EXPERT REVIEW OF PHARMACOECONOMICS & OUTCOMES RESEARCH
https://doi.org/10.1080/14737167.2021.1884546

Taylor & Francis
Taylor & Francis Group

PERSPECTIVE

Potential approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and the implications

Brian Godman [a,b,c,d], Andrew Hill[e], Steven Simoens [f], Gisbert Selke [g], Iva Selke Krulichová [h], Carolina Zampirolli Dias [i,j], Antony P Martin [k,l], Wija Oortwijn[m], Angela Timoney[b,n], Lars L Gustafsson[a], Luka Voncina [o], Hye-Young Kwon[b,p], Jolanta Gulbinovic[q], Dzintars Gotham[r], Janet Wale[s], Wânia Cristina Da Silva [i,t], Tomasz Bochenek[u], Eleonora Allocati[v], Amanj Kurdi [b,c,w], Olayinka O. Ogunleye [x,y], Johanna C Meyer [c], Iris Hoxha[z], Admir Malaj[aa], Christian Hierländer[bb], Robert Sauermann[bb], Wouter Hamelinck[cc], Guenka Petrova [dd], Ott Laius[ee], Irene Langner[g], John Yfantopoulos [ff], Roberta Joppi[gg], Arianit Jakupi [hh], Ieva Greiciute-Kuprijanov[ii], Patricia Vella Bonanno[b], Jf (Hans) Piepenbrink[jj], Vincent de Valk[jj], Magdalene Wladysiuk[kk], Vanda Marković-Peković [ll], Ileana Mardare [mm], Jurij Fürst[nn], Dominik Tomek [oo], Mercè Obach Cortadellas [pp], Corinne Zara [pp], Caridad Pontes [pp,qq], Stuart McTaggart[rr], Tracey-Lea Laba[ss], Øyvind Melien[tt], Durhane Wong-Rieger[uu], SeungJin Bae [vv] and Ruaraidh Hill [ww]

[a]Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, Stockholm, Sweden; [b]Division of Pharmacoepidemiology, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK; [c]Division of Public Health Pharmacy and Management, School of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, South Africa; [d]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia; [e]Institute of Translational Medicine, University of Liverpool, UK; [f]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium; [g]Wissenschaftliches Institut Der AOK (WIdO), Berlin, Germany; [h]Department of Medical Biophysics, Faculty of Medicine in Hradec Králové, Charles University, Hradec, Králové, Czech Republic; [i]Faculty of Pharmacy, Postgraduate Program in Medicines and Pharmaceutical Services, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil; [j]SUS Collaborating Centre for Technology Assessment and Excellence in Health (CCATES), Belo Horizonte, Minas Gerais, Brazil; [k]Faculty of Health and Life Sciences, Liverpool, UK; [l]QC Medica, Sim Balk Lane, York UK; [m]Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands; [n]NHS Lothian, Edinburgh, UK; [o]Faculty of Health Studies, Rijeka, Croatia; [p]Division of Biology & Public Health, Mokwon University, Daejeon, Korea; [q]Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; [r]Independent Researcher, Boston, MA, United States; [s]Independent Consumer Advocate, Brunswick, Victoria, Australia; [t]Data and Knowledge Integration Center for Health(CIDACS), Fundação Oswaldo Cruz (FIOCRUZ)/ Salvador, Bahia, Brazil; [u]Department of Nutrition and Drug Research, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland; [v]Istituto Di Ricerche Farmacologiche 'Mario Negri' IRCCS, Milan, Italy; [w]Department of Pharmacology, College of Pharmacy, Hawler Medical University, Erbil, Iraq; [x]Department of Pharmacology, Therapeutics and Toxicology, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria; [y]Department of Medicine, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria; [z]Department of Pharmacy, Faculty of Medicine, University of Medicine, Tirana, Albania; [aa]University of Medicine, Tirana, Albania; [bb]Department of Pharmaceutical Affairs, Federation of Social Insurances, Vienna, Austria; [cc]Statistics Department, Bruxelles, Belgium; [dd]Faculty of Pharmacy, Department of Social Pharmacy and Pharmacoeconomics, Medical University of Sofia, Sofia, Bulgaria; [ee]State Agency of Medicines, Tartu, Estonia; [ff]School of National and Kapodistrian University of Athens Athens Greece; [gg]Pharmaceutical Drug Department, Azienda Sanitaria Locale of Verona, Verona, Italy; [hh]Faculty of Pharmacy, UBT – Higher Education Institution, Prishtina, Kosovo; [ii]Department of Pharmacy, Ministry of Health of the Republic of Lithuania, Vilnius, Lithuania; [jj]National Health Care Institute (ZIN), XH, Diemen, Netherlands; [kk]HTA Consulting, Cracow, Poland; [ll]Faculty of Medicine, Department of Social Pharmacy, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina; [mm]Faculty of Medicine, Public Health and Management Department, "Carol Davila" University of Medicine and Pharmacy Bucharest, Bucharest, Romania; [nn]Health Insurance Institute, Ljubljana, Slovenia; [oo]Faculty of Medicine, Slovak Medical University in Bratislava, Bratislava, Slovakia; [pp]Drug Department, Catalan Health Service, Catalan Health Service, Barcelona, Spain; [qq]Department of Pharmacology, Therapeutics and Toxicology, Universitat Autònoma De Barcelona, Barcelona, Spain; [rr]Public Health Scotland, Edinburgh, UK; [ss]Centre for Health Economics Research and Evaluation, University of Technology Sydney, Broadway, Sydney, NSW; [tt]Reviews and Health Technology Assessments, Norwegian Institute of Public Health, Oslo, Norway; [uu]Health Data Science, Institute of Population Health, Liverpool, Canadian Organization for Rare Disorders, Toronto, Ontario, Canada; [vv]College of Pharmacy, Ewha Woman's University, Seoul, South Korea; [ww]Health Data Science, Institute of Population Health Liverpool Reviews and Implementation Group, Whelan Building, University of Liverpool, Liverpool, UK

CONTACT Brian Godman Brian.godman@strath.ac.uk Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom

ABSTRACT

Introduction: There are growing concerns among European health authorities regarding increasing prices for new cancer medicines, prices not necessarily linked to health gain and the implications for the sustainability of their healthcare systems.

Areas covered: Narrative discussion principally among payers and their advisers regarding potential approaches to the pricing of new cancer medicines.

Expert opinion: A number of potential pricing approaches are discussed including minimum effectiveness levels for new cancer medicines, managed entry agreements, multicriteria decision analyses (MCDAs), differential/tiered pricing, fair pricing models, amortization models as well as de-linkage models. We are likely to see a growth in alternative pricing deliberations in view of ongoing challenges. These include the considerable number of new oncology medicines in development including new gene therapies, new oncology medicines being launched with uncertainty regarding their value, and continued high prices coupled with the extent of confidential discounts for reimbursement. However, balanced against the need for new cancer medicines. This will lead to greater scrutiny over the prices of patent oncology medicines as more standard medicines lose their patent, calls for greater transparency as well as new models including amortization models. We will be monitoring these developments.

ARTICLE HISTORY
Received 17 August 2020
Accepted 29 January 2021

KEYWORDS
Alternative pricing approaches; cancer medicines; europe; managed entry agreements; multicriteria decision analyses; minimum effectiveness criteria; payers; transparent pricing approaches; tiered pricing approaches

1. Introduction

By 2023, it is estimated that global spending on medicines will reach US$1.5 trillion, growing at an annual compounded growth rate of 3–6% [1]. Approximately 50% of total expenditure will be on specialty medicines, including those for chronic, complex, or rare diseases incorporating oncology medicines [1]. As a result, oncology will continue to dominate spending on medicines especially in high income countries [2,3]. The cost of cancer care also now accounts for up to 30% of total hospital expenditure across Europe [4]. World-wide sales of oncology medicines are expected to grow to US$237 billion by 2024 [2], with this growth likely to continue with over 500 companies actively pursuing development of new oncology medicines in over 600 indications [5], and envisaged high price expectations [6].

We have seen the median annual cost for new oncology medicines exceed US$150,000 per person per year in 2017 compared with US$79,000 in 2013, with prices continuing to rise [3]. The price per life year gained for new oncology medicines has also risen in recent years, rising four-fold during the past 20 years after adjusting for inflation [7]. However, there are concerns with reimbursed prices for new oncology medicines, especially among higher-income countries and the actual level of health gain seen [8,9]. However, Molto et al. (2020) found that 40% of new oncology medicines recently received a breakthrough therapy designation, and were more likely than non-breakthrough therapies to provide a meaningful clinical benefit [10]. In addition, Lauenroth et al. (2020) found that the reforms in Germany led to reimbursed prices for new oncology medicines falling following evaluation; subsequently, more in line with the clinical benefit seen [11].

High requested prices for new oncology medicines though are resulting in appreciable disparity in their availability across Europe [9,12,13], mirroring the situation with biological medicines for arthritis and inflammatory bowel disease [14]. Alongside this, increasing concern with the sustainability of universal healthcare systems across countries [15]. The launch of new advanced therapy medicinal products (ATMPs), including new high-priced gene therapies, will put further pressure on countries' abilities to continue providing universal healthcare [16,17]. The current situation has already resulted in requests for price moderation for new oncology medicines in countries with high patient co-payment levels [18,19], and this will continue. We are already aware that current prices for new oncology medicines means they will be beyond the reach of the majority of low- and middle- income countries (LMICs) who struggle even to fund trastuzumab [20,21]. This is a concern that needs addressing as LMICs currently witness the fastest growth in mortality from cancer [22,23]. The growing availability of low cost biosimilars should help here [24].

Payers and their advisers are increasingly aware of the low production costs of a number of oncology medicines including those deemed cost ineffective by national authorities in Western Europe [25]. This is illustrated by price reductions up to 97.8% for oral cancer medicines once multiple sourced products become available [26], an 83% reduction in total expenditure on adalimumab in Denmark once biosimilars became available [27], and AbbVie in the Netherlands reducing the price of Humira® by 89% just before biosimilars became available [28]. However, there are concerns that cost-based pricing approaches can be difficult to implement especially with challenges in transparency and could result in disincentives to address areas of unmet need [29]. This is a concern given the level of unmet need with currently 9.6 million deaths annually from cancer globally and growing [22,30].

