OPINION

The high price of anticancer drugs: origins, implications, barriers, solutions

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Abstract | Globally, annual spending on anticancer drugs is around US$100 billion, and is predicted to rise to $150 billion by 2020. In the USA, a novel anticancer drug routinely costs more than $100,000 per year of treatment. When adjusted for per capita spending power, however, drugs are most unaffordable in economically developing nations, such as India and China. Not only are launch prices high and rising, but individual drug prices are often escalated during exclusivity periods. High drug prices harm patients — often directly through increased out-of-pocket expenses, which reduce levels of patient compliance and lead to unfavourable outcomes — and harms society — by imposing cumulative price burdens that are unsustainable. Moreover, high drug prices are not readily explained by rational factors, including the extent of benefit patients are likely to derive, the novelty of the agents, or spending on research and development. Herein, we summarize the available empirical evidence on the costs of anticancer drugs, probe the origins and implications of these high costs, and discuss proposed solutions.

The cost of anticancer drugs is increasingly being recognized as a global problem. In the USA, the average price of a novel anticancer drug routinely exceeds US$100,000 per year or course of treatment[1]. The absolute prices of many anticancer drugs are highest in the USA compared with those in other countries. When national drug prices are compared with per capita spending power in the same country, however, anticancer drugs are most unaffordable in economically developing nations, such as India and China[2].

Oncology drugs account for the largest spending of any specialty[3], and the global anticancer drug market, which currently exceeds US$100 billion per annum, is expected to grow to $150 billion by 2020 (REF. 4); patients in the USA account for nearly half (46%) of this market[5]. The growth in cancer drug prices is expected to exceed the growth in total cancer spending. From 2010–2020, total expenditure is estimated to increase by 26%[6], while expenditure on anticancer drugs surpasses this, rising by 50%[4].

Just 20 years ago, paclitaxel became the first anticancer drug with sales in excess of $1 billion annually[7]. By contrast, in 2013, the 10 highest-earning anticancer drugs had global sales ranging from $1.8 billion to $7.8 billion annually[8]. A comparison of the costs of 1 month of therapy among the 10 highest-earning cancer drugs between the USA and Norway illustrates the differences in both the price and affordability of these agents (FIG. 1). Prices of these drugs in the USA are consistently higher than those in Norway, despite similar median monthly incomes. Furthermore, broader variability in global drug prices is known to exist, as illustrated by a survey of prices in 16 European countries, Australia, and New Zealand, which shows variations in ex-factory prices of anticancer drugs of 28–388%[9] between these economically developed nations.

An analysis of changes in anticancer drug prices over time indicates that the median launch price of new drugs has increased in each decade from the 1960s to today[10]: from $100 to $10,000 per month of treatment[10]. Consider, as an example, the anti-programmed cell death protein 1 (PD-1) antibody pembrolizumab, a novel immunotherapeutic drug, for which administration to treat one person for 1 year (at a dose of 10 mg/kg) can now cost in excess of $1 million[11]. The trends in median launch prices of all anticancer drugs in the USA, relative to median household income from 1975–2014, demonstrate that while incomes have stagnated, prices have soared (FIG. 2).

Inflation-adjusted analyses show that the price of patented anticancer drugs is often increased after launch, by as much as 44% over the course of a decade[12]. An analysis of data on outpatient spending shows that median monthly spending on thalidomide and imatinib, for example, increased from $1,869 to $7,564 and $3,346 to $8,479, respectively[13] over 13–14 years. In both examples, prices have climbed despite the availability of similar, but more-advanced, next-in-class drugs (such as lenalidomide, dasatinib and nilotinib), and alternative classes of medications (such as bortezomib and omacetaxine). An inflation-adjusted analysis of all cancer drugs covered in Medicare Part B (a medical insurance plan that covers treatment services in a physician's office or outpatient setting for eligible US residents typically aged ≥65 years), including both patented and off-patent drugs, shows that from 2010 to 2015, 64% of drugs increased in price, with 12.7% increasing by more than 100% over this 5-year period[14].

Public payers have noted an increase of 367% in expenditure on all drugs covered by Medicare Part B, from $3 billion in 1997 to $18.5 billion in 2014 (REFS 10,15). In fact, oncology drug spending accounted for 42% of the Medicare Part B expenditures in 2014 (REF. 14). Medicare Part B is restricted to drugs administered in a physician's office or infusion centre, while an examination of total spending on drugs reveals that Medicare Part B expenditures account for 19% of all Medicare expenditures; however, precise figures are not available specifically
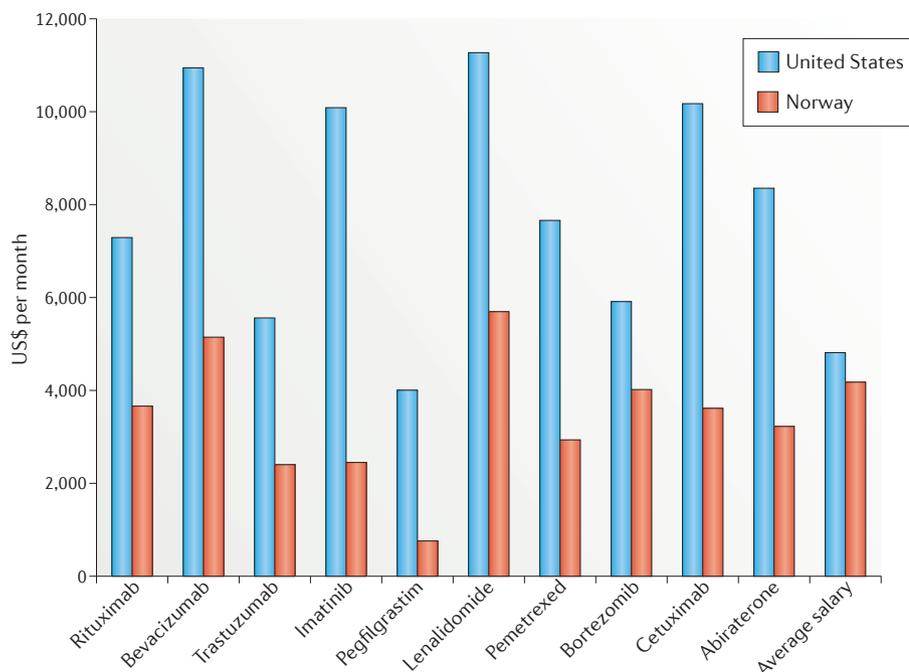
Figure 1 | **Cost of one month of treatment with the top 10 bestselling anticancer drugs in the USA[10] and Norway[127].** Drug prices are calculated for an adult weighing 70 kg, with a body surface area of 1.7 m². For drugs reimbursed through the Medicare part B programme, we obtained the average sales price (ASP) from the Centers for Medicare and Medicaid services[128]; for drugs reimbursed through Medicare part D, we obtained the 'full cost of the drug' (REF. 129).

