



Review

Cancer economics, policy and politics: What informs the debate? Perspectives from the EU, Canada and US[☆]Ajay Aggarwal^{a,*,1}, Ophira Ginsburg^{b,1}, Tito Fojo^{c,1}^a Institute of Cancer Policy, Kings College London, Guy's Hospital Campus, Department of Research Oncology, London SE1 9RT, United Kingdom^b Women's College Research Institute, Faculty of Medicine and Dalla Lana School of Public Health, University of Toronto, Canada^c Medical Oncology, National Cancer Institute, National Institutes of Health, Building 10, Room 12N226, 9000 Rockville Pike, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:

Available online 28 February 2014

Keywords:

Advocacy
Cancer economics
Policy
Access
Regional variations

ABSTRACT

In high-income countries the public policy consensus is that costs of delivering high-quality equitable cancer care present an increasing challenge to national budgets. In the U.S. alone it is estimated cancer care expenditures in 2020 will be 157 billion dollars. The increase is being driven by a number of factors including technological innovation, rising costs of medical and hospital care, expensive therapeutics and an increase in the proportion of individuals susceptible to malignancy as the population ages. In this article we review what factors are informing and influencing the political debate on cancer economics across Europe and North America.

We have undertaken a comprehensive analysis of the literature and supplemented this with key informant interviews within each region. An important theme is the increasing role of individual patients, organisations and physicians in advocating for greater access to and fairer prices for cancer therapies. Whilst health technology assessments (HTAs) are increasingly prevalent their role in informing reimbursement policy is influenced by public and political scrutiny, which impacts their ability to ensure access to high value cost effective care. Austerity measures following the global recession have created inequities in access to drugs with concern about the impact on subsequent outcomes. The cancer economics debate has largely centred on the provision of drugs, with access to radiotherapy and over-penetration of high cost radiation technologies under-represented in media outputs and political discussion.

Future work should enhance collaborative efforts to assess relative effectiveness and to provide real-world data. These debates are becoming increasingly complex, even as we face stagnating health budgets. We must also be aware of the key factors that play a significant role in cancer policy aside from economics including socio-cultural values, advocacy and political influence at the country and regional level.

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Contents

The case of Europe	2
Background	2
Breadth of the problem and the range of expenditures	2
The global recession: end of an era in cancer investment?	2
Barriers to drugs access – the role of HTAs	3
Heterogeneity in reimbursement mechanisms across EU-28	3
Formal collaboration across Europe	3
Where do radiation therapies stand in the cancer economics debate?	4
Cancer economics debate – the case of Canada	5

[☆] This paper is part of the Special Issue 'Delivering Affordable Cancer Care in High Income Countries: Papers from a Special Session of Oncology At The Limits, 13th – 15th February 2014'.

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Overview – the Canadian system	5
Canada – challenges and solutions	5
Cancer economics debate – the case of the United States	6
The US healthcare system – attributes, deficiencies and on-going changes	6
The current health care burden and where it may go	6
Cancer therapeutics: are we getting what we pay for?	6
Cancer patient outcomes in the United States	8
Conclusion	9
Conflict of interest	10
References	10

The case of Europe

Background

With respect to cancer care the US is estimated to spend approximately 100€ more per citizen compared to Europe as a whole where it is estimated that per person cancer expenditure is 196€ [1]. However there remains significant debate as to whether this has translated into improved patient outcomes [2,3]. Furthermore several EU-28 countries, despite less investment, are achieving comparable or superior outcomes by considering best practices, and assessing cost effectiveness [4].

However, within EU-28 countries the landscape is heterogeneous, with on-going debate as to the optimum strategy to achieve value in the provision of cancer care [5]. The report by the Lancet Oncology Commission on the affordability of cancer in high-income countries has conceptualised the debate and we have set out in this section to review the changes and ethos of EU-28 countries towards cancer economics [6].

Breadth of the problem and the range of expenditures

Across Europe there remain significant inequities in the incidence of specific tumour types and outcomes of care. The overall risk of dying is decreasing, in line with improvements in screening, diagnosis and treatment, however variation in the magnitude of change exists according to disease site and country [7]. The CONCORD study demonstrated that five-year relative survival for breast cancer in Europe ranged from 57.9% and 62.9% in Slovakia and Poland respectively to 75.5%, 79.8%, and 82% in Germany, France, and Sweden with regional variation evident [8]. Such trends have been established in other studies, notably the Eurocare 5 report and The International Cancer Benchmarking Partnership Study [9]. Factors implicated include late diagnosis associated with advanced stage at presentation [10].

These findings were widely reported in the media [11] and stimulated public debate and political action with the creation of new policies designed to ameliorate regional and international disparities. Early diagnosis was considered a key policy goal to improve cancer survival in the UK. Prevention, increasing awareness of cancer symptoms and dissemination of best practice were all identified as key goals in the government's white paper "Improving outcomes a strategy for cancer" [12]. Comparative data from observational studies on cancer outcomes has the ability to influence the debate and result in positive policy changes.

Although absolute cancer expenditures alone are not indicative of outcomes, significant differences are likely to reflect potential issues in access to essential screening, diagnostic and treatment services as well as the political priority afforded to cancer care. A recent study [1] demonstrated that per capita cancer care expenditure varies considerably across the EU, even for countries with the same level of national income. The UK, Italy, Sweden and France when adjusting for price differentials spend 92€, 96€, 92€ and 97€, respectively, per person on cancer specific health care. By compar-

ison Germany spends 171€ per person and The Netherlands 123€. However across Eastern Europe the differences are marked, with adjusted costs per person per annum for Bulgaria, Romania and Poland of 52€, 54€ and 78€, respectively.

The effects of variation in expenditure and the comparative effectiveness of health care interventions across Europe remain difficult to discern due to inconsistent poor quality data, and challenges of adjusting for case mix when interpreting observational studies [13]. Additionally factors other than wealth are important, and unwarranted variation can result from limitations in health insurance coverage, disparities in access, (e.g. radiotherapy), as well as differences in country-specific cancer epidemiology [14–17].

The global recession: end of an era in cancer investment?

A major factor influencing the current cancer economics debate has been the austerity measures rolled out across Europe in the face of the recession. Greece cut its health budget by 23.7% between 2009 and 2011, Spain by 14% in 2012 and Portugal cut its health spending for the first time in 2011 [18]. In the UK, additional pressure on NHS (National Health Service) budgets has been placed by the "Nicholson challenge" which is seeking efficiency savings of more than 20£ billion by 2015 in order to meet projected patient demand [19]. In Italy, poor control of regional health care expenditures had resulted in a cumulative deficit of over 38€ billion [20].

Countries have attempted to reduce expenditures by encouraging efficiency savings through the use of generic drugs. Spain has gone further with cuts to professional training (75%) as well as public health and quality programmes (45%). There have been cost shifts from the state to patients; with previously exempt groups (e.g. pensioners) now required to make co-payments [21]. Rationing of health services have led to lengthening of waiting lists for hospital procedures and tests and reduced availability of cancer drugs across several countries in Europe.

In Romania there has been a chronic shortage of basic cancer drugs over the last 2 years. Whilst under-investment in pharmaceuticals is a factor, it is the complex and fragmented procurement and distribution pathway for drugs that has resulted in inconsistent supply stimulating the black market and Internet sales. Furthermore, the costs of drugs in Romania are the lowest in the EU, resulting in parallel exports whereby drugs are sold to other European states where the same drugs are usually more expensive [22].

Drug companies have reacted by tightening their conditions for trading with European countries such as Greece [23,24]. However the overriding concern is the impact that inequities in drug availability could have on cancer outcomes particularly for those unable to pay privately. Exacerbating the situation is the fact that the costs of cancer care in EU-28 countries are increasing at an unprecedented rate, driven by demographic changes, innovation and consumerism within health care [6]. Fiscal sustainability of health care financing therefore remains a key public policy concern. Calls have been made to the European Commission to intervene on this issue given concerns regarding patient welfare.

The forum for the discussion has been the European Partnership for Action Against Cancer (EPAAC) [25]. EPAAC was set up by the European Commission in 2009 to engage relevant stakeholders across the EU to deal with the challenges European countries face in delivering cancer care. It encourages research collaboration, dissemination of evidence-based practice, measurement of outcomes of care and the creation legislation that promotes healthier lifestyles (e.g. anti smoking policies).

Barriers to drugs access – the role of HTAs

In Europe price-setting and reimbursement decisions are devolved to individual countries with EPAAC advocating the increasing role of Health Technology Agencies (HTAs) in this process [26].

