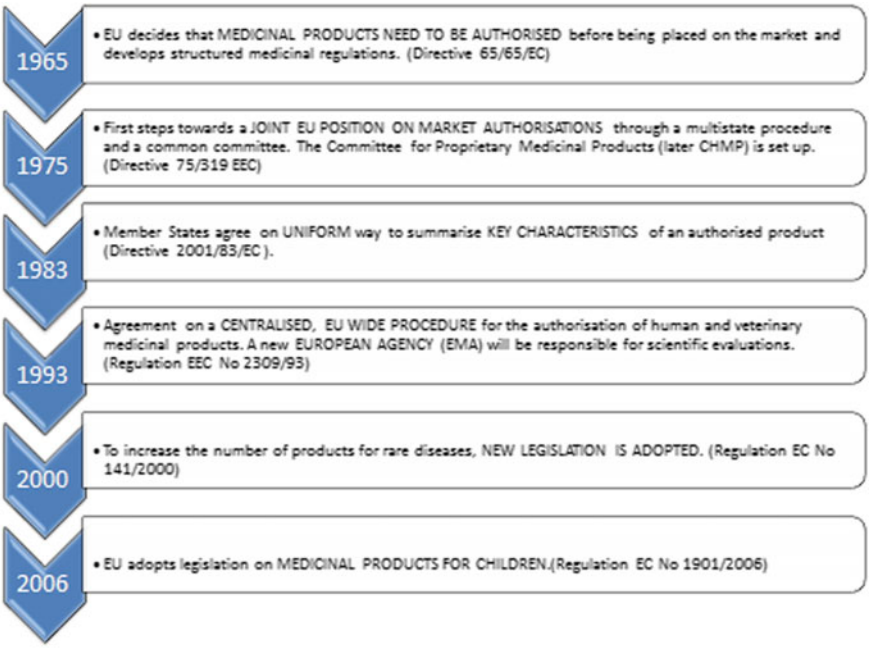

Fig. 1 Key milestones in European Union pharmaceutical legislation *Source* Modified from European Commission. 50 years of EU pharmaceutical legislation. Secondary 50 years of EU pharmaceutical legislation. https://ec.europa.eu/health/human-use/50years_en

2 Requirements for Marketing Authorisation

The requirements and procedures for the marketing authorisation for medicinal products for human use, as well as the rules for the constant supervision of products after they have been authorised, are primarily laid down in Directive 2001/83/EC and in Regulation (EC) No 726/2004 (Directive 2001/83/EC 2012, Regulation (EC) No 726/2004 2013). These texts additionally lay down harmonised provisions in related areas such as the manufacturing, wholesaling or advertising of medicinal products for human use.

The EU has established the European Medicines Agency (EMA) to help in the process by coordinating the scientific evaluation of the quality, safety and efficacy of medicinal products undergoing an authorisation procedure. The European Medicines Agency is responsible for the scientific evaluation of applications for EU marketing authorisations for human and veterinary medicines in the "centralised procedure". The centralised procedure is mandatory for human medicines containing a new active substance to treat cancer or orphan medicines. Other areas that fall in the mandatory scope of the centralised procedure include human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS); diabetes; neurodegenerative diseases; auto-immune and other immune dysfunctions; viral diseases. The same applies to medicines derived from biotechnology processes, such as genetic engineering; advanced therapy medicines, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The procedure is optional for other medicines containing new active substances for indications other than those stated above that are a significant therapeutic, scientific or technical innovation; or whose authorisation would be in the interest of public or animal health at EU level.

The Agency provides guidance for companies and individuals involved in developing and marketing medicines for human use (Pignatti et al. 2011). Scientific guidelines are prepared by the EMA's scientific committees, to help applicants prepare marketing authorisation applications for medicinal products for human use. Guidelines are also intended to provide a basis for practical harmonisation of the manner in which the EU Member States and the EMA interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community Directives.

The scientific evaluation of an application for marketing authorisation is carried out within the CHMP of the EMA, and a scientific opinion is prepared. A number of other committees are involved to various degrees during the scientific evaluation, such as the Pharmacovigilance Risk Assessment Committee (PRAC), which provides recommendations on questions on pharmacovigilance and risk management systems, including the monitoring of their effectiveness, the Committee for Advanced Therapies (CAT), responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and the Paediatric Committee (PDCO) to improve the health of children in Europe by facilitating the

development and availability of medicines for children aged 0 to 17 years (Regulation (EC) No 1901/2006 2007).

The scientific opinion on the granting of a marketing authorisation is sent to the European Commission which drafts a Decision. Having consulted the Member States through the relevant Standing Committee, the Commission adopts the Decision and grants a marketing authorisation. Such a marketing authorisation is valid throughout the Union and confers the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State. A standard approval is valid for 5 years and can be renewed (indefinitely or for another 5 years) on the basis of a re-evaluation of the benefit-risk balance.

A "standard" marketing authorisation is granted according to Art. 26 of Directive 2001/83/EC, which states that the marketing authorisation shall be refused if, after verification of the required particulars and documents, it is clear that

(a) the risk-benefit balance is not considered to be favourable; or
(b) its therapeutic efficacy is insufficiently substantiated by the applicant; or
(c) its qualitative and quantitative composition is not as declared.

The required particulars and documents include results of pharmaceutical (physico-chemical, biological or microbiological) tests, pre-clinical (toxicological and pharmacological) tests, and clinical trials (Directive 2001/83/EC 2012).

In general, for new applications, the primary evidence of therapeutic efficacy is derived from the main efficacy studies ("confirmatory" studies) submitted by the applicant of the marketing authorisation. According to the legal requirements, in general, clinical trials have to be done as controlled clinical trials if possible, randomized and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value. Other benefit criteria are derived from relevant non-pivotal ("supportive") studies. The risks are quantified based on observed adverse effects, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal and deaths.

EMA guidance addresses specific requirements for marketing authorisation for different therapeutic areas, including oncology. For anticancer drugs, randomized controlled trials (RCT) are generally required using mortality-related endpoints such as survival or progression-free survival. RCT are mostly active-controlled, with a minority of trials using placebo or best care. Double-blind placebo-controlled trials are often not feasible due to the unblinding effect of toxicity for the more traditional cytotoxic agents, but have become more frequent with less toxic targeted agents. The design is generally that of a superiority trial, whereas non-inferiority studies are infrequent due to the often marginal effect of available options, or lack of active treatment. Non-randomized studies using historical control have been accepted in some cases as a basis for standard approval if dramatic effect in terms of objective tumour response was shown in a homogenous population with predictable outcome and no alternative treatment, although more often these were approved under exceptional circumstances (Martinalbo et al. 2016).

The assessment of the relative effectiveness and cost-effectiveness is carried out by health technology assessment organisations and pricing bodies in EU Member States, in some countries by several different bodies using different approaches and often reaching different conclusions. Interactions between medicines' developers, regulators and HTA bodies or other possible stakeholders in the EU to discuss the development plan mean that evidence can be generated to meet the needs of respective decision-makers as efficiently as possible. This facilitates patient access to important new medicines and hence benefits overall public health.

3 Special Types of Marketing Authorisations

The conditional marketing authorisation is only provided for the centralised procedure (Article 14, Martinalbo et al. 2016) of Regulation (EC) No 726/2004. Commission Regulation (EC) No 507/2006 is laying down the rules on the granting of such marketing authorisation (Commission Regulation (EC) No 507/2006). Conditional marketing authorisation is seen as an important tool for fostering early access to medicines for patients, bringing forward the authorisation before comprehensive data are available, which on average took about four years (European Medicines Agency 2017). This approval is reserved for drugs that treat, prevent or diagnose seriously debilitating diseases or life-threatening diseases, or rare diseases (orphan medicinal products) or drugs to be used in emergency situations in response to threats recognised either by the World Health Organization or by the European Community.

Several criteria have to be fulfilled for granting of a conditional marketing authorisation, including (a) positive benefit-risk balance and benefits to public health of the immediate availability of the product; (b) likelihood that comprehensive data will be provided; and (c) fulfilment of unmet medical need.

This approval is granted under certain conditions (so-called specific obligations), whereby the applicant company is obliged to complete ongoing clinical trials, or to conduct new trials, or to collect additional pharmacovigilance data, with a view to confirming that the benefit-risk balance is positive.

Clear information has to be provided to patients and healthcare professionals on the conditional nature of such authorisations, including dates for when the conditional marketing authorisation is due for renewal in the summary of product characteristics.

A conditional approval is only valid for 1 year but can be renewed. The renewal is given on the basis of the confirmation of the benefit-risk balance, taking into account the specific obligations and the timeframe for their fulfilment. Once it is judged that remaining data have been provided or are no longer required, the marketing authorisation can be converted to a "standard" authorisation. If at any time, the benefit-risk is considered to be negative, the marketing authorisation can be suspended or revoked.