for anticancer drugs[16]. These increases in the price of anticancer drugs stand in contrast to the prices of other goods. For example, during the CARDIA study, the price of milk and restaurant hamburgers remained stable over a 20-year period[17].

The excessive costs of anticancer drugs have been criticized by >100 experts in haematological malignancies[18], and by 118 oncologists of all specialties[19]. Thus, the cost of anticancer drugs is clearly rising, this rise exceeds changes in prices in many other sectors of the economy, and the physicians that routinely administer these drugs to patients find these trends concerning. These issues are global concerns, although certain challenges facing patients and physicians in the USA are unprecedented, and warrant special consideration.

Value
The costs of anticancer drugs cannot be discussed without some consideration of the average benefit derived from treatment with these drugs, which unfortunately often remains marginal. Fojo and colleagues[20] found, in an analysis of 71 consecutive anticancer drugs approved for the treatment of patients with solid tumours between 2002 and 2012, that the median improvement in the duration of overall survival and

progression-free survival (PFS) was 2.1 months and 2.3 months, respectively[20]. In an analysis of 47 FDA anticancer drug approvals made between April 2014 and February 2016, only 9 (19%) met the modest standard of meaningful clinical benefit regarding overall survival set by ASCO[21], and in an analysis of 226 randomized trials, only 70 (31%) met the threshold of providing meaningful benefit proposed by ESMO[22]. Moreover, these marginal results have often come from pivotal randomized controlled trials that have supported the regulatory approval of these drugs. Some studies suggest that the benefits of these agents in a 'real world' patient population are even smaller than those observed in patients enrolled in clinical trials, given the generally older age and greater number of comorbidities among most real-world patients with cancer than in the carefully selected participants in clinical trials[23–26]. Of note, both ASCO and ESMO are currently incorporating value into their guidelines for the design and implementation of future clinical trials[21,27].

Given that the costs of anticancer drugs are high and that the benefits are typically limited, well-conducted analyses unsurprisingly indicate that many new anticancer drugs offer cost-effectiveness ratios that are immensely skewed in the

direction of cost. For instance, the cost-effectiveness ratio of regorafenib for the treatment of patients with metastatic colorectal cancer is $900,000 per quality-adjusted life year (QALY)[28]. Similarly, pertuzumab for those with metastatic breast cancer costs $710,000 per QALY[29], bevacizumab for patients with metastatic colorectal cancer costs >$500,000 per QALY[30], and necitumumab for those with metastatic squamous-cell lung cancer costs >$800,000 per QALY[31]. Even the most transformative drugs, such as imatinib, which nearly restores patient's life expectancies to that of the general population[32], costs $71,000 per QALY under the assumption of an annual cost of $79,000 (REF. 33). With the possible exception of imatinib, these figures exceed any and all thresholds of reasonable cost-effectiveness applied in the USA, the UK, and in every other nation on earth[31].

Analyses can be found that generally reach more-favourable cost-effectiveness estimates for anticancer drugs than those described above; however, these often have methodological limitations. For instance, an analysis by Saret et al.[34], using data from the Tufts Cost Effectiveness Analysis Registry, found that most drugs used to treat haematological cancer had cost-effectiveness ratios that fell below $50,000 per QALY (73%) or $100,000 per QALY (86%), two traditional thresholds for cost-effectiveness[34]. Subsequently, several limitations of this analysis have been identified[35,36]. Firstly, the analysis failed to include updated drug prices — given that prices generally increase after launch, updated pricing figures can alter cost-effectiveness calculations. Secondly, prices of drugs from outside the USA were used for calculations, although the final cost-effectiveness calculation was made in US$ (as opposed to calculations performed using US prices). Thirdly, the analysis relied on published cost-effectiveness analyses that might be selectively reported and might not constitute a systematically selected set of drugs. Fourthly, the analysis predominantly summarizes data from cost-effectiveness analyses sponsored by the pharmaceutical industry (22 of 29; 76%), which have been shown to yield more-favourable estimates than similar analyses that lack such conflicts of interest[37]. Finally, the analysis[34] used estimates of efficacy that were often assumed, rather than those that have been explicitly demonstrated, and subsequent trial follow-up data has failed to validate some of these assumptions[36].

After correcting for the first and second limitations described in the previous paragraph, independent authors found that only 9 of the 24 drugs (37.5%) analysed had cost-effectiveness ratios below $50,000 per QALY[35], and by examining the cost-effectiveness of anticancer drugs in a systematic fashion, Howard and colleagues[38] found that just 20 of 58 drugs (34%) had cost-effectiveness ratios of $100,000 or lower per QALY. Thus, in assessing the cost-effectiveness of anticancer drugs, caution is warranted.