However a review of market access of cancer drugs in Europe shows inconsistency in the mechanism of reimbursement, the use of cost effectiveness analysis in decision-making, and extent of pharmaceutical price regulation schemes [27]. This had led to inequities in drug access even amongst countries with similar levels of national income, although not necessarily causing differences in patient outcomes. A UK Department of Health report assessing the extent of international variation in drug usage in 14 countries found that Germany, France and the US were amongst the countries with the highest access, compared to the UK, Canada and Australia that had amongst the lowest [28].

In this regard, a poll of key stakeholders in the affordability debate at The Oncopolicy forum during the 2011 European Cancer Organisation (ECCO) conference is indicative of current political and public debate on the issue. Participants cited the following as causes of inequities in drug access across Europe: national funding and willingness to pay (42.2%), drug affordability (40.2%), clinicians' non-adherence to guidelines (11.8%), health technology assessment process (3.9%), and marketing authorisation (2%) [29].

Cancer drugs represent a rising proportion of the cancer care budget [30]. Governments have attempted to utilise HTAs to ensure rational and fair decisions are made regarding resource allocation, however, attempts to control the provision of drugs not deemed cost effective by HTAs such as NICE have met widespread public and professional discontent [31,32]. These difficulties are exacerbated when the same drugs that have been refused in the UK are widely available in the US and Europe. Between 2004 and 2008, 46 anticancer drugs were granted a European license following FDA approval. NICE made recommendations for 18 (39%) of these drugs to be freely available on the NHS with 11 (24%) still awaiting approval. In contrast all of these drugs were covered by the three main insurance providers in the US [33,34].

Another major concern is the time taken to review new cancer drugs. Relative to the FDA, the European Medicines Agency took longer and approved fewer drugs between 2003 and 2010 [35]. It is not surprising that anticancer drug coverage decisions that also consider cost effectiveness are associated with great restrictions and slower time to coverage. However despite these drawbacks, such rigorous evaluation ensures that co-payments are not required at the point of access for drugs granted approval, enhancing equity [34].

Heterogeneity in reimbursement mechanisms across EU-28

In Sweden, value based pricing has meant that no cost effectiveness thresholds are defined, instead applying a societal perspective to consider costs and benefits of healthcare [36]. Likewise in the Netherlands cost effectiveness thresholds are higher than for countries such as the UK (20–80,000€/QALY gained) and based on disease severity and medical need, meaning high cost drugs are often approved [36]. Provisional reimbursement for four years can

be arranged for drugs which have insufficient data to enable formal cost effectiveness evaluations or where uncertainty remains [37].

Most countries have some form of risk sharing agreement for high value drugs, be it financial based agreements where rebates are offered to third party payers for the cost of increased expenditure over an annual subsidisation cap, or performance or outcome based agreements [37]. In Italy, innovative new cancer drugs are classified as Class H stipulating their use in the hospital setting. Class H drugs are bought directly by hospitals from the manufacturers, enabling them to benefit directly from cost sharing agreements and minimum discounts of 50%. These have enabled expansion of patient access to pharmaceuticals [38]. Given national drug budgets are fixed, the utility of local or regional level HTA's are diminished [39].

France has the highest expenditure for cancer therapeutics in Europe however there is a reluctance to encourage explicit rationing despite the presence of a HTA body, to avoid denial of potentially life-saving drugs [40]. Disease severity and drug efficacy are the main criteria rather than cost effectiveness and therefore high price innovative cancer drugs with significant budget impact are still likely to be reimbursed [41]. However legislation introduced in 2012 is attempting to define indications for health-economic evaluation for those drugs with significant budget impact [42].

Eastern European countries are attempting to formalise the role of HTAs within strategic health decision making as noted by their involvement in international collaborative efforts. However some member states do not have the capacity or expertise to form an HTA agency namely, Slovenia, Slovakia, Estonia, Malta and Luxembourg [43].

The debate continually played out in the media is one of concern about access to drugs and the potential effect on outcomes. Public and political pressure has resulted in policy changes devised to increase access albeit at significant cost (Box1). A recent review estimated that between 2009 and 2011 the additional cost to the NHS of providing new interventions under the updated end of life criteria was 549€ million per annum [44]. The Cancer Drugs Fund has also required significant financial commitment with close to 1€ billion having been invested in the initiative. Definitive evidence on its role in improving patient outcomes is awaited but approximately 34,000 patients have gained access to high cost drugs through the scheme [45].

Formal collaboration across Europe

Greater emphasis needs to be placed on ensuring fiscal sustainability and the generation of policy ideas that will sustain spending proportional to the projected rise in number of cancer cases, whilst embracing technological innovations that could potentially improve outcomes. Formal collaborations have commenced across Europe to reduce this perceived disparity between nations and to develop synergies that can benefit what is politically sensitive decision making. Consideration needs to be given for more direct engagement of patients and public when setting the policy agenda so that they are aware of the trade-offs (e.g. lengthening waiting lists, co-payments) that may result should access become the sole priority [46].

Since 2006 the European Network for Health Technology Assessment (EUnetHTA) has brought together established regional and national HTAs across Europe as well as research groups performing HTA activities in countries with no formal national HTA agency [47]. The European commission supports this collaboration. All members of the European Union are represented with the exception of Bulgaria and Slovakia.

Box 1: Advocacy.

In numerous instances individual patients, organisations and physicians have garnered attention advocating for greater access to and fairer prices for cancer drugs. In the UK, there have been a series of challenges over the last 10 years to decisions by NICE. Legal challenges resulted in the approval of both trastuzumab and imatinib despite the fact both exceeded the 30,000£ QALY threshold.¹ These decisions were made against a background of legal action by patients, with its attendant publicity, and some political pressure. Following approval of sunitinib, NICE reviewed its policy for end of life drugs, specifically the value placed on gains in survival and quality of life for incurable conditions where there remains a paucity of reasonable alternatives.² The U.K. Government has also attempted to further improve access by initiating the Cancer Drugs Fund, which was officially due to finish in January 2014 and be replaced by value based pricing (VBP). However a further 400£ million investment has extended its role until March 2016.³ These changes are examples of the key role played by the public and importantly the media in the cancer economics debate.

However it is not necessarily a fair assumption that the public think coverage of new technologies irrespective of cost is appropriate. In a recent survey of societal preferences for NHS funding, respondents agreed with the premise of VBP, but the majority did not believe that extra value should be placed for specific groups such as children, cancer patients or those with reduced life expectancy.⁴ Another study reported that the majority of cancer patients and the general public did not believe the NHS should fund drugs that have not been approved by NICE.⁵

In Canada a growing number of high-profile cases of media and political influence have impacted drug approvals. A salient example is that of the 35-year old Ontario woman whose breast cancer was HER2-positive, but less than 1 cm in size without evidence of lymph node involvement. According to Cancer Care Ontario evidence based guidelines in 2011 she would not qualify for public funding of trastuzumab (Herceptin®). Citing the inter-provincial inequities to access, a massive letter-writing campaign to the Ontario Ministry of Health coordinated by patient advocacy groups⁶ led the provincial “public watchdog”, Ombudsman Ontario, to launch an investigation.⁷ Heavy media coverage ensued⁸ and within weeks the Ministry announced that it would fund trastuzumab for tumours less than 1 cm through Cancer Care Ontario’s new Evidence-Building Program.⁹ Ombudsman Ontario dropped their investigation.¹⁰

While in the US, physician advocacy may be increasing. Recent examples of vocal advocacy include: (1) the opinion piece co-authored by three Memorial Sloan Kettering (MSK) physicians in the New York Times that decried the planned charge for aflibercept (Zaltrap®), a “VEGF-trap”, that is neither better nor less toxic than bevacizumab but was to cost twice as much¹¹; and (2) an editorial signed by 119 chronic myeloid leukaemia (CML) experts that addressed “the multiple factors involved in cancer drug pricing and their impact on individual patients and health care policies”, and argued “for the need to (1) lower the prices of cancer drugs to allow more patients to afford them and (2) maintain sound long-term health care policies”.¹² In the case of aflibercept the company “reduced” prices by more than 50%, earning the MSK physicians praise from the New York Times¹³; while in the CML advocacy the outcome remains to be seen.

References

1. Steinbrook R. Saying no isn’t NICE—the travails of Britain’s National Institute for Health and Clinical Excellence. *New England Journal of Medicine*. 2008;359(19):1977–81.
2. Raftery JP. NICE and the challenge of cancer drugs. *BMJ*. 2009;338:271.