The EMA has recently published a review of its first 10 years of implementation of the conditional marketing authorisations (European Medicines Agency 2017). In this series, the main studies were randomised in 59% of applications (48% for oncology applications). Imposed specific obligations have mostly been clinical studies of various development phases. Limited number of specific obligations required extensions of the due date by more than one year (<15%). Although such changes can be driven by difficulties in the conduct of the study, in some cases they were required due to better than expected results (e.g. lower than expected rate of progression or death in the experimental group), and in all cases, formal extensions were substantiated with a justification supported by the CHMP. Submission of specific obligations results was often done in advance of the imposed due date, and only very few submissions were delayed. For the products that have already completed the specific obligations, the granting of CMA provided regulatory approval on average 4 years earlier, as compared to when a standard marketing authorisation could be granted.

One of the key issues, particularly in EU, is that early access based on reduced clinical data and a conditional approval may complicate subsequent relative effectiveness and cost-effectiveness evaluations by health technology organisations and payers. An analysis of reimbursement decisions for conditionally authorised medicines in oncology has been reported in the literature. Some delays have been observed in terms of the timelines for reaching a positive HTA recommendation, but the delays are clearly shorter than the average time required to generate comprehensive data for a "standard" authorisation (Martinalbo et al. 2016).

The conditional marketing authorisation must be distinguished from the marketing authorisation under "exceptional circumstances", based on Art. 14 (Commission Regulation (EC) No 507/2006) of Regulation (EC) No 726/2004 and Art. 22 of Directive 2001/83/EC. Authorisation under exceptional circumstances is a provision that is meant to accommodate situations where comprehensive data on the efficacy and safety under normal conditions of use cannot reasonably be provided, because the indications for which the product in question is intended are encountered too rarely, because in the present state of scientific knowledge, comprehensive information cannot be provided, or because it would be contrary to generally accepted principles of medical ethics to collect such information. This authorisation is also subject to specific obligations to the applicant and may require that the applicant completes an identified program of studies within a time period specified by the competent authority. Similar to the conditional approval, this type of authorisation is reviewed annually to reassess the benefit-risk balance. The fulfilment of any specific procedures/obligations imposed as part of the marketing authorisation under exceptional circumstances is aimed at the provision of information on the safe and effective use of the product and will normally not lead to the completion of a complete dossier form the point of view of evidentiary standards.

4 Demonstration of Efficacy and Positive Benefit-Risk Balance

The concept of benefit-risk balance was introduced progressively in legislation. Initially, safety and efficacy were considered separately (an authorisation was to be refused if, after verification of the particulars and documents the medicinal product was harmful in the normal conditions of use, or its therapeutic efficacy was lacking or is insufficiently substantiated). A preamble to legislation introduced in 1975 refers to the notion that harmfulness and therapeutic efficacy can only be examined in relation to each other and that therapeutic advantages must outweigh potential risks. Finally, Directive 2004/27/EC amended Directive 2001/83/EC by introducing benefit-risk as one of the criteria for marketing authorisation and providing a definition (an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, including risks relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health), putting the balance of benefits and risks is at the centre of drug licensing decisions (Directive 2004/27/EC 2004).

In the last decade, drug regulators, the pharmaceutical industry and academia have developed frameworks that might help benefit-risk analysis and communication (Pignatti et al. 2015). The aim has been to increase transparency and possibly to improve the methodology of assessment. A number of descriptive frameworks have been implemented, aiming at better definition of the decision context, drivers of the decision, and uncertainties. The EMA uses a framework called "PROACT-URL" that is based on decision analysis (Box 1) (Hammond et al. 1999). Quantitative frameworks go several steps further and may also combined data on multiple include analytical methods such as multi-criteria decision analysis that allow more sophisticated analyses and incorporate explicit value judgements, trade-offs and uncertainty using numerical algorithms. Such frameworks are currently being explored but have not yet reached wide implementation in the regulatory context.

Box 1. The PROACT-URL framework as implemented by EMA for structuring the benefit-risk assessment

- Problem: Determine if the benefit-risk balance of the medicinal product is positive for the population described by the therapeutic indication
- Objective: Consider what is the goal of therapy. Determine what are the attributes that measure best if such goals have been achieved (e.g. efficacy and safety endpoints, PROs)
- Alternatives: Identity the alternative choices in terms of regulatory decision (e.g. standard approval, conditional approval; restrict indication; reject)
- Consequences: Compare the alternatives in terms of the objectives based on the available data. Display in a table ("effects table")

- Trade-offs: Value judgments about the willingness to forego the achievement of one objective against the achievement of another objective in case of multiple conflicting objectives (e.g. maximise efficacy and minimise toxicity)
- Uncertainties (and how to cope with them)
- Risk-attitude (given the therapeutic context and available therapies)
- Linked decisions: impact in terms of similar decisions (e.g. ongoing or future approvals in similar setting)

The EMA has also been exploring stated preference studies to elicit the preferences of patients regarding the possible benefits and risks of treatments and how such data may be used to estimate the patients' acceptability of new treatments (Postmus et al. 2016). Stated preference studies provide a systematic approach to gain knowledge about the distribution of preferences in the population and about what this implies for the patients' acceptability of specific treatments. Although the usefulness of stated preference studies in drug regulation is still not well established, such studies along with other methods, such as focus groups and expert opinions, have the potential to become an important tool for gathering patient views in a systematic way to inform regulatory and treatment decisions (Levitan et al. 2017).

5 Experience Interpreting the Regulatory Requirements

According to general requirements in pharmaceutical legislation, clinical efficacy should be based on more than one randomised active and placebo-controlled trial measuring a valid and reliable endpoint of clinical benefit. However, in oncology, deviation from such general requirements is practically always justifiable. Indeed, due to the large unmet need (no established treatment options) and the rarity of most cancers, a higher level of uncertainty about the benefits and risks is generally acceptable and still allows concluding on a positive benefit-risk balance based on a single randomized controlled trial or even single-arm trials using a historical control.

When assessing the evidence, regulators need to strike a balance between early access for patients affected by conditions with high unmet medical need versus having as complete information as possible on the benefits and risks (Eichler et al. 2008). Also, due to the manifest side effects, placebo-controlled trials have rarely been feasible. These deviations are not unique to oncology and are particularly common for orphan medicinal products. For instance, considering all therapeutic areas, out of 104 orphan medicinal products approved by 2015, 3 (3%) were approved on the basis of case studies or compassionate use programmes, and 9 (9%) were approved on the basis of published data only. For the 37 oncology products in this series, 11 (30%) were approved on the basis of non-randomized controlled trials and 2 (5%) were based solely on bibliographical data. However,

for oncology applications submitted to EMA between (1995 and 2015), the probability of success associated with submissions based on non-RCTs (i.e. single-arm studies, published literature, case studies) as the main evidence of efficacy was 42/57 (74%) compared to 165/209 (79%) for RCTs.

To understand why such deviations are possible, it is important to stress that assessment of the benefit-risk balance is a much more comprehensive exercise than simply observing if the *P*-value of the primary treatment comparison of the pivotal study has met the 5% threshold. The benefit-risk balance is sometimes a complex problem of balancing multiple efficacy and safety outcomes from multiple non-clinical and clinical trials, the associated strength of evidence and uncertainty, using value judgments.

Whilst the purpose of this section is to highlight situations where deviations from the more conventional evidentiary standards are sometimes possible, a word of caution is inevitable. High unmet need and rarity of the disease cannot be used to justify poor data quality or insufficient evidence of efficacy and safety. Furthermore, the absence of adequately conducted RCTs has been the single most frequent reason for rejection of drug applications in the past (Pignatti et al. 2002). All phases of clinical investigation must be designed, implemented and reported in accordance with GCP although the implementation in the context of each trial may be proportional to the risks and complexity of the trial and prior knowledge of the product. GCP inspections may take place as part of the verification of applications for marketing authorisation or as part of the verification of applications for marketing authorisation.

6 Orphan Medicinal Products, Protection, Exclusivity and Other Incentives

The aim of the legislation on orphan medicinal products is to stimulate research and development of medicinal products for rare diseases by providing incentives to sponsors in order to ensure access to treatment for patients suffering from rare diseases. There are two EU Regulations covering orphan medicinal products: Regulation (EC) No 141/2000 and its implementing regulation, Commission Regulation (EC) No 847/2000 (Regulation (EC) No 141/2000, Commission Regulation (EC) No 847/2000). The former set up the Committee for Orphan Medicinal Products (COMP) within the Agency, responsible for evaluating applications for orphan designation, with three patient representatives elected as full members. The COMP adopts an opinion and forwards this to the European Commission for adoption of a decision.

For medicinal products designated as orphan and subsequently approved, there is a protection against direct competitors in the form of market exclusivity. If an orphan product is granted a marketing authorisation, the Agency and the Member States are prevented, for a period of 10 years, to accept another application for marketing authorisation or extension of indication of an already authorised product, in respect of substances with similar structure and mechanism of action, for the same therapeutic indication as the authorised orphan product (Table 1).

