Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

ELSEVIER

Teaser In highly politicised and heavily regulated markets for new anticancer drugs, the long-term value of extending life and reducing illness-related distress and disability is at risk of being underestimated: the fundamental goal of pharmaceutical price regulation should be to help assure universal access to continuously improving treatment.

The political economics of cancer drug discovery and pricing

David G. Taylor

UCL School of Pharmacy Offices, University College London, BMA House, Tavistock Square, London, WC1H 9JP, UK

David G. Taylor is an Emeritus Professor at UCL. Between 2000 and 2014, he held a personal chair in pharmaceutical and public health policy at the UCL School of Pharmacy. His previous positions included Associate Director for Health Care Quality at the Audit Commission for England and Wales and Director of Public and Economic Affairs at the Association of the British Pharmaceutical Industry. He has chaired or been a member of various NHS Boards and has also held Fellowships at the Kings Fund and the University of York.

Drug discoveries can, when used appropriately, save lives. Since 1970, cancer death rates among people aged under 65 have halved in countries such as the USA and the UK. Despite pharmaceutical market imperfections and fears about the prices of new treatments, further progress should be possible during the 2020s. Anticancer medicine outlays account for 0.1–0.2% of the gross domestic product (GDP) of developed countries. Total cancer service spending typically stands at ~0.8% of GDP. The affordability of these sums is a political calculation. Improvements in the efficiency of drug development and global access to effective therapies are desirable. However, from a public interest perspective, these goals should not be pursued in ways that understate the value of better treatment outcomes and threaten the funding available for ongoing innovation.

Introduction

Innovative drugs and vaccines, combined with improvements in living conditions and advances in technologies ranging from diagnostics to contraception, have facilitated demographic and epidemiological transition across the globe. Notwithstanding events such as the HIV global epidemic and the currently ongoing impacts of Coronavirus 2019 (COVID-19), infectious diseases have largely been brought under control in richer communities and the burdens they impose on poorer regions have been reduced [1].

This progress has opened the way to population ageing and increases in the occurrence of later life disorders. Yet, since the 1950s, age-standardised cardiovascular disease death rates have, in large part because of medical advances, dropped by around two thirds in regions such as North America and Western Europe. Although this trend might now be ending [2], declines in cardiovascular mortality have served to reveal the ill-health caused by cancers.

Malignancies now account for approaching 30% of deaths in the most developed countries [3]. By contrast, in settings such as India, this proportion is still around 10%. With regard to mortality reductions, it has proved harder to discover definitive treatments for advanced cancers than was anticipated at the beginning of the 1970s when Richard Nixon, who was also concerned with managing the political impacts of the Vietnam War, first launched America's 'war on cancer'.

E-mail address: david.g.taylor@ucl.ac.uk.

1359-6446/© 2020 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
https://doi.org/10.1016/j.drudis.2020.09.007

Nevertheless, in affluent nations, the cancer death rate among children and adults aged under 65 is currently about half that that recorded 50 years ago.

From the 1990s onwards overall age-standardised cancer mortality has fallen by ~1% per annum in countries such as the USA and the UK [4,5]. Key factors have included cuts in male tobacco smoking, increases in early diagnosis and treatment rates, improved surgical techniques and advances in radiotherapy and medical imaging, alongside the introduction of more effective anticancer drugs.

In the coming decade drug discoveries will contribute further health gains. However, there is controversy relating to the prices of new drugs. Critics say that innovative anticancer drugs are excessively expensive compared with the research and development costs involved and that paying for them is imposing unsustainable pressures on healthcare funders, providers, and users [6–8]. In the UK, about a quarter of the population believe that the cost of anticancer drugs is 'bankrupting the NHS' [9]. In the USA, there is evidence that the costs of cancer treatment inflict considerable harm on some patients and families [10].

It has been argued that drugs of inadequate clinical value are being licensed. There are also fears that, because of high prices, cancer treatments are not equitably available in affluent regions and are not accessible at all to large populations living elsewhere. It is on occasions suggested that, in the light of 'market failures', a fundamental restructuring of the mixed private and public system of funding drug discovery, development and supply is needed [11,12].

New drug pricing problems exist. But the quality of public and professional discussion on this topic is frequently poor. Lack of information, coupled with the technicalities of health economics, can exclude many people, even at the level of politicians responsible for health and industrial policy formation, from meaningful participation in discussions about what treatments should be judged 'cost effective' and how, and how much, societies ought to invest in fields such as drug discovery.

Against this background, this article seeks to provide an accessible overview of the political economics (Box 1) of drug development, pricing and access during the early 21st century, with special reference to anticancer treatments. It begins with a brief outline of relevant costs in nations such as the USA and UK, followed by analyses of the challenges involved in funding drug discovery and the strengths and weaknesses of current approaches to determining whether innovative therapies offer acceptable value for money. Key introductory points include: (i) *medicines alone cannot normally resolve major health problems*. Controlling the cancers more effectively will, in addition to drug discoveries, require a spectrum of interventions from social support and public health programmes through to further advances in diagnostics, radiotherapeutics and surgery; (ii) *concerns about drug costs on occasions link to the increased nonpharmaceutical spending their successful use can demand*; (iii) *markets for innovative medicines are complex, highly politicised and extensively regulated* [13,14]. Temporary monopolists in possession of intellectual property (IP) rights (granted because societies wish to incentivise ongoing research investment) typically sell to large public and private institutions with sufficient market power to secure price and/or cost reductions or, at the opposite extreme, to vulnerable individuals and families. In such circumstances, controversies often occur. Relatively high payments encourage further research investment, whereas lower prices might allow greater access to existing treatments; and (iv) *the extent and nature of the controls on how much is spent on drugs vary widely*. This analysis, although seeking to avoid overgeneralisations, provides a broad picture, albeit with respect to using cost-effectiveness evaluations to determine prices and justify rationing decisions it is especially concerned with the UK policy environment, in which setting the National Institute for Health and Care Excellence (NICE) is currently (during 2020) reviewing the methods it uses to evaluate innovative therapies.

The results of the NICE methods review might have international consequences. Modern economists often seek to predict policy impacts via mathematical modelling. This involves using aggregations, averages, probability estimates and other simplifying assumptions. It can also require phenomena that cannot be quantified to be ignored. Hence, economic assessments do not reflect all aspects of the human situation and are, on occasions, misleading. Their findings should not normally be regarded as statements of value-free fact. Neither can cost-effectiveness judgements appropriately substitute for the exercise of moral choice in deciding who should or should not have access to effective but expensive remedies for harmful diseases.

BOX 1

Political Economics

As a modern discipline economics dates back little more than 250 years, most notably to the work of the Scottish moral philosopher Adam Smith during the late 1700s. As belief in the God-guided right of Kings and aristocrats to determine the allocation of community resources faded, so 19th-century theorists (Thomas Malthus and Karl Marx were both described as political economists, along with individuals such as David Ricardo) began to address questions about how wealth is created through innovation and trading and to challenge its distribution. In today's terms, much of their work was an eclectic amalgam of history, sociology and political science.

However, as the 20th century progressed, the term 'political economics' was displaced by the briefer title 'economics'. This partly reflected an academic desire to create a clearly delineated discipline that could compete for funding with fields such as chemistry, engineering, physics and philosophy. It also stemmed from the development of mathematical modelling techniques, the use of which has helped to enhance the rigour and reproducibility of economic analyses at the cost of narrowing their focus (see main text). Some fear that modern economic studies are on occasions of value to policy-makers because they can be specified in ways that mean they are almost certain to provide desired answers without this being apparent to most audiences.