3. Health Do. Guidance to support operation of the cancer drugs fund in 2011–12. 2011 [2nd May 2013]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/152364/dh_133683.pdf.pdf [last accessed 09.02.14].
4. Linley WG, Hughes DA. Societal Views on NICE, Cancer Drugs Fund and Value-based pricing criteria for prioritising medicines: A cross sectional survey of 4118 adults in Great Britain. *Health Economics*. 2012.
5. Jenkins VA, Trapala IS, Parlour L, Langridge CI, Fallowfield LJ. The views of patients and the general public about expensive anti-cancer drugs in the NHS: a questionnaire-based study. *JRSM Short Reports*. 2011;2(9).
6. <http://rethinkbreastcancer.com/funding-for-herceptin-in-ontario/> [last accessed 06.12.13].
7. <http://www.ombudsman.on.ca/Files/Sitemedia/Documents/Investigations/SORT%20Investigations/pressreleasemar18-en.pdf> [last accessed 08.12.13].
8. <http://www.theglobeandmail.com/life/health-and-fitness/breast-cancer-patient-gets-access-to-costly-treatment/article594840/> [last accessed 08.12.13].
9. <https://www.cancercare.on.ca/toolbox/drugs/ebprogram/> [last accessed 08.12.13].
10. <http://www.ombudsman.on.ca/Newsroom/Press-Release/2011/Herceptin-coverage-extended-Ombudsman-suspends-i.aspx> [last accessed 08.12.13].
11. http://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html?_r=0 [last accessed 09.02.14].
12. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood*. 2013;121:4439–42.
13. <http://www.nytimes.com/2012/11/13/opinion/incredible-prices-for-cancer-drugs.html> [last accessed 09.02.14].

Since 2010 the EUnetHTa has been collaborating with the EMA following a direct mandate from the Pharmaceutical forum with the aim of improving the availability and best use of data relevant to Health Technology Assessment [48]. In November 2013 this collaboration announced a three-year work plan. Key areas include:

- (1) Developing approaches for collection of post-authorisation data to support activities of regulatory agencies and HTAs.
- (2) Facilitate clinical trial design to enable generation of data relevant for both benefit-risk and relative effectiveness assessments.
- (3) Orphan medicinal products – exploring ways of sharing information for the common benefit of patients with rare diseases whilst ensuring financial sustainability.

Where do radiation therapies stand in the cancer economics debate?

The debate on cancer economics has largely focused on expensive cancer drugs. However a less mature debate amongst EU-28 countries concerns the evaluation of radiation technologies, an area that has undergone significant development over the last 5–10 years. Radiotherapy is considered a necessary component of treatment in 52% of all newly diagnosed cancers [49]. Taking into account all costs across the life cycle of the resource, it is, broadly speaking more cost effective than surgery and chemotherapy [50]. However, the UK as with other European countries is in a paradoxical situation where delivering affordable radiotherapy over the next twenty years is being compromised by both current undercapacity and underinvestment in ‘standard’ radiotherapy and also

over-penetration of newer radiotherapy technologies that have far greater associated costs [51].

A recent analysis of Directory of Radiotherapy Centres (DIRAC) database demonstrated variation in radiotherapy capacity and quality across the EU [52]. The average number of megavoltage teletherapy machines per million of the population varies from 1.3, 2.8, 2.0 in Romania, Poland and Bulgaria respectively compared to 6.5, 7.6, 8.2 and 9.7 in France, The Netherlands, Sweden and Denmark respectively. In the former group of countries there is significant unmet radiotherapy need with a requirement to modernise capital infrastructure. The UK has 5.4 machines per million of the population however it is estimated that for the UK to meet projected demand by 2016, will require a 67% increase in current capacity requiring an extra 147 radiotherapy machines [53].

The quest to improve the therapeutic ratio (i.e. maximise tumour dose while limiting dose to normal tissues) has resulted in the development of innovative radiation technologies such as intensity modulated radiotherapy (IMRT), stereotactic radiotherapy and particle therapy e.g. proton therapy [54–56]. Whilst they offer the potential to reduce long term toxicity through improvement in dose deposition and accurate target localisation, there remains a paucity of randomised evidence of their benefit in achieving clinically relevant improved outcomes [49,57,58]. To inform the discussion, ESTRO (European Society for Radiotherapy and Oncology) has launched the HERO (Health Economics in Radiation Oncology) project to develop a knowledge base and a model for health economic evaluation of radiation treatments at the European level [59].

Of all the new technologies, the case of radiotherapy demonstrates the paradox of public policy towards affordable cancer care. A failure to deliver basic service needs, yet willingness to ‘overspend’ on technologies that have not been demonstrated to be cost effective. However stimulating debate in this area remains a challenge, as it appears the public identify more with concerns regarding drug access than radiotherapy. This despite evidence that the estimated impact of chemotherapy on 5-year survival for all cancers is 2% compared to 16% overall for radiotherapy [60,61]. The role of the pharmaceutical industry in driving the debate needs to be considered when reviewing this paradox, with pharmaceutical companies known to support patient lobbying groups when funding decisions of new technologies are being considered [62].

Cancer economics debate – the case of Canada

Overview – the Canadian system

As in the US and EU drug costs are rising and in Canada are the second largest health care expense (public and private) after hospitals [63]. Total health expenditure in Canada was \$CAD 200.1 billion in 2012. Per capita health expenditure was \$CAD 5803 in 2011, and is forecast to reach \$CAD 5988 for 2013 [63]. The Canadian Cancer Society estimated that in 2013, 187,600 Canadians would be diagnosed with cancer and 75,500 would die of cancer. Approximately 2 in 5 Canadians will develop cancer and 1 in 4 will die of their disease [64]. Fifty-two percent of new cases will be lung, breast, colorectal and prostate cancer.

A recent analysis of all healthcare costs for the province of Ontario estimated a mean of \$CAD 27,560 per patient in the year after diagnosis [65]. This included direct health care costs such as inpatient and outpatient care, intravenous chemotherapy, outpatient drugs, radiotherapy, same-day surgery and diagnostic tests. They did not estimate indirect costs, lost productivity or other expenditures. Costs varied considerably according to tumour site and 1-year survival. There was also variation according to geographical location with more remote areas of the province incurring

higher costs, which the study authors suggest may be due to a later stage at diagnosis. There is little reliable national data on direct or total health care expenditures for cancer. However, based on the Ontario data and assuming similar disease burden and costs in all Provinces, the same report estimated healthcare costs from the first year of diagnosis to be as high as \$CAD 484 million for colorectal cancer, \$CAD 453 million for lung cancer, \$CAD \$267 million for breast cancer and \$CAD 238 million for prostate cancer. Using 2009 GDP of \$CAD 1.5 trillion, the first-year costs for colorectal, breast, lung and prostate cancer combined would represent approximately 0.09% of Canada's GDP [65].

While cancer survival in Canada compares favourably with the US and the EU [8,11] new drug approvals by Health Canada remain slow [66,67], and the absence of a common pharmaceutical policy creates some inequities in access and pricing across the ten provinces. Canada's publicly funded health care system is based on the principle of universal coverage for “medically necessary health care services provided on basis of need, rather than the ability to pay” [68]. While public coverage for physician and hospital services is 100%, there is no legislated national coverage for drugs or home and community care services, with the exception of drugs administered in hospital. Provinces hold jurisdiction for decision-making regarding public funding of and pricing for new medicines including cancer drugs [68,69].

The national health system, known as “medicare”, can be best described as an “interlocking set of ten provincial and three territorial health insurance plans” [68]. However, unlike many other unitary states, Canada as a federation does not have a *national* health insurance plan but has 6 federal, 10 provincial and 3 territorial tax-payer funded plans in addition to thousands of private insurance plans. Health Canada, the government Ministry charged with setting and administering the principles of the Canada Health Act, assists in the financing of provincial/territorial health care services through fiscal transfers, in the form of cash or tax points, conditional on meeting the principles of the Act [70]. Tax points transfers occur when the federal government reduces some of its taxes enabling provinces to raise theirs by the same amount. The result is an increase in provincial revenues, with no increase in the total tax burden borne by Canadians. In effect the federal government steers policy through the indirect means of its spending power.

While Health Canada delivers health care services to specific groups including the aboriginal groups, First Nations and Inuit, for the vast majority of Canadians, provinces are responsible for the organisation, financing and delivery of health services including approvals and pricing for new drugs and technologies. Any drug approved by Health Canada can theoretically be paid for out of pocket, however many intravenous and oral cancer drugs are publicly funded, albeit with considerable variation across jurisdictions [71]. Those not publicly funded may be covered through private insurance/third party coverage (about 60% of Canadians), or through special provincial coverage for the elderly or those on social assistance [72]. Individuals may purchase some intravenous cancer drugs not publicly funded. In some provinces including Ontario, a few private chemotherapy infusion clinics were established in the mid 2000s [73]. Debate is on-going regarding the utilisation of public health infrastructure (i.e. pharmacy, nursing, and space resources) for patients who choose to pay for unfunded drugs; both Ontario and the UK have adopted a more permissive approach to this matter [74].