Table 1 Summary of market protection and data exclusivity in the EU pharmaceutical system

Type of MA	Period of protection	Extension of the protection	Other incentives
Standard MA (art 8(3))	8 years data exclusivity +2 years market protection	+1 year market protection for extension of indication with significant benefit or +6 months extension of the SPC for completed PIP 1 year data exclusivity for new indication for well-established substance (relative to indication only)	**SME**: 100% reduction to the total applicable fee for administrative services, post-authorisation activities (micro enterprises) 90% reduction to SA, scientific services, pre- and post-authorisation inspection 40% reduction to post-authorisation activities Fee deferral until the outcome of MA application (positive, negative or withdrawn application) Conditional fee exemption, where SA is followed and a MA application is not successful
Orphan MA	10 years market exclusivity	Separate 10 years market exclusivity for new indication covered by separate orphan designation +2 years market exclusivity for completed PIP	**SME**: 100% reduction to the total applicable fee for PA/SA, scientific services, administrative services, pre and post-authorisation activities (first year only), pre-authorisation inspection 90% reduction to post-authorisation inspection **Non-SME**: 100% reduction to the total applicable fee for PA (paediatric), pre-authorisation inspection 75% reduction to the total applicable fee for PA (non-paediatric) 10% reduction for application for MA
PUMA	8 years data exclusivity +2 years market protection	+ 1 year market protection for extension of indication with significant benefit 1 year data exclusivity (non-cumulative) for well-established use substance in a new indication (relative to the indication only)	**SME** (See Standard MA) **Non-SME**: 100% reduction to the total applicable fee for SA (adult indication not requested) 50% reduction to application for MA, pre-authorisation inspection, post-authorisation activities (only 1st year)

Source Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro-, small- and medium-sized enterprises

Abbreviations: *MA* marketing authorisation; *SPC* supplementary protection certificate; *SA* scientific advice; *PA* protocol assistance; *PIP* paediatric investigational plan; *SME* small- and medium-sized enterprises; *PUMA* pediatric use marketing authorization

For orphan medicinal products authorised for indications covered by different orphan designations (conditions), each will benefit from a separate period of market exclusivity starting from the date of the initial authorisation of the first therapeutic indication for each orphan designation. It is only possible for a similar medicinal product to be authorised if any of the derogations provided for in article 8(3) of Regulation (EC) No.141/2000 is met. These derogations may be met if the marketing authorisation holder of the orphan medicinal product gives consent, when it is unable to supply sufficient quantities of the authorised product in the EU market, or, if the subsequent applicant is in a position to establish that the similar product for which authorisation is sought is "safer, more effective, or otherwise clinically superior".

Incentives for orphan medicinal products also include "protocol assistance" in the form of scientific advice, eligibility for Union and Member State initiatives which support research and development of orphan medicinal products, and the possibility to request fee reductions from the EMA.

As of September 2017, over 1900 orphan designations have been issued by the European Commission, of which so far 174 have resulted in authorised medicinal products or extensions of indications (Fig. 2), of which 76 (44%) were for cancer indications.

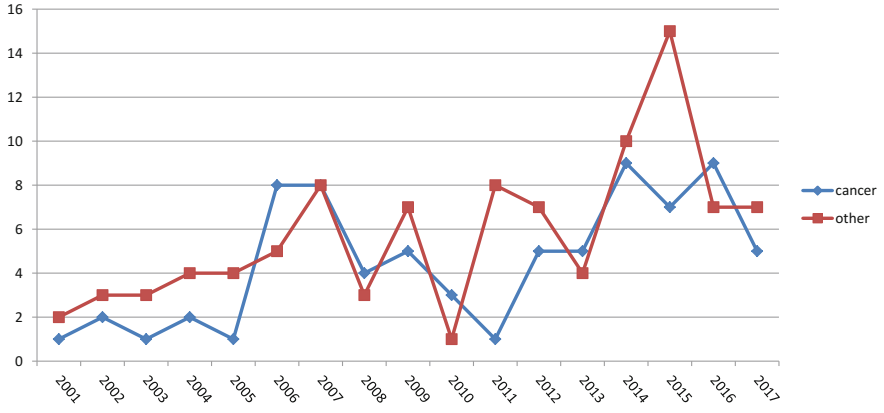

Fig. 2 Number of indication authorised for orphan medicinal products per year *Source* European Commission; pharmaceuticals—community register; http://ec.europa.eu/health/documents/community-register/html/index_en.htm

7 Paediatric Requirements for Medicinal Products

Regulation (EC) No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use entered into force on 26 January 2007 (Regulation (EC) No 1901/2006 2007). This was required since lack of authorised medicines and consequent off-label use is a significant problem in the paediatric population. The paediatric Regulation aims to promote and facilitate the development and availability of medicinal products for use in the paediatric population. To attain this goal, the Regulation places on applicants certain obligations, the main one being submission of data on the use of a medicinal product in children obtained in accordance with an agreed paediatric investigation plan (PIP) by EMA. Provided that the requirements of Regulation 1901/2006 are fulfilled, the applicants may be then eligible for a reward that may be an extension of the supplementary protection certificate (SPC), extension of market exclusivity, or data/market protection, as the case may be.

Additionally, Regulation (EC) No. 1901/2006 provides for a specific authorisation for medicinal products developed exclusively for use in the paediatric population: the paediatric use marketing authorisation—PUMA. This authorisation can be requested for a medicinal product no longer covered by intellectual property rights and may retain the existing brand name of the corresponding adult product. Medicinal products that have received a PUMA will benefit from the data and marketing protection periods set out in Directive 2001/83/EC (see Table 1).

New medicines for children with cancer that were recently authorised based on data from studies in agreed PIPs include everolimus (subependymal giant cell astrocytomas, 2011), imatinib (acute lymphoblastic leukaemia, 2013), dinutuximab (neuroblastoma, 2015), asparaginase (acute lymphoblastic leukaemia, 2016), vandetanib (medullary thyroid cancer, 2016) (Table 2). Overall, paediatric oncology has been identified as a neglected therapeutic area as little progress has been made with new and better treatments for childhood cancers especially if compared to adult cancers, and this was attributed in part to the difference in clinical conditions between adults and children (Table 2) (European Medicines Agency 2016a).

8 Efforts to Improve Timely Access to New Medicines

The "adaptive pathways" approach is part of the European Medicines Agency's (EMA) efforts to improve timely access for patients to new medicines. "Adaptive pathways" is a scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine. The approach makes use of the existing European Union (EU) regulatory framework for medicines and aims to improve patients' access to medicines in cases of high

Table 2 Active substances of centrally authorised medicines for paediatric oncology indications

Authorised before 2007	Authorised from 2008 onwards
Busulfan[IND]	Everolimus[IND PIP]
Clofarabine	Mifamurtide[NEW]
Nelarabine	Mercaptopurine[b NEW]
–	Asparaginase[a NEW]
–	Asparaginase (recombinant)[PIP NEW]
–	Temozolomide[IND]
–	Imatinib[IND PIP]
–	Dinutuximab [PIP NEW]
–	Daunorubicin[IND]
–	Etoposide[IND]
–	Idarubicin[IND]

Source EMA 10-year report to the European Commission on the experience acquired as a result of the application of the Paediatric Regulation. https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf

Note NEW = newly authorised including for paediatric use. PIP = authorised based on studies in an agreed PIP. IND = new paediatric indication for already authorised medicine

[a]Asparaginase was previously nationally authorised. In 2015, it was authorised via the centralised procedure

[b]PIP agreed. However, authorisation based on well-established use

unmet medical need. To achieve this goal, several approaches are envisaged: identifying small populations with severe disease where a medicine's benefit-risk balance could be favourable; making more use of real-world data where appropriate to support clinical trial data; and involving health technology assessment (HTA) bodies early in development to increase the chance that medicines will be recommended for payment and ultimately covered by national healthcare systems. Adaptive pathways are not new regulatory routes for medicines. The difference is in the way medicines development will be planned to better meet the needs of patients with serious conditions for whom there may be no suitable treatments. Between 2014 and 2016, the EMA conducted a pilot to explore the concept and published a report about a workshop on the evaluation of the pilot and planning of next steps (European Medicines Agency 2016b). The need for continued efforts to improve access to medicines and ensure healthcare systems are sustainable was recognised. EMA is expected to build on the experience gained from the adaptive pathways pilot within the existing mechanism of scientific advice, which provides for early multi-stakeholder dialogue.

Scientific advice is a voluntary procedure that allows non-binding discussions with EU regulators at any stage of the development process, e.g. on manufacturing issues, non-clinical testing and on the design of clinical trials. In order to address the increased complexity of market access of cancer drugs in the EU,

multi-stakeholder early dialogue pilots have been initiated recently, including developers, regulators, health technology assessment bodies and price and reimbursement decision-makers.

