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Delivering affordable cancer care in high-income countries

"We are at a crossroads for affordable cancer care, where our choices—or refusal to make choices—will affect the lives of millions of people."

Striking a balance between idealism and fatalism

See The Lancet Oncology Commission page 933

Great strides have been made over recent decades in the treatment of cancer. Outcomes are improving and the numbers of cancer survivors are rising rapidly. These advances have taken place on the back of remarkable research, which has fostered a much deeper understanding of the fundamental complexities of tumour and host biology and its translation to the clinic. New technologies, regimens, and care algorithms offer countless choices for screening, diagnosis, treatment, and prognosis, and have increased the customisation of cancer management allowing greater alignment with patients' individual needs. Advances in prevention and palliation have also taken place, albeit at a slightly less dramatic pace. These developments have placed extra demands on existing health-care systems—demands that many care infrastructures were not designed to meet. Long-term follow-up and care for cancer survivors, for example, is becoming an increasingly difficult dilemma. Moreover, these changes come at a price. The scale of this cost is fiercely debated, ranging from the idealistic, which advocates that everything is possible irrespective of cost, to the fatalistic point of view, in which health-care systems will collapse imminently. Neither of these two extremes will be correct, but what is certain is the current approach to the provision of cancer care is unsustainable, even for the wealthiest countries.

Many nations are limiting access to treatments and care services to ensure health-care budgets are met. The methods by which such decisions are made are multifarious and not always based on rational academic debate or sound clinical judgement, but many are increasingly being made on the basis of assessments of cost-effectiveness or comparative studies. These studies are technically, politically, and commercially challenging. And the elephant in the room is not the absolute sum of money ascribed to the latest drug or intervention, but rather, what value we as a society might place on the benefit it offers and what value a healthy population brings to a country's net worth.

With this in mind, and compounded by the current economic climate, *The Lancet Oncology* launched a Commission in 2010—which is reported here[1] in our first ever special issue—with the aim of engaging parties with a vested interest and role in the provision of cancer services to debate all aspects contributing to the challenges we face, and to draw conclusions and possible solutions. In the interests of keeping this vast topic focused, the scope for the Commission was defined as curative-intent, solid-tumour, adult oncology. Further, we decided to focus exclusively on high-income countries because many low-to-middle income countries have other social, political, and economic challenges to overcome.

Many opinions were invited when setting up this Commission: clinicians, pharmacists, academics, health economists, health-systems analysts, regulators, societies, trade bodies, the commercial sector, patient advocacy groups, and governmental organisations were all welcome. Additionally, we also encouraged other groups who had either decided not to participate directly in the Commission or had professional interests that fell outside of the immediate scope of the report, to also reflect on the issues. These thoughts are captured in the accompanying six Comments.

Remarkably, many representatives of these different groups were instantly willing to participate and to put aside their professional, political, or personal allegiances to form a unified voice. Unfortunately, the pharmaceutical industry decided not to contribute, despite numerous attempts to secure their involvement. Among the pharmaceutical companies we contacted, a reticence to participate did not come from the clinicians or scientists within the organisations, rather, it was from legal teams worried about company self-interests instead of the leadership role they should have in this important debate. The commercial sector is central to these discussions, and their input and vision will be essential in formulating solutions that all stakeholders can agree too. Inevitably, we have been unable to involve everyone; for example, the perspective of payers and educators would also be of interest. We therefore encourage continued discussion through our correspondence pages in the coming months.

A quote taken from the Commission sums up the scale of the problem we face: "We are at a crossroads for affordable cancer care, where our choices—or refusal to make choices—will affect the lives of millions of

people". We hope this Commission acts as a catalyst for further debate and helps deliver solutions before procrastination irreversibly damages the provision of high-quality care for patients with cancer.

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1 Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011; **12:** 933–80.

...And the only side-effects are good ones

See **The Lancet Oncology Commission** page 933

If we want to bend the cost curve—ie, reduce the rate of annual increases in health-care spending—many effective ways are outlined in the Commission for *The Lancet Oncology*[1] and in other recent reports.[2] However, one of the simplest yet most cost-effective approach may be encouraging patients to eat and live more healthfully. Prevention is not only better than cure, it's also cheaper and more compassionate.

Last year, US$2·5 trillion were spent on medical care in the USA, 95–98% of which was spent to treat disease after it had already occurred.[3] Chronic diseases, including cancer, account for 75% of health-care costs, yet these diseases may often be prevented or beneficially affected by making comprehensive lifestyle changes.

Although we tend to think of advances in medicine as being a new drug, device, or procedure—something high-tech and expensive—increasing evidence shows that comprehensive lifestyle changes are not only medically effective, but also cost-effective. Simple choices in lifestyle may cause powerful changes in outcomes.

For example, in the EPIC study,[4] patients who never smoked, had a body-mass index less than 30 kg/m^2, had at least 30 min a day of physical activity, and adhered to healthy dietary principles (high intake of fruits, vegetables, and whole-grain bread and low meat consumption) had a 78% lower overall risk of developing a chronic disease. This included a 93% reduced risk of diabetes, an 81% lower risk of myocardial infarction, a 50% reduction in risk of stroke, and a 36% overall reduction in risk of cancer, compared with participants without these healthy factors.[4]

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A healthy diet could help reduce cancer risk

Evidence shows that investment in comprehensive lifestyle changes yields a five-times greater return in cost savings than that documented for most clinical preventive services.[5] Some researchers believe that prevention does not save money,[6] but these reports often confuse the cost of teaching patients how to change lifestyle in formal programmes versus the costs of the lifestyle changes themselves.

Quitting smoking saves money for the individual and for society, since cigarettes are expensive. Walking, stress-management techniques (including yoga and meditation), and spending more time in social support with friends and family are free. Eating healthier generally costs less, although agriculture subsidies can create perverse incentives so that the cheapest calories (eg, fast food) are often the least healthful. These subsidies are policy decisions that can be changed, reducing government expenditures while improving health.

Changing reimbursement transforms medical practice and even medical education. Innovative approaches such as accountable care organisations and payments that reward keeping patients healthy shift the economic incentives from procedure-based interventions to ones based on quality and prevention. Medicare in the USA is now covering comprehensive lifestyle changes for reversing heart disease, for example, and other chronic diseases might later be covered.

Cost savings can be greatest and seen most quickly in those who are at highest risk or who have chronic diseases.[7] For example, 1410 men would need to be screened and 48 cases of prostate cancer would need to be treated to prevent one death from prostate cancer.[8] Since complications of treatment often include impotence,

incontinence, or both, there is a considerable quality-of-life cost as well as an economic cost from overtreatment. By contrast, a study of almost 3000 nurses with stage 1, 2, or 3 breast cancer reported that walking just 3–5 h per week at an average pace significantly reduced the risk of death from breast cancer by 26–40%.[9]

Further, comprehensive lifestyle changes might slow, stop, or even reverse the progression of early-stage prostate cancer after 1 year.[10] Changes in lifestyle alter gene expression in only 3 months, downregulating a set of *RAS* family oncogenes (*RAN*, *RAB14*, and *RAB8A*) that promote prostate cancer.[11]

In men with prostate cancer, these lifestyle changes also increased telomerase, an enzyme that repairs and lengthens telomeres.[12] Shortened telomeres are associated with poor clinical outcomes in breast cancer, worse prognosis in colorectal and prostate cancers, and with higher risk of bladder, head and neck, lung, and renal-cell cancers. Shortened telomeres also predict decreased survival in coronary heart disease and infectious diseases.

What you include in your diet is as important as what you exclude. Several studies have shown that diets higher in fruits, vegetables, soy, fibre, lycopene, and omega-3 fatty acids reduce the risk of breast and prostate cancers.[13] Social support might also help prolong life in women with metastatic breast cancer. In one study, survival from time of entry into the study was an average of 36·6 months for women who received support and only 18·9 months in the control group.[14]

Making comprehensive lifestyle changes substantially improves quality of life very quickly, which is what makes these changes sustainable and meaningful.

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Challenges related to palliative care

See **The Lancet Oncology Commission** page 933

Patients with cancer receive treatment from oncologists over long periods of time, with the intent of prolonging life in the first part of the disease trajectory and later with a palliative, symptomatic intent. During the last years of life patients suffer from many distressing symptoms, with pain being one of the most prevalent and feared symptom.[1] Patients also suffer from psychological and social distress.

Despite the palliative intent for most patients treated in oncology, the outcomes studied in clinical trials rarely address the potential effect of tumour-directed treatment on relieving or preventing distressing symptoms. Furthermore, the clinical effects of a combined symptomatic approach, consisting of chemotherapy, radiotherapy, and pure symptomatic treatment should be studied. How such a combined approach might reduce costs should also be investigated.

Progression-free survival (PFS) has been criticised as an invalid outcome, because it does not necessarily reflect a proxy outcome for overall survival.[2] The validity of PFS as an outcome might increase substantially if an international consensus could be reached to apply

standardised outcomes for symptom prevalence and symptom-relieving effects.[3] With information on somatic symptoms, psychological distress, physical performance, and overall quality of life, patients and their families (as well as health-care providers and physicians) could have a more comprehensive evidence base for making decisions about treatment.

The Lancet Oncology's Commission[4] reports that a substantial proportion of the cost of cancer care is spent during the last months and years of a patient's life. Furthermore, the authors note that patients should be offered full information about their treatment as part of oncology programmes, and that patients should be spared toxic effects and false hope. Ideally, oncologists should address these issues, although in most cases this might not be the case. An integrated and coordinated palliative medicine and oncology approach (based on collaboration) might be a better way to organise modern oncology care. How to set up such an organisational structure is undecided. Integration, collaboration, and the timing of switching from cancer care to palliative care need to be empirically tested. One key element should be that patients have only one responsible doctor at any given time. Such a structure will hopefully prevent futile treatment, improve symptom control and quality of life, and give patients access to high-quality home care.

WHO has addressed these observations and recently modified the definition of palliative care. The revised definition emphasises that the best care pathway is collaboration, and, when appropriate, integration of oncology and palliative care. Combining these two disciplines in a common treatment and care trajectory should be explored, by evaluating the quality and the cost of care.

A cost-effective health-care system needs to take into consideration the need for an integrated care pathway, particularly for cohorts receiving non-curative oncology care (roughly 60% of cancer patients). Several studies have shown that cancer patients choose to be treated at home during end-of-life-care, but they also expect that specialised oncology and palliative care is available when needed. Controlled studies have shown that such an organisation is beneficial to patients[5] and family members.[6] Further, such a system could also provide better ways to balance the benefits and risks of tumour-directed treatments, reduced costs of drugs, and improve psychological distress.[7]

The specialist cancer palliative care team may act as a link between tertiary or secondary and primary care. Collaboration is expected to improve the quality of care and reduce costs, by delivering high-quality care in patient's homes and in nursing homes as an alternative to inpatient care in high-cost oncology wards.[8] How different organisational structures affect cost is not well investigated. Transferring patients from intensive care units to homecare programmes is cost-saving; however, estimates of costs in palliative care (homecare *vs* hospital care) are typically evaluated retrospectively with a lack of information on all parts of the care trajectory. Furthermore, most of the existing data on costs are more than 10 years old. How different organisational structures within and between countries might affect costs should be prioritised as a research agenda in the near future.

Optimum collaboration calls for knowledge and skills by the clinicians involved. Palliative cancer medicine should be an integrated part of the oncology curriculum and specialists in palliative cancer medicine working in oncology care should have an appropriate and basic knowledge about oncology.

Finally, more real-life integrated research studies are needed. This research should be patient-centred and follow patients along the disease trajectory through oncology care, specialised palliative care, and community care. Appropriate designs need to be chosen and meaningful outcomes should be assessed and analysed in an appropriate way. Such research might shed new light on the benefit of a collaborative care approach to patients' symptom control, improved physical, social, and psychological function, and on family members' quality of life. This approach might also reduce costs for the health-care system.

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Paediatric oncology: are there ways to bend the costs?

The success of cancer treatment has markedly improved in developed countries within the past two decades. Since the costs of cancer care are rising, we now need to reconsider its affordability and objective patient benefits, as highlighted in a special Commission by *The Lancet Oncology*.[1]

Increased success in managing paediatric oncology was predicted by better anticancer treatment and the introduction of multicentre trials. One of these success stories is linked to the initiation of the Berlin-Frankfurt-Munich protocols in the 1970s, which became the universal gold standard for treatment of leukaemia in children.[2,3]

Care of children with cancer is very emotive, and involvement of parents and families in the decision process and their alliance with caregivers is essential. Parents will do everything they can to make sure their children receive the best available treatment and chance of cure. Therefore, close and repeated communication between caregivers and families is essential; this takes time and effort, but prevents wrong decisions and unnecessary costs.

Fortunately, for paediatric oncology, a system of comprehensive clinical trials and concepts of supportive care is in place for most cancers in developed countries.[4] These multicentre, and even multinational, trials ensure cost-effective treatment with the most benefit for patients in terms of survival, and include integrated documentation and follow-up of acute and long-term effects. Physicians and other caregivers can present parents with elaborate information on outcome and care, to give an objective base for decision making. The introduction of disease-related encoding (DRG) and the agreement between health-insurance services and hospitals to pay costs for care and treatment as a flat rate per case (eg, in Germany) can be used to reduce costs. In addition, there is a constant exchange of experience throughout the worldwide paediatric oncology community, for example through the International Society of Pediatric Oncology (SIOP) platform.

Nevertheless, other challenges to cost-effective cancer treatment have arisen, such as the EU clinical trials directive[5] that was translated into national practice in 2004. In Europe, the complex bureaucracy that must be navigated to launch investigator-led (non-commercial) national and international clinical trials consumes an essential part of research funding; and these funding resources are mainly from charity organisations who aim to collect money for the direct benefit of children with cancer. The much higher costs (eg, insurance, pharmacovigilance, and ethical review) add an additional financial burden and make the application for support of investigator-led clinical trials more and more unattractive. They also substantially prolong the process of initiating such trials.[6] Therefore, we need harmonisation of the implementation of the EU directive and a redefinition of what the directive should address, to make treatment safe for children, but not absorb important funding resources.[7]

Another issue to discuss is the danger of overtreatment in children, and to accept that adjusting to a palliative situation is very difficult for the child, family, and treating physician. In developed countries, available treatments are continually increasing with new, targeted therapies, and it is becoming difficult to accept that cure might not be the endpoint. In some cases, we need to put more effort into making the

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See **The Lancet Oncology Commission** page 933

residual lifetime as positive as possible for the patient and family, and to support families with a professional palliative team. Cost-effectiveness in this area also needs to be addressed. WHO defined this concept in 1996 with regard to control of pain, other symptoms, and psychological, social, and spiritual problems.[8,9] The awareness, concept development, and implementation of palliative care for paediatric oncology patients will help to avoid unnecessary prolongation of ineffective and cost-intensive treatments that have no benefit for patients, and will support the establishment of child-oriented or adolescent-orientated end-of-life care, which should be embedded in a non-hospital environment.