Where do high anticancer drug prices come from? A common justification for the high price of drugs, particularly anticancer drugs, is that the research and development (R&D) outlay required to develop and test these products is high. In a highly publicized analysis, researchers at Tufts Medical Center concluded that the total cost of developing a new pharmaceutical drug is approximately $2.6 billion[39,40]. This figure has been criticized, however, owing to a lack of transparency (the group does not disclose the specific products studied) and methodology — half of the $2.6 billion figure seems to be speculated earnings had the investment been placed in the hands of money managers[39]. Moreover, other groups have estimated the cost of developing a drug to be more than an order of magnitude lower, at approximately $160 million[41]. Both of these analyses consider the fact that many candidate drugs have to be pursued for only one agent to be approved. In other words, both analyses account for the costs of high failure rates[40].

Some critics argue that the cost of developing a medication is irrelevant to the price[42]. In no business sector is the cost of the product based entirely on the manufacturing cost or the cost of failed research but, rather, the cost is largely based on what a person is willing to pay for the value that the product provides, in the presence of alternative choices[43,42]. The expectations of profit by shareholders is another proffered explanation for the high prices of anticancer drugs, although economists argue that even the most rapacious capitalistic theories balance moral or ethical issues with pricing[44].

Data from empirical analyses suggest that federally funded research has a direct role in the innovation of approximately 10–40% of new drugs[45–47], and that the indirect role of federally funded science is more substantial than this[46]. Frankly, accurately estimating the cost of developing
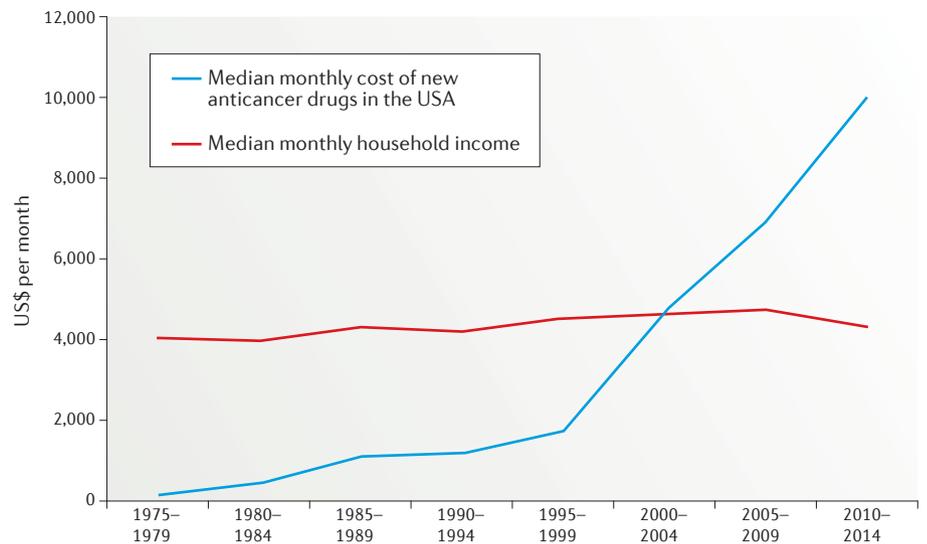

Figure 2 | **Median monthly launch price of a new anticancer drug, compared with median monthly household income from 1975–2014 in the USA.** Data on household incomes were obtained from the 2015 United States Census[130], and drug prices were obtained from Bach & Schnorr[131].

an anticancer drug, and whether and to what extent those costs are borne by public or private payers is currently difficult, if not impossible, without transparency and independent auditing of company records. Despite these difficulties, what is known is that when costs and expenses are balanced, the biopharmaceutical industry continues to report double-digit profit margins[48], suggesting that revenues often substantially exceed outlays. Furthermore, spending on marketing routinely exceeds R&D spending for these companies, and net profits are generally high (FIG. 3).

Some may feel that the focus on drug prices is disproportionate given that, in absolute numbers, more dollars are spent on hospital care[49] (FIG. 4). However, when accounting for profit margins, the absolute profits obtained from sales of prescription drugs exceed the aggregate profits made by hospitals over the same period of time. At first glance, therefore, the ability to achieve health-care savings by targeting drug prices might be substantially greater than the savings that could be made by targeting hospital care.

The findings of empirical analyses struggle to link the high costs of anticancer drugs with any rational considerations. For example, our analysis[1] of 51 drugs that received a total of 63 marketing approvals revealed that the price of anticancer drugs was not explained by their novelty — a measure of more extensive research and development — their basis of regulatory

approval, or their clinical benefit, as measured by PFS and overall survival durations. Instead, the cost of anticancer drugs seems to be driven by what companies believe the market will bear[1,10]. This market ceiling is further inflated owing to the presence of several restrictions on the ability of large payers, such as the Centers for Medicaid and Medicare Services, to exert downward pressure on prices. Specifically, by law, the Center for Medicare and Medicaid Services (CMS)[50] is prevented from negotiating the price of drugs, and must cover any drug that is either approved by the FDA, or that is endorsed by one of several compendia, such as that of the National Comprehensive Cancer Network[51].

The drug market, particularly in the USA, is a complex ecosystem in which prices begin with manufacturers, but are then altered by wholesalers, pharmacies, and pharmacy benefit managers, who themselves are incentivized by various rebates, discounts, and deductions[52]. The net result, however, is that high prices cause harm to both patients and society.