Canada – challenges and solutions

In 2005 Ontario published the first 3-year provincial cancer plan that included several hundred million dollars in capital and health services investment. The province also began to (1) report

systematically on system performance through the Cancer System Quality Index (CSQI [75]); (2) include indicators and targets across the cancer control continuum; (3) support a strategy for improved national surveillance, performance and risk assessment; and (4) identify areas of strategic priority for investment [75]. The Ontario-based Committee to Evaluate Drugs (CED) is the Ministry's independent expert advisory committee on drug-related issues. The CED evaluates the clinical value of drug products, interchangeability of generic drug products and cost-effectiveness of drugs through evidence-based reviews. These reviews result in recommendations being made to the Executive Officer regarding the coverage of these products through the Ontario Public Drug Programmes and ultimately the Executive Officer at the provincial Ministry of Health, makes final decisions whether or not to list a new drug in the public system and at what price.

Meanwhile, at the national level, in 2006 the Canadian Strategy for Cancer Control published the first national cancer plan [76]. To implement the new strategy the Canadian Partnership Against Cancer (CPAC), an independent non-profit organisation with federal government funding was launched, with \$CAD 250 million over 5 years; this has since been renewed. In March 2007 the inter-provincial Joint Oncology Drug Review (JODR) was developed and in 2010 became the Pan-Canadian Oncology Drug Review (pCODR), with a broader nationwide representation. pCODR provides clinical and pharmacoeconomic assessment of new drugs, at the request of provincial cancer agencies, pharmaceutical companies or other relevant stakeholders. With the exception of the initial price offered by pharmaceutical companies, pCODR processes are transparent and all reviews including details of deliberations and input from patient advocacy groups are publicly available online [77]. The pCODR publishes their final recommendations, which are then considered by individual provincial formulary mechanisms. In November 2013 an online lay-oriented tutorial was posted, to inform health professionals and the public on how cancer drug funding decisions are made [78].

To date the majority of pCODRs recommendations have been approvals, but these are almost always "conditional on the cost-effectiveness being improved to an acceptable level" (e.g. Ipilimumab for stage II/IV melanoma [79]). Despite mechanisms to ensure timely, equitable recommendations based on clinical evidence and cost-effectiveness, the adoption of pCODR recommendations is uneven across the country. Some provinces may decide against listing a new cancer drug for a variety of reasons, the most salient of which is the absence of conventional cost-effectiveness [74]. Despite the lack of national coverage standard for drugs, over a 2–3 year period following submission for consideration of a drug for funding, there does appear to be 'soft' harmonization of the formularies, as provinces tend to adopt common cancer drug coverage over time.

How each province sets the final price is coming under greater scrutiny with efforts underway to reduce inter-provincial differences. First, the Patented Medicine Price Review Board (PMPRB) sets a "ceiling price" nationally and this effectively becomes a floor price for a pharmaceutical company. PMPRB is an independent, quasi-judicial body established by Parliament in 1987 [80]. According to the PMPRB mandate a new brand-name drug in Canada can never be the most expensive in the world, and drugs already approved cannot increase by more than the Consumer Price Index. The cost of a new drug is considered as excessive if it exceeds the highest price of the same strength and dosage form of the same patented drug product for each country listed in the Regulations (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States) [81]. Upon considering pCODR's recommendation to list a new drug, it is then within each provincial Ministry of Health that closed door deliberations take place, leading to a final price being offered to the pharmaceutical company. In some cases,

such as erbitux (Cetuximab®) in Ontario, a pharmaceutical company may choose to withdraw their request for approval on the basis of this final price, leaving patients to seek funding through private insurance. This process too will soon be more transparent, and harmonized across the country via a new mechanism, the Pan-Canadian Pricing Alliance. The goals of the alliance are to: (1) increase access to drug treatment options; (2) improve the consistency of drug listing decisions across the country; (3) capitalise on combined buying power of jurisdictions; (4) achieve consistent pricing and lower drug costs; and (5) reduce duplication of negotiations and improve utilisation of services [82].

Cancer economics debate – the case of the United States

Finally, we examine the US system, exploring the efficacy of cancer therapeutics and the value and limitations of clinical trial results, important factors that should inform and influence health policy decisions.

The US healthcare system – attributes, deficiencies and on-going changes

The system for approving cancer therapeutics in the US is relatively straightforward. After initial consultations with the United States Food and Drug Administration (US FDA) the sponsor sets out to achieve previously agreed to endpoint(s). Approval will likely be granted if results are statistically valid and the drug generally tolerable. Importantly the US FDA does not discriminate against therapies similar to already approved therapies, as discussed below. Following US FDA approval the Centres for Medicare and Medicaid Services (CMS) grants its approval as do a majority of insurance companies often looking for guidance from groups such as the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). Unlike Europe where European Medicines Agency (EMA) approval requires subsequent approval by nations, US FDA approval covers all fifty states and the District of Columbia. Also because the US FDA does not consider costs and CMS is forbidden from negotiating prices, cost is not a factor neither in approval nor deployment of therapeutics. The law forbidding CMS from negotiating prices is a subject of debate. As in the EU and Canada, the US system is subject to both societal and political pressures. Nearly everyone agrees with this, although not everyone agrees whether this is harmful or beneficial.

The current health care burden and where it may go

A recent Council of Economic Advisers report noted that medical spending is slowing [83]. Per-capita health-care spending rose just 1.8 percent annually from 2007 to 2010 and even slower since then. While some of the slowdown can be explained by the recession and the slow recovery, many believe other factors may also be at work. As to the future, "structural changes" such as insurance plans with narrower networks of hospitals/doctors and changes in incentives may begin to have a salutary effect. Additionally, higher deductibles and co-pays will likely bring value into focus. In cancer, efficacy and novelty of therapies are likely to emerge as even more important factors.

Cancer therapeutics: are we getting what we pay for?

While much has been written about the cost of cancer therapeutics, the problem is not that therapies are expensive, but that for the benefit they deliver, their costs are excessive [84–87]. Looking at cancer therapies approved by the US FDA for solid tumours

between 2002 and 2012, one finds surprisingly small median benefits with progression-free and overall survivals prolonged 2.15 and 2.16 months, respectively [88]. Even more important: (1) combination therapies have repeatedly failed (inhibitors of BRAF and MEK in melanoma as exception [89,90]); and (2) their use sequentially has proven disappointing. Consider examples in metastatic colorectal cancer (mCRC) and metastatic renal cell carcinoma (mRCC). In mCRC, gains have stagnated. The recently published ML18147 trial, a prospective study in which bevacizumab was given with *all* chemotherapy regimens achieved a survival of 23.9 months [91]. This was disappointingly indistinguishable from survival a decade earlier in a GERCOR study without bevacizumab that reported similar survivals of 21.5 and 20.6 months [92]. While in mRCC one finds a similar stagnation in benefits even as the number of options has increased. To be sure, gains have been made. In the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registry survival between 2000 and 2003 before “targeted therapies” was 15 months compared to 20 months between 2005 and 2008 in the “targeted therapy” era [93]. But the evidence also indicates benefits may have reached a plateau. In a recently published trial the estimated survival of 29.3 months with sunitinib [94] overlapped the value of 26.4 months achieved with sunitinib in a trial that enrolled patients five years earlier [95].

Can this be true? Has improvement in overall survival in mCRC and mRCC reached plateaus? The SEER data shows gains in the community are much less than in clinical trials – survivals of 20 months in the era of targeted therapies, compared with 26.4–29.3 months in clinical trials bracketing this period [93–95]. Furthermore, the SEER data shows new therapies have had limited impact on both renal cell and colorectal cancer survival (Fig. 1). How can it be that in mRCC despite approval of seven drugs since 2005, improvement in survival rates has been disappointing? Amongst several explanations, the class of the drugs approved and the design of clinical trials stand out.

The impact of drug class underscores an attribute of the US FDA that is also a drawback – it largely ignores the class of the drug under review. Nearly identical drugs can seek approval for similar indications; and provided efficacy and safety are demonstrated, approval is likely. The FDA believes it is not in their purview to decide if a similar drug is or is not needed – marketplace forces will decide. Thus, four of seven drugs approved for renal cell carcinoma inhibit the vascular endothelial growth factor receptor (VEGFR) [96] and a fifth targets the ligand (VEGF) [97]. While the other two are derivatives of sirolimus [98]. Having very similar options has added little to survival. Patients are not living substantially longer, and receive drugs sequentially at no greater cost.