Payers and their advisers are also aware of an increasing number of medicines with small patient volumes, including targeted oncology medicines and those for orphan diseases, are reaching global sales of over €1billion (US$1.2bn) per year under the current system, with the number of medicines in this category continuing to rise [31]. In addition, up to the end of 2017 there were 33 oncology medicines with average annual sales exceeding US$1billion per year, with high sales often persisting after patent loss [9]. Alongside this, there is increasing

Article Highlights

- There is continued growth in medicine expenditure driven by increasing expenditure on speciality and complex treatments including those for cancer, which will soon account for 50% of total expenditure
- Concurrent with this, we are seeing new cancer medicines being launched at high prices with often considerable uncertainty regarding their future role. These concerns are leading to the development of different pricing approaches including establishing minimum effectiveness levels for new oncology medicines to be seen as an advantage, managed entry agreements, multicriteria decision analyses and fair pricing models to potentially reduce disparities in their availability and funding across Europe
- The value of existing patented oncology medicines will increasingly be re-evaluated as more standard treatments becoming available as low-cost generics or biosimilars

However, ongoing initiatives must be balanced against the need to still continuing to stimulate research into new oncology medicines including new gene therapies.

uncertainty with the value of new oncology medicines at launch. For instance, 50% of the new oncology drugs approved by the US Food and Drug Administration (FDA) in 2017 were solely based on data from a phase II trial with 21% based on phase I/II trials [3], and in 2018 the FDA granted accelerated approval for larotrectinib for adults and children with certain targeted tumors based on findings from only 55 patients across 12 cancers [32]. The majority of accelerated approvals (79%) are now for oncology medicines [33], and it is often left to European health authorities to fund these approved treatments under early access schemes until more data becomes available with limited opportunities to re-coup the monies spent if there are subsequent concerns with their effectiveness in practice [34,35]. In addition, fast-track oncology medicines are often associated with increased risk of safety-related issues [33].

Consequently, there is a recognized need especially among European health authorities to reevaluate pricing approaches toward new oncology medicines given these multiple challenges. European health authorities are also aware that expenditures on new oncology medicines in the US alone for those approved just in 2018 could be as high as US$39.5 billion if they were prescribed in all eligible patients that year [36]. This figure does not include expenditure on oncology medicines either side of this [36]. Such expenditures would pose a serious threat to the principals of equity and solidarity even among high income European countries. However, there are concerns that any potentially new proposed pricing approach may not always incorporate key issues for new valued oncology medicines. Key issues include their impact on productivity and/or current disabilities, reducing carer support, improving adherence rates where these are an issue as well as considering the impact of new knowledge gained on improving future treatments and the value of hope [37–39].

Current proposals to address concerns include establishing meaningful minimum effectiveness levels for new oncology medicines to be funded at higher prices than current standards, first proposed in the United Kingdom in 2000 [40,41], defining what is meant by innovation [42], and implementing fair and transparent approaches toward the pricing of new oncology medicines proposed by European payers, the World Health Organization (WHO) and others although there are concerns with issues including fully costing R. & D [43–45]. Potential proposals also include re-looking at managed entry agreements (MEAs) with countries concerned they may not always be getting optimal discounts in practice with rebates continuing to be confidential [46,47]; however, balanced against increased opportunities of reimbursement with such schemes combined with the potential to gain valuable evidence of the performance new oncology medicines in routine clinical care [46,48]. This is important given concerns with the lack of subsequent studies confirming effectiveness aspirations using clinical outcomes contained in the initial approval of novel new medicines following their launch [49].

Other proposals include the development of new multicriteria decision analyses (MCDAs) models [50,51] as well as potentially de-linkage models combining academic consortia with separate manufacturers to make new oncology medicines available at low prices [52]. Alongside this, we are already seeing countries and regions in Europe and wider become appreciably more pro-active in their approaches to funding new medicines in designated populations starting up to three years pre-launch and continuing post-launch to assess their role and value in routine clinical care [53,54]. Some authors are also arguing for differential pricing to enhance access to new oncology medicines in LMICs as well as further stimulate innovation, which could be based on economic indicators [55,56]. Alongside this, argue for differential pricing by indication to broaden reimbursed indications. However, there are reservations with the practicalities of these approaches [57].

Consequently, the principal aim of this perspective paper is to summarize, frame and debate potential approaches to the pricing and reimbursement of oncology medicines given current concerns. As such, help lay a foundation for the future.

2. Body of the paper

2.1. General considerations

The views expressed and debated will principally be from a European payer's perspective as they are the key personnel involved in funding and reimbursement decisions for new oncology medicines across Europe. We have chosen to concentrate principally on Europe in view of continuing debates about possible ways of valuing new medicines including those for cancer and orphan diseases, ongoing initiatives to improve the managed entry of new medicines, current controversies surrounding adaptive pathways and MEAs as well as a plethora of demand-side measures to enhance the prescribing of multiple source products and biosimilars when available [26,35,57,58]. We are aware this contrasts with the U.S.A. with its absence of single-payer health care systems where patients or families who can afford it often demand expensive oncology therapies despite marginal survival expectations, although there are concerns among some with potentially high expenditures on new oncology medicines [36]. However, we believe our deliberations will be of interest to all countries, and especially LMICs, given continual pressure on healthcare resources exacerbated by the COVID-19 pandemic.

We will principally use the knowledge and experience of the senior level coauthors from across Europe typically working for health authorities or health insurance companies or advisers to them to debate potential pricing approaches and their ease of administration.

2.2. Defining innovation

The Expert Panel on effective ways of investing in Health (EXPH) suggested 'value-based healthcare (VBHC)' should be built on four pillars, namely (i) appropriate care to achieve patients' personal goals – personal value; (ii) technical value incorporating the achievement of best possible outcomes with available resources; (iii) allocative value including the equitable resource distribution across all patient groups which is seen as very important in Europe with its universal healthcare and opportunity costs a key consideration; and (iv) societal value including the societal contribution of any healthcare intervention to social participation and connectedness [59]. This mirrors some of the considerations of Garrison et al. [38,60]. Opportunity costs is a key consideration for cancer care as discussed by Barrett et al. (2006) when Herceptin® first became available in the United Kingdom [61]. However, it is recognized that additional considerations should be given to reimburse and fund new premium priced treatments that address unmet need in patients with severe diseases such as cancer to stimulate innovation [51,62].

We are also aware that Berdud et al. (2020) have recently suggested implementing variable cost/QALY limits for new medicines for orphan diseases, which could include new oncology medicines for targeted populations, depending on the size of the patient population [63]. These build on existing approaches in countries including Sweden and the UK [62,64]. However, there are concerns that such approaches could be abused as seen in the Netherlands, where there was considerable pressure for the Government to fund new medicines for Pompe's disease up to €15 million/QALY as well as concerns with their moral justification [64,65].

2.3. Minimum effectiveness criteria

Ferguson et al., in the UK in 2000, suggested that a minimum of 3–6 months of additional survival compared with current standards should be the threshold level for hospitals and health authorities to consider authorizing and funding any new oncology medicine at a higher price than current standards [40]. Others have suggested similar considerations although there are concerns that an additional three months may be considered a marginal benefit by clinical experts whilst expressing concerns with the value of surrogate markers in decision making [9,41,66–68].

Lower thresholds have been suggested [69]. However, this is a concern with Kantarjian et al. (2013) noting that of the twelve oncology medicines approved by the US FDA in 2012 only three actually prolonged survival and in only one was this by more than two months. However, among the 12, 9 were priced at more than US$10,000 per patient per month [70]. Davis et al. (2017) in their analysis also found that 57% of new oncology medicines approved by the EMA between 2009 and 2013 had no evidence of a quality of life or a survival benefit at the time of approval, or if present, these were not clinically meaningful in most cases with many new cancer medicines approved on the basis of only surrogate markers [71]. Cohen, in an accompanying editorial in the BMJ, highlighted that despite often limited health gain, these medicines were often associated with high prices [8], and warned against potential overestimation of the clinical benefits of new oncology medicines when approval is granted in the context of early access policies. Having said this, Salas-Vega in their analysis found that 43% of new oncology medicines approved either by the FDA or the European Medicines Agency (EMA) between 2003 and 2013, and subsequently reviewed by health technology agencies, did improve overall survival by 3 months or longer [72]. In addition, as mentioned, Molto et al. (2020) found that 40% of new treatments recently received a breakthrough therapy designation, and were more likely than non-breakthrough therapies to provide a high clinical benefit [10]. Consequently, minimum thresholds of three to six months are likely to remain.

However, payers are aware they need to look more critically at important factors for patients including issues of toxicity and quality of life along with caution when appraising requested prices if only surrogate endpoint data is available during negotiations and the data is still immature [33,34,41]. Health authorities and patients can play a key role in future funding decisions especially across Europe by agreeing what is meant by meaningful clinical benefit to establish baselines for granting higher prices for new cancer medicines versus current standards, building on current examples [41,59].

2.4. Managed Entry Agreements (MEAs)

There has been an increase in the number of MEAs in recent years especially for new oncology medicines given pharmaceutical company requests for high prices coupled with concerns with affordability [48,73].

MEAs can generally be divided into financial-based schemes, which typically involve confidential rebates, discounts, or price volume agreements, and performance or outcomes-based schemes, which typically include outcome guarantee schemes or agreed prices based on agreed outcomes [47]. Financial-based schemes are increasingly seen in practice as they are viewed as easier to administer and are more suited to manage uncertainty regarding overall budgets [46,47].

In its recent report addressing the challenges in access to oncology medicines, the OECD (2020) suggests that the design of outcome- or performance-based MEAs should be improved to better support the generation of real-life clinical data to reduce the uncertainty regarding the effectiveness and safety of new oncology medicines in routine clinical care [74]. This is because financial-based agreements typically only help control the economic impact of new medicines and do not address clinical uncertainty. This is a concern with, as mentioned, new cancer medicines increasingly launched with immature data and the high failure rates of translating promising Phase II into positive findings in Phase III and beyond

Table 1. Summary of advantages and disadvantages of MEAs [adapted from Al-Omar et al, Antonanzas et al., Carlson et al., Hampson et al., Toumi et al., and Zampirolli Diaz et al. [46,48,86–89]].