There is also discussion of whether quality-adjusted life-years should be viewed differently in paediatric cancer patients compared with adults. This is a complex question, and the answer should include economical considerations, as well as ethical aspects, and the subjective views of patients.

In summary, the objective and subjective patient benefit is the main measure for economic evaluation of cancer care for children. Treatment regardless of survival or optimum care as the endpoint has to be evidence-based and established in structured settings.[10]

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Caring for patients with haematological malignancies

See **The Lancet Oncology Commission** page 933

In view of the relevance and implications of the topic, *The Lancet Oncology* should be praised for their timely initiative in covering delivery of affordable cancer care in high-income countries, in a specially commissioned issue of the journal.[1] The contributors to the report, who work in different high-income countries worldwide, dissected the theme in a broad, integrated, comprehensive, and visionary manner, with particular emphasis on the remarkable changes that have taken place over the years and are continuously occurring in the management of patients with cancer.

As the report correctly identifies, there are many reasons for the progressive rise in costs for cancer care. A key point is the constant increase in median life expectancy in high-income countries, associated with an era of improved biological research and treatments. In addition, in many countries a large proportion of the population is older than 70 years. In this age range, cancers (including haematological malignancies) are more common.[2] In many countries, individuals who have reached 70 years are expected to live another 15–20 years. Measures must be taken to enable access to adequate management for all patients. Broader use of routine diagnostic tests, which means earlier diagnoses, also contribute to increased costs. This is more common in haematological malignancies. Although earlier diagnosis does not always translate into treatment, it does imply that patients have to be monitored and have repeat tests.

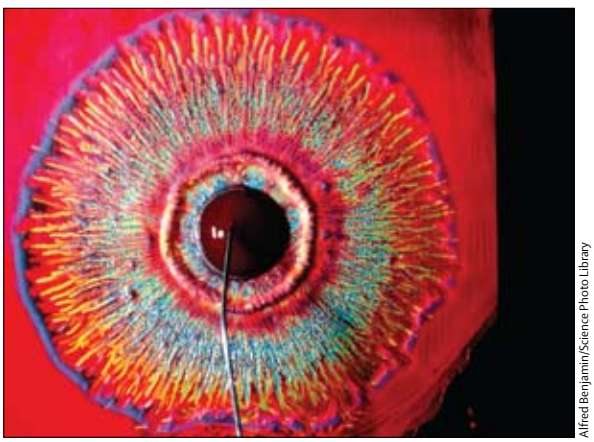
In the era of more sophisticated technologies and new drugs and compounds, the challenge will be to identify objectively those that really affect survival. Are all tests necessary? Are all new drugs and combinations truly effective? At a time when many patients are elderly, the issue of compliance and quality of life are essential. Broader use of guidelines

for patient management would be welcome, as well as higher enrolment of patients in clinical trials aimed at optimising clinical management.

Haematological malignancies are the most common cancer in children, increasing with age and often seen as late side-effects of treatment for other cancers.[3,4] Novel therapies for haematological malignancies have often changed paradigms in cancer treatment. Examples include the introduction of stem-cell transplantation or targeted drugs for leukaemias and lymphomas, which have increased cure rates or prolonged life by transforming life-threatening diseases into manageable chronic illnesses. One result is that expensive drugs for maintenance treatment might have to be supplied for many years.[5,6] In parallel, genetic and molecular diagnostics for prognostication, outcome prediction, and drug pretesting have become more sophisticated. This includes monitoring of minimal residual disease.

These technologies have enhanced costs in the short term, but could pay off in the future because of their potential to personalise treatment. Patients with haematological cancers live longer and might have late complications (second malignancies or cardiovascular diseases).

In addition to the costs associated with treatment of cancer, there are also financial returns. One example is the many patients with chronic myeloid leukaemia whose disease can be controlled with tyrosine-kinase inhibitors, without chemotherapy or transplant, who live much longer and lead a normal life.[6] Ultimately, it would also be relevant to develop rehabilitation programmes for the roughly 50% of haematological patients who are cured, so that they can return to an active working life.[7] Despite advances in treatment, outcome of patients with identical diseases is not the same in all developed countries, not even within Europe.[8] The European Hematology Association is developing strategies in line with those proposed in the commissioned report, including the following: harmonisation of haematology training in Europe in conjunction with national haematology societies and accreditation authorities to ensure high-level education and mobility;[9] on-site and online continuing medical education and postgraduate education programmes, including cost-awareness; interaction with international stakeholders involved in research, drug approval, and health-care delivery; and active participation in programmes enhancing non-commercial clinical trials, and basic and translational research.



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An electrical field blood test for leukaemia

Paradoxically, it is rewarding that we are witnessing these financial issues because it underlines the fact that, in general, individuals in high-income countries live longer and have better lives, and it also implies that management of patients with different malignancies has substantially improved over the years.

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For more on the **European Hematology Association's ongoing programmes** see http://www.ehaweb.org

Regulators, payers, and prescribers: can we fill the gaps?

See The Lancet Oncology Commission page 933

The approval of new cancer drugs in Europe is built on the benefit–risk paradigm, based on objective criteria of efficacy and safety, to the exclusion of economic considerations. This limits the extent to which the European Medicines Agency (EMA) can contribute to the debate on cost-effectiveness. Still, EU regulators share the growing concerns about sustainability of expenditure on cancer drugs. Regulators are exposed to challenges from stakeholders who often have opposing views, such as the need to increase early access to new medicines and improve the efficiency of drug development versus the need to avoid exposing patients to unnecessary risks or possibly ineffective treatments. Concerning the latter, regulatory agencies are under increasing criticism for allowing drugs on the market too soon. Health economists and third-party payers advocate more premarketing data, with information on relative efficacy and drug effectiveness.[1]

The Lancet Oncology's Commission, by Sullivan and colleagues,[2] echoes some of these concerns about the limitations of randomised trials of cancer therapy and subsequent regulatory decisions, seemingly driven by statistical rather than clinical significance, coupled with a too liberal use of non-validated surrogate endpoints, such as progression-free survival (PFS). We argue that the evidentiary standards for regulatory decisions are based on established scientific and statistical principles. Accordingly, statistical significance is a requirement where possible, but is by no means a sufficient criterion to license new drugs, whereas clinical significance is a prerequisite to establish the benefits of any new drug. Furthermore, regulators in Europe have moved away from the concept that non-validated surrogates such as PFS might be used for approval with the expectation that relevant benefits in terms of overall survival (OS) would later materialise.

Although the relevance of the magnitude of observed effects can always be debated, and acknowledging that OS remains the most objective and clinically convincing endpoint, the rationale for using PFS is that this endpoint could be considered as reflecting clinical benefit, provided the treatment effect is sufficiently large to offset treatment toxicity. Progression is assumed to be associated with worsening symptoms, an overall deterioration in quality of life, poor long-term prognosis, and the prospect of additional, less-effective, and possibly more toxic treatments. Thus, requiring evidence of improved OS at the time of approval may limit patient access to useful, albeit not necessarily life-prolonging, drugs. A possible solution is to further develop ways to measure the clinical relevance of progression, to better define the associated gains in terms of other outcomes of concern to the patient, and to better inform relative effectiveness and cost-effectiveness analyses.

Although approval of new cancer drugs in Europe will probably continue to be based on the current paradigm, there is an opportunity for regulators and payers to agree on pre-marketing and post-marketing evidentiary standards for relative effectiveness, and when relative-effectiveness trials should be available at the time of licensing (eg, for life-threatening conditions when placebo-controlled trials lead to uncertainty regarding whether the new drug is inferior to a treatment). Furthermore, regulators and payers could provide joint guidance and advice on clinical development to avoid multiplication of trials due to divergent requirements. Indeed, the EMA has recently begun a collaboration with the European Network for Health Technology Assessment (EUNetHTA) to consider how the scientific assessment reports published by the Agency could contribute better to the assessment of relative effectiveness by HTA bodies. A pilot programme for parallel scientific advice is also now available for drug developers who want to address the needs of both regulators and HTA early in drug development. Convergence of the needs of regulators and payers will help sustain interest and investment in drug development, and will allow patients to have earlier access to information and treatment alternatives. Better alignment is also needed between prescribers' practice and regulatory decisions (eg, to reduce off-label drug use) which has been shown to contribute to the efficacy versus effectiveness gap, because of more frequent adverse events or reduced benefit with off-label use.[3] In any case, off-label use should contribute to the evolving knowledge base of a drug, either through observational studies or, where possible, through post-licensing randomised controlled trials.

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FP, XL, and H-GE are employed by the European Medicines Agency. The views expressed in this article are the personal views of the authors and do not necessarily reflect those of the European Medicines Agency, or one of its committees or working parties.

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The opportunity cost of cancer care: a statement from NICE

The Lancet Oncology's commissioned report on delivering affordable cancer care in high-income countries valiantly attempts to outline how developed countries might deliver reasonably priced cancer care to all their citizens.[1] Even with its narrow focus—omitting people with cancer in lower and middle income countries and neglecting preventive measures—it has merit.

There are, unquestionably, parts of the report that comprise a thorough, evidence-based review of available data on the development and use of effective treaments for cancer. The section on affordable cancer surgery (Part 4), for example, provides a thoughtful discussion in an area that has been neglected. However, there are three issues with which we take exception.

The first issue is the cost of new anticancer drugs. The report does not adequately address the underlying reasons for the increasing costs of anticancer drugs. Over the past 40 years the median monthly costs, at launch (and adjusted to 2007 prices), has risen from less than US$100 in 1965–69 to more than $5000 in 2005–09.[2] Why?

The cost of developing new drugs, generally, has increased substantially over the past decades and is becoming unsustainable.[3,4] This is partly due to the escalating costs and inefficiencies of clinical trials themselves, together with the increasing additional burdens imposed by national drug regulatory authorities. The lengthening development times, and resulting erosion of products' patent lives, mean that companies must necessarily charge high prices to recoup their investment in research and development. Moreover, drug discovery is becoming more difficult. The sums spent on research and development have increased three times over the past two decades but, as judged by the number of drugs licensed per dollar of research and development, the innovative performance of the drug industry has declined.[5]

Even more importantly, the pharmaceutical industry faces a very substantial loss of income over the next 4 years, as a result of the loss of patents on many of its blockbusters. For example, analysts[6] predict that in the USA, sales of branded medicines will fall by $42 billion in 2011–12. To offset this loss of income the industry is charging premium prices for its newer products.

A second issue is that in several places the report is critical of health technology assessment (HTA) agencies. None (including the National Institute for Health and Clinical Excellence [NICE] in the UK) are perfect and it is true that incompetent agencies could do great harm to patients. Nevertheless, some of the criticisms are purely polemic and without an evidence base to support them. For example, in Part 2, it is claimed that NICE's decisions—unlike those in Scotland and Northern Ireland—are economist directed rather than physician led. Aside from the fact that Northern Ireland does not have its own arrangements for appraising new interventions, and relies on advice from NICE, NICE's appraisal committees mainly comprise clinicians working in the National Health Service with each committee having only two or three economists among its 25 members.

The third issue is that the report takes too little account of the opportunity costs often incurred by use of some expensive new anticancer drugs that offer modest benefits. Countries seeking to provide universal access to health care for all citizens have finite resources at their disposal. These resources have to meet the needs of people with cancer and all those


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See **The Lancet Oncology Commission** page 933

with other health conditions. Moreover, resources will become even more constrained as a result of the financial difficulties facing almost all developed countries.

The problem is simple yet real. If large (and increasing) sums of a health-care system's finite resources are to be devoted to cost-ineffective cancer care, then other patients with other diseases—often lacking the vocal support of pharmaceutical companies and patient advocacy groups—will be denied access to cost-effective care. The solution to this over-riding problem is one we all need to seek.

The commissioned report offers little in the way of effective solutions. The list in table 7 does not get to the heart of the matter. What is needed is for new, effective anticancer treatments to be priced at a level that is affordable in a cold economic climate. This requires the industry to operate in a much more efficient manner, for the costs of drug development to be slashed, and for oncologists and patient advocacy groups to start asking tough questions of both regulators and the pharmaceutical industry.

We have some suggestions for practical implementation of effective solutions. First, recent proposals by an international group of academic clinical investigators suggest that clinical trial costs could be decreased by 40–60% without detriment to their quality.[7,8] Simple measures to reduce costs include electronic data capture, reduction in the length of case-management forms, and modified site-management practices. The latter should include greater use of statistical techniques to detect fraud, rather than over-reliance on site visits by regulators and sponsors.[9] Second, greater use of Bayesian techniques in the design and analysis of randomised controlled trials[3,4] holds real promise in reducing trial duration and numbers of patients needed. Third, oncologists and patient advocacy organisations should start challenging the data requirements demanded by regulatory authorities. Fourth, rather than criticise organisations such as NICE for declining reimbursement on grounds of cost-effectiveness, clinicians and patient advocates should start challenging pharmaceutical companies about the high prices they seek for products with modest benefits. Finally, we should all be more concerned about the difficulties facing low and middle income countries in accessing affordable cancer care, rather than constantly focusing on the problems facing developed countries.

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Delivering affordable cancer care in high-income countries

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The burden of cancer is growing, and the disease is becoming a major economic expenditure for all developed countries. In 2008, the worldwide cost of cancer due to premature death and disability (not including direct medical costs) was estimated to be US$895 billion. This is not simply due to an increase in absolute numbers, but also the rate of increase of expenditure on cancer. What are the drivers and solutions to the so-called cancer-cost curve in developed countries? How are we going to afford to deliver high quality and equitable care? Here, expert opinion from health-care professionals, policy makers, and cancer survivors has been gathered to address the barriers and solutions to delivering affordable cancer care. Although many of the drivers and themes are specific to a particular field—eg, the huge development costs for cancer medicines—there is strong concordance running through each contribution. Several drivers of cost, such as over-use, rapid expansion, and shortening life cycles of cancer technologies (such as medicines and imaging modalities), and the lack of suitable clinical research and integrated health economic studies, have converged with more defensive medical practice, a less informed regulatory system, a lack of evidence-based sociopolitical debate, and a declining degree of fairness for all patients with cancer. Urgent solutions range from re-engineering of the macroeconomic basis of cancer costs (eg, value-based approaches to bend the cost curve and allow cost-saving technologies), greater education of policy makers, and an informed and transparent regulatory system. A radical shift in cancer policy is also required. Political toleration of unfairness in access to affordable cancer treatment is unacceptable. The cancer profession and industry should take responsibility and not accept a substandard evidence base and an ethos of very small benefit at whatever cost; rather, we need delivery of fair prices and real value from new technologies.

