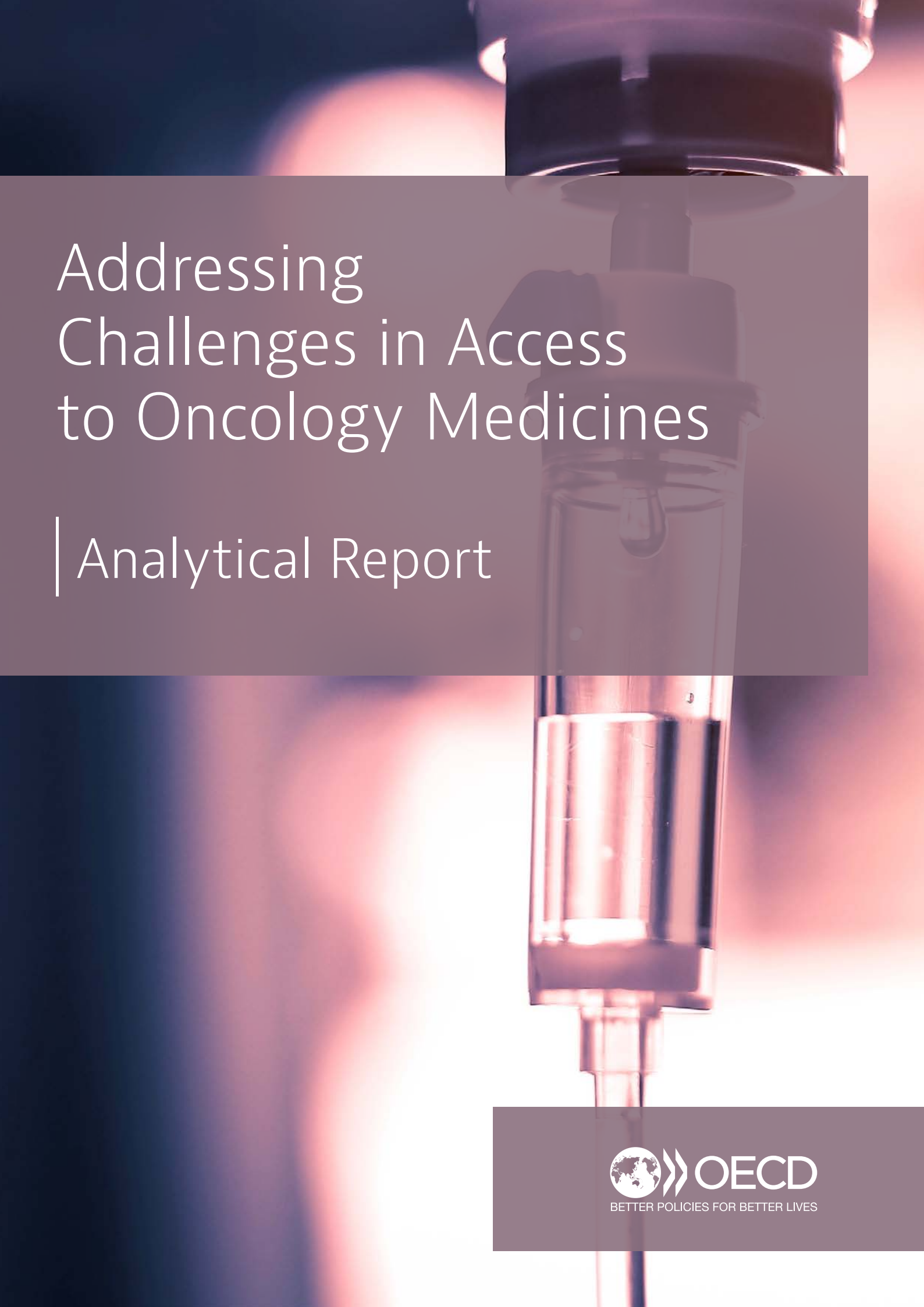

Addressing Challenges in Access to Oncology Medicines

Analytical Report

OECD

BETTER POLICIES FOR BETTER LIVES

ADDRESSING CHALLENGES IN ACCESS TO ONCOLOGY MEDICINES

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List of acronyms and abbreviations

ABPI	Association of the British Pharmaceutical Industry
AIFA	Italian Medicines Agency
ASCO	American Society of Clinical Oncology
ASP	Average sales price
ATC	Anatomical Therapeutic Chemical classification
ATMP	Advanced therapy medicinal products
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR-T	Chimeric antigen receptor T-cell therapy
CDF	Cancer Drugs Fund (England)
CHMP	Committee for Medicinal Products for Human Use
CMS	Centers for Medicare & Medicaid Services (United States)
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DDD	Defined daily dose
DHSC	Department of Health & Social Care (England)
dMMR	Deficient mismatch repair
DRG	Diagnosis related group
EBP	Evidence Building Program (Canada)
ECL	European Cancer Leagues
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EML	Essential Medicines List (i.e. 21st WHO *Model List of Essential Medicines*)
EOPYY	National Organization for the Provision of Health Services (Greece)
ESMO	European Society for Medical Oncology
ESMO-MCBS	European Society for Medical Oncology Magnitude of Clinical Benefit Scale
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
Euripid	European Integrated Price Information Database
FDA	Food and Drug Administration (United States)
GDP	Gross domestic product
GP	General practitioner

GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Haute Autorité de Santé (France)
HER-2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
IBP	Indication-based pricing
INCa	French National Cancer Institute
MEA	Managed entry agreement
MfE	Medicines for Europe
MOH	Ministry of Health
MSI-H	Microsatellite instability-high
NHS	National Health Service
NHSE-I	National Health Service England & Improvement
NICE	National Institute for Health and Care Excellence
NoMA	Norwegian Medicines Agency
NTRK	Neurotrophic Tyrosine Receptor Kinase
OOP	Out-of-pocket payments
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PBS	Pharmaceutical Benefits Scheme (Australia)
pCODR	pan-Canadian Oncology Drug Review
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PMPRB	Patented Medicine Prices Review Board
PPRI	Pharmaceutical Pricing and Reimbursement Information network
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RWD	Real world data
TKI	Tyrosine kinase inhibitor
TLV	Dental and Pharmaceutical Benefits Agency (Sweden)
WHO	World Health Organization
WHOCC	WHO Collaborating Centre for Drug Statistics Methodology
WTP	Willingness to pay

Country abbreviations

AUS	Australia
BEL	Belgium
CAN	Canada
CHE	Switzerland
CHL	Chile
CYP	Cyprus[1]
CZE	Czech Republic
DEU	Germany
DNK	Denmark
EST	Estonia
FRA	France
GBR	United Kingdom (England only)
GRC	Greece
HUN	Hungary
IRL	Ireland
ISR	Israel
ITA	Italy
JPN	Japan
KOR	Korea
LTU	Lithuania
LVA	Latvia
MLT	Malta
NOR	Norway
SWE	Sweden
USA	United States

[1] Note by Turkey: The information in this document with reference to "Cyprus" relates to the southern part of the Island. There is no single authority representing both Turkish and Greek Cypriot people on the Island. Turkey recognises the Turkish Republic of Northern Cyprus (TRNC). Until a lasting and equitable solution is found within the context of the United Nations, Turkey shall preserve its position concerning the "Cyprus issue".

Note by all the European Union Member States of the OECD and the European Union: The Republic of Cyprus is recognised by all members of the United Nations with the exception of Turkey. The information in this document relates to the area under the effective control of the Government of the Republic of Cyprus.

Executive summary

1. Faced with rapid advancements in oncology treatments, even the wealthiest countries around the globe have raised concerns about providing and sustaining access to new medicines. This report, based on a series of initial interviews, and augmented by an extensive survey to which 25 countries in total responded, describes **policies and practices adopted by countries to address a number of challenges that are specific to oncology medicines**.

2. One of the key challenges is the **often significant uncertainty surrounding the degree of clinical benefit offered by a new medicine** at the time of market entry. In oncology, new products and new indications are frequently approved in earlier phases of development, on the basis of surrogate endpoint data, or on evidence from non-randomised trials—all of which can lead to the overestimation of clinical benefit. This is driven in large part by the desire to facilitate rapid access to promising therapies in areas of unmet or inadequately met need, but with the result that payers and Health Technology Assessment (HTA) entities may struggle to determine the value of these products and make confident decisions on coverage and pricing. Thus far, a common approach to addressing uncertainty has been the use of managed entry agreements, mainly with the objective of managing *financial* risks. However, for the most part, these agreements have not helped reduce uncertainties surrounding the clinical benefits of the treatments concerned (and by extension, their cost-effectiveness), though this might be possible with greater attention to the design of the agreements and more harmonised approaches across countries.

3. Another major challenge is that **many products have multiple indications, which may have been approved in quick succession, and with varying degrees of clinical benefit**. This generates considerable debate about the appropriateness of setting prices by indication to reflect differences in value. Indication-based pricing (IBP) is expected to provide better access (in comparison with a single "high" price leading to coverage restrictions) and allow companies to capture a larger share of the surplus generated (in comparison with a single "low" price), thus sending "appropriate" signals to innovators. Some of the countries surveyed do not agree with IBP principles, and among those that do and use it (generally via confidential agreements)[2], few are able to track the use of the products by indication. The coverage of each additional indication of a product often leads to a price reduction to reflect the anticipated volume increase, even in countries willing to take into account differential values across indications.

4. The **pricing of products used in combination** with other treatments is also an emerging challenge, with 16 'combination' therapies approved in Europe at the end of 2019, and a myriad of ongoing clinical trials, notably combining novel immunotherapies with other targeted therapies. Frequently, an application for coverage is filed by the sponsor of a new product (the 'add-on' therapy), for use in combination with an existing product (the 'backbone' therapy). HTA entities assess the value[3] of the combination therapy relative to a comparator (usually the backbone therapy), and payers determine their willingness to pay (WTP) for the combination. When the two products are already marketed in other indications, the sum of the two prices is often well above the payer's WTP, necessitating downward price adjustments for one or both constituent therapies. In an ideal world, the price would be set in a way that reflected the respective contributions of the constituent medicines to the overall clinical benefit of treatment, but there is no consensus on a defined framework by which to attribute these shares. In addition, where products used together are sold by different companies, competition law may preclude the negotiation of agreements between companies on the prices to be charged for individual products. **Only a few countries have methods for the pricing of combination products**, among them France, the United Kingdom

[2] Australia, Belgium, Estonia, France, Germany, Italy, Latvia, Switzerland

[3] "Value" may be defined differently across countries.

(England), and Switzerland, which, after having determined their WTP for a combined therapy, then negotiate with the individual companies. Price adjustments generally take the form of confidential rebates on list prices.

5. Confronted with the growing number of new therapies entering the market at high prices, **many OECD countries have raised concerns about their ability to reconcile access to oncology treatments with spending efficiency and sustainability**. Expenditure on oncology medicines has steadily increased over time, not only due to higher launch prices, but also to steady increases in the number of patients being treated (a combination of rising prevalence, new treatment options, and increasing duration of treatment). That said, in OECD member countries, retail pharmaceutical expenditure as a proportion of gross domestic product (GDP) has, on average, remained stable over the past decade, at around 1.5%, even though some countries have seen greater growth in expenditure on medicines administered in hospital or ambulatory care settings. This relative stability is due to the fact that many countries have implemented policies to contain pharmaceutical costs, including overall budget constraints or spending caps. To guarantee access to a selection of new high-cost oncology medicines in that context, both Italy and the United Kingdom (England) have set up earmarked funds, with caps beyond which companies selling products financed through these funds are required to pay rebates.

6. In this study, **access to oncology medicines was assessed using information provided by 23 of the 25 responding OECD/EU countries on the approval and coverage status of a sample of 109 product/indication pairs used across five cancer types**, as at the end of 2019. Time to access (i.e. time between the date of submission of a marketing authorisation application and the date of coverage decision) was then computed for a subset of 31 product/indication pairs approved in the United States since 2014. Information on cost-sharing requirements was also used to provide an indication of affordability for patients.

7. From these data **it is clear that access to oncology medicines remains unequal across OECD/EU countries**, an observation that has been documented in previous studies. Of the 109 product/indication pairs in the sample, the United States had the largest percentage of product/indications approved and covered (by Medicare), followed by Denmark and Germany (96%, 91%, and 88%, respectively). Chile and Malta had the lowest percentage of pairs approved and covered (47% and 46% respectively). Access was more homogeneous across countries for a subset of *essential medicines*[4]*,* but more heterogeneous for the 31 newer product/indication pairs, some of which are not yet approved (or launched) in all countries.

8. The average proportion of medicines approved and covered varied with cancer type (metastatic breast cancer 77%, non-small cell lung cancer 69%, colorectal cancer 69%, melanoma 62%, multiple myeloma 75%, and supportive care 83%). However, across these indications, all medicines included in the WHO Essential Medicines List, and at least one in each pharmacological subgroup, were covered in nearly all countries.

9. **Time to marketing and coverage decisions by public payers[5] for new oncology product/indications varied widely across OECD/EU.** Of the 31 new product/indication pairs approved since 2014, 26 (84%) received their first marketing authorisation in the United States. Across the sample, the average time between date of first marketing authorisation (usually in the United States) and subsequent authorisation in other countries/regions ranged from 12 to 17 months. For individual product/indications, the time elapsed between date of first marketing authorisation and coverage decision in a given country ranged from 1 to 66 months (more than 5 years). This reflects both companies' launch sequences, and processing times for marketing approval, pricing, and coverage decisions.

[4] A subset of 32 product/indication pairs that are included in the World Health Organization's (WHO) 21st *Model List of Essential Medicines* (EML).

[5] This indicator could only be computed for countries which provided complete responses.

10. At country level, the time between application for marketing authorisation and granting of coverage was decomposed into separate periods. The regulatory review period, including any clock-stops (i.e. time taken by the company to provide additional information requested by the regulator to inform the assessment of the application), ranged from 7 months in the United States, to 13 months in the European Economic Area. The time between application and granting of coverage ranged from 4 months in Sweden to 27 months in Malta. In some cases, application for coverage may be filed prior to regulatory approval, which shortens the time to access. The average total time from application for marketing authorisation to coverage ranged from 9 months in Israel and 11 months in Japan, to 52 months in Malta.

11. **Inequities in access within countries were also reported. These can be attributed to variations in coverage across regions or sub-national levels of government, health care settings and population groups, as well as to cost-sharing policies**. While most OECD/EU countries make coverage decisions at the national level, and which are generally valid across all settings of care, regions or population groups, there are some exceptions (e.g. Australia, Canada, some Nordic countries and United States). In oncology, where medicine prices can be particularly high, cost-sharing requirements can substantially affect affordability for patients. Where patient contributions are required, fixed co-payments are, in principle, more effective in providing financial protection than co-insurance, where contributions are set as a percentage of the cost of the medicine. Based on the OECD survey, countries were categorized according to the type of cost-sharing applied to cancer care. In 13 countries, patients access oncology medicines for self-administration free of charge, or with a fixed co-payment. In other countries, patients are subject to co-insurance, so individual costs **increase** with the prices of the medicines. In most countries, inpatient and outpatient cancer care services, including administration of injectable products, are provided free of charge when delivered by public providers. Almost all countries have a cap on user charges. These caps are defined in absolute or relative terms (e.g. a fixed amount or proportion of household income). They typically represent less than 1%-2% of the average wage in European countries, but may exceed 9% and 10% in the United States and Korea respectively.

12. Patients and clinicians are increasingly interested in international comparisons of access to medicines, and these can provide useful benchmarks for policy makers. However, these comparisons should not be limited to simple counts of numbers of medicines approved and covered, as many other factors affect access to appropriate treatments (e.g. access to providers, levels of cost-sharing, reliability of supply chains etc.). **Access needs to be understood within the context of each country's health care system.** Where several medicines are available for a given indication, it may be possible to prioritise the use of certain medicines, based on evidence of burden of disease, clinical and cost-effectiveness, without disadvantaging patients.

13. Drawing on the results of the survey, countries could consider a number of policy options to address the identified challenges in access to oncology medicines:

- **Enable the tracking of use by indication through routinely collected data, registries or post-marketing studies.** This could serve a number of purposes, including informing ex-post price adjustments where needed, and supporting the monitoring of expenditures linked to oncology medicines, as well as contributing to 'real world' evidence of the performance of medicines.
- **Improve the design of performance-based managed entry agreements to support the generation and collection of on-market evidence**. This would require the collection of information on both utilisation and relevant clinical outcomes for products subject to these agreements. Harmonisation of outcome measures, data aggregation, and information-sharing across payers and countries would be highly desirable, particularly for products targeting small populations.
- **Set cost-sharing arrangements**, where unavoidable, **as fixed co-payments rather than co-insurance, and ensure that these do not undermine access or impose catastrophic costs on households with cancer patients**.

1 Introduction

14. Cancer represents a high and increasing burden worldwide, in part reflecting an ageing population and to some degree, the success of countries' health care systems. In some countries the lifetime risk of developing some form of cancer exceeds 50% (Tanday, 2015[1]), and the costs of care, especially of pharmacotherapies, are burgeoning (World Health Organization, 2018[2]; IQVIA, 2018[3]). Within the European Union (EU) the cancer burden was estimated to be 3.1 million new cancer cases and 1.4 million cancer deaths in 2018, with direct health costs of cancer of EUR 103 billion, of which cancer medications accounted for 31% (Hofmarcher et al., 2019[4]). In the United States, the Agency for Healthcare Research and Quality estimated the direct medical costs of cancer care in 2015 at over USD 80 billion (Islami et al., 2019[5]).

15. Recent decades have seen significant advances in cancer care, stemming from progress in prevention, early detection, pharmacotherapies, and other treatment modalities. In Europe, although cancer deaths increased from 1.2 million in 1995 to 1.4 million in 2018, the rate of increase has been slowing and deaths have been decreasing in age groups below 65 years (Hofmarcher et al., 2019[4]). Hofmarcher et al. (2019[4]) estimated that in all European countries, the five-year survival rates between 1995 and 2014 increased for most common cancer types. Within this same period, Arnold et al (2019[6]) found that five-year net survival increased in almost all of seven cancer types in seven high-income countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway and the United Kingdom). The highest observed increases in five-year survival were 16.6 and 21.0 percentage points for colorectal cancer in Denmark between the periods 1995-1999 and 2010-2014, respectively (Arnold et al., 2019[6]). However, the contribution of oncology medicines to these improvements in survival is challenging to estimate. Moreover, many cancer medicines that are now considered the standard of care have been approved since 2014, and recent data on five-year survival rates are lacking.

16. The collective understanding of the underlying biology and pathophysiology of many cancers is also driving substantive changes in approaches to care. Increasingly, genomic profiling of tumours is enabling the identification of individual patients or sub-populations more likely to respond to treatment with specific medications. Drug development is progressively targeting particular molecular pathways, in order to identify treatments that can inhibit growth or destroy tumour tissue, while minimising the toxicity associated with conventional chemotherapeutic regimens. Major progress has come with the development of treatments that recruit the body's own immune system to fight some forms of cancer for which there were previously few meaningful treatment options (Page et al., 2014[7]).

17. These developments have created multiple challenges for countries in achieving and sustaining affordable access to oncology care. A number of informal preliminary discussions were undertaken with a subset of countries, to attempt to identify the most pressing issues. Not surprisingly, increasing launch prices and potential budget impact of new oncology medicines, and the concomitant issues of pricing, expenditure and managing financial risks, were prominent. These create difficulties for payers even in the presence of sound evidence of effectiveness, cost-effectiveness, and identifiable downstream cost offsets. A related issue was that of uncertainty in clinical benefit, cost-effectiveness and budget impact, in part the result of efforts to promote early and rapid approval for new medications, often based on clinical trials not designed to provide evidence relevant to informing decisions on coverage and payment. A third issue raised was referred to as the "cascade'' of indications, indicating the tendency for oncology medicines to

gain marketing approval for multiple indications, often reflecting different degrees of clinical benefit, and thus representing varying levels of cost-effectiveness at a given price. A corollary to this is the challenge of determining the appropriate place in therapy for a new medication, particularly given the increasing use of complex treatment regimens. The use of multiple medicines with distinct but complementary mechanisms of action, in combination or in close sequence, creates particular challenges both for health technology assessment (HTA) and price negotiation. Differences in coverage policies, purchasing mechanisms, and willingness to pay (WTP) can create inequity in access and lead to 'postcode prescribing'. Finally, all of the preceding challenges contribute to the challenge of meeting patient expectations of timely access to new oncology medicines. A summary of the identified challenges is shown in Table 1.1.

Table 1.1. Summary of challenges identified in managing oncology medicines

Key Issues	Elements	Description
Up-front costs, affordability and sustainability	• Rapidly increasing launch prices • Challenge of upfront payment especially if pent-up demand, delayed benefits	Escalating launch prices have been widely documented. These create difficulties for payers even in the presence of sound evidence of effectiveness, cost-effectiveness, and downstream cost offsets.
Uncertainty in clinical benefit, cost-effectiveness and budget impact	• Early/rapid approval with immature/paucity of data • Clinical trials not designed to address key issues for HTA/payers • Use of surrogate endpoints of uncertain validity renders uncertainty in clinical benefit • Pan-tumour indications • Transition from acute to chronic treatment	Nature and level of evidence presented to/accepted by regulatory agencies to support marketing approval creates uncertainties in estimating clinical benefit for HTA entities/payers with flow on to assessments of cost-effectiveness, budget impact. This may necessitate the use of MEAs and real world data collection to attempt to overcome these uncertainties.
Cascade of indications	• Multiple indications in populations of varying size	Multiple indications for a given medication reflecting differences in degrees of benefit, thus presenting varying levels of cost-effectiveness at a given price.
Place in therapy[1]	• Increasing use of combination therapies and complex treatment regimens	Increasing use of multiple medicines with distinct but complementary mechanisms of action in combination or in close sequence can be challenging for HTA and price negotiations.
Inequity in access	• Coverage and access (and societal willingness to pay) may vary at national, regional and institutional level ('postcode prescribing')	Differences in willingness and capacity to pay across countries, regions and even institutions, leads to inequities in access.
Meeting patient expectations	• Rapid approval of multiple new therapies	Patient expectations of timely access to new oncology medicines are not being met; challenges for HTA/payers in assimilating rapid entry of multiple new treatments, particularly in the presence of clinical/economic uncertainty and lack of clarity about place in therapy.

Note: HTA health technology assessment, MEA managed entry agreement
1. Place in therapy refers to whether a medicine is to be used by itself or in combination, in what line of treatment, or in what sequence of treatment for a given stage of disease etc.
Source: Authors based on preliminary interviews for 2019 OECD survey on challenges in access to oncology medicines.

18. In September 2019, a survey was sent to OECD member countries and EU Member States with the aim of reviewing the current state of access to oncology medicines across OECD and EU countries, and informing an analysis of the ways countries and health systems are attempting to manage access and respond to these and related challenges. The survey comprised three parts: 1) a questionnaire on challenges encountered in access to oncology medicines; 2) a document collecting information on cost-

sharing; and 3) a spreadsheet in which to record information regarding a sample of 109 product/indication pairs used in five cancer types and in supportive care. Further details are provided in Annex A.

19. A total of 25 countries[6] responded in whole or in part to the survey (see Annex A. Table A A.1), with 24 countries responding to Part 1, 22 to Part 2 and 23 to Part 3. This report draws extensively on information from all parts of the survey. Chapter 2 describes the different approaches taken by countries in attempting to address the challenges described above, while pursuing sustainability and efficiency in expenditure. Chapter 3 presents data on availability of more than 100 product/indications used in five cancer types in 23 OECD/EU countries, as well as information on time to access (i.e. time between the date of submission of an application for marketing authorisation and the date of coverage decision) and on cost-sharing requirements for patients.

[6] Australia, Belgium, Canada, Chile, Cyprus, the Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Malta, Norway, Sweden, Switzerland, the United Kingdom (England only), and the United States.

2 Country approaches to challenges in oncology medicines

20. In a series of preliminary interviews, a number of issues were identified, several of which are either specific to oncology medicines, or are particularly challenging in this therapeutic area. The sections below substantiate these challenges and, based on 24 country responses to Part 1 of the OECD survey[7], describe approaches used by these countries to cope with them. Sections successively address the challenges of uncertainty in the assessment of clinical benefits (2.1); managing the cascade of indications (2.2); managing place in therapy and pricing of combination products (2.3); and lastly managing increasing treatment costs within budget constraints (2.4).

2.1 Mitigating increasing uncertainty in the assessment of clinical benefit

21. In all therapeutic classes, a mismatch has been observed between the nature and level of evidence required and accepted by regulatory agencies to support marketing authorisation, and that desired by Health Technology Assessment (HTA) entities and payers to make evidence-informed coverage or reimbursement decisions.

22. Regulatory agencies are required to assess safety, quality, and efficacy and to establish that in the population targeted, the benefits of a drug outweigh the risks associated with its use. They evaluate the data from clinical trials submitted for regulatory approval, trials that are often limited to subjects from narrowly-defined populations (i.e. generally excluding the very old, very young and very sick), thus limiting the generalisability of the results. Frequently, these trials measure or report *efficacy* results using surrogate endpoints[8] or biomarkers rather than clinical endpoints (Johnson, Williams and Pazdur, 2003[8]; Kim and Prasad, 2015[9]; Kim and Prasad, 2016[10]). The trials do not always involve an active comparator (though active comparators are more common in oncology than in other therapeutic areas). They may not measure or report changes in health-related quality of life.

23. By contrast, HTA entities are usually interested in assessing comparative or relative effectiveness, as well as incremental cost-effectiveness or value for money. A key question is how does the new medicine compare with the existing standard of care, and how will it perform in the wider population? Evidence from

[7] Australia, Belgium, Canada, Chile, Cyprus, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Malta, Norway, Sweden, Switzerland, the United Kingdom (England only), the United States

[8] A surrogate endpoint is an indirect measure of the effect of a specific treatment that is expected to predict a final clinical outcome of interest such as overall survival and/or quality of life (Kemp and Prasad, 2017[91]). A surrogate endpoint may be considered to be valid if it is in the causal pathway of the disease process and is correlated with the clinical endpoint in such a way that the change in the surrogate *fully captures* the net effect of the intervention on the final clinical endpoint (Fleming, 2005[92]). The use of surrogate endpoints is often favoured when the measurement of more patient relevant or final clinical endpoints would be difficult or invasive, or would require larger and longer trials. However, not all surrogate endpoints used in clinical trials are well validated.

clinical trials used for regulatory purposes is generally not sufficient to address the key questions of interest to HTA and payers. In the absence of trial designs more suited to generating evidence for HTA there may be considerable residual uncertainty around the comparative value of a new therapy. Products for which the clinical benefits and target population are uncertain will be associated with concomitant uncertainty in both cost-effectiveness and expected utilisation, and by extension, in budget impact.

In oncology, uncertainty in the assessment of clinical benefit is particularly high

24. In oncology, this mismatch is worsened by the fact that medicines are often approved via expedited or 'fast-track' processes intended to accelerate patient access to promising treatments. These processes often rely on the use of surrogate endpoints or biomarkers rather than final, clinical outcomes, and frequently require post-marketing studies to confirm evidence of benefit. There are many sound reasons for using surrogate endpoints: endpoints measured soon after the intervention of interest are less prone to 'contamination' by other factors (such as co-interventions, or death from unrelated causes) before the clinical endpoint of interest is reached; measurement of a final, clinical outcome may be excessively invasive or expose patients to excessive risk; and patient survival may require lengthy follow-up and/or large numbers of patients to render concrete evidence of benefit, particularly in early disease. Thus, surrogate endpoints may be relied upon in order to expedite approval and patient access.

25. The surrogate endpoints used, however, have not always been well validated, so that the extent to which a change in the surrogate predicts the extent of change in the more clinically relevant endpoint may not always be clear. For example, in 2018, a systematic review found that there was no significant association between the frequently used surrogate endpoint of progression-free survival and measurements of quality of life in cancer trials (Kovic et al., 2018[11]). A 2019 systematic review of trial meta-analyses found low or only modest correlation between surrogate endpoints and overall survival (Haslam et al., 2019[12]). Correlation between surrogate endpoints and overall survival may be better in some settings than in others. In 2018, a large-scale meta-analysis provided an overview of the current evidence of surrogate endpoints for overall survival in randomised controlled trials (RCTs) across a range of cancer types and settings. The authors found that disease-free survival has adequate surrogate properties for overall survival in adjuvant treatment for non-small-cell lung cancer, gastric cancer, head and neck cancer, and colon cancer. In advanced settings, the study found that progression-free survival may be appropriate for metastatic colorectal cancer, lung cancer, and head and neck cancer (Savina et al., 2018[13]). However, uncertainty in the interpretation of results may also be exacerbated in trials designed to allow participants to cross over to another therapy once a favourable result is recorded against the surrogate endpoint. While there will often be sound ethical and scientific reasons for permitting crossover within such trial, this can nevertheless introduce additional complexity in the interpretation of the data and can undermine attempts to clarify or confirm the validity of the surrogate marker.

26. The confirmation of benefits through post-marketing studies is thus important for policy makers. Two studies, looking at cancer indications approved by the US Food and Drug Administration (FDA) and through the European Medicines Agency (EMA) provide some insights into post-marketing benefit assessment. The most recent and complete study, from May 2018, reviewed information from post-marketing studies for 93 cancer drug indications that received accelerated approval from the US FDA between December 1992 and May 2017. Clinical benefit was confirmed for two-thirds of the indications (58), measured on clinical outcomes such as overall survival for 20% and measured on surrogate outcomes for 41%. Benefit was not confirmed in 9% and post-marketing studies were ongoing for 10% of the sample, pending for 11% and delayed for 5% (Gyawali, Hey and Kesselheim, 2019[14]). Another study looked at evidence available for the 68 cancer indications approved by the EMA between 2009 and 2013. At the time of approval, significant improvement in survival was demonstrated for 24 (35%) of these indications and improvement in quality of life in 7 (10%). For the remaining 44 product indications, post-marketing studies provided evidence of life extension for 3 (7%) and of improvement in quality of life for 5 (11%). The authors concluded that pre and post-market evidence available for these 68 drug indications

showed improvement in survival or quality of life for 51%, while the benefits remained uncertain for the remaining 49% (Davis et al., 2017[15]).

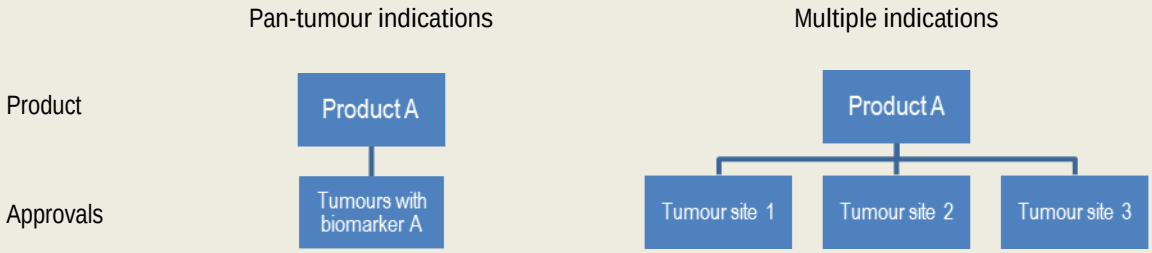
27. Particularly challenging in this respect are 'pan-tumour' products[9] that are mutation- rather than organ- or tissue-targeted, as it may be unclear how, and in whom they will be used and effective (see Box 2.1). While recent approvals, by several regulatory agencies, of cancer treatments based solely on the presence of a genetic feature in a solid tumour, rather than the site, tissue or cancer type, are an important advance in cancer management informed by tumour-specific genetic profiles, it remains the case that responses will be heterogeneous (and still measured on surrogate endpoints). For example, although patients with certain cancer types (e.g. lung cancer and melanoma) typically have good responses to immune checkpoint inhibitors such as pembrolizumab (Keytruda®), not every patient responds to the same extent to the treatment. One particular challenge encountered in the value assessment of products with pan-tumour indications may be the choice of an appropriate comparator. These products are often evaluated in "basket" trials – trials in which a targeted therapy is evaluated for multiple diseases that have common molecular alterations – which are often single-arm studies (Park et al., 2019[16]). More traditional, disease-specific follow-up studies may ultimately be needed to inform both clinical guidelines and HTA (Tao, Schram and Hyman, 2017[17]).

28. While the gold standard of evidence is data on final, clinical endpoints (e.g. overall survival) from RCTs, these may be neither feasible nor ethical in rare tumour types. There are often also challenges in undertaking RCTs of these types of products; these include a limited understanding of the natural history and epidemiology of rare tumours; the absence of standard companion diagnostic tests; difficulties in subject accrual; and population heterogeneity; as well as the inherent difficulty in interpreting outcomes measured using surrogate endpoints of uncertain validity. More broadly, the growing trend within regulatory agencies to accept single-arm studies as the basis for expedited approval not only weakens the evidence base for any subsequent comparative assessment, but, by definition these studies cannot be used to generate comparative evidence of the progression of the cancer in the absence of the new medicine, (though in some cases comparisons can be made using historical controls). Importantly, any additional evidence generated for drugs approved on the basis of non-randomised studies must be considered in the knowledge that important biases cannot be excluded. Gyawali et al (2020[18]) assessed the response rate and durations of response measured in non-randomised versus randomised controlled trials for a sample of 19 oncology product/indication pairs approved by the FDA on the basis of changes in biomarker. Response rates did not differ significantly between the two types of trials (pooled ratio 1.06 with 95% Confidence Interval of 0.95-1.20), but duration of response was significantly higher in the non-randomised studies (pooled ratio 1.17 with 95% Confidence Interval 1.03-1.33). The authors concluded that the effects of drugs approved on the basis of duration of response in non-randomised trials may be overestimated, and a poor proxy for overall survival (Gyawali et al., 2020[18]).