Advantages	
General	• Provide access to new medicines where affordability is an issue and/or where there are concerns with the uncertainty of the effectiveness or cost-effectiveness of the new oncology medicine when introduced into routine use. • Potentially improve prescribing in a more predictable, transparent and rational way to a defined patient population enhanced by subsequent monitoring of prescribing against agreed guidance, e.g. Italy and Sweden, and that agreed outcomes are being reached in practice [77,90–92] • Offers flexibility in terms of the potential budget impact and value when considering new oncology medicines characterized by appreciable levels of uncertainty especially as more biological medicines are losing their patents, with the potential for payback mechanisms if outcomes and subsequent value are less than expected [48,86]
Financial-based schemes	• Easier to implement than outcome-based schemes, helping to contain costs and keep expenditure within agreed limits. • Potential for cross product agreements among Pharmaceutical Companies and health authorities to help keep annual expenditures within agreed limits • Potential to improve the cost-effectiveness of new oncology medicines through lowering the incremental cost-effectiveness ratio (ICER)
Outcome-based schemes	• Potentially provides new oncology medicines to patients including those most likely to benefit, e.g. CAR-T cell therapies among EU countries including future re-assessment of prices and/or rebates based on agreed outcomes in France, Germany, and the UK, with re-assessments of staged payments in Italy and Spain [93] • Potentially incentivize R&D activities more than reimbursement and funding policies based on cost effectiveness criteria • Provide additional 'real-world' evidence – especially important when new medicines are approved with limited Phase I and II data • Can help consolidate the development of a set of meaningful data that can be routinely collected in busy oncology clinics to improve future decision making such as the CMOP program in Scotland [80] • Potentially provide evidence about a new oncology medicine in different patient populations • Can in time help to update guidelines within a country on appropriate medicine use as more data becomes available. • Potential to prolong the time for capturing meaningful data on the effectiveness, safety and cost-effectiveness of a new oncology medicine in a more restricted environment with clinicians adhering to agreed protocols and no off-label use. As a result, more rapidly enhance the evidence base. This is increasingly important in the case of oncology medicines if initial data sets are based on surrogate markers such as progression-free survival rather than overall survival and impact on quality of life
Disadvantages	
General	• Whether countries are getting the optimal discount in reality and concerns with good governance [9] • Volume agreements do not necessarily ensure the most appropriate patients receive the new medicine – the concomitant instigation of demand-side measures including prescribing against agreed protocols can help here • In pertinent countries, patient co-pays will be higher in ambulatory care if co-payments are based on list rather than actual prices – balanced though against wholesalers, distributors and retail pharmacists typically paid on list rather than actual prices across countries • Potentially higher administrative and transaction costs including the length of time for negotiations especially for outcome-based schemes, lack of expertise, and potentially a lack of regulations. • In multiple-payer healthcare systems, data tracking is challenging when members move from one plan/insurance company to another. • Early approval and funding via MEAs for new oncology medicines could potentially be considered by physicians and patients as improvements compared to current standards without necessarily being the case [34]
Financial-based schemes	• Companies potentially asking for higher prices initially especially if they believe discounts are inevitable. • The confidential nature of discounts and rebates could mean companies seek a high list price in a reference priced country, especially in a country with considerable economic power to negotiate good discounts, to the detriment of other countries with less economic power
Outcome-based schemes	• Information collected in outcome-based schemes may not necessarily enhance the evidence base especially where there are concerns with trial design • Patient accessibility may be compromised if the new oncology medicine is only available in a limited number of centers, and the temporary nature of certain agreements may make companies cautious about progressing with them. • The confidential nature of data captured/privacy issues adds to the difficulties with transparency when analyzing the findings with typically strict criteria within health authorities for accessing patient level data under governance issues • Issues of transparency are also important in discussions with patients about the temporary nature of any funding for new medicines under outcome-based MEAs. • Concerns with the length of time of some outcome-based schemes – especially important in rapidly changing disease areas or where generics/biosimilars will become available by the time the outcome-based scheme is finished. • Who pays for the cost of the oncology medicine during the evaluation period – seen as a particular issue with olaratumab [34] • Health authorities may not always be fully compensated in payback schemes when the new oncology medicine is not as effective or cost-effective in routine clinical care as expected • Possible difficulties at the time of finishing agreements to lower prices if pertinent to reflect the actual observed effectiveness in clinical practice if there is a reluctance among companies to reduce the prices of their patented medicines (especially in reference priced countries) alongside pressure from clinicians who have already incorporated the new medicine into their clinical protocols

[75,76]. Alongside this, only a relatively limited number of European countries and regions have good patient level data infrastructures to routinely capture outcome data in practice without the need to design specific schemes for each new oncology medicine. Concerns with the latter have resulted in a plethora of MEAs in Italy failing to collect any meaningful clinical data, alongside disputes with manufacturers regarding any payback, with current MEA arrangements principally demonstrating that healthcare professionals followed prescribing guidance [77]. Consequently, key stakeholder groups including payers and patient groups will need to decide in advance if the value of information retrieved through MEAs will be clinically meaningful and compensate for the cost of any subsequent data collection [78]. Agreements between payers and pharmaceutical companies will also need to be strengthened given concerns with continued reimbursement for new medicines despite at times issues with their value as more evidence becomes available [79].

Potential ways forward especially in Europe include the harmonization of the clinical data that can routinely be

collected in busy oncology clinics for any future outcome-based MEA. This builds on approaches such as the Cancer Medicines Outcome Project (CMOP) program in Scotland starting with prostate cancer [80,81], as well as the Data the Systemic Anti-Cancer Therapy (SACT) dataset project in England [82]. This also builds on recent initiatives in the United Kingdom that pharmaceutical companies need to start collecting outcome data for any new oncology medicines targeted for consideration for funding within the UK Cancer Drug Fund, with such situations likely to grow [83]. However, this must be balanced against the considerable costs that can occur with increased monitoring of patients especially where there is uncertainty regarding the role and value of new treatments [84]; however, costs can be reduced with initiatives such as CMOP and SACT.

Potential advantages and disadvantages of MEAs have recently been summarized by Zampirolli Diaz et al. (2020) with payers and their advisers from a number of countries and continents involved in such activities (Table 1), building on deliberations by Antonanzas et al., Carlson et al., Hampson et al., Toumi et al., and others [46,48,85–87].

It is likely there will be a growth in MEAs in the coming years given the likely increase in the number of new high cost oncology medicines being launched including personalized medicine approaches such as CAR-T therapies, with MEAs seen as a viable means of addressing concerns with immature data at launch alongside high requested prices, increasing pressure on available resources exacerbated by the COVID-19 pandemic, and the absence of other approaches to enhance the affordability of new oncology medicines in Europe and wider. In addition, reassess potential rebates under value-based pricing schemes when the initial standards used in reimbursement and funding negotiations become available as either low cost generics or biosimilars as a pragmatic way forward [9].

Greater knowledge about the outcome of current schemes would be beneficial going forward to aid all key stakeholder groups. However, timelines for any schemes have to be reasonable for all key stakeholder groups. There are also considerations for the introduction of independent platforms for outcome-based contracting which aligns the interests of all key stakeholders and promotes inclusivity and transparency. We will be looking to explore this feasibility in Europe going forward [94].

The formation of purchasing consortia especially in Europe (progressing) and South America via PAHO (as seen with new medicines for Hepatitis C) may help to address the current lack of transparency with prices, discounts, and rebates fulfilling recent WHO recommendations for increasing pricing transparency for medicines across countries [45,59,95]. Alongside this, enhance the concomitant instigation of demand-side measures across countries, including prescribing against agreed protocols, to optimize the use of new oncology medicines as part of any agreement [9].

It is also likely we will see more outcome-based schemes as IT-infrastructures become more sophisticated across countries. Lastly, there is growing recognition that the appraisal of the value of new oncology medicines is more a continuum than a 'one-off' evaluation; however, mindful of the concerns (Table 1) [46,54]. The continuum will be helped by an increasing number of centers collaborating together including research agendas from basic science to the collection of outcome data [96].

2.5. Multicriteria decision analyses (MCDA)

In formulating recommendations for reimbursements, appraisal committees typically interpret the results of an assessment in a broader perspective to inform decision-makers sometimes making use of MCDAs. This is an intrinsically complex and a value-laden task that requires careful judgment. It is likely we will see a growth in MCDAs including for new oncology medicines in view of concerns with current approaches including transparency [97]. These models may well build on suggested models for new medicines for orphan diseases [55–57,98,99], as well as the deliberations of Lakdawalla et al. who discuss additional considerations for valuing new medicines including the value of hope and the real option value. The 'real option value' is generated whereby the prescribing of a new medicine that extends life potentially creates opportunities for patients to benefit from future advances, improves equity, and may result in scientific spill overs from one new medicine to another [37].

We are aware that several public agencies and health insurers are already using, or proposing, MCDA approaches in healthcare decision making including an MCDA introduced by the reimbursement authorities in Italy to help define the level of innovation of new medicines, and this is likely to grow including LMICs [42,100–102].

Hsu et al. (2019) recently developed a MCDA for targeted therapies for colorectal cancer centering on clinical, economic and social values (Table 2) [50].

Angelis et al. (2020) also recently developed an advanced value framework for new medicines for prostate cancer [103]. Their key criteria are presented in Table 3. Perhaps not surprisingly, the level of therapeutic benefit consistently ranked first in relative importance among the studied countries (Belgium, Poland, Spain, Sweden). While there were some differences in value preferences between respondents (assessors and experts) in the given countries, drug rankings in terms of the relative value of the different medicines for prostate cancer

Table 2. Multicriteria for assessing the value of targeted therapies for colorectal cancer [adapted from Hsu et al. [50]].

Dimension	Criteria
Clinical	• Comparative efficacy – overall survival and progression-free survival (months) • Overall safety, e.g. incidence of adverse events including severe adverse events and potential for drug:drug interactions • Convenience (including length of treatment) and impact on health-related quality-of-life
Economic	• Cost-effectiveness – incremental cost-effectiveness ratio (ICER) • Number of patients – number of patients by indication who could potentially be treated • Expenditure – overall expenditure (budget impact)
Society values	• Degree of innovation – including likely approval times by the authorities • Societal concerns and patient needs – including the extent of alternatives • Experience/funding – Extent funded within other countries

Table 3. Criteria for assessing the value of therapies for prostate cancer [adapted from Angelis et al. [103]].