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See **Comment** pages 923–32

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Introduction

The ability to deliver affordable cancer care is at a crossroads. A volatile mixture of demographics (ageing and expanding populations), rapid development of new technologies (such as medicines and surgery), and increasing health-care expenditure is driving cancer-care costs upwards. Furthermore, as the overall cancer burden gathers pace, we are seeing significant economic losses due to premature cancer-induced morbidity and mortality. The hard numbers are stark. The worldwide cost of cancer due to premature death and disability (not including direct medical costs) has been estimated to be US$895 billion (in 2008 figures).[1] It is also clear from an analysis of survival and mortality data that there is little direct relationship with the overall spend on cancer in developed countries. The Economist Intelligence Unit estimates the costs associated with new cancer cases alone in 2009 to be at least $286 billion.[2] Medical costs make up more than half of the economic burden, and productivity losses account for nearly a quarter of the total. These figures reflect today's reality. By 2030, there will be an estimated 27 million new patients with cancer per year worldwide.[2] Patient numbers (due to the ageing population) will increase, and treatment protocols will be more complex, and therefore more expensive. The challenge to developed countries is how to collectively deliver reasonably priced cancer care to all citizens—ie, make cancer care affordable to individuals and society.

To inform and guide this essential public debate, leading members of the cancer community, from patient advocates to economists and health-care professionals, have contributed their knowledge and viewpoints in this *Lancet Oncology* Commission. In focusing on developed countries we have not forgotten that the global cancer burden is radically shifting to low-income and middle-income countries, but the unique health and disease trajectory in the latter group (many experience the added burden of significant acute, infectious, and chronic disease) necessitates a separate policy approach and discussion. There are also missing voices—namely the regulatory authorities and health-technology assessment agencies—but none agreed to contribute. What this silence says from a public policy perspective we leave the reader to judge. In the following chapters, a diverse and expert faculty grapple with key issues, from the perspectives of classical economics to fundamental principles of justice and equity. All major issues are dealt with head on. Their conclusions and solutions have commonalities and surprises.

Part 1: Framing the challenge—the cost of cancer care

Why are we concerned with the cost of cancer care?

Reducing the morbidity and mortality caused by cancer is a global priority. Cancer affects an estimated 12 million new patients worldwide and leads to more than 7·5 million deaths annually.[1] Many patients with cancer would otherwise experience years to decades of good health. Thus, devoting appropriate resources to the prevention and treatment of cancer, and to research aimed at eradicating cancer in all forms, is essential.

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	Percent of GDP
USA	15·7
France	11·0
Germany	10·4
Canada	10·1
Australia	8·9
UK	8·4

GDP=gross domestic product.

Table 1: **Percent of GDP spent on health care in 2007[7]**

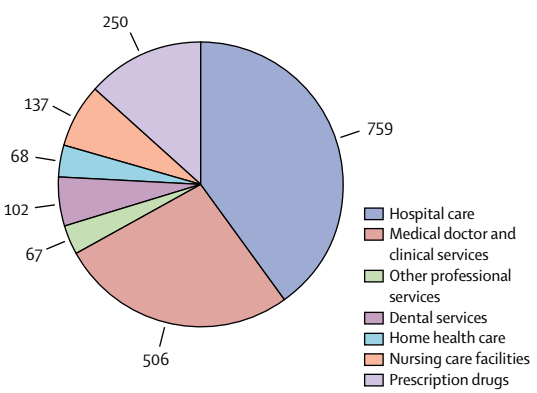

Figure 1: **US total health-care spending by service in 2009 (US$ billion)[5]**

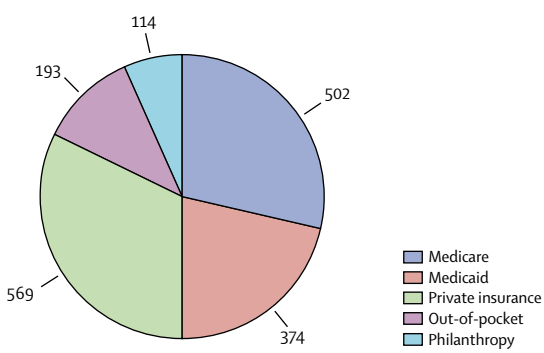

Figure 2: **US total health-care spending by source of funds in 2009 (US$ billion)[5]**

However, in a world of finite resources and competing societal priorities related to health and other areas, we need to consider how much we are actually spending on cancer control (prevention and treatment), whether this is reasonable in relation to other priorities, and whether we are allocating resources efficiently and appropriately.

Health care in general and cancer care in particular can be expensive.[2] Moreover, costs are rising at a rate that outpaces inflation and consumes an increasing share of expenditures at all budgetary levels, from national to individual, in almost all countries. Many new cancer treatments and technologies are available, and outcomes have improved in many areas, but we are increasingly faced with the question of whether the sometimes minor benefits of proven interventions are worth the cost to individuals or society. Novel, more effective, and less toxic interventions are needed, but the price of innovation contributes further to the costs of care.[3] We are thus at a crossroads where our choices, or refusal to make choices, have clear implications for our ability to provide care in the future. How can we provide care, improve options and outcomes for patients with cancer, and do so within a socially responsible, cost-effective, and sustainable framework?

How expensive is cancer care?

The economic impact of cancer care can be measured as total spending, percent of national gross domestic product (GDP), or the cost to care for a single patient. Concerns around escalating costs for cancer care include all of the above, but estimating precise costs and calculating total spending is challenging.[4]

In the USA, it is estimated that total health-care spending in 2009 was US$2·5 trillion, accounting for 18% of the GDP.[5] By comparison, in Australia, total health-care expenditures were $112·8 billion—roughly $5000 per capita versus $11000 per capita in the USA.[6] Health-care spending in the USA as a percent of GDP greatly exceeds that of other countries, with the closest among developed nations being France at 11% (table 1). The total costs of cancer care in the USA were estimated to be more than $124 billion for 2010, representing roughly 5% of total health-care spending.[8] The UK National Health System (NHS) reports that total cancer spending was £5·86 billion in 2009–10, representing 5·6% of total health spending for the year.[9] Despite diverse health-care systems, the US figure is remarkably consistent with 2004 data from Europe, Canada, Australia, and New Zealand, where cancer costs as a percentage of total health-care spending ranged from 4·1% in the Netherlands to 7% in Sweden.[10] In Japan, cancer costs accounted for a slightly higher percentage of total health-care spending, at 9·3% in 2004.[10]

The US Centers for Medicare and Medicaid Services (CMS) provides a breakdown of spending by services (hospital, physician services, drugs) and by funding source (figure 1 and figure 2).[5] A comparable breakdown of spending on components of cancer care is not currently available; it is estimated that the most expensive cancers in 2010 were breast ($16·5 billion), colorectal ($14·1 billion), lymphoma ($12·1 billion), lung ($12·1 billion), and prostate cancer ($11·9 billion).[8]

The issue that concerns economists and policy makers is not just the amount of money currently spent on health care, but also the rate of increase in health-care spending, or what has become known as the cost curve. CMS reports that in 1965, health-care spending was only 5% of GDP. By 2020, total health expenditures are estimated to rise to 20% of GDP, or a fifth of the US economy. Total spending on cancer is estimated to have grown from $27 billion in 1990 to $90 billion in 2008.[11] It is projected to reach $157 billion (in today's dollars) by 2020; roughly a 600% increase in 30 years.[8]

Although the percentage of health-care spending on cancer has been consistent in the USA for decades,[10] increases in costs for cancer treatment could begin to outpace health-care inflation as a whole, and become responsible for a rising percentage of total health-care spending. Evaluating data for treatment of common cancers among Medicare recipients, Warren and colleagues[12] found substantial increases in spending for lung, colorectal, and breast cancer between 1991 and 2002, driven by a marked increase in use of chemotherapy and radiation therapy, and by increases in cost for these services and for hospital care. For example, the percentage of patients with breast cancer receiving chemotherapy increased from 11% to 24% during this period, while the cost of chemotherapy increased from around $6000 per patient to close to $13 000.[12] In the UK, total spending for breast-cancer care has increased by about 10% in each of the past 4 years.[9]

Use of imaging for patients with cancer is also increasing and becoming more expensive. Dinan and colleagues[13] found that PET scans and MRI were being used increasingly among Medicare beneficiaries for many cancer types. Between 1999 and 2006, the cost of cancer care increased from 1·8% to 4·6% each year, while the cost of imaging for cancer increased by 5·1% to 10·3% each year.[13]

Although inflation and the availability of new cancer diagnostics and treatments contribute to rising costs for cancer care, the net effect of these changes on total costs partly depends on the downstream effect of these interventions, which can be difficult to assess accurately. Costs for curative adjuvant therapy might be offset by reductions in hospitalisation and treatment for recurrent disease. Interventions that delay time to progression among patients with advanced cancer might reduce costs for symptom management, or merely defer costs to later in the course of illness.

What drives the cost of cancer care?

To bend the cost curve, we must understand what drives the cost of cancer care, and which, if any, components of high or rising costs we can reduce or eliminate with minimal effect on health outcomes. We need reliable data on the magnitude of total costs and expenditures for different components of care (eg, therapeutic interventions, diagnostic studies, and professional services), but perhaps most importantly, we need to begin to consider the costs of care in terms of what they yield for patients. Are the costs related to a proven aspect of care that improves outcomes, and if so, with what likelihood and by how much? Alternatively, are there costs that are not associated with proven improvement in outcomes, and if so, can they be eliminated? Similar to the breakdown in total health-care spending supplied by CMS, we need to identify specific components of health-care spending, including disease-directed and supportive-care therapeutics, diagnostics, and professional services, and

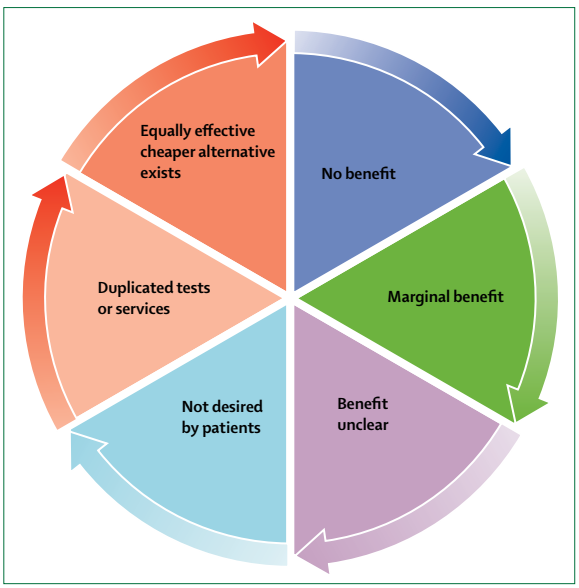

Figure 3: **Classes of interventions to target for decreased utilisation**

determine which components of these expenses are evidence based and cost effective, evidence based but not cost effective, not evidence based, and not yet studied.

Notably, different societies set different thresholds (both explicit and implicit) for what is considered good value or cost effective. Different approaches are required for evaluating and reducing costs in these distinct categories, and the effect on clinical care and outcomes varies. Figure 3 shows how we might subdivide aspects of cancer care in terms of evidence and value, so that we can identify major expenses and those that can be addressed with minimal effect, or perhaps improvement, in health outcomes. At a minimum, closer attention to interventions that are either unproven, or of very low value, provides an immediate opportunity for responsible health-care decisions that might bend the cost curve. Comparative-effectiveness research methods promise to assist in such decisions. When assessing efficient use of health dollars, consideration should be given to the entire spectrum of interventions, including prevention and screening strategies as well as diagnosis, treatment, and hospital care.

In many cases, defining interventions as ineffective or marginally effective in a particular medical context requires clinical evidence and socially derived assignment of value to clinical outcomes. The process of trying to assign interventions to the categories listed in figure 3 could help define the policy and societal debates that are needed in health systems around the world. If an intervention is proven to be ineffective or inferior in a clinical trial, then assigning it to the ineffective category is straightforward. However, is an intervention that is proven to shrink a tumour or slow progression in the metastatic setting without improvement in overall survival viewed as ineffective, marginally effective, or clinically beneficial? How do we view an intervention that

yields a dramatic response among a small subset of patients, but minimal or no response among most? The answers can vary according to medical context, culture, and budgetary constraint.

In the UK, the National Institute for Health and Clinical Excellence (NICE) evaluates the clinical and cost-effectiveness of oncology interventions, explicitly considering cost per quality-adjusted life-year (QALY) gained, and provides the NHS with advice on which treatments should be covered. In the USA, passage of the 2010 Patient Protection and Affordable Care Act established a Patient Centered Outcomes Research Institute (PCORI) to support development of an evidence base to guide policy makers' decisions on health-care coverage and access. However, unlike NICE, this institute cannot provide actual recommendations or establish a cost–benefit threshold for health care.[14]

Why is total spending increasing?

From a societal perspective, total spending on cancer care is driven by the cost to treat an individual patient and the number of patients treated. Cancer incidence rises as the population ages, and in view of demographic projections, coming decades will see increases in both the number and percentage of elderly people and corresponding increases in the number of cancer cases. In developing countries, increased cancer incidence and attendant increases in the cost of cancer care are the result of success in treating infectious diseases and improving infant mortality and paediatric care.[15] In the USA, this changing demographic and success in preventing and treating cardiovascular disease means that cancer is now the leading cause of death in people younger than 85 years.[16]

In addition to increases in spending due to increased disease prevalence, spending can increase as more people gain access to care or as the pool of treated patients broadens, based on differences in diagnostic categories or treatment decisions. All of these factors contribute to increased spending, although to different degrees in each nation.

Why are costs of care for individual patients increasing?

We need to consider the cost of care for each patient as a separate issue. On a simple level, this cost consists of screening and diagnostic studies, treatment interventions, and supportive interventions. These categories are not independent, since diagnostic decisions can lead to treatment, treatment decisions can have implications for supportive measures, and additional diagnostic studies might be needed to assess the effect and safety of treatment.

In general, increases in the cost of health care are driven by innovation. In the case of cancer care, innovation takes many forms, including new approaches to early detection, new drugs or established drugs in new indications, new surgical devices, new methods to deliver radiation treatments, and new technologies to diagnose and monitor patients. We spend more because we can do more to help patients. The past decade has seen a marked increase in the number of novel systemic interventions, many of which are molecularly targeted agents. In the UK, there were 35 approved oncology drugs available in the 1970s; there are currently close to 100. The cost of a course of systemic therapy in the UK has increased from 34% of per-capita GDP in 1995, to 67% in 2009.[17] Although molecularly targeted therapies (the vast majority of new agents in the past decade) are revolutionising the treatment of cancer in many areas, they can be exceedingly expensive. For example, sipuleucel-T, a novel immunotherapy for metastatic prostate cancer, was found to improve survival by several months in a population of patients with few proven options. However, it costs more than $100 000 per patient for a three-dose course of treatment.[18] The treatment is proven to be effective, but how should we determine its value?[19] Additionally, new technology is expanding our ability to diagnose cancer, predict prognosis, and select therapy. Imaging costs for CT scans, PET, and MRI are increasing twice as fast as the overall cost of cancer care.[13]

Doing more for patients does not always equate to spending more. When used selectively, novel interventions can save money. For example, if a new drug is used in the adjuvant setting and prevents recurrence of cancer, this saves a life and eliminates the cost of treating advanced disease in the future. Similarly, if a diagnostic test costs several thousand dollars, but identifies a group of patients at very low risk of recurrence who can forgo chemotherapy that would otherwise be recommended, this can greatly benefit the patient and yield a net saving.[20] Therefore, novel interventions and technologies need to be evaluated on a case-by-case basis, taking into account cost, benefit, and downstream implications (including medical costs from other conditions). Few treatments or tests are clear clinical winners, with many falling into the category of substantial cost for limited benefit.