29. Another layer of uncertainty is associated with the short duration of clinical trials for the introduction of advanced therapy medicinal products (ATMP), such as Chimeric antigen receptor T-cell therapy (CAR-T). From a payer point of view and for price setting, it is unclear whether these treatments are in fact 'one-off' or whether re-treatment will be required, which adds uncertainty in estimates of clinical benefit, cost-effectiveness and budget impact. Residual uncertainty regarding the extent and duration of benefit from treatment also arises from the transition of some drugs from acute or episodic treatment to chronic therapy (e.g. trastuzumab emtansine - Kadcyla®).

[9] These are medicines that are approved on the basis of targeting specific mutations or genomic alterations in different tumours, also known as "tumour-agnostic" or "histology-independent" therapies, because they target the genomic alteration within a tumour, regardless of where in the body it has formed.

Box 2.1. Medicines approved with pan-tumour indications



One approval for a single indication on the basis of targeting specific mutations or genomic alterations in different tumours i.e. « *tumour-agnostic* » or « *histology-independent* »

Separate approvals for multiple indications by cancer type, stage, line of therapy etc.

Note: A pan-tumour approval may be an additional indication for a product already approved for use in multiple indications. The pan-tumour indication does not necessarily overlap with existing indications.
Source: Authors based on definition of pan-tumour indications.

Examples of medicines recently approved:

United States Food and Drug Administration (May 2017)

Keytruda® (pembrolizumab) is indicated for the treatment of adult and paediatric patients with unresectable or metastatic solid tumours that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

Note that this is an additional indication for pembrolizumab and does not replace existing indications.

European Medicines Agency (July 2019)

Vitrakvi® (larotrectinib) as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

Note that this is the initial marketing authorisation for larotrectinib, although it had previous orphan designations in the treatment of soft tissue sarcoma, salivary gland cancer, glioma, and papillary thyroid cancer.

Japan Pharmaceuticals and Medical Devices Agency (June 2019)

Rozlytrek® (entrectinib) is indicated for the treatment of adult and paediatric patients NTRK fusion-positive, advanced/recurrent solid tumours. This is the initial marketing authorisation for entrectinib in Japan.

Source: https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature ; https://www.ema.europa.eu/en/news/first-histology-independent-treatment-solid-tumours-specific-gene-mutation; https://www.pmda.go.jp/files/000232794.pdf, consulted on 18 March 2020.

Countries have so far focused on limiting financial risks associated with uncertainty

30. Sixteen[10] respondents to the survey (67%) confirmed that the issue of "high uncertainty" has been flagged in their countries, either in individual assessment reports or in other documents.

31. The OECD survey mainly explored policy responses from HTA entities and payers and did not specifically address the role of regulatory agencies. The latter can, however, play a key role in reducing the gap between evidence available at the time of marketing authorisation and that needed for both payer and clinical decision making. For example, to address the issue of lack of representativeness of subjects in clinical trials, the US FDA will shortly publish a guidance document for industry on the inclusion of older adults in cancer clinical trials.[11] On another front, regulatory agencies and HTA bodies now offer opportunities of "early dialogue" with companies to help them develop research plans that are more responsive to the needs of all evaluators. In Europe since 2010, pharmaceutical companies can receive parallel scientific advice from regulatory both EU regulators and HTA entities on their medicine development plans. Tafuri et al. (2018[19]) investigated the uptake of such advice on two key aspects of medicine development relevant to both regulators and HTA entities: clinical endpoints and choice of comparator. While all included studies that received advice between 2010 and 2015 implemented endpoints that met the needs of both regulators and at least one HTA entity, just over half used comparators that satisfied both regulators and at least one HTA entity.

32. A few countries have addressed the question of uncertainty in recent updates to their guidelines for evaluation and/or priority setting. For example, France's Haute Autorité de Santé (HAS) updated its principles of assessment in 2018, specifying the circumstances in which the clinical benefit may be assessed despite a high degree of uncertainty. These circumstances are: severe disease; unmet medical need; where initial data suggest benefits to patients; and there is a development plan to reduce uncertainty in the short term, through further clinical trials or use of real-world data (HAS, 2018[20]). In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has been invited to provide guidance in its assessments on how to manage the types of uncertainty that matter most for cost-effectiveness studies (Department of Health and Social Care and ABPI, 2018[21]). To our knowledge, these recommendations have not yet been published. In Norway, the recent report *Principles for Priority Setting in Health Care* stipulates that a high level of uncertainty in the assessment of benefit must in principle lead to a lower level of priority (i.e. a lower cost-effectiveness threshold) (Norwegian Ministry of Health and Care Services, 2017[22]). However, the document also calls for the application of less stringent requirements when assessing interventions targeted to small patient groups. A higher cost-effectiveness threshold may be accepted for medicines targeting very small patient groups with an extremely severe condition. The Norwegian Medicines Agency (NoMA) further published guidelines to define medicines eligible for this analytic framework: they must target a very small patient group (global prevalence of less than 1/100,000 and less than 50 patients in Norway); they must be for the treatment of an extremely severe condition (absolute loss of 30 quality-adjusted life years [QALYs] in the absence of treatment); and the expected benefit must be substantial (i.e. at least 2 QALYs gained in comparison with standard treatment) (NoMA, 2018[23]).

33. Respondents were asked what policies and/or approaches, if any, they use to address uncertainty in coverage and/or pricing decisions (see Figure 2.1). Almost all countries (21 of 24 respondents) reported using financial and/or performance-based managed entry agreements (MEAs). A recent OECD report on country experiences with MEAs (Wenzl and Chapman, 2019[24]) found that oncology medicines are often the subject of such agreements. In general, most of the agreements are financial in nature and aim to keep

[10] Australia, Belgium, Canada, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Norway, Sweden, Switzerland, the United Kingdom (England only), the United States

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/inclusion-older-adults-cancer-clinical-trials, consulted on 12 March 2020

actual prices paid confidential or to mitigate risks on budget impact (e.g. volume-price agreements). The report also notes that to date, performance-based agreements have not really clarified the performance of products in health care settings.

34. Eight countries reported relying on post-marketing studies to address uncertainty at the time of marketing approval (see Figure 2.1). This is the case for medicines funded through the 'new' Cancer Drugs Fund (CDF) in England[12], for example. Under this scheme, Managed Access Agreements rely heavily on post-marketing studies requested by the EMA for the generation of evidence to address uncertainties (Wenzl and Chapman, 2019[24])

35. 'Real world data' (RWD)—data collected in routine clinical practice—can also be used to address some of the uncertainties inherent in assessments of efficacy, safety, comparative effectiveness and cost-effectiveness. Nine countries use clinical registry data in this way (see Figure 2.1). In Italy, for example, nation-wide web-based registries have been created for each product/indication or line of treatment. While the principal aim of the Italian Medicines Agency (AIFA) is to monitor the appropriate use of the medicines in clinical practice and the application of the financial terms of MEAs, the data are also useful in addressing some uncertainties, for example, concerning the length of treatment or duration of effect (Montilla et al., 2015[25]). Moreover, Italy has implemented a pricing policy which assigns medicines to one of three different categories according to the perceived level of innovation they represent (innovative, potentially innovative, not innovative), based on the outcomes of an evaluation that takes into account clinical need, added therapeutic value, and quality of evidence (using the Grading of Recommendations Assessment, Development and Evaluation [GRADE] criteria). In Greece, the national health insurance fund maintains a registry for multiple myeloma. Hungary also has registries for high cost oncology medicines.

36. Six countries reported relying on routinely collected data to reduce uncertainty surrounding the clinical benefits of new products (see Figure 2.1). Australia, for example, uses routinely collected data to manage financial MEAs, and on a range of sources to reduce uncertainty surrounding the comparative effectiveness of new products in performance-based MEAs. In Germany, recent legislation allows the HTA entity to ask a pharmaceutical company to collect data from clinical practice for the purposes of the benefit assessment. This is, however, limited to medicines with conditional or exceptional approval and orphan medicines, as these products often receive market authorisation with less data from clinical trials. In Canada, a number of payers have introduced initiatives to collect RWD. Cancer Care Ontario, for example, runs an Evidence Building Program (EBP), through which patients can gain access to existing medicines for use in indications not yet accepted for routine funding because of a high degree of uncertainty. Medicines are only eligible for this programme if they fulfil a number of conditions, two in particular: that the collection and analysis of the real-world data are expected to be sufficient to inform a future funding decision, and that there are no studies already underway that are expected to address the issue within the EBP funding period. [13]

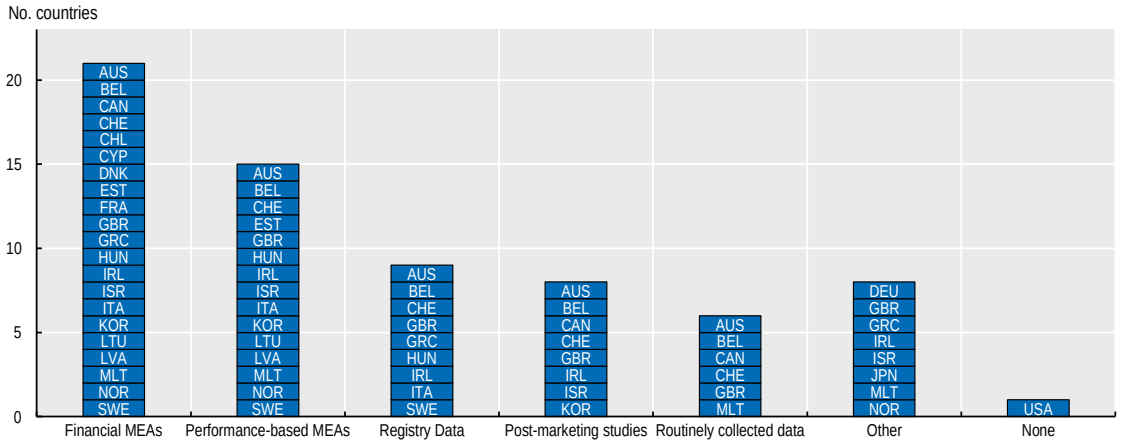
37. Switzerland reported that post-marketing studies, collation of routinely-collected data, and registries may be required for temporary reimbursement. In Japan, HTA may be used *after* initial coverage and pricing decisions for medicines with high budget impact, in order to adjust prices according to the cost-effectiveness of the product/indication.

[12] See https://www.england.nhs.uk/cancer/cdf/, consulted on 18 March 2020.

[13] See https://www.cancercareontario.ca/en/Funding/Evidence_Building_Program, consulted on 18 March 2020.

Figure 2.1. Policies and approaches to address uncertainty in coverage and/or pricing decisions across OECD/EU countries

Based on responses from 24 countries to the OECD survey (multiple options possible per country).



Note: MEA managed entry agreement
In Cyprus, formal MEAs do not exist but the Ministry's procurement unit can negotiate discounts.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

38. All responding countries reported that they would see value in international collaboration or information sharing to address clinical and/or economic uncertainties. Countries mentioned existing collaborative initiatives such as BeNeLuxA, Health Technology Assessment International (HTAi), the European Network for Health Technology Assessment (EUnetHTA), FINOSE, the Valletta Declaration, the European Integrated Price Information Database (Euripid) and the Pharmaceutical Pricing Reimbursement Information (PPRI) network (see Box 2.2 for brief descriptions of these initiatives). However, concerns were raised by a number of countries regarding the feasibility of information sharing and the generalisability of national data across health care systems and populations.

39. To improve their collective capacity to address uncertainty, countries suggested they could consider: engaging in joint data collection or building cross-country registries, especially for orphan medicines; aggregating national routinely-collected data sources; developing a global approach to performance-based managed entry agreements; harmonising approaches to the assessment of clinical and economic outcomes, including relative effectiveness assessments (for instance through the EUnetHTA initiative); and joint efforts to addressing evidence gaps (e.g. requirements for post-marketing studies or other types of evidence generation).

Box 2.2. Existing international collaboration initiatives

BeneluxA: Five countries (Belgium, the Netherlands, Luxembourg, Austria and Ireland) contribute to this initiative, whose aim is to improve access to "ensure sustainable access to innovative medicine at affordable cost for […] patients". To achieve this aim, countries have agreed to cooperate in the following activities: horizon scanning, information sharing and policy exchange; HTA (with EUnetHTA). Technical experts have been collaborating to produce HTA reports; as well as a common template for submission of a dossier. See: https://beneluxa.org/

European Network for Health Technology Assessment (EUnetHTA) aims to "contribute to a sustainable model for the scientific and technical cooperation on HTA in Europe in close collaboration with the stakeholders and the European Commission". It comprises 80 organisations from 30 countries. Key objectives include early dialogues with manufacturers, joint HTA reports, and post launch evidence generation. See: https://eunethta.eu/

Euripid collaboration is a "voluntary and strictly non-profit cooperation between mostly European countries on building up and maintaining a database with information on national prices and pricing regulations of medicinal products in a standardized format". The online database, which contains data on official prices of publicly reimbursed medicines, is not publicly accessible. See: https://www.euripid.eu/aboutus

Health Technology Assessment International (HTAi) is a global non-profit, scientific and professional society for all those who produce, use or encounter health technology assessment. They represent over 80 organisations and 2 500 individual members from 65 countries worldwide. Members include "researchers, policy makers, industry, academia, health service providers, agencies and patients". See: https://htai.org/about-htai/

The International Horizon Scanning Initiative (IHIS) was launched in 2018 to organise a formal cooperation around horizon scanning between countries willing to become members of this initiative https://ihsi-health.org/.

The Pharmaceutical Pricing and Reimbursement Information (PPRI) Network is an informal network of experts involved in pharmaceutical policy from 47 countries, mostly but not only European. Members of this network meet twice a year to exchange information on challenges and policy responses https://ppri.goeg.at/

Valletta Declaration: The Valletta Declaration was signed on 8th May 2017. This regional cooperation scheme now includes the Ministries of Health of Cyprus, Croatia, Greece, Ireland, Italy, Malta, Portugal, Romania, Slovenia, and Spain, covering 160 million citizens, representing 32% of the total EU population. According with the Declaration, the Valletta Technical Committee was established. The Committee aims to explore new areas of activity, such as mechanisms for joint negotiation and procurement as well as information and best practice sharing.

Source: Authors as above, consulted March 2020.

2.2 Managing the 'cascade' of indications

40. Globally, between 2013 and 2017, 45 new oncology drugs entered the market, many of them approved for multiple indications or for use within a combined therapy regimen. The number of approved indications increased by 265 to 935 during this period, an average of five indications per new active substance. In 2018, 75% of targeted therapies were used in multiple indications, and checkpoint inhibitors were approved for 10 indications (IQVIA, 2018[3]).

41. Beyond the targeted disease itself (e.g. tumour type, cancer site, genetic mutation), an approved indication or formulary listing may also specify disease severity, patient status, line of treatment (e.g. first line, second line), or use within a combined treatment regimen. New indications may be added over time and others may also evolve. For example, a treatment initially approved or covered only in second line therapy may move to first line as evidence accumulates.

42. The following sections discuss issues in the pricing of medicines used across multiple indications, as well as the management of the use of these medicines outside their covered indications.

Pricing products with multiple indications is challenging

43. The degree of clinical benefit and value may vary significantly between indications, and as a result so will the cost-effectiveness. This creates a substantial challenge both for companies in setting a price acceptable to payers, and for payers in seeking to ensure cost-effectiveness. Pricing and reimbursement are also particularly challenging when multiple indications, or extensions of indications, for a given product are approved successively. Some oncology products may be approved for several indications with small populations. Some recent examples include nivolumab (Opdivo®) and pembrolizumab (Keytruda®), both with orphan designation in the United States for 6 and 10 indications respectively.[14,15]

44. In the literature, indication-based pricing (IBP)—also known as indication-specific pricing—refers to pricing mechanisms that enable payers to vary the price paid for a drug according to its perceived value when used in different indications. IBP has been described as a way of ensuring both static and dynamic efficiency. It is expected to improve access for drugs in those indications in which use would not be cost-effective (and thus not covered or reimbursed) if the drugs were priced at a level reflecting the value of its use in the most cost-effective indication. At the same time, it is also expected to encourage investment in research and development supporting the use of drugs in indications of lesser value, and which would be unlikely to be developed if the risk of a coverage denial or price reduction not fully compensated by increase in volume was high (Neri, Towse and Garau, 2018[26]). There is, however, no consensus definition of the term (Cole, Towse and Zamora, 2019[27]; Bach, 2014[28]; Campillo-Artero et al., 2019[29]) The broader concept of indication-based pricing can include: a) discrete branding of products in different indications; b) different prices charged at the point of sale; c) different prices applied ex-post through managed entry agreements or rebates; and d) a blended price based on a population-weighted average value across indication. Options b) and c), however, depend on payers' ability to track both utilisation and the indications for which drugs are prescribed, which for many countries may not be achievable within current data management infrastructures and information systems. If tracking utilisation were to be implemented solely for payment purposes (rather than for other sound policy reasons such as promoting rational use and good prescribing), there is likely to be a trade-off between the benefits of this monitoring and the administrative overhead for the party (company or payer) bearing the cost of data collection.

45. Fifteen[16] of the 24 countries (63%) who responded to the survey reported that the issue of the cascade of indications had been given particular attention in that country.

46. Based on the OECD survey, responding countries were categorised according to their willingness to take into account differential values when pricing multi-indication products, as well as their capacity to track use by indication in their systems (see Table 2.1).

Table 2.1. Pricing products with multiple indications in OECD/EU countries

Pricing mechanism	Ability to track use by indication	No ability to track use by indication
Differential prices per indication applicable up-front: e.g. simple financial discounts at the point of sales according to intended usage	Estonia, Latvia	
Differential prices per indication applicable ex-post through rebates	Belgium[1], France[1], Italy	Belgium[1], France[1], Switzerland
Blended / single weighted price		Australia, Germany

[14] See https://www.accessdata.fda.gov/scripts/opdlisting/oopd/, consulted on 10 February 2020.

[15] Note that due to differences in orphan drug criteria, these medicines do not have orphan designation in Europe.

[16] Australia, Belgium, Canada, Denmark, France, Hungary, Ireland, Israel, Italy, Japan, Malta, Norway, Sweden, Switzerland, and the United Kingdom (England only).

Pricing mechanism	Ability to track use by indication	No ability to track use by indication
Single price not taking into account differential values of multiple indications	Hungary[2]	Canada, Chile, Cyprus, Denmark, Greece, Ireland, Israel, Japan, Korea, Lithuania, Malta, Norway[3], Sweden[3], United Kingdom[3]

Note: 1. In Belgium and France, tracking use by indication is only possible for some product/indications but not for all.
2. In Hungary, usage of products can be tracked by indication in most cases.
3. In Norway, Sweden and the United Kingdom (England), the price of the product is unique but based on the fact that the medicine should be cost-effective in all indications (and not on a weighted average of value-based prices per indication).
Source: Authors' synthesis based on 2019 OECD survey on challenges in access to oncology medicines.

47. The majority of respondents reported single prices for products with multiple indications irrespective of varying benefit and value (see bottom, right-hand, grey cell of Table 2.1). To be covered in Norway and the United Kingdom (England), a product must be cost-effective at the price proposed across *all* indications. One third of responding countries (8 out of 23) reported setting different prices across indications according to value. Australia and Germany described calculating a blended or 'shadow' price based on the weighted average price per indication in the anticipated treatment populations. Italy, Belgium, France and Switzerland negotiate prices per indication but use a single list price, with ex-post confidential rebates. In Italy, where use is tracked through cancer registries, ex-post rebates can be based on actual use in each indication. In France, use by indication can only be tracked for new products paid for outside Diagnosis Related Groups (DRG) payments to hospitals, as hospitals must claim reimbursement by indication for these products. In Belgium, the capacity to track use by indication is limited, while in Switzerland tracking use by indication is not currently possible. Finally, Estonia and Latvia are able to apply differential prices per indication ex-ante.

48. In order to clarify payers' willingness to consider value when regulating pharmaceutical prices, countries were asked to report the effect, if any, on an existing product's price of the addition of a new indication. The responses are shown in see Table 2.2.

Table 2.2. Price change likely to occur following approval and coverage of a new indication of an existing product in OECD/EU countries

Multiple options possible per country.

What is likely to happen when a new indication is added for a product already covered?	Country
Product price likely to remain unchanged, no reference to value or population per indication	Canada (max. price set at Federal level)[1], Cyprus, Israel, Lithuania, Malta, Sweden
Product price likely to be reduced to account for increase in volume / market expansion / budget impact	Chile, Belgium, Denmark (company's decision), France, Israel, Italy, Japan (if large volume increase), Korea, Latvia, Lithuania, Malta, Sweden, Switzerland
List product price remains unchanged, but new or existing MEA may be (re)negotiated (e.g. simple discount, price-volume agreements, etc.)	Australia, Belgium, Denmark (volume-based discounts), France, Greece (volume rebates), Hungary (volume-based), Italy, Latvia, Switzerland
Product price might need to be reduced if new indication is less cost-effective than existing ones	Norway, United Kingdom (England, with possible MEA if this would cause a net loss in revenue)
Price might change to reflect value and volume per indication	Australia, Belgium[2], Estonia, Germany, Ireland, Switzerland

Note: MEA managed entry agreement
1. In Canada, third-party payers (private insurers and public plans) are free to negotiate prices below the maximum price established at the national level.
2. This is not the most common situation in Belgium.
Source: Authors' synthesis based on 2019 OECD survey on challenges in access to oncology medicines.

49. In most countries, the price of a product is likely to be reduced to take into account increases in sales volumes. Thirteen countries reported that a medicine's price was likely to be reduced in response to an increase in volume, although in Denmark this would generally be a decision of the manufacturer. In nine countries, the *list price* of the product is likely to remain unchanged but new (or existing) product-specific agreements (formal managed entry agreements or other forms of contracts) may be (re)negotiated. Both Norway and the United Kingdom (England) reported that the price might need to be reduced to ensure that the product remains cost-effective across all indications. This could potentially deter companies from applying for coverage of less cost-effective indications if it could lead to a net loss of revenue, but the framework agreement signed between the England National Health Service (NHS) and the pharmaceutical industry stipulates that a managed entry agreement can be signed to avert such situations (see art. 3.36 in (Department of Health and Social Care and ABPI, 2018[21])).

50. What is likely to happen in the United States is difficult to predict. For medicines covered under Medicare Part B (those administered as part of a physician service), reimbursement to providers is set at 106% of the average sales price (ASP) of the product.[17] The approval of a new indication would not directly lead to a variation in the Medicare Part B reimbursement amount, however sales of the product in the new indication could potentially impact the ASP if other payers renegotiated their prices. For medicines covered under Part D (medicines self-administered in primary and ambulatory care), prices are negotiated by private Part D plans; it is therefore not possible to determine the impact of a new indication on prices.

Managing "off-label" and "off-coverage" use of oncology medicines

51. The use of medicines outside the indications approved by the regulator ('*off-label use*') is very common in cancer. Because oncology remains a therapeutic area of high unmet need, prescribers and patients are often willing to accept the use of medicines in circumstances in which their efficacy and safety profiles have not yet been clearly established. A systematic review of the literature showed that off-label use of oncology medicines was in the range of 18% to 41% for hospitalised patients and of 7% to 50% for patients treated in ambulatory care. In total, 13% to 71% of adult patients with cancer received at least one off-label chemotherapy during the course of treatment. This was more likely to happen in patients who had exhausted all standards lines of treatment. The main reasons for off-label use were use in an unauthorised indication for a specific tumour and use in an unauthorised line of treatment (Saiyed, Ong and Chew, 2017[30]).

52. While prescribing off-label is unregulated in most, if not all, health systems, medicines may not be covered by third-party payers when used outside their approved indications for marketing. Medicines may also be prescribed for approved, but not (or not yet) covered, indications (referred to as '*off-coverage use*'). In some countries so-called early access schemes enable patients to access medicines for which formulary selection or coverage decisions have not yet been made. When a coverage decision was negative, patients may be expected to cover the full cost of care, unless they can use any mechanism providing exceptional access to this product/indication. Importantly, off-label and off-coverage use are of a very different nature; drugs approved for marketing but not (or not yet) covered or reimbursed have been determined to have a positive risk/benefit balance in the relevant (on-label) indication. Products used off-label may not be supported by sound evidence of benefit and may thus present greater risks to patients.

53. The results of the OECD survey pertaining to the off-label use of medicines in health systems are presented in Table 2.3. While off-label use is not covered in a number of countries, it can be covered in some circumstances, and in others in exceptional circumstances, most often unmet medical need, and with prior authorisation. In some countries, coverage of off-label use depends on the health care setting (e.g. Canada, Sweden).

[17] The ASP reflects the average price, net of all price concessions (such as discounts and rebates), for all sales of the product in the U.S. market (with limited exceptions), for any indication.

Table 2.3. Management of off-label use of oncology medicines in OECD/EU countries

Off-label use possible, but not covered/reimbursed
Australia, Chile, Israel, Japan, Korea, Latvia, Lithuania, United Kingdom (England)
Sweden for outpatients.
Off-label use possible, and covered/reimbursed
Belgium, only for unmet need for new medicines. There are no reimbursement restrictions for older off-patent medicines used off-label.
Canada for inpatients. For outpatients, it depends on insurer/plan.
Cyprus
France: off-label used is covered by a temporary authorisation for use programme or under exceptional individual circumstances.
Estonia, via hospital service list, ambulatory list, or for individual patients under exceptional circumstances
Germany, if off-label indication approved by an expert group and health technology assessment body
Hungary and Greece with individual prior authorization
Italy: off-label use is covered if there is unmet need, the company is not conducting clinical trials or there is no active compassionate use programme. Off-label access requires approval based on evidence of potential benefit and regulatory requirements.
Lithuania for ultra-rare diseases
Malta: cancer cases can be managed through exceptional treatment schemes, which are not specific to off-label use but may include it.
Norway, hospitals cover off-label use in their budgets
Sweden for inpatients
Switzerland for unmet need and with prior authorisation by insurer
United States: off-label use can be funded by Medicare if the product is deemed reasonable and necessary for treatment.
Other
Denmark: Off-label use is possible for all public hospital medicines, but is not included in treatment guidelines (The Danish Medicine Council).
Ireland: off-label use can be incorporated into 'standard of care' treatment and related costs. For high-cost medicines, off-label use is only covered by private insurers
Norway: access in private hospitals

Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

2.3 Managing place in therapy and pricing combination regimens

54. Increasingly, approaches to treating many cancers involve the administration of a number of medicines with distinct but complementary mechanisms of action in combination or in close sequence, as part of a regimen that also seeks to minimise the emergence of drug resistance. In some circumstances, standard approaches to HTA (determining whether an incremental cost-effectiveness ratio for an individual drug falls under an acceptable willingness to pay threshold) may conclude that a new product used in combination cannot be cost-effective even at zero cost, generating results that may be counterintuitive, or inconsistent with societal preferences.

Most countries use HTA to determine place in therapy of new medicines

55. Respondents to the OECD survey were asked what policies or approaches, if any, they use to address the challenge of determining the place in therapy of new medicines[18]. The objective was to understand who makes decisions about place in therapy, and by what criteria (see Figure 2.2). In most countries, decisions are based on HTA. Thirteen countries reported that place in therapy was determined on the basis of clinical data, and nine that it was determined by cost-effectiveness considerations. Eight

[18] Place in therapy refers to whether a medicine is to be used by itself or in combination, in what line of treatment, or in what sequence of treatment for a given stage of disease etc.

countries said that place in therapy was determined by clinical guidelines, and not specified in coverage conditions.

56. Some countries appear in several categories. For example, in Australia, place in therapy is determined by the HTA process based on clinical as well as cost-effectiveness evidence. Coverage conditions are determined via the HTA process. If cost were not a factor, or the decision were cost-neutral, the preferred option would be to have prescribers determine the place in therapy based on clinical judgement. Canada and Belgium indicated that HTA entities provide recommendations on place in therapy to inform coverage conditions and potential restrictions. In Belgium this is more likely to apply to high-priced medicines.

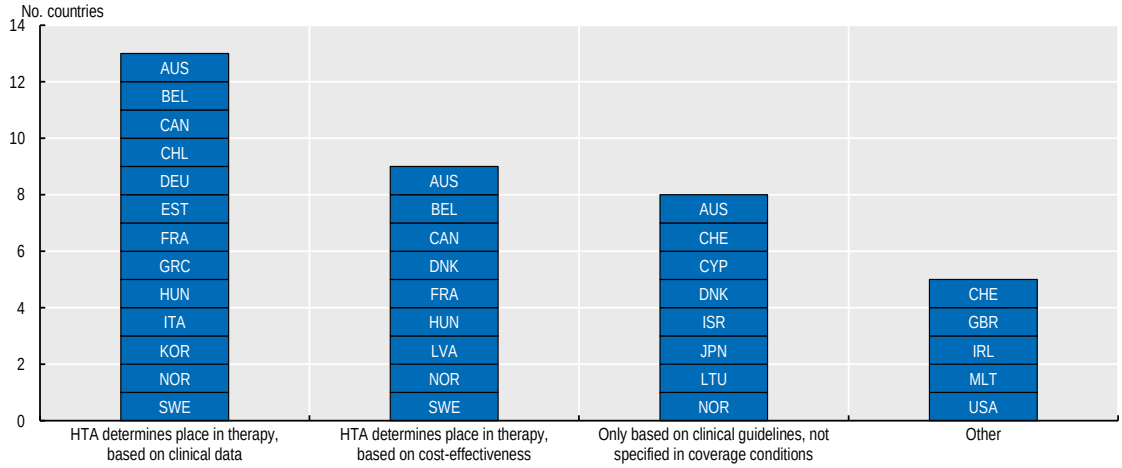
57. In Norway, while the use of a drug may be described in clinical guidelines, the Decision Forum[19] determines the conditions surrounding each new medicine's use. In some circumstances, the HTA process restricts coverage conditions to specific subgroups because of differences in cost-effectiveness. Place in therapy may be determined by cost-utility analysis. Where clinical trials show equi-effectiveness between medicines these may be subject to tendering. The oncology expert group then makes recommendations on place in therapy depending on the results of the tender.

58. In France, HAS determines the place of the drug in therapy as part of the HTA informing the coverage decision and pricing negotiation. To do so, HAS uses clinical practice guidelines published by the French National Cancer Institute (INCa), which is responsible for issuing clinical practice guidelines.

59. In the United States, under Medicare Part D, plans are permitted to use formularies and step therapy. The Centers for Medicare & Medicaid Services (CMS) issue guidance on how to determine the adequacy of a plan's formulary, but the plans themselves set the step therapy requirements. Medicare Advantage plans are also permitted to use step therapy for their enrolees. Other private health insurance plans can freely determine coverage rules.

Figure 2.2. Approaches to determining place in therapy of new drugs across OECD/EU countries

Based on responses from 24 countries to the OECD survey (multiple options possible per country).



Note: HTA health technology assessment
In Chile, HTA determines place in therapy only for medicines covered through the High Treatment Cost Law, not for the private sector.
In Denmark, place in therapy is primarily determined by clinical guidelines, but can be determined by cost if two products have the same effectiveness.
Source: Authors based on 2019 OECD challenges in access to oncology survey.

[19] In Norway, coverage decisions for hospital drugs (all oncology treatments) are devolved to the four regions, but they have delegated this responsibility to a Decision Forum, whose decisions are de facto national ones.

The pricing of products used in combination treatment regimens remains a challenge

60. A related issue is the growing use of combination treatment regimens[20] in oncology. Increasingly, approaches to treating many cancers involve the concurrent administration of a number of products with distinct but complementary mechanisms of action in combination or in close sequence, as part of a regimen that also seeks to minimise the emergence of drug resistance. Combination approaches to oncology treatment have become the norm for both solid tumours and haematological malignancies. Some recent examples include the addition of pertuzumab to trastuzumab for the treatment of human epidermal growth factor receptor 2 positive (HER-2) breast cancer, and the use of programmed cell death protein (PD-1) and programmed cell death ligand (PD-L1) inhibitors in combination with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapies in metastatic melanoma. For HTA bodies and payers, this trend presents serious challenges.

61. Standard approaches to HTA (determining whether an incremental cost-effectiveness ratio falls under an acceptable willingness to pay threshold) may produce results that are counterintuitive, or inconsistent with societal preferences. This was the case when the addition of a medicine to an existing treatment offering meaningful clinical benefit was nonetheless be found to be 'not cost-effective at zero price' (Davis, 2014[31]). Pertuzumab for HER-2+ metastatic breast cancer offered an incremental overall survival benefit of 15.9 months when added to trastuzumab (Herceptin®), but NICE did not initially consider it to be cost-effective for use in the NHS even if the drug were provided free of charge.[21] This was because the use of additional health resources (concomitant to improved survival) over and above the cost of the 'backbone' therapy, pushed the total treatment costs beyond what was considered acceptably cost-effective at the margin.

62. Combination regimens are expected to proliferate over the next few years. Dankó et al. identified 16 products approved by the EMA for use in combination with other products until February 2019 (Dankó, Blay and Garrison, 2019[32]) and a recent study counted more than 1700 clinical trials for regimes involving anti-PD-1/PD-L1 with other cancer therapies (drug or non-drug) (Tang et al., 2018[33]). From payers' and decision makers' points of view, the most common situation can be described as follows (illustrated in Figure 2.3): products A and B are already in the market and have different modes of actions or targets. The sponsor of product B gets a marketing authorisation for the use of its product in association with product A and files an application for coverage of the combination. Product A is usually referred to as the backbone therapy (without prejudice of its role in clinical benefit) and product B as the "add-on therapy", both products are "the constituents" of the combination (Dankó, Blay and Garrison, 2019[32]).