Dimension	Key criteria
Clinical (outcome)	• Overall survival (months) • Health-related quality-of-life (stable and progressive disease) – utility scores (EQ5D)
Clinical (surrogate)	• Radiological progression-free survival (months) • PSA response (%)
Clinical (side-effects, etc.)	• Treatment discontinuation (%) • Contra-indication (type)
Other clinical/value considerations	• ATC level (mechanism of action) • Experience – number of patients enrolled into Phase II and III trials for given indications • Delivery posology
Economic	Medical costs/budget impact

NB: ATC = Anatomical, Therapeutic, Chemical'

including abiraterone, cabazitaxel, and enzalutamide, remained the same across the studied countries [103].

Ezeife et al. (2020) used a multi-stakeholder approach incorporating 2 patients, 2 public members, 2 patient advocacy group leaders, 2 pharmacists, 1 industry representative, 6 oncologists, 1 ethicist, 3 health economists, 3 members of an appraisal committee (pCODR), 2 cancer agency members, and a Ministry of Health government representative. They identified the criteria through published literature, and let the stakeholders assign weights equaling 100 [104]. The highest weights assigned included quality of life (weight of 19), overall survival (weight of 15), and unmet clinical need (weight of 15), with the lowest weights being for disease severity (weight of 5) and caregiver well-being (weight of 4) [104].

However, there are concerns that quantitative MCDA approaches may not be that transparent in reality and may not necessarily lead to good quality recommendations [105]. This has resulted in more structured deliberative approaches including those used by the pan-Canadian Oncology Drug Review (pCODR) in Canada [106], and ongoing initiatives in the Netherlands and the UK [107]. This means that appraisal committees make judgments on the overall value of a technology using some rules. These rules subsequently guide trade-offs between explicitly defined criteria such as disease severity and cost per quality adjusted life years (QALYs) [108]. We will continue to monitor such activities to provide future direction, similar to ongoing activities regarding MEAs.

2.6. Differential/tiered pricing including multi-indication pricing

We also see growing debates regarding indication-based prescribing, i.e. differential pricing by indication, especially if there are appreciable differences in the value of a new medicine by indication [55,109–111]. However, there are a number of concerns with this approach.

These include the fact that at maximum prices per indication, this favors pharmaceutical companies over health authorities [112]. This approach could potentially lead to higher prices for the patients who benefit the most, which is an issue where there are already high patient co-payments [56,113]. In addition, monitoring against manipulated diagnoses ('up-coding') is challenging, as experiences from introducing hospital payment schemes based on diagnosis-related groups (DRGs) have shown. There are also concerns among companies that if the low value indication is launched first, the cost of developing the high value indication may be prohibitive [55].

However, improved planning and proactivity within countries as well as robust IT systems that collect data on indications alongside utilization data can help address some of these concerns. Alternatively, through requirements to collect data through registries [55,109,114]. However, different European countries are at different stages with their IT systems especially regarding linking medicines dispensed with an indication [115]. Consequently, it may be that a review of existing discounts and rebates is a practical approach in the short term since R&D costs have already been accounted for during pricing negotiations for the first indication [112]. Subsequently, re-visit the situation as health authorities further develop their IT system.

Mestre-Ferrandiz et al. (2018) recently identified six key issues when key stakeholders consider multi-indication pricing (Table 4) [114]. A review of potential discounts for new medicines where companies are seeking additional indications would appear to be the most prevalent and possible approach to date to address indication-based pricing (IBP) as this takes into consideration issues of higher profitability with new indications as R&D costs have already been accounted for [112]. This is also consistent with a recent systematic review by Campillo-Artero et al. (2020) who found no application of indication-based pricing (IBP) systems in practice and their practical consequences [112]. The authors concluded that MEAs most closely resemble the IBP approach; however, such arrangements are generally confidential [112], which is a continual concern.

2.7. Fair and Transparent Pricing Models

There are ongoing discussions across Europe and in other countries concerning what is considered a fair price for a new medicine, including a new oncology medicine, depending on the perspective of the stakeholder [43,118,119].

This includes concepts surrounding fair pricing incorporating proposed models from payer groups such as the International Association of Mutual Benefit Societies (AIM) and others [43,44,119,120]. Moon et al. (2020) believe the price of a new medicine should allow for the societal need for that medicine; however, government interventions are usually needed to ensure a fair and equitable price to benefit all key stakeholder groups [119]. Typically, this means greater transparency around key issues including R&D, production costs, and pricing approaches [118]. The aim is to stimulate and reward the development of new medicines in areas of unmet need including new innovative oncology medicines whilst limiting funding for new oncology medicines where high prices are sought for limited health gain. The WHO (2020) in their recent guidelines on country pharmaceutical policies also ask for increased price transparency as well as potentially a cost-plus approach to pricing if the lack of transparency in price setting continues [45].

Table 4. Key considerations when considering multi-indication pricing (adapted from Mestre-Ferrandiz et al. [114]).

Key consideration	Implication
Incentives	Incentives need to be designed to encourage the collection and use of reliable data including indication data, e.g. in Italy it is in the hospitals' interest to collect utilization data by indication as part of MEAs for new medicines [116,117]
Registries	Registries need to be improved and allow for the incorporation of real world evidence into reimbursement and funding decisions
Co-ordination	• Co-ordination needs to be enhanced at all levels for effective systems. This includes the national level, but may also include the regional level data if there are already different prices for medicines across regions in a country • There also needs to be co-ordination at the hospital level to monitor usage by patient and indication if this is linked to managed entry and other schemes
Transparency	There needs to be greater transparency regarding who actually benefits from such approaches as part of any future situation
Contractual pricing arrangements	Any contractual pricing arrangements need to be flexible in order to take account of any new evidence surrounding existing and new indications as well as changes in the prices of medicines being used to treat that tumor and stage. This is especially important if pertinent medicines become available as low cost multiple sourced medicines or biosimilars
Modeling the impact of differential pricing approaches	• There is also a recognized need for further research to help model the potential budget impact of differential pricing especially if this leads to lower overall expenditure • If subsequently greater expenditure – how can this be equitably and transparently shared between payers and pharmaceutical companies with companies seeking to maximize prices for each indication [109]

Table 5. Key information and analysis requirements needed in order to apply a fair pricing framework [adapted from Moon et al. [119]].

Factors to consider	Information and analysis requirements
Sellers (including those conducting R&D as well as the manufacturers/companies)	
Cost of R&D	Typically this information is not disclosed and is contentious to estimate as seen by appreciable differences in published sources for bringing new medicines to the market ranging from US $200million and US$2.9billion [9]
Cost of manufacturing and distribution	Generally this information is not disclosed although it is seen as feasible to estimate and usually disclosed in competitive markets as seen by some of the low costs for generics and biosimilars and other estimates of production costs [26,28,122,123]
Fair profit	• Typically aggregate profits are disclosed by companies but these are typically not product specific • Such activities will typically entail a judgment as there have been concerns among health authority personnel that companies typically set prices for new medicines for cancer and orphan diseases based on previous benchmarks and what they feel are attainable prices irrespective of the health gain involved [8,124–127]
Other costs including registration, administration and pharmacovigilance	Again, usually such information is typically not disclosed by companies but is feasible to estimate based on previous benchmarks
Buyers (including health authorities and patients)	
Affordability of new medicines	Additional analytical work will generally be required to identify concrete affordability ceilings for health authorities and patients given concerns with ever increasing prices for new cancer medicines and those for orphan diseases [7,126,128]
Value to health systems across continents	• HTA can contribute to such analyses [129]. However, different methods may be needed to fully incorporate the benefits and value of new medicines for cancer into future pricing considerations given affordability constraints that exist within countries, especially LMICs. • Willingness-to-pay studies have been conducted among the public in Brazil to help establish possible prices for new vaccines serving as potential benchmarks [130,131]
Supply security	Information on potential volumes and producers (for multi-sourced products) are needed to maintain competition and supply for specific products, which such data seen as feasible to collect. This is because supply shortages are becoming a key issue across countries [132]

Whilst Moon and colleagues discussed in general terms what they mean by fair pricing, there currently appears no standard definition of what actually constitutes a fair price for new oncology medicines [119]. Having said thus, the European Cancer Leagues recently defined a fair price for a new oncology medicine as '*A fair price is transparent, understandable, affordable, proportionate and based on objective factors such as R&D investment, delivery, marketing and sales costs, and a clearly defined profit margin connected to the proven therapeutic value (if available compared with other treatments). They believed a fair price was profitable enough to steer innovation in the long term, but would not pose a threat to the long term sustainability of healthcare systems'* [121]. Overall, they believed proposed prices should combine economic aspects such as the cost-effectiveness and budget impact of any new oncology medicine as well as likely estimates of the costs associated with R&D [121]. However, there is currently an absence of reliable published data on development costs which is a concern although most commonly accepted estimates lie between US$200million and US$2.9billion [9]. In their model, Moon et al. (2020) proposed the concept of a 'fair pricing zone' that lies between a price floor and a price ceiling. The price floor for a new medicine, including a new oncology medicine, should be the lowest sustainable price at which suppliers, typically pharmaceutical companies, can sell a medicine and still incentivize innovation. This includes R&D costs, manufacturing, and distribution costs as well as a fair profit

Table 6. Potential parameters proposed by the International Association of Mutual Benefit Societies (AIM) for pricing considerations for new medicines [43] as well as by Uyl-de Groot et al. for new oncology medicines [44].