Overutilisation

The costs of cancer care are also increased through overutilisation. Even the best interventions and tests can be valuable in one setting and wasteful in another. Treating patients who do not need or will not respond to treatment yields costs without clinical benefit (not to mention needless toxicity).

One factor driving overutilisation in oncology is time. It is sometimes quicker and easier to discuss a plan of treatment than to discuss why treatment might not be indicated. Similarly, exploring the likely basis for a new symptom in the office takes time and clinical diagnostic skills that are emphasised less and less in an age of technology, and it is often easier to order a scan than to reassure the patient or physician on the basis of a careful history and a physical examination.[21,22]

Overutilisation can also occur when the physician is unaware of the evidence. For example, for most patients

with breast cancer there is no proven benefit in following asymptomatic patients after initial therapy, with tumour markers or routine surveillance studies. In fact, two large randomised trials showed no benefit in terms of survival or patient quality of life with use of an aggressive, testing-based follow-up approach versus periodic visits with the physician and mammography.[23,24] However, routine use of these tests in practice remains common.[25]

In the USA, overutilisation is partly driven by medicolegal concerns and the fear, on many levels, of missing something or failing to do everything.[21] Estimates of the effect of defensive medicine on health-care spending vary, with several studies showing that tort-reform would have little effect on cost.[26,27] However, physicians report that the legal climate has a large effect on their practice and utilisation, which suggests that the effects of defensive medicine on utilisation and cost might be underappreciated.[28]

Finally, it must be recognised that as in most businesses, physicians and hospitals are paid for what they do and not for what they don't do. Thus, financial incentives can potentially drive overutilisation.

Consumer demand, willingness to pay, and insurance

Patient demand might be a driver of overutilisation, and can affect diagnostic studies and treatment in oncology. In the presence of insurance, patients might be more willing to accept interventions with marginal benefits since they are personally shielded from the costs. The effect of insurance on the value equation has been termed moral hazard by economists. To overcome the effect of moral hazard on utilisation, insurers are increasingly turning to cost sharing through co-payments and higher deductibles. In a survey of patients' willingness to pay for cancer treatment, there was sensitivity to the value of treatments.[29] Patients indicated a greater tolerance for out-of-pocket expenses for more effective treatments. Exploratory analyses showed that patients who were employed or more educated had higher willingness to pay for treatment. In settings where treatment is highly effective, cost-sharing might discourage use that would be of high personal and societal value. This consideration could be particularly important in the setting of oral cancer therapies (including supportive-care medications) where patient cost-burden can be substantial. At the same time, however, cost-sharing can be an important mechanism for controlling waste.

Futile care

Special consideration must be given to costs of cancer care at the end of life. Many forms of cancer are currently incurable and patients will eventually die from their disease. If we could accurately predict when further disease-directed therapy would be futile, we clearly would want to spare the patient the toxicity and false hope associated with such treatment, as well as the expense. In fact studies suggest that a substantial portion of the total cost of cancer care is for care delivered in the last weeks or days of life, and that much of this care is futile and potentially inconsistent with patients' wishes.[30–32] Providing futile disease-directed care, such as chemotherapy in the last weeks of life, has financial consequences for the patient's family and society, and might also compromise the patient's quality of life and distract from a focus on palliative care that can improve quality of life and even prolong survival.[33]

Lowering the cost of interventions and services

In general, there are two primary mechanisms to control costs. We can lower the cost of cancer-care services or interventions, or we can reduce utilisation. Lowering costs might be accomplished through several mechanisms. Reducing the costs of production of cancer care would, theoretically, translate into lower costs for delivery. Technological breakthroughs such as improved preclinical models for screening compounds might improve the efficiency of new drug discovery, although the magnitude of effect on costs of care is uncertain. Decreasing the time and cost of clinical trials through regulatory reform might also have an effect, particularly with the rapidly increasing per-patient costs to do clinical research.[34] Improving the efficiency of clinical trials at all phases, from study design, to site selection, to patient accrual, could also help reduce the costs of bringing new interventions to the clinic. Study designs that preselect patients most likely to benefit can reduce sample size, minimise the potential of missing a benefit restricted to a particular population, and accelerate the development process overall. At the same time, we must be cautious of rushing to judgment on the association between a putative predictive marker and treatment, since there are many examples where an active therapy had relevant target effects unappreciated at the time of early development.

The cost of professional services can be reduced by lowering training costs for oncology care providers, and by redistribution of services so that physicians have a supervisory role where appropriate, with midlevel and nursing providers delivering care that does not directly require a physician. With projected oncologist workforce shortages, changes in the models of care delivery will likely be needed, irrespective of cost, but many practices and institutions have already begun to implement such models, and both experience and research will contribute to improving efficiency and maintaining quality of care.[35]

Costs can also be controlled through improving the power of the payer or consumer in the market place. In the USA, allowing the largest government payer, CMS, to negotiate payments for diagnostics, pharmaceuticals, and other interventions could bring costs down as it has in other countries.[36] Regardless of the government's role, all efforts to aggregate consumer power, through insurers, and employers for example, can have the same effect [as

Federal authorities] on at least moderating the cost of treatments and physician and hospital services.

Although price controls are a readily available means to control cost in oncology and in other areas of medicine, there is an important and vulnerable link between pricing and innovation.[37] Thus, there is increasing interest in value-based pricing that would reward and incentivise development of drugs that substantially improve outcomes, but not subsidise development of me-too or marginally effective new treatments.[38,39] How best to do this, and balance support for innovation, cost control, and continued evidence development, is the subject of active debate.[40]

There is ongoing tension over whether and to what extent health care can and should be operationalised as an open market. Health care clearly lacks many features of an ideal market, such as information equality and an equal power relationship between buyers and sellers. Furthermore, the consumer patient is not generally in control of purchasing decisions. The catastrophic nature of a cancer diagnosis and the presence of insurance also distinguish this setting from other economic models. As noted above, making individual patients more sensitive to costs of care is likely to reduce utilisation, but this might have the unintended consequence of reducing use of highly effective and marginally effective interventions.[41]

Improving efficiency and value of cancer care

Education

The cornerstone of evidence-based medicine is physician education. Such education could be expanded to include review of evidence for interventions and tests that are widely used in routine practice without clear benefit. In an effort to control costs, it makes sense to identify components of care that might be ineffective or marginally effective, but with high cost. Through systematic reviews, meta-analyses, decision modelling, and analyses of administrative data—the tools of comparative-effectiveness research—in addition to randomised clinical trials, we can increase the evidence base relevant to everyday practice.

Clinical education is often focused on technical skills and clinical decision making, without attention to cost. This focus can encourage use of therapies with marginal benefit as the most effective approach to care. There is a need to incorporate knowledge of costs and understanding of cost-effectiveness analysis into primary and continuing medical education. The communication of cost and cost-effectiveness to patients is becoming increasingly relevant as patients share an increasing burden of the cost of care.[42]

We can also use technology to support evidence-based decision making and efficient care. Electronic access to clinical guidelines and trial data is a minimum requirement in modern oncology practice. Systems that link computer-based orders to evidence, cost information, and alternatives will probably further enhance care and cost-effectiveness. High-cost, marginal-yield interventions and tests can be linked to specific flags and checks to enhance appropriate use. Finally, electronic medical records and ability to transfer imaging and other information digitally should reduce duplication of tests.

Personalised medicine

The era of personalised medicine is clearly upon us. Diagnostic tests are now routinely used to select treatment in patients with breast, lung, and colon cancers, as well as less common malignancies such as gastrointestinal stromal tumours (GIST) and leukaemias. The list of relevant classifiers and their platforms (eg, immunohistochemistry, in-situ hybridisation, genotyping, and gene-expression profiling) grows daily. The promise of personalised approaches includes more effective therapies and improved treatment outcomes, and sparing patients the toxicity and cost associated with ineffective treatment. For example, investigators in Japan estimated that implementing *KRAS* testing in selected patients with colorectal cancer before cetuximab therapy yields health-system savings of more than $50 million per year, compared with use of cetuximab without *KRAS* testing.[43] Whether the incremental costs of using the therapy even in molecularly selected patients (reported as $160 000 per QALY) can be justified is an important, though distinct question.[43] In some cases, although diagnostic tests themselves might be expensive, their use may be cost-saving from a societal perspective.[20,44]

To accelerate progress in achieving more personalised approaches to cancer care, the development process for diagnostics must begin early in clinical development. This fact has implications for regulatory science as well as clinical trial design. Additionally, the effect of more personalised approaches on the pharmaceutical industry must be recognised, especially with the potential for disincentives that might exist (panel 1).

***Panel 1:* Potential effects of personalised medicine on pharmaceutical industry drug development**

Clear advantages

- Longer treatment duration
- Potential new indications, new market
- Competitive advantage with personalised approach
- Co-marketing of diagnostics

Clear disadvantages

- Reduced market size

Uncertain

- Development time of new therapies
- Success in bringing pipeline therapy to market
- Effect of higher-value therapy on pricing and willingness to pay

Barriers to overutilisation

For interventions that are ineffective or substantially more expensive than equally effective interventions, establishing barriers to utilisation is appropriate on both clinical and economic grounds. Such barriers can occur at the regulatory level through drug or device approval, the payer level through coverage decisions, or at the institutional level through use of evidence-based formularies. With the complexity of cancer care, some interventions might be highly valuable in rare settings, but inappropriate for routine use in general practice. In these cases, there must be specific exceptions to facilitate appropriate use, or transparent and efficient mechanisms for appeal (or both).

Research

Research investment to improve or maintain level of care while controlling costs requires a multifaceted approach that supports the following: basic, translational, and clinical research focused on development of new (ideally more effective) interventions; comparative-effectiveness and health-services research aimed at defining the most efficient way to deliver care and improve delivery of evidence-based care; and prevention and life-style modification (eg, smoking cessation, weight loss, and exercise) research that might reduce cancer risk or risk of recurrence. Improved infrastructure for development of outcomes data and a rapid learning health-care system, where we can learn from each patient to guide practice, is increasingly viewed as crucial to guide rational health policy and to contain costs by providing head-to-head comparisons and add-on health economic studies. Many countries struggling with rising costs of health care are being forced to direct resources towards care delivery instead of research. In the USA, this debate is occurring over entitlement reform (payments for Medicare and Medicaid) versus discretionary spending, which includes cancer research through the National Institutes of Health (NIH). Politically, reductions in discretionary spending seem to be more feasible, but as policy, this is the equivalent of buying a farm by selling the seeds you will need for the harvest.

Focus on end-of-life care

Evidence shows that a substantial percentage of cancer-care spending occurs in the last weeks and months of life, and that in a large percentage of cases, such care is not only futile, but contrary to the goals and preferences of many patients and families if they were adequately informed of their options. Therefore, empowering patients through education and shared decision making can potentially improve care and lower costs. Specifically, when patients are informed that their cancer is life threatening, but there is a treatment available, many choose to be treated irrespective of personal costs, and certainly of costs borne by their insurer. However, there is potential to improve care and reduce spending by empowering patients to forgo expensive and futile, or low-probability care when this matches their goals and preferences, and by empowering physicians to discuss these issues with their patients, and to recommend stopping disease-directed care when appropriate.[45]

Summary

Concern over the costs of health care are nearly universal, across a broad range of national health-care systems and diverse ideological approaches to issues of access to care, regulation, and innovation. Cancer is a leading cause of death and morbidity throughout the world, and a large and potentially increasing component of total health-care spending. Consideration of the cost of cancer care raises questions regarding how we balance access, quality, equity, and cost. Not all societies take the same approach to prioritising values in this area or controlling costs, but we can learn from each other. In the UK, access to health care is universal, but access to specific interventions is subject to explicit considerations of cost and value. In the US, access to interventions (ie, US Food and Drug Administration [FDA] approval) in the marketplace is governed primarily by safety and efficacy evaluation, not cost, but access to the marketplace (ie, health care of any kind) is not guaranteed and the principal of universal access is highly contested.[46] Societal debates in these areas will probably continue, but improved understanding of the magnitude of costs of cancer care, factors driving these costs, effect on patients and societies, and potential approaches to controlling cost while sustaining or expanding both access and quality should have international appeal.

Part 2: Research and cost-effectiveness in cancer care

Cancer incidence is rising and expenditure on cancer therapy has increased substantially, leading to a focus on more affordable cancer care. Cost-effectiveness analyses provide the basis for defining affordability; they are usually based on results of randomised controlled trials (RCTs), although these trials might not predict benefits and costs when a new treatment is used more widely. Such analyses should be supplemented by cost analyses based on health-outcomes databases, so that resource utilisation and longer-term toxicity are better elucidated. Defining the value of cancer therapy remains difficult, and individual countries should involve key stakeholders in decisions regarding the definition of affordable treatment. Cancer has a high societal burden, and the proportion of total health-care expenditure on cancer does not always reflect this. Furthermore, although utilisation of health-care resources is the main contributor to the cost of cancer care, access to drugs is typically rationed even though drugs account for a small proportion of total cancer expenditure. Value-based pricing of drugs or approval based on incremental cost-effectiveness in relation to average national income are promising methods for

setting limits on the cost of new treatments. Methods of limiting resource utilisation might also allow for increased expenditure and access to novel therapies.

Worldwide projections suggest that by 2030 there could be 26 million new cases of cancer diagnosed, with around a third occurring in developed or high-income countries.[47] The economic burden of cancer is high because of direct costs (eg, screening, diagnosis, and treatment) and indirect costs (eg, loss of productivity).[48,49] Expenditure on cancer therapy has risen substantially: in Europe, between 1993 and 2004, total sales for cancer drugs alone increased from €840 million to €6·2 billion,[48] while in the USA, global expenditure on all cancer treatment (including screening, diagnosis, and treatment) increased from US$41 billion in 1995 to $72 billion in 2004.[50,51] As a result, health-care policy is attempting to contain spending on cancer care and treatment.

Cancer care encompasses a wide range of costs, including financial, social, and psychological costs, which are difficult to estimate. Furthermore, not all costs are incurred during interactions with medical services. There may be early reductions in quality of life brought about by cancer symptoms, and there are costs involved in visits to the primary-care physician before a cancer diagnosis is made. Stress and days lost from work occur during prediagnosis, diagnosis, and treatment. After treatment and during palliative and terminal care, there is also the possibility of early retirement.

Direct costs to patients, insurers, or health services include expenditure on diagnosis, such as laboratory and other diagnostic tests, and also for treatment. In this setting, the cost of drugs is important but there are many other costs such as hospitalisation, surgery, and radiotherapy. Indirect costs associated with cancer care include costs of managing side-effects, pain, fatigue, and loss of mobility. There are also costs associated with the involvement of social services. Finally, the costs of cancer care can also affect patients' social network, financially and in psychological terms. Therefore, it is difficult to estimate the total cost of cancer care and to determine what is affordable. Cancer drugs are one of the costs where estimates can be made and a model outlined of how to determine affordable costs of care.