In addition, the EMA has recently launched a new scheme (PRIME for PRIority MEdicines) to strengthen support to drugs that target an unmet medical need. The scheme focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. To be accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. This scheme is open to all companies including micro-, small- and medium-sized enterprises (SMEs) and applicants from the academic sector.

9 Guidelines on Clinical Drug Development of Anticancer Medicinal Products

The CHMP guidelines on the evaluation of anticancer medicinal products in man provide guidance on all stages of clinical drug development for the treatment of malignancies, including drug resistance modifiers or normal tissue protective compounds (European Medicines Agency 2012a). The guideline was first adopted in 1996 and revised in 2001 and 2003, focussing on conventional cytotoxic compounds. In 2005, a major revision was undertaken, aiming at covering non-cytotoxic compounds, to expand on the sections on exploratory trials and to provide more guidance with respect to methodological issues. Later, various appendixes followed, including methodological issues related to the use of PFS (European Medicines Agency 2012b), the use of patient-reported outcomes (European Medicines Agency 2016c) and various disease-specific guidelines, including non-small cell lung cancer (NSCLC), prostate cancer, chronic myeloid leukaemia (CML), myelodysplastic syndormes (MDS), haematopoietic stem cell transplantation (HSCT), breast cancer, pathologic complete response (pCR), neoadjuvant treatment, surrogate endpoint, minimal residual disease (MRD) and chronic lymphocytic leukaemia (CLL) (European Medicines Agency 2016d). A recent revision (revision 5) has focused on safety collection, reporting and communication. The revision was motivated by changes in the therapeutic landscape, new classes of drugs, new regimens and with other types of adverse drug reactions, requiring additional analyses to evaluate the risks (e.g. time-dependent, off-treatment). Also, guidelines for reporting of toxicity in the summary of product characteristics have been introduced.

Over the years, one of the most debated aspects has been the choice of endpoint in RCTs designed to establish the efficacy of cancer drugs and that will form the basis for regulatory approval. For regulators, the choice is driven by the need to be able to perform a benefit-risk assessment, i.e. to be able to quantify what is the treatment effect in terms of clinically relevant effects, in order to demonstrate that the investigational product provides clinical benefit. Acceptable primary endpoints

include cure rate, OS and PFS/DFS, and QoL. Convincingly demonstrated favourable effects on survival are, from both a clinical and methodological perspective, the most persuasive outcome of a clinical trial. However, there are many reasons why differences in survival are often difficult to observe. Apart for the more obvious reasons (cancers that are too rare; trials in which control group patients cross over to the experimental treatment after progression), multiple subsequent lines of effective treatments may make the effect of a drug used in earlier lines difficult to detect (unless the effect or the trials are unrealistically large). More importantly, when there is early evidence of dramatic activity based on objective response and duration, and no good therapeutic alternatives are available, early approval mechanisms are used to bring the drug to patients even in the absence of evidence from randomised clinical trials. QoL is also often difficult to assess for a number of reasons, including when double-blind trials cannot be conducted or missing data; multiplicity also makes it difficult to draw conclusions on the basis of single items or domains of a QoL instrument. Therefore, QoL is rarely used as the primary efficacy endpoint in cancer clinical trials and convincing clinical benefits in terms of QoL are only rarely shown. This however does not mean that EMA does not value such studies, which are encouraged in EMA guidelines even if often they do not lead to robust conclusions (European Medicines Agency.2016b).

Prolonged PFS/DFS as such, however, if of sufficient magnitude is considered to be of benefit to the patient. PFS has been the efficacy outcome on which many cancer drug approvals are based for both solid tumours and haematological malignancies (Fig. 3), with the justification that, if of sufficient duration, with acceptable toxicity and no detriment in overall survival, prolonging PFS will delay worsening and onset of symptoms. This is considered to reflect an intrinsic clinical benefit and not a "surrogate" for overall survival requiring subsequent confirmation. Objective response rate is generally not an accepted endpoint of intrinsic clinical benefit. Approvals based on this endpoint are often based on dramatic activity in terms of response rate and duration in single-arm trials in situations of high unmet medical need. Such approvals, which are more frequent for haematological malignancies than solid tumpours, are generally conditional and are followed by confirmatory data in related indications or approvals under exceptional circumstances.

The choice of primary endpoint should also be guided by the relative toxicity of the experimental therapy, but e.g. expected survival after progression, available next-line therapies and the prevalence of the condition must also be taken into account. Irrespective of chosen primary endpoint, it is emphasised that it is the magnitude of the treatment effect on all relevant outcome measures that forms the basis in the benefit—risk assessment. When OS is reported as secondary endpoint, the estimated treatment effect on OS should ensure that there are no relevant negative effects on this endpoint, in most cases by showing trends towards superiority. In situations where there is a large effect on PFS, or if there is a long expected survival after progression, and/or a clearly favourable safety profile, precise estimates of OS may not be needed for approval. When OS is reported as primary endpoint, consistency is expected as regards effects on PFS.

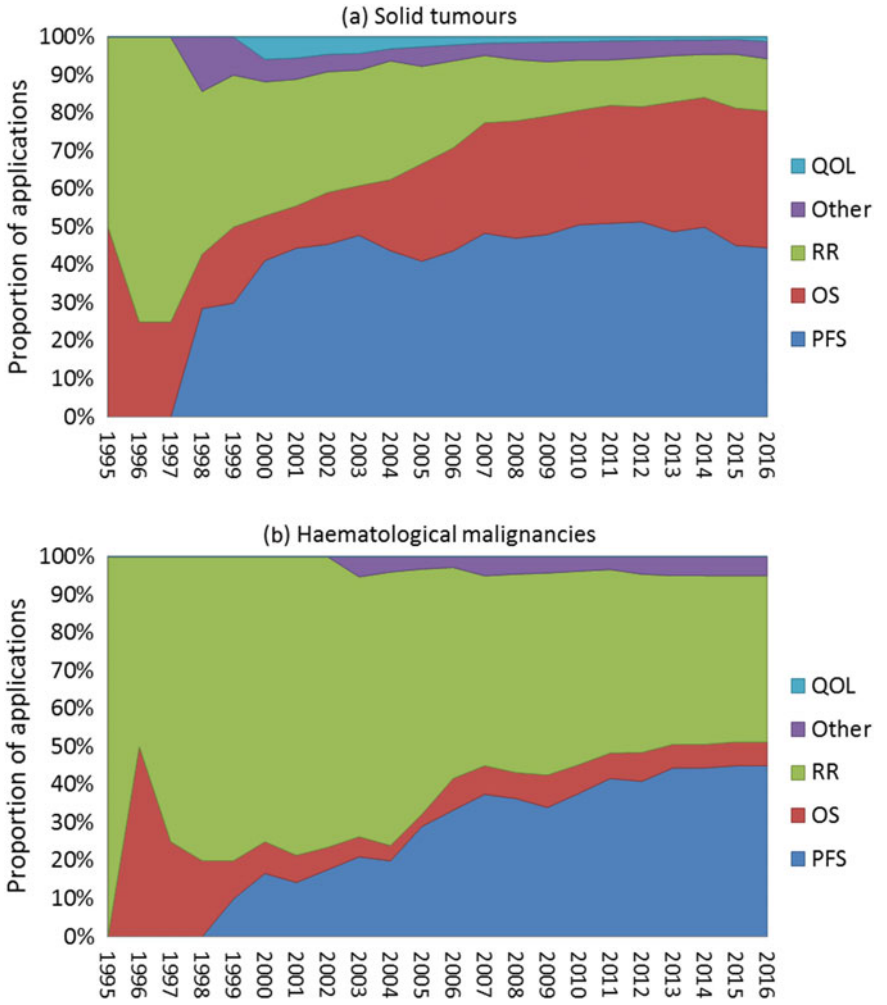

Fig. 3 Cumulative proportion of approved indications by main endpoint for new cancer products or additional indications, by year of approval

In patients with tumour-related symptoms at baseline, symptom control, if related to anti-tumour effects, is a valid measure of therapeutic activity and may serve as primary endpoint in late line therapy studies, provided that sources of possible bias can be minimised. In certain cases, time to symptomatic tumour progression may also be an adequate primary measure of patient benefit.

There are also examples where tumour response-related activities, e.g. limb-saving surgery may be reasonable primary measures of patient benefit. Analyses of location- or cause-specific events, however, should in general be

avoided as the focus may be drawn away from the main objective, namely the overall success of the treatment strategy in question.

Biomarkers convincingly demonstrated to reflect tumour burden can be used, in combination with other measures of tumour burden, to define tumour response and progression, an example being multiple myeloma and the M-component. For new classes of compounds, however, it has to be demonstrated that the marker is a valid measure of tumour burden and that no bias in the assessment is introduced, e.g. through differential suppression of the tumour marker.