Potential parameters AIM Model	Potential considerations model of Uyl-de Groot et al.
(1) R&D costs – a lump sum of €250 million for each new medicine. Higher amounts if these can be justified using a specific approved methodology (incorporating issues such as expenses incurred minus sponsor/government money, costs of failure and buyouts) up to a total amount of €2.5 billion (2) Amount of R&D allocated to Europe (which represents 42% of the population of the main markets for new innovative medicines) (3) Target population, i.e. whether ultra rare, rare, or for a chronic disease treatment rate, market share, and likely duration of treatment (4) Whether a new indication or the 2nd or 3rd indication (5) Alternatives for the same indication, i.e. are there already alternative medicines on the market or will this new medicine be a first in the class (6) Production and overhead costs (7) Sales and marketing costs – 20% of R&D costs will be allowed and gradually reduced (8) Basic profit of 8% based on the upper range of returns in risky industries (9) Innovation bonus ranging from 5% to 40% depending on the expected added therapeutic value of the new medicine versus current standards (10) Differential price depending on issues such as GDP per country	• R&D costs incorporating medicines that have been abandoned during their development (attrition rate) • Costs including manufacturing, sales and marketing and overheads • A profit margin linked to the level of clinical benefit versus current treatments to stimulate innovation based on for instance ASCO and ESMO criteria which are linked to the length of additional survival and other key parameters, e.g. 20–40% margins • The envisaged number of patients likely to be treated with the new medicines • The length of patent (years) after registration

[119]. The price ceiling is the maximum price that a buyer, e.g. a European health authority, can afford [119]. Moon et al. identified seven key information and analysis requirements that are needed in order to apply their fair pricing framework (Table 5) [119].

The International Association of Mutual Benefit Societies (AIM) was more specific in their recent approach [43] (Table 6) believing their suggested model ensures fairness to pharmaceutical companies in view of the unmet need that still exists, for example, for new oncology medicines whilst considering fairness toward European healthcare systems struggling to cope with competing demands including the consequences of increased prevalence rates for cancer [43].

However, there are concerns that such approaches disincentivize R&D efficiency, do not factor in failures, may not sufficiently encourage innovation and may be highly disruptive [29,51,133,134]. In view of this, the AIM approach (Table 6) may be more applicable; however, this remains to be seen. In addition, the instigation of cross-border purchasing consortia among European countries such as the Beneluxa, Nordic and the Valetta consortia, may lead to greater transparency in pricing approaches; however, there are concerns whether such collaboration will fully work in practice [9,135,136].

2.8. Other approaches

Suleman et al. (2020) have recently proposed new business models for R&D to help achieve fair pricing building on previous publications [57,120,137]. These include 'push' models that typically provide grants for research projects in advance; 'pull' mechanisms that provide rewards for agreed research accomplishments at various stages of the drug development process, and pooling mechanisms that facilitate access to knowledge to help advance scientific knowledge and hence shorten development timelines and costs [120]. Pooling mechanisms include collaborative initiatives that share R&D as well as open source initiatives that apply open source, open access, open data, or open knowledge principles, to progress R&D in key areas [137]. Interest in pull mechanisms, or combining push and pull mechanisms, has risen in recent years with a number of schemes now in operation [120,137]. These include initiatives to develop new antimicrobials including those for HIV and tuberculosis, new vaccines, as well as new medicines for orphan diseases and cancer [137].

Other pricing approaches include amortization or leasing scheme approaches for new high priced medicines as well as seeking to de-link the costs of R&D from a medicine's price [134]. De-linkage models have been proposed for new cancer medicines to help lower their costs given increasing recognition that most basic research for new cancer medicines is now predominantly undertaken in universities or funded by public sources [52,110]. However, there is concern that such approaches may disincentivise companies in the future.

Concerns with requested prices for new ATMPs, as well as regenerative medicines, coupled the envisaged number in development and the uncertainty surrounding their performance, is also leading to suggestions for performance-based annuity payments [138]. However, such models need to take into account the current legal and other frameworks within a country as emphasized recently in Belgium when appraising potential options for funding new ATMPs [139,140]. They also need to take into account concerns among payers about potential rebates if 'one-off' treatments such as gene therapies fail to achieve their desired effect. However, greater evidence generation alongside appropriate MEAs may help here [141].

Two-part pricing approaches have also been proposed to help spread the costs of new premium-priced but valued medicines [134]. Under this system, manufacturers and payers agree an entry fee for a population or subpopulation and for every treatment, with the manufacturer receiving a 'user fee' for every patient treated. However, for such schemes to work, there has to be a degree of certainty surrounding the outcome with new treatments such as schemes proposed for hepatitis C [134,142].

Consequently, such schemes may be difficult to implement for new oncology medicines, especially those for solid tumors where only surrogate data is available at launch, given the considerable uncertainty that exists regarding their future effectiveness at launch [3]. However, greater knowledge with the help of a growing number of oncology databases should help here.

Finally, Chalkidou and colleagues (2020) recently proposed the development of an Innovation Uptake Institute (IUI) to address key issues including affordability of medicines for LMICs as well as stimulating research to address unmet need in neglected or de-prioritized disease areas [143]. This includes focusing more on demand-side strengthening, and includes new HTA mechanisms as well as investing in IT systems to collect real-world evidence alongside the development of cost conscious clinical guidelines [143]. The authors envisage that IUI would be financed via a mixed funding model [143]. However, methodologies for obtaining valid 'real-world evidence' are still in their infancy, and more input is needed before such developments can become realities

3. Conclusion

We are likely to see a growth in alternative pricing models given concerns with the current system, the level of unmet need, and the desire to maintain the sustainability of healthcare systems especially among European countries. This will include reevaluating prices or rebates of existing patented oncology medicines as more standard oral and biological medicines become available as generics or biosimilars.

Likely additional activities among payers will include a greater focus on MCDAs for new oncology medicines building on recent developments including those in Italy, the Netherlands, and the UK, as well as MEAs especially with the development of IT systems and a potential consensus regarding pragmatic patient-level data to collect during routine oncology clinics. In addition, health authorities and insurers are likely to become more critical when negotiating rebates and discounts for MEAs, building on growing knowledge of the low cost of goods of many oncology medicines and biologicals with prices falling considerably once patents have been lost. However, this must not be at the detriment of incentivizing innovation given the level of unmet need that still exists for new cancer medicines.

Ongoing activities especially among health authorities and their advisers are also likely to include continual reevaluation of proposed models for fair pricing including those from AIM building on recent proposals by the WHO and others. Multi-indication pricing is also a potential consideration going forward as patient level database systems grow across Europe.

We will continue to monitor and debate the situation to provide future guidance to all key stakeholder groups.

4. Expert opinion

There is likely to be an increasing scrutiny over the value of new oncology medicines among health authority personnel in the future. This especially with likely continued requests for higher prices as new oncology therapies become available and are likely to be more targeted and more complex. This scrutiny will be enhanced by greater knowledge of the effectiveness and safety of new oncology medicines in routine clinical care with developments in health services databases, data collection methods, and electronic health records. We are already seeing health service records and databases being adapted to collect more clinical data to aid decision making and this will grow building on current systems and proposals such as the ongoing SACT program in England and the CMOP program in Scotland. Greater scrutiny will also be driven by the increasing number of oncology medicines currently used as first and second line treatments becoming available as either low-cost generics or biosimilars, with originator companies also increasingly likely to lower their prices once biosimilars become available to help maintain market share as seen with AbbVie in the Netherlands. This is likely to lead to greater scrutiny regarding rebates offered by Companies of still patented oncology medicines for continued reimbursement under existing MEAs and value-based pricing approaches once the medicines they used for price justifications during negotiations become available as multiple sourced medicines or biosimilars. In addition, greater consideration for fair pricing models.

Increasing scrutiny over potential prices for new oncology medicines is also likely to lead to greater discussions over potential clinical threshold levels for reimbursement and funding of new premium priced cancer medicines at various stages of the disease, coupled with restrictions of use and/or greater discounts where there are initial concerns until more data becomes available. In addition, there is likely to be increasing discussions regarding fair pricing for new oncology medicines as more models are proposed. These build on the suggestions of AIM and others along with greater evaluation of new MCDAs especially those for new oncology medicines. Concurrent with this, accelerated discussions regarding the potential for spreading the cost of new high-priced medicines over a number of years to enhance their affordability across Europe including new ATMPs

We are already seeing new cancer medicines being given conditional approval based on a limited number of patients in Phase II trials, and this trend is likely to grow to accelerate access to potentially new innovative therapies. Consequently, payers will need to become increasingly vigilant over such developments and potentially reflect this in their pricing negotiations and deliberations during any conditional approval or MEA; however, mindful of existing unmet need.

Overall, we are likely to see greater transparency in all aspects of pricing of new oncology medicines with the development of new pricing models and purchasing consortia especially with new proposals from the WHO, and in time potential convergence of prices across Europe. It is also likely that there will be an increase in the reevaluation of the value, prices and rebates of existing patented medicines once the comparator medicines used for negotiations lose their patent. However, such deliberations have to be balanced against

sufficient incentives in the system to develop new oncology medicines to address areas of unmet need.

Funding

There was no funding for this research and no assistance with the write-up.

Declaration of interest

Most of the authors work directly for health authorities or health insurance companies or are advisers to them (GS, CZD, WO, AT, LH, LV, JG, WC d S, TB, JCM, IH, AM, CH, RS, WH, OT, IL, RJ, AJ, IG-K, PVB, HFP, V de V, V M-P, JF, MOC, CZ, CP, ST, OM, RH). Steven Simoens has previously held the EGA Chair 'European policy towards generic medicines.' All the authors have no other conflicts of interest to declare.