How high anticancer drug prices harm patients. The high price of anticancer drugs has negative consequences for patients with cancer. For example, in the USA, patients with cancer who require treatment that incurs a high level of medical expense might be forced to declare personal bankruptcy. Research by Ramsey and colleagues[53] suggests that a diagnosis of cancer is
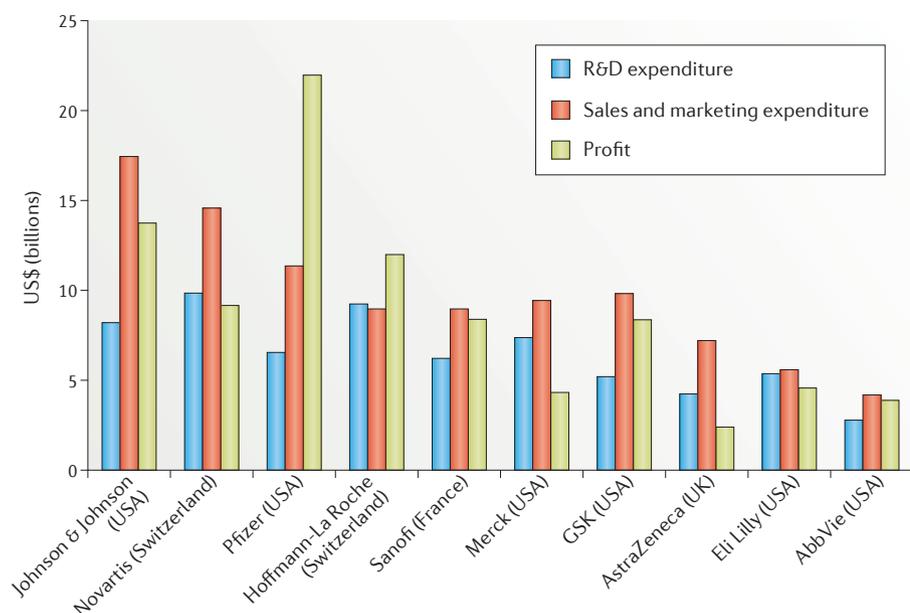
Figure 3 | **Annual profits, and annual expenditure on research and development (R&D) and marketing for the 10 largest pharmaceutical companies in 2013** (REF. 48).

associated with a 2.65 times increased risk of going bankrupt. Subsequent research has demonstrated that bankruptcy can, in turn, have adverse health-related consequences. In a propensity score analysis, Ramsey and colleagues[54] found that the hazard ratio for mortality was 1.79 (95% confidence interval (CI) 1.64–1.96) among patients with cancer who filed for bankruptcy compared with matched individuals who did not. These demanding financial circumstances following a cancer diagnosis increase the risk of bankruptcy, which in turn increases the risk of mortality.

Patients receiving imatinib, a tyrosine-kinase inhibitor (TKI) that is vital to the treatment of chronic myeloid leukaemia, have a longer time to initiation of therapy when they do not have a cost-sharing subsidy[55], and are 42% more likely to discontinue treatment if they had higher (≥75th percentile for cost) co-payments (adjusted risk ratio (aRR) 1.42; 95% CI 1.19–1.69)[56]. Other findings confirm that 10% of all patients receiving a new prescription of an oral anticancer drug fail to collect their drugs from the pharmacy[57]. Such abandonment of medication is associated with having a high level of cost-sharing (>$500 per prescription) and lower income, compared with a lower level of cost-sharing (<$100 per prescription, odds ratio (OR) 4.46; *P* <0.01)[57]. Among Medicare Part D users, the receipt of a low-income subsidy is associated with greater persistence with

anticancer medication than those who are not eligible for such subsidies, despite the fact that those receiving a subsidy are of a lower socioeconomic status than those who do not[58]. Research by other groups has shown that patients who had already filled five or more previous prescriptions are most likely to abandon use of their medications[57]. Patients with non-small-cell lung cancer (NSCLC) receiving erlotinib are more likely to be adherent to therapy if they have lower monthly co-payments (<$30), compared to those with copayments of $45–65 (OR 0.54, 95% CI 0.30–0.96)[59]. The findings of a further analysis suggest that for each $10 increase in out-of-pocket expense, 13% more patients will discontinue or delay their use of an oral anticancer drug[60]. The results of an ESMO survey[61] indicated that cost is also a major barrier to the use of potentially life-prolonging medications in Europe (particularly in the relatively less-economically developed nations of eastern Europe), and many patients do not have access to novel anticancer drugs. In short, a diverse set of research data are available linking the costs of therapy, and the out-of-pocket costs, with the ability to initiate and continue cancer therapy. Non-adherence by patients prescribed oral anticancer drugs risks both negative clinical outcomes of individual patients, and paradoxically, might also raise health-care spending when these patients later present to the hospital with advanced-stage disease.

How high anticancer drug prices harm societies. Beside direct effects on patients with cancer, the costs of anticancer drugs can also have effects on both insurance programmes[9] and, more generally, on the economy of a country[62]. Per capita spending on anticancer drugs has increased in many countries globally[63], and anticancer drug spending is expected to continue to rise to 6–8% more than current costs by 2018 (REF. 64). As an example, the lifetime cost to treat just one patient with chronic lymphocytic leukaemia is estimated to rise from $147,000 to $604,000 between 2011 and 2025 (a 310% increase), which, coupled with an increase in the prevalence of the disease, will push total spending in the USA from an estimated $0.74 billion to $5.13 billion (a 590% increase) for this one type of cancer alone[65]. No national health system anywhere in the world can afford to make all new anticancer drugs available to patients, and even in some economically developed countries (such as Spain or Japan) fewer than half of all newly approved drugs are available to patients[66].

The costs of anticancer drugs are projected to continue to increase; therefore, it is only a matter of time before costs become unsustainable for all world economies. If we routinely allow expenditure on drugs that cost $800,000 per QALY, the total projected cost annually in the USA — if all patients with cancer received treatment with such drugs — would be $440 billion[67]. This figure translates to 18% of current total health care spending for a single, noncurative drug[68]. If we extrapolate the costs of treatment with certain forms of immunotherapy to all patients in the USA who die of cancer annually, the cost of that intervention alone would be $174 billion[11]. In short, if noncurative anticancer drugs were given to all patients with cancer, and if we also allow for such drugs to potentially be given sequentially — as is the common treatment paradigm for most patients with cancer — all nations, even wealthy ones, will be bankrupted.