Cost-effectiveness analyses and randomised trials of cancer therapy

RCTs are the gold standard for showing the efficacy (effect under ideal conditions) of new therapies. Once a treatment is shown to be efficacious, data are usually presented to bodies such as the US FDA or the European Medicines Agency (EMA) for regulatory approval. Such bodies consider the balance between benefits and risks of interventions, but do not consider the associated cost of treatment. This process is independent of decisions to fund therapy. In the EU, judgments about medical costs, including funding of drugs and reimbursement policies, remain the remit of member states. For example, NICE considers costing issues in the UK. Funding decisions are usually based on cost-effectiveness analyses applied to specific national settings. Cost-effectiveness is typically evaluated using an incremental cost-effectiveness ratio (ICER) comparing the new treatment with the treatment used in the control group of a pivotal RCT, usually a less efficacious and less costly alternative. Usually, the ICER is expressed as an incremental cost per life-year, or per QALY gained, and calculated as:

$$\text{ICER} = \frac{\text{Cost(new)} - \text{Cost(old)}}{\text{Effectiveness(new)} - \text{Effectiveness(old)}}$$

The growing use of cost-effectiveness analyses to evaluate the costs and health effects of specific interventions is dominated by prospective comparison of new interventions with current practice in RCTs. The estimated cost-effectiveness of a new intervention is compared with either the reported cost-effectiveness of existing interventions or with a fixed price cut-off representing the assumed social willingness to pay for an additional unit of health. The implicit assumption that the required additional resources would need to be transferred from another health intervention or from another sector is rarely addressed. To be complete, cost-effectiveness analyses must not only consider short-term costs and benefits (eg, those observed during an RCT), but must also assess longer-term outcomes.[52]

Limitations of randomised trials of cancer therapy

Statistical significance does not imply clinical significance

Randomised trials rely heavily on statistical significance between the experimental and control intervention, with less attention paid to the clinical importance of the treatment effects. For example, investigators of the National Cancer Institute of Canada PA.3 trial reported a significant benefit in overall survival (OS), with a median gain of 0·33 months for erlotinib plus gemcitabine compared with gemcitabine alone as first-line treatment of advanced pancreatic cancer.[53] This small survival gain was achieved with increased risk of toxicities such as diarrhoea, interstitial lung disease, and treatment-related death. Although the clinical value of erlotinib in this setting seems limited,[54] it has been approved by the FDA and EMA. The estimated incremental cost per life-year gained is almost $500 000.

Surrogate endpoints

Surrogate endpoints are often used to allow for quicker reporting of results and to reduce the requisite sample size of an RCT. Thus, disease-free survival (DFS) and progression-free survival (PFS) are used as surrogates for OS in RCTs evaluating adjuvant therapy, and therapy for metastatic disease, respectively. For example, DFS was chosen as the primary endpoint in two large RCTs comparing upfront aromatase inhibitors with tamoxifen

as adjuvant therapy in post-menopausal women with early breast cancer. It was expected that early differences in DFS would predict later differences in OS, but updated results from both trials[55,56] and a meta-analysis[57] have shown that this assumption was invalid. Survival remains similar between the intervention groups despite substantial differences in DFS. Evaluation of bevacizumab used with chemotherapy compared with chemotherapy alone in RCTs for several types of metastatic cancer provides a further example: several trials showed significant differences in PFS, and were reported as positive when this was selected as their primary endpoint, but most did not show significant differences in OS. All of the trials recorded increased toxicity.[58] QALYs might be lost rather than gained with such treatment.

The above limitations can lead to inaccurate estimates of the ICER. Using trials of upfront aromatase inhibitors versus tamoxifen as an example, several studies suggested that aromatase inhibitors were cost effective,[59–61] but these studies were based on the assumption that improvements in DFS would lead to improvements in OS. However, longer follow-up showed that these assumptions were invalid, and so results of cost-effectiveness analyses are void. In the absence of any measurable survival benefit, the ICER of aromatase inhibitors in this setting is infinite.

The reverse situation has been noted in a few trials of cancer immunotherapy, where the effect on OS is larger than that on DFS.[62,63] In studies of cost-effectiveness, it is important to use valid estimates of OS whenever possible, to avoid misleading results from modelling costs with surrogate endpoints.

Selection of patients for randomised trials

Another problem in estimating cost-effectiveness from RCTs is the modelling of costs associated with prevention or management of toxicities. Patients enrolled on RCTs are usually highly selected and might not be representative of patients treated in general oncological practice. Such RCTs usually have multiple exclusion criteria, which include comorbidities or the use of many concomitant medications.[64] For example, the PACS-01 trial compared six cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) with three cycles of FEC followed by three cycles of docetaxel (FEC-D) as adjuvant therapy for women with breast cancer. Results showed that FEC-D led to improvement in DFS and OS with an acceptable toxicity profile, including a rate of febrile neutropenia of 11·2%.[65] However, two subsequent reports of unselected patients treated at cancer centres showed rates of febrile neutropenia in excess of 25%.[66,67] Analyses based on data from PACS-01 suggested that FEC-D is cost effective,[68,69] but these studies did not model the costs of treatment for the higher rate of febrile neutropenia found subsequently, or for prevention of myelosuppression by using granulocyte colony stimulating factors. The results from such analyses might not apply to the wider population of patients with cancer.

Guidelines for reporting studies of cost-effectiveness

To address the above problems, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force published good practice guidelines for the reporting of cost-effectiveness analyses based on data from RCTs.[70] Task force members emphasised that RCTs measure efficacy rather than effectiveness (ie, effect of an intervention in a highly controlled setting rather than in a real-world scenario); therefore, cost-effectiveness in routine clinical practice might be inaccurately estimated using data from RCTs. The task force suggested that investigators adjust their analysis to accommodate this. It also recommended that cost-effectiveness analyses based on RCTs should obtain health-resource use and health-state utilities directly from study participants. The collection of economic data should be fully integrated into RCTs, and analyses should be guided by hypotheses and a pre-established statistical plan.[71]

The above guidelines do not address the larger issue of relevance to more general practice due to the selection of healthier patients for participation in RCTs. Ideally, pragmatic RCTs would follow pivotal RCTs that have established efficacy of a new treatment in a restricted population. Pragmatic trials would be simple and would assess the treatment groups under conditions that reflect daily medical practice, but they would face at least two problems. First, even if simpler than the original RCTs, these trials would be expensive and difficult to perform. Second, there are ethical issues in denying treatment to a control group when efficacy has been acknowledged by regulatory bodies, although equipoise might be maintained if the benefit is marginal and the new treatment increases toxicity.

Cost-effectiveness and health-outcomes research

Cost-effectiveness analysis can produce markedly different results depending on the source of data used in the modelling. These analyses are highly sensitive to the health-system context, because diagnosis and patient management vary considerably across countries and even within countries. Also, although the internal validity of RCTs is high because of randomisation and blinding, their external validity is limited because, as discussed above, the probabilities of benefit and of toxicity in an RCT do not necessarily represent those in clinical practice.[72]

Decision makers involved with health coverage and payment are increasingly developing policies that seek information about real-world outcomes. Health-outcomes methods are able to provide such data and can contribute important evidence. Panel 2 lists areas where health-outcomes methods can contribute to cost-effectiveness as defined by the ISPOR task force.[73] A key problem for real-world information about patient management and outcome is the rarity of high-quality databases that include relevant data from diagnosis to long-term outcomes, including patient characteristics, medical history, and concomitant illnesses. The EUROCAN project (an

Panel 2: **Benefits of health-outcomes data for cost-effectiveness analysis**

- Estimates of effectiveness (effect of drug in real-world setting) rather than efficacy (effect of drug in ideal or highly controlled setting) in a variety of typical practice settings
- Comparison of several alternative interventions (eg, older *vs* newer drugs) or clinical strategies to inform choice of optimum therapy beyond placebo comparators
- Estimates of the evolving risk–benefit profile of a new intervention, including long-term (and rare) clinical benefits and harms
- Examination of clinical outcomes in a diverse study population that reflects the range and distribution of patients seen in clinical practice
- Results on a broader range of outcomes (eg, patient-reported outcomes, quality of life, and symptoms)
- Data on resource use for the costing of health-care services and economic evaluation
- Information on how a product is dosed and applied in clinical practice and on levels of compliance and adherence to therapy
- Data in situations where it is not possible to do an RCT
- Substantiation of data collected in more controlled settings
- Data in circumstances where there is an urgency to provide reimbursement for some therapies because it is the only therapy available and may be life-saving
- Interim evidence—in the absence of RCT data—upon which preliminary decisions can be made
- Data on the net effects of clinical, economic, and patient-reported outcomes after implementation of coverage or payment policies, or other health management programmes (eg, the kind of data CMS expects to collect under its policy of coverage with evidence)

RCT=randomised controlled trial. CMS=Centers for Medicare and Medicaid Services.

EU-funded project for improving the coordination of cancer research in Europe[74]) has documented that the problem is not really technical, since information technologies increasingly facilitate connection between databases, and statistical methods can handle complex datasets. Rather, the problems are ethical, political, and administrative. Stricter rules governing access to data have reinforced barriers that hinder the linkage between databases. Public authorities request more and more evidence of the effectiveness of medical technologies, but gathering of useful data is increasingly limited. The enormous expenses for health care in high-income countries are not paralleled by data gathering programmes that could inform about the effectiveness of these expenses. Ideally, a small proportion of public spending on drugs should be devoted to evaluation of their effectiveness at a population level, and to pharmacoepidemiology. The Drug Effectiveness Review Project, initiated in Oregon, USA, as an alliance between 15 US states and two private organisations, is an example of such a project.[75]

Although health-outcomes data are able to provide the closest estimation of real world cost-effectiveness, their key weakness is the difficulty in defining adequate control groups for comparisons between interventions. Therefore, such data should be used in conjunction with results of RCTs rather than in isolation.

Defining value in cost-effectiveness research

A major challenge is for countries to establish threshold values on which to base funding decisions for new interventions. NICE has established a maximum threshold for drug coverage at £30 000 (around $50 000) per QALY gained, although a higher threshold is used for end-of-life drugs.[76] A $50 000 cost per QALY threshold has been used in many other jurisdictions.[77] These figures are based on a 1982 valuation. After adjustment for health-care inflation (around 5·5% annually over the last 30 years[78]), this cutoff would now be equivalent to about $200 000 per QALY.

WHO has proposed using the wealth of an individual country when deciding on thresholds for economic value—specifically, multiples of a country's per-capita GDP.[79,80] New treatments with an ICER of less than or equal to the per-capita GDP would be considered very cost effective, one to three times the GDP would be cost effective, and more than three times would be cost ineffective. For example, for high-income countries such as in western Europe and the USA, the cost per QALY threshold would be about $100 000 and $140 000, respectively.[81] The use of thresholds based on per-capita GDP in combination with pharmacoeconomic modelling to establish a value-based price for a new drug is an intriguing approach, and could set the foundation for providing consistent and transparent drug funding decisions.[82]

Cost-effectiveness and rationing of cancer therapy by public health-care systems

Rationing is a reality in publicly funded health systems. Indeed, many countries require health-technology assessments when deciding on adoption of new health-care technologies. However, a major hurdle in many countries is the lack of expertise for performing these cost-effectiveness estimations. In England and Wales, formal cost-effectiveness analyses are required before approval for funding. In 1999, NICE was established to ensure that patients receive the most effective treatments. Its remit includes balancing the financial costs and clinical benefits of health technologies and evaluating their cost-effectiveness.[83] In this respect, NICE could become the de-facto health technology expert institution for many countries that would simply adjust work done by NICE to their specific context, a process that could lead to recommendations different to those issued by NICE for the UK. Countries such as Azerbaijan and Brazil have adapted NICE guidance. Furthermore, NICE includes a non-profit consultancy group (NICE International) that does contract work in Canada, Bosnia, and

other countries, where its guidelines may be adapted or similar bodies established.[84] Recently, the American College of Physicians recommended establishment of an organisation to generate and review cost-effectiveness studies in the USA.[85]

With the rising cost of cancer therapy, many countries need a process to assess cost-effectiveness, and this process is easier to implement in countries that have a national health service or a national health-insurance scheme. In countries with a limited public health-care system, such as the USA, treatments are approved for use if they are deemed to be safe and effective for the licensed condition; cost is not a factor. However, even in situations where treatments are funded largely by consumers or their private insurers, continuing rises in costs of treatment, often for minimal gains, will ultimately require guidelines for limits on incremental costs.

Value-based pricing has been advocated as a method for improving the affordability of cancer therapy. In this setting, a cost-effectiveness appraisal would be done and the ICER per QALY threshold would be defined for individual drugs. Approved drug prices would then be set on the basis of an explicit assessment of the drug's value. Determining this value would require political and public debate, with formal acceptance of a limit on ICER for new treatments. Individual pharmaceutical companies would then decide whether or not to market their drugs at that price. These methods are gaining considerable interest in the UK, and NICE is expected to apply them to future decisions. Such a method could also be instituted when drugs are reviewed for approval by the FDA or EMA, but would require a major change in policy. The main advantage would be to limit costs of drugs that provide small gains. A main disadvantage might be to hinder approval of useful drugs that would ultimately become less expensive, since the price of drugs generally decreases with time, particularly when patents expire. Furthermore, such limitation might discourage drug development. New drug development is increasingly done by for-profit industries, with government contribution falling in the past 30 years.[86] In Europe, this trend has been encouraged by the advent of the European Directive on Clinical Trials in 2001, which has boosted trial costs and administrative requirements and discouraged academic clinical research.[87] Regulation and over-administration—ranging from controls over patient tissue to onerous regulations across a range of other areas—is now blighting research in all developed countries. The inability of national governments and supranational organisations such as the European Commission to conduct proper impact assessments and engage in joined up regulation is a major threat to cancer care. Furthermore the inability to reverse regulation has created a detrimental negative tightening effect on research and development. Since the private sector requires a profit or return on investment, substantial control of this return could affect investment in drug research and development and ultimately lead to fewer drugs entering clinical care. A balance between the requirement for health-care systems to limit cost of cancer care and industry's need for profit will have to be reached.