ORCID

Brian Godman http://orcid.org/0000-0001-6539-6972
Steven Simoens http://orcid.org/0000-0002-9512-2005
Gisbert Selke http://orcid.org/0000-0002-9614-9875
Iva Selke Krulichová http://orcid.org/0000-0002-6815-0780
Carolina Zampirolli Dias http://orcid.org/0000-0003-2181-4268
Antony P Martin http://orcid.org/0000-0003-4383-6038
Luka Voncina http://orcid.org/0000-0002-1864-2381
Wânia Cristina Da Silva http://orcid.org/0000-0002-5108-5724
Amanj Kurdi http://orcid.org/0000-0001-5036-1988
Olayinka O. Ogunleye http://orcid.org/0000-0002-8921-1909
Johanna C Meyer http://orcid.org/0000-0003-0462-5713
Guenka Petrova http://orcid.org/0000-0001-8116-5138
John Yfantopoulos http://orcid.org/0000-0003-0424-6887
Arianit Jakupi http://orcid.org/0000-0002-7719-9690
Vanda Marković-Peković http://orcid.org/0000-0001-8963-5720
Ileana Mardare http://orcid.org/0000-0002-4725-9808
Dominik Tomek http://orcid.org/0000-0003-0838-5550
Mercè Obach Cortadellas http://orcid.org/0000-0002-2756-6181
Corinne Zara http://orcid.org/0000-0002-6831-2233
Caridad Pontes http://orcid.org/0000-0002-3274-6048
SeungJin Bae http://orcid.org/0000-0002-8993-8884
Ruaraidh Hill http://orcid.org/0000-0002-2801-0505

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. IQVIA. The Global Use of Medicine in 2019 and Outlook to 2023 - Forecasts and Areas to Watch. 2019. [cited 2020 Dec 10]. Available at URL: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023.pdf.
2. Waters R, Urquhart L. EvaluatePharma® World Preview 2019, Outlook to 2024. 2019. [cited 2020 Dec10]. Available at URL: https://info.evaluate.com/rs/607-YGS-364/images/EvaluatePharma_World_Preview_2019.pdf.
3. IQVIA Institute for Human Data Science. Global Oncology Trends 2018. [cited 2020 Dec9]. Available at URL: https://www.iqvia.com/institute/reports/global-oncology-trends-2018.
4. Simoens S, van Harten W, Lopes G, et al. What Happens when the Cost of Cancer Care Becomes Unsustainable. Eur Oncol Haematol. 2017;13(2):108–113.
5. IMS Institute for Healthcare Informatics. Global Oncology Trend Report. A Review of 2015 and Outlook to 2020. June 2016. [cited 2020 Dec 11]. Available at URL: https://www.scribd.com/document/323179495/IMSH-Institute-Global-Oncology-Trend-2015-2020-Report.
6. Haycox A. Why Cancer? PharmacoEconomics. 2016;34(7):625–627.
7. Howard DH, Bach P, Berndt ER, et al. Pricing in the market for anticancer drugs. J Econ Perspect. 2015;29(1):139–162.
8. Cohen D Cancer drugs: high price, uncertain value. BMJ. 2017;359:j4543.
•• Key paper discussing concerns with high prices and limited benefits of most new oncology medicines
9. WHO. Pricing of cancer medicines and its impacts. Geneva: world Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO. [cited 2020 Dec 10]. Available at URL: https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?sequence=1&isAllowed=y.
10. Molto C, Hwang TJ, Borrell M, et al. Clinical benefit and cost of breakthrough cancer drugs approved by the US Food and Drug Administration. Cancer. 2020;126(19):4390–4399. .
• Interesting paper documenting potential sales of new oncology medicines in one year in the US
11. Lauenroth VD, Kesselheim AS, Sarpatwari A, et al. Lessons from the impact of price regulation on the pricing of anticancer drugs in Germany. Health Affairs. 2020;39(7):1185–1193.
12. Wilking N, Bucsics A, Kandolf Sekulovic L, et al. Achieving equal and timely access to innovative anticancer drugs in the European Union (EU): summary of a multidisciplinary CECOG-driven roundtable discussion with a focus on Eastern and South-Eastern EU countries. ESMO Open. 2019;4(6):e000550–e.
• Interesting paper discussing disparities in oncology medicines across Euroope
13. Association of European Cancer Leagues. LET'S TALK ACCESS! WHITE PAPER ON TACKLING CHALLENGES IN ACCESS TO MEDICINES FOR ALL CANCER PATIENTS IN EUROPE. 2018. [cited 2020 Dec 9]. Available at URL: https://www.europeancancerleagues.org/wp-content/uploads/ECL-Lets-Talk-Access-White-Paper.pdf.
14. Baumgart DC, Misery L, Naeyaert S, et al. Biological therapies in immune-mediated inflammatory diseases: can biosimilars reduce access inequities? Front Pharmacol. 2019;10:279.
15. Ghinea H, Kerridge I, Lipworth W If we don't talk about value, cancer drugs will become terminal for health systems. 2015. [cited 2020 Dec 10]. Available at URL: http://theconversation.com/if-we-dont-talk-about-value-cancer-drugs-will-become-terminal-for-health-systems-44072 [
16. Shukla V, Seoane-Vazquez E, Fawaz S, et al. Landscape of cellular and gene therapy products: authorization, discontinuations, and cost. Hum Gene Ther Clin Dev. 2019;30(3):102–113.
17. Barlow JF, Yang M, Teagarden JR. Are payers ready, willing, and able to provide access to new durable gene therapies? Value Health. 2019;22(6):642–647.
18. Gyawali B, Sullivan R. Economics of Cancer Medicines: for Whose Benefit? 2017;23(1):95–104. The New Bioethics: A Multidisciplinary Journal of Biotechnology and the Body.
19. Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: understanding and stepping-up action on the financial toxicity of cancer treatment. CA. 2018;68(2):153–165.
20. Gershon N, Berchenko Y, Hall PS, et al. Cost effectiveness and affordability of trastuzumab in sub-Saharan Africa for early stage HER2-positive breast cancer. Cost Eff Resour Allocation. 2019;17:5.
21. Al-Ziftawi NH, Shafie AA, Mohamed Ibrahim MI Cost-effectiveness analyses of breast cancer medications use in developing countries: a systematic review. Expert review of pharmacoeconomics & outcomes research. 2020:1–11.
22. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. 2018;68(6):394–424.
23. Atieno OM, Opanga S, Martin A, et al. Pilot study assessing the direct medical cost of treating patients with cancer in Kenya; findings and implications for the future. J Med Econ. 2018;21(9):878–887.
24. Godman B. Biosimilars are becoming indispensable in the management of multiple diseases although concerns still exist. Bangladesh J Med Sci. 2021;20(1):5-10.

25. Hill A, Redd C, Gotham D, et al. Estimated generic prices of cancer medicines deemed cost-ineffective in England: a cost estimation analysis. BMJ Open. 2017;7(1):e011965.
26. Godman B, Hill A, Simoens S, et al. Pricing of oral generic cancer medicines in 25 European countries; findings and implications. GaBI J. 2019;8(2):49–70.
    • **Critical paper discussing low prices for generic oral cancer medicines in Europe**
27. Jensen TB, Kim SC, Jimenez-Solem E, et al. Shift From Adalimumab Originator to Biosimilars in Denmark. JAMA Intern Med. 2020;180 (6):902–903.
28. Sagonowsky E. AbbVie's massive Humira discounts are stifling Netherlands biosimilars: report. 2019. [cited 2020 Dec 9]. Available at URL: https://www.fiercepharma.com/pharma/abbvie-stifling-humira-biosim-competition-massive-discounting-dutch-report.
29. Lee Mendoza R. Incentives and disincentives to drug innovation: evidence from recent literature. J Med Econ. 2019;22(8):713–721.
30. Jarosławski S, Toumi M, Auquier P, et al. Non-profit Drug Research and Development at a Crossroads. Pharm Res. 2018;35(3):52.
31. Marselis D, Hordijk L. From blockbuster to "nichebuster": how a flawed legislation helped create a new profit model for the drug industry. BMJ. 2020;370:m2983.
32. FDA. FDA approves larotrectinib for solid tumors with NTRK gene fusions. 2018. [cited 2020 Dec 9]. Available at URL: https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-0.
33. Gyawali B, Hwang TJ, Vokinger KN, et al. Patient-Centered Cancer Drug Development: clinical Trials, Regulatory Approval, and Value Assessment. American Society of Clinical Oncology Educational Book. 2019(39):374–387.
34. Pontes C, Zara C, Torrent-Farnell J, et al. Time to Review Authorisation and Funding for New Cancer Medicines in Europe? Inferences from the Case of Olaratumab. Appl Health Econ Health Policy. 2020;18(1):5–16.
    • **Good paper discussing potential implications of early funding of new oncology medicines**
35. Vella Bonanno P, Ermisch M, Godman B, et al. Adaptive Pathways: possible Next Steps for Payers in Preparation for Their Potential Implementation. Front Pharmacol. 2017;8:497.
36. DeMartino PC, Miljkovic MD, Prasad V. Potential Cost Implications for All US Food and Drug Administration Oncology Drug Approvals in 2018. JAMA Intern Med. 2021;181(2):162-16.
37. Lakdawalla DN, Doshi JA, Garrison LP Jr., et al. Defining Elements of Value in Health Care-A Health Economics Approach: an ISPOR Special Task Force Report [3]. Value Health. 2018;21(2):131–139.
38. Garrison LP Jr., Kamal-Bahl S, Towse A. Toward a Broader Concept of Value: identifying and Defining Elements for an Expanded Cost-Effectiveness Analysis. Value Health. 2017;20(2):213–216.
39. McKenna I How do we Measure the "Value" in Value-Based care? OHE Seminar Briefing 31. London.2019. [cited 2020 Dec 10]. Available at URL: https://www.ohe.org/publications/how-do-we-measure-%E2%80%9Cvalue%E2%80%9D-value-based-care.
40. Ferguson JS, Summerhayes M, Masters S, et al. New treatments for advanced cancer: an approach to prioritization. Br J Cancer. 2000;83(10):1268–1273.
41. Wild C, Grossmann N, Bonanno PV, et al. Utilisation of the ESMO-MCBS in practice of HTA. Ann Oncol. 2016;27(11):2134–2136.
42. Fortinguerra F, Tafuri G, Trotta F, et al. GRADE methodology to assess innovation of new medicinal products in Italy. Br J Clin Pharmacol. 2020;86(1):93–105.
43. AIM. AIM PROPOSES TO ESTABLISH A EUROPEAN DRUG PRICING MODEL FOR FAIR AND TRANSPARENT PRICES FOR ACCESSIBLE PHARMACEUTICAL INNOVATIONS. [cited 2020 Dec 11]. Available at URL: https://www.aim-mutual.org/wp-content/uploads/2019/12/AIMs-proposal-for-fair-and-transparent-prices-for-pharmaceuticals.pdf
44. Uyl-de Groot CA, Lowenberg B. Sustainability and affordability of cancer drugs: a novel pricing model. Nat Rev Clin Oncol. 2018;15 (7):405–406.
45. WHO. WHO guideline on country pharmaceutical pricing policies, second edition. Geneva: World Health Organization; 2020. [cited 2020 Dec 9]. Available at URL: https://apps.who.int/iris/bitstream/handle/10665/335692/9789240011878-eng.pdf.
46. Zampirolli Dias C, Godman B, Gargano LP, et al. Integrative Review of Managed Entry Agreements: chances and Limitations. PharmacoEconomics. 2020;38(11):1165–1185.
    • **Recent review of MEAs across countries and issues/ concerns**
47. Ferrario A, Arāja D, Bochenek T, et al. The Implementation of Managed Entry Agreements in Central and Eastern Europe: findings and Implications. PharmacoEconomics. 2017;35(12):1271–1285.
48. Carlson JJ, Chen S, Garrison LP Jr. Performance-Based Risk-Sharing Arrangements: an Updated International Review. PharmacoEconomics. 2017;35(10):1063–1072.
49. AM P, HM K, NS D, et al. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. BMJ. 2017;357:j1680.
50. Hsu JC, Lin J-Y, Lin P-C, et al. Comprehensive value assessment of drugs using a multi-criteria decision analysis: an example of targeted therapies for metastatic colorectal cancer treatment. PloS One. 2019;14(12):e0225938–e.
51. Annemans L. A proposal for value informed, affordable ("via") prices for innovative medicines. J Med Econ. 2019;22 (11):1235–1239.
52. Workman P, Draetta GF, Schellens JH, et al. How Much Longer Will We Put Up With $100,000 Cancer Drugs? Cell. 2017;168 (4):579–583.
53. Kemp-Casey A, Pratt N, Ramsay E, et al. Using Post-market Utilisation Analysis to Support Medicines Pricing Policy: an Australian Case Study of Aflibercept and Ranibizumab Use. Appl Health Econ Health Policy. 2019;17(3):411–417.
54. Eriksson I, Wettermark B, Persson M, et al. The Early Awareness and Alert System in Sweden: history and Current Status. Front Pharmacol. 2017;8:674.
55. Towse A, Cole A, Zamora B The Debate on IndicationBased Pricing in the U.S. and Five Major European Countries. 2018. [cited 2020 Dec 10]. Available at URL: file:///C:/Users/mail/Downloads/OHE%20IBP%20Final%20Report%20May%202018%20(Revised).pdf
56. Campbell JD, Kalo Z. Fair global drug pricing. Expert review of pharmacoeconomics & outcomes research. 2018;18(6):581–583.
57. Godman B, Bucsics A, Vella Bonanno P, et al. Barriers for Access to New Medicines: searching for the Balance Between Rising Costs and Limited Budgets. Front Public Health. 2018;6:328.
58. Moorkens E, Vulto AG, Huys I, et al. Policies for biosimilar uptake in Europe: an overview. PloS One. 2017;12(12):e0190147.
59. European Commission. DEFINING VALUE IN "VALUE BASED HEALTHCARE". Report of the Expert Panel on effective ways of investing in Health (EXPH). 2019. [cited 2020 Dec 9]. Available at URL: https://ec.europa.eu/health/sites/health/files/expert_panel/docs/024_defining-value-vbhc_en.pdf
60. Garrison LP, Towse A. Value-Based Pricing and Reimbursement in Personalised Healthcare: introduction to the Basic Health Economics. J Pers Med. 2017;7(3):10.
61. Barrett A, Roques T, Small M, et al. How much will Herceptin really cost? BMJ. 2006;333(7578):1118–1120.
62. Svensson M, Nilsson FO, Arnberg K. Reimbursement Decisions for Pharmaceuticals in Sweden: the Impact of Disease Severity and Cost Effectiveness. PharmacoEconomics. 2015;33(11):1229–1236.
63. Berdud M, Drummond M, Towse A. Establishing a reasonable price for an orphan drug. Cost Eff Resour Allocation. 2020;18(1):31.
64. McHugh N, van Exel J, Mason H, et al. Are life-extending treatments for terminal illnesses a special case? Exploring choices and societal viewpoints. Soc Sci Med. 2018;198:61–69.
65. Simoens S, Picavet E, Dooms M, et al. Cost-effectiveness assessment of orphan drugs: a scientific and political conundrum. Appl Health Econ Health Policy. 2013;11(1):1–3.
66. Paoletti X, Lewsley LA, Daniele G, et al. Assessment of Progression-Free Survival as a Surrogate End Point of Overall Survival in First-Line Treatment of Ovarian Cancer: A Systematic