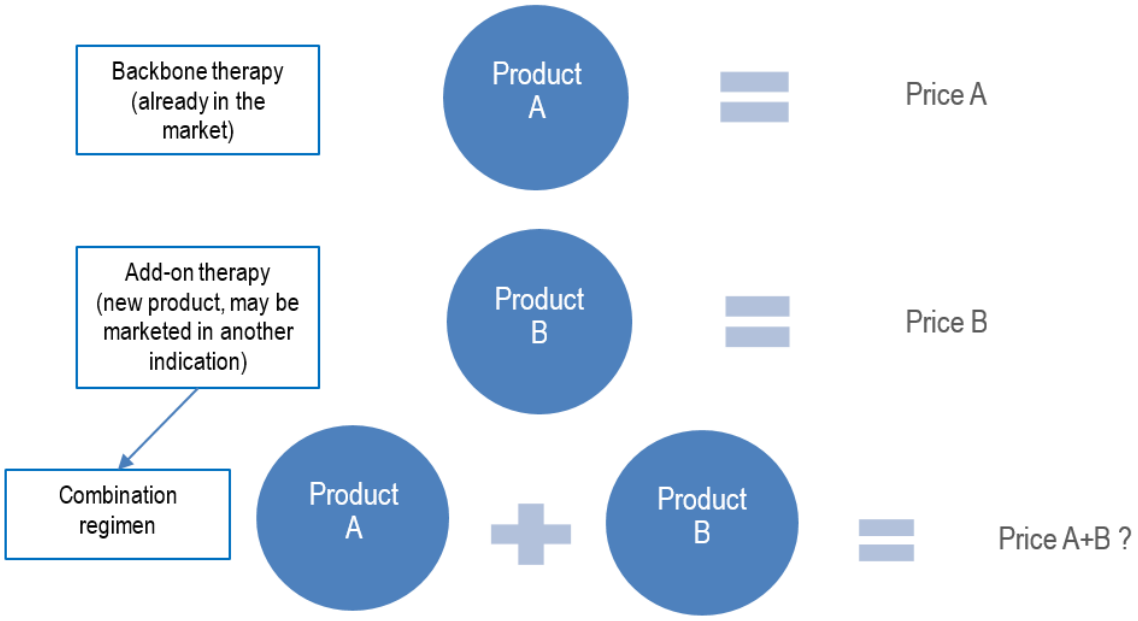
63. What generally happens is that the sum of the respective prices of drugs A and B exceeds the willingness to pay for the combination regimen. Decision makers may decide not to cover the combination, or they may choose to restrict access to it, but if there is a benefit for patients, a solution is likely to be sought. If the two products are made by the same manufacturer, a pricing agreement may be easier to reach even though it may still be challenging to operationalise, just as with indication-based pricing. However, the issue is more complex when the two products are marketed by different companies. The first issue is determining the price of each product when used in combination.[22] The second is compliance with competition law.

[20] Combination regimens refers to different medicines being used in combination, but not in a fixed dose product.

[21] NICE was ultimately able to issue a positive recommendation in the final guidance, and the initial assessment is intended to be illustrative.

[22] Value is used here as a generic term. It may refer to clinical benefit, to cost-effectiveness, or to any metric chosen to represent value in a specific environment.

Figure 2.3. Setting prices of products used in combination regimens



Source: Authors.

64. The company selling the backbone product has in general an interest in the combination being covered because it is expected to increase sales of its product. The company may therefore be willing to reduce the price of A in that indication if it does not affect the price of A in other indications. If the price of A is affected in all circumstances (because the payer is unable or unwilling to use indication-based pricing), the company may be reluctant to accept a lower price not fully compensated by the anticipated increased uptake arising from the use of the combination of A+B.

65. In any case, the question is how should the prices of A and B in the combination regimen be determined? The approaches reported by countries are described in Table 2.4. It appears that combination regimens are generally assessed with standard methods of evaluation, and with the possible exception of Australia, HTA entities do not, as a rule, attempt to attribute value shares to the individual constituents of the combination. In some countries, for example Belgium, the company filing the application for coverage or pricing is expected to adjust its price to make the price of the combination acceptable to payers. In France and Switzerland, the price of the combination is determined and public authorities then negotiate (confidential) prices with individual companies.

66. From a legal perspective, competition law generally prohibits companies from agreeing on prices for their products, particularly if they are in competition, unless there are demonstrable benefits to consumers from doing so. Companies agreeing on prices of products used in combination regimens are breaking the law if (i) the products are competitors, rather than complements; or (ii) if they are complements but the combination is used to foreclose access to one of the products or competitors of the suppliers. Within these constraints, pharmaceutical industry associations (both regional and national) within Europe have been working to identify practical solutions for adapting the prices of constituents of combination regimens.[23] So far, countries have adopted a variety of approaches. In France, the pricing committee determines its willingness to pay for the combination and then negotiates individually with each of the companies. In the United Kingdom (England), the Department of Health and Social Care (DHSC) and NHS England is waiting for solutions proposed by Association of the British Pharmaceutical Industry (ABPI) “to

[23] See for instance (EFPIA, 2018[94]) (Sandmeier, 2017[95]).

allow company-to-company engagement, to ensure that the combined cost of combinations can be developed for NICE appraisal, at the standard NICE threshold, in line with competition law" (Department of Health and Social Care and ABPI, 2018, p. 27[21]).

Table 2.4. Approaches to attributing value to constituents of combination regimens in OECD/EU countries

Country	Approaches to attribute value to constituents
Australia	This is highly context specific. First, the cost-effectiveness of the combination is determined based on the price proposed. Attributing value to the constituent parts will be influenced by relevant factors, including: • whether used concomitantly at all times, whether used in an overlapping way (e.g. use of one medicine extended as "maintenance"), or whether used entirely in sequence • whether one medicine is already listed for the target population and thus has an already established price, and if so, whether this price is likely to change in the near future • whether the constituent medicines are supplied by the same company, or by competing companies. Relevant factors such as these influence first the PBAC deliberations in deciding whether to recommend listing, and subsequently the government negotiations and decisions about whether to implement the PBAC's recommendation to list.
Belgium	No specific approach. In general if a company applies for coverage of its product B to be used with A, it will be expected to cover the cost of A, whose price is unlikely to change.
Canada	The HTA body assesses the combination therapy to issue a recommendation for public plans. The review looks at the product as a combination and does not focus on the constituent parts individually, to develop a funding recommendation. Typically, economic analyses by the Canadian Agency for Drugs and Technologies in Health (CADTH) ensure that public plans are not paying more than the aggregate of the current costs of the individual components.
Chile	No approach to attribute value to individual constituents of the combination. Budget impact is taken into account in price negotiations, which typically consider volumes rather than value.
France	The HTA body assesses the application for coverage of B, used in association with A and determines the added therapeutic benefit of A+B over the comparator (which might be A alone). The pricing committee then negotiates the price of the combination - If the combination has a minor added benefit (level IV), the cost of (A+B) must be = previous cost of A. - If the combination has a greater added benefit (from moderate III to major I), the cost of (A+B) may be = to the cost of A + 10% or more. In all cases, both prices must be negotiated. Treatment costs are based on net cost if any rebate. The price negotiation is done for each indication. Authorities do not attribute a share of the 'value' to constituents; the pricing committee negotiates with individual companies separately and may use confidential discounts.
Germany	The comparator therapy is the basis to determine the benefit for a new medicinal product and negotiate price if needed.
Hungary	Based on cost-effectiveness analysis and budget impact analysis and recommendations of Therapeutic Committee (financing protocols).
Italy	AIFA negotiates the price of a new product, regardless of its use in combination with other medicines. However, different types of MEAs can be applied to the product used in combination with other medicines, through the implementation of a patient monitoring registry. In such cases, the net price (i.e. list prices minus any agreed discounts) of the combination regimen may be different from the price of the single components used in other indications. When one of the medicines in the combination regimen is already reimbursed by the national health service, its price is generally considered a fixed parameter (although price negotiations can occur) and the price of the second part of the combination is defined so that the total cost of the combination reflects its added value. This approach is not mandatory for pricing decisions made by the Pricing and Reimbursement Committee.
Latvia	If both products are from the same company, the price is set for the combination and reimbursement restrictions may be applied stating that the products are reimbursed only if used in combination. If the new product is added to an existing therapy (which is the comparator) the price of a new product is approved based on cost-effectiveness data.
Lithuania	The combination is assessed as it would be for a monotherapy
Norway	No specific approaches used to valuing constituent parts of combination treatment regimens.
Sweden	The Dental and Pharmaceutical Benefits Agency (TLV) is currently working on the development of a method to price combinations therapies, with consultation in relevant stakeholders, including regions and industry.
Switzerland	Comparison of the combination therapy with the existing Standard of Care. For clinically relevant additional benefits, an innovation premium can be considered (max. 20 % over the price of the comparator). The cost-effective price per month of progression-free survival is used to calculate the price of the combination and then the payback for single agents.

Country	Approaches to attribute value to constituents
United Kingdom (England)	NICE does not undertake value attribution between constituents of combination therapies; this needs to be established prior to appraisal submission to NICE. Along with the Department of Health and Social Care, NHS England and NHS Improvement, NICE expects to support ABPI's efforts to enable companies to engage with one another where health-improving combination therapies face challenges coming to market, and ensure that the aggregate cost of combinations can be developed for NICE appraisal, within the standard NICE threshold, and in line with competition law.

Note: PBAC Pharmaceutical Benefits Advisory Committee, HTA health technology assessment, CADTH Canadian Agency for Drugs and Technologies in Health, AIFA Italian Medicines Agency, MEA managed entry agreement, TLV The Dental and Pharmaceutical Benefits Agency, NICE National Institute for Health and Care Excellence, NHS National Health Service, ABPI Association of the British Pharmaceutical Industry. Ireland and Malta, responded that no specific approach has been defined yet.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

2.4 Managing increasing treatment costs within budget constraints

67. While fast-paced innovation in oncology is good news for patients and societies, health policy makers can only worry about its impact on health expenditures and on the allocation of resources within the health sector, i.e. on spending efficiency. After a short introduction on price trends, the sections below look at general trends in pharmaceutical expenditures, and at special financing arrangements for oncology medicines existing in a few countries.

Many new medicines with increasing launch prices

68. The number of new medicines and indications has been increasing rapidly, especially since 2010. The EMA has approved 10 cancer medicines per year in the past decade (see Figure 2.4 panel A and (Hofmarcher et al., 2019[4])). In parallel, the prices of oncology medicines have also increased. In the United States, the monthly cost of treatment with individual medicines has constantly increased over time and some new treatments cost nearly USD 85 000 per month (see Figure 2.4 panel B and (Bach, 2019[34]). The figure does not feature two of the new CAR-T treatments, Kymriah® and Yescarta®, both approved in 2017, costing USD 216 564 and 170 060, respectively for one-off treatments. These new treatments, which in some cases bring important benefits to patients, are quickly adopted in clinical practice, raising the average costs of treatments. In Canada, the share of medicines with monthly treatment costs exceeding CAD 10 000 now accounts for almost one third of oncology sales (see Figure 2.4 panel C and (NPDUIS, 2019[35]).

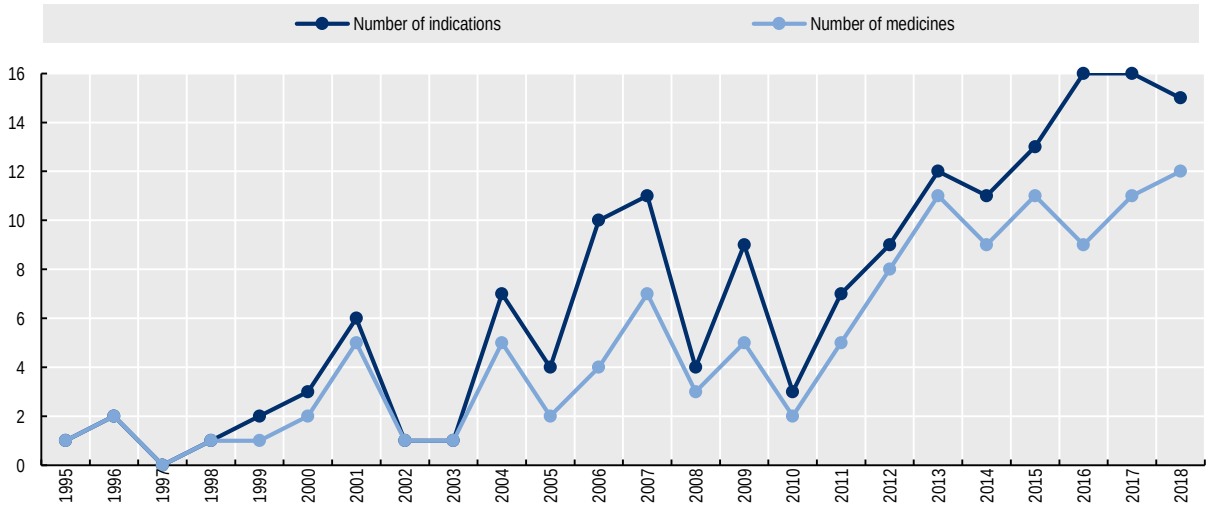
69. The prices of new oncology medicines have been questioned by many stakeholders, including prescribers, third-party payers, and civil society, and echoed in conference proceedings, media coverage[24] and investigations by various institutions.[25] In April 2019, the UK Institute for Cancer Research (ICR) published a very strong position statement, identifying "fundamental problems with the way that cancer drugs are priced, […] many innovative new medicines end up being unaffordable for health care systems" and calling for "a new approach to pricing that sets a fair price for each drug – taking into account the need for a return on investment, but without pushing health care systems to the limits of what they can afford." (ICR, 2019, p. 1[36])

[24] See for example: http://sante.lefigaro.fr/actualite/2016/03/14/24739-lurgence-maitriser-prix-nouveaux-medicaments-contre-cancer; https://www.theguardian.com/science/2017/dec/20/drug-giants-hefty-prices-nhs-vital-medication-pharma-profits; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6745980/pdf/hs9-1-e12.pdf; https://www.irishexaminer.com/breakingnews/ireland/cancer-patients-under-siege-from-treatment-costs-936549.html; consulted on 18 March 2020.

[25] See https://www.lecese.fr/travaux-publies/prix-et-acces-aux-medicaments-innovants, consulted on 18 March 2020.

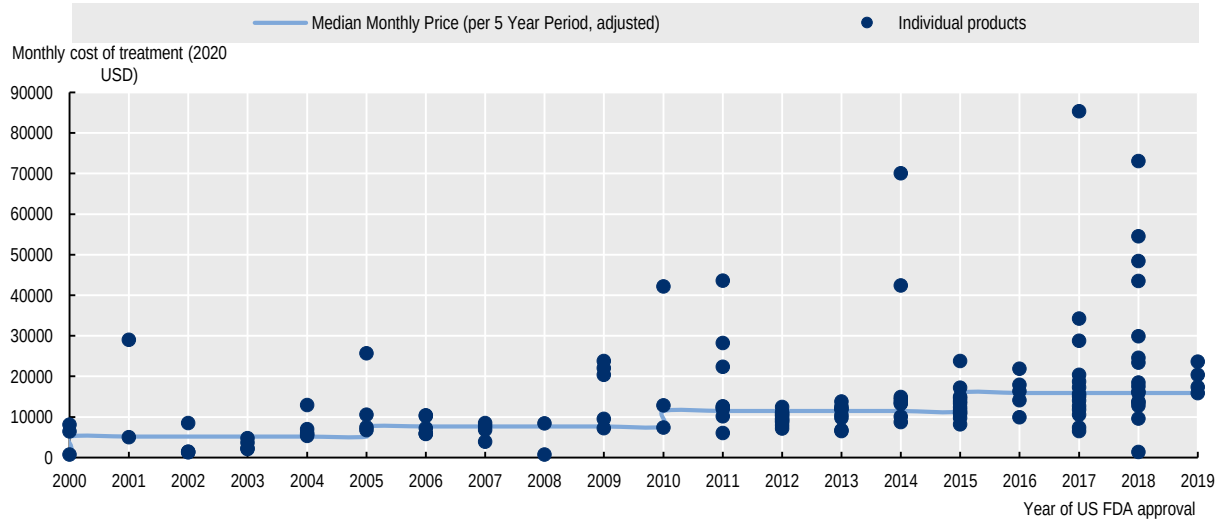
Figure 2.4. Trends in the number of oncology medicines approved and their prices

A: Number of cancer medicines and indications approved by the European Medicines Agency, 1995-2018



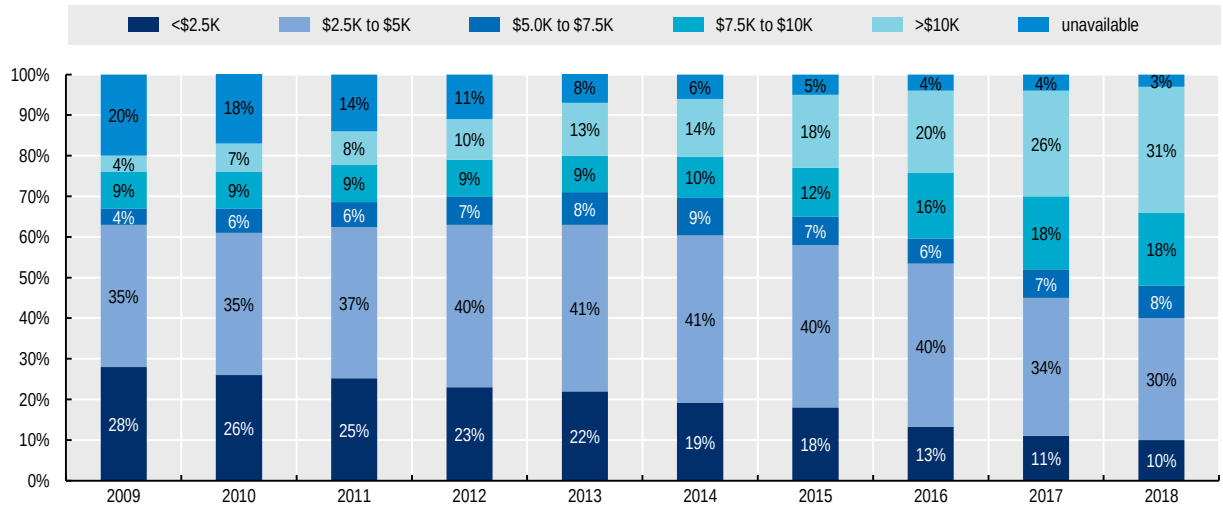
Source: Reproduced from (Hofmarcher et al., 2019[4]), Comparator Report on Cancer in Europe 2019, https://ihe.se/en/publicering/comparator-report-on-cancer-in-europe-2019/, on 26 February 2020.

B. Monthly costs of cancer drugs at time of US FDA approval, 2000-2019



Note: Based on Medicare reimbursement rates and by year of drug approval. Median cost is computed for 5-year period. Figure excludes Kymriah® and Yescarta®, both approved in 2017.
Source: Reproduced from (Bach, 2019[34]), Prices & Value of Cancer Drugs, https://www.mskcc.org/research-programs/health-policy-outcomes/cost-drugs, on 17 March 2020.

C: Sales revenue share by 28-day treatment cost (CAD) of oncology medicines, Canada, 2009 to 2018



Source: Reproduced from the Patented Medicine Prices Review Board (PMPRB) (NPDUIS, 2019[35]), The oncology drug market: A high-growth, high-price therapeutic area, http://www.pmprb-cepmb.gc.ca/view.asp?ccid=1453&lang=en, on 27 February 2020. The reproduction is a copy of an official work that is published by the Government of Canada and that the reproduction has not been produced in affiliation with, or with the endorsement of the Government of Canada.

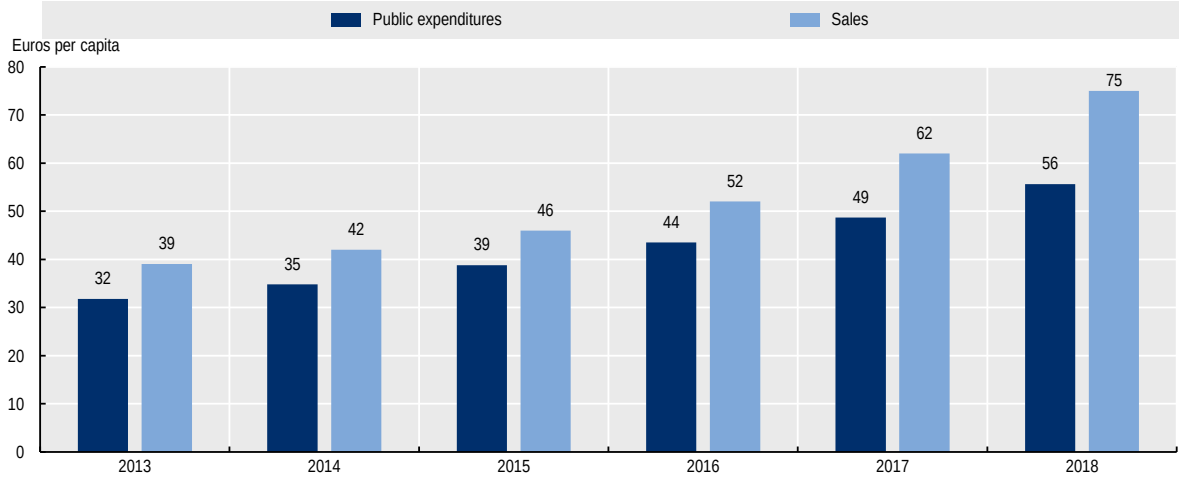
Increases in expenditures have been partly compensated by savings in other parts of the health system

70. Expenditures on oncology medicines are not only impacted by increasing prices but also by an increasing number of patients treated, due to higher cancer prevalence and new treatment options (Hofmarcher et al., 2019[4]). As a result of these trends in volumes and prices, the value of sales of oncology medicines more than doubled in Europe in the past decade[26], and in the United States in just five years[27] (Hofmarcher et al., 2019[4]; IQVIA, 2019[37]). Available sales data, however, are not ideal for estimating pharmaceutical expenditures. To begin with, they do not include distribution mark-ups and taxes on medicines sold to outpatients for self-administration (thereby underestimating the impact on health care budgets). Nor do they take into account confidential ex-post rebates, which are particularly important in oncology markets (thereby overestimating the impact on health expenditures). As a matter of fact, only a handful of countries are able to report trends in expenditure on oncology medicines. In Italy, where data on sales and public expenditures can be compared, the differences between sales and public expenditures are not negligible (public expenditures are 26% lower in 2018) (see Figure 2.5). In oncology, the difference is unlikely to be due to private expenditures. This can be attributed in part to product-specific rebates, since public expenditures by therapeutic classes published by AIFA are net of these rebates - but not net of rebates paid by all companies when the total pharmaceutical expenditure ceiling is exceeded (Osmed/AIFA, 2019[38]).

[26] Sales growth at list prices, in real term between 2008 and 2018, according to (Hofmarcher et al., 2019[4]). These series do not take into account ex-post rebates.

[27] Sales growth at list prices, current prices according to (IQVIA, 2019[37]).

Figure 2.5. Comparisons of sales and expenditures per capita for oncology medicines in Italy

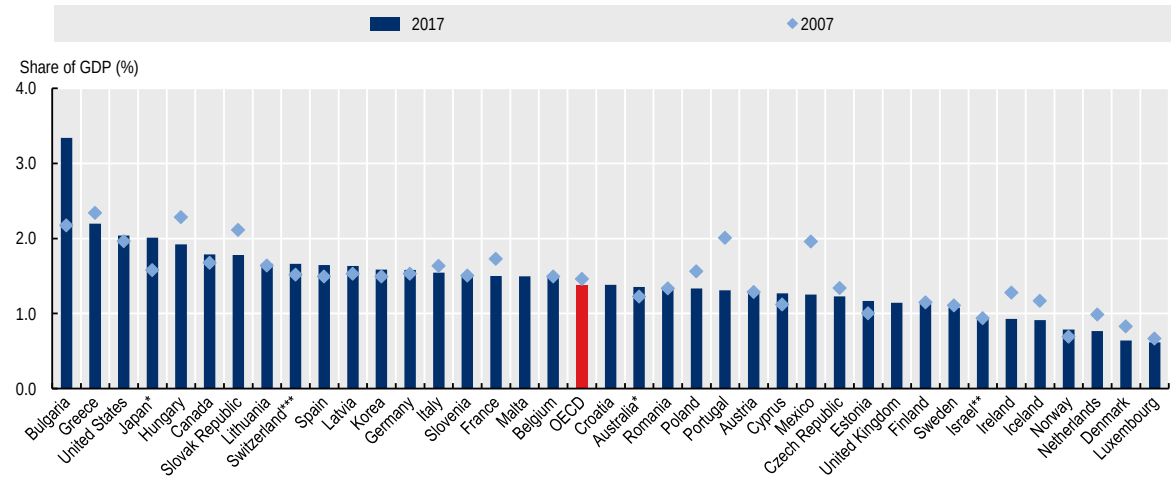


Source: Authors based on per capita public expenditure on oncology medicines, in current euros, taken from (Osmed/AIFA, 2019[38]); and per capita sales in current euros taken from (Hofmarcher et al., 2019[4]).

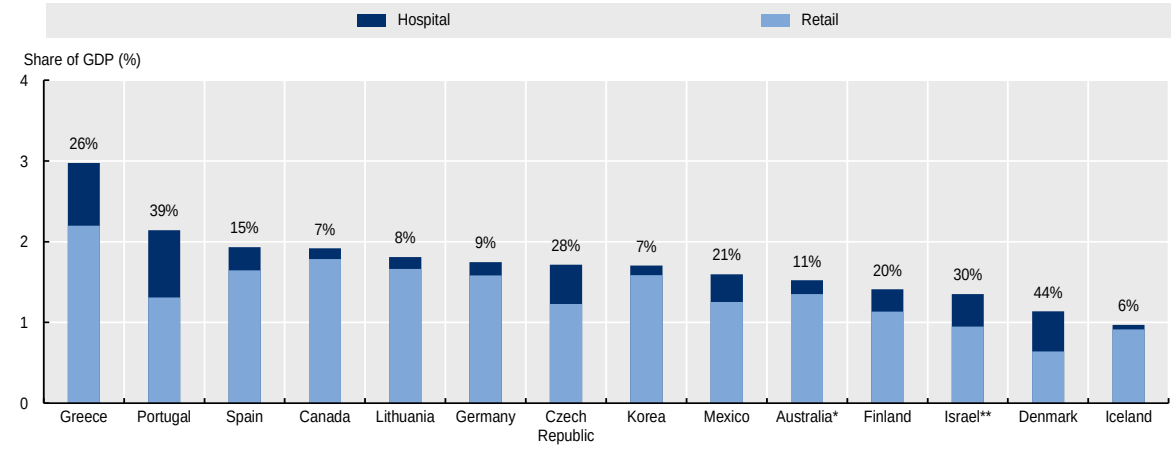
71. Without appropriate monitoring of expenditure on oncology medicines, the impact of consumption and price trends on total pharmaceutical or total health expenditures is not easy to discern, and requires a lot of estimation and assumptions (Hofmarcher et al., 2019[4]). What can be observed is that expenditure on retail pharmaceuticals as a share of Gross Domestic Product (GDP) has remained stable over the past decade in OECD countries. This is due in part to a combination of market dynamics (generic and biosimilar competition) and cost-containment policies. However, this does not provide a complete picture of current trends. In several countries, expenditure reported for pharmaceuticals administered as part of outpatient or inpatient services, account for a large share of total pharmaceutical expenditures (e.g. 26% in Greece, 30% in Israel, 39% in Portugal, and 44% in Denmark). Moreover, this spending is increasing much more rapidly than it is for retail pharmaceuticals (see Figure 2.6).

Figure 2.6. Trends in pharmaceutical expenditure

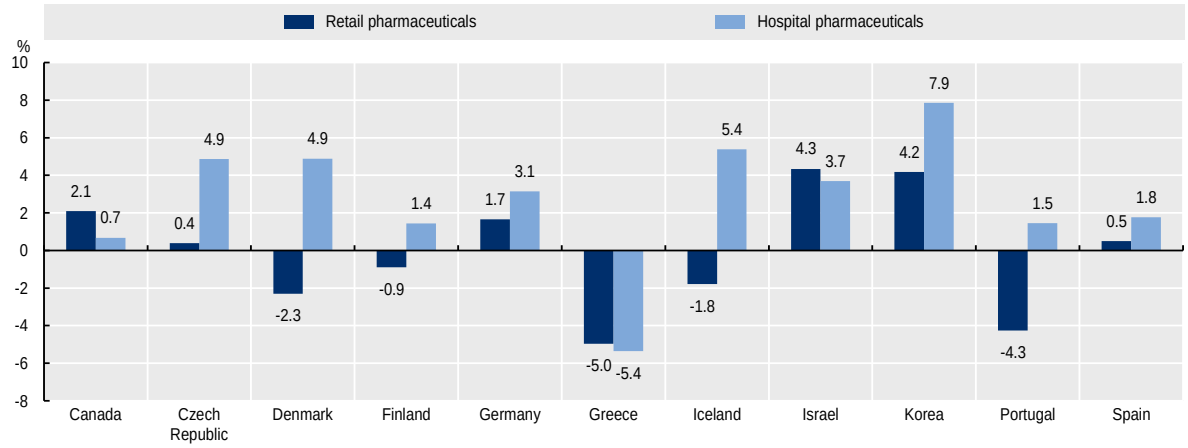
A: Retail pharmaceutical expenditure, as share of GDP, 2007-2017



B: Total pharmaceutical expenditure, as share of GDP, in 2017



C: Growth of expenditure of retail and hospital pharmaceuticals 2007-2017



Note: Panel A: Retail pharmaceutical expenditure includes medical non-durables. * latest year available 2016; ** 2014; *** first year available 2010. Panel C: Average annual growth of expenditures, in real terms

Source: OECD Health Statistics 2019

A few countries have special financing arrangements for oncology medicines

72. In response to the OECD survey, only a few countries reported having *specific arrangements* for the financing, pricing and procurement of oncology medicines. More countries reported having specific arrangements for all high-cost medicines, but these are not systematically described below.

73. Six countries[28] responded that **financing arrangements** for oncology medicines differed from those of other medicines:

- In Canada, provincial and territorial governments are responsible for the delivery of health services, including what is reimbursed and under what conditions. Some of them use cancer agencies to delivery cancer treatments, with earmarked budgets. These budgets typically cover all cancer care, including medicines.
- Italy and England have both adopted approaches to earmark funds towards new oncology medicines, *before their inclusion in regular health care budgets*.
    - In Italy, an annual fund of EUR 500 million, renewable every three years, has been made available for *new innovative* oncology medicines since 2017. Medicines eligible to this fund must be innovative, according to well-defined criteria including added therapeutic value compared to existing treatments (see Box 2.3). First-in class medicines may benefit from this status for a maximum of 36 months. Follow-on products may be eligible but only for the residual period up to 36 months. The system is demand-driven. If the financing of eligible treatments exceeds EUR 500 million in a given year, companies have to pay rebates. In 2018, expenditures for new innovative oncology medicines (net from MEAs rebates) but before fund-specific rebates was EUR 613.8 million (Osmed/AIFA, 2019[38]). Medicines funded through this mechanism are not included in the estimation of pharmaceutical expenditures subject to the existing capping for total pharmaceutical expenditures (OECD, 2019[39]).The renewal of this earmarked fund is currently being discussed.
    - In England, the 'new 'Cancer Drugs Fund (CDF) covers new oncology medicines in three scenarios (see Figure 2.7): medicines with a marketing authorisation awaiting NICE appraisal (through Interim Funding Arrangements); medicines with Managed Access Agreements through the CDF while further data are collected to reduce uncertainty (usually for a period of two years); and medicines approved by NICE for routine NHS commissioning for a period of 90 days after the decision. The annual budget for the CDF is GBP 340 million, beyond which all companies with medicines funded through the CDF must pay rebates in proportion to their own sales (NHS England Cancer Drugs Fund Team, 2016[40]; NICE, 2018[41]; NICE, n.d.[42]).
- In Chile in 2016, the "Ricarte Soto law" set up a fund for high cost treatments and diagnostics and a specific fund for cancer drugs is under discussion in Parliament at the time of reporting. The system enables the financing of one type of medicine or device per disease and invites companies to submit confidential proposals to the Ministry of Health (MOH). Once the medicine is selected, the MOH sends the information (prices and conditions) to the National Procurement Agency (CENABAST) who opens a public bidding process or purchases directly when there is only one possible provider. All companies can participate, but they have to present at least the same offers that were presented to the MOH before.[29]

[28] Greece and Malta reported earmarked funding for oncology medicines. In Malta, a specific oncology financial vote was introduced in 2017 for new oncology medicines to be introduced on the Government Formulary List as approved and prioritised by the Ministry for Health

[29] https://www.minsal.cl/ley-nacional-de-cancer-fue-aprobada-en-general-por-el-senado/

Box 2.3. Criteria used to determine eligibility for funding through **Italy's** Fund for Innovative Medicines in Oncology

"Innovative" oncology medicines are currently financed through a specific fund "Fondo per i farmaci innovativi oncologici" (Law n. 232/2016, art.1), established at EUR 500 million per year for three years and renewable every three years since 2017. The Italian Medicines Agency (AIFA) has defined criteria for identifying "innovative" medicines (Det. 1535/2017) taking into account: (1) therapeutic need; (2) added therapeutic value; and (3) the quality of evidence and robustness of clinical studies.