Health economics and, within it, the cost per QALY methodology emerged during the second half of the 20th century [42]. Its establishment mirrored the evolutionary path followed by economics as a whole. Whether there will in coming decades be a return to more multidisciplinary research in fields such as determining appropriate health and social care spending and incentivising activities such as drug discovery is uncertain. An advantage of a broader sociopolitical approach might be that it could better inform long-term policy formation. A possible disadvantage is that it would challenge established authorities and interests.

There are valid concerns about '$100,000 treatments' seeming unaffordable [15]. Yet progress towards better cancer outcomes is occurring. As a starting point, care should be taken not to confuse imperfect markets working with limited efficiency to deliver benefits with those failing to achieve anything worthwhile, or those that could quickly or easily be replaced by superior alternatives.

Spending on cancer care

Around 80% of child cancers are now cured in 'developed' nations, where two thirds of all cancer fatalities today occur among people aged over 65 years. Both childhood and young adult cancer mortality rates are higher in poor communities, where tumours resulting from infections are more prevalent and treatment facilities comparatively sparse [16]. Even so, cancers are the largest single cause of death among children and young adults in the 'rich world', where many cancer survivors live on with long-term adverse effects from their therapies and little post-cancer support.

Among older populations, cancers in aggregate cause larger losses of potential life years than they do in young people. Through the impacts of grief and the other sequelae of loss, they also inflict much hidden suffering. Yet, despite being responsible for over a quarter of all mortality in wealthier nations, the financial costs of cancer services are relatively modest. In affluent countries, they account for 5–8% of gross health spending [3].

The latter averages ~10% of GDP, albeit in the USA this proportion is 17% [17]. In the UK, NHS and social service cancer care is likely to account for some 0.6–0.7% of GDP [18,19]. By contrast, the equivalent proportion in the USA is about twice that.

In high-income nations, an estimated 25–30% of overall cancer care costs take the form of drug outlays. World-wide spending on anticancer drugs was, for 2019–2020, estimated to be US$180 billion a year, or 0.2% of world gross product (WGP) before the 2020 coronavirus 'lockdowns' [20,21].

High drug prices cause problems for pharmacy budget holders and individual purchasers. However, in the case of drug outlays, there is a danger of overstatement, because the published figures are derived from market research surveys that do not take account of discounts. This has, on occasions, led to inaccurate claims that pharmaceutical spending has risen faster than other healthcare costs [22]. Data gathered by the Organisation for Economic Co-operation and Development (OECD) show that overall drug outlays have in many countries fallen as a proportion of health spending in recent decades, despite innovations in fields such as cancer [23,24]. One reason why overall net NHS medicine costs presently represent little more than 10% of UK health service spending is because while new high unit price but low volume hospital use products have been introduced spending on high volume older drugs used in primary care has fallen significantly.

There can be public interest focused reasons why discount levels are not made public. In European countries such as the UK the actual amounts paid for intellectual property (IP) protected medicines, including anticancer products, can be 50% or more below published 'list' prices. In the differently structured US market discounts (which are typically retained by institutional health care providers) on many drugs reach similar levels [25]. However, this is not usually the case with novel anticancer drugs in the US setting.

Regulations such as those controlling Medicare and Medicaid drug cost reimbursement practices and US legal provisions relating to the treatment rights of insured patients with cancer help explain this last observation. Some other nations, most notably Germany, pay comparable amounts for new anticancer treatments. Yet the available data indicate that the US market accounts for well over 40% of current global anticancer medicine sale revenues. For some, this statistic is problematic. However, it is also of note that the USA is responsible for one third of global health spending of all types, as expressed in nominal (exchange rate adjusted) currency terms. The OECD estimates that, as a proportion of its gross health outlays, overall US spending on pharmaceuticals is relatively low. At ~12%, it is comparable to that of the UK (Fig. 1) [17]. Where the USA differs from countries such as the UK is in the proportion of its GDP spent on health services and the extent to which individuals and families pay directly for items such as cancer treatments. Along with relatively high spending on cancer care the USA is, similar to Switzerland and Japan, a world centre of commercially as well as publicly and charitably funded biomedical research. The extent to which the post discount domestic prices paid for patent-protected therapies determine local life science industry investment levels is unknown. But to the degree that relatively low profits and difficult market conditions, such as those associated with complicated economic evaluation requirements, discourage investment, there is a risk that the long-term costs of some cost-cutting 'economies' will exceed their short-term, more readily measurable, benefits.

Research investments

Given improvements in cancer outcomes among those below retirement age and the fact that relatively few patients with cancers (compared with those experiencing disorders such as heart failure) live for long periods with disabilities that prevent their working, cancers also impose limited lost production costs. Most national estimates put these at a similar level as cancer service spending: that is, at between 0.5 and 1% of GDP [3].

Such observations might be taken to mean that, in contrast to what is known about the public's priorities [9,26], cancer research should not receive as much funding as work on diseases such as the dementias and other neurological disorders. Yet, at present, out of a global pharmaceutical industry research and development annual spend of approaching US$200 billion~40% (i.e., between US $70 and US$80 billion, or just under 0.1% of WGP) is directed towards anticancer projects [20]. This is a greater proportion than that devoted to any other goal. In addition to the fact that, at this point in history, oncology provides many of the research targets available, this pattern is linked to expected levels of return. Given its size, the US market is particularly influential in determining research priorities and investments.

Likewise, cancer has for some time been a key field of non-commercially funded biomedical research [27]. Current North American and European spending by government, charitable, and other not-for-profit organisations, such as the National Cancer Institutes (NCI) in the USA and France, Cancer Research UK, and the German Cancer Research Centre, is in total around US$20 billion a year. The largest actor in this category, the USA's NCI, has a (2020) budget of just under US$6.5 billion [28]. Even allowing for additional outlays in settings such as universities and investments