Review and Meta-analysis. JAMA Network Open. 2020;3(1): e1918939.
67. Prasad V, Kim C, Burotto M, et al. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. JAMA Intern Med. 2015;175(8):1389–1398.
68. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32 (12):1277–1280.
69. Dreicer JJ, Mailankody S, Fahkrejahani F, et al. Clinically meaningful benefit: real world use compared against the American and European guidelines. Blood Cancer J. 2017;7(12):645.
70. Kantarjian HM, Fojo T, Mathisen M, et al. Cancer drugs in the United States: justum Pretium–the just price. J Clin Oncol. 2013;31 (28):3600–3604.
71. Davis C, Naci H, Gurpinar E, et al. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ. 2017;359:j4530.
72. Salas-Vega S, Iliopoulos O, Mossialos E. Assessment of Overall Survival, Quality of Life, and Safety Benefits Associated With New Cancer Medicines. JAMA Oncol. 2017;3(3):382–390.
73. Pauwels K, Huys I, Vogler S, et al. Managed Entry Agreements for Oncology Drugs: lessons from the European Experience to Inform the Future. Front Pharmacol. 2017;8:171.
74. OECD. Addressing Challenges in Access to Oncology Medicines - Analytical Report. 2020. [cited 2020 Dec 10]. Available at URL: https://www.oecd.org/health/health-systems/Addressing-Challenges-in-Access-to-Oncology-Medicines-Analytical-Report.pdf
75. Gyawali B, Addeo A. Negative phase 3 randomized controlled trials: why cancer drugs fail the last barrier? Int J Cancer. 2018;143 (8):2079–2081.
76. Grignolo A, Pretorius S Phase III Trial Failures, Costly But Preventable. Applied Clinical Trials. 2016. [cited 2020 Dec 9]. Available at URL: https://www.parexel.com/application/files_previous/5014/7274/5573/ACT_Article.pdf
77. Garattini L, Curto A. Performance-Based Agreements in Italy: 'Trendy Outcomes' or Mere Illusions? PharmacoEconomics. 2016;34(10):967–969.
78. Edlin R, Hall P, Wallner K, et al. Sharing risk between payer and provider by leasing health technologies: an affordable and effective reimbursement strategy for innovative technologies? Value Health. 2014;17(4):438–444.
79. Makady A, van Veelen A, de Boer A, et al. Implementing managed entry agreements in practice: the Dutch reality check. Health Policy. 2019;123(3):267–274.
80. Bennie M Cancer Medicines Outcome Project (CMOP). [cited 2020 Dec 10]. Available at URL: https://cancerchallengescotland.com/sites/default/files/documents/event_item/PROMsPREMs_Info_Session_190417/cic_info_session_190417_marion_bennie.pdf
81. Baillie K, Mueller T, Pan J, et al. Use of record linkage to evaluate treatment outcomes and trial eligibility in a real-world metastatic prostate cancer population in Scotland. Pharmacoepidemiol Drug Saf. 2020;29(6):653–663.
82. Bright CJ, Lawton S, Benson S, et al. Data Resource Profile: the Systemic Anti-Cancer Therapy (SACT) dataset. Int J Epidemiol. 2019;49(1):15–l.
83. NICE. Cancer Drugs Fund Managed Access Agreement Axicabtagene ciloleucel for treating diffuse large Bcell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA559]. January 2019. [cited 2020 Dec 11]. Available at URL: https://www.nice.org.uk/guidance/ta559/resources/managed-access-agreement-january-2019-pdf-6660053245.
84. Kefalas P, Ali O, Jorgensen J, et al. Establishing the cost of implementing a performance-based, managed entry agreement for a hypothetical CAR T-cell therapy. J Mark Access Health Policy. 2018;6(1):1511679.
85. Nazareth T, Ko JJ, Sasane R, et al. Outcomes-Based Contracting Experience: research Findings from U.S. and European Stakeholders. J Manag Care Spec Pharm. 2017;23(10):1018–1026.
86. Antonanzas F, Juarez-Castello C, Lorente R, et al. Use of Risk-Sharing Contracts in Healthcare: theoretical and Empirical Assessments. PharmacoEconomics. 2019;37(12):1469–1483.
87. Toumi M, Jaroslawski S, Sawada T, et al. The Use of Surrogate and Patient-Relevant Endpoints in Outcomes-Based Market Access Agreements: current Debate. Appl Health Econ Health Policy. 2017;15(1):5–11.
88. Al-Omar HA, Alghannam HH, Aljuffali IA Exploring the status and views of managed entry agreements in Saudi Arabia: mixed-methods approach. Expert review of pharmacoeconomics & outcomes research. 2020:1–9.
89. Hampson G, Towse A, WB D, et al. Real-world evidence for coverage decisions: opportunities and challenges. J Comp Eff Res. 2018;7 (12):1133–1143.
90. Frisk P, Aggefors K, Cars T, et al. Introduction of the second-generation direct-acting antivirals (DAAs) in chronic hepatitis C: a register-based study in Sweden. Eur J Clin Pharmacol. 2018;74(7):971–978.
91. Eriksson I, Wettermark B, Bergfeldt K. Real-World Use and Outcomes of Olaparib: a Population-Based Cohort Study. Target Oncol. 2018;13(6):725–733.
92. Clopes A, Gasol M, Cajal R, et al. Financial consequences of a payment-by-results scheme in Catalonia: gefitinib in advanced EGFR-mutation positive non-small-cell lung cancer. J Med Econ. 2017;20(1):1–7.
93. Jørgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. J Mark Access Health Policy. 2020;8(1):1715536.
94. Alkhatib NS, Abraham I. The six Delta platform for outcome-based contracting for pharmaceuticals. J Med Econ. 2020;23(11):1209-14.
95. Eatwell E, Swierczyna A Emerging voluntary cooperation between European healthcare systems: are we facing a new future? Medicine Access@Point of Care 2019; 1–8.
96. Berns A, Ringborg U, Celis JE, et al. Towards a cancer mission in Horizon Europe: recommendations. Mol Oncol. 2020;14 (8):1589–1615.
97. Howard S, Scott IA, Ju H, et al. Multicriteria decision analysis (MCDA) for health technology assessment: the Queensland Health experience. Aust Health Rev. 2019;43(5):591–599.
98. Hughes-Wilson W, Palma A, Schuurman A, et al. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? Orphanet J Rare Dis. 2012;7:74.
99. Roldán Ú, Bradia X, Marcos-Rodríguez JA, et al. MULTI-CRITERIA DECISION ANALYSIS AS A DECISION-SUPPORT TOOL FOR DRUG EVALUATION: A PILOT STUDY IN A PHARMACY AND THERAPEUTICS COMMITTEE SETTING. Int J Technol Assess Health Care. 2018;34(5):519–526.
100. Youngkong S, Baltussen R, Tantivess S, et al. Multicriteria decision analysis for including health interventions in the universal health coverage benefit package in Thailand. Value Health. 2012;15 (6):961–970.
101. Kaur G, Prinja S, Lakshmi PVM, et al. Criteria Used for Priority-Setting for Public Health Resource Allocation in Low- and Middle-Income Countries: A Systematic Review. Int J Technol Assess Health Care. 2019;35(6):474–483.
102. Kapiriri L, Baltussen R, Oortwijn W. Implementing evidence-informed deliberative processes in health technology assessment: a low income country perspective. Int J Technol Assess Health Care. 2020;36(1):29–33.
103. Angelis A, Linch M, Montibeller G, et al. Multiple Criteria Decision Analysis for HTA across four EU Member States: piloting the Advance Value Framework. Soc Sci Med. 2020;246:112595.
104. Ezeife DA, Dionne F, Fares AF, et al. Value assessment of oncology drugs using a weighted criterion-based approach. Cancer. 2020;126 (7):1530–1540.
105. DiStefano MJ, Krubiner CB. Beyond the numbers: a critique of quantitative multi-criteria decision analysis. Int J Technol Assess Health Care. 2020;1–5.
106. CADTH. The pCODR Expert Review Committee (pERC). 2020. Available at URL: https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/pcodr-expert-review-committee-perc.