9.1 Summary

Over more than 50 years of EU pharmaceutical legislation and more than 20 years since the EMA came in operation, a great deal has been achieved in terms of medicine development and in terms of setting up a robust regulatory framework. Learning from the thalidomide tragedy that acted as catalyst, the most evident achievement has been providing Europe with the centralised procedure for assessment and authorisation. This is possible thanks to thousands of experts from the national competent authorities in the EU Member States and a number of key players such as the EMA and the European Commission, working together to provide European citizens with safe and effective medicinal products.

Transparency and patient involvement have naturally evolved within the system. In 2000, the COMP was created, with three patient representatives elected as full members, an innovative response to patients' involvement in the authorisation processes. Research into paediatric medicines has also benefited greatly from the EU pharmaceutical legislation although oncology has been somewhat neglected owing to the different biology of many cancers between adults and children. Alongside legislation, a number of new concepts have been developed such as "adaptive pathways" that allow regulators to inform drug development by planning ahead together with other stakeholders and gather supportive evidence from observational studies and other sources in the real world.

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Prioritization not Rationing in Cancer Care

Nikolaus Knoepffler, Jürgen Zerth and Martin O'Malley

Abstract

Conditions of scarcity impact healthcare services for cancer patients. This is the unpleasant reality for nations, local governments, hospitals, and even individual doctors. This means that medical services judged by objective standards as potentially effective by medical professionals are limited because of financial or access scarcity. With this situation of scarcity as premise, one must raise the ethical question of how to deal with scarcity while respecting fundamental principles of human dignity and human rights. This chapter focuses on the German healthcare context where dignity and rights form the basis and framework for medical ethics. Accordingly, in Germany, rationing medical services for life-threatening diseases has been traditionally and appropriately criticized and prohibited. Granting a situation of scarcity, however, some prioritization becomes increasingly necessary. Thus, there is present need for careful ethical analysis of non-emergency regulatory prioritization principles and protocols. Above all, analysis and conclusions must preserve and foster society's deepest moral commitments.

Keywords

Prioritization · Rationing · Human dignity · Ethics · Oncology
Scarcity of resources · Healthcare

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1 Introduction

This chapter focuses specifically on the German healthcare system that is presently faced with particular financial strains of a legally mandated but privately provided health insurance system. Health insurance costs are limited by legal and market restrictions, while demographic trends indicate increasingly disproportionate geriatric participation in the system.[1]

Stated simply, more elderly patients need more cancer care, and that care is becoming increasingly sophisticated and expensive. The probability of developing cancer increases with age, and increasing life expectancy leads to more frequent malignant prognoses. Additionally, medical advances in cancer therapy, including potentially personalized medicine, are offering hope in the form of successful therapies, but often at great expense. Some advances actually reduce costs, as the following example from Guttmacher et al. (2004) shows. A four-year-old John has acute lymphoblastic leukaemia and tolerates chemotherapy well with minimal side effects. A key part of his follow-up is daily oral mercaptopurine, which is associated with diminished life expectancy. However, a genetic test showing that John has a genetic mutation that limits the enzyme that metabolizes mercaptopurine allows him to receive a reduced daily follow-up dosage. Without this new screening capacity, normal administration of mercaptopurine would have diminished his prognosis, but the genetic screening and adjusted treatment result in complete remission. Such cases of advanced science reducing health costs do not characterize overall trends, however, and cancer-care costs are expected to increase significantly in the near future.

In the foreseeable future, financial costs will increase as new drugs are launched to address specific disease groups and subgroups. These costs are associated with high development costs and price developments resulting from strategic actions in a market segment. For example, orphan drugs for patients with very rare genetic dispositions for specific kinds of cancer are publically supported in an effort to encourage research and development (cf. Hatz et al. 2014; Greiner and Knittel 2011). Public support includes exemptions from certain testing requirements, extended patent exclusivity, and financial compensation. Such support involves a benefit calculus that balances significant per patient costs against minimal expected health outcomes. A prominent example of high-priced cancer drugs is Provenge (from Dendreon), costing 99.000 dollars in the USA for a prostate cancer treatment with an expected benefit of four additional months of life (Anassi and Ndefo 2011). Barring other expected benefits of public support for such treatment, how can one make an ethical argument that suggests limits to investment in extending human life?

Two points must guide an approach to answering this question:

[1]The article covers with much greater elaboration the same ground as Knoepffler (2015), Knoepffler and Daumann 2017: 105–113.

The first assumption is that everything possible has been done to use scarce resources responsibly. For example, active surveillance of a diagnosed prostate carcinoma often presents much better outcome options than an expensive and often chosen prostatectomy (Gigerenzer 2013).

Secondly, social solidarity cannot mean that healthcare resources must be allotted to every candidate that can benefit even marginally from a medical treatment. Along these lines, as president of the German Medical Association Jörg-Dietrich Hoppe stated: "The gap between what we can afford and what we can pay is continually changing. […] In the current system, I see only one way out of rationing, and that involves a discussion about prioritization" (Bundesärztekammer Pressemitteilung 2010). Hoppe's recommendation remains relevant and this discussion engages questions regarding rationing and prioritization as relevant specifically to Germany's healthcare system, and thus not as a global justice question (See Knoepffler 2008). In a first step, a number of key concepts are clarified and the ethical framework is outlined with respect to the economics of health care. After showing why rationing is a violation of the principle of equality, criteria are developed according to which prioritization can be ethically integrated into Germany's healthcare system according to an "order ethics" approach. Decisions regarding prioritizing ought not to be shouldered by individual medical health providers or even managers of such care. Rather, this approach seeks to inform regulatory frameworks that support optimizing doctor–patient care in a way that conforms to existing ethical principles and respects the challenges of economic scarcity. Such a framework recognizes limits to care posed by economic realities, but simultaneously integrates incentive systems for healthcare providers to innovate in providing services to optimally meet individually discerned treatment plans and developing new organizational solutions for upcoming healthcare problems.

2 Clarifying Terms

The terms prioritization, rationing, and rationalization often lack careful differentiation. For example, prioritization and rationing are often used synonymously. For the German context, a significant opinion by the German Ethics Council established a basic reference point for present terminological discussion, "Medical benefits and costs in health care: The normative role of their evaluation" (cited here as Deutscher Ethikrat 2011). This chapter carefully advances the definitions of that opinion and maintains a strict differentiation between rationing and prioritization.

"Rationalization" is the judicious and ethically obligated form of discerning the most efficient and effective medical management in the context of a scarcity (See Knoepffler and Daumann 2017: 107). The German Ethics Council defines it as "the complete utilization of economic efficiency reserves" (Deutscher Ethikrat 2011: 2.3:17). Rationalization can be understood as a reasonable and therefore compelling

approach that saves valuable resources in scarcity context while providing basic and needed services and therapies according to evidence-based principles.

"Rationing" is used here, in contrast to rationalization, to describe medical decision-making reasoning in a scarcity context that limits services or therapies despite well-established medical need or evidence-based benefits, despite the fact that in principle, all persons have a right to that service or therapy.

This rationing concept should not to be confused with classic economic rationing, according to which each person decides their own distribution of limited resources, or in another version, according to which the state decides, using its limited resources (Weissberger 2008).

"Prioritization", in distinction to rationing, describes "the systematically justified establishment of ranking—in health care, the drawing up of ranking lists, or league tables, of medical interventions" (Deutscher Ethikrat 2011: 2.5, 22). Prioritization as defined in the German Ethics Council Opinion is potentially ethically neutral insofar as the decision-making model it outlines does not necessarily indicate a situation of limiting medical interventions with low priority on the basis of scarcity. Rather, prioritization establishes category differentiation first in a vertical axis with respect to a single condition, disease, or problem. For example, the vertical axis deals with a single diagnosed malignant cancer type and differentiates the full scope of potential management paths according to a set of criteria such as medical benefit. Within a prioritization decision-making model, certain treatment regimens have greater or lesser relative value for a given patient.

Secondly, prioritization establishes a differentiation on a horizontal axis among groups of conditions or patients: "an overarching ranking is effected across a number of different groups of conditions and patients and/or care objectives (e.g. the treatment of persons suffering from heart disease or of tumour patients)" (Deutscher Ethikrat 2011: 2.5, 22). The best-known example of such a horizontal prioritization occurred in Oregon at the end of the 1980s. In this highly controversial first prioritization, the state was directed to use its (government-funded) Medicaid programme for dental treatment, but not for appendicitis (Perry and Hotze 2011).

The German Ethics Council describes prioritization neutrally, noting that it could be used as a preparation for rationing if, in a second stage, lower ranked treatments (vertical) or disease groups (horizontal) received denied-funding recommendations. The Ethics Council excludes this possibility in Germany however, because "given the comprehensive access to medical treatments … such a situation is unlikely to arise" (2.5, 23). This optimistic viewpoint evades rather than addresses the situation of scarcity, potentially pushing the reality of rationing underground. A more adequate and ethically transparent approach is to recognize the situation of scarcity and develop implementable prioritization models that prevent implicit rationing. The present recommendation is that prioritization treats all patients equally according to their medical conditions. With equity assured, patients would receive services and therapy according to a regime sequence that may in no way contradict principles of human dignity and human rights, while scarcity concerns could influence decisions regarding potential interventions.