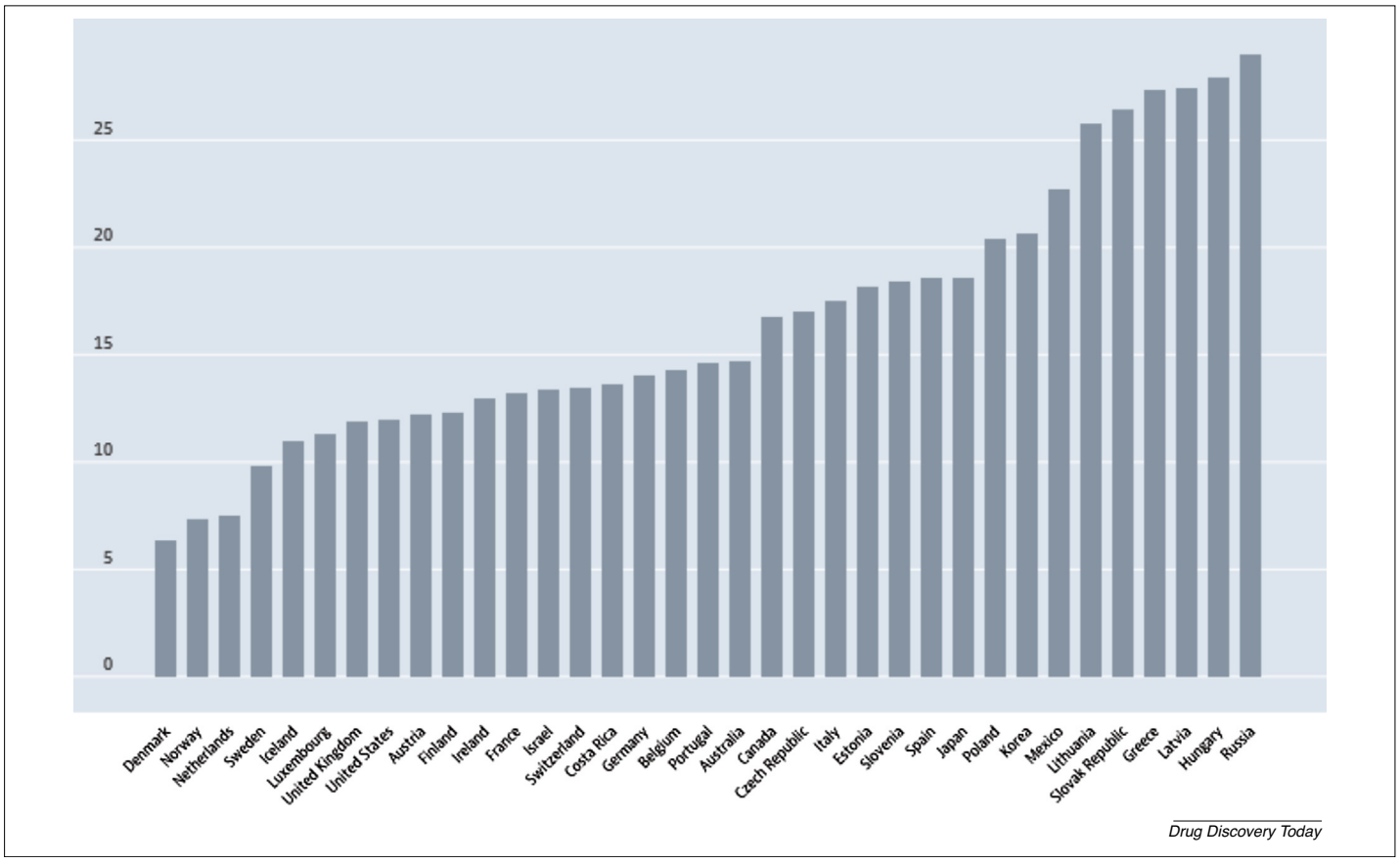

FIGURE 1

Pharmaceutical spending as a percentage of all health spending in selected countries in 2018 or nearest year. Data from Ref. [17].

being made in countries such as the People's Republic of China and Japan, present total global investment in biomedical cancer research by public and private agencies combined probably stands at no more than 0.15% of WGP.

Individuals working in less well-resourced areas might see this figure as high, especially if they believe there is a fixed pool of funding that, if not spent on cancer research, would be allocated to their fields. Likewise, a proportion of health professionals might regard anticancer medicine costs as excessive compared with the resources available for, say, prevention and social care. However, it is not necessarily the case that if money were withdrawn from cancer research and treatment it would be available for use in domains that lack similar political and public attention.

Funding policies

Despite the investments made since the end of World War II, most advanced cancers remain incurable. To date prevention and early-stage detection leading to surgery and radiotherapy have often provided the most effective ways of extending life. But as the range of anticancer pharmaceuticals increases and their use in drug combinations and with other technologies becomes more sophisticated greater benefits will be generated. From a research-funding perspective, the central challenges facing societies relate to making appropriate overall sums available and to creating incentives that, via pricing freedoms or controls, grant giving and allied strategies (including offering 'research prizes') and mechanisms such as tax relief, enhance productivity.

Whether publicly or privately funded, discovery and development programmes require regulation and patient and public needs-focused scrutiny to prevent profiteering and avoid problems such as 'cronyism' and institutionalised resource wastage. Furthermore, neither market-based nor public funding systems can themselves answer questions about how much of their resources societies should spend on seeking better cancer treatments for the future, as opposed to optimising present wellbeing via good use of existing technologies. Informed political judgement is needed for policy direction.

At the extreme, it might be argued that introducing an entirely nonmarket funding system could facilitate patterns of research and development (R&D) more in line with public interests than is presently possible in settings such as the USA and UK. However, just as it would be wrong to think that 'free markets' can, without counter-balancing mechanisms and appropriate regulation, be relied upon to deliver community ends such as health improvement, unchecked State direction can also fail to promote better outcomes.

In Western Europe every aspect of drug development and marketing is already heavily regulated [29]. In the UK, for instance, there are multiple levels of pharmaceutical price and cost control (Box 2). Suggestions that systems such as the NHS are at risk of spending more than planned on drugs and allied products

BOX 2

Pharmaceutical cost control in the NHS

Net of discounts, the UK NHS spends about 10% of its resources on drugs and related items [19]. This proportion has been relatively stable for several decades, partly because of the inherent dynamics of the pharmaceutical market (similar if somewhat higher spending levels are found in other comparable nations) and partly because of regulatory interventions.

In addition to the local work of doctors, pharmacists and other health professionals aimed at promoting appropriate drug prescribing and use, pharmaceutical cost control structures and provisions in the English NHS include: (i) *The Voluntary Pricing and Access Scheme (VPAS) for branded drugs*. The VPAS replaced the final version of the NHS Pharmaceutical Price Regulation scheme in 2019. Among other things, it presently confines total (UK) health service pharmaceutical cost increases to 2% a year. All excess industry earnings are returned to the DHSC and its devolved nation equivalents; and (ii) *NICE*. Since 1999, NICE has conducted an increasing range of work related to improving health outcomes and maximising value for money. Its interventions limit the unit prices of selected medicines but do not control their total cost to the health service in England and Wales. In this last context NHS England has also gained pharmaceutical cost control powers. Since 2017, NHS England has been able to apply to NICE for permission to curb the uptake of new drugs that might otherwise cost in excess of £20 million per annum and/or negotiate further price reductions.

Similar cost control arrangements apply in Scotland, Wales, and Northern Ireland. In addition, the Cancer Drug Fund (CDF) provides a mechanism for supplying innovative drugs at negotiated prices for a period during which further evidence of effectiveness can be gathered. Given the existence of the VPAS and NICE, it could be argued that agencies such as NHS England should not be able to slow the introduction of treatments with the potential to benefit health service users. Nevertheless from an overall cost control perspective the system now in place ensures that, across the UK, the NHS is at no significant risk of its spending on pharmaceuticals exceeding planned levels.

are often ill-informed. They can fail adequately to acknowledge the differences between the pharmaceutical market in the USA and its counterparts in Europe or regions such as, for example, Australasia.

Even in the USA, where anticancer drug producers have more unilateral power to set product prices, there is extensive governmental control of activities such as sales promotion. The conclusion offered here is that there is no 'magic bullet' solution available for overcoming the challenges of drug discovery funding and new medicine affordability. Seeking to incrementally improve combinations of well-regulated private, public and charitable inputs is likely to provide the most viable way forward.

Cancer medicine development as a special case?

The economics of drug research and manufacture are such that the 'sunk' costs of pharmaceutical development and supply are typically high relative to the marginal costs of production. A key consequence of this is that while drugs are under patent or otherwise in receipt of IP protection (IPP; intended by policy makers to promote ongoing spending on R&D) the average price charged by innovators will, subject to regulatory controls and market limitations, be multiples of or even orders of magnitude greater than the price at which efficient generic manufacturers could supply similar items.

One implication of this is that new drugs of all types normally become cheaper over time, as IPPs fade. This is evidenced by the fact that overall pharmaceutical costs have remained broadly stable as a proportion of health expenditure in many countries for some decades [23]. Figure 2 shows that, during the period since the 2008 financial crisis, pharmaceutical spending across the OECD nations increased less than that of any other key care element [24].