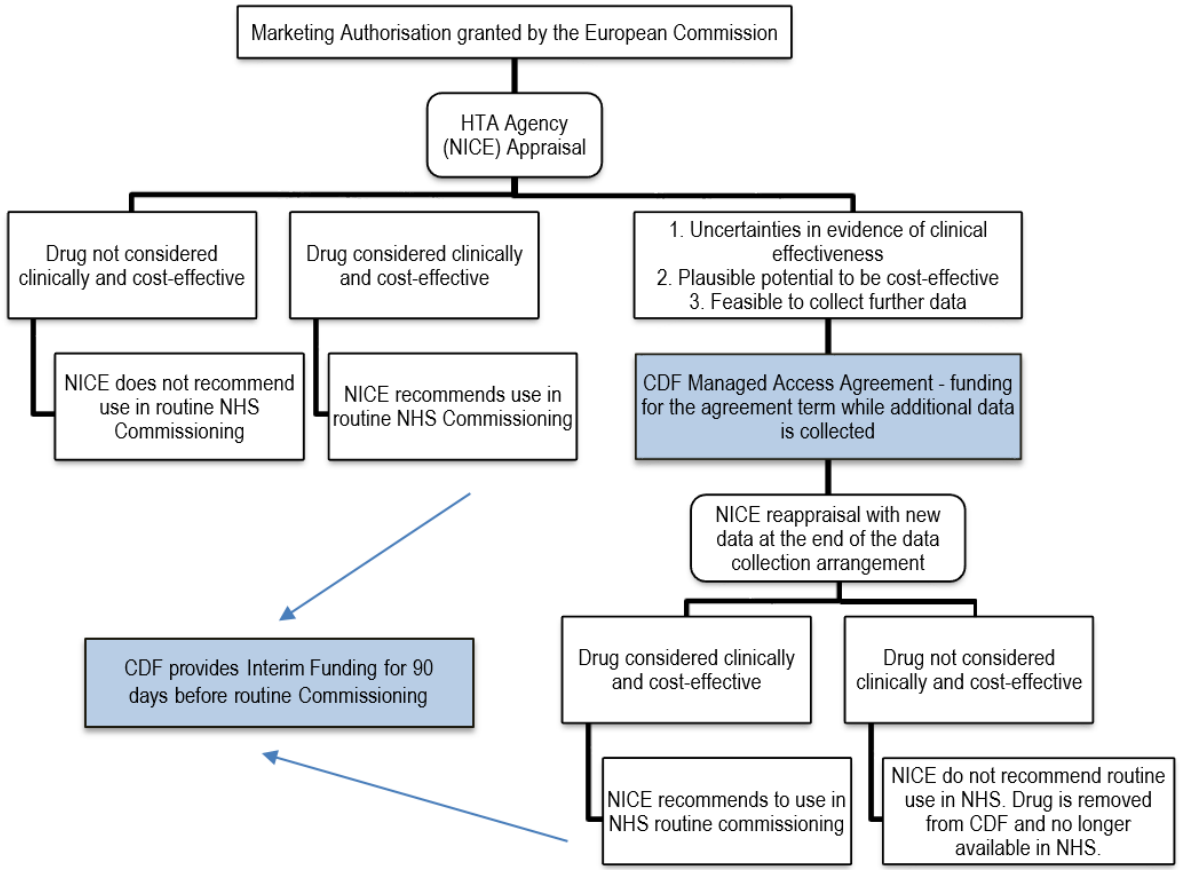
(1) Therapeutic need is scored on a 5-level scale from "maximum" (absence of any therapeutic option) to "absent" (presence of therapeutic alternatives for the specific indication able to modify the natural history of the disease and with a favourable safety profile).

(2) Added therapeutic value is defined as the extent of the clinical benefit offered by the new medicine compared to existing alternatives, assessed against outcomes that are clinically relevant and validated for the condition treated. The added therapeutic value is also scored on a 5-point scale from "maximum" (greater efficacy demonstrated on clinically relevant outcomes; the medicine is able to cure the disease or change its natural history) to "absent" (absence of an additional clinical benefit compared to therapeutic alternatives available).

(3) Quality of evidence and robustness of clinical studies. For the evaluation of this parameter, AIFA uses the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to assess the quality as High, Moderate, Low, or Very low.

Source: http://www.agenziafarmaco.gov.it/content/criteri-la-classificazione-dei-farmaci-innovativi-e-dei-farmaci-oncologici-innovativi-180920 ; http://www.jclinepi.com/content/jce-GRADE-Series

Figure 2.7. The role of the Cancer Drugs Fund in the English National Health System



Note: HTA health technology assessment, CDF Cancer Drugs Fund (England), NICE National Institute for Health and Care Excellence, NHS National Health Service (England)
Source: Authors, based on information provided by NHS England and NICE (NHS England Cancer Drugs Fund Team, 2016[40]; NICE, 2018[41]; NICE, n.d.[42]).

74. These earmarked funds seem to function as a “double guarantee”: a guarantee that selected new treatments will be available in the system, and at the same time, a guarantee that they will not capture a disproportionate amount of resources. However, concerns have been raised by other countries on the equity of such earmarked funds.

75. Other countries mentioned special financing arrangements which are not specific to oncology medicines but aim to fund *early* or *derogatory* access to some medicines. In Belgium, for example, an Early Temporary Authorisation for use and an Early Temporary Reimbursement schemes can be used to provide subsidised access to promising therapies used in severe/fatal diseases with no reimbursed alternative treatment. The indication must be included in the “Unmet Medical Need list”, updated annually. The system is demand driven. In addition, a Special Solidarity Fund provides an additional safety net to cover high cost treatment for rare diseases excluded from the universal insurance system. Several criteria have to be met to be eligible for reimbursement and the budget of this fund is limited.

76. Finally, two countries responded that **procurement processes** for oncology medicines differed from that of other medicines (Canada and Latvia). In Canada (except in Quebec), hospitals go through their own procurement processes and often have dedicated budgets for cancer care. In Latvia, centralised procurement is organised by the National Health Service for chemotherapy medicines.

Promoting competition in off-patent markets can save costs and increase access

77. At the end of a period of market exclusivity, competition from generics or biosimilars is expected to result in lower prices and cost savings. Usually, the price difference between originator and generic is higher than that between originator and biosimilar (up to 80% versus 15-30%, respectively) (Simoens, 2011[43]; Nabhan et al., 2018[44]). However, given that prices of biologics are general higher than prices of small molecules and that the market share of biologics is increasing, the potential savings are high.

78. Recent studies have looked at generic prices and savings after generic entry for simple molecules or groups of molecules. Lejniece et al. showed that, in Latvia, the annual cost of a generic version of imatinib was reported to be 96% lower than that of the originator (Lejniece, Udre and Rivkina, 2017[45]). In the United Kingdom, the uptake of generic versions of imatinib saved the NHS GBP 66.3 million in the year 2017-2018 (NHS England, 2018[46]). Godman and Simoens (2019[47]) looked at nine generic oral cancer medicines included in the World Health Organization’s (WHO) *Model List of Essential Medicines (EML)* across 25 EU countries. They observed that differences between originator and generics prices varied widely across countries, as a result of generics policies. For example, for capecitabine in Norway, France, Spain and Sweden the differences were 45%, 53%, 67% and 80%, respectively (Godman and Simoens, 2019[47]). In Japan, where generic market penetration was relatively high for oncology medicines between 2010 and 2016, it was relatively low for antimetabolites, protein kinase inhibitors, hormones, and with no penetration of monoclonal antibodies (likely not yet off-patent) (Shibata et al., 2017[48]).

79. In Europe, at least one biosimilar is available for each of three biologics used in oncology and four used in supportive care (European Medicines Agency, 2019[49]). Hofmarcher et al. (2019[4]) estimated the potential cost savings from biosimilars from the three biologics (bevacizumab, rituximab and trastuzumab) at EUR 2.4 billion in Europe per year, based on sales in 2016 (before the first biosimilar was approved) and assuming a 45% price reduction compared to the reference product. In 2018 in Europe, these three medicines accounted for 15% of all cancer medicine sales.

80. A range of contextual factors may influence the magnitude of price reductions following the introduction of generic / biosimilar medicines, and the extent of generic / biosimilar uptake (World Health Organization, 2018, pp. 64-67[2]; Godman and Simoens, 2019[47])

81. In 2014, Kanavos outlined a methodological framework for measuring performance in off-patent drug markets in 12 EU Member States (the United Kingdom, Germany, Finland, Austria, France, Spain, Sweden, Italy, Greece, and Portugal). Performance indicators include generic availability (12 and 24

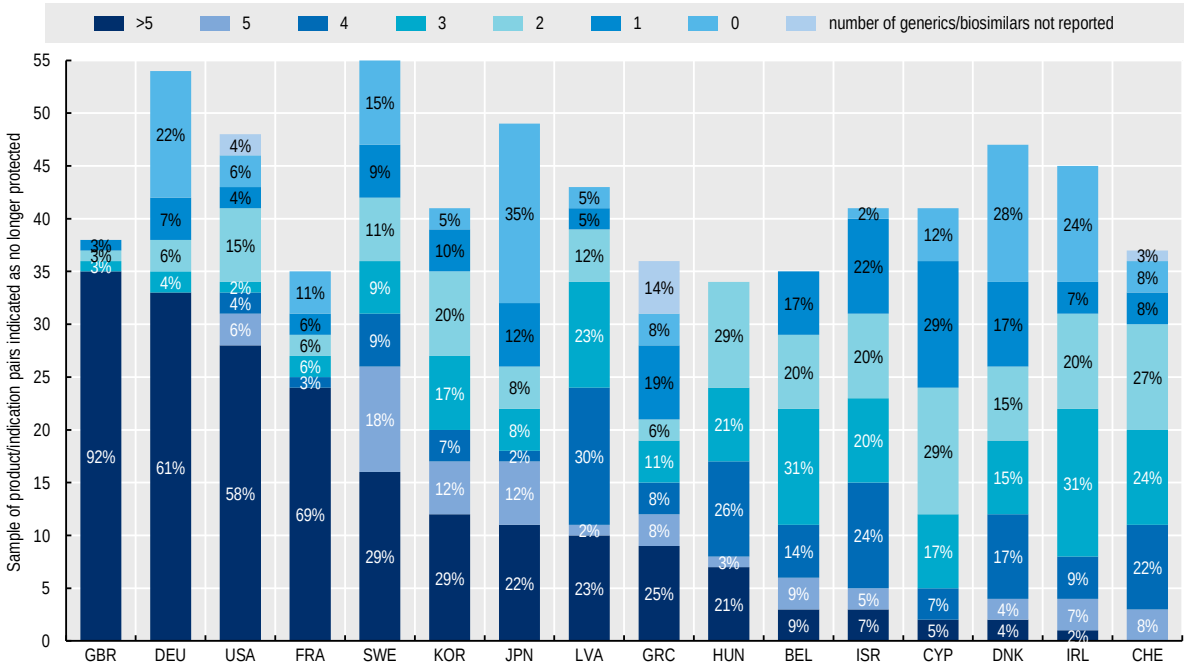
months after patent expiry), time delay to generic entry, number of generic competitors, generic price development and impact, and generic volume market share. According to these indicators, the Netherlands, Denmark, Germany and the United Kingdom have high performing generic markets (Kanavos, 2014[50]).

82. In Part 3 of the OECD survey, for each of the 109 product/indication pairs of the sample, respondents were asked if the originator / reference product was currently protected from generic or biosimilar competition, and if not, the number of generic/biosimilar products available for that indication (see Annex A. for further details). Responses to this part of the survey were incomplete: of those product/indication pairs approved in each country, the numbers reported as no longer protected ranged from 34 (in Hungary) to 55 (in Sweden).

83. For the pairs reported as no longer protected in each country, at least one generic / biosimilar was available in most countries (see Figure 2.8). The United Kingdom (England), Germany and the United States had the highest proportions of product/indications with more than five generics / biosimilars available, with 92%, 61% and 58% respectively. This confirms what is already known about the strength of generic markets in these countries. What is more intriguing are the proportion of products/indications reported as "no longer protected" but for which no competitor has entered the market, i.e. 28% in Denmark, and 35% in Japan.

84. The number of product/indications no longer protected may vary across countries for a number of reasons. Firstly, the duration of the protection from competition depends on national or regional legislation (differences in dates of patent expiration, duration of regulatory data and market exclusivity periods). In addition, data or market exclusivity terms begin on the date of marketing approval in the country or region (Copenhagen Economics, 2018[51]). Once product/indications are no longer protected, the time to generic entry will depend in part on local policy settings. Some countries (for example Germany) have no formal pricing and reimbursement procedures for generics and biosimilars, and can therefore benefit from competition immediately following marketing approval.

Figure 2.8. Percentage of products reported as no longer protected from competition, by number of generics/biosimilars available across OECD/EU countries



Note: Data from Chile, Estonia, Lithuania, Malta, and Norway were excluded as data were not representative.
Source: Authors based on 2019 OECD challenges in access to oncology survey.

Wastage reduction and dosage optimisation may also create savings

85. Savings can also be achieved by minimizing wastage of high-cost (injectable) cancer medicines. Dosage are often individualised, based on patient body weight or surface area. Each dose must be made up specifically for the patient, using a combination of vial sizes (where available). As a result, there may be leftover drug that is subsequently wasted as it must be discarded within a short time (based on the stability data of the drug, and often within a few hours). Bach et al (2016[52]) examined the top 20 cancer drugs that are dosed by body size and packaged in single-use vials and estimated the extent of leftover product, based on 2016 US sales. The proportion of leftover drug varied from 1% to 33% across products, representing 10% of companies' revenues from these medicines, or USD 1.8 billion. The cost for consumers and third-party payers was higher since it included supply chain mark-ups (Bach et al., 2016[52]). Pearson, Ringland, & Ward (2007[53]) examined wastage of trastuzumab, used for the treatment of metastatic breast cancer, in Australia. Trastuzumab is dosed by patient body size and was only available in one vial size at the time. An estimated 24% of trastuzumab dispensed over a 40-month period from December 2001 to March 2005 was discarded. This equated to AUD 21.1 million. Alternative dosing schedules and the availability of another vial size were estimated to reduce wastage to 5% of volume dispensed (Pearson, Ringland and Ward, 2007[53]).

86. Two studies highlighted a number of strategies that have been proposed to reduce wastage, generally aimed at pharmaceutical companies (Gilbar and Chambers, 2017[54]; Gilbar et al., 2019[55]). They included: 1) increasing the range of vial sizes available in countries; 2) ensuring vials contain excess or overage of the drug to compensate for loss during manufacture resulting in insufficient volume of the drug for a patient dose; 3) further research to provide extended stability data, as most oncology medicines are given short expiry dates once reconstituted due to lack of information on stability; and 4) ensuring medicines are available in the most appropriate form (e.g. pre-filled syringes or pens) (Gilbar and Chambers, 2017[54]; Gilbar et al., 2019[55]). An additional method aimed at pharmaceutical companies would be to encourage vial sizes that reflect fixed dosage regimens. Other proposed methods include vial sharing, whereby leftover drug from one patient can be used in the preparation of a dose for another patient. While vial sharing reportedly occurs in Australia, it is not a specific Australian strategy to reduce wastage. In addition, optimising treatment doses may be another step in reducing the financial toxicity of cancer medicines. This includes optimization of dose, duration, or type of drug (The Lancet Oncology, 2018[56]; Norris, 2018[57]).

87. Since 2011 in Australia, the Efficient Funding of Chemotherapy Program aims to minimise wastage and reduce payer and patient costs of injectable cancer medicines administered in public and private hospitals. Prescribers order per treatment doses for each patient (e.g. in milligrams), rather than by vial; the programme provides national Pharmaceutical Benefit Scheme (PBS) reimbursement to pharmacies based on supplying the lowest cost combination of vials for this dose (Australian Government Department of Health, 2019[58]; 2013[59]). Even though a 2013 review of the programme found that the funding arrangements did not align with the complexity of chemotherapy pharmaceutical provision models in Australia and highlighted the complexity and administrative burden of PBS reimbursement, the programme remains in place (Australian Government Department of Health, 2013[59]).

3 Access to oncology medicines in OECD/EU countries

88. Differences in access to oncology medicines across countries may arise as a result of the varying capacities of health care systems (administrative, technical, and financial), willingness to pay for oncology medicines, and societal priorities regarding cancer care *vis a vis* other diseases. They may also arise because of the issues discussed previously, such as uncertainty regarding benefits and high launch prices. Additionally, countries may vary in terms of the level at which coverage decisions are made and subsequent coverage provided. The following section discusses dimensions of access, before presenting results from the OECD survey on regulatory approval and coverage status of a sample of medicines, as well as time to access[30] for a subset of this sample. Potential reasons for differences in countries are described, followed by a discussion on sources of inequity and patient expectations.

3.1 Access is multi-dimensional

89. Access to oncology medicines can be assessed across three major dimensions: availability, affordability, and accessibility, defined below. Broad access to *all* cancer medicines is often assumed to be ideal, but is not essential. Access needs to be understood within the context of each country's health care system. For example, if several medicines are potentially available for a given indication, procurement methods may result in only some of them being available, without disadvantaging patients. In addition, in many countries, even those without significant or absolute budget constraints, it may be difficult (or even illegal) for payers to provide coverage of medicines not considered cost-effective.

Availability

90. Availability in the market is the first condition for access to medicines. It generally requires *marketing authorisation* for a product (for a specific indication), followed by *launch of the medicine* by the company. While companies may launch their products as soon as marketing authorisation is granted, in some countries, they may choose to wait for a decision on funding by one or more third-party payers (government or health insurance), and which will often be linked with price regulation. In terms of availability and timeliness of the availability of a medicine in a given country, the following indicators are interesting:

- Whether the medicine has marketing authorisation;
- Whether the product has been launched;
- The elapsed time between marketing authorisation and launch; and
- The elapsed time between first approval/launch and approval/launch in a given country. This is influenced by two factors: the launch strategy of the company (in turn influenced by market size

[30] In this study, "time to access" for a medicine (or an indication) was generally measured as the time between submission of the application for marketing authorisation in the country (or region for EU) and the date of the coverage decision.

and pharmaceutical policies in each country, as shown in (Danzon and Epstein, 2012[60])), and the performance of the regulatory and coverage decision-making processes.

Affordability

91. Affordability can be considered at the individual level, for patients or their families, and at the societal level (for public budgets). For most oncology medicines, funding by third-party payers is essential for individual affordability. In most OECD countries, these medicines are covered by government or health insurance schemes, albeit often with user charges or co-payments. For affordability for patients it is essential that 1) the medicine is covered, and that 2) user co-payments, where they exist, are not excessive. Affordability for health care systems will be influenced by government priority setting and resource allocation, which in turn are influenced by societal values and the priority afforded to health relative to other social policy areas such as education and social welfare.

92. Indicators of affordability include the coverage status of the medicine and the insurance status of the patient, as well as the type and level of cost-sharing for different goods and services (e.g. co-payments, co-insurance, deductibles, extra-billing, safety nets or caps), other out-of-pocket costs to patients, and individual drug prices. These are defined and discussed in section 3.6.

Accessibility

93. Accessibility encompasses the ability to obtain a prescription for the medicine, but also factors associated with the pharmaceutical supply chain, such as marketing authorisation, pricing, coverage or reimbursement status, and inclusion in clinical guidelines and treatment protocols. The extent of use of a medicine by patients who could potentially benefit from it would arguably be the best metric of accessibility, but unfortunately, this is not readily measurable. Other indicators may include:

- Utilisation, measured in a standard unit, such as defined daily dose (DDD[31]) per 1000 population per day. This, however, does not take prevalence of disease into account.
- Proportion of eligible patients treated by the medicine. This indicator would measure accessibility more accurately, but the number of eligible patients may be difficult to ascertain. Information on prevalence is most often insufficiently granular (by cancer type, stage, line of treatment) to compute the exact number of patients eligible for a given treatment.
- "Sales per dying patient", has been used in the *Comparator Report on Cancer in Europe* (2019[4]). It is the ratio of quantity sold (in milligrams) to the number of deaths from the cancers for which the medicine has an indication, as a proxy for incidence. Mortality data, however, may not reflect the number of patients treated.

3.2 Measuring access to oncology medicines

94. Experts from 23 OECD countries and EU Member States[32] responded to the section of the OECD survey that sought information on aspects of access such as regulatory approval (i.e. marketing authorisation) and coverage for a sample of 109 oncology product/indication pairs across five cancer types (including supportive care).

[31] The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults.

[32] Responses were received from Australia, Belgium, Chile, Cyprus, the Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Japan, Korea, Latvia, Lithuania, Malta, Norway, Sweden, Switzerland, the United Kingdom (England only), and the United States.

Sample of 109 products/indications pairs covering 5 cancer types

95. The list of products and indications in the survey drew on the results of two European Society for Medical Oncology (ESMO) surveys that, to date, have produced the most comprehensive dataset on availability and coverage of cancer medicines across countries (Cherny et al., 2016[61]; Cherny et al., 2017[62]). The selection of medicines was narrowed to cancers with significant prevalence in OECD countries and EU Member States, albeit with the addition of medications for one haematological malignancy. In order to capture the availability of novel medicines, the Secretariat added to the sample all oncology medicines for the selected indications that had been approved by the United States or Europe as of July 2019 and those included in the 21st World Health Organization (WHO) *Model List of Essential Medicines (EML)* (2019[63]). The final list of indications comprised metastatic breast cancer, non-small cell lung cancer, colorectal cancer, melanoma, and multiple myeloma. Further details about the survey are presented in Annex A, with the final sample of products and indications shown in Table A A.2. Product/indications included in the EML, as well as those medicines approved in the United States since 2014 are flagged.

96. Product/indication pairs were further classified in order to facilitate the interpretation of availability of medicines and make a qualitative assessment of access. A qualitative judgement requires a framework for the classification of medicines into relevant categories. Hofmarcher et al. (2019[4]) proposed several options, such as the class of the medicine (Anatomical Therapeutic Chemical [ATC] subgroups); the type of therapy (chemotherapy, targeted therapy, immunotherapy); the indication (lung cancer, colorectal cancer); the extent of unmet need or target population size (orphan drugs); the "vintage" (older vs newer medicines); and the therapeutic value (e.g. using classification systems proposed by ESMO, the American Society of Clinical Oncology [ASCO], and others).

97. For this analysis, two options were considered, in addition to inclusion in the EML, to provide a qualitative assessment of access:

- The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS): This scale measures the therapeutic value of medicines (see Box 3.1 for more detail) (Cherny et al., 2015[64]). It was created to highlight the most important drugs in terms of clinical benefit, in order to assist countries in prioritising access to these medicines. The Essential Medicine List Cancer Medicines Working Group, an informal advisory group who convened on 22-23 March 2018 to assist in the preparation of the WHO report *Pricing of cancer medicines and its impacts*, proposed the use of this scale in considering therapies for listing on the EML (World Health Organization, 2018[2]). However, the ESMO-MCBS could not be used for the OECD sample, as it does not provide scores for all products contained in the sample, and also because the ESMO establishes scores for individual indications at a very detailed level (e.g. different line of therapy, different comparators). It was not possible to aggregate these scores to reflect the indications specified in the sample.
- The ATC classification system developed by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) (WHO Collaborating Centre for Drug Statistics Methodology, 2019[65]): Medicines were grouped by therapeutic class (ATC 4 level) in tables presenting information on availability and accessibility. At this level medicines have similar modes of actions and can often be considered as therapeutic alternatives.

Box 3.1. ESMO – Magnitude of Clinical Benefit Scale (ESMO-MCBS)

The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a standardised, generic, validated tool to classify new cancer medicines according to their therapeutic value (Cherny et al., 2015[64]; Cherny et al., 2017[66]). The scale grades cancer medicines in curative and non-curative settings, based on their quality, efficacy and safety; it does not take cost into account. It was created in order to highlight the most important drugs in terms of clinical benefit, and increase access to such drugs. The table below outlines the grading system. A different form is completed based on the intent of the treatment (curative and non-curative) and the primary endpoints used to assess clinical benefit (e.g. overall survival, progression free survival, response rate etc.) Scores A and B in the curative setting, and 5 and 4 in the non-curative setting indicate grades with substantial improvement.

Table 3.1. ESMO-MCBS Treatment Scores

	Curative intent	Non-curative intent	
Scores	A	5	} High level of clinical benefit
	B	4	
	C	3	
		2	
		1	

Source: Adapted from (Cherny et al., 2015[64]; Cherny et al., 2017[66]).

ESMO-MCBS can be used by Health Technology Assessment bodies for coverage decision-making, by prescribers and patients in daily practice, and in the design of clinical trials. Australia, for example, references this scale when prioritising oncology medicines for national medicine listings. Users can filter results of grading system by therapeutic agent, tumour type/sub-type and score. At present, however, the tool is only available for solid tumours.

Source: Authors based on sources cited.

Information collected on marketing authorisation and coverage status as at the end of 2019

98. The data present a cross-sectional view of availability and coverage of medicines *at one point in time, near the end of 2019* (ranging from 20 September 2019 for Cyprus to 15 January 2020 for Chile)[33]. The data reflect regulatory approval (i.e. marketing authorisation) and coverage determinations, and do not take actual utilisation into account. Unfortunately, no data on dates of market launch were collected. Respondents were asked to provide information for each medicine by indication(s) for which it is used (i.e. pembrolizumab for non-small cell lung cancer). The survey did not take into account any coverage restrictions (such as population limits, line of therapy, use alone or in combination, requirements to demonstrate a therapeutic response etc.) which differ between countries. It also did not take into account differences in coverage by treatment setting (dispensed to patients for self-administration, administered in hospitals and ambulatory care settings as part of outpatient services, or administered to hospitals inpatients) as countries were permitted to provide only one response for each product/indication pair. It is acknowledged that in some countries, coverage may vary between settings of care.

[33] Note that responses to this part of the survey were incomplete, and as such, data on all indicators are not presented for all respondent countries.

European Member States (plus Norway)

99. Since 1995, oncology medicines in Europe have been subject to the centralised procedure of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP), with subsequent decisions on marketing authorisation made by the European Commission. Through that centralised procedure, the medicine is approved in all European Union Member States[34] as well as in Iceland, Liechtenstein and Norway. However, having a valid central marketing authorisation does not necessarily mean that a product is or will be marketed in a given country. Additionally, many older medicines, marketed before the establishment of the EMA, may have been authorised at national level, or may have only been approved for a subset of indications. As a result, where a product is classified as "not approved" in one country but "approved" in another, it may mean that 1) it is an older product not approved in all countries, or 2) the product has not been launched on the market in that country, either at all, or for that indication. Examples were reported by several countries including Cyprus, Greece, and Norway, and may explain some of the differences in responses regarding regulatory approval status of product/indication pairs across EU countries.

Country-specific

100. Country-specific reporting details are presented in Table A B.1 of Annex B. The table outlines limitations of the data, and assumptions made by countries when completing the survey. It also includes dates of survey submission (ranging from 20 September 2019 for Cyprus to 15 January 2020 for Chile), which are relevant since the evolution of approvals and coverage decisions in oncology is rapid. Thus a medicine indicated as "not approved" or "not covered" may in fact be a medicine which is *not yet* approved or covered, or it may be a medicine for which an application for marketing authorisation or (more likely) coverage/reimbursement was rejected.

101. Unless otherwise specified, information on coverage reflects the nationwide coverage status for the product/indication. This is the case in all countries in which coverage decisions are made at the national level, and apply to all patients in the country, independent of the setting of care in which the medicine is administered (hospital, ambulatory care, home, etc.). In other countries, the information collected does not necessarily apply to all patients, all care settings, or all regions. In Australia, for example, the information provided only pertains to the Pharmaceutical Benefits Scheme, which provides national-level coverage for medicines supplied in all settings other than public hospital inpatients. Decisions on coverage of medicines administered to public hospital inpatients are taken at regional level and thus vary between States and Territories. In Sweden, the information fully reflects nationwide coverage of medicines used in outpatient care but may be less comprehensive for medicines used in inpatient care, for which coverage is determined at regional level. These differences are discussed in section 3.5.

"Time to access" covers the entire period between application for marketing authorisation and (national) coverage decision

102. "Time to access" for a medicine (or an indication) is generally measured as the time between submission of the application for marketing authorisation in the country (or region for EU) and the date of the coverage decision. Indeed, application for marketing authorisation is the first step to gaining market access, though in many countries, companies may only launch a medicine once it has coverage (often at a regulated price). There are some exceptions; in the United States, Canada, England, and Germany, companies generally launch their products just after the marketing authorisation, either because every

[34] Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom.

medicine authorised is covered by default (England, Germany) or because coverage decisions are made by individual insurers or public plans for their beneficiaries (Canada and the United States).

103. In oncology, two other factors are likely to influence time to access.

- First, in many countries, some patients can gain access to oncology medicines through early access schemes, before the medicine/indication is covered or sometimes before it is approved. Such schemes may be limited to medicines treating severe diseases, for which no effective treatments are available. Oncology products often meet these criteria, making them eligible for early access mechanisms. In addition, where coverage (or inclusion in a positive list) is denied for any reason, in some countries individual patients may be granted exceptional access on request. As these exceptional access schemes that require prior authorisation for individual patients[35] are limited in scope, and access to medicines is significantly more complex for prescribers and patients, they are clearly no substitute for general coverage. In this study, early access schemes were not taken into account in the calculation of time to access.[36]
- Second, even where a new indication for an existing product is not (yet) approved or covered access may be possible through off-label prescribing. This however, will be subject to the financing arrangement for these prescriptions.

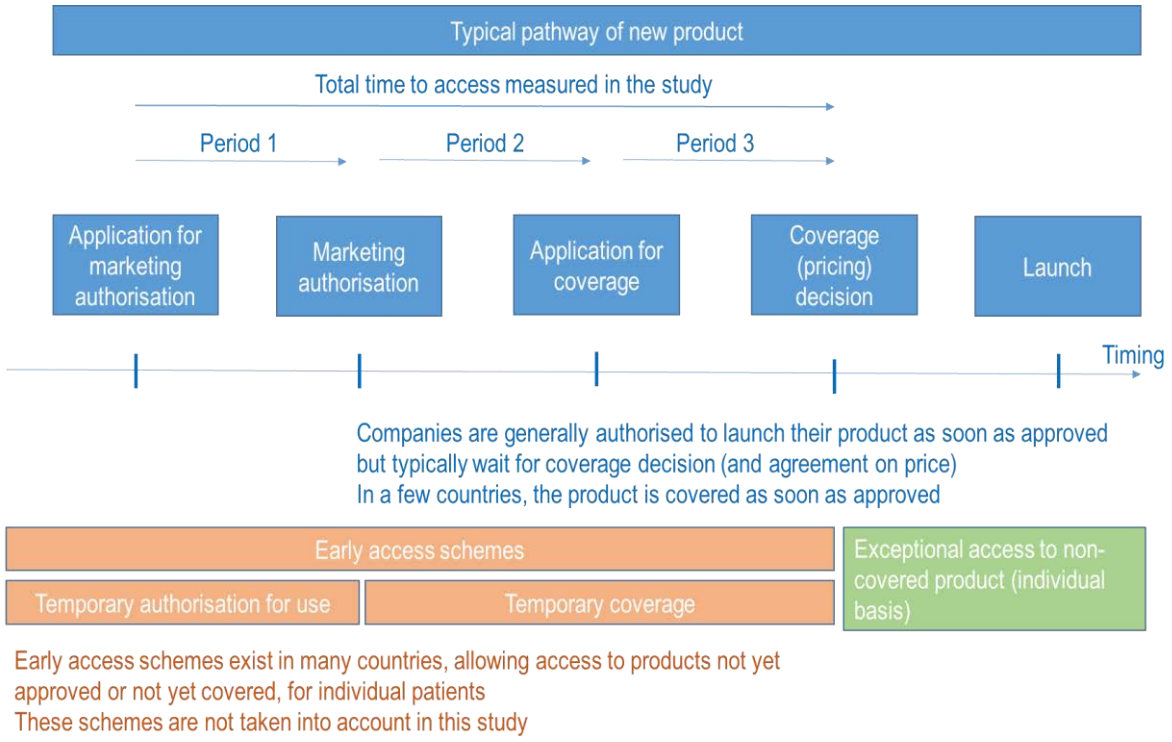
104. In this study, time to access was measured as the time (in months) between the submission of an application for marketing authorisation and a coverage decision (see Figure 3.1). It was decomposed into three periods.

- Period 1 is defined as the time between the date of submission of the application for marketing authorisation and the date of marketing authorisation. It includes the regulatory agency processing time, including any "clock stops", i.e. time taken by the company to provide additional information requested by the regulator to inform the assessment of the application. This indicator was calculated for all pairs that were reported as approved.
- Period 2 is defined as the time between the date of marketing authorisation and the date of application for coverage. This information is relevant in countries where a "coverage decision" is made at the national level, less so for others (see Table 3.4, the contents of which will be discussed in section 3.5). In order to accelerate access, in some countries, including Australia, Belgium, Cyprus, Estonia, Ireland, and Norway, companies may submit applications for coverage before they receive marketing authorisation. In Israel, coverage decisions for the whole country and all care settings are made once a year for all applicants (during October-December), and take effect in January of the following year; in some cases, coverage decisions may also precede formal marketing authorisation. This indicator was calculated for all pairs that were reported as approved and covered.
- Period 3 is defined as the time between the date of application for coverage and the date of coverage decision, which is only relevant for countries where such a process exists at central level and if the medicine is covered. Time to launch, as used in other studies, would have been more informative, but could not be elicited. This indicator was calculated for all pairs that were reported as approved and covered.