The decisive factor for dealing with this question is the structure of the ethical framework insuring respect for human dignity and human rights. Before this, ethical reference framework can be further elucidated; however, a reference to the health-economic perspective must address the issue of scarcity.

3 Economic Discussion Regarding Scarcity and Medical Decision-Making

Rationing in health policy context is understood as broad limitations of potentially medically necessary measures due to scarcity. As argued above, rationing is a disproportionately economic approach to society-level issues of scarcity. Though rationing garden water use during a drought is a potentially legitimate approach, such justification is far from the situation of healthcare resource allocation and its limitation frameworks that apply to situations of non-discretionary needs (cf. Olsen 2011). Rationing that limits health care is objectionable and deserves resistance. The reasoning behind the objection is that rationing approaches to scarce resource allocation is too short-sighted and does not take account of the specific ethically established social needs that health care addresses (cf. Dietz 2011). Such social needs are integrated in principles of dignity, equality, respect, etc., and must be integrated into the decision-making evaluation as much as market demands such as costs and availability of services. Social claims, including the principle of non-dependent access to health care, serve as a complement to individually tradable property rights (cf. Schüller 2002).

A society such as Germany values and appropriately protects the institutional structures that insure minimal standards of living. Some institutionalized social structures (including ethical and legal structures) protect minimal standards of life quality, and some structures insure freedoms to hold and use resources with significant discretion. There is value in conceptually differentiating the spheres of health care, markets, and law. And yet, our concepts cannot disregard the inherent interdependence of these spheres. Separating economic from social values is what rationing tends to do and is the marker for differentiating rationing and the prioritization principles that will be outlined below.

Order ethics as an economic approach focuses upon legal frameworks that do not ignore market realities, but rather integrates social values on a level of rule-setting so that the market incentives and limitations are ordered to function effectively. A social contract or contractarian view underlies this approach such that legitimate social organization must ultimately serve the interests of citizens. These interests include basic protections of ethics and law, but also include interests of material well-being that a productive market can serve. The contractarian approach, such as outlined in Rawls and others, recognizes the existence of various levels of rule-setting that are relevant to health care. As a basically contractarian approach, order ethics pays careful attention to differentiating the rule frameworks of each of these levels. It is important, according to this view, to set the rule frameworks to

incentivize rule-abiding appropriate to each level such that socially desired outcomes are achieved. Thus with respect to health care, pharmaceutic firms should be given a rule framework that applies equally to all firms so that they are incentivized to invest in drug development. There is overlapping interest in having improved drugs in the market with prices that are competitive, feasible, effective, and contributing to both public health and market vigour. Patent laws and market completion need to be balanced along with other pressures, and the telos of public health remains overriding. This macro-level rule structure is distinct from the micro-level of individual medical decision-making of doctors and patients.

A basic axiom of medical ethics, passed down in the Hippocratic Oath, is "first, do no harm"—primum nil nocere. The axiom not only warns against dangerous or harmful care, but also gives support to legitimately refrain from medical services that cannot be reasonably expected to provide benefit in terms of overall life quality. Health care presents many economic pressures and dynamics that are unique to the industry. For example, the Dartmouth Atlas Project studies distribution and use of health care and argues a strong correlation between availability and use of treatments and services. This supply-sensitive dynamic essentially means that rather than perceived need or science-based decision-making, resources are employed regionally according to the services which happen to be available (Dartmouth Atlas Project 2007). If more expensive acute-care services are available, those resources will most likely be used without a necessary improvement in desired medical outcomes.

With respect to economics, two distinct points are relevant:

(1) An expansion of medical capacities and/or services is associated with higher opportunity costs in various alternative uses if
(2) There is no clear consensus regarding the best direction for further development of health care (cf. Zerth 2015: 127). The situation remains in flux because of the diversity regarding need and demand for health care within groups relevant to this issue, namely medical experts and health industry, patients, and society more generally. Defining an overall benefit basket as a current interpretation of rationing must be adjusted to diversities of healthcare demand and supply mentioned above. Decentralized healthcare demand catches the diversity of complex demands more appropriately when a rule-based form of competition and evaluation is in place and institutionalized to improve the level Q. With social pluralism as background, the issue at stake is planning a move from the present environment Q1 (representing a kind of a benefit-basket system), to a future a high-level public healthcare environment Q2 that is socially legitimate and as efficient and effective (rationalized) as possible. Moving from Q1 to Q2 will be achieved in the most efficient way with a clear and science-based approach that integrates realistic considerations of healthcare economists (cf. Oberender et al. 2016: 155). Thus, the decision-making models necessary for achieving Q2 need to take into consideration the micro-economic realities that are at play in relationships among patients, doctors, insurance agencies, and the constraints public policy officials have to cope with by defining and

enhancing social claims. Here, a regulated form of "managed competition" (cf. Enthoven 1993) can be an efficient instrument to include various interests and the need of an overall implementation of innovation in health care. Patient wishes are very relevant in these considerations, but so are the financial realities of scarce resources in a situation of spiralling costs. In the German healthcare system, the idea of a "solidary-based competition order" is an attempt to combine competition with social claims.

With respect to priority-setting principles, an ethical decision-making framework must be structured (and judged as legitimate) by the degree to which the rule system itself is designed to efficiently and productively incentivize socially desirable results, and to limit or de-incentivize socially undesirable results.

4 Ethical Decision-Making Framework

If ethical and legal issues and questions are not clearly differentiated, analyses are susceptible to error. This is especially the case with analysis of health policy. This paper is concerned primarily with ethical considerations and does not propose legal recommendations even as the relevance of law and politics is recognized for rule-setting in health care. Nevertheless, attention will be focused here upon scope of ethical possibilities and considerations relevant to decision-making in multi-levelled organized health systems. The ethical framework is also intentionally developed to be relevant to and consistent with existing legal framework of Germany's Federal Republic. As such, it is appropriate that the guiding ethical principle is the principle of human dignity according to which every human being has subject status, and a principle of equality as regards to every person's fundamental rights (cf. Knoepffler 2004). The challenge of prioritization for oncology is clearly protecting three fundamental and closely linked rights, namely, the right to life, physical integrity, and self-determination. The right to life is not a purely defensive claim, but is linked to the right to receive adequate medical care. For example, a person diagnosed with life-threatening cancer has a right to life-preserving care. Following the principle of fundamental equality, patients with comparable oncological disease are entitled to comparable treatment—not better or worse based upon some sorting criteria such as profession, race, gender, or income. This equity claim goes much further than the general social claim to sufficient, necessary, and effective treatment, as it could be formulated in a social code, for example. The equality principle does not exclude context differences relevant to prioritizing care, however. Thus, a 25-year-old patient with a pancreatic head tumour has a greater priority claim to treatment than a 92-year-old patient suffering from numerous life-threatening conditions. The decision-making model respects the principle of equality even in giving priority to the 25-year old and recommending more palliative cancer therapy for the 92-year-old multi-morbid patient.

The Swedish solution uses a similar approach, now well-established and carefully studied after twenty years, although it does not specifically refer to "prioritization in oncology" (SOU 1995). The report by the Swedish Parliamentary Priorities Commission is based on human dignity as the central and anchoring principle, which is supplemented by the principles of need and solidarity: those patients who have the greatest need are given priority. Vulnerable persons must be given special consideration. It is only in the third place that the criterion of cost efficiency is given. It is a question of a reasonable relationship between the costs involved and the associated effects: improving the state of health or improving the quality of life. These are issues for the context of vertical prioritization. Different disease categories cannot be easily and meaningfully compared, but the report clarifies that life-threatening diseases receive priority over chronic diseases. And chronic diseases might receive priority over diseases that lack urgent care, despite very positive prognoses with treatment, and accompanied with significant life-quality benefits.

Similar to the German Ethics Council (Deutscher Ethikrat 2011), Germany's Central Ethics Committee (ZEKO) at the German Medical Association drafted a recommendations report in 2007, but it, like the German Medical Association in 2011, was unable to achieve comprehensive progress analogous to Sweden (SOU 1995) with respect to prioritization. ZEKO's recommendations report (2007) essentially adopts the three "Swedish" principles as the basis for prioritization, though it does so in five stages. Formal criteria are placed alongside them: transparency, comprehensible reasoning, evidence-based, consistency, respect for the equality principle, discernment of prioritization decisions and their regulation by legitimate institutions, disclosure and balancing of conflicts of interests, effective legal protection for patients who are denied benefits. Against this backdrop, the ZEKO (2007) develops a graduated model of permissible prioritization: The first-stage priority is the protection of life, protection from severe suffering and severe pain, though the protection from suffering is not really relevant to prioritization. The second-stage priority protects against failure or impairment of essential organs and body functions. Here, too, ZEKO calls for the primary use of resources, even in the case of a resource shortage. In both cases, strictly the equality and, therefore, the non-discrimination requirement apply. In the first two stages, rationing is distinctly excluded; in subsequent stages, limitation dynamics call for vigilance. The third stage deals with less serious cases or temporary impairments of well-being. The fourth stage concerns for non-life-threatening healthcare services often described as elective or discretionary. In the case of cancer care, level discernment is context-relevant. Cosmetic interventions, for example, could be judged level three for a patient post-surgery or undergoing chemotherapy. This form of discernment is integral to the art of medical care, and prioritization protocols are not intended to interfere with medical judgement of need, but rather to respect the medical decision-making judgement and its ability to discern distinctions in care necessity. Based upon that prioritized judgement, however, it is reasonable to maintain that some services could receive limited financial support.