Discrepancies between the prices of innovative products and those of generic copies can be difficult to accept. So too can be the fact that the IP-based market value of novel medicines does not, as in the case of gold, primarily lie in their innate rarity, the past costs of their development or even their current clinical utility [30]. It rests fundamentally on the importance that advanced societies attach to incentivising the generation of new biomedical knowledge and enhanced therapeutic opportunities.

Communicating this, and the case in favour of funding ongoing innovation via the amounts paid for recent innovations, is difficult in the absence of equitably resourced universal healthcare and when public trust in the agencies funding drug discovery is under-

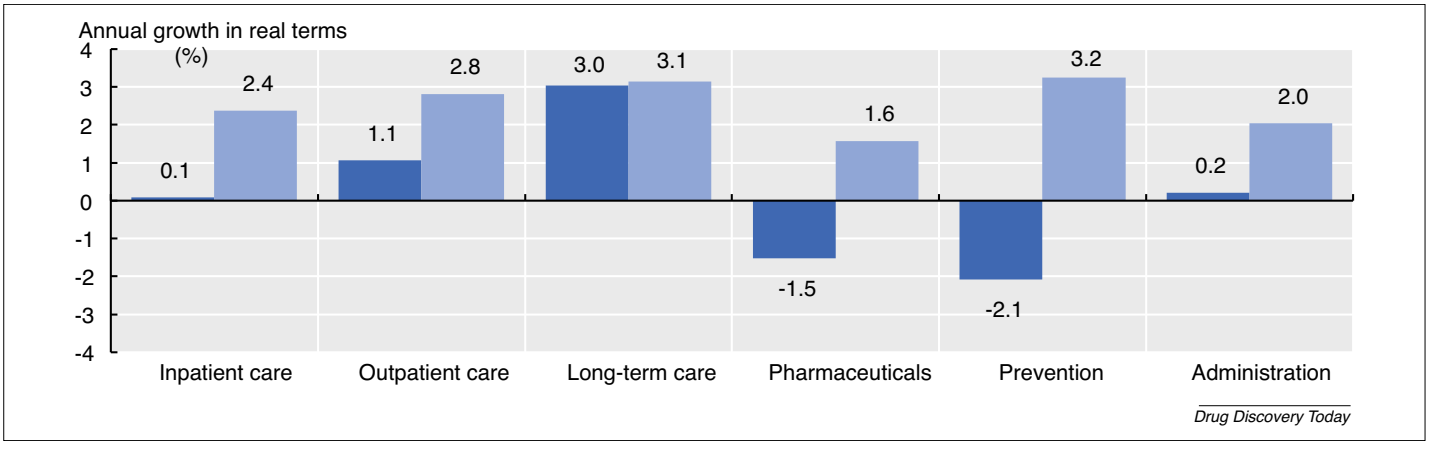

FIGURE 2

Annual growth in health expenditure for selected services (real terms) based on the Organisation for Economic Co-operation and Development (OECD) average for 2009–2013 (dark blue) and 2013–2017 (light blue). Data from Ref. [24].

mined by charges of profiteering. Disputes about how much is spent on bringing new pharmaceutical therapies to market reflect this. Critics have claimed that the process of discovering, testing and licensing new drugs costs 'only' $200–$700 million per product [31]. Against this, other sources cite figures in excess of US $2000 million per licensed drug [32]. Currently, a cost of between US$1500 and US$2000 million is in line with published information on the numbers of innovations launched each year and global R&D outlays, given the challenges involved in making accurate estimations and that recent evidence suggests that the productivity of pharmaceutical research has risen over the past 5–10 years [33–35].

The technical reasons why drug discovery and development cost estimates vary relate, in part, to how money invested in failed research projects is taken into account and the ways in which capital 'locked-in' during periods before successful innovations can generate income is costed. The mix of products analysed in surveys and the sizes of the firms developing them are also significant factors: rare disease drugs produced by smaller companies are typically less expensive to bring market than common disease treatments offered by major companies [36]. However, in realpolitik terms, the central factors underlying conflicts about how much innovative drugs cost to develop have little to do with disputes about academic costing methods.

Commentators concerned with enhancing access to anticancer therapies in poor countries or opening the pharmaceutical markets of rich countries to lower cost competition from nations such as India might well believe that they will strengthen their position by saying that harmful overcharging is occurring in the USA and elsewhere. They might also claim that interventions that drive down revenues derived from innovative treatments will not lead to cuts in research investment. Calling for the funding of healthcare systems in ways that assure universal access and also (via, for instance, well-structured mechanisms for facilitating lower costs in poorer economies via Ramsey-differential-pricing) protect global public interests in R&D investment can be more problematic from a political and public communications standpoint.

Other controversial topics relating to the political economics of anticancer medicines development include: (i) *the high prices of new drugs for rare indications, including cancer subtypes*. Developing treatments for rare diseases costs, on average, only a third or so of the amount normally needed because of factors such as reduced clinical trial costs [37]. But large financial outlays are still involved. Given that sales volumes will be low comparatively high unit prices are, from an investor's perspective, needed to deliver a satisfactory return on capital and, from a public interest viewpoint, to incentivise future investment. There is a case for return on capital based pricing in the case of orphan disease treatments [38]. There are also concerns about (ii) *the low levels of patient benefit generated by new anticancer drugs*. Health Technology Assessments (HTAs) might find that innovative cancer medicines on average extend the lives of those taking them by only weeks or months. However, aggregated figures can hide the fact that some individuals enjoy better outcomes than others. Also, trials undertaken to gain initial marketing approvals are normally focussed on late-stage cancer treatment for patients close to death. Much longer periods of time are required to demonstrate with statistical confidence potentially greater benefits during early-stage and adjuvant treatment settings. This in some ways makes cancer drug development a special case.

Additional questions relate to whether noncommercial drug developers could work with generic drug makers to offer lower price innovations [15] and to suggestions that the costs of clinical trials could be significantly reduced via better use of 'real-world' patient data. The first of these options is already possible, assuming that investors in generic manufacturing and supply would accept lower returns on the resources needed to bring new products to market than the agencies (such as pension funds) that invest in established research-based pharmaceutical companies.

It could be wrong to believe that generic drug companies are more public spirited or less commercially minded than research-based pharmaceutical companies [39]. The second option, extending real-world data use, might prove more viable. Yet reducing research costs would not automatically lead to cuts in the prices of new treatments or to lower total spending on them. An alternative outcome might be an increase in the productivity of drug discovery programmes that could lead to increased pressures on healthcare funders.

If simply limiting pharmaceutical outlays were (along with curbing the associated non-drug health expenditures that can accompany successful pharmacological innovation) the immediate policy goal, then introducing cost-effectiveness analysis linked pricing controls, coupled with narrow interpretations of concepts such as 'evidence based', 'value based', and 'societal benefit', would be more likely to provide a sustainable way of intervening. This is especially true if such an approach to value-based pricing were backed by an overall expenditure cap and/or targeted controls on the annual amounts spent on successful products.

The strengths and weakness of 'cost per QALY' based pricing

The origins of health economics as it exists today date back to the 1950s. After World War II healthcare budgets began to account for larger proportions of GDP than defence. This led policy-makers to start asking how they could limit health outlays while improving outcomes. American initiatives, such as the establishment in 1972 of the Congressional Office of Technology Assessment (OTA), had an important early role. However, funding for the OTA was stopped during the mid-1990s. It was left open for the UK to lead subsequent developments. NICE was established in 1999.