[35] Prior authorisation may also be required for medicines in general coverage schemes.

[36] In addition, in countries where early access schemes provide access to *subsidised* medicines, companies may be less eager to conclude price negotiation to obtain general coverage. This may in turn increase "time to access" as measured in this study.

Figure 3.1. Time to access as measured in this study



Source: Authors.

3.3 Access to oncology medicines remains unequal across OECD/EU countries

105. The proportion of the 109 product/indication pairs in the sample approved (i.e. with a marketing authorisation) and covered varied substantially across OECD/EU countries (Figure 3.2 panel A). The United States reported the largest percentage of product/indications covered (by Medicare), followed by Denmark and Germany (96%, 91%, and 88%, respectively). Chile and Malta reported the smallest proportion of pairs approved and covered (47% and 46% respectively). Latvia and Hungary had the largest proportion of medicines approved but not covered (43% and 40%, respectively).

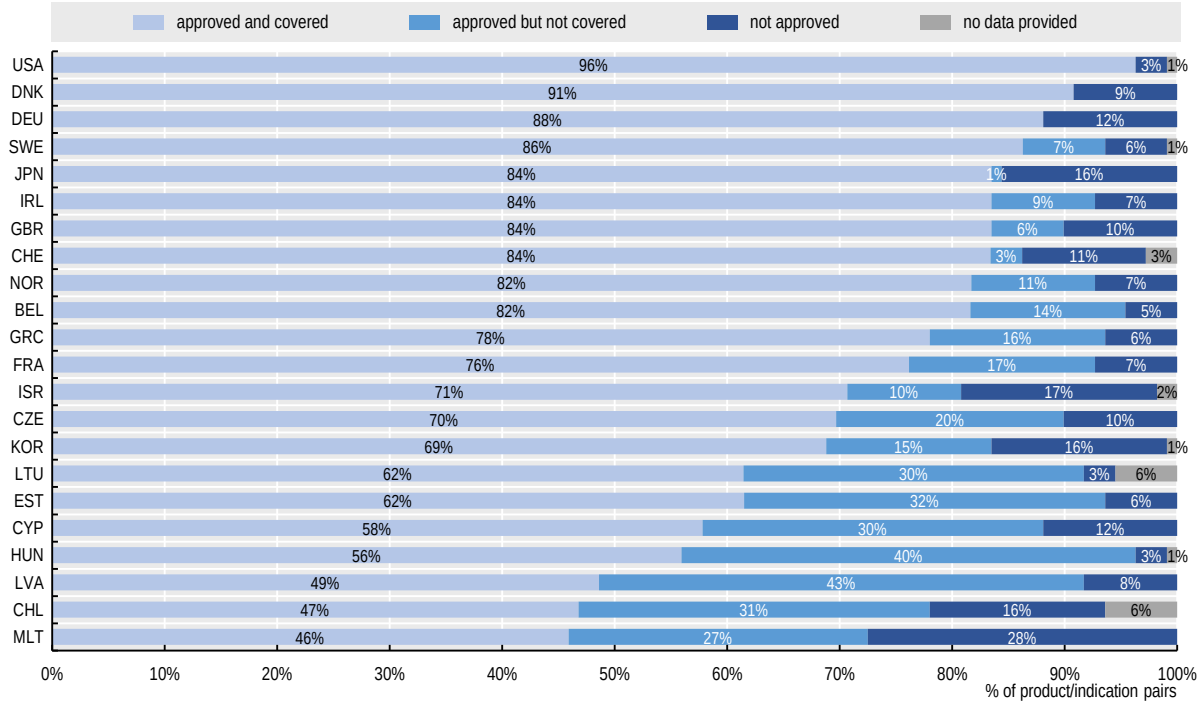
106. Access was better and more homogeneous for the 32 product/indication pairs listed on the 21st WHO *Model List of Essential Medicines,* (Figure 3.2 panel B). With the exception of Hungary and Australia[37], at least 80% of the 32 product/indication pairs were approved and covered in all responding countries.

107. For the 31 newer product/indication pairs, regulatory approval and coverage status varied considerably (Figure 3.2 panel C). In the United States, Germany and Denmark, more than 90% of these newer product/indications were covered, while in Japan, the United Kingdom (England), Switzerland, and Sweden, the figure was 70 to 80%. Other countries had fewer product/indications covered; while in Korea and Chile, this is partly explained by the fact that some medicines were not yet approved, in the remaining countries, it is more likely that coverage decisions had not yet been made or coverage was denied.

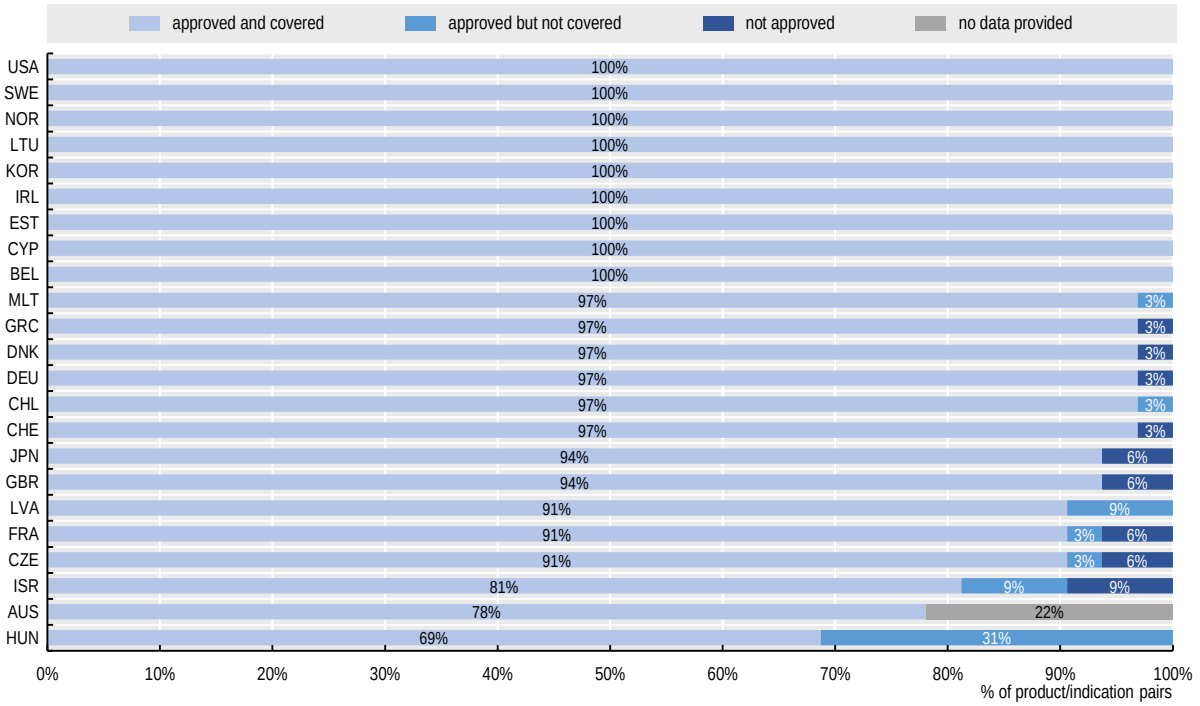
[37] No data for Australia were provided for 22% of the 32 product/indication pairs.

Figure 3.2. Percentage of sample product/indication pairs by approval and coverage status across OECD/EU countries

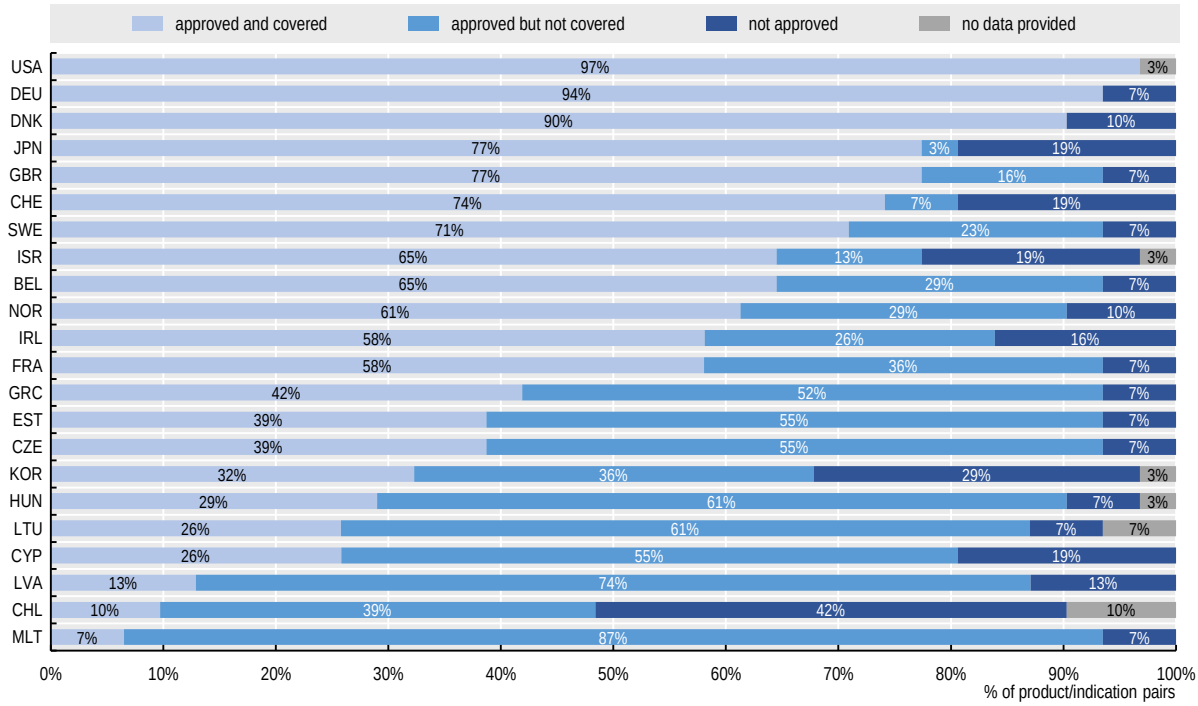
A: Based on total sample of 109 product/indication pairs



B: Based on sample of 32 product/indication pairs included on the 21st WHO *Model List of Essential Medicines*



C: Based on sample of 31 product/indication pairs approved by the US FDA since 2014



Note: Data for Australia were not included in panel A and C as many data were missing.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

108. Regulatory approval and coverage status of medicines also varied across OECD and EU countries by cancer type (see Table A C.1 to Table A C.6 in Annex C). The average proportion of product/indications approved and covered by cancer type was 77% for metastatic breast cancer, 69% for non-small cell lung cancer and colorectal cancer, 62% for melanoma, 75% for multiple myeloma, and 83% for supportive care in oncology, respectively.

109. For the treatment of **metastatic breast cancer**, countries generally reported coverage for at least one medicine in each class of products, with the exception of platinum compounds[38] and protein kinase inhibitors, with the latter not covered in Chile or Lithuania (Table A C.1). Most countries reimbursed all EML medicines. Not surprisingly, newer medicines were less likely to be available because some may have not yet been approved in some countries (Chile, Korea, Switzerland and Japan) and others may not yet have been covered (Chile, Korea, Eastern European countries).

110. Disparities were noted in the coverage of medicines for **non-small cell lung cancer (**Table A C.2**)**. Generally, older medicines and those on the EML were available and covered, with the exception of carboplatin, cisplatin and etoposide in some countries. In all countries, at least one protein-kinase inhibitor and one monoclonal antibody were reported as subsidised, with the exception of Latvia, with no covered monoclonal antibody.

111. Management of **colorectal cancer** often involves fluorouracil, capecitabine, irinotecan and oxaliplatin, all of which are included in the WHO EML. With the exception of Hungary, all were reported as available and subsidised in all countries (Table A C.3). Of the newer medicines, neither nivolumab nor pembrolizumab had marketing authorisation for colorectal cancer in the EU, and were thus not available

[38] This, however, may be due to a reporting issue. Platinum compounds are old products, approved at national level and their Summary of Product Characteristics does not necessarily specify indications.

for that indication. However, both were indicated as available and covered in Chile, Israel and the United States.

112. Nivolumab and pembrolizumab are the only two medicines on the WHO EML indicated for **melanoma**. Both have been approved in the EU or US in the last five years, and at least one was reported as approved and covered in all countries (Table A C.4). In addition, at least one drug from the protein-kinase inhibitor class was subsidised in all countries except Chile. Talimogene laherparepvec is a novel oncolytic immunotherapy for melanoma; among the countries that provided data for this medicine, it was covered only in Switzerland, Germany, Denmark, the United Kingdom (England), and the United States.

113. Nearly every country subsidised all EML medicines for **multiple myeloma** (except Latvia, Israel and Hungary) (Table A C.5). There was less disparity in approval and coverage status for the older medicines than in the newer ones. None of the newer medicines for this indication received subsidy in Chile, Lithuania, Latvia or Malta; all were covered in Belgium, Denmark, Germany, Japan, and the United States.

114. With regard to medicines used in **supportive care** in oncology, all countries subsidised calcium folinate and at least one colony-stimulating factor and corticosteroid (Table A C.6).

115. These results from the OECD survey are consistent with previous studies on coverage of cancer medicines across countries. The two ESMO studies mentioned previously surveyed the national formulary availability, out-of-pocket costs and accessibility of cancer medicines for solid tumours across 49 European countries in 2014 and 63 non-European countries in 2015 (Cherny et al., 2016[61]; Cherny et al., 2017[62]). In Europe, the EMSO study showed differences in availability across countries, particularly for targeted agents approved in the last 10 years, which were not available in less economically developed countries (e.g. Eastern Europe). The situation in Eastern Europe has improved for all cancers included in the OECD survey. Many product/indications that were categorised as having no coverage in Eastern European countries in the ESMO survey now have coverage (i.e. Czech Republic, Estonia, Hungary, Latvia, and Lithuania). This suggests that availability in such countries may be related to time from marketing authorisation. That being said, in the ESMO survey, major disparities in national formulary availability were observed for medicines to treat melanoma, which still remains the case. For lung cancer, colorectal cancer, and breast cancer, disparities were limited to distinct subgroups of patients (e.g. by disease status). Consistent with the OECD survey, less variations were found among EML medicines. For those high-income, non-European OECD countries, most EML medicines were available. Discrepancies in access to cancer care were the greatest in those severely economically challenged countries.

116. Several articles evaluated the actual utilisation of oncology medicines using different measures. A longitudinal analysis on the determinants of utilisation of 31 cancer drugs approved between 2000 and 2012 in three European countries (Belgium, Scotland and Sweden) measured utilisation of the drugs in DDD per 1000 population between 2008 to 2013 (Ferrario, 2017[67]). The number of indications and the number of years since EU-wide marketing authorisation had a positive impact on utilisation, while price per DDD and the average rating of clinical added value across all indications (with a higher score when the added value was low or zero) had a smaller, but negative impact on utilisation.

117. The Swedish Institute for Health Economics *Comparator Report on Cancer in Europe* (2019[4]) examined the uptake of cancer medicines in seven cancer types (plus immunotherapy) across Europe in 2018. Uptake was measured as the number of standard weekly doses per case (in mg), using the number of deaths of the considered cancer type as the definition of a case. Countries were categorised into three groups based on GDP/capita. Lower tier included Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Slovenia. Mid-tier included the “big 5” – France, Germany, Italy, Spain, and the United Kingdom. Upper tier countries were Austria, Belgium, Denmark, Finland, Iceland, Ireland, the Netherlands, Norway, Sweden and Switzerland. Unsurprisingly, the report showed that uptake varied across countries, relating to economic status, with usage in poorer countries being one third to one half of the uptake in the big 5 and wealthier countries. Among the big 5, France and

Germany had the highest level of uptake while the United Kingdom had the lowest across all cancer types and immunotherapy. Among the high-tier countries, Switzerland had a consistently high uptake across the cancers studied. For breast cancer, uptake of newer medicines other than trastuzumab was slow, with almost no uptake in some countries (e.g. Lithuania). Uptake for medicines for colorectal cancer varied across countries, with some lower tier countries having usage above those mid-high tier countries. The largest differences in uptake between countries were seen for immunotherapy and medicines used for multiple myeloma and prostate cancer. Austria, Belgium and Switzerland had high uptake for immunotherapy, and Lithuania, Latvia and the Czech Republic had the lowest uptake. The smallest disparities between countries were seen in those medicines used for lung cancer.

3.4 Time to access for new oncology products/indications varies across OECD/EU countries

118. Times to access were computed for the 31 new product/indication pairs in the sample across a number of OECD/EU countries. New products and/or indications were reportedly most often first approved in the United States, and obtained marketing authorisation in other countries between 12 months and 17 months after, on average. Coverage decisions were typically taken a few months later, with a total time from first approval up to 66 months (more than 5 years). Time between marketing authorisation and coverage decision also varied across OECD/EU countries, reflecting different regulatory, health technology assessment (HTA), reimbursement and pricing processes.

On average, product/indications are approved in OECD/EU countries 12 to 17 months after the first marketing authorisation

119. Among 31 new product/indication pairs in the sample approved since 2014, 26 obtained their first marketing authorisation in the United States, while 4 were first approved in Japan and 1 in Switzerland (see Table 3.2). Table 3.2 shows the elapsed time between date of first marketing authorisation (out of the sample countries) and marketing authorisation in subsequent countries/regions for each product/indication pair. All European countries except Switzerland have been grouped into the European Economic Area (EEA)[39], as marketing authorisation is centralised for oncology products. Market launch sequences varied for each product/indication pair in the sample. On average, products and indications were approved in individual countries/regions 12 to 17 months after their first marketing authorisation in the sample of countries surveyed (range 2 to 52 months for individual pairs). This reflects both patterns arising from companies' launch strategies and the duration of the regulatory process. The latter is likely to be longer for initial approvals of new medicines than for subsequent extensions of indications.

[39] The European Economic Area (EEA) includes EU countries and also Iceland, Liechtenstein and Norway. It allows them to be part of the EU's single market.

Table 3.2. Time between first marketing authorisation and marketing authorisation in subsequent countries/regions for product/indications approved since 2014 (n=31 pairs)

Indication	Active substance	First marketing approval		Time since first marketing approval and subsequent approval in each country/region in months (number of pairs approved, with information on dates[1])						
		Country	Date	USA (31)	EEA (29)	JPN (25)	ISR[2] (20)	CHE (25)	KOR (21)	CHL (9)
Metastatic breast cancer	abemaciclib	USA	Sep-17	0	12	12	15	20	20	27
	olaparib	USA	Dec-14	0	52	43	b	13	8	a
	palbociclib	USA	Feb-15	0	21	31	b	23	18	b
	ribociclib	USA	Mar-17	0	5	a	b	7	a	b
	talazoparib	USA	Oct-18	0	8	a	a	a	a	a
Non-small cell lung cancer	alectinib	JPN	Sep-15	3	17	0	7	16	13	c
	atezolizumab	USA	May-16	0	16	20	13	12	8	9
	brigatinib	USA	Apr-17	0	19	a	19	a	19	a
	ceritinib	USA	Apr-14	0	13	23	13	16	9	8
	dacomitinib	USA	Sep-18	0	7	4	a	11	a	a
	durvalumab	USA	May-17	0	16	14	9	13	19	a
	lorlatinib	JPN	Sep-18	2	8	0	a	a	a	a
	necitumumab	USA	Nov-15	0	3	43	17	a	a	a
	nivolumab	USA	Dec-14	0	10	12	3	11	3	12
	osimertinib	USA	Nov-15	0	3	4	6	8	6	31
	pembrolizumab	USA	Oct-15	0	9	14	c	16	c	c
	ramucirumab	USA	Apr-14	0	21	26	25	9	12	12
Colorectal cancer	nivolumab	USA	Dec-14	0	a	a	3	11	3	12
	pembrolizumab	USA	Sep-14	0	a	51	5	29	6	a
	ramucirumab	USA	Apr-14	0	21	25	25	18	12	12
	trifluridine / tipiracil	JPN	Mar-14	18	25	0	a	41	a	a
Melanoma	binimetinib	USA	Jun-18	0	3	7	a	a	a	a
	cobimetinib	CHE	Aug-15	3	3	a	10	0	3	8
	encorafenib	USA	Jun-18	0	3	7	b	a	a	a
	nivolumab	JPN	Jul-14	5	11	0	8	16	8	b
	pembrolizumab	USA	Sep-14	0	10	24	5	29	6	b
	talimogene laherparepvec	USA	Oct-15	0	2	a	28	9	a	a
Multiple myeloma	daratumumab	USA	Nov-15	0	6	22	14	13	24	b
	elotuzumab	USA	Nov-15	0	6	10	10	13	12	b
	ixazomib	USA	Nov-15	0	12	16	9	15	20	a
	panobinostat	USA	Feb-15	0	6	5	a	10	24	b
Average length of time per country/region for pairs studied				*1*	*12*	*17*	*15*	*15*	*12*	*15*
Median length of time per country/region for pairs studied				*0*	*10*	*14*	*13*	*13*	*12*	*12*

Note: a = product/indication pair not approved (or not launched); b = product/indication pair approved but marketing authorisation date not provided; c = no data provided for that product/indication pair

All European countries except Switzerland have been grouped as marketing authorisation in the European Economic Area (EEA) is centralised for oncology products. Australia did not provide data on dates.

1. Israel and Chile provided information on dates only for a subset of product/indication pairs indicated as "approved and covered"
2. For products with several indications, data represent product-level dates only. Indication-specific dates are not available.

Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

120. Former studies used sales data to estimate time elapsed between first global launch and launch in a given country. Varol et al. (2012[68]) estimated the time between first global launch and launch in 20 individual countries, for several cohorts of products. The study found a reduction of the median time from four years for medicines launched in 1984-1995 to two years for medicines launched in 1995-2008. In the latter period, medicines were launched first in the United States, then in Germany, the United Kingdom and the other three big European markets (France, Italy, Spain), and finally in Japan. The reduction in launch delays was explained by the creation of the EMA and harmonisation in regulatory requirements in OECD countries (Varol, Costa-Font and McGuire, 2012[68]).

121. This harmonisation and cooperation between regulatory authorities has increased in the past years and new initiatives may further accelerate access (OECD, 2018[69]). The Orbis project, an initiative by the US FDA provides a framework for concurrent submission and review of oncology products among international partners. The first review through this process involved regulatory agencies from Australia, Canada and the United States and led to the simultaneous approval of the use of combination immunotherapy for a particular form of endometrial cancer.[40] Each country defines the terms of approval. For this specific product/indication, Australia granted a provisional approval and Canada a conditional approval, which both require the provision of further confirmatory evidence.[41] Although to date it has only been applied to "supplemental indications" in oncology, this collaboration has the potential to support more rapid access for patients in the countries involved. However, it does not guarantee that the new indication will be covered and affordable for patients.

Time from first marketing approval to coverage in a given country ranges from 1 to 66 months

122. For covered product/indications for which data were available, the time from the date of first marketing authorisation (most often in the United States) and a coverage decision in individual countries varied between countries and across products, from 1 to 66 months (see Table 3.3). The average time across all indications ranged from 10 months in Israel, followed by 17 months in Japan, to 56 months in Malta (where only 2 product/indications were covered at time of reporting)[42]. Part of this time difference is an artefact of company launch strategies (which determine when marketing approval is applied for) but more than half of it reflects differences after marketing authorisation, such as the time companies take to apply for coverage, and the time it takes to complete coverage and pricing processes, where relevant.

[40] Both medicines were already approved in other indications.

[41] https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis; https://www.tga.gov.au/media-release/provisional-application-receives-approval-through-first-international-collaborative-review-initiative-between-tga-fda-and-hc, consulted on 18 March 2020

[42] Time to access could not be computed for a number of countries that did not provide the necessary information, including Australia, Chile, Germany, Lithuania, and the United States.

Table 3.3. Time between first marketing authorisation and granting of coverage in subsequent OECD/EU countries for product/indications approved since 2014 (n=31 pairs)

Indication	Active Substance	First marketing approval		Time since first marketing approval and subsequent granting of coverage in each country in months (number of pairs approved and covered, with available information on date of coverage decision[1])															
		Country	Date	BEL (18)	CYP (8)	CZE (12)	EST (12)	FRA (17)	GBR (20)	GRC (12)	HUN (8)	IRL (18)	LVA (4)	MLT (2)	NOR (17)	SWE (19)	CHE (23)	ISR[2] (20)	JPN (24)	KOR (10)
Metastatic breast cancer	abemaciclib	USA	Sep-17	21	b	b	b	17	17	b	b	b	a	b	24	21	22	16	14	b
	olaparib	USA	Dec-14	b	b	b	b	b	b	b	b	b	a	b	b	b	20	13	43	b
	palbociclib	USA	Feb-15	34	38	b	55	37	34	40	44	40	b	b	42	28	25	35	33	33
	ribociclib	USA	Mar-17	17	13	b	30	c	9	15	19	23	25	b	13	10	27	10	a	a
	talazoparib	USA	Oct-18	b	a	b	b	b	b	b	b	a	b	b	b	b	a	a	a	a
Non-small cell lung cancer	alectinib	JPN	Sep-15	29	b	48	b	35	35	b	37	26	b	b	33	26	23	4	2	25
	atezolizumab	USA	May-16	22	b	b	42	33	c	b	29	34	b	b	21	21	14	8	23	20
	brigatinib	USA	Apr-17	b	b	b	b	b	23	b	b	26	b	b	30	20	a	9	a	24
	ceritinib	USA	Apr-14	32	b	64	56	31	26	22	b	32	b	b	52	20	41	9	25	28
	dacomitinib	USA	Sep-18	b	b	b	b	b	11	b	b	14	b	b	14	9	b	a	5	a
	durvalumab	USA	May-17	24	b	b	30	b	24	b	b	b	b	b	29	20	16	8	15	b
	lorlatinib	JPN	Sep-18	b	b	b	b	b	b	b	b	13	b	b	b	12	a	a	2	a
	necitumumab	USA	Nov-15	b	b	b	b	b	c	b	b	a	b	b	a	b	a	b	b	a
	nivolumab	USA	Dec-14	25	33	39	b	52	35	c	46	45	b	53	36	38	16	1	12	32
	osimertinib	USA	Nov-15	13	26	38	40	44	12	15	b	b	b	b	b	46	33	2	6	25
	pembrolizumab	USA	Oct-15	c	26	40	38	19	15	16	d	30	b	b	11	28	23	d	16	d
	ramucirumab	USA	Apr-14	b	b	b	b	b	c	b	b	a	b	b	b	c	23	b	26	b
Colorectal cancer	nivolumab	USA	Dec-14	a	a	a	a	a	a	a	a	a	a	a	a	a	16	1	a	b
	pembrolizumab	USA	Sep-14	a	a	a	a	a	a	a	a	a	a	a	a	a	60	4	51	b
	ramucirumab	USA	Apr-14	b	b	b	b	31	b	b	b	b	b	b	b	c	23	b	25	b
	trifluridine / tipiracil	JPN	Mar-14	43	b	42	66	42	29	45	b	35	57	b	41	30	43	a	2	a
Melanoma	binimetinib	USA	Jun-18	17	a	b	b	14	8	b	b	11	b	b	15	9	a	a	8	a
	cobimetinib	CHE	Aug-15	28	b	34	b	18	c	18	38	32	34	b	c	b	9	17	a	b
	encorafenib	USA	Jun-18	17	a	b	b	14	8	b	b	11	b	b	15	9	a	7	12	a
	nivolumab	JPN	Jul-14	21	22	29	28	29	19	19	28	39	b	58	16	33	21	6	2	43

Indication	Active Substance	First marketing approval		Time since first marketing approval and subsequent granting of coverage in each country in months (number of pairs approved and covered, with available information on date of coverage decision[1])															
		Country	Date	BEL (18)	CYP (8)	CZE (12)	EST (12)	FRA (17)	GBR (20)	GRC (12)	HUN (8)	IRL (18)	LVA (4)	MLT (2)	NOR (17)	SWE (19)	CHE (23)	ISR[2] (20)	JPN (24)	KOR (10)
Melanoma (cont.)	pembrolizumab	USA	Sep-14	20	20	40	26	28	13	17	26	21	48	b	14	31	36	4	29	41
	talimogene laherparepvec	USA	Oct-15	b	a	b	b	b	11	b	b	b	b	b	b	b	26	b	a	a
Multiple myeloma	daratumumab	USA	Nov-15	c	33	45	36	43	28	18	c	29	b	b	23	c	19	14	24	41
	elotuzumab	USA	Nov-15	22	b	34	b	b	b	b	b	b	b	b	b	b	21	14	12	b
	ixazomib	USA	Nov-15	23	b	39	b	35	27	25	b	37	b	b	b	30	29	14	18	b
	panobinostat	USA	Feb-15	22	b	b	37	b	23	24	b	b	b	b	47	b	b	a	6	b
Average length of time per country for pairs studied				*24*	*26*	*41*	*40*	*31*	*20*	*23*	*33*	*28*	*41*	*56*	*27*	*23*	*25*	*10*	*17*	*31*
Median length of time per country for pairs studied				*22*	*26*	*40*	*38*	*31*	*20*	*19*	*31*	*29*	*38*	*54*	*24*	*21*	*23*	*9*	*15*	*30*

Note: a = product/indication pair not approved (or not launched); b = product/indication pair approved but not covered; c = product/indication pair approved and covered but no information on date; d = no data provided for that product/indication pair.

Australia, Chile, Denmark, Germany, Lithuania and the United States did not provide sufficient data to calculate this time difference. In Israel, coverage decisions are made once a year (during October-December) for the whole country and all care settings, and take effect in January of the following year. In some cases, coverage decisions may precede formal marketing authorisation.

1. Belgium, France, the United Kingdom (England), Greece, Hungary, Norway, and Sweden provided information on dates only for a subset of all pairs indicated as “approved and covered”.

2. For products with several indications, data represent product-level dates only. Indication-specific dates are not available.

Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Time from application for marketing authorisation to coverage decision varies across OECD/EU countries

123. For a few countries, available information allowed to decompose the time between dates of marketing authorisation and coverage decisions for approved product/indications (see Figure 3.3, and Figure 3.1 for the definition of periods).

Period 1

124. The average time between application for marketing authorisation and approval (Period 1) varied across the 5 countries/regions that provided data, with the shortest period being 7 months in the United States, followed by 8 months in Chile, 10 months in Israel and Japan, and 13 months in the European Economic Area (see Figure 3.3 panel A). Observed time differences were longer than the maximum time required by the regulator to process an application for marketing approval, as the data included "clock-stops", and thus cannot be considered regulatory processing times.

125. Previous studies have examined the time between application and marketing approval across countries. For 29 cancer drugs approved by the EMA between 2006 and 2011, one study looked at approval times in three major jurisdictions. Median approval time was shorter in the United States (6.0 months) than in Japan and Europe (15.0 and 13.3 months respectively). While the time difference between the United States and Japan was not explained, the difference between the EU and the United States was attributed to "clock stops' and to the time taken by the European Commission to make a decision after a positive opinion from the CHMP (Hartmann, Mayer-Nicolai and Pfaff, 2013[70]). Another study, focusing on 16 tyrosine kinase inhibitors (TKIs)[43] approved by the US FDA as of 30 September 2012, shed some light on the factors influencing the differences in average time spent on review and approval between the United States (205.3 days) and the EU (409.6 days) (Shah, Roberts and Shah, 2013[71]). The active review time was similar in both jurisdictions, 205.3 days in the United States and 225.4 days in the EU, with the differences attributed to longer clock stops during the review process to collect additional information from sponsors, and the time from recommendation by the CHMP, an EMA's expert advisory opinion, and the decision of the European Commission. These factors also contributed to the longer approval time in the EU found in the aforementioned study by Hartmann, Mayer-Nicolai and Pfaff (2013[70]).

126. Additionally, for 37 cancer medicines approved between 2005 and 2013 by Health Canada, the time from date of submission to approval was much longer for the EMA and Health Canada than for the FDA, by an average of 6.7 months and 6.4 months, respectively (Samuel and Verma, 2016[72]). The differences were attributed to the more frequent use of expedited review processes in the United States, as well as differences in administrative procedures applying in the EU. Submissions to the FDA were also made on average 12.9 and 28.4 months earlier than submissions to Health Canada and to the EMA, respectively.

127. A more recent study showed that the overall median approval time for anti-cancer drugs and immunomodulators varied across six major regulatory agencies in the EU, the United States, Japan, Canada, Switzerland, and Australia, from 240 days (the FDA) to 423 days (the EMA and Swissmedic) in 2014-2018 (The Centre for Innovation in Regulatory Science (CIRS), 2019[73])

Period 2

128. The time between marketing authorisation and application for coverage (Period 2) varied across countries (see Figure 3.3 panel B). This period is often interpreted as a reflection of companies' launch strategies, which may in turn be influenced by national pharmaceutical policies. For example, in some

[43] For these 16 TKIs, 19 applications were approved in total during the period. Review time was only computed for first applications. It would be shorter if computed for all applications.

countries, application for coverage may be made prior to the receipt of marketing authorisation of the product for a specific indication (e.g. in Australia, Belgium, Ireland, Norway). This may shorten or even negate the duration of the Period 2 for some products. In the sample of countries considered, Ireland had the shortest average time between marketing authorisation and application for coverage (one month), followed by Belgium, and Hungary. Malta had the longest delay, 18 months (computed on the only 2 product/indications covered at the time of reporting).