Already, evidence is emerging that the costs of anticancer drugs are unsustainable. Since being introduced in 2011, the UK Cancer Drug Fund (CDF) has struggled to remain solvent[62]. The CDF was initially created as a way for the UK National Health Service (NHS) to treat patients using anticancer drugs with cost-effectiveness ratios exceeding the thresholds set by the UK National Institute of Health and Care Excellence (NICE). This fund, from the outset, violated the principle of doing

the most good with the available money; therefore, many felt it was counterproductive and antithetical to the NHS model[69]. Over the past 6 years, this fund has progressively grown in magnitude, but increasingly excluded drugs from its list[62], many of which offer more certain or greater benefits than those of most newly approved anticancer drugs in the USA[62]. Thus, if costs were not a limiting factor, many oncologists would likely treat patients with the excluded drugs[62]. In the spring of 2016, an announcement was made stating that the UK CDF would be discontinued. Notably, the many challenges to the CDF arose despite the fact that the organizers were able to negotiate drug prices with manufacturers.

Despite the end of the UK CDF, anticancer medications continue to be used and funded through NICE. This public body performs a cost-effectiveness analysis in order to determine the true value that anticancer drugs provide: specifically, the costs of providing 1 year of good-quality life to patients. NICE then compares a drug's cost-effectiveness ratio with an established threshold, which is equivalent to approximately $25,000–$40,000 (REF. 70). Some drugs meet this threshold, thus permitting their continued use by the NHS.

Using cost-effectiveness analysis to prioritize the use of cancer drugs provides some advantages. Firstly, the calculation of an anticancer drug's cost-effectiveness is often more straightforward than a similar calculation for other types of medical intervention, owing to the availability of precise estimates of gains in survival and duration of treatment. Secondly, the process ensures that health-care spending is preferentially applied to achieve the most benefit. In other words, low-cost, high-value interventions are funded at the expense of high-cost, low-value interventions. As a result, some beneficial drugs are not available in the UK, but the average life expectancy nevertheless remains higher in the UK than in the USA[71] — a testament to the more rational application of a limited budget. A disadvantage of this approach is that such analyses of cost-effectiveness can vary in terms of the methodology used and, as described earlier, they must be conducted by impartial groups using clear, prespecified methods, and draw upon published evidence of efficacy, rather than relying on assumptions of efficacy. When conducted in this way, such cost-effectiveness analyses sometimes lead to the conclusion that drugs, even important ones, should not be funded. Ultimately, however, rationing

the use of anticancer drugs based on their cost-effectiveness takes cost as an absolute, immutable term, which is likely not correct. Moreover, this approach is akin to treating the symptoms of the problem, without addressing the root cause.

In less economically developed and developing nations, even though prices of anticancer drugs are usually lower than those of the same drugs in economically developed countries, treatments are more unaffordable when considering the average purchasing power of citizens in those countries[2]. For example, in an advanced medical centre in India, only one of 107 women with HER2-positive breast cancer received treatment with trastuzumab[72], a drug that provides unequivocal benefit to this patient group. Furthermore, the high prices of anticancer drugs globally enable pharmaceutical sponsors to test next-in-class drugs against comparators that, despite being known to be inferior, are considered the standard of care because local patients cannot afford treatments of the best available standard[73]. In one example, sponsors were able to test the efficacy of a novel EGFR inhibitor in patients with *EGFR*-mutant NSCLC compared with chemotherapy several years after the superiority of EGFR inhibitors had already been established, because an alternative EGFR inhibitor was unaffordable[73]. This scenario would not have happened in the USA, where an older EGFR inhibitor had been the standard-of-care treatment for several years.

Finally, high anticancer drug prices serve to protect the market share of a given agent, and prevent the generation of patient-centred research[74]. Several novel, yet expensive drugs are considered the next-in-class agent, and have been demonstrated to provide clinical benefit for an indication for which the parent drug was never tested. For instance, nab-paclitaxel is used in the treatment of pancreatic cancer, while paclitaxel was never tested to a similar extent in patients with this disease. In these situations, independent groups might wish to conduct non-inferiority studies to ascertain whether or not the older, cheaper alternatives perform similarly. Such trials have the potential to yield considerable financial savings for health-care systems; however, the cost of purchasing sufficient quantities of the study drug for such trials is tens of millions of dollars, according to several hypothetical comparisons[74]. Thus, high anticancer drug prices also preclude robust, independent comparisons of clinical benefit[74].
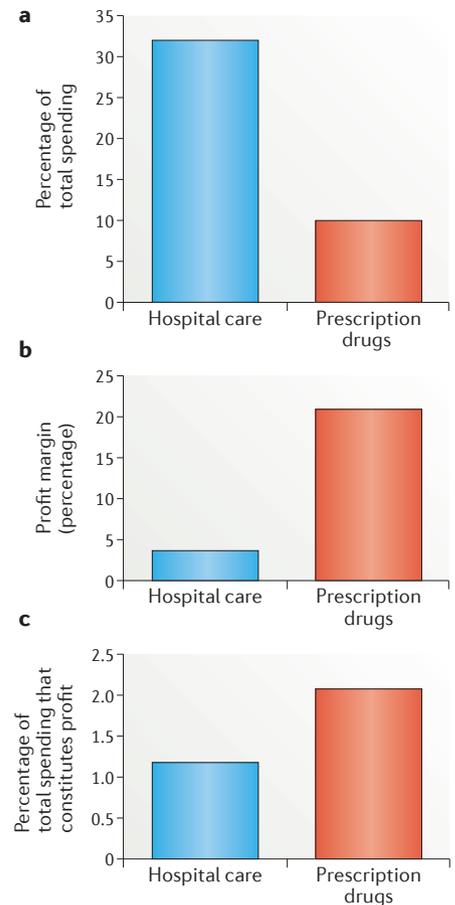
Figure 4 | **Spending on hospital care versus spending on prescription drugs. a** | Percentages of total US health-care spending on hospital-based care versus prescription drugs[49]. **b** | Annual profit margins of hospitals versus those of drug manufacturers, as a percentage of total income distribution[132]. **c** | Pharmaceutical manufacturers obtain more money in profit, despite a smaller share of total health-care spending.