The formation of NICE followed lobbying by groups seeking to replace the then Pharmaceutical Price Regulation Scheme (the PPRS, which historically limited the overall returns of companies on capital and controlled the amounts spent on items such as research and promotion in relation to NHS sales) with product-specific drug pricing based on the cost per incremental quality adjusted life year (QALY) generated [40]. This methodology (Box 3) uses affordability thresholds to determine whether cancer and other therapies provide adequate value [41]. Although in the UK neither NICE nor its Scottish equivalent, the Scottish Medicines Consortium (SMC), have formal price-setting powers, they can decline to recommend products if supplying them exceeds the 'cost per QALY' limit.

Political and practical cases can be made in support of this way of defining drug prices, given the inherent imperfections of markets for innovative medicines. The disadvantages of

BOX 3

Defining Quality Adjusted Life Years

A QALY is a generic unit of the value of healthcare interventions. When the financial dimensions and outcomes of therapies are known, comparing QALY costs allows best value options to be identified. A QALY is the sum of two factors: the extra years of life generated and the 'objective' quality of life gain experienced as a result of being treated [41]. Quality of life is measured via questionnaires such as the EQ5D. This contains simple scales relating to various aspects of disability and distress. Typically, healthy individuals rather than people with relevant diseases are asked about their personal preferences for differing (imagined) health states, with the results being aggregated to give reproduceable population responses.

The incremental cost efficiency ratio (ICER) is the cost per new (i.e., incremental or marginal, as distinct from the average) QALY generated. In cost-effectiveness analyses, the ICER value is compared with an preset affordability threshold to determine whether a treatment provides enough 'value for money'. In wealthier or more health-oriented environments, affordability thresholds are normally higher than in lower cost systems, allowing (all other things being equal) more treatments to be judged 'cost effective'.

From a practical political perspective, determining the cost per incremental QALY can provide a useful step towards establishing a form of value-based pricing. However, its utility is questionable in dynamic situations where there is a probability (which is not empirically assessable) of ongoing innovation leading to radical (but not yet specifically quantifiable) outcome improvements and where a central pricing related objective is to incentivise risky R&D investment. One set of concerns relates to the extent to which anticipated health gains should be discounted. Others range from the claim that cost effectiveness-based decision-making is biased against the interests of older and disabled individuals through to fears that it can be used to legitimate low spending on tax funded or otherwise collectively resourced welfare services relative to other areas of economic activity.

alternatives, such as unregulated bargaining or international comparison based 'reference pricing' systems, arguably make some form of value-based price control an attractive option for all 21st century pharmaceutical sector stakeholders. The NICE system, which is now augmented by nationwide and product-specific spending caps set independently by purchasers such as NHS England, is particularly significant in the centralised and overtly tax (rather than insurance) funded NHS environment where there has since the 1940s been visible tension between the desire to provide good quality healthcare and the wish to keep taxation low.

In such circumstances there is a political need for a publicly credible body to take responsibility for high-level rationing and cost-limitation decisions. Despite there being evidence that the UK's approach to health economics was developed without full political oversight [42], this is what today's system effectively offers. Other European countries also use cost effectiveness-based approaches to determining pharmaceutical payments, as do many American organisations along with, for instance, Canadian Provinces and Australia. However, there are significant variations in the ways in which national systems function [43]. The UK has been unusually reliant on a narrow, relatively inflexible, interpretation of the 'cost per QALY' methodology. By contrast, the US has to date been a global outlier with regard to its rejection of pharmaceutical price controls.

It is sometimes argued that those seeking to foster private sector research should devote more energy to ensuring that the drug discoveries brought to market deliver major health benefits and less on disputing details relating to how new treatments are evaluated [44]. But as the history of 'targeted' anticancer medicines illustrates, progress towards desired therapeutic end-points is at times difficult and slow. Whether discovery and development programmes are privately or publicly resourced, it is in the long-term interests of the world community that each new step towards better therapies liberates sufficient funds in time to support the next.

Theoretical concerns

The theoretical foundations of the York/NICE methodology are derived from Benthamite utilitarianism and the belief that good governance should aim to achieve the greatest possible aggregated happiness for the population being served. This ethic has been translated by modern health economists into a 'tool set' that measures individuals' health-related preferences and then indicates how most efficiently to pursue their realisation, given the quantum of resources available.

Yet people have imperfect knowledge about health and its links to personal and society-wide happiness. Hence policies shaped by the health preferences identified by health economists might well fail, however carefully conducted the research they are based on, to achieve optimal levels of wellbeing. In parallel with this, fairness is a widely shared priority located outside the sphere of individual health preferences and conventional efficiency criteria [45]. Taking it into account indicates a need for positively weighted levels of investment in rare, severe and presently untreatable disease therapies. Accepting this in turn implies that the value of each new QALY is a function of the context in which it is generated, rather than being the same in all circumstances.

In response to past political prompting, NICE now in effect ascribes increased values (via applying a multiplier of 2.5) to QALYs generated at the end of life and, via a different mechanism, to treatments for some rare conditions. However, the extent and consistency of the adjustments made to date have been arbitrary and arguably inadequate. It can also be suggested that in incremental discovery fields, where repeated investments are needed over long periods of time, 'fit-for-purpose' policies should seek to differentially reward steps such as the introduction of new mechanisms of therapeutic action [46]. This is so even when the immediate clinical gains yielded are limited. Waiting for major outcome improvements before recognising the value of investing in research could fail to provide incentives in a sufficiently timely manner.

Threshold setting

With regard to the affordability thresholds normally used by NICE, some commentators have maintained that £20,000–30,000 per incremental QALY is too much for the NHS to pay and that an appropriate amount would be between £10,000 and £15,000 [47]. The latter range reflects, its proponents claim, the average amount of money spent by the NHS per new QALY gained. However, against this, the available research shows that there are large

variations between different fields of activity. In some instances the NHS costs incurred approach £1 million per new QALY.

Also, the UK Treasury has specified an affordability threshold figure of £60,000 [48]. The Treasury 'Green Book' also recommends a discount rate of 1.5%, as opposed to the 3.5% per annum employed by NICE. Using a raised discount rate drives down the presently perceived value of lives saved and suffering relieved in the future [49,50]. The impacts of this are particularly likely to undermine the economic viability of curative and other long-term treatments given to children or young adults to prevent long-term harm.

It is reasonable for individuals to prefer immediate personal rewards over delayed gains. Yet it is ethically and logically questionable for health benefits that benefit entire communities to be subject to the same degree of discounting.

Pharmaceutical purchasing costs typically fall as IP protections expire and competitive supply ensues. In addition, the clinical value of drugs increases as their optimal use becomes better understood. This means that costly cutting-edge innovations can eventually become highly affordable 'work-horses'. Such factors make the economic life cycle of an innovative drug very different from that of labour-intensive forms of care, which when real salaries increase tend to become more expensive over time. Typically, labour accounts for two thirds of all health spending.

Pegging the market entry prices of new medicines to the average cost per new QALY generated in the NHS (which is not particularly well funded in advanced nation terms) would drive down UK payments compared with those of other countries and risk harming public interests in incentivising biomedical innovation and associated investment. Drugs are paid for via health sector budgets. However, the communities funding and using them also have employment, science and trade policy concerns. Allowing the unregulated monopsony (dominant purchaser) power of entities such as NHS England (or, perhaps in future, similar health service purchasers in the USA) to depress the amounts paid for pharmaceuticals (or indeed inputs such as nursing or social care labour) to below the levels paid for equivalents in other sectors would, over time, reduce rather than increase overall wellbeing.

Such observations raise a variety of complex issues [51–53]. In essence, advocates of 'cost per QALY' based pricing accept that it does not take into account value considerations outside the health sphere or necessarily reflect the full amount that people would be willing to pay for life-saving or changing therapies. (Even within the health arena, some dimensions, such as the creation of 'insurance value', have been neglected; Box 4.) Basing their case on what can be referred to as extra-welfarist theory, they argue that the pursuit of goals other than QALY defined health improvement should not influence the allocation of fixed health system resources. Some believe that separate provisions, such as compensatory tax incentives, can compensate for unwanted aspects of this approach.