Period 3

129. The time between application and coverage decision (Period 3) is influenced by HTA processes and pricing mechanisms[44], and varied on average from 4 months in Sweden to 27 months in Malta (see Figure 3.3 panel C). In Sweden the short time difference may be explained in part by the fact that reimbursement decisions are made at the product level and not for individual indications, which means that all subsequent indications are covered automatically once the initial indication is covered. Observed delays are in many cases longer than the six-month maximum for EU countries' reimbursement and pricing procedures set by the Transparency Directive.[45] However, in this study, the time measured includes "clock-stops", and cannot be interpreted as administrative processing time.

130. The survey results are generally aligned with those of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Patient WAIT Indicator 2018 survey, with the exception of Hungary, the United Kingdom and Sweden (IQVIA, 2019[74]). The WAIT indicator computed delays between marketing authorisation and national coverage (Periods 2 and 3) for 31 oncology products granted EMA approval for a new active substance between 1 January 2015 and 31 December 2017, with a cut-off date for coverage of 19 December 2018. Some differences between the two studies remain to be elucidated, but there are at least two reasons for different results. EFPIA used a product-based sample while the OECD survey included products/indications over a different period of time. In the OECD survey, the number of product/indications for which the time difference was computed varied across countries, with a maximum of 31 pairs.

Period 1 to 3

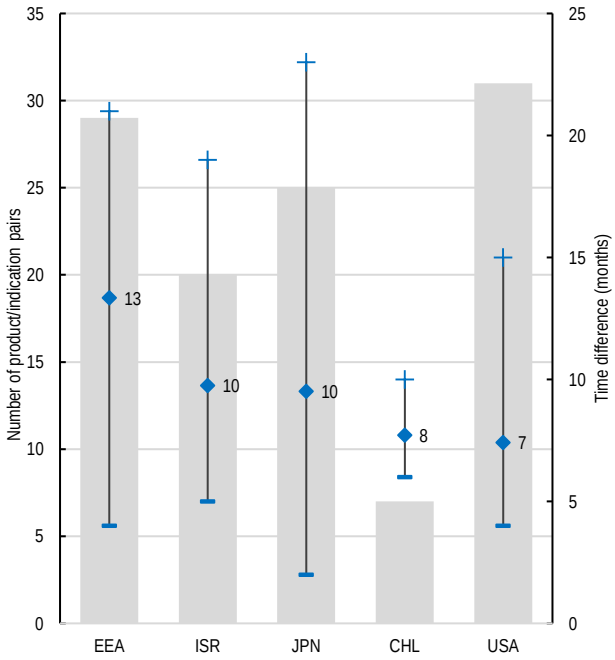
131. Given the variations observed in the decomposed periods, it is not surprising that disparities were evident in the aggregate times between application for marketing authorisation and granting of coverage (Periods 1, 2, and 3). Times ranged from 9 and 11 months on average in Israel and Japan respectively, to 52 months in Malta (see Figure 3.3 panel D). As noted previously, in Israel coverage decisions are made only once a year (during October-December), and take effect in January of the following year. Japan reported the shortest time between marketing authorisation and coverage decision (i.e. Periods 2 and 3), an average of two months. In Japan, reimbursement of a new pharmaceutical generally commences within 60 days (or within 90 days at the latest) from the time of approval. The reimbursement process starts immediately after approval of the medicine, and additional indications are covered by health insurance from the day of approval. Prices are not negotiated with companies; reimbursement prices are set by the government.

[44] These mechanisms have been described elsewhere, for example in (Panteli et al., 2016[93]) or in country profiles available here https://ppri.goeg.at/publications, consulted on 18 March 2020.

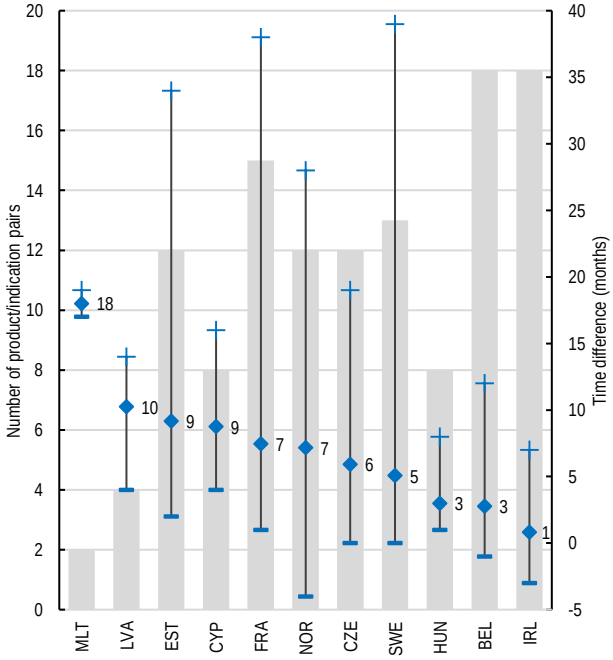
[45] EU's Transparency Directive (Council Directive 89/105/EEC), available here: https://ec.europa.eu/growth/sectors/healthcare/competitiveness/products-pricing-reimbursement/transparency-directive_en, consulted on 18 March 2020.

Figure 3.3. Time between approval and coverage dates across OECD/EU countries

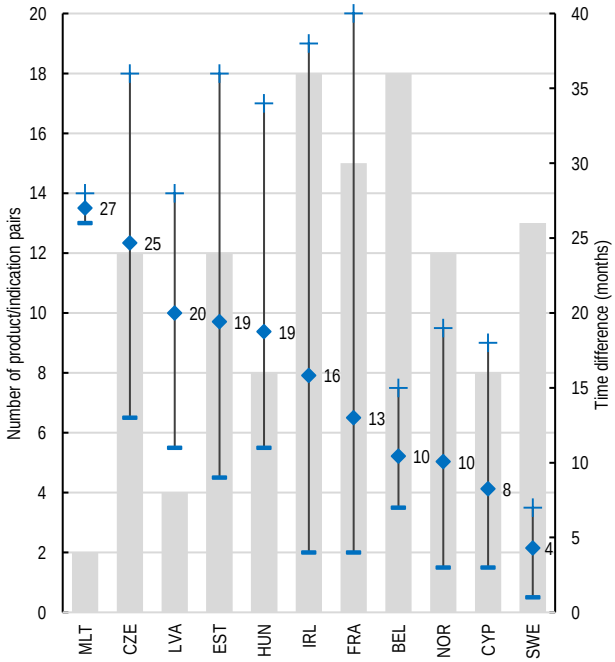
A: Application for and granting of marketing authorisation (Period 1)



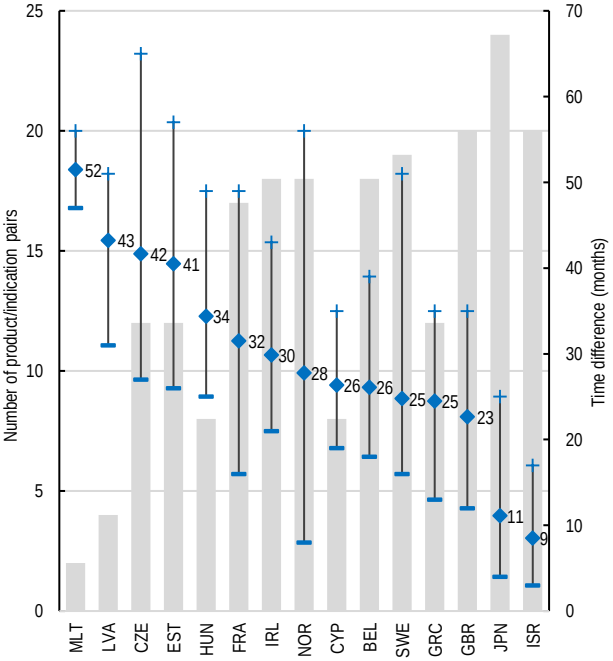
B: Marketing authorisation and application for coverage (Period 2)



C: Application for coverage and granting of coverage (Period 3)



D: Application for marketing authorisation and granting of coverage (Periods 1, 2, and 3)



Note: ♦ average time; + maximum time; - minimum time; grey bars represent the number of product/indication pairs for which the time difference was computed for each country, with the maximum possible being 31 pairs.
Times elapsed were not computed for all 23 countries who responded to the survey due to missing date information.
In Israel, for products with several indications, data represent product-level dates only. Indication-specific dates are not available.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

3.5 Countries report inequities in access and difficulties in meeting patient expectations

132. Half of the 24 respondents to the policy questionnaire confirmed that inequities in access exist within their countries.[46] These inequities vary in nature and extent, and may be due to differences in coverage across regions, heath care settings or population groups as well as cost-sharing policies.

Pharmaceutical coverage is not always uniform within countries

133. Inequity in access within countries may arise from non-uniform coverage across regions or population groups. While most OECD and EU countries make coverage decisions at the national level, a few countries take more decentralised approaches (see Table 3.4). In some countries, funding of cancer medicines, including inpatient and outpatient treatment, is a regional or even municipal responsibility, and coverage decisions are made at this level. This is the case in Nordic countries, for example. Local or regional administrations may have variable capacity—both administrative, technical and financial—to respond to the pressures that cancer medicines pose to their systems. In some countries, health care coverage is provided by different entities (national and sub-national governments, private health insurers, etc.), with differences in the content of formularies[47], conditions of access, and the type and level of co-payment. This can all create significant disparities in access across populations.

134. In Australia, the Pharmaceutical Benefits Scheme (PBS) provides national coverage decisions for medicines supplied in settings other than inpatients of *public* hospitals.[48] States and territories are responsible for providing hospital care and make their own decisions about medicines to be used for inpatient care in public hospitals; in some states and territories, decisions are made at the level of the hospital. New South Wales and the Australian Capital Territory also subsidise medicines supplied on discharge from public hospitals, supplied via an outpatient clinic, or supplied to day-admitted patients. In all other states and territories the PBS subsidises these.

135. In Canada, access to oncology medicines is non-uniform across provinces and territories, and inequity in access is a frequent topic of public discourse (Chafe et al., 2011[75]). The federal government makes coverage decisions at the national level for certain groups of Canadians covered by federal public plans (members of the Canadian forces, veterans, First Nations peoples living on reserves, Inuit people in northern communities, certain classes of immigrants and refugees, and persons incarcerated in the federal correctional system). Provincial governments make coverage decisions for those residents that qualify for public plans, and for all inpatient medicines. Individual private insurers make decisions on medicines used in outpatient care for their enrolees. Public coverage of outpatient drugs is usually linked to patient age and/or income, but only accounts for roughly 40% of retail pharmaceutical expenditure. In 2011, the pan-Canadian Oncology Drug Review (pCODR) was introduced to address uneven coverage and lack of transparency in provincial review processes of cancer medicines in Canada. The pCODR assesses clinical evidence and cost-effectiveness of new cancer medicines in order to make recommendations to the provinces and territories (McDonald et al., 2016[76]). These recommendations guide the allocation of publicly funded resources. Ultimately, however, reimbursement depends on the willingness of the province or territory to consider a product for listing. With resource limitations, provinces and territories must inevitably make choices, taking into account local opportunity costs (McDonald et al., 2016[76]). Nevertheless, since the implementation of pCODR, there has been greater concordance among provinces

[46] Canada, Chile, Denmark, Ireland, Israel, Italy, Latvia, Malta, Norway, Sweden, Switzerland, the United States.

[47] A formulary is a list of medicines covered by a specific coverage scheme. The term is also used in hospitals for the list of medicines available to prescribers.

[48] Medicines dispensed to inpatients of private hospitals are covered by PBS.

in cancer drug funding decisions, and the time to funding decisions has been reduced (Srikanthan et al., 2017[77]).

Table 3.4. Level of coverage decision making across OECD/EU countries

Multiple options possible per setting of care.

Level of coverage decision making for medicines	Country
Dispensed to patients for self-administration	
National	AUS, BEL, CAN (Federal public plans), CHE, CYP, DEU, EST, FRA, GBR, GRC, HUN, IRL, ISR, ITA, JPN, KOR, LVA, LTU, NOR, SWE
State/Provincial	AUS, CAN (Provinces & Territories' public plans), USA (Medicaid)
Regional	AUS, DNK, ITA, NOR[1]
Municipal	
Individual health coverage schemes	CAN (private insurance), ISR, USA (private plans, Medicare part D)
Insurer-provider network	ISR
Other	
Administered in hospitals or ambulatory care settings as part of outpatient care services	
National	AUS, BEL, CAN (certain groups), CHE, CYP, DEU[2], EST, FRA, GBR, GRC, HUN, IRL, ISR, ITA, JPN, KOR, LVA, LTU, NOR, USA (Medicare Part B)
State/Provincial	AUS, CAN (public plans)
Regional	AUS, BEL (for prevention products), DNK, ITA, SWE, USA
Municipal	IRL, LTU
Individual health coverage schemes	CAN, IRL, ISR
Insurer-provider network	
Other	
Administered in hospitals during inpatient stays	
National	AUS (private hospitals), BEL, CAN (certain groups), CHE ,CYP, DEU[3], EST, FRA, GBR, GRC, HUN, IRL, ISR, ITA, JPN, KOR, LVA, LTU, NOR, USA (Medicare part A)
State/Provincial	AUS (public hospitals), CAN (Provinces & Territories' public plans)
Regional	AUS (public hospitals), DNK, ITA, SWE
Municipal	IRL, LTU
Individual health coverage schemes	IRL, ISR
Insurer-provider network	CHE
Other	USA

Note: 1. Although coverage decisions are a competency of regions, the four regions have delegated this responsibility to a Decision Forum, which makes decisions de facto national.
2. In general, all products administered in hospitals and ambulatory care settings as part of outpatient care services are covered.
3. The national representation of sickness funds makes coverage decisions for inpatient medicines for all people in statutory health insurance.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

136. In some countries in which coverage decisions are decentralised, recent initiatives have promoted more uniform coverage. In Norway, coverage decisions for hospital drugs (all oncology treatments) are devolved to the four regions, but they have delegated this responsibility to a Decision Forum, whose decisions are *de facto* national ones. In Italy, where positive lists exist at both the national and regional level, innovative medicines (not limited to oncology) must be included in all regional lists, in order to reduce regional variations.

137. In the United Kingdom (England), NHS England and NHS Improvement support the national commissioning of cancer medicines according to national service specifications. Decisions on the delivery setting (self, direct general hospital, tertiary hospital) fall outside marketing authorisation and coverage

decisions. As such, NHS England's policies set out pathway arrangements, and the associated impact assessments provide information on the delivery setting and prices of both drugs and their administration.

138. Variations in coverage of oncology medicines or cancer care may also exist within individual health coverage schemes in some countries. For example, differences between patients with private or public insurance were mentioned by Ireland and Chile. In the United States, the health care system is very complex and gives rise to significant variations in patient access due to the type of insurance, the products covered, and ability to pay out of-pocket costs. Self-administered drugs are covered under Medicare Part D; plans that contract with Medicare Part D are authorised to decide whether products are reasonable and necessary for the diagnosis or treatment of an illness of injury, subject to certain statutory and regulatory limits. Formulary design must be adequate and non-discriminatory, and therefore formulary plans must be reviewed and approved by CMS. Oncology medicines nevertheless belong to "protected classes", for which Medicare Part D plans are required to cover all medicines. For medicines administered in hospital and physician settings (covered under Medicare part B), national coverage determinations for medicines are very rare, but do happen occasionally. Such coverage decisions are usually made by private regional contractors, based on general non drug-specific national instructions. Hospitals generally decide what products are used for inpatients through a hospital committee. Medicare reimbursement to hospitals is typically provided as a lump sum on the basis of diagnosis, and is not broken down into different components of treating the particular illness or injury. Note that as available insurance plans vary from state to state, regional differences may also play a role in disparities in access in the United States.

139. Other factors that may affect access within and across countries include regional differences in prices and inconsistent policies across service delivery settings within a health care system, as well as differences in purchasing power, procurement processes, ability and willingness to pay. Geographic variations may also arise due to limited access to prescribers and cancer centres in rural and remote areas (e.g. Australia, Chile).

Meeting patient expectations for access can be challenging

140. The final issue elicited in the preliminary discussions was the challenge of meeting patient expectations for timely access to new and promising medicines. Twenty[49] of the 24 respondents to the survey (83%) reported that concerns about access to oncology treatments, affordability, and sustainability had been raised in public position statements or in the media. With the recent uptick in the number and speed at which new oncology medicines (and new indications) have gained regulatory approval, there is increasing pressure on HTA agencies and payers to assess and approve these. HTA agencies/payers may thus need to prioritise among a number of cancer medicines which to evaluate/negotiate first. The arrival of competing products launched within a short time span adds to the pressure, though it can also present potential opportunities for payers. One approach several countries have adopted to address patient expectations around access to oncology medicines is to involve patients or patient groups in the HTA process, in one capacity or another, as has been done in Australia, France, Ireland, Lithuania, Norway, Sweden, Switzerland, and the United Kingdom (England).

141. While facilitating rapid access to treatments for sub-populations of patients who might otherwise have no or limited treatment options available to them is desirable, it must be acknowledged that introducing drugs with limited evidence of efficacy or effectiveness may in some circumstances put patients at risk and generate excess costs to the health care system.

[49] Australia, Belgium, Canada, Denmark, Estonia, France, Germany, Hungary, Ireland, Israel, Italy, Korea, Latvia, Lithuania, Malta, Norway, Sweden, Switzerland, the United Kingdom (England only), the United States.

3.6 Cost-sharing and medicine prices affect affordability

142. In most OECD countries, the whole population is covered for a core set of health services, which generally includes medicines. There are few exceptions: 8.5% of the population was uninsured in the United States in 2018, around 7.5% in Poland, and between 5% and 6% in Chile, the Slovak Republic, Estonia, and Hungary (Berchick, Barnett and Upton, 2019[78]; OECD, 2019[79]). Nevertheless, even when covered, patients may face significant user charges or cost-sharing when accessing services and products covered by third parties. These can constitute a substantial barrier to access or cause financial distress to patients and their families, especially when prices are high. The situation is seen as so critical in some countries it has led to coining of a new term "financial toxicity", which the US National Cancer Institute defines as[50]:

> *In medicine, a term used to describe problems a patient has related to the cost of medical care. Not having health insurance or having a lot of costs for medical care not covered by health insurance can cause financial problems and may lead to debt and bankruptcy. Financial toxicity can also affect a patient's quality of life and access to medical care. For example, a patient may not take a prescription medicine or may avoid going to the doctor to save money. Cancer patients are more likely to have financial toxicity than people without cancer. Also called economic burden, economic hardship, financial burden, financial distress, financial hardship, and financial stress.*

143. User charges are often uniform or very similar in countries where health benefits are defined centrally, even though exemptions or reduction of cost-sharing requirements may apply for specific population subgroups, such as children or low-income populations. In the United States, both benefits covered and cost-sharing requirements vary widely across health plans.

Cost-sharing requirements can compromise access or cause financial toxicity

144. The OECD survey collected information on cost-sharing requirements for three categories of goods and services involving the use of oncology medicines, with the objective of producing a qualitative assessment of coverage beyond the dichotomous coverage status of individual medicines. Three types of information were collected:

- For each category of care (medicines dispensed to patients for self-administration; outpatient specialist cancer services including the administration of a medicine; hospital inpatient care for cancer including the administration of a medicine), countries were invited to report the type and the level of cost-sharing (see Box 3.2 for definitions);
- Where relevant, the existence of exemptions or reductions in co-payments for some population groups (e.g. children, low-income, patients with certain diseases);
- Information on the existence of a cap on user charges.

[50] See https://www.cancer.gov/about-cancer/managing-care/track-care-costs/financial-toxicity-pdq, consulted on 18 March 2020.

Box 3.2. Types of user charges or cost-sharing requirements - definitions

The participation of patients to the cost of care, commonly referred to as "user charges", "cost-sharing requirements" or "cost-sharing arrangements" can take many forms. In this report, they are defined as follows:

- Co-insurance: cost-sharing requirement whereby the insured person pays a share of the cost of the medical service (e.g. 10%);
- Co-payment: fixed sum (e.g. USD 15) paid by an insured individual for the consumption of itemized health care services (e.g. per hospital day, per prescription item);
- User fee (prescription fee is sometimes used as synonymous) is actually a fixed co-payment, but this term is only used for pharmaceuticals dispensed to outpatients;
- Deductible: lump sum threshold below which an insured person must pay the full cost of health goods and services out-of-pocket before insurance coverage begins. It is defined for a specific period of time: one year, one quarter or one month. Deductibles can apply to a specific category of care (e.g. doctors' visits, pharmaceutical spending) or to all health expenditures (general deductible).
- Extra-billing: refers to any difference between the price charged and the price used as a basis for reimbursement purpose. Extra-billing exists for example where medical practitioners are allowed to charge fees beyond a negotiated fee serving as the base of reimbursement or payment of the practitioner by a third party. In some countries such as Australia, this is referred to as a "gap payment" for a professional service. In the pharmaceutical sector, where "reference prices" are often used, a fixed reimbursement amount is set for a cluster of products, while sellers remain free to charge a higher price. The patient pays any difference between the price of a medicine and the reference price out-of-pocket.
- Safety net: refers to thresholds beyond which a person (or family) may receive prescription medicine items at lower cost or at no cost (e.g. Australia, see Annex D). In some countries, these are referred to as "stop-loss provisions".
- In many countries, patients may face several types of user charges, for instance the combinations of a deductible or co-payment or co-insurance.

In the system of health accounts, out-of-pocket costs or expenditures include user charges but also expenditures for goods and services not covered at all.

Source: (Auraaen et al., 2016[80])

145. In oncology, where medicine prices can be very high, cost-sharing requirements can significantly affect affordability for patients. Fixed co-payments, which do not increase with the price of the medicine, are in principle to be preferred over co-insurance. More broadly, affordability is improved when vulnerable populations are exempted from, or entitled to lower cost-sharing, and where patient contributions are capped. Based on the information from the survey (see Table A D.1 in Annex D), countries were categorised according to the type of cost-sharing applied to cancer care, along a gradient of increasing financial burden (see Figure 3.4 to Figure 3.6).

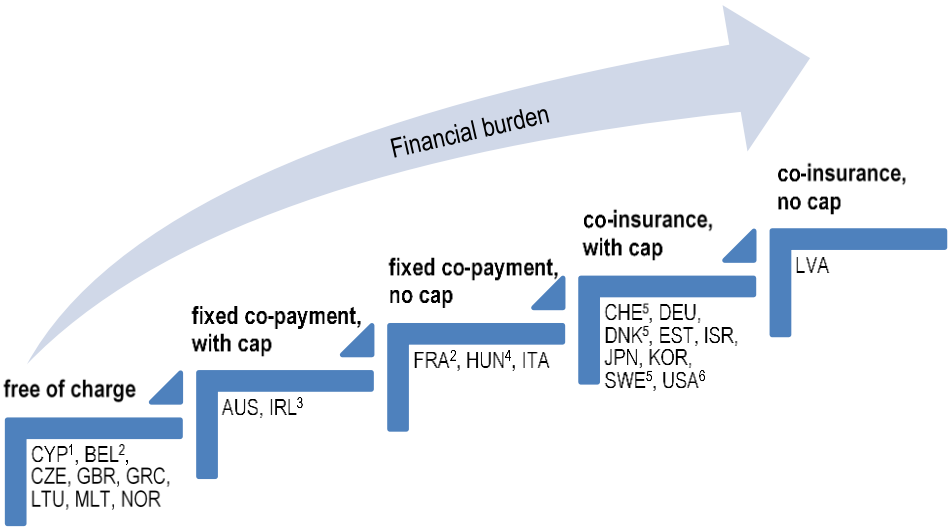
- In 13 countries, patients can access *oncology medicines dispensed for self-administration* free of charge or with a low fixed co-payment (see Figure 3.4). This is the case for example in Australia, where patients have to pay up to a maximum co-payment of AUD 41.00 per prescription item, with the amount reduced to AUD 6.60 for vulnerable population. In 10 countries, patients are required to pay a share of the costs – from 10% in Switzerland to 30% in Japan. In Germany, there is co-insurance of 10% of the cost of a medicine but capped at EUR 10 per item. In some countries, oncology treatments have lower cost-sharing than other medicines. For example, in Belgium and France, oncology medicines carry no co-insurance. In England patients do not pay anything for oncology treatment, while there are prescription fees for other types of medicines.
- In most responding countries, *outpatient cancer care services* are free of charge, at least when delivered by public providers (see Figure 3.5). Where public providers are available, affordability

for patients is not an issue in these countries. Patients in Switzerland, Korea, Japan and the United States are required to pay co-insurance amounts for these services (respectively 10%, 5%, 30% and around 20% in typical health plans).

- The situation is very similar for *inpatient cancer care*, except that in many cases, patients must also pay fixed co-payment per day for accommodation (see Figure 3.6).

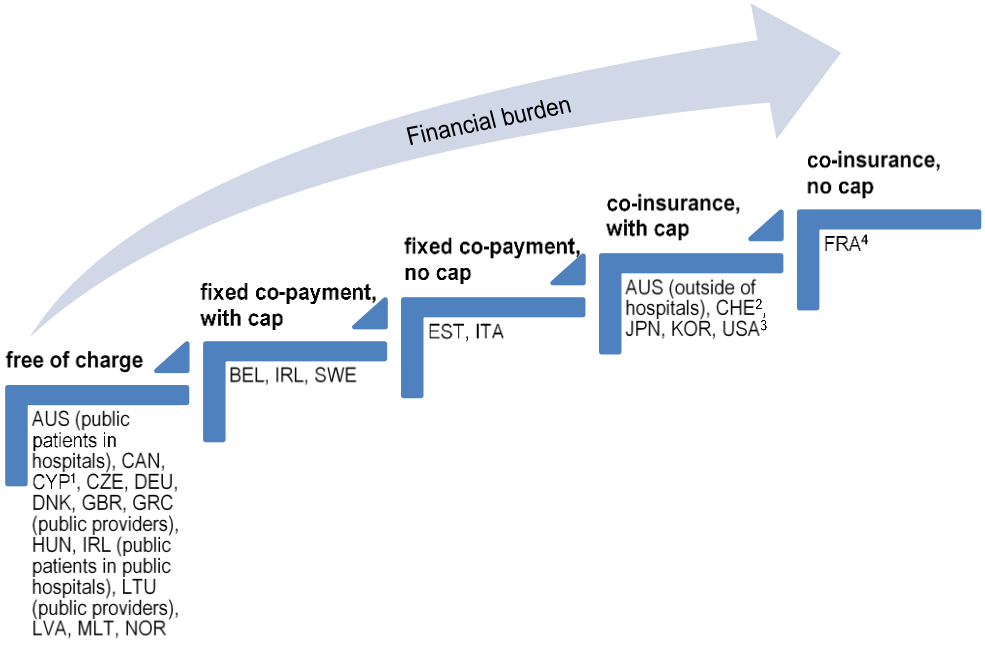
146. Many countries apply caps on user charges, either for the category of care or for the total user charges accumulated in one year. Caps may be expressed as fixed amounts of out-of-pocket payments (e.g. Australia, Denmark) or as a share or household income (e.g. Germany). Caps commonly represent around 1% of the average wage in European countries, while they can exceed 9% in the United States and 10% in Korea.

Figure 3.4. Cost-sharing for oncology pharmaceuticals dispensed to patients for self-administration in OECD/EU countries



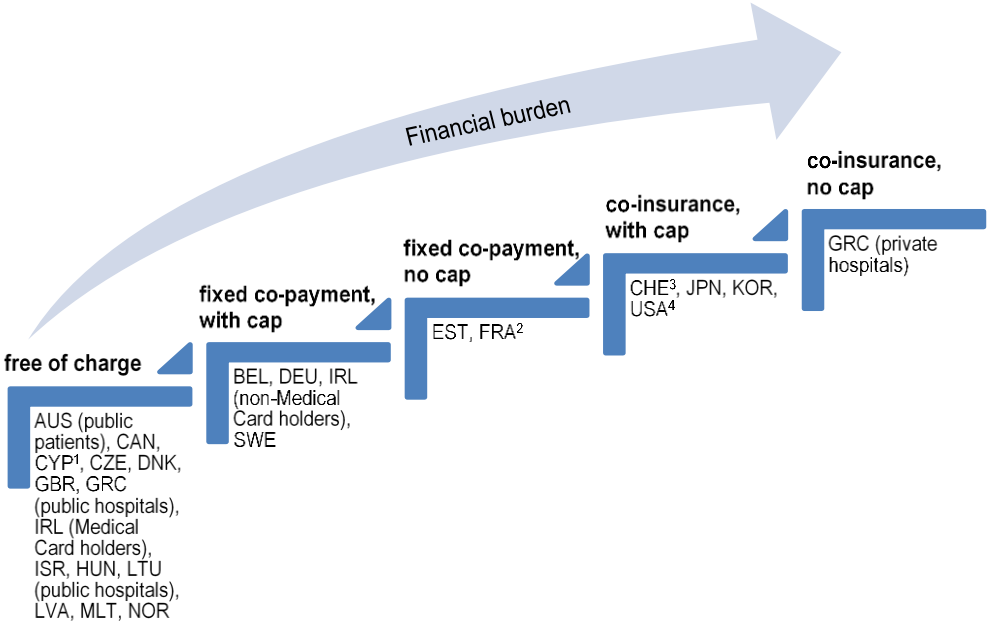
Note: This figure does not take into account potential user charges linked to the use of "reference prices".
1. In Cyprus, people earning less than EUR 135 000 do not share the costs. Beyond this limit, they pay the full cost of care. 2. Belgium and France have co-insurance for some other medicines, but no co-insurance for oncology medicines. 3. In Ireland, there is a fixed co-payment for Medical Card Holders, with deductible for other groups. 4. In Hungary, there is a co-payment of HUF 300 per pack for self-administered products. 5. In Denmark, Sweden, and Switzerland there is a deductible before co-insurance applies. 6. In the United States, there is no cap on out-of-pocket payments for Medicare beneficiaries.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Figure 3.5. Cost-sharing for outpatient specialist cancer care services including the administration of a medicine in OECD/EU countries



Note: This figure does not take into account potential user charges linked to the use of "reference prices".
1. In Cyprus, people earning less than EUR 135 000 do not share the costs. Beyond this limit, they pay the full cost of care. 2. In Switzerland there is a deductible before co-insurance applies. 3. In the United States, there is no cap on out-of-pocket spending for Medicare beneficiaries unless they have supplemental coverage or they have opted for a Medicare Advantage plan. 4. In France, patients may face extra-billing.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Figure 3.6. Cost-sharing for hospital inpatient care for cancer including the administration of a medicine in OECD/EU countries



Note: This figure does not take into account potential user charges linked to the use of "reference prices".
1. In Cyprus, people earning less than EUR 135 000 do not share the costs. Beyond this limit, they pay the full cost of care. 2. France has both co-payment and co-insurance on hospital care, but no co-insurance for hospital services related to cancer care. 3. In Switzerland there is a deductible before co-insurance applies. 4. In the United States, there is no cap on out-of-pocket spending for Medicare beneficiaries unless they have supplemental coverage or they have opted for a Medicare Advantage plan.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

147. In the two ESMO studies previously mentioned, the results of a 2014 survey of availability of antineoplastic medicines across 49 European countries and 63 non-European countries were stratified using the level of out-of-pocket spending ("Free", "<25% cost", "25-50% cost", "50-100% cost", "Full cost (i.e. no coverage)" (Cherny et al., 2016[61]; Cherny et al., 2017[62]). The results showed wide disparities across the world. In lower-middle- and low-income countries patients had to pay the full costs of about 32% and 58% of anti-cancer medicines included in the WHO *Model List of Essential Medicines*. In metastatic cancer, including epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer, renal cell carcinoma, melanoma, RAS/RAF wild-type metastatic colon cancer, castration-resistant prostate cancer and HER-2 amplified metastatic breast cancer, recently approved medicines for these conditions were only available with large out-of-pocket expenses in less economically developed countries. However, while this approach method enables comprehensive analysis on both availability and the "normal" degree of coverage for each medicine, it does not account for the more nuanced elements of co-payment policies, such as the exemption or reduction of co-payments for vulnerable groups, or annual caps on user charges.

148. Various studies have assessed the impact of different cost-sharing mechanisms on access to treatment (Carrera, Kantarjian and Blinder, 2018[81]; Doshi et al., 2018[82]; Lentz, Benson and Kircher, 2019[83]; Lee and Yoon, 2019[84]). In the United States, for example, higher out-of-pocket costs for Medicare and commercial insurance enrolees have been found to be associated with higher rates of oral anti-cancer prescription abandonment and delayed treatment initiation (Doshi et al., 2018[82]). A study of the association between high cost-sharing and treatment initiation for metastatic renal cell carcinoma among US Medicare beneficiaries found that those without low-income subsidies were less likely to initiate oral and injected/infused medications than those with subsidies (26.7% vs. 40.4%) (Li et al., 2018[85]). In Korea, another study found that catastrophic health spending in households with cancer patients was more frequent among those with National Health Insurance than those receiving medical care benefits[51], and more frequent among those with private health insurance compared to those without insurance (Lee and Yoon, 2019[84]). In Ireland, a report by the Irish Cancer Society highlighted the financial challenges experienced by 514 cancer patients and their carers who responded to an online survey between May and June 2019 (Irish Cancer Society, 2019[86]). The challenges included issues such as income and the workplace, the cost of medicines and hospital stays, additional bills at home, and medical card insurance. The average cost per month for medicines was EUR 158 per person.

Medicines prices may affect affordability for patients

149. Cost-sharing design certainly affects the affordability of medicines, but medicine prices also matter, especially when cost-sharing requirements take the form of co-insurance, i.e. a fixed proportion of the price of the medicine. While a co-insurance rate of 10 or 20% may be manageable for a large share of the population taking low-cost medicines, it quickly becomes unaffordable for high cost treatments.