What about the design of clinical trials? Unfortunately they do not represent the general population. The importance of this is underscored by a report from the International Metastatic RCC Database Consortium study [99]. Trial eligible patients survived 28.4 months, but the 35% of patients that did not satisfy standard trial eligibility criteria had a discouraging 12.5 months survival. The authors concluded, “The number of patients ineligible for clinical trials is substantial and their outcomes are inferior. Specific trials addressing the unmet needs of protocol ineligible patients are warranted.”

Patients enrolled in clinical trials are “better fit” and younger [100] underscoring the flaw in extrapolating clinical trial results to all patients, especially in policy decisions. The US SEER data cited above [93], for example, found age older than 65 a predictor of a shorter survival. And in the fifty-seven trials supporting the forty-eight FDA approvals between 2002 and 2012, enrolled patients were generally younger than those in the community with the same cancer and in the majority older patients achieved less benefit [88]. An additional consequence of this disparity is poorer tolerability in the community as seen in an observational study of patients with hepatocellular carcinoma treated with sorafenib in which the rates of dose reduction and discontinuation were 50–100% higher in the

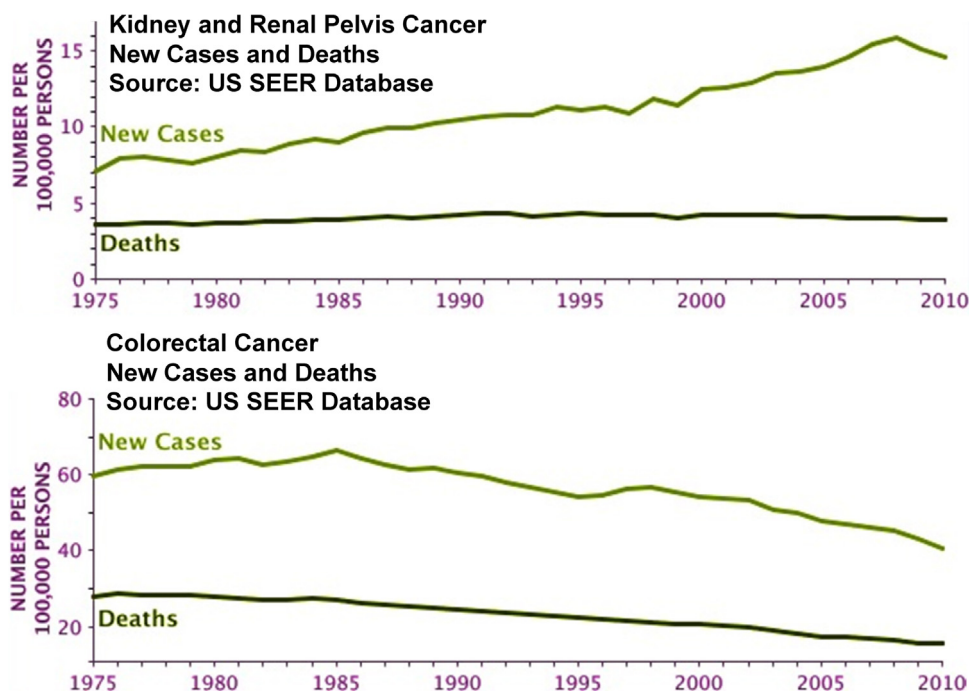


Fig. 1. Survival rates for renal cell and colorectal cancers in the era of targeted therapies. Using statistical models, the SEER data finds the rates for new kidney and renal pelvis cancer rose on average 1.7% each year from 2000 to 2010 with death rates falling on average 0.6% each year over the same period – a trend that antedates the start of “targeted therapies” and could be explained by earlier detection and better surgical interventions. While for colorectal cancer death rates have fallen on average 2.8% each year during this period, coincident with a 2.9% fall in the rates of new colon and rectum cancer cases.

observational study [101] than in the original report [102]. The elderly can also be expected to gain less from ensuing therapies.

These facts are important for society and pharmaceutical companies. In mRCC, for example, initial surgical costs are “built into the system” so that going forward the administration of expensive therapies to patients with metastatic disease will drive higher costs. Unfortunately, as discussed, the length of that time has not increased appreciably despite seven new therapies and outlays by individuals and society will not change much in the near term – indeed as drug patents expire, costs may decrease. Novel therapeutics may yet add some benefit and cost, but this will likely be incremental. For society this offers the possibility the rate of increase of oncology drug prices for some cancers may now fall. As for pharmaceutical companies one would think the experience in mRCC with “me too drugs” that do not substantially prolong survival when used sequentially but must compete for market share would be instructional. But unfortunately “me too” drug development is not likely not to go away – inhibitors of the anaplastic lymphoma kinase (ALK) in non-small cell lung cancer (NSCLC) as an example in a very small market. And although “me-too drugs” may be viewed as a safe investment, for society it is unacceptable to have patients enrolled in clinical trials involving drugs that are either never approved or do not yield the needed gains in survival.

Cancer patient outcomes in the United States

Finally we turn to allegations cancer patient outcomes in the US are less than would be expected for its investment. Let's begin by first looking at some of the data within the United States that speaks to these allegations, then consider very basic facts, and conclude by “assigning responsibility”.

Data from the World Cancer Research Fund International [103] shows the rate for all cancers (excluding non-melanoma skin cancers) was 1.73 times higher in more developed compared with less developed countries (255.8 versus 147.8 per 100,000 population). Such data imply greater wealth leads to greater cancer risk, but the United States data suggests a threshold exists, and that all Americans exceed this threshold (Fig. 2). Furthermore, wealth confers only limited advantages suggesting gains in cancer survival have a threshold above which additional expenditures bring diminishing returns (Fig. 3). Consistent with this, SEER-Medicare linked data found no consistent association between mean regional Medicare spending and survival [104].

Why do greater US expenditures not bring better outcomes or at least outcomes commensurate with outlays? Expensive therapeutics conferring modest or marginal benefits is one explanation. But pharmaceutical companies bristle at this focus, arguing this is only a fraction of health care expenditures. Admittedly self-serving, this argument has some validity since doctor's fees, expensive diagnostics, excessive procedures by innumerable consultants and skyrocketing intensive care unit costs contribute enormously. And more importantly, a large percentage of these outlays occur at what many might consider inappropriate times. For example, the data show a quarter of total cancer care expenditures occur in the last year of life with a large portion in the last 30 days [105]. Given healthier cancer patients derive the greatest benefit from any intervention much is being spent when the return on investment can be expected to be very low, and current data is not encouraging for a solution in the near term [106].

Consider recent data from the Dartmouth Atlas Project [105], an endeavour that uses Medicare data to provide information and analysis about hospitals and their affiliated physicians at a local, regional and national level. Its 2010 report (Table 1) found mixed results when looking at trends in end-of-life cancer care across the country: (1) fewer days hospitalized but increased number in intensive care in the last month of; (2) Increase in hospice days but often beginning in the last three days of life; (3) increase in percentage of patients who saw ten or more physicians during the last six months of their lives; (4) not much change in endotracheal intubation, feeding tube placement, and cardiopulmonary resuscitation during the last month of life or percentage of patients receiving chemotherapy during the last two weeks of life. The report concluded: “Despite the increased frequency of end-of-life discussions, cancer treatment has become more aggressive in general. It could be that some patients prefer more aggressive care, or do not fully understand – or accept – that their life expectancy is limited when expressing their preferences. Alternatively, end-of-life discussions may occur too late in the course of illness to have a serious impact on treatment ... the findings ... suggest that there is more work to be done to ensure the wishes of cancer patients facing the end of their lives are elicited, understood, and honored.”