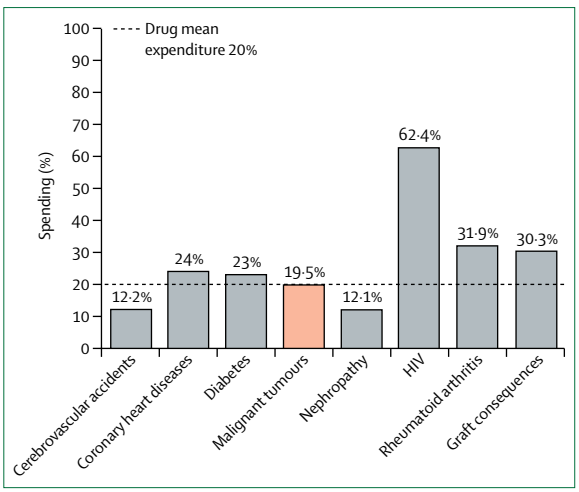

Figure 4: **Mean annual expenditure per patient for selected chronic diseases in France[89]**

Improving access to effective cancer care

Overall spending on cancer care has increased substantially during the past 15 years, raising the question of the capacity of some countries to finance universal access to the latest treatment. The French National Cancer Institute recently completed an audit of cancer-related expenses, which showed that the annual direct costs of cancer care, including screening, treatment, and government-funded research, were around €14 billion. Annual indirect costs such as lost productivity and premature disability or death and their effect on the general economy were around €17 billion.[88]

The report of this audit argued that better access to cancer treatment should be provided through several strategies. First, cancer accounts for about 30% of all deaths and 36% of premature deaths in France, but despite this, direct government expenditure on cancer was only about 10% of total health-care expenditure. Second, the annual per-patient expenditure on cancer treatment was close to the average expenditure for all diseases (figure 4) and substantially lower than for some other chronic diseases, such as nephropathy or infection with HIV. Furthermore, the contribution of drug costs to total expenditure on cancer care was less than 20%, with around 70% accounted for by health-care resource utilisation, such as hospitalisation. Compared with other chronic diseases, 20% of total expenditure on drugs was low (figure 5).

The audit concluded that public spending on cancer should increase in an attempt to reduce the burden of the disease relative to other illnesses. Furthermore, it recommended that access to drug therapy be increased with reciprocal cost savings gained from reducing health-care resource utilisation.

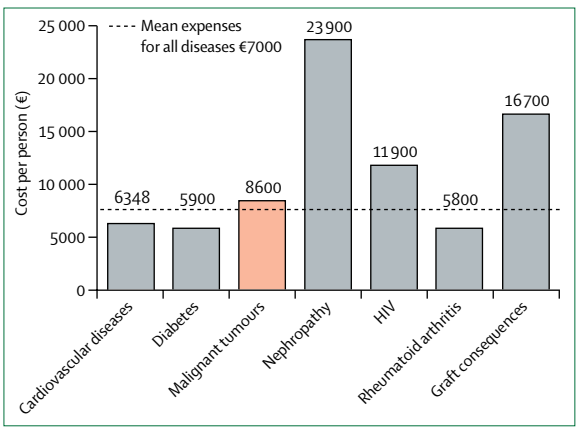

Figure 5: **Contribution of drug cost to total spending for selected chronic diseases in France[89]**

Defining affordable cancer care in high-income countries

The decision to implement a new cancer intervention should require that it increases survival or quality of life (or both) and that it is financially viable. This requirement involves a trade-off between the risks and benefits to the patient as well as between the potential effectiveness to be gained and the limited resources available. Establishing the value of a cancer treatment requires assessment of whether the additional health expected to be gained exceeds the health expected to be lost as other treatments are displaced by its additional cost.

Data from RCTs often do not apply to the general population, therefore analyses of cost-effectiveness based on RCTs should be supplemented by health-outcomes databases so that health-resource utilisation and longer-term toxicity are better elucidated. Furthermore, to improve the usefulness of such analyses, reports should be based on clinically meaningful endpoints and not surrogates.

The definition of value remains a divisive area. Economic incentives are powerful drivers of new cancer therapies, but the fruits of such research can be unaffordable even in high-income countries. Although many jurisdictions have set official or unofficial thresholds for the definition of value, these rarely have input from important stakeholders such as patient groups or the general public. As a result, many treatments are rationed for not meeting prespecified levels of cost-effectiveness. The development of value-based pricing, where drugs will be approved only at prices that ensure that their expected health benefits exceed the benefits that might be obtained by applying the same resources to other health strategies, could lead to more affordable cancer care and improve access to cancer drugs for many patients.

Part 3: Strategies for affordable cancer care—a medical oncology perspective

Lessons from the past

The first cancer drugs were discovered in the 1940s, and from mid-20th century to the 1980s, alkylating agents (oral and intravenous), several antibiotics, and two stalwart antimetabolites (methotrexate and fluorouracil) were developed. Costs were not an issue, since the only successes (cures) were achieved in rare tumours such as lymphomas, choriocarcinoma, and several leukaemias, mostly in children. The use of platinum compounds was important, but only in terms of cure in testicular tumours. Side-effects of renal failure, aggressive peripheral neuropathy, and nausea and vomiting worse than with mustine highlighted the issue of costs of managing or preventing drug side-effects. Subsequent calculations of the costs of cancer care have not emphasised the now routine use of expensive hydration schemes, cold caps, antiemetics, and myelopoietic stimulating factors. On the positive side, chemotherapy has moved almost completely from an in-patient setting to the day-bed ward, home delivery, or mobile unit.

During the 1980s, anthracyclines proved to be useful drugs, although mainly in empiric cocktails of cytotoxic drugs in metastatic solid tumours. It is a sobering thought that 30 years later, patients with metastatic tumours arising in breast, lung, colon, rectum, ovary, or pancreas are still not cured, apart from rare situations when surgery or radiotherapy (or both) for isolated late-onset metastases is possible. Rather, we are now faced with novel antibodies and small molecules, the so-called targeted agents (they still cause off-target toxicity), which are used more and more, in sequence rather than in combination. Small wonder that leading health economists (who are seeing considerable growth in their university departments as demographic changes lead to an increase in incidence of age-related cancers) now label cancer as a chronic disease. By definition, this implies no likelihood of cure.

The other area of increase in costs has been the addition of systemic therapies to locoregional treatment of early cancers after (adjuvant) or before (neoadjuvant) surgery or radiation. The main problem with this approach can be the lack of benefit; most patients only have side-effects, early and late. The promise of prognostic and predictive markers has not been easily forthcoming and we need, for example to still treat ten women with breast cancer with adjuvant chemotherapy when probably only around two of these will actually benefit. Cost–benefit models (eg, of adjuvant cyclophosphamide, methotrexate, and fluorouracil [CMF] in breast cancer) were deficient in overlooking this uncalculated toxicity. Cost–benefit analysis in these situations can only be done with artificial models, which are largely unvalidated by the people who matter—ie, cancer patients. The advent of trastuzumab as a targeted drug that improved 5-year survival in patients with early breast cancer, whose tumour cells were HER2 positive by immunochemistry or fluorescence in-situ hybridisation (FISH), was a distinct improvement in selecting patients most likely to benefit. However, the cost of this drug is high, and the costs of prerequisite tissue testing

has added to the bill. It is worth noting that barely half of patients whose cancer is HER2 positive actually respond, reminiscent of the failure of the first targeted agent, tamoxifen, to benefit all women with oestrogen-positive breast cancers. More sophisticated tests, not only in molecular pathology but also using expensive imaging tools, such as ^{18}F-fluorodeoxyglucose (FDG)-PET and MRI angiogenesis markers, will probably improve the percentage of patients responding to the appropriate targeted medicines. Here, we compare the cost of cancer drugs today in three high-income countries (the UK, US, and Australia), and highlight the main challenges for keeping the cost of cancer care affordable in the next decade.

Cost of cancer care today: UK

In the UK, the high cost of cancer medicines has been a controversial issue. NICE controls which drugs and treatments are available on the NHS in England and Wales (Scotland and Northern Ireland have separate organisations that are physician led, rather than economist directed, to make decisions). NICE was developed to eliminate the so-called postcode lottery, where some drugs and treatments were available in some parts of the UK, but not in others. NICE has been repeatedly criticised by oncologists for its decisions to deny approval for cancer medicines.[90,91]

NICE makes decisions by utilising the QALY as its measure of cost-effectiveness, and has an upper limit of £30 000 per QALY above which it is unlikely to approve a drug.[92] Many cancer medicines are not approved by NICE, since their high acquisition cost and marginal benefits in improving OS result in QALYs higher than £30 000. This restriction of access to cancer medicines has caused controversy for UK patients, clinicians, payers, providers, and politicians.[93,94] The QALY values generated by the pharmaceutical industry in their submissions to NICE are often different than those calculated by NICE, leading to appeals and delays.[95] NICE responded to concerns over access to expensive cancer medicines by adopting controversial end-of-life criteria, which enabled cancer drugs to be valued more highly than other types of drug. This allowed some cancer medicines with a QALY greater than £30 000 to be approved.[96] Following a change of government in 2010, and further evidence that the UK was slow to adopt new cancer drugs compared with other countries in Europe, a new approach to funding high-cost cancer medicines based on value-based pricing has been introduced in the UK. Value-based pricing starts with a basic price threshold, expressed as cost per QALY or other outcome metric, and incorporates all the components that contribute to a treatment's effect on health and quality of life.[97]

A £200 million per year cancer drugs fund has also been introduced, to allow patients to receive treatments they are unable to access through usual local funding arrangements by NHS payers. However, because these decisions are regional, it reintroduces the postcode lottery.[98] This fund has allowed drugs deemed not cost effective by NICE, such as bevacizumab for colorectal cancer, to be prescribed in the UK. The fund is to run for 3 years, until April 2014, when it will be replaced by a value-based pricing system of approval for medicines in the UK. It is proposed that such a system will recognise innovation, unmet need, and burden of disease, factors that should favour funding of cancer medicines. The role of NICE in the next few years is unclear.[99,100]

	Date	Drug	Title	PAS (Y/N)	End of life (Y/N)	Approved	QALY*
TA 212	December, 2010	Bevacizumab	First-line metastatic colorectal cancer	Yes	No	No	£68 000–103 000
TA 208	November, 2010	Trastuzumab	HER2-positive metastatic gastric cancer	No	Yes	Yes	£45 000–50 000
TA 209	November, 2010	Imatinib	600–800 mg for progressive unresectable or metastatic GIST	No	No	No	£39, $63
TA 202	October, 2010	Ofatumumab	Chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab	No	Yes	No	£60 000–81 000
TA196	August, 2010	Imatinib	GIST (adjuvant)	No	No	No	£19 000–171 000
TA 192	July, 2010	Gefitinib	Advanced or metastatic non-small-cell lung cancer, first line	Yes	No	Yes	£27 000
TA 193	July, 2010	Rituximab	Relapsed or refractory chronic lymphocytic leukaemia	No	No	Yes	£20 000–30 000
TA 191	July, 2010	Capecitabine	Advanced gastric cancer	No	No	Yes	NA (dominates comparator)
TA 190	June, 2010	Pemetrexed	Maintenance treatment of non-squamous non-small-cell lung cancer	No	Yes	Yes	£47 000

NICE=National Institute for Health and Clinical Excellence. PAS=patient access scheme. QALY=quality-adjusted life years. HER2=human epidermal growth factor receptor 2. GIST=gastrointestinal stromal tumour. NA=not applicable. *NICE guidance typically presents a range of possible QALYs rather than a single definitive value. The QALYs listed are the consensus values from NICE TA documents.

Table 2: **NICE cancer-medicine technology appraisals (TA) from June–December 2010**[101]

The UK pharmaceutical industry responded to drug-access problems by adopting a different approach to pricing of cancer drugs and other high-cost medicines for the UK market. The industry acknowledged that many of its products are too expensive for the UK, but was reluctant to directly lower drug costs, since UK prices are a reference against which drug prices in other countries are set. The solution to this pricing dilemma was the development of risk share, or patient access schemes (PAS), which have allowed drug companies to reduce the transaction price of a drug to the NHS while maintaining the list price of the drug. PAS are seen as a way of improving access to new medicines that would otherwise be deemed not cost effective by NICE. However, PAS present an administrative burden, which still increases cost overall, and their complexity can lead to the discounts and rebates not being claimed.[98] Table 2 outlines NICE decisions in the past 2 years and highlights the effect of end-of-life criteria and PAS on NICE approvals.

Cost of cancer care today: Australia

In Australia, the cost of most prescription medicines is subsidised by the government through the pharmaceutical benefits scheme (PBS). Drugs approved by the Therapeutic Goods Administration (TGA) are assessed for PBS subsidy by an independent body of medical practitioners and pharmacists, the Pharmaceutical Benefits Advisory Committee (PBAC). The committee considers several issues before recommending a drug, including the conditions for which the drug has been approved for use in Australia, the conditions in which use has been shown to be effective and safe compared with other therapies, the costs involved, and a range of other factors and health benefits. These factors can include costs of hospitalisation or other alternative medical treatments that might be needed, as well as less tangible factors such as patients' quality of life. In 1993, Australia was one of the first countries to add economic analysis to the criteria for listing drugs on the PBS. Decisions on PBS listing are generally made from a health-economics perspective, using cost-effectiveness analysis. Drugs that provide little health benefit at considerable additional expense, such as expensive cancer chemotherapy drugs, might not be listed on the basis of poor cost-effectiveness. WHO adopted this Australian concept as a key mechanism of ensuring equity of access to necessary drugs. However, this robust system can result in long delays from the time of TGA approval of a drug to its listing on the PBS. The PBS can be described as a dominant or single-payer universal health-care system, in which the government is the only buyer of health-care services. This system has resulted in Australian drug prices being at least half as expensive as in the USA, Canada, and Sweden, and similar to prices in France, Spain, and New Zealand, which show comparable drug pricing with the UK.[102] However, Australian prices for new innovative pharmaceuticals are much closer to those in most other countries. The largest price differences between Australia and other countries are for pharmaceuticals with minor chemical variations that lack major benefits compared with an innovator brand, and generic drugs. PBS price negotiations have been good for Australian consumers, but over the years, the cost of the PBS to the government has escalated. Patient co-payments, brand premiums, therapeutic group premiums, and other strategies have been used to provide price signals and transfer some of the cost to consumers. Nonetheless, the comparative cost-effectiveness processes of the PBS ensures that it provides Australian citizens with more equitable access to medicines than in many other developed nations. In 2007, changes to the National Health Act divided the PBS formulary into an F1 (for patented, single-brand medicines) and F2 category (for generic medicines), with reduced reference pricing between them. This has led to a considerable reduction in costs for generic medications. Like many other countries, the pharmaceutical industry in Australia offers many programmes to facilitate deferred cost, cost-free, or subsidised access to medicines, before the PBS listing or implementation of other relevant funding arrangements. The programmes have different names (product-familiarisation programmes, expanded-access programmes, risk-share programmes), but the principles are similar. These programmes are an acknowledgment by pharmaceutical companies that their therapies are expensive. Although they are unrestricted, Medicines Australia's Code of Conduct and the Council of Australian Therapeutics Advisory Group's (CATAG) has guiding principles for such programmes.[103]

Cost of cancer care today: USA

As in other countries, the cost of cancer care in the USA continues to rise. A recent study estimates costs of $124 billion in 2010 and $158 billion in 2020, with the latter estimate increasing to $173 billion if costs of care increase annually by 2% from the initial phase of care to the last year of life.[8] As in other countries, the largest increases are envisioned for continuing care for prostate cancer (42%) and female breast cancer (32%). But more than in other countries, the cost of cancer care in the USA is increasingly burdened by off-label use of expensive therapies that provide marginal or no benefit.[104,105]

What is off-label use? In the USA, after a drug's approval, the FDA works with the manufacturer to create a drug label that contains information about the drug, how it should be administered, and the indications for which it has been approved. Any use of the drug in a manner different from that described in the FDA-approved drug label is an off-label use. In oncology, off-label use includes uses for a different cancer or at a different time in the course of the disease, or in a dose or schedule different from that in the approved label.