Such a position has attractions, especially from the perspective of healthcare budget holders. However, from a global drug discovery standpoint it is at best unclear as to whether the use of current forms of 'cost per QALY' pricing is beneficial or acts to further complicate an imperfect world market in ways that threaten the public purpose underlying the granting of intellectual property rights. Seeking to improve the use of health resources is a desirable goal. But if pursued in ways that, on the grounds of 'scientific' cost effectiveness analysis, legitimise unfair rationing or inappropriately discount the value of investing in research for the future, then harm will result.

Simply because a body such as NICE judges a treatment non-cost effective does not necessarily mean that it should not or cannot be afforded. In addition, given possibilities such as shifting money from one sector to another or taking advantage of low interest rates, neither should it always mean that funding for other desirable forms of care would have to be reduced if a relatively expensive innovation were provided to those able to benefit.

BOX 4

Neglected dimensions of healthcare value

Conventional cost-effectiveness analyses take into account a narrow range of health and healthcare value dimensions [52]. Examples of useful aspects of treatment and care that are often neglected include:

- Removing uncertainty. Knowing what symptoms are being caused by can be of value to affected persons, even if an accurate diagnosis does not immediately open the way to better treatment.
- Fear reduction. If people know that were an event such as an epidemic to occur it can be effectively contained, this generates value via curbing anxiety and fear.
- Insurance value. The existence of medical technologies insures individuals and societies against physical and financial risks. This can increase willingness to spend in ways that increase wellbeing.
- Disease severity. The more harmful conditions are the more individuals and families are likely to value cures or radical improvements in their control.
- Hope. Individuals living with incurable diseases can gain from the hope that, in future, definitive drug or other treatments will become available to them or others important to them.
- Real option value. Medical technologies that extend survival for limited periods give their beneficiaries opportunities to benefit from additional advances made during the extra time they live.
- Fairness and equity. Many people value fairness (although not imposed absolute equality) as an addition to the efficient pursuit of health and wealth (see main text).
- Scientific 'spillovers'. If biopharmaceutical and other forms of innovation are seen as linked event chains then the main value of what might in clinical outcome terms be small individual advances can lie in their being incremental precursors to more effective interventions.

It can be argued from a financial perspective that part of the value of existing IP law-protected drugs lies in their capacity to provide funding for developing the next generation of therapies. If so, during periods in which major therapeutic steps are unusually difficult to achieve, it might be appropriate to pay more for each new unit of health gain created than when innovation is more rapid. NICE is conducting a methods review that might change the ways it values innovative treatments. However, if the affordability thresholds applied remain constant or are reduced, recognising previously neglected health related value dimensions might not have a significant effect on permitted prices.

Discussion: drug discovery in the aftermath of COVID-19

There are many other important areas of debate relating to how much societies should pay for services such as healthcare or drug discovery and products such as drugs. For example, there is evidence, including work from the European Commission, that challenges claims that research-based pharmaceutical industry profits are excessive compared with those made in other sectors, allowing for the financial risks incurred [34,36,54,55]. Stakeholders in drug discovery should also be aware that pharmaceutical industry research funding would, all other things remaining constant, decrease or at least become more risk averse if anticipated profitability was cut in the USA or other key settings and that there is no evidence that reductions in private R&D spending would lead to compensatory increases in public outlays.

Linked questions relate to whether competition between drugs with the same or similar modes of action (so-called 'me-too' products) increases or decreases the overall costs and benefits of drug development and use. Claims about this have been intensely disputed. Yet since the onset of the global COVID-19 pandemic in early 2020 the world-wide health policy agenda has become mainly centred on controlling the spread of the new coronavirus and limiting the harm it directly causes. In this context there is presently little questioning of the value of plural research efforts aimed at producing effective vaccines and therapeutics.

Over the next few years the protection of public interests in areas such as improving cancer treatment will, to a considerable degree, depend on how the economic and social sequelae of COVID-19 are managed. The severity of the impacts of this infection offers a warning of the dangers of failing to make timely investments in discovery programmes, diagnostic testing and service provision. The pandemic has also revealed a high political willingness to pay for the prevention of avoidable mortality when it occurs in association with acute, publicly visible, threats. This is despite the fact that, in countries such as the UK, approaching 90% of COVID-19 deaths have been among individuals past normal retirement age [56]. The equivalent proportion among people who die from cancer is ~70%.

Such figures could suggest that there should in future be increased spending on cancer research, prevention and care. Every year, cancers impose (in developed countries) losses comparable to those that could have been caused by the 2020 COVID-19 outbreaks among virus-naïve populations had they been less effectively mitigated. However, in practice, political and economic pressures generated by increased public debt and socioeconomic disruption could precipitate new restrictions on future health spending, particularly if the need for better treatments for disorders such as cancers is publicly regarded as nonacute and hence politically less urgent.

In the UK, Cancer Research UK announced in April 2020 cuts in the value of the grants that it was able to award [57]. Looking forward, reducing the amounts paid for innovative drugs could, from the standpoint of political economics, be a comparatively attractive way of saving because of the sensitivities associated with alternatives such as wage cuts coupled with the perceived unpopularity of pharmaceutical companies. If inflated claims about the costs of new drugs and underestimates of their long-term value are accepted uncritically, the risk of expenditure reductions that will slow drug discovery will increase.

Towards balanced judgements

Cancers now cause up to 30% of deaths in parts of Europe and countries such as the USA, Japan, and Australia, despite the fact that cancer care accounts for no more than 8% of rich world health and allied service spending. This is under 1% of the GDP of the average OECD nation [19,58]. Within that, spending on anticancer drugs of all types represents 0.1–0.2% of the GDP of the typical developed country.

These are considerable sums. However, given sufficient public and political willingness to pay, they are not unaffordable. Raising research and development productivity and finding methods of agreeing prices for new therapies in ways that protect health system viability while also protecting patients and the public from avoidable fears about their ability to access the most effective treatments are laudable ends. Enhancing cancer care in poor nations is a particularly important challenge. Nevertheless, there are good reasons for concluding that solutions to such problems ought not to be pursued in ways that risk cutting funding for ongoing innovation. Neither should it be assumed that appropriate treatment costs are always lower costs.

Considerable intellectual effort has been put into developing the 'cost per incremental QALY'/ICER based approach to determining the extent to which patented and similarly protected treatments provide value. It is possible that, without a broadly agreed approach to value-based pricing, the current IP system underpinning much biopharmaceutical research funding will come under severe challenge. Nevertheless, the theories and techniques underpinning this strategy have a variety of limitations, including, for example, the arbitrary nature of affordability threshold setting. Their inflexible application could deliver the short-term maximisation of a narrowly specified form of health sector efficiency at the expense of a more balanced pursuit of welfare.

Complex evaluations can themselves be costly and draw resources away from investment in more beneficial activities. Yet there are no simple solutions to the problems surrounding the pricing of innovative drugs early in their life cycles. In the aftermath of the COVID-19 pandemic few if any governments or healthcare providers will wish to accept unregulated drug spending. Furthermore, alternatives to a cost per QALY approach, such as using reference pricing, could well prove more harmful to the funding of drug discovery and therapeutic evolution than well-specified cost-effectiveness based strategies [59].