Finally we turn to “assigning responsibility”, and in the US system there is plenty of “responsibility” to assign. Consider the following: As a society the US expects results too often fuelled by hype in the lay press. Patients and their families, read about the imminent cure of cancer, the personalising of medicine and how cancer can now be a chronic disease and feel hopeful [107–109]. They present

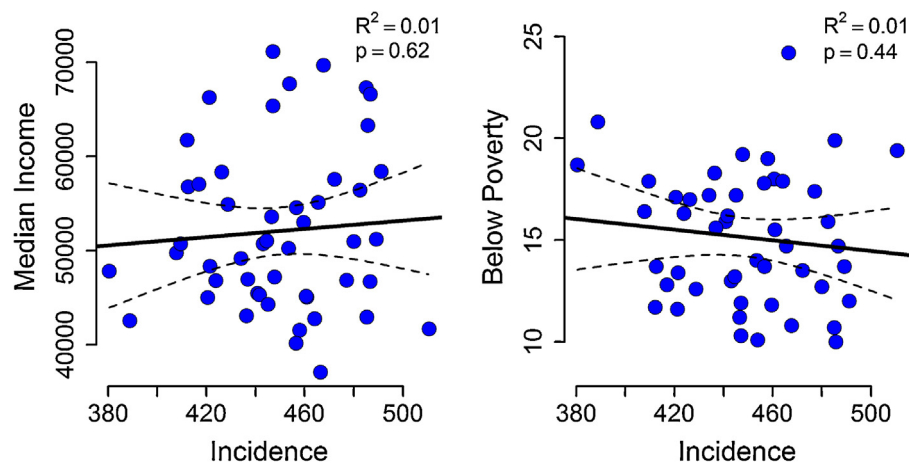


Fig. 2. US data showing plots of cancer incidence across the fifty states and the District of Columbia as a function of median income or percent of households below the poverty level. The data show that in the US cancer is not a disease of the wealthy, but a disease of Americans. Median income: In USD. Incidence: Age-Adjusted Invasive Cancer Incidence Rates by State, 2010 data. All Cancer Sites Combined for both Males and Females. Rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25-1130).

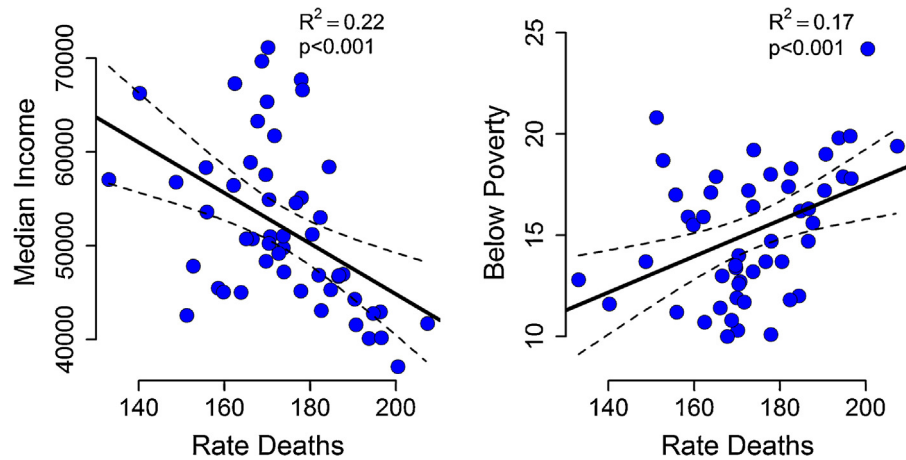


Fig. 3. US data showing plots of cancer death rates as a function of median income or percent of households below the poverty level. The data show that in the US greater wealth confers only limited advantages. Although the correlations are statistically significant, the data show that wealth (or percent of households below the poverty level as a surrogate) can only account for at most 17–22 percent of the variance. The latter may be explained if gains in cancer survival have a threshold above which additional expenditures bring diminishing returns. *Median Income:* In USD. *Rates Death:* Age-Adjusted Cancer Death Rates by State, 2010 data. All Cancer Sites Combined for both Males and Females. Rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25-1130).

Table 1

National trends in selected measures of the care of cancer patients near the end of life.

Measure	2003–2007	2010	Percent change, 2003–2007 to 2010
Number of deaths among cancer ill patients ^a	235,821	212,322	–10.0%
Percent of deaths occurring in hospital	28.8	24.7	–14.4%
Percent hospitalized, last month of life	61.3	62.2	+1.5%
All hospital days per patient, last month of life	5.1	4.8	–5.2%
Percent admitted to ICU, last month of life ^b	23.7	28.8	+21.6%
ICU days per patient, last month of life ^b	1.3	1.6	+21.2%
Percent receiving life-sustaining treatment, last month of life	9.2	9.4	+3.1%
Percent receiving chemotherapy, last two weeks of life	6.0	6.0	+0.7%
Percent enrolled in hospice, last month of life	54.6	61.3	+12.2%
Hospice days per patient, last month of life	8.7	9.1	+4.3%
Percent enrolled in hospice within three days of death ^c	8.3	10.9	+30.9%
Percent seeing 10 or more physicians, last six months of life ^d	46.2	58.5	+26.8%

Adapted from the Dartmouth Atlas of Health Care Brief [105].

^a The estimate for 2003–2007 was created by summing a 20% sample over five individual years.

^b Previous research has shown use of ICU resources is in part driven by the “supply”.

^c Time period too brief to provide patients full benefit of hospice care.

^d Although the Dartmouth Report authors interpreted this diversity of physicians as a suggestion “more patients may have experienced fragmented care”, an equally likely possibility implicates an increase in the number of specialists recruited to consult on dying cancer patients for whom little that is meaningful can be done.

to their oncologist expecting a cure or at a minimum a decade of life – often with expensive, “personalised results” that have not been validated but that they think will ensure success [110,111]. Many options will be “me-too drugs” one can argue should never have been but were developed and are often very expensive – in part because many other “me-too drugs” did not succeed adding cost to company ledgers that must be “recovered”. Additional expenses were incurred because academicians with pharmaceutical company support conducted large multi-institutional trials. These were needed because participation in clinical trials has reached intolerable lows [112] and large numbers were needed quickly to achieve statistical significance for the expected marginal benefits before the competition. Additional expenses occurred because the trials have become increasingly burdened by regulations, the majority of which, many have argued, have not made patients safer, but have made trials difficult and expensive [85,113].

Unfortunately expensive therapies are not curative, too often deliver only marginal benefits, and in the majority the cancer recurs. Hard-working, dedicated oncologists wanting to help their patients who wish to “continue fighting”, all too often demure and continue treating when they should not. They reach for unproven drugs or combinations, many extraordinarily expensive, or for regimens proven only in first line but found in various guidelines as a

fourth line alternative where it provides little or more likely no benefit, but at great cost – financially and in terms of toxicity. Or the oncologist administers “off-label”, often at great expense to the patient, a “novel therapy” that has never been proven beneficial in the setting being used. The oncologist knows nothing has worked in the past and in desperation looks to something “novel”. But the problem is not drugs from the past were ineffective; the problem is the cancer is refractory and will not respond to this novel, expensive therapy. The oncologist knows the remote chances of a meaningful outcome; the patient encounters the certainty of financial costs and toxicities that impact the quality of their remaining lives. Only in the end, when less than two weeks of life remain, does the “average cancer patient” in the US seek out hospice.

Conclusion

Significant heterogeneity exists in both expenditure and outcomes of cancer care. The demographic transition means that cancer remains at the forefront of the public and political consciousness with numbers expected to rise as populations’ age. Austerity following the global recession has brought its own unique set of challenges with concerns regarding cuts to cancer spending to reduce public expenditure. HTAs have been initiated across

much of Europe and have started to collaborate in order to identify high value drugs which are likely to improve outcomes over and above those currently used, taking into account resources and disease characteristics within the population. However the degree of uptake of these decisions and their impact on prescribing policy is variable, with challenges to several decisions resulting in a change to reimbursement policy in countries such as the U.K.

A less mature debate is the impact of new radiation technologies in driving the costs of cancer care. Due to methodological limitations of conducting radiotherapy trials, evaluation of relative effectiveness remains limited however greater attention needs to be given to rigorous evaluation of new technologies coming to market in the EU, as per pharmaceuticals. Imaging modalities similarly require tighter budgetary controls given their myriad of indications.

Throughout the world how to deal with the cost of cancer care remains a work in progress. It is clear all countries are earnestly trying to achieve equitable availability of therapeutic options, as efficiently as possible, mindful of the increasingly limited resources. Future work should enhance collaborative efforts on assessing relative effectiveness. Unfortunately this is as much a cultural and political issue as one related to affordability.

Conflict of interest

No conflict of interest.