Because the FDA does not regulate professional standards, off-label use of FDA-approved cancer drugs is not regulated and is legal in the USA (panel 3).

Indeed, once a drug receives FDA approval, a licensed doctor can use it for any indication they consider appropriate, governed only by professional medical standards and the licensing authorities of each state. Furthermore, the practice of off-label use of cancer therapies has the tacit endorsement of the National Cancer Institute (NCI),[108] and the FDA has acknowledged that in some circumstances, off-label uses of approved products are appropriate, rational, and accepted medical practice.[109] Off-label use of drugs is not a new phenomenon—oncologists caring for terminally ill patients with cancer have long resorted to this practice. Nearly 20 years ago, the US General Accounting Office found that about 33% of all cancer drugs administered were used off-label, with more than half of patients with cancer (56%) prescribed at least one drug off-label as part of their treatment regimen.[110] This 1991 report described a practice that today is commonplace, reporting higher off-label use in treating more difficult cases (advanced incurable cancers, those in which chemotherapy is ineffective, and in second and third lines of treatment). Similarly, a 1997 study found that 60% of medical oncologists had prescribed a chemotherapy drug off-label, a number that today is likely closer to 100%.[111] Although some off-label use is supported by clinical data, oncologists increasingly use off-label cancer drugs in patients that are no longer experiencing benefit from standard approved treatments—clinical scenarios where there is little supporting data and therefore little reason to expect benefit, with accumulating evidence of harm.[112,113] Furthermore, unlike the 1990s when drug prices were more restrained, off-label use today involves increasingly expensive drugs that do not provide any greater benefit or lower toxicity than much less expensive alternatives. One example is the use of chemotherapy in patients with platinum-refractory ovarian cancer. Expensive targeted and cytotoxic therapies do not always provide greater benefit than drugs that cost much less, nor do they provide this benefit with less toxicity.

Who pays for these therapies? Medicare coverage reimburses such costs for elderly patients, with younger Americans relying on private insurers.[114] Insurance companies might not reimburse charges for an indication not listed in the approved drug label, on the grounds that its use is experimental or investigational (large portions of the US population are uninsured, an issue we do not address here). However, in 1993, federal legislation was enacted requiring coverage of medically appropriate cancer therapies off-label (panel 3). Since its initial implementation, the law has been generously expanded so that it currently provides great latitude in support of off-label use, provided the therapy has been carefully evaluated clinically and reported in respected medical literature. By reporting clinical trials, including those that are not part of the FDA approval process, medical literature is the main source of information for off-label use. Increasingly, this information is catalogued as treatment guidelines that effectively codify off-label uses, which in the absence of an evidence base seems contradictory. The treatment guidelines provided by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) are examples of such catalogues. Clearly, a guideline should be based on substantial evidence, from robust randomised trial results to convincing phase 2 experience, as was the case for adopting imatinib for chronic myeloid leukaemia (CML) and GIST.

As reported above, health economists have been slow to involve consumers (ie, patients and caregivers) in research regarding the costs they deem acceptable for specified but uncertain benefit, nor have patients' values been explored in a systematic way. This is particularly true for elderly patients, who will make up the vast majority of the cancer burden by 2030, since they have been systematically deselected from clinical trials. Thus,

Panel 3: Legal remedies enacted by US Congress to cover off-label use

Concerns about the quality of cancer care prompted Congress to require federal health-care programmes, such as Medicare, to cover payment of off-label uses of drugs used to treat cancer, provided the drugs were deemed medically appropriate. The first legislative remedy was a provision in 1993 that required Medicare to cover off-label uses of anticancer drugs found in standard medical compendia. The Social Security Act recognised three compendia as authoritative sources for use in the determination of medically accepted indications of drugs and biological agents that are used off-label in an anticancer chemotherapeutic regimen: American Medical Association Drug Evaluations (AMA-DE), US Pharmacopoeia–Drug Information (USP-DI) or its successor publication (amended in the Deficit Reduction Act of 2005), and American Hospital Formulary Service–Drug Information (AFHS-DI).[106]

Through the years, Congress continued to rely on a system of compendia in several other legislative initiatives. In 2008, the Centers for Medicare and Medicaid Services (CMS) established a process for revising the list of compendia, and also established a definition for compendium,[107] as a comprehensive listing of US Food and Drug Administration (FDA)-approved drugs and biological agents or a comprehensive listing of a specific subset of drugs and biological agents in a specialty compendium (eg, a compendium of anticancer treatment). A compendium includes a summary of the pharmacological characteristics of each drug or biological agent, and may include information on dosage and recommended or endorsed uses in specific diseases, is indexed by drug or biological agent, and has a publicly transparent process for evaluating therapies and identifying potential conflicts of interest.

there is scant evidence to discuss and a void of information about what elderly patients value and would be willing to trade off.[115] In children, off-label use is a prerequisite for treatment of many malignancies, since many drugs have not been evaluated in younger patients. In Europe, however, recent legislation will ensure that this is done in the future.[116]

Cost of cancer care tomorrow: challenges and policy strategies

The rapidly escalating cost trajectory of the past decade has been partly driven by pricing new therapies based on the costs of existing therapies, rather than rational economic models. The alarming pace might seem to be moderating, but the trajectory continues upwards at a speed that is not sustainable. Everyone can agree that there are many causes of skyrocketing therapy costs, but we continue to sow the seeds that risk exacerbating the problem.[117,118] Phase 3 studies done to garner regulatory approval routinely enrol hundreds of patients, the large numbers needed to ensure statistical validity, and these trials that are powered to ratify marginal differences enhance the problem of escalating drug costs. The problem might begin much earlier, as therapies with marginal effects early in their development continue to be advanced. Table 3 shows the results in early development of therapies that eventually gained approval based on marginal benefits in phase 3 trials. It is not surprising that marginal results early in development lead to marginal outcomes in phase 3 trials.

Deciding how to allocate resources to treat cancer needs more discipline among professional caregivers, but it is also a patient, moral, and political issue. Several scientific strategies are aimed at lowering the costs of oncological drug development and cancer care. First, tailoring novel therapies by use of prescreening with molecular biomarkers should become the norm. By restricting the use of new drugs to patients who will have the maximum benefit, costs will be reduced. Second, imaging techniques could potentially have a greater effect on cost reduction than tailored therapy, by selecting patients for appropriate medicines or excluding patients with no chance of clinical benefit. Third, we need to change the focus from large phase 3 trials to more intelligently designed phase 0, 1, randomised phase 2, and intermediate phased 1–2 trials, to discard marginally effective drugs quickly. New guidelines were released by the FDA in 2006, and in 2007 and 2008, the first phase 0 trial of a poly ADP-ribose (PARP) inhibitor was done at the NCI-NIH.[131] In 2009, the International Conference on Harmonisation released comprehensive guidelines on exploratory phase 0 trials and adaptive clinical trials.[132] The industry, though, needs to catch up with these guidelines.

Scientific advancements are not the only factor to consider when devising strategies for affordable cancer care. Other components that affect the burden and cost of cancer need to be taken into account in policy making. The effect of treatments on quality of life, treatment costs in terms of patients' time, burden on caregivers, productivity losses, and other aspects of the cancer-care continuum, such as primary prevention and screening,

	Study design	N	Patient population	RR or difference in RR*	PFS or difference in PFS* (months)	OS or difference in OS* (months)
Panitumumab in colorectal cancer						
Panitumumab[119]	Phase 2	148	Heavily pretreated mCRC†	9%	3·5	9
Panitumumab *vs* BSC[120]	Randomised phase 3	463	mCRC refractory to fluorouracil, oxaliplatin, and irinotecan†	8%	<2	HR 0·93‡
FOLFIRI ± panitumumab[121]	Randomised phase 3	1186	Second-line mCRC§	25%	2	2
FOLFOX4 ± panitumumab[122]	Randomised phase 3	1183	First-line mCRC§	7%	1·8	4·2‡
Cetuximab in colorectal cancer						
Cetuximab[123]	Phase 2	57	Prior irinotecan	8·8%	1·4	6·4
Cetuximab ± irinotecan[124]	Randomised phase 3	329	Progressed during or within 3 months after treatment with an irinotecan regimen	10·8%¶	1·5¶	6·9¶
FOLFIRI ± cetuximab[125]	Randomised phase 3	1198	First-line mCRC	8·2%	0·9	1·2‡
FOLFOX4 ± panitumumab[126]	Randomised phase 3	354	First-line mCRC	8%	0‡	NA
Cetuximab in NSCLC						
Cetuximab[127]‖	Phase 2	18	Recurrent NSCLC with progression on oral EGFR TKIs gefitinib or erlotinib	0%	1·8	7·5
Cisplatin + vinorelbine ± cetuximab[128]	Randomised phase 2	86	First-line NSCLC	7%	0·4‡	1·0‡
Cisplatin + vinorelbine ± cetuximab[129]	Randomised phase 3	1125	Advanced (stage IIIB or IV) EGFR-positive NSCLC	7%	0‡	1·2
Taxane + carboplatin ± cetuximab[130]	Randomised phase 3	676	Chemotherapy-naive patients with stage IIIB (pleural effusion) or IV NSCLC	8·5%	0·16‡	1·31‡

N=number of patients. RR=response rate. PFS=progression-free survival. OS=overall survival. mCRC=metastatic colorectal cancer. BSC=best supportive care. HR=hazard ratio. FOLFIRI=folinic acid, fluorouracil, irinotecan. FOLFOX=folinic acid, fluorouracil, oxaliplatin. NA=not applicable. NSCLC=non-small-cell lung cancer. EGFR=epidermal growth factor receptor. TKI=tyrosine kinase inhibitor. *Single agent data are shown as absolute RR, PFS or OS. For randomised trials, the difference between the two groups is shown. †Wild-type and mutant KRAS tumours. ‡Not significant. §Only wild-type *KRAS* tumours. ¶Values are for the cetuximab-only group. ‖Data not available for randomised phase 2 and 3 trials.

Table 3: **Outcomes of early and phase 3 studies of cancer drugs**

will need to be included to improve our understanding of the societal impact of cancer. We recommend a greater degree of patient empowerment, which will require more than just token recognition, because in the end it is the patient who pays for care, either directly or indirectly via taxation or insurance premiums. Also, proper considerations must be given to the problem of off-label use; the increasing burden of the cost of cancer care in the USA, due to use of expensive therapies that provide marginal or no benefit off-label, is a practice that might foreshadow a similar problem in other parts of the world.

Finally, a policy-making approach focused only on high-income countries would be incomplete. Although here we focused on a comparison of three high-income countries, the perception of cancer as a disease only of high-income countries leads to an underestimation of the costs associated with premature death and disability in low-income and middle-income countries,[15] and we support a call for action on a global scale to allocate resources and increase awareness of cancer care in such countries.[133]

Part 4: Affordable cancer surgery

Surgery remains the main method for control and cure of solid tumours globally. 70% of patients with solid tumours that are cured have surgery as part of their management. We have made considerable progress since the late 18th century when John Hunter described surgery as being "like an armed savage trying to render by force that which a civilised man would render by strategem". With the increasing incidence of cancer due to ageing, and better early detection accompanied by advances in molecular diagnostics, profiling, and targeted therapy, surgery will continue to constitute the backbone of cancer management for most patients with solid cancers.[134] Major issues in evaluating of the benefits of cancer surgery are the paucity of data from high quality trials that assessed surgical and related imaging technology and the associated costs, geographical variation in utilisation of surgery, and surgical effectiveness in relation to overall clinical outcomes and quality of life.

Using data from the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked database, Warren and colleagues[12] evaluated trends in costs of initial cancer treatment and showed that the substantial increase in costs is a result of more patients receiving surgery and adjuvant therapy, and the rising costs for these treatments. It is anticipated that these trends will continue in the near future. One way of mitigating the overall effect of this trend is more efficient use of costly therapies,[12] and a willingness to place a value index on such therapy.

Cost of cancer surgery today

There is a paucity of data on the cost of surgery as a percentage of the total cost of cancer care. The only detailed data are from Warren and colleagues,[12] who examined the cost of surgery, chemotherapy, radiation therapy, and other hospitalisations, during the period of initial cancer care (2 months before to 12 months after diagnosis), for 306 709 patients aged 65 years or older treated between 1991 and 2002 for four common cancers. The cost of cancer-related surgery relative to the total cost of treatment and other hospitalisations was 53% for breast, 28% for lung, 53% for colorectal, and 34% for prostate cancer.

Since surgery is performed for patients with early-stage disease, the cost of lives saved would be expected to be in favour of surgery. In the absence of metastatic disease, surgical treatment of cancer is curative. It is therefore important to rule out metastatic disease by suitable diagnostic imaging before attempts at curative surgery. Current diagnostic modalities include ultrasound, CT, MRI, and PET. The indications for staging and the method used vary, depending on tumour type and clinicohistopathological stage of disease. A fine balance is achieved between diagnostic yield, false-positive rates, and cost-effectiveness. Quantifying the benefit of radiological staging investigations is difficult, and in many cases impossible. Some studies have attempted to evaluate the cost-effectiveness of diagnostic staging investigations in patients with cancer.[135] The study methods have varied and results are not easy to interpret. What is without doubt is that complex investigations are more expensive, and as a result of greater patient and clinician expectations, these investigations continue to be done without clearly quantifiable patient benefit, possibly making the increasing demand on health care in this area irreversible and unaffordable.

Although surgical techniques have become more cost effective in terms of shorter inpatient stay and decreased morbidity, they have also allowed for wider indications for surgery that were previously not possible. This wider use of surgery has been enabled by greater sophistication of techniques. Several studies have shown that minimally invasive surgery, particularly robotics, is much more costly than conventional open surgery. However, a shorter length of hospital stay might balance the higher cost. With increasing volumes of surgery done for a physiologically healthy, but ageing, population with an increased incidence of cancer, in real terms, the costs might actually rise.

There has been an explosion in the number of robot-assisted procedures. Paradoxically, while there has been a decrease in the underlying incidence of prostate cancer, there has been an increase in the number of robot-assisted prostatectomies (figure 6).[136] This suggests that the introduction of this technology has been the driver for the increased number of cases treated surgically, thereby increasing costs with no clear evidence of long-term improved patient outcome or quality of life.[137] This form of treatment is unaffordable in most countries, for all but the privileged few.