150. The impact of different approaches to pricing on the cost, availability and affordability of cancer medicines was extensively reviewed in the WHO report *Pricing of cancer medicines and its impacts* (World Health Organization, 2018[2]). The report highlights that many countries have a form of price regulation, with the objective of providing necessary treatment to patients at affordable prices, and to ensure financial sustainability of health systems. Some authorities set prices directly, while others indirectly regulate prices by setting thresholds for public funding. The United States does not utilise price regulation except in a small number of federal programmes, which may in part account for the recent rapid growth in cancer drug prices.

[51] In Korea, national health insurance provides coverage for all citizens, with Medical Aid further supporting lower income groups. See https://www.hira.or.kr/dummy.do?pgmid=HIRAJ010000006002, consulted on 18 March 2020.

151. Many studies have found that prices of new oncology medicines in the United States are higher than in other countries, even though price differences vary across studies. For all medicines approved by the FDA between 2000 and 2009 for cancer indications, the Australian PBS price was on average 41% lower than the sales price in the United States (Wilson and Cohen, 2011[87]).[52] For 29 drugs with cancer indications approved by both the FDA and the EMA between 2000 and 2011, in 2013 the average *list* prices in four European countries (England and Wales, France, Germany, and Netherlands) were 8% lower than the average sales price in the United States, on a per dose or treatment cycle basis (Cohen, Malins and Shahpurwala, 2013[88]).

152. Other studies have assessed the affordability of medicines by adjusting drug prices for differences in wealth. In a 2017 study, the monthly costs of treatment with individual cancer medicines were adjusted by GDP per capita to compare affordability among seven countries, including the United States and the United Kingdom (Goldstein et al., 2017[89]). The results showed that *affordability* in middle-income countries (India, China, and South Africa) was poorer than in high-income countries (Australia, Israel, the United States and the United Kingdom), suggesting that prices were only being partly adjusted for capacity to pay. The study was, however, based on list prices and not on actual transaction costs, and the metric does not provide information on affordability for individual patients, which may vary within countries.

[52] Both studies converted prices into US dollars to compare prices in multiple countries. The pricing data were retrieved from IMS Health and/or national authority websites.

4 Conclusions

153. Various strategies have been adopted by countries to address the identified challenges to managing oncology medicines i.e. increasing uncertainty at the time of marketing authorisation; pricing of products with multiple indications of variable cost-effectiveness; pricing of products used in combination regimens; and budget impact driven by increasing volumes and prices of oncology medicines. The first section of the report shows that:

- The main response to uncertainty about clinical benefits at the time of launch is the use of managed entry agreements, some of which are based on the performance of products in "real-life". As shown in a previous OECD report (Wenzl and Chapman, 2019[24]), however, through these agreements, payers have mostly sought to mitigate financial risks, without paying much attention to the generation of new evidence.
- Countries do not necessarily have the information infrastructure to track the use of oncology products by indication. Hence, while some countries adhere to the concept of indication-based pricing (i.e. pricing mechanisms that enable payers to vary the price paid for a drug according to its perceived value in different indications), they can only adjust product prices based on expected utilisation. The problem is naturally the same when price adjustments are needed for products used in combination regimens.
- While expenditures for oncology products have steadily increased over time, retail pharmaceutical expenditures, as a proportion of gross domestic product (GDP), have been stable on average over the past decade, the result of a number of factors that include the application of budget constraints and spending caps. This indicator, however, does not take into account expenditures for medicines administered in hospitals and ambulatory care settings.
- A few countries have established capped, earmarked budgets for the funding of innovative oncology medicines (Italy) or for the temporary funding of medicines of uncertain cost-effectiveness, pending the generation of further evidence (England). Their impact on the overall efficiency of pharmaceutical expenditures remains unknown.

154. Countries could consider a number of policy options to reduce uncertainty about the benefits of oncology medicines present at the time of market launch, and to improve the monitoring of use and associated expenditures:

- **Enable the tracking of use by indication through routinely collected data, registries or post-marketing studies.** This could serve a number of purposes, including informing ex-post price adjustments where needed, and supporting the monitoring of expenditures linked to oncology medicines, as well as contributing to 'real world' evidence of the performance of medicines.
- **Improve the design of performance-based managed entry agreements to support the generation and collection of on-market evidence**. This would require the collection of information on both utilisation and relevant clinical outcomes for products subject to these agreements. Harmonisation of outcome measures, data aggregation, and information-sharing across payers and countries would be highly desirable, particularly for products targeting small populations.

155. The second part of this report presents important new information on accessibility and coverage for a sample of oncology medicines across 5 cancer sub-types in 23 countries, as well as new information on time to access for a subset of recent 31 product/indication pairs (comprising products approved in the United States since 2014). The information confirms that access to oncology medicines remains unequal across OECD/EU countries.

- Of the 109 product/indication pairs in the sample, the United States had the largest proportion approved and covered (by Medicare), followed by Denmark and Germany (96%, 91%, and 88%, respectively). Chile and Malta had the lowest proportion approved and covered (47% and 46% respectively). Access was more homogeneous across countries for products/indications included in the WHO 21st *Model List of Essential Medicines* (EML), but, conversely, more heterogeneous for recently approved product/indication pairs, due to the fact that not all of them are yet approved (or launched) in all countries. The number of medicines approved and covered also varied according to cancer type. However, all medicines included in the EML, and at least one medicine in each pharmacological subgroup, were covered in almost all countries in each cancer type.
- Marketing and coverage decisions for the 31 recent product/indications occurred at different times across OECD/EU countries, with first marketing authorisation granted in the United States in 84% of cases. On average, product/indications were approved in individual countries/regions 12 to 17 months after their first marketing authorisation in the sample of countries surveyed. For individual product/indications, the time between first marketing authorisation and coverage in a given country ranged from 1 to 66 months (more than 5 years). This reflects both companies' launch sequences, as well as processing times for marketing approval, and pricing and coverage decisions.
- At country level, the regulatory review period (including any clock-stops) ranged from 7 months in the United States, to 13 months in the European Economic Area. The time between application and granting of coverage ranged from 4 months in Sweden, to 27 months in Malta. The average total time from application for marketing authorisation to coverage ranged from 9 months in Israel and 11 months in Japan, to 52 months in Malta.

156. A number of countries also reported inequities in access *within* countries. These can be attributed to several factors:

- While most OECD/EU countries make coverage decisions at national level, and which are generally valid across all settings of care, regions or population groups, there are some exceptions (e.g. Australia, Canada, some Nordic countries and United States). Beyond this, when sub-national governments have responsibility for inpatient care, variable budget constraints and financing arrangements may lead to differences in access. In some of them, however, efforts are being made to harmonise coverage decisions (e.g. Canada, Norway) or access (e.g. Italy).
- The design of cost-sharing can also potentially affect access. In 13 countries, patients can access oncology medicines for self-administration free of charge, or with a fixed co-payment. In other countries, user charges take the form of co-insurance, with contributions increasing with the price of the medicine. In most countries, inpatient and outpatient cancer care services, including administration of injectable products, are free of charge when delivered by public providers. Almost all countries have a cap on user charges. These caps, where they exist, are defined in absolute or relative terms (e.g. a fixed amount or a proportion of household income); they typically represent less than 1%-2% of the average wage in European countries but may exceed 9% and 10% of the average wage in the United States and Korea respectively. In these two countries, high co-payments have been shown to impair access or lead to catastrophic health spending in households of patients with cancer.

157. Patients and clinicians are increasingly interested in international comparisons of access to medicines, and these can provide useful benchmarks for policy makers. However, **access needs to be understood within the context of each country's health care system** and the information collected on

access in this study has several limitations. First, in most cases, it does not take into account early access schemes, which provide access to promising medicines for high unmet medical needs prior to marketing authorisation, and/or coverage decisions. Moreover, individual drug availability and coverage data do not provide a complete picture of access to appropriate treatments for patients in need. Hofmarcher et al. (2019[4]) showed in a recent report on EU countries that consumption levels, even for covered medicines, vary widely across countries, probably beyond what could reasonably be explained by differences in burden of disease and clinical practice guidelines. They noted that consumption in Eastern European countries was well below that of wealthier European countries. This suggests that, beyond availability and coverage, access is likely to be impaired by funding arrangements.

158. In addition to marketing authorisation, coverage, and financing, access to oncology medicines may also be impaired by the increasing occurrence of supply interruptions and shortages. Seventeen of 24 respondent countries (71%) reported having experienced shortages of oncology medicines within the preceding three years. Only four countries reported that they had not experienced shortages (Germany, Japan, Sweden, and Switzerland).[53] Shortages reported by countries were not always similar, but were more common among older drugs and generics.

159. All the challenges met when assessing access to oncology medicines confirm that tracking their utilisation—by indication, where possible—would be invaluable. It would inform an assessment of actual uptake, and of differences in access across regions and/or coverage programmes. In addition, countries could consider **setting cost-sharing arrangements**, where unavoidable, **as fixed co-payments rather than co-insurance, and ensuring that these do not undermine access or impose catastrophic costs on households with cancer patients.**

[53] The three remaining countries did not respond to the question.

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Annex A. OECD data collection

The content of this paper is based on information available from public sources, including the peer-reviewed literature, grey literature and documents published by payers and government agencies, survey data, and experience from stakeholders collected by the OECD Secretariat during a two-day workshop on oncology medicines.

Expert interviews and survey

The key challenges identified in managing and accessing oncology medicines were elicited from a series of preliminary discussions with experts from a sample of OECD member countries (France, Canada, Poland and the Netherlands).

In September 2019, the OECD Secretariat sent a survey to a total of 41 countries, including OECD member countries and EU Member States, comprising

1. a MS-word document with questions on challenges encountered in access to oncology medicines and policies and approaches adopted to address them;
2. a MS-word document with prefilled information on cost-sharing requirements for oncology medicines and other health care services for review, update, and amendment; and
3. a MS-excel tabular spreadsheet with information to complete on several aspects of access to a subset of oncology medicines for five cancer types.

A total of 25 countries responded to at least one part of the survey Table A A.1.

Table A A.1. Responses to OECD survey

Country	1. Policy questionnaire	2. Cost-sharing	3. Access survey
Australia	yes	no[1]	yes
Belgium	yes	yes	yes
Canada	yes	yes	no
Chile	yes	no	yes
Cyprus	yes	yes	yes
Czech Republic	no	yes	yes
Denmark	yes	yes	yes
Estonia	yes	yes	yes
France	yes	yes	yes
Germany	yes	yes	yes
Greece	yes	yes	yes
Hungary	yes	yes	yes
Ireland	yes	yes	yes
Israel	yes	yes	yes
Italy	yes	yes	no
Japan	yes	yes	yes
Korea	yes	yes	yes
Latvia	yes	yes	yes

Country	1. Policy questionnaire	2. Cost-sharing	3. Access survey
Lithuania	yes	yes	yes
Malta	yes	yes	yes
Norway	yes	yes	yes
Sweden	yes	yes	yes
Switzerland	yes	yes	yes
United Kingdom (England only)	yes	no[1]	yes
United States	yes	yes	yes
Count of countries	*24*	*22*	*23*

Note:
1. Information on cost-sharing requirements was updated by the Secretariat using publicly available sources.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Part 1, the policy questionnaire on key challenges in managing oncology medicines, contained 30 questions based around themes arising from a literature review and a series of preliminary discussions with experts from a sample of OECD member countries (France, Canada, Poland and the Netherlands).

Part 2, a pre-filled document with information on cost-sharing was sent to countries for revisions and update. Initial information was based on information collected by the OECD as part of the *Health Systems Characteristics Survey* in 2012 and updated for the working paper on *Health care coverage in OECD countries* in 2012 published in 2016 (Paris et al., 2016[90]). Countries were asked to update information specifically related to covered oncology medicines or to inpatient services / specialist services including the administration of covered oncology medicines.

For Part 3, the list of products in the MS-excel spreadsheet built on information presented in the recent WHO Report *Pricing of cancer medicines and its impacts* (World Health Organization, 2018[2]), which was based on the results of two ESMO surveys (Cherny et al., 2016[61]; Cherny et al., 2017[62]), adding to the sample all oncology medicines that had been approved by the United States or Europe as of July 2019, and those included in the 21st WHO *Model List of Essential Medicines* (EML) (2019[63]). The selection of medicines was narrowed to cancers with significant prevalence in OECD countries and EU Member States, adding a haematological malignancy, and aiming to capture those indications for which there are a large number of new medicines including immunotherapies. The list was refined in order to define a workable sample, with no value judgement made on the final indications and medicines chosen. This analysis could be extended in the future. The final sample included 101 oncology product/indication pairs and 8 ancillary products (for supportive care) used in the following indications: metastatic breast cancer, non-small cell lung cancer, colorectal cancer, melanoma, and multiple myeloma (see Table A A.2). Medicines were classified by WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) Anatomical Therapeutic Chemical (ATC) code (2019[65]). Information requested for all 109 sample pairs included: regulatory approval and coverage status, setting of administration, generic / biosimilar protection and, if no longer protected, subsequent number of generic / biosimilar products available. Detailed information was requested for those 31 product/indication pairs that had been approved in the United States since 2014. This included date of application for marketing authorisation, date of granting of marketing authorisation, date of application for coverage decision, date of granting of coverage, as well as coverage restrictions. The Secretariat added dates for marketing authorisation for those countries with central authorisation by the European Commission.

Inconsistencies in initial survey responses were clarified with relevant experts.

Table A A.2. Final product/indication sample for OECD access survey

109 product/indication pairs included in the final sample, across five cancer types and supportive care

Indication	Active substance	ATC Code	ATC-4 Level	EML	Vintage[1]
Metastatic breast cancer	abemaciclib	L01XE50	protein kinase inhibitors	no	new
Metastatic breast cancer	anastrozole	L02BG03	aromatase inhibitors	yes	old
Metastatic breast cancer	bevacizumab	L01XC07	monoclonal antibodies	no	old
Metastatic breast cancer	capecitabine	L01BC06	pyrimidine analogues	yes	old
Metastatic breast cancer	carboplatin	L01XA02	platinum compounds	no	old
Metastatic breast cancer	cisplatin	L01XA01	platinum compounds	no	old
Metastatic breast cancer	cyclophosphamide	L01AA01	nitrogen mustard analogues	yes	old
Metastatic breast cancer	docetaxel	L01CD02	taxanes	yes	old
Metastatic breast cancer	doxorubicin - liposomal	L01DB01	anthracyclines and related substances	no	old
Metastatic breast cancer	doxorubicin	L01DB01	anthracyclines and related substances	yes	old
Metastatic breast cancer	eribulin	L01XX41	other antineoplastic agents	no	old
Metastatic breast cancer	everolimus	L01XE10	protein kinase inhibitors	no	old
Metastatic breast cancer	exemestane	L02BG06	aromatase inhibitors	no	old
Metastatic breast cancer	fluorouracil	L01BC02	pyrimidine analogues	no	old
Metastatic breast cancer	fulvestrant	L02BA03	anti-oestrogens	no	old
Metastatic breast cancer	ixabepilone	L01DC04	other cytotoxic antibiotics	no	old
Metastatic breast cancer	lapatinib	L01XE07	protein kinase inhibitors	no	old
Metastatic breast cancer	letrozole	L02BG04	aromatase inhibitors	no	old
Metastatic breast cancer	olaparib	L01XX46	other antineoplastic agents	no	new
Metastatic breast cancer	paclitaxel	L01CD01	taxanes	yes	old
Metastatic breast cancer	palbociclib	L01XE33	protein kinase inhibitors	no	new
Metastatic breast cancer	pertuzumab	L01XC13	monoclonal antibodies	no	old
Metastatic breast cancer	ribociclib	L01XE42	protein kinase inhibitors	no	new
Metastatic breast cancer	talazoparib	L01XX60	other antineoplastic agents	no	new
Metastatic breast cancer	tamoxifen	L02BA01	anti-oestrogens	yes	old
Metastatic breast cancer	toremifene	L02BA02	anti-oestrogens	no	old
Metastatic breast cancer	trastuzumab emtansine	L01XC14	monoclonal antibodies	no	old
Metastatic breast cancer	trastuzumab	L01XC03	monoclonal antibodies	yes	old
Metastatic breast cancer	vinorelbine	L01CA04	vinca alkaloids and analogues	yes	old
Non-small cell lung cancer	afatinib	L01XE13	protein kinase inhibitors	no	old
Non-small cell lung cancer	alectinib	L01XE36	protein kinase inhibitors	no	new
Non-small cell lung cancer	atezolizumab	L01XC32	monoclonal antibodies	no	new
Non-small cell lung cancer	bevacizumab	L01XC07	monoclonal antibodies	no	old
Non-small cell lung cancer	brigatinib	L01XE43	protein kinase inhibitors	no	new
Non-small cell lung cancer	carboplatin	L01XA02	platinum compounds	yes	old
Non-small cell lung cancer	ceritinib	L01XE28	protein kinase inhibitors	no	new
Non-small cell lung cancer	cisplatin	L01XA01	platinum compounds	yes	old
Non-small cell lung cancer	crizotinib	L01XE16	protein kinase inhibitors	no	old
Non-small cell lung cancer	dabrafenib	L01XE23	protein kinase inhibitors	no	old
Non-small cell lung cancer	dacomitinib	L01XE47	protein kinase inhibitors	no	new
Non-small cell lung cancer	docetaxel	L01CD02	taxanes	no	old
Non-small cell lung cancer	doxorubicin	L01DB01	anthracyclines and related substances	no	old
Non-small cell lung cancer	durvalumab	L01XC28	monoclonal antibodies	no	new
Non-small cell lung cancer	erlotinib	L01XE03	protein kinase inhibitors	yes	old
Non-small cell lung cancer	etoposide	L01CB01	podophyllotoxin derivatives	yes	old

Indication	Active substance	ATC Code	ATC-4 Level	EML	Vintage[1]
Non-small cell lung cancer	gefitinib	L01XE02	protein kinase inhibitors	no	old
Non-small cell lung cancer	gemcitabine	L01BC05	pyrimidine analogues	yes	old
Non-small cell lung cancer	lorlatinib	L01XE44	protein kinase inhibitors	no	new
Non-small cell lung cancer	necitumumab	L01XC22	monoclonal antibodies	no	new
Non-small cell lung cancer	nivolumab	L01XC17	monoclonal antibodies	no	new
Non-small cell lung cancer	osimertinib	L01XE35	protein kinase inhibitors	no	new
Non-small cell lung cancer	paclitaxel	L01CD01	taxanes	yes	old
Non-small cell lung cancer	pembrolizumab	L01XC18	monoclonal antibodies	no	new
Non-small cell lung cancer	pemetrexed	L01BA04	folic acid analogues	no	old
Non-small cell lung cancer	ramucirumab	L01XC21	monoclonal antibodies	no	new
Non-small cell lung cancer	trametinib	L01XE25	protein kinase inhibitors	no	old
Non-small cell lung cancer	vinorelbine	L01CA04	vinca alkaloids and analogues	yes	old
Colorectal cancer	aflibercept	L01XX44	other antineoplastic agents	no	old
Colorectal cancer	bevacizumab	L01XC07	monoclonal antibodies	no	old
Colorectal cancer	capecitabine	L01BC06	pyrimidine analogues	yes	old
Colorectal cancer	cetuximab	L01XC06	monoclonal antibodies	no	old
Colorectal cancer	fluorouracil	L01BC02	pyrimidine analogues	yes	old
Colorectal cancer	irinotecan	L01XX19	other antineoplastic agents	yes	old
Colorectal cancer	mitomycin C	L01DC03	other cytotoxic antibiotics	no	old
Colorectal cancer	nivolumab	L01XC17	monoclonal antibodies	no	new
Colorectal cancer	oxaliplatin	L01XA03	platinum compounds	yes	old
Colorectal cancer	panitumumab	L01XC08	monoclonal antibodies	no	old
Colorectal cancer	pembrolizumab	L01XC18	monoclonal antibodies	no	new
Colorectal cancer	raltitrexed	L01BA03	folic acid analogues	no	old
Colorectal cancer	ramucirumab	L01XC21	monoclonal antibodies	no	new
Colorectal cancer	regorafenib	L01XE21	protein kinase inhibitors	no	old
Colorectal cancer	trifluridine / tipiracil	L01BC59	pyrimidine analogues	no	new
Melanoma	high-dose IL-2 - aldesleukin	L03AC01	interleukins	no	old
Melanoma	binimetinib	L01XE41	protein kinase inhibitors	no	new
Melanoma	cobimetinib	L01XE38	protein kinase inhibitors	no	new
Melanoma	dabrafenib	L01XE23	protein kinase inhibitors	no	old
Melanoma	dacarbazine	L01AX04	other alkylating agents	no	old
Melanoma	encorafenib	L01XE46	protein kinase inhibitors	no	new
Melanoma	fotemustine	L01AD05	nitrosoureas	no	old
Melanoma	interferon	L03AB	interferons	no	old
Melanoma	ipilimumab	L01XC11	monoclonal antibodies	no	old
Melanoma	nivolumab	L01XC17	monoclonal antibodies	yes	new
Melanoma	pembrolizumab	L01XC18	monoclonal antibodies	yes	new
Melanoma	talimogene laherparepvec	L01XX51	other antineoplastic agents	no	new
Melanoma	temozolomide	L01AX03	other alkylating agents	no	old
Melanoma	trametinib	L01XE25	protein kinase inhibitors	no	old
Melanoma	vemurafenib	L01XE15	protein kinase inhibitors	no	old
Multiple myeloma	bortezomib	L01XX32	other antineoplastic agents	yes	old
Multiple myeloma	carfilzomib	L01XX45	other antineoplastic agents	no	old
Multiple myeloma	cyclophosphamide	L01AA01	nitrogen mustard analogues	yes	old
Multiple myeloma	daratumumab	L01XC24	monoclonal antibodies	no	new
Multiple myeloma	doxorubicin	L01DB01	anthracyclines and related substances	yes	old
Multiple myeloma	elotuzumab	L01XC23	monoclonal antibodies	no	new

Indication	Active substance	ATC Code	ATC-4 Level	EML	Vintage[1]
Multiple myeloma	interferon alfa-2b	L03AB	interferons	no	old
Multiple myeloma	ixazomib	L01XX50	other antineoplastic agents	no	new
Multiple myeloma	lenalidomide	L04AX04	other immunosuppressants	yes	old
Multiple myeloma	melphalan	L01AA03	nitrogen mustard analogues	yes	old
Multiple myeloma	panobinostat	L01XX42	other antineoplastic agents	no	new
Multiple myeloma	plerixafor	L03AX16	other immunostimulants	no	old
Multiple myeloma	pomalidomide	L04AX06	other immunosuppressants	no	old
Multiple myeloma	thalidomide	L04AX02	other immunosuppressants	yes	old
Ancillary treatments used in oncology	calcium folinate - leucovorin	V03AF03	detoxifying agents for antineoplastic treatment	yes	old
Ancillary treatments used in oncology	dexamethasone	H02AB02	corticosteroids	yes	old
Ancillary treatments used in oncology	epoetin alfa	B03XA01	other anti-anaemic preparations	no	old
Ancillary treatments used in oncology	epoetin zeta	B03XA02	other anti-anaemic preparations	no	old
Ancillary treatments used in oncology	filgrastim	L03AA02	colony stimulating factors	yes	old
Ancillary treatments used in oncology	lipegfilgrastim	L03AA14	colony stimulating factors	no	old
Ancillary treatments used in oncology	pegfilgrastim	L03AA13	colony stimulating factors	no	old
Ancillary treatments used in oncology	prednisolone	H02AB06	corticosteroids	yes	old

Note: ATC Anatomical Therapeutic Chemical, EML Essential Medicines List
Pairs were classified by ATC-4 code and level (2019[65]), according to whether they were included in the 21st WHO *Model List of Essential Medicines* (EML) (2019[63]), and whether they had entered the United States market after 2014.
1. New refers to product/indication pairs approved in the United States since 2014.
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Workshop

The *Workshop on Oncology Medicines* took place on 2-3 December 2019 at the European Commission, Brussels. Twenty-two experts from 17 EU Member States attended the meeting; as well as representatives of European Commission DG Santé, WHO, invited experts from regulatory and HTA agencies and the OECD Secretariat. Experts from Member States were invited to provide feedback and advice around the current OECD project on *Challenges in Access to Oncology Medicines* and share their experience. The last session on Day 2 was opened to stakeholders; six representatives from European Federation of Pharmaceutical Industries and Associations (EFPIA), two from Medicines for Europe (MfE), and two from European Cancer Leagues (ECL - patient association) attended to share their perspectives on the oncology topic. The primary focus of this workshop was to discuss preliminary results of the OECD oncology survey.

Annex B. OECD access survey – limitations and country-specific caveats

Table A B.1 below outlines limitations to the data, or assumptions made by the 23 countries who responded to Part 3 of the OECD survey on access to the sample of 109 product/indication pairs. The table also indicates the dates of survey submission by respondents (ranging from 20 September 2019 for Cyprus to 15 January 2020 for Chile), which is important since the evolution in approvals and coverage decisions in oncology is rapid. A medicine indicated as "not approved" or "not covered" in a country may be a medicine which is *not yet* approved or covered or for which an application for marketing authorisation or (more likely) coverage led to a negative outcome. This table should be read in conjunction with Table 3.4 on level of coverage decisions.

Table A B.1. Country-specific caveats

Country	Submission date	Notes
Australia	08/12/19	- Information was only provided for some pairs - Information provided only covers the Pharmaceutical Benefits Scheme, which provides national-level coverage for medicines supplied in settings other than to public hospital inpatients. Coverage of medicines administered during to public hospital inpatients of public hospitals may vary across States and territories.
Belgium	08/10/19 (amended 09/03/20)	- For products that are "approved and covered", the originator may no longer be reimbursed or available, or the product may only be covered under certain conditions. - Coverage was granted for two product/indication pairs after 20/09/19 (the date of the first respondent submission) - National-level coverage decision
Chile	15/01/20	- Marketing authorisation was granted for one product/indication pair after 20/09/19 (the date of the first respondent submission)
Cyprus	20/09/19	- Application for coverage can be made by pharmaceutical companies and doctors prior to EU marketing authorisation date (e.g. based on FDA approval). Once a medicine is approved by EMA, it is available for patients to access without any coverage scheme; in many cases, the government covers the cost of these medicines. - Some medicines with an EU marketing authorisation may be listed as "not approved" as they have not been launched on the market in Cyprus. - National-level coverage decision
Czech Republic	27/11/19	- Two products listed as "not approved" as relevant indication not in Summary of Product Characteristics (products are listed for use in these indications in national guidelines) - National-level coverage decision
Denmark	07/11/19 (amended 09/03/20)	- National-level coverage decision
Estonia	23/09/19	- Coverage was granted for two product/indication pairs after 20/09/19 (the date of the first respondent submission) - National-level coverage decision
France	18/11/19 (amended 06/03/20)	- National-level coverage decision and coverage - Delays in coverage may be due to price negotiation
Germany	25/11/19 (amended 27/02/20)	- National-level coverage decision and coverage

Country	Submission date	Notes
Greece	30/09/19	- For new oncology medicines authorised through the EMA centralised procedure, the answer "not approved" implies that the new medicines has not yet been launched in Greece, either because the company has not yet applied for a price, or because the pricing procedure is still in progress. - The answer "approved but not covered" may mean that the product does not yet have a price, the product is approved through a type of early patient access scheme, the product has a price but has not yet been included in the positive list, or the product could be reimbursed in limited cases as an imported medicine or for off-label use etc - National-level coverage decision
Hungary	28/10/19	- Medicines may have restricted and/or conditional availability in a named -patient programme - It is not possible for the marketing authorisation holder to apply for coverage prior to the date of marketing authorisation of the product - National-level coverage decision
Ireland	19/11/19 (amended 03/12/19)	- The answer "approved but not covered" may mean that the company has not yet applied for coverage or that the application is being processed. - Coverage was granted for two product/indication pairs after 20/09/19 (the date of the first respondent submission) - National-level coverage decisions for high-cost medicines administered in outpatient and inpatient care settings
Israel	12/01/20	- National-level coverage decisions are made once a year (during October-December), with decisions put into effect in January of the following year - Date of marketing authorisation reflects the final approval date for a pharmaceutical. It may have received a positive opinion from the Advisory Committee prior to this date, at which point it may be included in the National List of Health Services. Thus the date of marketing authorisation may be after the date of coverage decision.
Japan	14/10/19	- Reimbursement of a new pharmaceutical is listed within 60 days (within 90 days at the latest) from the time of approval. The reimbursement process starts immediately after approval of the medicine, with an additional indication being covered by public health insurance from the day of approval of the medicine. Prices are not negotiated; reimbursement prices are set by the government's official pricing formula. - National-level coverage decisions
Korea	21/10/19	- National-level coverage decisions
Latvia	21/10/19 (amended 11/03/20)	- The answer "not approved" may mean that the product has not been launched in Latvia - In 2018, only ~23% (608) of 2637 names of products authorised through the centralised procedure at EU level were launched in Latvia. On the one hand some marketing authorisation holders are not interested in launching their products in Latvia (small market, low purchasing power etc.). On the other hand, affordability is the cornerstone of access. Usually the medicines are available to patients only if the costs are covered by the state i.e. if the medicine is included in the Positive List (i.e. the medicine is cost-effective and the state can afford it). In order to decide whether to include the medicine in the Positive list, the cost-effectiveness and budget impact of the medicine need to be evaluated by the competent authorities. If the medicine is not cost-effective at the offered price or there is insufficient budget for reimbursement the medicine does not receive coverage. - National-level coverage decision
Lithuania	15/10/19 (amended 05/11/19)	- National-level coverage decision
Malta	08/10/19 (amended 09/03/20)	- The answer "approved but not covered" may mean that the product was approved but is in the process of being procured through tender - National-level coverage decision
Norway	17/10/19 (amended 06/03/20)	- National-level coverage decision, regional financing - For hospital drugs (all oncology treatments), the four regions are responsible for access to medicines for patients. The four regions participate in a Decision Forum. The regions have formally delegated their decision authority to the Decision Forum. The Decision Forum must reach a common decision for all regions that is a national decision. - To complete the survey for the new novel medicines, the web page nyemetoder.no in addition to in house registries were used. For the older medicines, information from the tender was used to complete the survey; information about whether these drugs actually are used for the specific cancer types or not was not available for these drugs. - If the company can provide a dossier at an early stage, application for coverage is possible prior to marketing authorisation - The answer "not approved" may mean that the drug has not been marketed in Norway.

Country	Submission date	Notes
Norway (cont.)		- The answer "approved but not covered" may mean that it was not covered at the time of survey completion, awaiting documentation from the company, ongoing assessments or awaiting decisions. - The answer "approved and covered" mainly means covered by hospitals. However in some special cases it may mean that it is covered by primary care sector, in combination with one thing but not another, or a subgroup may be covered but not all groups (e.g. line of therapy, biomarker etc), or temporary coverage has been applied. - Coverage was granted for six product/indication pairs after 20/09/19 (the date of the first respondent submission)
Sweden	14/10/19 (amended 18/12/19)	- Information includes both national and, where possible, regional-level coverage decisions. Information for regions was found online and from sales data. - Product-based national-level coverage decisions for outpatient medicines by TLV; all approved indications are subsidised. - Coverage for inpatient medicines is decided by regions, sometimes as soon as it is approved. The regions in Sweden have a process called managed introduction with the New Therapies Council to make sure equal access to medicines to all patients, which is used for some medicines, but not for all. For some medicines, the regions' New Therapies Council asks TLV for an evaluation and makes a recommendation based on that. In some cases, the date of such a relevant recommendation has been used as date of coverage decision.
Switzerland	04/10/19 (amended 19/11/19)	- National-level coverage decision and insurer provider network
United Kingdom (England only)	18/10/19 (amended 29/11/19)	- The answer "approved and covered" may also mean that the product/indication pair has a patient access scheme or is in the Cancer Drugs Fund with a managed access agreement - National-level coverage decision
United States	20/12/19	- The data presented are for Medicare; anti-neoplastics are a protected class under Medicare Part D. - The US has a complex system based around individual health coverage schemes

Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Annex C. OECD access survey – indication-specific results

Table A C.1 to Table A C.6 below present a summary of regulatory approval and coverage status of the 109 sample product/indication pairs by indication (for the 23 countries who responded to this part of the OECD survey). Below is a note on how to read information presented in the tables:

- Colour code:

	Not approved (no marketing authorisation for this indication) or not (yet) launched
	Approved but not covered
	Approved and covered
	No information provided

- * = product/indication pair included in the 21st *WHO Model List of Essential Medicines* (2019[63]).
- † = product/indication pair has been approved since 2014 in the United States.
- ‡ = European Medicines Agency (EMA) marketing authorisation withdrawn.
- § = There is no central marketing authorisation at EU level for this product/indication pair.
- Note for EU members states (and Norway)
  - When a medicine appears as “approved” in one country and “not approved” in another country, it might mean either 1) that the product has been approved before 1995 through national procedures (before systematic centralised marketing authorisation of all oncology medicines); or 2) that the product, although authorised for marketing in all EU countries, has not (yet) been launched on the market in that country for that indication.