References

- [1] Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol* 2013;14:1165–74.
- [2] Philipson T, Eber M, Lakdawalla DN, Corral M, Conti R, Goldman DP. An analysis of whether higher health care spending in the United States versus Europe is 'Worth It' in the case of cancer. *Health Aff* 2012;31:667–75.
- [3] Furlow B. Expensive US cancer care: value for money? *Lancet Oncol* 2012;13(5):e193.
- [4] Drummond MF, Mason AR. European perspective on the costs and cost-effectiveness of cancer therapies. *J Clin Oncol* 2007;25:191–5.
- [5] Whalen J. Europe targets drugs price cuts. *Wall Street J* 2010.
- [6] Sullivan R, Peppercorn J, Sikora K, Zalcberg J, Meropol NJ, Amir E, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–80.
- [7] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer (Oxford, England: 1990)* 2013;49:1374–403 [Epub 2013/03/15].
- [8] Coleman MP, Quaresma M, Berrino F, Lutz J-M, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9:730–56.
- [9] De Angelis R, Sant M, Coleman M, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *Lancet Oncol* 2014;15:23–34.
- [10] Coleman M, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* 2011;377:127–38.
- [11] Martin N. UK cancer survival rate lowest in Europe. *The Daily Telegraph* 2007.
- [12] Health Do. In: Health Do, editor. Improving outcomes: a strategy for cancer. 2011.
- [13] Lyman GH. Counting the costs of cancer care. *Lancet Oncol* 2013;14:1142–3.
- [14] Halpern MT, Ward EM, Pavluck AL, Schrag NM, Bian J, Chen AY. Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis. *Lancet Oncol* 2008;9:222–31.
- [15] Gray M, Naredi P, Bacon N, Kerr D. Better value cancer care for the 21st century. *Ann Oncol* 2011;22:2541–5.
- [16] Marmot M, Wilkinson R. Social determinants of health. Oxford University Press; 2009.
- [17] Vrdoljak E, Wojtukiewicz MZ, Pienkowski T, Bodoky G, Berzinec P, Finek J, et al. Cancer epidemiology in Central and South Eastern European countries. *Croat Med J* 2011;52:478–87.
- [18] Stuckler D, Basu S. *The Body Economic: Why Austerity Kills—Recessions, Budget Battles, and The Politics of Life and Death*. Harper Collins; 2013.
- [19] Kmietowicz Z. New health secretary warns further NHS efficiency savings may be needed. *BMJ* 2010;340(May):c2600-c.
- [20] de Belvis AG, Ferré F, Specchia ML, Valerio L, Fattore G, Ricciardi W. The financial crisis in Italy: implications for the healthcare sector. *Health Policy* 2012;106:10–6.
- [21] Legido-Quigley H, Otero L, la Parra D, Alvarez-Dardet C, Martin-Moreno JM, McKee M. Will austerity cuts dismantle the Spanish healthcare system? *BMJ* 2013;346:f2363.
- [22] L.C. Romanian politics – A shortage of cancer drugs. *The Economist* 2013.
- [23] Sukkar E. Greeks feel effects of drug shortages caused by austerity measures. *BMJ* 2012;344:e3589.
- [24] Rada AG. "A generation of cancer patients is being sacrificed" because of drug shortages in Europe, expert says. Tavistock Square, London, England: BMJ Publishing Group British Med Assoc House; 2012.
- [25] Communities CotE. Communication from the commission to the European parliament, the council, the European economic and social committee and the committee of the regions on Action Against Cancer: European Partnership. Brussels, 24.06.2009.
- [26] Jönsson B. Technology assessment for new oncology drugs. *Clinical Cancer Res* 2013;19:6–11.
- [27] Pauwels K, Huys I, Casteels M, De Nys K, Simoons S. Market access of cancer drugs in European countries: improving resource allocation. *Target Oncol* 2013;November [Epub ahead of print].
- [28] Richards M. In: Health Do, editor. Extent and causes of international variation in drug usage. 2010.
- [29] Organisation EC, editor. *Oncopolicy Forum 2011: Inequalities in Access to Cancer Drugs in Europe*. Oncopolicy Forum; Stockholm Sweden. 2011.
- [30] Zambrowski J. Cost of cancer in France: pharmaceutical expenditure as part of global patients' care. *Bull Cancer* 2008;95:535.
- [31] Mayor S. NICE recommends kidney cancer drug it previously rejected on cost grounds. *BMJ* 2009;338:b499.
- [32] Dyer O. Oncologists protest about NICE's decision on cancer drugs. *BMJ* 2002;324:1413.
- [33] Malin JL. Wrestling with the high price of cancer care: should we control costs by individuals' ability to pay or society's willingness to pay? *J Clin Oncol* 2010;28:3212–4.
- [34] Mason A, Drummond M, Ramsey S, Campbell J, Raisch D. Comparison of anti-cancer drug coverage decisions in the United States and United Kingdom: does the evidence support the rhetoric? *J Clin Oncol* 2010;28:3234–8.
- [35] Roberts SA, Allen JD, Sigal EV. Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the United States than in Europe. *Health Aff* 2011;30:1375–81.
- [36] Sorenson C. Use of comparative effectiveness research in drug coverage and pricing decisions: a six-country comparison. *Issue Brief (Commonwealth Fund)* 2010;9:1.
- [37] Cheema P, Gavura S, Migus M, Godman B, Yeung L, Trudeau M. International variability in the reimbursement of cancer drugs by publically funded drug programs. *Curr Oncol* 2012;19:e165.
- [38] Folino-Gallo P, Montilla S, Bruzzzone M, Martini N. Pricing and reimbursement of pharmaceuticals in Italy. *Eur J Health Econ* 2008;9:305–10.
- [39] Lo Scalzo A, Donatini A, Orzella L, Cicchetti A, Profili S, Maresso A. Italy: health system review. *Health Syst Transit* 2009;11:1–216.
- [40] Lochouart M. The state of chemotherapy in France. *Lancet Oncol* 2012;13:761.
- [41] Le Pen C, Priol G, Lilliu H. What criteria for pharmaceuticals reimbursement? *Eur J Health Econ* 2003;4:30–6.
- [42] Sante-HAS HAD. In: Sante. HAD, editor. La commission evaluation economique et de sante publique (CEEPS). 2012.
- [43] Turk E, Albrecht T, Prevolnik Rupel V. The institutionalisation of Health Technology Assessment in Slovenia. *Eurohealth* 2010;16:27.
- [44] Collins M, Latimer N. NICE's end of life decision making scheme: impact on population health. *BMJ* 2013;346:f1363.
- [45] Marshall H. UK Cancer Drugs Fund receives £400 million boost. *Lancet Oncol* 2013;14:e494.
- [46] Aggarwal A, Sullivan R. Affordability of cancer care in the United Kingdom – is it time to introduce user charges? *J Cancer Policy* 2013, <http://dx.doi.org/10.1016/j.jcpo.2013.11.001>
- [47] Assessment ENFHT. EUnetHTA project – Overview of Results – Years 2006–2008; 2009 [29.11.13]. Available from: <http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Overview%20of%20the%20EunetHTA%20Project%20Results%202006-2008.0.pdf> [last accessed 09.02.14].
- [48] EUnetHTA EMAa. European Medicines Agency and EUnetHTA agree joint work plan; 2013 [29.11.13]. Available from: <https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/EMA-EUnetHTA%20press%20release%20-%20final%20version.pdf> [last accessed 09.02.14].
- [49] Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment. *Cancer* 2005;104:1129–37.
- [50] Ploquin NP, Dunscombe PB. The cost of radiation therapy. *Radiother Oncol* 2008;86:217–23.
- [51] van Loon J, Grutters J, Macbeth F. Evaluation of novel radiotherapy technologies: what evidence is needed to assess their clinical and cost effectiveness, and how should we get it? *Lancet Oncol* 2012;13:e169–77 [Epub 2012/04/04].
- [52] Rosenblatt E, Izewska J, Anacak Y, Pynda Y, Scalliet P, Boniol M, et al. Radiotherapy capacity in European countries: an analysis of the Directory of Radiotherapy Centres (DIRAC) database. *Lancet Oncol* 2013;14:e79–86.
- [53] Health Do. Radiotherapy services in England in 2012; 2012 [06.04.13]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/127213/Radiotherapy-Services-in-England-2012.pdf [last accessed 09.02.14].
- [54] Cozzi L, Fogliata A, Lomax A, Bolsi A. A treatment planning comparison of 3D conformal therapy, intensity modulated photon