107. Baltussen R, Marsh K, Thokala P, et al. Multicriteria Decision Analysis to Support Health Technology Assessment Agencies: benefits, Limitations, and the Way Forward. Value Health. 2019;22 (11):1283–1288.
108. Wahlster P, Goetghebeur M, Kriza C, et al. Balancing costs and benefits at different stages of medical innovation: a systematic review of Multi-criteria decision analysis (MCDA). BMC Health Serv Res. 2015;15(262).
109. Cole A, Towse A, Lorgelly P, et al. Economics of Innovative Payment Models Compared with Single Pricing of Pharmaceuticals. Available at URL: https://www.ohe.org/publications/economics-innovative-payment-models-compared-single-pricing-pharmaceuticals-0.
110. European Commission. INNOVATIVE PAYMENT MODELS FOR HIGH-COST INNOVATIVE MEDICINES. Report of the Expert Panel on effective ways of investing in Health (EXPH). 2018. Available at URL: https://ec.europa.eu/health/expert_panel/sites/expertpanel/files/docsdir/opinion_innovative_medicines_en.pdf.
111. Yeung K, Li M, Carlson JJ. Using Performance-Based Risk-Sharing Arrangements to Address Uncertainty in Indication-Based Pricing. J Manag Care Spec Pharm. 2017;23(10):1010–1015.
112. Campillo-Artero C, Puig-Junoy J, Segu-Tolsa JL, et al. Models for Multi-indication Drugs: A Systematic Review. Appl Health Econ Health Policy. 2020;18(1):47–56.
113. Chandra A, Garthwaite C. The Economics of Indication-Based Drug Pricing. N Engl J Med. 2017;377(2):103–106.
114. Mestre-Ferrandiz J, Zozaya N, Alcalá B, et al. Multi-Indication Pricing: nice in Theory but Can it Work in Practice? PharmacoEconomics. 2018;36(12):1407–1420.
115. Hoffmann M, Vander Stichele R, Bates DW, et al. Guiding principles for the use of knowledge bases and real-world data in clinical decision support systems: report by an international expert workshop at Karolinska Institutet. Expert Rev Clin Pharmacol. 2020;13 (9):925–34.
116. Garattini L, Curto A, van de Vooren K. Do the current performance-based schemes in Italy really work? "Success fee": a novel measure for cost-containment of drug expenditure. Value Health. 2015;18(2):352.
117. Mestre-Ferrandiz J, Towse A, Dellamano R, et al. Multiindication pricing: pros, cons and applicability to the UK. OHE 2015. Available at URL: https://www.ohe.org/publications/multi-indication-pricing-pros-cons-and-applicability-uk.
118. WHO. Fair Pricing Forum 2017 Meeting Report. 2017. Available at URL: https://www.who.int/medicines/access/fair_pricing/FairPricingForum2017MeetingReport.pdf?ua=1.
119. Moon S, Mariat S, Kamae I, et al. Defining the concept of fair pricing for medicines. BMJ. 2020;368:l4726–l.
120. Suleman F, Low M, Moon S, et al. New business models for research and development with affordability requirements are needed to achieve fair pricing of medicines. BMJ. 2020;368:l4408–l.
•• Key paper discussing new business models for new medicines
121. Prokupkova A Tackling challenges in access to innovative cancer medicines - societal perspective. 2019. [cited 2020 Dec 10]. Available at URL: https://www.aim-mutual.org/wp-content/uploads/2019/12/Anna-Prokupkova_The-societal-perspective-Tackling-challenges-in-access-to-innovative-cancer-medicines.pdf
122. Hill A, Gotham D, Fortunak J, et al. Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. BMJ Open. 2016;6(1):e009586.
123. Hill AM, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. BMJ Glob Health. 2018;3(1):e000571.
124. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood. 2013;121(22):4439–4442.
125. Kaiser J. Personalized medicine. New cystic fibrosis drug offers hope, at a price. Science (New York, NY). 2012;335(6069):645.
126. Luzzatto L, Hyry HI, Schieppati A, et al. Outrageous prices of orphan drugs: a call for collaboration. Lancet. 2018;392(10149):791–794.
• Critical paper discussing current prices for new medicines for orphan diseases and concerns
127. Hollis A. Orphan Drug Pricing and Costs: A Case Study of Kalydeco and Orkambi. Healthcare Policy. 2019;15(1):70–80.
128. Tefferi A, Kantarjian H, Rajkumar SV, et al. In Support of a Patient-Driven Initiative and Petition to Lower the High Price of Cancer Drugs. Mayo Clin Proc. 2015;90(8):996–1000.
129. De Oliveira GL, Guerra Junior AA, Godman B, et al. Cost-effectiveness of vildagliptin for people with type 2 diabetes mellitus in Brazil; findings and implications. Expert Rev Pharmacoecon Outcomes Res. 2017;17(2):109–119.
130. Godoi IP, Santos AS, Reis EA, et al. Consumer Willingness to Pay for Dengue Vaccine (CYD-TDV, Dengvaxia(R)) in Brazil; Implications for Future Pricing Considerations. Front Pharmacol. 2017;8:41.
131. Muniz Júnior RL, Godói IP, Reis EA, et al. Consumer willingness to pay for a hypothetical Zika vaccine in Brazil and the implications. Expert Rev Pharmacoecon Outcomes Res. 2019;19(4):473–482.
132. Acosta A, Vanegas EP, Rovira J, et al. Medicine Shortages: gaps Between Countries and Global Perspectives. Front Pharmacol. 2019;10:763.
133. Popa C, Holvoet K, Van Montfort T, et al. Risk-Return Analysis of the Biopharmaceutical Industry as Compared to Other Industries. Front Pharmacol. 2018;9:1108.
134. Franzen N, Retèl VP, Schats W, et al. Evidence Underlying Policy Proposals for Sustainable Anticancer Drug Prices: A Systematic Review. JAMA Oncol. 2020;6(6):909–916.
135. O'Mahony JF. Beneluxa: what are the Prospects for Collective Bargaining on Pharmaceutical Prices Given Diverse Health Technology Assessment Processes? PharmacoEconomics. 2019;37 (5):627–630.
136. Tvd G, Uyl-de Groot CA, Pieters T. Addressing the challenge of high-priced prescription drugs in the era of precision medicine: A systematic review of drug life cycles, therapeutic drug markets and regulatory frameworks. PloS One. 2017;12(8):e0182613–e.
137. Kiddell-Monroe R, Greenberg A, Basey M Re:Route: a map of the alternative biomedical R&D landscape. Universities Allied for Essential Medicines, 2016. Available at URL: http://altreroute.com/assets/download/UAEM_Reroute_Report.pdf.
138. MIT NEWDIGS FoCUS Project. Designing financial solutions to ensure affordable access to cures - An overview of the MIT FoCUS project. 2018. Available at URL: https://newdigs.mit.edu/sites/default/files/NEWDIGS%20FoCUS%20Frameworks%2020180823.pdf
139. Maes I, Boufraioua H, Van Dyck W, et al. Innovative funding solutions for paradigm changing advanced therapy medicinal products (ATMP) in Belgium - Multi-stakeholder consensus on gene therapy funding solutions. Nov 2019. [cited 2020 Dec 11]. Available at URL: https://www.vlerick.com/~/media/Corporate/Pdf-knowledge/Policy-Paper-Innovative-Solutions-For-Paradigm-Changing-New-Therapiespdf.pdf.
140. AMCP Partnership Forum: designing Benefits and Payment Models for Innovative High-Investment Medications. J Manag Care Spec Pharm. 2019;25(2):156–162.
141. Towse A, Fenwick E. Uncertainty and Cures: discontinuation, Irreversibility, and Outcomes-Based Payments: what Is Different About a One-Off Treatment? Value Health. 2019;22(6):677–683.
142. Trusheim MR, Cassidy WM, Bach PB. Alternative State-Level Financing for Hepatitis C Treatment-The "Netflix Model". Jama. 2018;320(19):1977–1978.
143. Chalkidou K, Towse A, Silverman R Unpacking the Black Box of Payer Policy: A Demand-Side Approach for Equitable Uptake of Cost-Effective Health Innovation. CGD Note 2020. [cited 2020 Dec 10]. Available at URL: https://www.cgdev.org/sites/default/files/Chalkidou-Innovation-Uptake.pdf.