5 Heterogenization and Comparison Analysis Provide Innovation-Oriented and Value-Generating Framework

Both the Swedish Commission's Report and ZEKO convincingly demonstrate that rationing medically-necessary or at least evidence-based-effective services and therapies cannot be an acceptable solution in oncology for life-threatening diseases. The rationing of scarce resources in an equal distribution system merely with reference to economic scarcity is incapable of establishing a decision-making regimen that protects fundamental social and ethical principles as well as the freedom of individual healthcare providers to provide care that optimally meets patients' needs in cost-effective ways. It might theoretically integrate the equality principle in attempting to distribute scarce goods equally, but human dignity requires integration of individually-tailored care.

One can appreciate the attractiveness rationing may represent as a seemingly simple solution to the scarcity issue. However, rationing in healthcare contexts has proven ethically unsupportable given the human dignity principle as understood in the German context. Rationing is not merely a recognition of scarcity—it is limiting resources to individuals based upon generalized per-person allotments, whether that is calculated in fixed monetary, service/treatment units, or percentage calculations. Such de-personalized, generalized, and limiting approaches are clearly suboptimal for many reasons. Ethicists in Germany have successfully articulated the need to protect human dignity, but ethics must be more than a practice of error avoidance. Non-rationing, person-centred approaches allow much greater creativity in effective care that may nevertheless also integrate cost-effectivity measures. Ethics can also be a force for aiding innovation in creating value in terms of the conditions of social and material well-being, in addition to public health goals (see O'Malley 2013).

Constructing priority systems for health care that integrate the full range of social, ethical, and market principles is significantly more complex than rationing (see Diederich et al. 2015). For example, does a patient with blood in their stool receive a gastroscopy, because such a treatment could reveal a malignant tumour, though this is not a high probability? If a rationing system were in place, perhaps every patient presenting such symptoms would have a right to such treatment and be placed on the waiting list for screening. In Germany's present system, doctors have incentives to grant quicker appointments to patients with private insurance over state-mandated insurance. A difference in patient appointment conferrals would confer a proportionate equity challenge because private insurance patients' timelier diagnosis would lead to timelier treatment for potentially rapidly advancing stomach tumours. Paradoxically, the equity logic of equity rationing (as opposed to prioritization) can present perverse incentives, and limits for doctor decision-making, rather than freedom and creativity to judge whether other factors indicate more or less likelihood of stomach cancer and thus the need for expensive tests or other specific treatments. Such limitations effectively contradict the medical ethos, which includes the principle of care and justice. Thus, doctors are pressed to ration themselves and thus have to make decisions for budgetary reasons rather than

medical indications. Patients depend upon expertise of medical and insurance experts, and thus transparency is an issue. Another issue at stake is the related goal of self-determination in situations of covert or implicit rationing, which is experienced temporally in the form of waiting periods, and regionally insofar as some regions are better served by sufficient healthcare providers and medical centres.

Healthcare decision-making models based upon rationing are not only ethically problematic, such designs are also inherently structurally flawed. With models integrating rationing, patients and doctors tend to experience healthcare services as limiting, falling short, and thus failing to provide desired goods. Rationing practices and dispositions require that practitioners and patients envision (1) healthcare services as a basket of potential but scarce goods, (2) patients as deserving but insatiable consumers, and (3) doctors as gatekeepers tasked to distribute limited goods and deny those goods when the basket is empty.

A more dynamic healthcare decision-making paradigm could be developed by testing various provider models utilizing distinct prioritization protocols for both axes, vertical and horizontal, but especially the latter. By allowing various models to exist in conditions conducive to careful monitoring over time for ethical compliance, effectiveness, and efficiency, there is much potential for long-term gains in goals that serve the public health (development from Q_1 to Q_2) (cf. Oberender and Zerth 2014). Comparison studies on nation-level healthcare provision and costs are abundant and insightful. Would it be possible to allow experimentation on models within Germany? Reluctance to do so is perhaps a result of an unwillingness to deal with the ethical implications of recognizing healthcare scarcity. Yet there is an ethical duty to gain knowledge and experience for long-term effectiveness and efficiency.

For example, competitive health system models can be designed such that the horizontal differentiation is increased at a time t_0, with a clear goal of improving the prioritizing rules in order to provide the best possible care for all eligible persons. It is precisely with regard to recent developments in oncological care that longitudinal experimentation and decision-making model deliberation is warranted. Given supply-sensitive nature of healthcare economics and present and expected future growth in oncology expenditure, cost-effectiveness with respect to specific oncological therapies and achievement of clear outcome goals is needed. A decentralized competition-based strategy for a "controlled experimentation" would help to generate needed knowledge about outcome research as well as participation feedback of the defined users. However, such form of controlled experimentation within a managed care environment is only allowed subsequent to the prior market authorization. In consequence, such decentralized effectiveness experiments must recognize the tension between the further development of diagnostic and therapeutic options on the one hand, and the need for priority setting on the other hand. If the reluctance to experiment with priority systems is related to anxiety regarding ethical questions, then the discipline of ethics becomes a hindrance to innovation and value creation. There is some urgency for organizational innovation complementary to prioritization (cf. Cutler 2011); however, it must respect the distinctions among levels of physician–patient, institutions, and social/political decision-making.

What is needed, in sum, is heterogenization in prioritization ranking and rule-setting regimens within healthcare decision-making models. Ethical reflection can and must be integrated in a way that protects societies' deepest moral commitments, including the commitment to social flourishing (O'Malley 2013). To foster this goal, heterogenization must be part of a well-designed strategy open to continuous science-based evaluation of each respective organizational level with respect to clear benchmark, public health, and economic-efficiency goals.

Temporal/longitudinal studies can be supplemented with regional studies comparing care access, especially the difference between major urban and more rural areas, concentrating acute care in competency centres, and public health measures and strategies over and against intensive and expensive state-of-the-art medical interventions. Another common public debate concerns diminishing access to health care in rural areas; the diminishing numbers of doctors, nurses, and medical centres implies an implicit rationing experience for cancer patients. At the very least, some cancer patients may have difficult access to treatment. Does this violate equity (cf. Aggarwal et al. 2014)?

Although certain oncologic centres in Germany have particularly good reputations, the equity principle is not necessarily violated for cancer patients in rural areas as long as they receive care that meets minimum recognized standards. Additionally, major urban cancer centres that usually also function as research and development institutions play an important role in improving cancer care more regionally. Questions regarding equity may raise ethical concern if certain groups of people are excluded from the major cancer centres. However, if the access is limited because of patients' freely determined choice to live far from centres or simply to remain with local centres and familiar medical professionals, there is less ethical urgency. Times of medical emergency may also limit access at least temporarily, but that too is not an equity challenge. The key here is insuring high minimum healthcare standards that prohibit sortal (unequal differentiation based upon some sorting of human qualities such as race, gender, class, income) difference in services, therapies, or expected medical outcomes.

These prioritization considerations have dealt with health care from the perspective of care-claimant pressure, but there is also an important issue regarding the structures and incentives systems from the side of care providers. Restricting wide healthcare therapy options and capacity on the basis of evidence-based medicine would likely provide better medical outcomes. If there is a correlation between complex procedure outcomes and repetition of such services, that would be a reason to establish focused competency medical centres. Planning these centres would require priority balancing that overtly compensates for perceived and real diminishment of equal access to state-of-the-art health care. Robust testing regimens coupled with equity-sensitive priority rules and region-targeted quality standards could be developed. Moreover, heterogeneous care-provision models could be allowed to emerge that integrate regulated competition among models based upon elaborate benchmarks for care provision. Based upon cross-sectional, regional, and longitudinal studies, evidence could be established to support optimal single approaches, or even to allow continuation of pluralistic approaches. The ethical

commitments to basic principles and transparency of supporting these principles provides policy makers with the trust, expertise, and social as well as financial resources to achieve optimal care based upon carefully predetermined long-run public health goals.