- therapy and proton therapy for treatment of advanced head and neck tumours. *Radiother Oncol* 2001;61:287–97.
- [55] Staffurth J. A review of the clinical evidence for intensity-modulated radiotherapy. *Clin Oncol* 2010;22:643–57.
- [56] Wolff D, Stieler F, Welzel G, Lorenz F, Abo-Madyan Y, Mai S, et al. Volumetric modulated arc therapy (VMAT) vs. serial tomotherapy, step-and-shoot IMRT and 3D-conformal RT for treatment of prostate cancer. *Radiother Oncol* 2009;93:226–33.
- [57] Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. *Lancet Oncol* 2008;9:367–75.
- [58] Brada M, Pijs-Johannesma M, De Ruyscher D. Proton therapy in clinical practice: current clinical evidence. *J Clin Oncol* 2007;25:965–70.
- [59] Lievens Y, Grau C. Health economics in radiation oncology: introducing the ESTRO HERO project. *Radiother Oncol* 2012;103:109–12.
- [60] Morgan G, Ward R, Barton M. The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. *Clin Oncol* 2004;16:549–60.
- [61] Barton M, Gebiski V, Manderson C, Langlands A. Radiation therapy: are we getting value for money? *Clin Oncol* 1995;7:287–92.
- [62] Colombo C, Mosconi P, Villani W, Garattini S. Patient organizations' funding from pharmaceutical companies: is disclosure clear, complete and accessible to the public? An Italian survey. *PLoS One* 2012;7:e34974.
- [63] National Health Expenditure Trends 1975–2012, Canadian Institute for Health Information (CIHI).
- [64] <http://www.health.gov.on.ca/en/public/programs/drugs/> [last accessed 08.12.13].
- [65] de Oliveira C, Bremmer K, Pataky R, Gunraj N, Chan K, Peacock S, et al. Understanding the costs of cancer care before and after diagnosis for the 21 most common cancers in Ontario: a population-based descriptive study. *CMAJ Open* 2013.
- [66] Rawson NSB. Access to new oncology drugs in Canada compared with the United States and Europe. Fraser Institute; 2012.
- [67] Rawson NSB. Fraser research bulletin: Potential impact of delayed access to five oncology drugs in Canada, November. Fraser Institute; 2013 <http://www.fraserinstitute.org/uploadedFiles/fraser-ca/Content/research-news/research/publications/potential-impact-of-delayed-access-to-five-oncology-drugs-in-canada.pdf> [last accessed 08.12.13].
- [68] <http://www.hc-sc.gc.ca/hcs-sss/index-eng.php> [last accessed 09.02.14].
- [69] <http://www.health.gov.on.ca/en/public/programs/drugs/> [last accessed 09.02.14].
- [70] <http://www.hc-sc.gc.ca/hcs-sss/delivery-prestatiion/fedrole/index-eng.php> [last accessed 09.02.14].
- [71] Chafe R, Culyer A, Dobrow M, Coyte PC, Sawka C, O'Reilly S, et al. Access to cancer drugs in Canada: looking beyond coverage decisions. *Healthcare Policy* 2011;6(February (3)):27–36.
- [72] <http://www.drugcoverage.ca/en-ca/private-insurance.aspx> [last accessed 09.02.14].
- [73] <http://www.ctvnews.ca/private-chemotherapy-clinics-on-the-rise-in-canada-1.227764> [last accessed 26.01.14].
- [74] Chafe R, Dhalla I, Dobrow MJ, Sullivan T. Accessing unfunded cancer drugs in publicly funded hospitals. *Lancet Oncol* 2009;10(April):306–7.
- [75] Cancer System Quality Index (CSQI). <http://www.csqi.on.ca/> [last accessed 28.01.14].
- [76] <http://www.partnershipagainstcancer.ca/wp-content/uploads/CSCC.CancerPlan.20061.pdf> [last accessed 06.12.13].
- [77] http://www.pcodr.ca/wcp/portal/Home?_afLoop=5669010530854452&_afWindowMode=0&_adf.ctrl-state=i2qbjrg55.4 [last accessed 06.12.13].
- [78] <http://www.pcodr.ca/idc/groups/pcodr/documents/pcodrdocument/pcodr-funding-tutorial.pdf> [last accessed 08.12.13].
- [79] <http://www.pcodr.ca/idc/groups/pcodr/documents/pcodrdocument/pcodryervoy-adv-mel-fn-rec.pdf> [last accessed 08.12.13].
- [80] <http://www.pmprb-cepmb.gc.ca/english/View.asp?x=1433> [last accessed 06.12.13].
- [81] <http://www.pmprb-cepmb.gc.ca/english/view.asp?x=1733&mid=1644> [last accessed 27.01.14].
- [82] http://www.health.gov.on.ca/en/public/programs/drugs/publications/opdp/docs/odb_report.12.pdf [last accessed 25.01.14].
- [83] http://www.whitehouse.gov/sites/default/files/docs/erp2013/ERP2013_Chapter_5.pdf [last accessed 08.02.14].
- [84] Fojo T, Grady C. How much is life worth: cetuximab, non-small cell lung cancer, and the \$440 billion question. *J Natl Cancer Inst* 2009;101:1044–9.
- [85] Stewart DJ, Whitney SN, Kurzrock R. Equipoise lost: ethics, costs, and the regulation of cancer clinical research. *J Clin Oncol* 2010;28:2925–35.
- [86] Danzon PM, Taylor E. Drug pricing and value in oncology. *Oncologist* 2010;15:24–31.
- [87] Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: Justum Pretium – the just price. *J Clin Oncol* 2013;31:3600–4.
- [88] Fojo AT, Noonan A. Why RECIST works and why it should stay – counterpoint. *Cancer Res* 2012;72:5151–7.
- [89] <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm381159.htm> [last accessed 09.02.14].
- [90] Flaherty KT, Infante JR, Daud A, Gonzalez R, Keefe RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012;367:1694–703.
- [91] Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, et al., ML18147 Study Investigators. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013;14:29–37.
- [92] Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229–37.
- [93] Vaishampayan U, Vankayala H, Vigneau FD, Quarshie W, Dickow B, Chalasani S, et al. The effect of targeted therapy on overall survival in advanced renal cancer: a study of the National Surveillance Epidemiology and End Results Registry Database. *Clin Genitourin Cancer* 2013;S1558–7673(13):00218–228.
- [94] Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013;369:722–31.
- [95] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *New Eng J Med* 2007;356:115–24.
- [96] Drugs approved for metastatic renal cell carcinoma that inhibit the vascular endothelial growth factor receptor (VEGFR): (1) sorafenib (Nexavar®); (2) sunitinib (Sutent®); (3) pazopanib (Votrient®); and (4) axitinib (Inlyta®).
- [97] Drug approved for metastatic renal cell carcinoma that target the vascular endothelial growth factor (VEGF): bevacizumab (Avastin®).
- [98] Drug approved for metastatic renal cell carcinoma that are derivatives of an inexpensive generic, sirolimus: (1) temsirolimus (Torisel®); and (2) everolimus (Afinitor®).
- [99] Heng DY, Choueiri TK, Rini BI, Lee J, Yuasa T, Pal SK, et al. Outcomes of patients with metastatic renal cell carcinoma that do not meet eligibility criteria for clinical trials. *Ann Oncol* 2014;25:149–54.
- [100] Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003;21:1383–9.
- [101] Iavarone M, Cabibbo M, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. *Hepatology* 2011;54:2055–63.
- [102] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in Advanced Hepatocellular Carcinoma. *N Engl J Med* 2008;359:378–90.
- [103] <http://www.wcrf.org> [last accessed 09.02.14].
- [104] Brooks GA, Li L, Sharma DB, Weeks JC, Hassett MJ, Yabroff KR, et al. Regional variation in spending and survival for older adults with advanced cancer. *J Natl Cancer Inst* 2013;105:634–42.
- [105] <http://www.dartmouthatlas.org> [last accessed 09.02.14].
- [106] Chen RC, Royce TJ, Extermann M, Reeve BB. Impact of age and comorbidity on treatment and outcomes in elderly cancer patients. *Semin Radiat Oncol* 2012;22:265–71.
- [107] <http://www.cnn.com/2013/12/07/health/cohen-cancer-study/> [last accessed 09.02.14].
- [108] <http://www.cancer.gov/aboutnci/recovery/recoveryfunding/personalized> [last accessed 09.02.14].
- [109] http://www.nytimes.com/2011/01/18/health/18cancer.html?pagewanted=all&_r=0 [last accessed 09.02.14].
- [110] Rubin EH, Allen JD, Nowak JA, Bates SE. Developing precision medicine in a global world. *Clinical Cancer Res* 2014 [in press].
- [111] Parkinson DR, McCormack RT, Keating SM, Gutman SI, Hamilton SR, Mansfield EA, et al. Evidence of clinical utility: an unmet need in molecular diagnostics for cancer patients. *Clin Cancer Res* 2014 [in press].
- [112] <http://www.cancer.gov/cancertopics/aya/treatment> [last accessed 09.02.14].
- [113] Kantarjian H, Stewart DJ, Zwelling L. Cancer research in the United States: dying by a thousand paper cuts. *Cancer* 2013;119:3742–5.