Solutions

Current and newly approved anticancer drugs are unaffordable in some nations and by many people around the globe, but, if allowed to continue, the trends in anticancer drug costs will likely ensure that it is only a matter of time before these drugs are unaffordable in all nations and for all people. Solutions intended to lower or, at a minimum, curb the rise in anticancer drug prices are desperately needed to ensure widespread access to these medications. Here, we summarize ongoing proposals and efforts.

Changes in how drugs prices are negotiated. In the USA, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 established the Medicare Part D programme, and prohibits the CMS from

negotiating price reductions and rebates for drugs purchased under this programme[75]. Several experts and key stakeholders have recommended legislative action to permit the CMS to negotiate drug prices.

One suggestion of the effect negotiation might have on drug prices comes from the Medicaid Drug Rebate Program. This programme was authorized by section 1927 of the Social Security Act in 1990, and requires a drug manufacturer to enter into a national rebate agreement with the Secretary of the Department of Health and Human Services (HHS) in exchange for coverage of the manufacturer's drugs by the Medicaid programme[76]. Drug manufacturers are required to provide a rebate of at least 23.1% of a drug's average price, plus an additional rebate for price increases after the drug's introduction that exceed the rate of inflation[77]. The Congressional Budget Office (CBO) has estimated that Medicaid's average price of drugs was 27–38% lower than the Medicare part D average in 2010 (REF. 78).

Simply expanding the availability of these rebates to individuals who are eligible for both Medicare and Medicaid coverage would yield savings[77]. In 2011, approximately 20% of Medicare beneficiaries were also eligible for Medicaid[79]. Compared with the non-dual-eligible Medicare population, dual-eligible beneficiaries tend to be poorer, have a lower level of education, are more limited in terms of conducting activities involved in daily living, and account for a higher proportion of Medicare spending. Dual-eligible beneficiaries have received drug coverage through the more expensive Medicare Part D programme since its introduction in 2006. Thus, the CBO estimates that savings of approximately $123 billion could be made in 10 years by expanding the availability of Medicaid rebates to these dual-eligible beneficiaries[79].

Beyond the use of fixed rebates, some researchers have suggested that the CMS and HHS should be allowed to formally negotiate drug prices and formulary placements. Using this approach, many experts have suggested health-care savings of approximately $150–540 billion could be obtained over a period of 10 years[80–82]. Improvements in the ability of the CMS to negotiate pricing might also have global repercussions, leading to a fall in prices in other nations, given that health-care systems in many other nations use CMS prices as a starting point for negotiations.

Several potential challenges to the successful implementation of policies designed to reduce the costs of anticancer drugs exist, not the least of which is the need for legislative action in order to alter current laws. Additional concerns include the details regarding which drugs to include in proposed cost-saving plans, how drug prices are negotiated, and whether decisions on formulary placement can be made by the HHS[80]. However, the Medicaid drug-rebate programme provides a roadmap for the successful implementation of this policy at a larger scale, and should be considered to help address the increasing costs of anticancer drugs.

Drug price transparency. The pharmaceutical industry has often cited R&D costs as a key driver of the high costs of anticancer drugs[39]. As previously noted, however, the R&D costs associated with introducing a new drug are largely unknown and/or speculative. In the USA, several states are now proposing drug price transparency laws aimed at providing clarity; on 3 June 2016, Vermont became the first state in the country to enact a drug price transparency law[83], and other states have similar legislation forthcoming. These laws require that pharmaceutical manufacturers provide details on R&D, manufacturing, and marketing costs associated with their drugs, in addition to information on financial assistance for patients and rebates provided by the manufacturers[43]. Some states, such as Massachusetts, have also proposed considering whether or not the price of a prescription drug is overly high given: the likely clinical benefit of the drug; the costs of development and manufacturing; and the prices charged by health-care systems in other countries[84]. Opinion is currently divided on the likely effects of implementing such drug price transparency laws; however, it is hard to argue that increasing transparency by providing more information relating to drug pricing is not desirable.

Introduction of generic and biosimilar drugs. Generic drugs are similar to brand-name drugs, and are typically used at comparable dosing levels and in similar treatment schedules for the approved indication. In the USA, the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch–Waxman act) governs the approval of generic drugs. Manufacturers submit an abbreviated new drug application (ANDA) to the FDA, which is designed to ensure that the generic drug meets the same standards as those of the brand-named equivalent. Generic drugs are, on average, approximately 80–85% lower in price than their brand-named equivalents[85]. The CBO has estimated that the use of generic drugs instead of their brand-named equivalents reduced Medicare part D prescription drug costs by about $33 billion in 2007 (REF. 86). Thus, a considerable level of interest exists in ensuring the early and safe introduction of generic drugs, especially in oncology.

Biosimilar drugs are products that are highly similar to an FDA-approved biological agent, with no clinically meaningful differences in terms of safety, efficacy, or purity[87]. On 6 March 2015, filgrastim–sndz became the first FDA-approved biosimilar drug, for use as an alternative to filgrastim for the amelioration of neutropenia in patients receiving treatment for cancer[88]. The cost of the biosimilar filgrastim–sndz is approximately 30% lower in Europe and 15% lower in the USA compared with filgrastim[89]. The financial consequences of the introduction of biosimilar drugs has been debated and the CBO initially estimated a saving of $25 billion over 10 years[90], while others estimate savings to be higher, for instance, $250 billion for just 11 biosimilars over 10 years[91].