In the face of this and current economic uncertainties, no precise prescription can be offered here. However, in addition to informing country level and international debates about the long term value of investing in biomedical and biopharmaceutical innovation and addressing concerns relating to issues such as inappropriate future benefit discounting, reform options include introducing incremental improvements to the current 'cost per new QALY' drug pricing model. Adjustments for factors that exist within the health sphere but are not acknowledged in current methodologies (such as insurance value) could add to the sensitivity of decision making without, unless they led to significant increases in the number of QALYs produced, major cost implications. Likewise, instituting 'outcomes-based pricing' and allied

BOX 5

The Cancer Drug Fund

The CDF originated from an idea promulgated by David Cameron during the 2010 general election campaign in the UK. In response to concerns about access to new anticancer drugs, an initial £200 million per annum fund was established and, in the period to 2015–2016, was used in England to purchase cancer drugs that had not been recommended by NICE for NHS use. Up to 100,000 patients may have benefited, although no outcome records were kept. The amounts paid for the drugs supplied appear to have been higher than might otherwise have been possible. The fact that the CDF did not benefit UK citizens living outside England or those with diseases other than some cancers created equity issues. It is also possible that its existence fostered delays affecting the NICE anticancer treatment appraisal programme.

Despite benefiting some health-service users and innovative pharmaceutical companies, the CDF represented a threat to several interests related to NHS drug purchasing and use. It could have been that, with a more positive approach among those involved, early action would have been taken to improve aspects of its functioning. However, as it was, the cost of the CDF rose and in 2016 significant reforms were introduced.

The CDF is now administered by NHS England. It provides access to selected treatments at negotiated costs and for limited periods, during which additional evidence relating to their effectiveness can be gathered. This revised approach is widely regarded as useful and desirable. But with regard to the further evolution of 'coverage with evidence' arrangements in oncology and other fields (in Scotland, for example, there is a general New Medicines Fund resourced via VPAS rebates) questions remain as to for how long they should ensure access and how fair levels of overall financial return for innovators should ultimately be determined.

approaches in ways that make paying for novel treatments conditional on the realisation of intended results can eliminate uncertainties about how well they will work and so help permit their timely use. [This is partly how the UK Cancer Drug Fund (CDF) already functions, albeit under tight restraints; Box 5.] This too would have limited cost implications if the amount paid per new QALY gained remains within existing limits.

A second reform option could involve raising affordability thresholds to more adequately recognise both health and non-health value generation. NICE already pays a premium for QALYs gained towards the end of patients' lives and from treating selected rare diseases. In The Netherlands, adjustments related to the proportion of a patient group's remaining life that a new therapy saves have been proposed [60]. Looking beyond severity measures to take into account the public policy objectives underlying IPPs such as patents, a systematic scale of incremental QALY affordability designed to allow the prices of innovative therapies to more fully reflect their societal value could be advantageous to all stakeholders, assuming that the healthcare or alternative funding available is sufficient to accommodate resultant cost increases.

A third option is that of radical simplification. Part of the political attraction of health economics-based systems for determining drug prices is that their complexity can provide an aura of 'science-based' authority that is difficult to challenge. However, they also require the investment of considerable resources to generate what are at best no more than limited estimations. A simplified approach to setting fair prices for new drugs and allied items based on variables such as projected volume usage, proven and/or projected capacity to confer benefit, the degree of scientific innovation achieved and the type of production process involved (in each case, a three-level scale could apply) might prove viable, given sufficient commitment to health improvement and agreed purpose regarding the role of pricing in incentivising further research investment.

Finally, developing a world-wide consensus on the application of Ramsey pricing for innovative treatments may be key to future progress. In areas such as oncology, outcomes depend on multiple factors. Unlike the situation with, for instance, HIV infection during the 1990s, access to recently discovered drugs might not by itself be centrally important in increasing cancer survival in poor countries. Nevertheless, there is a strong ethical case for minimising the extent to which high unit prices prevent the appropriate use of anticancer drug discoveries. Differential pricing mechanisms could, if well-designed, promote international equity while protecting the public and private funding of innovation.

In this last context, a core policy goal would be for richer economies to continue paying the full costs of the drugs they use and incentivising ongoing investments in innovation at levels consistent with national priorities and capacities, while allowing the most vulnerable communities to be supplied at or (if aid were to be given) below marginal manufacturing costs. However, there are many vested interests gravitating against the establishment of a workable global system aimed at achieving this end. They include those of entrepreneurs seeking to sell items available at low cost in poor countries in higher price settings. Similar points apply to the possibility of introducing simplified ways of setting fair prices: some groups have sectional interests in creating and maintaining complexity.

Concluding remarks

Drug discoveries and therapeutic advances stemming from them contribute to health, wealth, and wellbeing in many ways. They will further improve the treatment of most if not all diseases, including cancers, as the 21st century proceeds and will also act as a bridgehead to advances outside the healthcare arena. The rate and precise nature of such progress cannot be accurately predicted. However, its value should not be ignored by policy makers seeking to serve public purposes.

The affordability of new drugs is a widely discussed concern, although this is not necessarily indicative of failures on any side. There are always likely to be tensions between the buyers and sellers of products that can be both life saving and costly, especially when tax-payers' money is used to purchase them. From a drug discovery viewpoint it is significant that pharmaceutical and allied spending has, in the industrialised world, been broadly stable as a proportion of health outlays in recent decades. As their life-cycles unfold, effective drugs and vaccines usually fall in price and add to the cost-effectiveness of healthcare.

With regard to cancer research and treatment, overall spending is relatively modest in macro-economic terms, despite individual treatments having high unit prices. People living in modern communities have the right to expect that abuses of market power are prevented. Yet this should not obscure the legitimacy

of questions about whether enough is being spent in affluent societies on drug discovery and drug purchasing, compared with less worthwhile forms of consumption. Neither should opportunities for promoting constructive collaboration and productive ways of working together across public and private sector boundaries be missed because of ideological disputes or prejudiced assumptions.

Across the world, markets for innovative medicines are complex and imperfect. So too are systems for research funding and care provision. However, benefits are being delivered. In the final analysis it is important not to lose sight of this fact and to seek further health gains in ways that build on the value of today's scientific, industrial and health service heritages.

Declaration of Competing Interest

The author declares the following financial interests/personal relationships which may be considered as potential competing interests: Work contributing to this review was in part funded via an independent grant from Merck and Co awarded to Professors David Taylor and Mark Emberton via University College London. Other than that the author has no relevant interest to declare and does not believe himself to have been improperly influenced.

Acknowledgements

This article was in written in 2020. It draws on the findings of research undertaken in 2019 that was supported by a grant awarded via UCL by Merck & Co to Professor Mark Emberton and D.G.T. Thanks are due to all those colleagues who contributed to this analysis, including Tom Lee, Duncan Sim and others at Cancer Research UK and Aris Angelis, Leela Barham, Paul Catchpole, Adam Hutchings, Panos Kanavos, Paula Lorgelly, Chris Pickard, Jack Scannell, Michael Schlander, Brendan Shaw and Richard Torbett.