Table A C.1. Regulatory approval and coverage status of medicines for *metastatic breast cancer*

Active substance	ATC Code	ATC-4 Level	AUS	BEL	CHE	CHL	CYP	CZE	DEU	DNK	EST	FRA	GBR	GRC	HUN	IRL	ISR	JPN	KOR	LTU	LVA	MLT	NOR	SWE	USA
doxorubicin -liposomal	L01DB01	anthracyclines and related substances																							
doxorubicin*	L01DB01	anthracyclines and related substances																							
fulvestrant	L02BA03	anti-estrogens																							
tamoxifen*	L02BA01	anti-estrogens																							
toremifene	L02BA02	anti-estrogens																							
anastrozole*	L02BG03	aromatase inhibitors																							
exemestane	L02BG06	aromatase inhibitors																							
letrozole	L02BG04	aromatase inhibitors																							
bevacizumab	L01XC07	monoclonal antibodies																							
pertuzumab	L01XC13	monoclonal antibodies																							
trastuzumab emtansine	L01XC14	monoclonal antibodies																							
trastuzumab*	L01XC03	monoclonal antibodies																							
cyclophosphamide*	L01AA01	nitrogen mustard analogues																							
carboplatin	L01XA02	platinum compounds																							
cisplatin	L01XA01	platinum compounds																							
abemaciclib†	L01XE50	protein kinase inhibitors																							
everolimus	L01XE10	protein kinase inhibitors																							
lapatinib	L01XE07	protein kinase inhibitors																							
palbociclib†	L01XE33	protein kinase inhibitors																							
ribociclib†	L01XE42	protein kinase inhibitors																							
capecitabine*	L01BC06	pyrimidine analogues																							
fluorouracil	L01BC02	pyrimidine analogues																							
docetaxel*	L01CD02	taxanes																							
paclitaxel*	L01CD01	taxanes																							
vinorelbine*	L01CA04	vinca alkaloids and analogues																							
eribulin	L01XX41	other antineoplastic agents																							
olaparib†	L01XX46	other antineoplastic agents																							
talazoparib†	L01XX60	other antineoplastic agents																							
ixabepilone	L01DC04	other cytotoxic antibiotics																							

Note: Dark blue = not approved i.e. no marketing authorisation for this indication or not (yet) launched; medium blue = approved but not covered; light blue = approved and covered; white = no data provided. * product/indication pair included in the 21st WHO *Model List of Essential Medicines* (2019[63]); † product/indication pair has been approved in the United States since 2014; ‡ EMA marketing authorisation withdrawn. For EU members states (and Norway), when a medicine appears as "approved" in one country and "not approved" in another country, it might mean either 1) that the product has been approved before 1995 through national procedures (before systematic centralised marketing authorisation of all oncology medicines); or 2) that the product, although authorised for marketing in all EU countries, has not (yet) been launched on the market in that country for that indication. Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Table A C.2. Regulatory approval and coverage status of medicines for *non-small cell lung cancer*

Active substance	ATC Code	ATC-4 Level	AUS	BEL	CHE	CHL	CYP	CZE	DEU	DNK	EST	FRA	GBR	GRC	HUN	IRL	ISR	JPN	KOR	LTU	LVA	MLT	NOR	SWE	USA
doxorubicin	L01DB01	anthracyclines and related substances																							
pemetrexed	L01BA04	folic acid analogues																							
atezolizumab†	L01XC32	monoclonal antibodies																							
bevacizumab	L01XC07	monoclonal antibodies																							
durvalumab†	L01XC28	monoclonal antibodies																							
necitumumab†	L01XC22	monoclonal antibodies																							
nivolumab†	L01XC17	monoclonal antibodies																							
pembrolizumab†	L01XC18	monoclonal antibodies																							
ramucirumab†	L01XC21	monoclonal antibodies																							
carboplatin*	L01XA02	platinum compounds																							
cisplatin*	L01XA01	platinum compounds																							
etoposide*	L01CB01	podophyllotoxin derivatives																							
afatinib	L01XE13	protein kinase inhibitors																							
alectinib†	L01XE36	protein kinase inhibitors																							
brigatinib†	L01XE43	protein kinase inhibitors																							
ceritinib†	L01XE28	protein kinase inhibitors																							
crizotinib	L01XE16	protein kinase inhibitors																							
dabrafenib	L01XE23	protein kinase inhibitors																							
dacomitinib†	L01XE47	protein kinase inhibitors																							
erlotinib*	L01XE03	protein kinase inhibitors																							
gefitinib	L01XE02	protein kinase inhibitors																							
lorlatinib†	L01XE44	protein kinase inhibitors																							
osimertinib†	L01XE35	protein kinase inhibitors																							
trametinib	L01XE25	protein kinase inhibitors																							
gemcitabine*	L01BC05	pyrimidine analogues																							
docetaxel	L01CD02	taxanes																							
paclitaxel*	L01CD01	taxanes																							
vinorelbine*	L01CA04	vinca alkaloids and analogues																							

Note: Dark blue = not approved i.e. no marketing authorisation for this indication or not (yet) launched; medium blue = approved but not covered; light blue = approved and covered; white = no data provided. * product/indication pair on 21st *WHO Model List of Essential Medicines* (2019[63]); † product/indication pair has been approved in the United States since 2014. For EU members states (and Norway), when a medicine appears as "approved" in one country and "not approved" in another country, it might mean either 1) that the product has been approved before 1995 through national procedures (before systematic centralised marketing authorisation of all oncology medicines); or 2) that the product, although authorised for marketing in all EU countries, has not (yet) been launched on the market in that country for that indication. Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Table A C.3. Regulatory approval and coverage status of medicines for *colorectal cancer*

Active substance	ATC Code	ATC-4 Level	AUS	BEL	CHE	CHL	CYP	CZE	DEU	DNK	EST	FRA	GBR	GRC	HUN	IRL	ISR	JPN	KOR	LTU	LVA	MLT	NOR	SWE	USA
raltitrexed	L01BA03	folic acid analogues																							
bevacizumab	L01XC07	monoclonal antibodies																							
cetuximab	L01XC06	monoclonal antibodies																							
nivolumab†§	L01XC17	monoclonal antibodies																							
panitumumab	L01XC08	monoclonal antibodies																							
pembrolizumab†§	L01XC18	monoclonal antibodies																							
ramucirumab†	L01XC21	monoclonal antibodies																							
oxaliplatin*	L01XA03	platinum compounds																							
regorafenib	L01XE21	protein kinase inhibitors																							
capecitabine*	L01BC06	pyrimidine analogues																							
fluorouracil*	L01BC02	pyrimidine analogues																							
trifluridine / tipiracil†	L01BC59	pyrimidine analogues																							
aflibercept	L01XX44	other antineoplastic agents																							
irinotecan*	L01XX19	other antineoplastic agents																							
mitomycin C	L01DC03	other cytotoxic antibiotics																							

Note: Dark blue = not approved i.e. no marketing authorisation for this indication or not (yet) launched; medium blue = approved but not covered; light blue = approved and covered; white = no data provided.

* product/indication pair on 21st *WHO Model List of Essential Medicines* (2019[63]); † product/indication pair has been approved in the United States since 2014; § There is no central marketing authorisation at EU level for this product/indication pair.

For EU members states (and Norway), when a medicine appears as "approved" in one country and "not approved" in another country, it might mean either 1) that the product has been approved before 1995 through national procedures (before systematic centralised marketing authorisation of all oncology medicines); or 2) that the product, although authorised for marketing in all EU countries, has not (yet) been launched on the market in that country for that indication.

Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Table A C.4. Regulatory approval and coverage status of medicines for *melanoma*

Active substance	ATC Code	ATC-4 Level	AUS	BEL	CHE	CHL	CYP	CZE	DEU	DNK	EST	FRA	GBR	GRC	HUN	IRL	ISR	JPN	KOR	LTU	LVA	MLT	NOR	SWE	USA
interferon	L03AB	interferons																							
high-dose il-2 - aldesleukin	L03AC01	interleukins																							
ipilimumab	L01XC11	monoclonal antibodies																							
nivolumab*†	L01XC17	monoclonal antibodies																							
pembrolizumab*†	L01XC18	monoclonal antibodies																							
fotemustine	L01AD05	nitrosoureas																							
binimetinib†	L01XE41	protein kinase inhibitors																							
cobimetinib†	L01XE38	protein kinase inhibitors																							
dabrafenib	L01XE23	protein kinase inhibitors																							
encorafenib†	L01XE46	protein kinase inhibitors																							
trametinib	L01XE25	protein kinase inhibitors																							
vemurafenib	L01XE15	protein kinase inhibitors																							
dacarbazine	L01AX04	other alkylating agents																							
temozolomide	L01AX03	other alkylating agents																							
talimogene laherparepvec†	L01XX51	other antineoplastic agents																							

Note: Dark blue = not approved i.e. no marketing authorisation for this indication or not (yet) launched; medium blue = approved but not covered; light blue = approved and covered; white = no data provided.

* product/indication pair on 21st *WHO Model List of Essential Medicines* (2019[63]); † product/indication pair has been approved in the United States since 2014.

For EU members states (and Norway), when a medicine appears as "approved" in one country and "not approved" in another country, it might mean either 1) that the product has been approved before 1995 through national procedures (before systematic centralised marketing authorisation of all oncology medicines); or 2) that the product, although authorised for marketing in all EU countries, has not (yet) been launched on the market in that country for that indication.

Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Table A C.5. Regulatory approval and coverage status of medicines for *multiple myeloma*

Active substance	ATC Code	ATC-4 Level	AUS	BEL	CHE	CHL	CYP	CZE	DEU	DNK	EST	FRA	GBR	GRC	HUN	IRL	ISR	JPN	KOR	LTU	LVA	MLT	NOR	SWE	USA
doxorubicin*	L01DB01	anthracyclines and related substances																							
interferon alfa-2b	L03AB	interferons																							
daratumumab†	L01XC24	monoclonal antibodies																							
elotuzumab†	L01XC23	monoclonal antibodies																							
cyclophosphamide*	L01AA01	nitrogen mustard analogues																							
melphalan*	L01AA03	nitrogen mustard analogues																							
bortezomib*	L01XX32	other antineoplastic agents																							
carfilzomib	L01XX45	other antineoplastic agents																							
ixazomib†	L01XX50	other antineoplastic agents																							
panobinostat†	L01XX42	other antineoplastic agents																							
plerixafor	L03AX16	other immunostimulants																							
lenalidomide*	L04AX04	other immunosuppressants																							
pomalidomide	L04AX06	other immunosuppressants																							
thalidomide*	L04AX02	other immunosuppressants																							

Note: Dark blue = not approved i.e. no marketing authorisation for this indication or not (yet) launched; medium blue = approved but not covered; light blue = approved and covered; white = no data provided.

* product/indication pair on 21st *WHO Model List of Essential Medicines* (2019[63]); † product/indication pair has been approved in the United States since 2014.

For EU members states (and Norway), when a medicine appears as "approved" in one country and "not approved" in another country, it might mean either 1) that the product has been approved before 1995 through national procedures (before systematic centralised marketing authorisation of all oncology medicines); or 2) that the product, although authorised for marketing in all EU countries, has not (yet) been launched on the market in that country for that indication.

Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Table A C.6. Regulatory approval and coverage status of medicines used as *supportive care*

Active substance	ATC Code	ATC-4 Level	AUS	BEL	CHE	CHL	CYP	CZE	DEU	DNK	EST	FRA	GBR	GRC	HUN	IRL	ISR	JPN	KOR	LTU	LVA	MLT	NOR	SWE	USA
filgrastim*	L03AA02	colony stimulating factors																							
lipegfilgrastim	L03AA14	colony stimulating factors																							
pegfilgrastim	L03AA13	colony stimulating factors																							
dexamethasone*	H02AB02	corticosteroids																							
prednisolone*	H02AB06	corticosteroids																							
calcium folinate – leucovorin*	V03AF03	detoxifying agents for antineoplastic treatment																							
epoetin alfa	B03XA01	other antianaemic preparations																							
epoetin zeta	B03XA02	other antianaemic preparations																							

Note: Dark blue = not approved i.e. no marketing authorisation for this indication or not (yet) launched; medium blue = approved but not covered; light blue = approved and covered; white = no data provided.

* product/indication pair on 21st *WHO Model List of Essential Medicines* (2019[63]); † product/indication pair has been approved in the United States since 2014.

For EU members states (and Norway), when a medicine appears as "approved" in one country and "not approved" in another country, it might mean either 1) that the product has been approved before 1995 through national procedures (before systematic centralised marketing authorisation of all oncology medicines); or 2) that the product, although authorised for marketing in all EU countries, has not (yet) been launched on the market in that country for that indication.

Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines.

Annex D. OECD survey – cost sharing requirements

Table A D.1. Patient cost-sharing requirements for oncology medicines and medical services potentially including the administration of an oncology medicine

This table includes information on patient cost-sharing requirements for each country. It is based on information collected by the OECD as part of the *Health Systems Characteristics Survey* in 2012 and 2016. It has been updated with country responses to the survey focused on access to oncology medicines.

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
Australia	Co-payment per item of AUD 41.00, reduced to AUD 6.60 for patients with concession card.	Free at the point of care for patients treated as public patients in public hospital. Patients treated as private patients in public or private hospitals have to pay a share of the cost, often paid by their private health insurance (with some services being partly funded via the Medicare system).	Outpatient specialist contacts are fully covered when provided in public hospitals, and generally covered with a 20% co-insurance when provided outside hospitals and financed by Medicare.	Co-payment reduced to AUD 6.60 for patients with concession card (low income). Reduction or exemptions for people with certain medical conditions and disabilities and for seniors; for children, war veterans and eligible Aboriginal and Torres Strait Islander patients.	Cap on OOPs for medicines: - When OOPs reach AUD 1486.80 (~1.8% of average wage), patients are entitled to concession card. - After that, annual cap of AUD 316.80 (~0.4% of average wage) for concession card holders. Separate safety nets exist for services other than medicines. Cap on out-of-pocket costs for outpatient services covered by Medicare (i.e. services provided by GPs, specialists, private clinics and private emergency departments). Beyond an expenditure threshold, which varies with income and family situation (between approximately AUD 690 and 2200), Medicare pays 80% of the out-of-pocket costs. People on low incomes qualify for this Safety Net at a lower threshold.

54 In many countries, pregnant women are exempted from cost-sharing for all care related to pregnancy. We did not include this information as it does not relate to cancer care.

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
Belgium	Cost-sharing ranging from 0% up to 100% according to drug category (drugs of high therapeutic value used in the treatment of severe diseases – diabetes, cancer – are free of charge but a co-payment is applied for other categories); patient status (preferential or not) and ex-factory price of the drug.	Co-payment per day, plus the costs of some non-reimbursable medical products or pharmaceuticals.	Co-payments between EUR 3.00 and EUR 12.00, depending on service type and patient status (GMD/preferential reimbursement). In general, patients pay the full price and are reimbursed afterwards.	Children, seniors and patients with certain medical conditions are exempted from co-payments for outpatient specialist care and inpatient care. Vulnerable populations are also exempted from co-payments and "up-front costs".	Annual cap on cost-sharing. The amount depends on the annual income. Additional measures are foreseen for patients with preferential reimbursement, children (up to 18 years old) and chronically ill.
Canada	Varies across health insurance plans.	Free at the point of care.	Free at the point of care.	Most provincial and territorial governments fund a range of supplementary benefits that are not covered under the Canada Health Act for certain groups (incl. low-income residents). Outpatient-pharmaceuticals are covered in some provinces for all residents, while others focus on particular groups, incl. those on social assistance.	
Cyprus	Cancer therapy is provided free of charge to all patients whose annual income does not exceed EUR 135 000.00. Other patients cover all pharmaceutical expenditures by their own or from a private insurance.	Cancer therapy is provided free of charge to all patients whose annual income does not exceed EUR 135 000.00. Other patients cover all pharmaceutical expenditures by their own or from a private insurance.	Cancer therapy is provided free of charge to all patients whose annual income does not exceed EUR 135 000.00. Other patients cover all pharmaceutical expenditures by their own or from a private insurance.	Cancer therapy is provided free of charge to all patients whose annual income does not exceed EUR 135 000.00. Other patients cover all pharmaceutical expenditures by their own or from a private insurance.	
Czech Republic	Co-payment of any difference between pharmacy retail price and reimbursement price.	Free of charge	Free of charge	Exemptions for some groups of patients (patients receiving social benefits, children living in orphanages, *etc.*) in paying emergency/dental emergency visit fee. There are various age-related reductions of co-payments (annual caps) on partially reimbursed pharmaceuticals (see next column).	Annual caps on co-payments on partially reimbursed pharmaceuticals: ≤18 years – EUR 40 19–64 years – EUR 198 65–69 years – EUR 40 ≥70 years + 2nd and 3rd level of disability – EUR 20.

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
Denmark	Deductible of DKR 980 beyond which co-insurance rate applies, diminishing stepwise as spending increases (50%, 25%, 15%).	Free at the point of care.	Free at the point of care.	Reduction or exemptions of co-payments on pharmaceuticals for people with certain medical conditions and disabilities and for seniors.	Annual cap for pharmaceuticals of DKK 4110 (~1% of average wage). Other services of medical diagnostic and curative care are virtually free of charge.
Estonia	For general prescription medicines, co-payment of EUR 2.50 per prescription, and co-insurance of at least 50%. For prescription medicines for chronic diseases, co-payment of EUR 2.50 per prescription, and co-insurance of 0 to 25%.	Co-payment of EUR 2.50 per day, up to 10 days per episode. Co-payments charged for above-standard accommodation.	Co-payment of EUR 5.00 for visits to specialists contracted with the health insurance fund, with a GP referral (exceptions are dermato-venerologist, gynecologist and psychiatrist where no GP referral required). Visits without referral are not reimbursed. Specialists not contracted with health insurance determine their fees.	Reduced co-insurance (10%) on prescription medicines for chronic diseases for people with disability benefits or pensioners over 63 or children up to 16 years. Children under 18 exempted from co-payments for inpatient care. Children under 4 only pay EUR 2.50 per prescription medicine and no co-insurance.	Complementary reimbursement applies when patients cost-sharing is over EUR 100.00 per year (50% of costs exceeding the EUR 100.00 will be reimbursed) and 90% of costs exceeding EUR 300.00 per year will be reimbursed complementary)
France[55]	Co-insurance of 0%, 35%, 70%, 85%, depending on drug category, plus co-payment of EUR 0.5 per item. For some medicines subject to reference prices, any difference between retail price and "reference price" is paid by the patient.	Co-insurance of 20%, not applicable for diagnostic or surgical procedures whose cost exceeds a certain threshold (EUR 120). Co- payment of EUR 20/day for acute in-patient care.	Co-payment of EUR 1 fee per consultation, plus cost-sharing of 30% with a GP referral, 70% otherwise. Patients may be exposed to extra-billing (allowed for 45% of private specialists). Patients pay the full price and are reimbursed afterwards.	Patients with malignant tumour or malignant affection of lymphatic or hematopoietic system are exempted from co-payments for all treatments related to this condition. People benefitting from a disability pension are fully covered for treatment of illness.	No
Germany	Co-insurance of 10% of cost with a minimum of EUR 5 and a maximum of EUR 10 per item; co-payment cannot exceed the total drug price. For medicines subject to reference prices, any difference between retail price and "reference price" is paid by the patient.	Co-payment of EUR 10 /day, limited to 28 days/year.	Free at the point of care for patients with statutory health insurance and patients with selected private health insurance contracts.	Chronically ill and patients with disabilities have a lower cap on co-payments. Children are exempt from all co-payments.	Co-payments are capped at 2% of gross household income, reduced to 1% for the chronically ill.

[55] In France, more than 95% of the population is covered by complementary insurance, which often covers co-payments left by social health insurance.

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
Greece	Statutory co-insurance of 0%, 10% or 25% depending on drug category. Medicinal products for cancer and its consequences are fully covered. For medicines subject to reference prices, any difference between retail price and "reference price" is paid by the patient, up to 20€. 1€ prescription fee is also applied in private pharmacies.	Free of charge for patients treated in public hospitals. High-cost medicinal products for cancer are provided free of charge from EOPYY to private clinics. Higher level of cost-sharing and potential extra-billing for patients in private hospitals.	Free at the point of care for public providers.	Some Chronically ill and patients with paraplegia, tetraplegia have exemptions for pharmaceutical cost-sharing. Patients belonging to low income/vulnerable groups are exempted from co-payments for pharmaceuticals. Women during pregnancy and lactation are exempted from co-payments on pharmaceuticals.	
Hungary	Co-payment of HUF 200 per pack. Any difference between retail price and "reference price" for products subject to reference pricing.	Free at the point of care.	Free at the point of care.	Reduction or exemption for people with certain medical conditions and disabilities.	Entitlement to free pharmaceuticals for those whose medical expense exceeds 10% of the minimum pension (for households with income per capita < minimum pension = EUR 100 in 2010).
Ireland	For medical card holders: Under the age of 70 years there is a prescription charge of €2 for each item, up to a maximum of €20 per month, for each person or family. Over 70 years, the prescription charge is €1.50 for each item, up to a maximum of €15 per month, for each person or family. For other groups, deductible of EUR 124 per family and per month before full reimbursement	Free at the point of care for medical card holders and certain other categories. Co-payment of EUR 80 per day for public patients, capped at EUR 800 in any period of 12 consecutive months.	Attendances at planned outpatient clinics in public hospitals are free at the point of care for public patients. Patients attending an emergency department are subject to a EUR 100 charge subject to a number of exemptions.	Exemption for outpatient specialist care and pharmaceuticals for patients with certain medical conditions or disabilities (eligibility for Medical Card). 40% of the population is entitled to the preferential status with no or lower co-payments for health services (Eligibility for Medical Card; Low-income, elderly, students, foster-care children etc.). Children and Students up to 25 are exempt from co-payments for acute inpatient care, outpatient specialist contacts and pharmaceuticals. Pregnant women are exempt for acute inpatient care and outpatient specialist contacts.	Annual cap on inpatient care, primary care and pharmaceuticals, as indicated in relevant columns.

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
Israel	Patients pay a co-payment fee based on a three tier plan starting from a minimum of 17 ILS, to 10-15% of the public maximum price. Quarterly caps and discounts apply for certain target populations: elderlies, patients with HIV, Cystic Fibrosis, cancer, tuberculosis, etc.	Free at the point of care.	Co-payment of approximately ILS 25 once every quarter.	Reduction or exemptions for people with certain medical conditions and disabilities; for low-income patients and recipients of social benefits. Exemptions for holocaust survivors and those with disabilities due to active resistance to the Nazi regime, as well as victims of traffic accidents.	Annual cap on inpatient and outpatient primary care.
Italy	Co-payment per prescription or per package determined at regional level Patients wishing to get a higher-priced medicine (e.g. an originator brand) have to pay the difference between the reference price and the pharmacy retail price	Free at the point of care for patients treated as "public" patients in public and private hospitals.	Facilities and services included in the national health care entitlements ("*Livelli essenziali di assistenza*"(LEA)) have a co-payment of up to EUR 36.15 + EUR 10 fixed cost per prescription[56] defined by the National legislation, which varies regionally (some regions do not apply it).	Reduction or exemptions for people with certain medical conditions and disabilities and for seniors under designated income thresholds. Reduction or exemptions for low-income patients and patients receiving social benefits. Reductions or exemptions for children under a certain income threshold.	
Japan	Co-insurance rate of 30% of costs.	Co-insurance of 30% of costs.	Co-insurance of 30% of costs.	Co-insurance rates reduced to: - 20% for infants and children before the school-age; - 20% for people aged 70-74 and 10% for people over 75 years, unless their income exceeds an annual threshold The recipients of public assistance benefits are exempted from paying the co-insurance.	Monthly cap depending on age and income
Korea	Co-insurance of 30% (reduced to 5% for patients with severe diseases, incl. cancer).	Co-insurance of 20%, reduced to 5% for cancer-related medical services provided for severe diseases Co-insurance of 50% for meals, 10-50% for	Co-insurance rate varies according to hospital type (60% for tertiary hospitals; 50% for general hospitals: (reduced to 45% in rural area); 40% in other hospitals (35% in rural area)	Co-insurance rates reduced for patients with severe illness (incl. cancer), see relevant categories. In addition, Medical Care Cost Support programmes provide subsidies to high-risk patients (disease	Cap on annual cost-sharing, depending on income level (KRW 2 to 4 million, i.e. 5-10% of average annual wage).

[56] This extra-ticket ("super ticket") will be removed from September 2020, according to a recent decision that will be included in the budget law.

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
Korea (cont.)		accommodation, depending on room type, 50~80% for oriental medical services, 30~90% for benefits with provisional coverage.	Co-insurance of 30% in doctors'. Co-insurance reduced to 5% for patients with cancer; except for 50~80% for oriental medical services, 30~90% on benefits with provisional coverage.	included in a list of 132) whose income is below 300% of the established minimum cost of living, or who are enrolled in the nation-wide Medical Aid programmes. Seniors (>65) have reduced cost-sharing for primary care consultations. Children are exempt from co-payment for acute inpatient care, outpatient specialist care, and pharmaceuticals. Patients under a certain income threshold have reduced cost-sharing. Low income patients with cancer pay no co-insurance, except for meals (20%), benefits with provisional coverage (30~90%), and cost-sharing for accommodation (30-50% depending on room type), and for oriental medical services (30~80%).	
Latvia	Co-insurance rate of 50%, 25% or 0% % for drugs used for chronic diseases and included in the Positive list. A co-payment of EUR 0.71 per prescription applies when the medicine is fully reimbursed. Any difference between retail price and reference price for products subject to reference pricing is paid by the patient.	Free at the point of care.	Free at the point of care.	No co-payment for children up to 18 years, vulnerable people, and asylum seekers, except any difference between retail price and reference price for products subject to reference prices. 50% reimbursement for all nationally registered prescription medicines (beyond those listed in the positive list) for children up to 24 months.	

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
Lithuania[57]	No co-payment for medicines included in list A, used to treat specific conditions, including cancer. Other medicines (List B) are fully paid by patients, unless they are children, people with severe disabilities and people with specific conditions (no co-insurance) or for pensioners and people with less severe disabilities and reduced capacity to work (50% co-insurance). Patients may have to pay the difference between retail price and reimbursed price, with a cap of EUR 4.71 per prescription.	Free for patients treated in public hospitals.	Free at the point of care for public providers	No	No
Malta	No cost sharing. Free at point of care for all patients entitled according to the Social Security Act and Government Formulary List policies and entitlement protocols.	No cost sharing. Free at point of care for all patients entitled to free health care and according to the Social Security Act and Government Formulary List policies and entitlement protocols.	No cost sharing. Free at point of care for all patients entitled to free health care and according to the Social Security Act and Government Formulary List policies and entitlement protocols.	Not applicable	Not applicable
Norway	Co-insurance rate of 39%, capped to NOK 520 per prescription, with total patient cost-sharing (for all services) capped at NOK 2 369 in 2019. All anti-cancer drugs are financed by hospitals and free of charge for the patient.	Free at the point of care. Also includes outpatient care (tablets and injections) where hospitals are responsible for treatment. All anti-cancer drugs are financed by hospitals.	Annual ceiling for total user charges of NOK 2 369 in 2019.	Chronically ill and those with disabilities have reductions or exemptions from co-payment for outpatient specialist care. Certain groups of pensioners/retirees in Norway are exempted from co-payments on prescriptions which are reimbursed by the state. Children and victims of occupational injuries or diseases are exempted from co-payments.	Annual cap (ceiling 1) of NOK 2 369 (0.4% of average wage) in 2019 for the combination of expenses on pharmaceuticals, consultations with primary care physicians, psychologists and psychiatrists, outpatient services in hospitals, physiotherapists, laboratory tests, x-rays. Another annual cap of NOK 2 085 in 2019 (ceiling 2) includes physical therapy, some forms for dental treatment that are subject to reimbursement and accommodation fees at rehabilitation centres and treatment abroad.

[57] From the Lithuanian Health Profile (OECD/European Observatory on Health Systems and Policies, 2019)and survey response.

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
Sweden	Deductible of SEK 1 150 (€ 105), beyond which co-insurance applies, diminishing stepwise (50%, 25%, and 10%). Patient annual OOP spending is capped to SEK 2 300.	Co-payment determined by each region, approx. SEK 100 per day.	Co-payment determined by each region, between SEK 230 and 350, with an annual cap on cost-sharing for outpatient care of SEK 1 150.	Those with certain medical conditions and disabilities; and children, are exempted for all cost-sharing. Low-income people are entitled to reduced hospital co-payments in some countries.	Annual cap for all cost-sharing requirements. Annual cap on co-payments for pharmaceuticals, set at SEK 2 300 (~0.5% of average annual wage).
Switzerland	Co-insurance of 10% up to an annual cap once the general deductible has been met. The deductible varies across insurance plans within a range of CHF 300 to CHF 2 500 per year Co-payment is increased to 20% for off-patent drugs with cheaper (generic) alternatives.	Co-insurance of 10% after deductible, subject to annual cap. + Contribution to the costs of a hospital stay of CHF 15.00 per day. Children, young adults up to the age of 25 in training and women receiving maternity benefits are exempt from the hospital contribution.	10% cost-sharing after general deductible, with an annual cap.	Children under 18 have no deductible.	Patients' co-payments capped at CHF 700 (~0.8% of average wage) for an adult and CHF 350 for a child under 18 years.
United Kingdom (England only)	Co-payment of GBP 9 per prescription, no co-payment for cancer patients.	Free at the point of care.	Free at point of care.	The following categories are exempted from prescription fees: seniors and those affected with certain diseases, low-income people, children and pregnant women. Other medical diagnostic and curative services are typically free of charge. Low income groups receive further assistance via the NHS Low Income Scheme, which covers notably prescriptions, and health care related travel costs.	
United States[58]	Cost-sharing requirements vary across health insurance plans. Medicare beneficiaries can obtain coverage for self-administered medicines through Medicare Part D. Part D sponsors offer plans with either	Cost-sharing requirements vary across health insurance plans. Medicare beneficiaries can obtain coverage for medicines through Medicare Part A. In 2020, Medicare Part A, enrollees face a deductible of USD 1,408 for each hospital admission	Cost-sharing requirements vary across health insurance plans. Medicare beneficiaries can obtain coverage for certain medicines and their administration through Medicare Part B. In 2019 Medicare, enrollees face a USD 185 annual deductible and then, 20% of	Medicaid programmes may impose cost-sharing (co-payments, co-insurance and deductibles), which vary in nature and amount depending on income[59]. Additionally, in Medicare Part D, beneficiaries with lower incomes are eligible	Most Medicare and Medicaid programmes have co-payments and deductibles, with exemptions for people who have paid for health expenditure above a certain threshold. In employer-sponsored health insurance plans, 99% of enrollees have cost-sharing caps. In

[58] Information on employer-sponsored health insurance extracted from (Claxton *et al.*, 2019).

[59] https://www.medicaid.gov/medicaid/cost-sharing/out-of-pocket-costs/index.html

Country	Pharmaceuticals dispensed to patients for self-administration	Hospital inpatient care for cancer including the administration of a medicine	Outpatient specialist cancer services including the administration of a medicine	Exemptions or reductions of co-payments for some population groups[54]	Annual cap for cost-sharing
United States (cont.)	a defined standard benefit or an alternative equal in value ("actuarially equivalent"), and can also offer plans with enhanced benefits. The standard benefit in 2020 has a USD 435 deductible and 25% coinsurance up to an initial coverage limit of USD 4,020 (~6.4% of average wage) in total drug costs, followed by a coverage gap. During the gap, enrollees pay a 25% coinsurance until their total true out-of-pocket spending reaches USD 6 350 (~10.1% of average wage). Thereafter, enrollees pay either 5% of total drug costs or USD 3.60/USD 8.95 for each generic and brand-name drug, respectively. In 2019, in employer-sponsored health insurance plans, 86% of covered workers face a deductible (USD 1,200 for single coverage). 91% of workers have plans with "tiered cost-sharing" for prescription drugs, with different average monthly co-payments across drug categories. In plans with 3 or more tiers of cost-sharing, co-payments are, on average: USD 11 for generics, USD 33 for "preferred drugs", USD 59 and USD 123 for drugs of the third and fourth tiers. In plans where cost-sharing takes the form of co-insurance, the average rates are respectively 18%, 24%, 34% and 29% for the first, second, third and fourth tiers.	and then no cost-sharing up to 60 days. Then, a co-payment of USD 352 per day applies up to the 90th day. Once in lifetime, patients can benefit from a per diem co-payment of USD 704 for an additional 60 days. After this, patients have to pay the full costs of inpatient care. In employer-sponsored health insurance plans, and after deductible, most workers face user charges when hospitalised (sometimes in addition to the general deductible): 66% pay co-insurance (20% on average); 14% pay fixed co-payments (USD 326 per hospital admission on average), 7% pay both types, and 5% per diem co-payments (USD 475 on average). 15% of insured have no additional cost-sharing after the general deductible has been met	Medicare-approved payment (plus 15% extra-billing if the provider does not accept Medicare rates). In certain situations, for example if providers do not agree to accept Medicare payment, or do not participate in Medicare, beneficiaries may have to pay higher amounts. Beneficiaries may also buy supplemental insurance coverage to help pay for Part B cost sharing amounts. In employer-sponsored health insurance plans, 72% of covered workers have a co-payment for a primary care office visit (USD 35 on average) and 20% have co-insurance (19% on average). In employer-sponsored plans, after deductible, 66% of patients pay fixed co-payment per visit (USD 40) and 26% pay co-insurance (19% on average). 5% pay no cost-sharing.	for low-income subsidies that significantly reduce patient cost-sharing.	individual plans, 29% of covered workers have a cap below USD 3,000 (~4.8% of average wage) and 20% a cap of USD 6 000 (~9.5% of average wage) or more.

Note: OOP out-of-pocket payments, GP general practitioner, EOPYY National Organization for the Provision of Health Services (Greece), HIV human immunodeficiency virus
Source: Authors based on 2019 OECD survey on challenges in access to oncology medicines and (Auraaen et al., 2016[80]).

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