Pharmaceutical companies, however, use several strategies to delay or prevent the introduction of generic and/or biosimilar drugs. These have been reviewed in detail by Jones *et al.*[92] and are summarized here. Patent holders for the branded drug might pay potential manufacturers of generic agents to delay the introduction of generic equivalent drugs. Jones *et al.*[92] illustrate this practice using several examples with particular relevance to oncology, such as the situation with imatinib. Novartis AG, which holds the patent for imatinib, a drug used for the treatment of chronic myelogenous leukaemia, successfully convinced the generic drug manufacturer Sun Pharma to delay the introduction of generic imatinib by 7 months[93].

Another strategy deployed to delay the introduction of generic drugs involves the Risk Evaluation and Mitigation Strategy (REMS) programme[94]. For drugs with substantial safety issues, the FDA requires prescribers and patients to be informed of the potential risks and benefits associated with use. Some drug manufacturers patent their own REMS programme, and subsequently deny REMS access to generic manufacturers who seek to conduct bioequivalence studies. The proposed

Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act introduced by the US Senate on 14 June 2016 aims to prevent delays in the introduction of such generic medications[95]. The CREATES Act has two important components: a requirement that patent holders provide drug samples to generic manufacturers in order to conduct studies that are required to obtain regulatory approval; and a requirement that patent holders negotiate the implementation of a shared REMS programme with the manufacturers of generic drugs.

Balancing speedy approval while ensuring the efficacy and safety of each agent is yet another challenge with the introduction of generic and biosimilar drugs. Owing to backlogs and delays in approving such medicines, the Generic Drug User Fee Amendments of 2012 (GDUFA) were enacted to collect fees from drug companies and use these additional resources to speed the approval processes for generic agents[96]. The FDA has reported more rapid approvals of generic drugs, and in 2016, 75% of original ANDA requests were approved within 15 months (compared with 60% in 2015)[97]. Some policy experts have called for further shortening of the time required for this decision to be made[98]. Finally, a remaining challenge is that, even though generic drugs are often cheap to manufacture (manufacturing 1 years' worth of imatinib for the treatment of one patient is estimated to cost between $350–750 (REF. 99)), the price of generic drugs remains high. As of August 2016, Sun Pharma, the manufacturers of generic imatinib, were charging 90% of the price of brand-name imatinib for their agent — an annual cost of $140,000 a year according to their listed Redbook prices[100]. The solution is to enable multiple generic manufacturers to supply agents to this market; notably, the available evidence shows that four or more generic manufacturers have developed generic versions of just 133 of 210 (63%) of drugs, for which generic versions are eligible[101].

Patent length. No discussion of generic and biosimilar drugs is complete without consideration of drug patent length and market exclusivity. The US Patent and Trademark Office issues patent exclusivity for novel inventions, including drugs[102]. Furthermore, the FDA grants a regulatory exclusivity period of 5–7 years for small molecules and 12 years for biologic agents before a generic competitor can be introduced[103]. In an analysis of 437

top selling drugs, the median period of market exclusivity was 12.5 years; for drugs classified by the FDA as being in the haematology/oncology category, this period was 14.3 years[104]. Drug patents and market exclusivity both provide companies with a time-limited monopoly that blocks competition, permitting greater profits, and given with the goal of incentivizing companies to conduct R&D and discover further innovative products. Several researchers have suggested, however, that a market exclusivity period of >10 years might be too long[105,106], and as noted previously, profits are large among the biopharmaceutical industry. Legitimate impetus then exists to argue for reductions in patent length, which would still preserve profit margins, although such a step might diminish these. We must not forget that without market exclusivity — a form of government interference with the market — high profits could not be sustained for long periods of time.

Proposed experiments to improve drug reimbursement. Early in 2016, the CMS announced six pilot programmes aimed at lowering drug spending for Medicare part B medications. Medicare Part B covers the cost of drugs delivered either in a doctor's office or in an outpatient setting, and has annual expenditures of $20 billion[50]. The six proposals were intended to reduce the financial incentive that encourages oncologists to prescribe more-expensive anticancer drugs by reducing payments that are currently proportionate to the cost of the drugs; reducing or eliminating patient cost-sharing; providing doctors with feedback on their prescription patterns; reimbursing a single medication at different rates according to the specific use and relative benefit of the drug for that purpose; limiting reimbursement to the cheapest, equipotent drug (reference-based pricing); and by matching rates of reimbursement with real-world outcomes[107]. All of these proposals would have been tested prospectively, with randomized or staggered implementation. The proposed reference-based pricing limits the extent of reimbursement to the cost of the lowest-priced, equipotent medication; Medicare has previously used this strategy to guide the reimbursement of hormonal therapy for patients with prostate cancer, and data suggest that this decision alone resulted in $30 million in savings[108]. Data published in a CBO report indicate that these reforms, if implemented, are likely

to save approximately $395 million over 10 years[109]. However, these proposals faced a strong political backlash[110] — and the CMS ultimately backed away from them[111]. The lesson then is twofold: firstly, the CMS under the Obama administration had demonstrated a willingness to consider a diverse range of alternatives to the problem of drug costs; secondly, entrenched interests, who opposed these changes, have formidable political clout and were able to stop it.

In the UK, experimentation has also been proposed as a means to mitigate the various challenges encountered by the CDF. Following the close of the CDF, NICE has proposed to provisionally fund the use of certain drugs that fall at the bounds of cost-effectiveness thresholds, and to collect real-world data from the use of such agents in order to make more accurate estimates of their cost-effectiveness[112]. Others, however, recognize this as an opportunity for NICE to instead conduct pragmatic, real-world randomized trials of these agents, data from which would enable even better estimates of cost-effectiveness[112]. Randomization overcomes the many challenges associated with observational data, including residual confounding and confounding by indication; and, emerging evidence suggests that anticancer drugs might not perform similarly in the real world as they do in the idealized setting of clinical trials[24,113].