The present course of action, based upon reluctance to honestly face the reality of scarcity, is a default passive response to unrestrained cost escalation. Given the supply-sensitive dynamic of healthcare systems, medical centres tend to efficiently utilize at-hand medical services, even if those services do not provide proven benefit. Thus, an incentive system for medical centres to invest in evidence-based medical service capacities can free up resources for perhaps less expensive but more effective care. It is ethically acceptable to exclude controversial treatment methods and remedies for which there is no proven need or effectiveness. But even in marginal cases, rationing is still not the recommended solution in the area of a solidarity-based health system. Rather, there is even value in marginal cases being integrated into priority-based models, as long as such marginal cases are at least integrated into the evidence-generating evaluation systems. The discussion above demonstrates that the difference between rationing and priority is more than differing criteria; as developed here, they represent fundamentally different approaches to managing public health resources.

A critical question remaining for discussion is this: Who decides what kind of treatment is necessary or not?

6 Order Ethics Provides Framework for Responsible Cancer-Care Prioritization

Rationing, as argued above, is simply not appropriate for cancer-care decision-making, as ethical commitments bind the medical community to provide equal and non-sortal access to fundamental levels of cancer therapy. In non-planned situations of resource shortages, rationalization in the forms of emergency triage strategies may provide sanction for emergency vertical prioritization measures. However, in order for such a prioritization to be appropriate, the above criteria must be respected, that is, respecting human dignity linked to the basic rights to life and physical integrity; neediness and cost-effectiveness are relevant only after the first two criteria are satisfied.

The following example shows how difficult it is to obtain a clear statement of vertical prioritization, assuming these criteria: In a clinical Phase III study, stereotactic body radiation therapy (SBRT) is compared to external beam radiation therapy (EBRT). The working hypothesis of the study assumes that SBRT is more effective for pain caused by spinal metastases than the currently used EBRT. According to current results, SBRT seems to be about 20% better than EBRT. In an accompanying study, which carries out a cost-benefit analysis, Kim et al. (2015) show that SBRT is only useful in cases where the prognostic survival is at least

eleven months; in all other cases, a quality-adjusted life year (QALY) would be more expensive than $100,000, making it a threshold decision.

Another example shows the difficulties of vertical prioritization. According to the Swedish criteria and the criteria of ZEKO, the principle of pain relief is more important than the criterion of the cost-effectiveness. However, in this case, it is not just a matter of choosing between pain relief and costs, but between improved pain relief and the associated costs. Valuing incremental effects in quality and accompanying costs is the main challenge facing post-industrialized healthcare systems.

It is even more problematic in the case, for example, of a certain, very expensive drug for the treatment of melanomas for patients with BRAF mutation (about half of all patients), vemurafenib. According to the German Medicines Commission, its costs are more than €12,500 per month (Juni 2012). This drug prolongs lifetime by approximately three months, according to a study published in The New England Journal of Medicine (Chapman et al. 2011). In combination with cobimetinib, it appears even possible to increase the survival time by further three months (Larkin et al. 2014), but cost increases are likely to increase accordingly. In February 2015, the Roche Pharmaceutical Group received the "Priority Review" status from the FDA for this drug.

The example of the treatment possibilities of melanom patients with BRAF mutation excellently shows the problems of vertical prioritization because all options are problematic with a capped budget: While there has been a procedure since 2014 to get additional resources for the use of vemuratenib, currently cobimetinib has not yet been paid for, since it is not yet on the list. If the chief physician uses these resources for this drug, resources must be limited in another place. He could, for example, reduce nursing care costs in order to remain cost neutral. The alternative would be to administer the standard medication. The regulatory response to this issue is not separate from the structure of the health system. In the case of state-financed systems of the Beveridge type, the idea of optimizing a "virtual" total budget is taken into account and thus a cost/QALY threshold value can be deduced directly. However, insurer-related healthcare systems—Bismarckian type—use indirect measures for controlling stakeholders' behaviours, namely by institutional arrangement for risk allocation between insured persons, providers, and health insurances. For both types of health systems, however, the transfer of such a decision to the medical director of the dermatology clinic is not ethically justifiable. Here, a doctor is compelled to refrain from the medical ethos, either on an evidence-based drug that prognostically triggers three months of life, or else to shrink his team, which is likely to increase the overall mortality in his clinic, so that probably also three months of life distributed. In any case, if the personnel rationalization measures are already exhausted, a deficit situation is created for nursing staff and/or physicians.

There is another ethically important problem. Suppose the director in question could administer this drug to some of the affected patients, but not to all patients, as this would blow up his budget—would it be permissible to do so? This raises the question as to whether it can be ethically appropriate to withhold an effective drug

from all patients because it is not possible to give it to all patients, so to say, it is better to give all the standard therapy to the equality injury, as some better.

Or is the alternative preferable to give all patients only the standard medication, but also all patients to point out the possibility of the new better drug? But then only the really financially strong patients can afford this medicine. Can it be reversely ethically permissible to conceal an evidence-based, successful treatment option for patients, in order not to jeopardize equality?

Against the background of the ethical framework, it is clear that concealment of a better treatment alternative is not permissible because the formal criterion of transparency is violated here. However, if society is not willing to invest more resources in health care, at least for a certain period of time, the budget of the dermatology clinic is not increased, although the evidence-based studies offer better but unfortunately more expensive treatments The condition of equality is maintained only in so far as the less effective drug is made available according to solidarity principle. This leaves open the possibility, of course, to privately purchase more expensive medication, granted that the patient is aware of such options. The delegation of healthcare expenses to the private purchase raises equity questions. Sortal differentiation of human life valuation, in this case based upon wealth, raises questions regarding equal protection of life, which is linked to human dignity. This has also been emphasized by ZEKO (2007).

Germany could tackle the equity problem like France, for example, and impose price limits on medical drugs produced by pharmaceutical companies. Whether this is enforceable remains to be seen. However, the basic problem remains that the best possible treatment will not be affordable for everyone. Alternatively, QALYs would have to be used for vertical prioritization, which would be the response of a state-financed healthcare system. In a Bismarck-style system, like Germany, the risk-sharing scheme is set up within the regulatory system (cf. Ellis and Fernandez 2013). Solution options in this context could lie in the conscious design of heterogenization in the contractual context of patient-provider health insurance, for example via the idea of developed selective contract arrangements between health insurance companies and patients, then also with limited choice of medical capacities, or by regional differentiations, for example the differences in the utilization behaviour. Important in all rather competitive concepts is the feedback of designed heterogenization to the further development of the supply level (development from Q1 to Q2). Especially in the case of innovative pressure in oncological care, it will be shown how difficult this can be. At the same time, heterogenization in the care system, while at the same time respecting the principle of the basic requirement for performance in cancer therapy, also offers an opportunity to further develop personal and patient-related care concepts with regard to the patient and quality aspects. Perhaps non-aggressive end-of-life care can be achieved that meets life-quality goals without significantly reducing or even prolonging life expectancy. Priority setting can more dynamically integrate such goal-setting strategies than rationing—or wilful avoidance of scarcity dilemmas (Temel et al. 2010).

In any case, the decisions on how to achieve vertical prioritization in oncology should be conducted in dialogue with oncologists as those who have the relevant treatment competence. However, there is also a clear differentiation between the principles of a macro-priority (which is fundamentally possible) and the impact on the micro-level, namely the specific physician–patient relationship (which is, e.g., cost coverage at the hospital level). Thus, an interdisciplinary dialogue, for example with health economists and other representatives of society, is necessary. In any case, prioritization is not a Bogeyman, and it is ethical cowardice to burden medical professionals with essentially social and political responsibilities allocating scarce resources. Healthcare decision-making models will always depend upon medical expertise, of course, but solidarity with medical professionals is also relevant here.

7 Conclusion

If one proceeds from the principle of human dignity, neither race nor gender and neither age nor self-fault are criteria to violate the equality principle. This means that in the case of cancer therapy, neither an ageing population nor other possibilities of discrimination as a means of saving money are possible in order to solve the scarcity problem. Against the background of the potential for innovation, especially in the field of cancer care, a wise regulatory approach between the general framework—definition of social claims—and micro-allocation is imperative. Decentralized health systems would have the chance, for example, to develop heterogeneous risk-sharing mechanisms with integrated analysis tools—and to use them in the patient's interest through the principle of a "managed competition". Care management strategies, which see risk management not only in the immediate financial sector, but in the overall context of a care strategy, should greatly benefit from integrating science-based decision-making principles. If one assumes that not physicians at the clinic or doctors' office should decide how a just vertical prioritization could be accomplished, but society as a whole, we should compare problem-solving among international models and examples.

Jörg-Dietrich Hoppe articulated an important future-oriented need in 2010 before he died—warning of the pressures of scarcity. Health care should be focused on the patient, and not on power, politics, or economic emergency. The argument in this paper recognizes not only the warning, but also the great potential for healthcare achievements if our ethical responsibilities recognize not only the potential pitfalls of scarcity, but the great value to be gained with courageous future-oriented healthcare analysis.

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