References

1 GBD 2017 Causes of Death Collaborators (2018) Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017, a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392, 1736–1788

2 Lopez, A.D. and Adair, T. (2019) Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics. *Int. J. Epidemiol.* 48, 1815–1823

3 Hofmarcher, T. *et al.* (2019) *Comparator Report on Cancer in Europe 2019 – Disease Burden, Costs and Access to Medicines*. IHE

4 American Cancer Society (2019) *Facts and Figures 2019. US Cancer Death Rate Has Dropped 27% in 25 Years*. ACS

5 Cancer Research UK (2020) *Cancer Mortality Statistics*. Cancer Research, UK

6 Experts in Chronic Myeloid Leukaemia (2013) The price of drugs for chronic myeloid leukaemia is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood* 121, 4439–4442

7 WHO (2019) *Pricing of Cancer Medicines and Its Impacts*. WHO

8 Tay-Teo, K. *et al.* (2019) Comparison of sales income and research and development costs for FDA-approved cancer drugs sold by originator drug companies. *JAMA Netw. Open* 2, e186875

9 Taylor, D.G. and Heller, M. (2019) *British Public Attitudes Towards Cancer Research and Treatment in 2019*. The UCL School of Pharmacy

10 Yabroff, R.K. *et al.* (2019) Minimizing the burden of cancer in the United States: goals for a high-performing health care system. *CA Cancer J. Clin.* 69, 166–183

11 UCL Institute for Innovation and Public Purpose (2018) *The People's Prescription. Re-Imagining Health Innovation to Deliver Public Value*. IPP

12 Labour Party (2019) *Medicines for the Many*. The Labour Party

13 Comanor, W.S. (1986) The political economy of the pharmaceutical industry. *J. Econ. Lit.* 24, 1178–2117

14 Taylor, D.G. and Maynard, A. (1990) *Medicines, The NHS and Europe*. The Kings Fund Institute

15 Workman, P. *et al.* (2017) How much longer will we put up with $100,000 cancer drugs? *Cell* 168 (4), 759–583

16 GBD 2017 Childhood Cancer Collaborators (2019) The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. *Lancet Oncol.* 20, 1211–1225

17 OECD (2019) *OECD Health Statistics*. OECD

18 Richards, M. *et al.* (2018) *Unfinished Business: An Assessment of the National Approach to Improving Cancer Services in England 1995-2015*. The Health Foundation

19 Taylor, D.G. (2020) *Cancer Policy Update: Agenda for the 2020s*. UCL School of Pharmacy

20 EvaluatePharma (2019) *World Preview 2019, Outlook to 2024*. EvaluatePharma

21 IQVIA Institute for Human Data Science (2019) *The Global Use of Medicine in 2019 and Outlook to 2023*. IQVIA

22 Espin, J. *et al.* (2018) Projecting pharmaceutical expenditure in EU5 to 2021, adjusting for the impact of discounts and rebates. *Appl. Health Econ. Health Policy* 16, 803–817

23 OECD (2015) Average annual growth in pharmaceutical and total health expenditure per capita, in real terms, average across OECD countries, 1990 to 2013. In *Health at a Glance 2015 OECD Indicators*. OECD Publishing

24 OECD (2019) *Health at a Glance 2019 OECD Indicators*. OECD Publishing

25 Berkeley Research Group (2017) *The Pharmaceutical Supply Chain: Gross Drug Expenditures Realised by Stakeholders*. Berkeley Research Group

26 Incisive Health (2018) *The State of Cancer*. Incisive Health

27 Kanavos, P. *et al.* (2010) The role of funding and policies on innovation in cancer drug development. *Ecancermedicalscience* 4, 164

28 NCI (2020) *NCI Budget and Appropriations*. NCI

29 Schweitzer, S.O. and Lu, Z.J. (2018) *Pharmaceutical Economics and Policy Perspectives, Promises, and Problems*. Oxford University Press

30 Scannell, J.W. (2015) Four reasons drugs are expensive, of which two are false. *Forbes* (October),

31 Prasad, V. and Mailankody, S. (2017) Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern. Med.* 177, 1569–1575

32 DiMasi, J.A. *et al.* (2016) Innovation in the pharmaceutical industry: new estimates of R&D costs. *J. Health Econ.* 47, 20–33

33 Ringel, M.S. *et al.* (2020) Breaking Eroom's Law. *Nat. Rev. Drug Discov.* Published online ahead of print April 16, 2020. https://doi.org/10.1038/d41573-020-00059-3

34 Cutler, D.M. (2020) Are pharmaceutical companies earning too much? *JAMA* 323, 829–830

35 Wouters, O.J. *et al.* (2020) Estimated research and development investment needed to bring a new medicine to market 2009-2018. *JAMA* 323, 844–853

36 Frazier, K.C. (2020) Affording medicines for today's patients and sustaining innovation for tomorrow. *JAMA* 323, 831–833

37 Berdud, M. *et al.* (2018) *Establishing a Reasonable Price for an Orphan Drug*. Office of Health Economics

38 Drummond, M. and Towse, A. (2019) Is rate of return pricing a useful approach when value-based pricing is not appropriate? *Eur. J. Health Econ.* 20, 945–948

39 Eban, K. (2019) *Bottle of Lies*. HarperCollins

40 Claxton, K. (2007) OFT, VBP: QED? *Health Econ.* 16, 54–548

41 Devlin, N.J. and Lorgelly, P.K. (2017) QALYs as a measure of value in cancer. *J. Cancer Policy* 11, 19–25

42 MacKillop, E. and Sheard, S. (2018) Quantifying life: the history of quality-adjusted life-years (QALYs). *Soc. Sci. Med.* 211, 359–366

43 Angelis, A. *et al.* (2018) Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur. J. Health Econ.* 19, 123–152

44 Paterson, K.R. (2017) Value and cancer medicines – a personal view. *J. Cancer Policy* 11, 26–31

45 Richardson, J. and Schlander, M. (2019) Health technology assessment (HTA) and economic evaluation: efficiency or fairness first. *J. Mark Access Health Policy* 7, 1557981

46 Sharpe, E. *et al.* (2020) From patent to patient: analysing access to innovative cancer drugs. *Drug Discov. Today*. Published online ahead of print January 29, 2020. https://doi.org/10.1016/j.drudis.2020.01.004
47 Claxton, K. *et al.* (2015) Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol. Assess.* 19, 1–503
48 HM Treasury (2018) *The Green Book*. HM Treasury
49 Catchpole, P. and Barrett, V. (2020) Keeping pace with pharmaceutical innovation: the importance of the NICE methods review. *PharmacoEconomics* 38, 901–903
50 Sculpher, M. and Palmer, S. (2020) After 20 years of using economic evaluation, should NICE be considered a methods innovator? *PharmacoEconomics* 38, 247–257
51 Garrison, L.P. *et al.* (2018) An overview of value, perspective, and decision context—a health economics approach: an ISPOR Special Task Force report. *Value Health* 21, 124–130
52 Lakdawalla, D.N. *et al.* (2018) Defining elements of value in health care – a health economics approach: an ISPOR Special Task Force Approach. *Value Health* 21, 131–139
53 Danzon, P.M. *et al.* (2018) Objectives, budgets, thresholds, and opportunity costs: an ISPOR Special Task Force Approach. *Value Health* 21, 140–145
54 Scannell, J.W. *et al.* (2015) Financial returns on R&D: looking back at history, looking forward to adaptive licensing. *Rev. Recent Clin. Trials* 10, 28–43
55 European Union (2019) *The 2019 EU Industrial R&D Investment Scoreboard*. Publications Office of the European Union
56 OpenSAFELY Collaborative, *et al.* (2020) OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. MedRxiv. Published online May 7, 2020. https://doi.org/10.1101/2020.05.06.20092999
57 Butler, P. and Morris, S. (2020) Cancer charities say coronavirus shortfall will set back research. *The Guardian* April 7
58 Gill, J. *et al.* (2014) *Overcoming Cancer in the 21st Century*. UCL School of Pharmacy
59 Kanavos, P. *et al.* (2017) *External Reference Pricing Within and Across Countries*. LSE Consulting
60 Netherlands Healthcare Institute (2018) *Disease Burden in Practice - The Theory and Practice of Calculating Disease Burden in Package Assessment*. Zorginstituut Nederland