Importation of drugs from foreign countries. As discussed earlier, absolute drug prices are often higher in the USA than elsewhere in the world. For instance, a 100 mg vial of trastuzumab, as used in the treatment of patients with breast cancer, costs US$848 in the USA and US$493 in Ontario, Canada[114]. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 permits the importation of drugs from Canada, but requires certification from the HHS secretary regarding safety and potential cost savings. In reality, the FDA has not permitted importation of foreign drugs thus far, citing concerns regarding safety[115]. As with the other examples illustrated earlier, the potential savings that could be achieved by importation of anticancer drugs is unclear, although, in 2004, the CBO estimated $40 billion in potential savings over 10 years[115]. The costs of drugs have since continued to increase substantially and the price differences between the USA and other countries remain high, suggesting that potential

exists for additional savings to be made. Importation of drugs from foreign countries might have other unintended consequences, such as leading to price increases for such anticancer drugs in other countries, and even a potential shortage of medicines in less economically developed and economically developing countries from which these drugs might be imported.

Legal solutions to a fiscal problem. The rising cost of cancer drugs has prompted academics and policy-makers to look at existing laws — predominately in the USA — that could potentially be leveraged to help lower pricing. For instance, the Bayh–Dole act[116], which was passed in 1980, enables small businesses and not-for-profit organizations, as well as the researchers involved, to patent inventions funded by the federal government[117]. 35 United States Code (U.S.C.) Section 203, or 'march-in rights' is also included in the law; this legislation allows the federal government (or specifically the federal agency that funded the research leading to the invention) to revoke patents in order to alleviate health or safety needs that are not reasonably satisfied by the patent holder[118]. Some have argued that for drugs developed primarily using federal funding that are now being priced exorbitantly by for-profit companies, the federal government could invoke march-in rights to ensure reasonable pricing[119].

Others have pointed to section 202 of the act that requires patent holders of federally funded inventions to confer nonexclusive licensing to the US government for use on the government's behalf. In the case of drugs developed using federal funding that are now exorbitantly priced, the government could make a case for invoking section 202 to use the drug in government health-care programmes, such as Medicare[120]. For instance, enzalutamide, an agent used in patients with advanced-stage prostate cancer was developed with federal funding and is currently priced at $7,298 for one month of treatment. Engelberg and Kesselheim have estimated that using a generic manufacturer to supply the drug could potentially save the government approximately $57,000 per patient[120].

Another law, 28 U.S.C. Section 1498, would enable the US government to use patented inventions without a need for licensing from the owner by paying reasonable and entire compensation to the patent owner[121]. Kapczynski and Kesselheim[122] have suggested that in

instances when anticancer drug prices are excessive, the US government could pay patent holders a 'more reasonable' royalty and obtain generic equivalents. A key issue here would be to determine what constitutes 'reasonable and entire compensation' — as Kapczynski and Kesselheim[122] point out, this definition would include the R&D costs of developing the drug as well as reasonable profit margins. If we looked at the top ten anticancer drugs by revenue[123], the annual earnings range from $1.58–7.55 billion (FIG. 2). Considering that an average patent lasts for 20 years, and taking into account the upper estimate of the drug-development costs of these agents[40], these figures would account for substantial profits. The strict enforcement of Section 1498 could potentially lower the costs of these medications significantly, while maintaining reasonable profit margins for the manufacturers.

Other countries, particularly less economically developed and economically developing countries, such as India, have used compulsory licensing to facilitate access to anticancer drugs[124]. Use of compulsory licensing enables a third party to manufacture patented products without the consent of the patent holder. Article 31 of the World Trade Organization agreement on trade-related aspects of intellectual property rights enables compulsory licensing under certain circumstances in order to enable affordable access to potentially life-saving drugs[125].

Conclusions

Data from a broad range of empirical research suggest that the prices of many anticancer drugs are excessively high, and that current pricing trends are unsustainable. Anticancer drug pricing affects patients and payers globally. Given the complexity of this topic and its broad origins, clearly, no single solution will suffice. Instead, at best, we might hope that some, or all of these solutions, which individually might only have a modest effect, implemented together will have a meaningful cumulative effect on drug pricing.

As is always the case with policy measures, the introduction of untested changes is prone to leading to unintended consequences[126]. Thus, we favour the programmes that include appropriate test proposals before implementation. The proposed (and since abandoned) changes to Medicare Part B[107], which include staggered and randomized implementation, meet this criteria.

Reducing the price of anticancer drugs will likely reduce the profit margins of most major biopharmaceutical firms from their current levels[48]. Some experts believe that doing so will curb the development of innovative new drugs. Yet, the reality is that 60% of new anticancer drugs are next-in-class agents, rather than entirely novel therapeutics[1], and the majority of these drugs offer only marginal benefits[20]. Others argue that reducing prices might even encourage innovation. The argument here is that high anticancer drug prices, which are reaped no matter how novel or how good the drug, diminish the level of incentives to develop innovative drugs, and instead encourage sponsors to pursue the development of lucrative, but low-risk 'me too' drugs that provide few additional benefits[20,126]. In our literature search, we were unable to identify empirical evidence on this topic in either direction; thus, policy makers should evaluate the effects of pricing policies on both affordability and access to anticancer drugs, as well as on the anticancer drug-development pipeline.

As outlined in this Perspectives, the impetus required to address the issue of excessive costs of anticancer drugs is strong, and proposals on how best to address this issue have been both diverse and creative. We believe the only untenable option is the status quo.

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Author contributions

Competing interests statement