Martin and colleagues[138] investigated the point at which robotic cystectomy becomes more expensive than open cystectomy. They found that robot-assisted

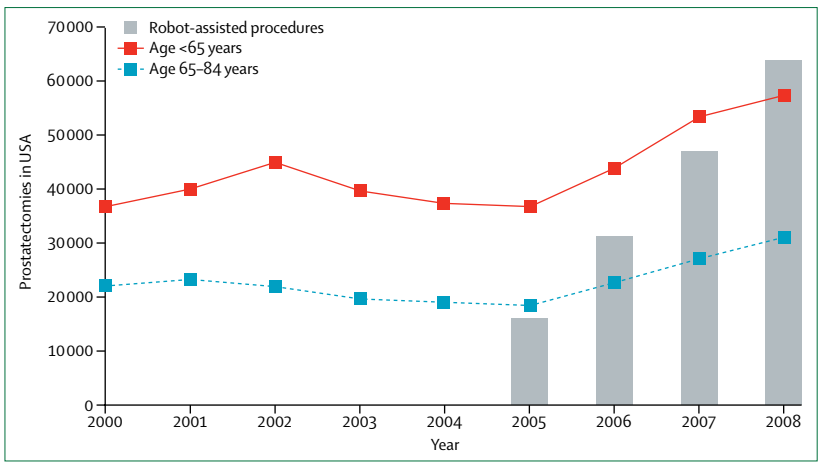

Figure 6: **Prostatectomies in the USA from 2000–08**
Reproduced with permission from reference 136.

radical cystectomy was 16% more expensive than the open procedure when direct operative costs were compared. However, when the complication rate and associated increase in hospitalisation cost in the open surgery cohort was taken into account, this increased operative cost for the robotic procedure was reversed. This lower cost has to be balanced against amortisation of the robot, which is facilitated by a high case volume. Also, robotics are not available for most of the world's population.

Clearly, the minimally invasive and robot-assisted approaches are the most likely to be proven efficacious when the objective is removal of a lesion with limited requirement for intracorporeal reconstruction—eg, they are more likely to be successful with hysterectomy than with pancreatoduodenectomy. One clear advantage for the minimally invasive approach, whether robotic or laparoscopic, compared with open surgery is avoidance of incisional hernia, which can cause substantial long-term morbidity with reported rates that vary from 5 to 15%. This negative cost could argue against open surgery. In the short term, minimally invasive surgery causes less trauma than open surgery, which is important in cost-efficient enhanced recovery after surgery (ERAS) programmes that are designed to shorten hospital stay.

The robotic surgical community has a responsibility to design large-scale, multicentre RCTs to identify which patients will benefit from open surgery versus robotic-assisted procedures, and to refine indications for the latter. This has been done for laparoscopic versus open colorectal cancer surgery with no substantial cost-benefit for either procedure.[139]

Changing surgical approaches with improved biological understanding and systemic treatment

The use of surgery has evolved because of better insights into the biology of cancer. A prominent example is Halsted's radical mastectomy versus the current breast-conserving approach of wide local excision and sentinel-node biopsy, followed by an axillary lymph-node dissection (ALND) only in patients with proven tumour involvement of the sentinel node. Even this current approach is likely to change. At the 2010 ASCO annual meeting, long-term follow-up results (median follow-up 6·3 years) of the ACOSOG Z0011 trial[140] were presented. This trial showed that in 891 patients with clinically node-negative breast cancer and one to three positive sentinel nodes, there was no benefit from ALND (*vs* no ALND) for women who had a positive sentinel-node biopsy. No difference was observed between the two groups in terms of 5-year breast, nodal, or total locoregional recurrence. The DFS curve for patients who did not undergo completion ALND for positive sentinel lymph nodes was always above the curve for ALND patients throughout the follow-up period—ie, no suggestion of a benefit for ALND. The potential cost benefit of avoiding long-term lymphoedema increases the benefit of not performing ALND. For this trial not to be accepted solely on inherent surgical bias would be unfortunate.

Ageing

With an ageing population and increased incidence of cancer, cancer care is becoming a greater proportion of health care. Yabroff and colleagues[141] used SEER Medicare files to estimate net costs of care for elderly patients with cancer in the USA, for the 18 most prevalent cancers and for all other tumour sites combined. They concluded that the costs of cancer care to Medicare are substantial, and vary by tumour site, phase of care, stage at diagnosis, and survival. Ageing adds additional challenges in terms of treatment options, physical comorbidity, quality of life, tolerability of surgery, increased perioperative risks, and balancing the natural history of disease with proportion of remaining normal life. Elderly women with breast cancer are often offered suboptimum treatment despite good evidence for surgery as standard care.[142] By contrast, active treatment for prostate cancer can be questioned. For hypothetical cohorts of 65-year-old men, the quality-adjusted life expectancy (QALE) was longer for active surveillance than for brachytherapy, intensity-modulated radiation therapy (IMRT), or prostatectomy.[143] The health economics of cancer care in the elderly population requires more detailed research from clinical, psychological, and social-impact perspectives.

Why is cancer surgery becoming unaffordable?

There are many reasons why cancer surgery is becoming unaffordable, here we discuss a few. First, the medical profession and the health-care industry have created unrealistic expectations of arrest of disease and death. This set of expectations allows inappropriate application of relatively ineffective therapies, including surgery, in the name of care. In developed countries, cancer

treatment is becoming a culture of excess. We overdiagnose, overtreat, and overpromise. This extends from use of complex technology, surgery, and drugs to events related to the acceptance of treatment side-effects.

Second, we are a society that focuses almost exclusively on benefit, and such benefit is often small. For example, a 20% improvement in survival for a patient with a non-resectable metastatic solid tumour translates into a benefit of 4–6 weeks at best. Perspective is almost exclusively absent as we focus solely on what is perceived as benefit. Benefit is often measured as improvement in PFS, which often does not translate into OS. We undertake prospective randomised trials of large numbers of patients to provide benefits measured in single percentages, losing sight of the clinical significance of such change. For example, in early-stage breast cancer where survival is higher than 90%, large trials can be done to show improved survival from 92% to 94%; while this may be a statistically valid improvement in survival it is nevertheless very small. We ignore the fact that all interventions have side-effects and financial costs. This situation can apply for an added chemotherapy drug, the application of an extraordinarily costly technology, a novel surgical technique, or the utilisation (overutilisation) of a diagnostic test.

Third, in the USA and in other countries, cancer care (including surgery) is already rationed, by the lack of availability or access. In some situations, patients with no insurance or the most basic form of Medicaid, if they can gain access, are provided with better cancer care than that of the most expensive insurance policy. Such premium care is reimbursed at less than the cost by the state or federal government, and supported by the health-care provider, physician, or hospital who absorb the loss.

Finally, we are a compliance-ridden society. We seem to believe that we can mandate good behaviour, good clinical care, and social responsiveness. Process and oversight are important, but overzealous administrative compliance is burdensome, costly, and stifles initiative and personal responsibility.

Clearly, there are examples of excellent progress and noteworthy advances in selected diseases. It is exciting to see a lethal disease such as GIST become a chronic illness because of progress in molecular biology and use of targeted agents. But key successes are overwhelmed by the trivial focus on small benefit and total ignorance of potential costs. Such failures, for example in the management of pancreatic adenocarcinoma, are compounded by constant rearrangement of ineffective therapies, with no evidence that a new scheduling will alter the outcome.

Way forward

There is acknowledgment that the economic burden of health care in general, and high-quality cancer care in particular, will become unaffordable without genuine effort to address these issues. ASCO has established a cost-of-care task force, which has developed a guidance statement on the cost of cancer care.[42] In addition to providing an overview of the economic issues relevant to cancer care, it recommends a series of measures addressing immediate needs. These include increased awareness, education, and communication regarding the cost of cancer care to help guide patients and physicians on treatment decisions. It is important to understand the drivers contributing to the burgeoning cost of cancer care and develop policy to address these factors. We believe that society can be educated. The recent transition following the economic crisis, where credit-card usage has decreased and savings increased, shows that a crisis can be used as an opportunity to influence behaviour (and we are heading towards a crisis in medical-care delivery).

Incredibly, most physicians and surgeons in major institutions are unaware of the cost of their own services or the technology and investigations that they order. The simple approach of educating physicians, by making it mandatory that charges for every test, and procedure, are cited, would help educate us all. Most important would be studies designed to show the relative benefit of a particular intervention, whether it is a surgical or new imaging technique. If we could define performance of a modality or treatment (ie, outcome) first based on clinical outcome and then based on cost, it would be a major step forward.

Part 5: Appropriate assessment of radiation oncology technology and treatment

In the early 1970s, radiation and medical oncology were just emerging as clinical specialties in Europe and the USA. Few systemic therapies were available, and rudimentary linear accelerators were entering into general use. The costs of these emerging technologies were a small portion of health-system budgets, and their promise lay in the future. Today, early detection and cancer-specific treatment advances have resulted in increased cancer survival and substantially higher costs.[42,144] Although population ageing, increased cancer prevalence, and cancer prescription drug costs are important drivers of rising costs, technological advances in diagnostic and therapeutic modalities, including radiation therapy, have also contributed.[42]

Radiation therapy is a well established, essential component in the curative and palliative treatment of malignancy. Roughly 60% of US patients with cancer receive radiotherapy during their course of treatment.[12] Nevertheless, there is mounting concern that undiscerning analysis of medical evidence could lead to asymmetric allocation of resources away from this discipline. We address these concerns and propose a progressive method for evaluation of the effectiveness of radiation oncology treatments, and for demonstration of the discipline's patient-determined value.

Progress in radiation therapy

Tremendous advances in radiation therapy technology, particularly in the past decade, have allowed for remarkable precision in treatment delivery and for the realisation of dose escalation with a concomitant decrease in treatment-related morbidity. IMRT uses advanced computer-based treatment planning and delivery to modulate the radiation beam across the target volume, creating highly conformal dose distributions with steep dose gradients.[145] Image-guided radiation therapy (IGRT), used with IMRT, incorporates advanced real-time and near real-time target imaging and localisation by use of ultrasound, stereoscopic shift imaging, CT, and soon MRI to precisely guide radiation delivery.[146,147] Stereotactic radiation delivery, including stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT), uses advanced planning and treatment equipment and complex methods of patient immobilisation, tumour localisation, and radiation delivery to deliver large, precise radiation doses to treatment targets.[148] Although associated with questions of cost and incremental benefit, proton and hadron beam radiotherapy exploits heavy charged particles to minimise dose deposition distal to the tumour volume, with the potential for improved dose conformity and a reduction in adverse events, provided anatomical variations can be monitored and controlled during dose deposition.[149–151] Image guidance, high-precision dose delivery, increasingly accurate target definition with improved anatomical and biological imaging, and the possibility of dose verification during treatment via dose-adaptive radiation therapy permit dose escalation and higher probability of tumour control.

There has been an evolution in our understanding of radiation therapy. Long considered to be a physical intervention, radiation therapy is now mathematically understood, and is more accurately conceptualised as a biological intervention with profound effects at the cellular and molecular level, modulated through cellular signalling pathways and the immunological axis.[152,153] Accordingly, combinations of radiation therapy with targeted biological agents have proven efficacy and hold tremendous promise for future advances.[154,155]

Improved outcomes associated with technological advances

These scientific and technological advances in radiation therapy add complexity and cost, yet show promise for improved outcomes for a growing number of malignancies. Results of radiation oncology clinical trials with and without systemic therapy have shown survival improvement for most common cancers.[156–163] Radiation therapy has supplanted surgery as the definitive treatment for many head and neck and gynaecological malignancies, and is an equally effective alternative treatment for prostate cancer.[164–166] Additionally, when coupled with chemotherapy, radiation exerts the dominant effect. Concurrent chemoradiotherapy is often associated with improved locoregional control; however, development of distant metastases is not affected, suggesting that the true benefit of chemotherapy is in radiosensitisation.[160] Recent meta-analyses of the relative effect of chemotherapy and hyperfractionated radiation in head and neck cancer reported an absolute survival improvement of 4·5% with chemotherapy versus 8% with hyperfractioned radiotherapy.[167,168]

Technological advances in radiation oncology also hold promise for achieving rates of locoregional tumour control that could obviate the need for surgery or chemotherapy in select settings. SBRT delivery of large doses of radiation causes a greater radiation-induced inflammatory response, increased danger signalling, and more antitumour immunity, leading to an otherwise unpredicted improved clinical response.[169–171] Additionally, the shorter overall treatment time associated with SBRT enhances clinical control by minimising the effect of accelerated tumour repopulation, and it decreases in-patient costs. A recent multicentre cooperative group study of lung SBRT reported 3-year primary tumour control of 97·6%, significantly higher than historical rates of 30–40% achieved with conventional radiotherapy approaches.[172]

Social and economic context of cancer care

Scientific and technological progress comes at a high cost, and there are many concerns regarding the value of that progress. Patients in Europe and the USA often believe that advanced technology and new treatments equate to better care. Dissonance among providers, payors, and government agencies, as a result of disagreement over interpretation of evidence for treatment coverage decisions, is amplified by patients, who often neither embrace nor understand the validation of medical technology.[173] In health-delivery systems in Europe and managed-care systems in the USA, efforts to slow rising costs or to increase profits (in some cases in the USA) have led to underfunding or non-coverage of advanced radiation therapy procedures. The reality is that advanced radiation therapy is complex and costly to deliver. It requires direct supervision by a radiation oncologist throughout the treatment process and is associated with increased equipment cost, paramedical personnel, quality control, and quality assurance essential for safe and consistent treatment delivery. Serious breaches in quality and safety have resulted from short cuts, underfunding, or cost cutting in these processes.[174]

When increased patient demand and physician enthusiasm for cutting-edge treatment is opposed by payers because of an overriding agenda of cost control, what is often overlooked are the potential cost savings to the system and improved patient outcomes afforded by new advanced treatments. Increased equipment and resource costs associated with cutting-edge radiation oncology technologies can be partly mitigated by shortened treatment courses. Additionally, improved tumour control, less toxicity, and reduced treatment

courses decrease the indirect costs of cancer care, including lost time and economic productivity secondary to treatment-related and cancer-related illness and death.[175] The NIH estimates that 53% of the total cost of cancer care in 2010 was attributable to indirect mortality costs, and 8% to indirect morbidity costs.[176] Advances in radiation therapy can potentially result in substantial direct and indirect cost savings. To attain outcome benefits and realise these cost savings requires a new approach and sensibility towards incorporation of new technology and treatment into routine medical care.

Regulatory effects on device development and routine use

The FDA requires drugs to show efficacy in a clinical trial before approval for routine use. Although medical device approval can require a clinical trial, the most common pathway for approval of radiation oncology technologies is the so-called 510K process. This process requires only that the device vendor shows the device to be safe for patient use. Therefore, although the safety and mechanical dependability aspect of the 510K process can be daunting, the process does not require that the device show efficacy or an enhanced health outcome beyond its predicate device in a controlled clinical trial. By contrast with drug development and approval for use, which is supported by an extensive and costly clinical trial infrastructure funded by a well capitalised pharmaceutical industry, no comparable system exists in the technology arena.

Because of the unique nature of medical device development, use of the same criteria to evaluate pharmaceuticals and medical devices is inappropriate. Medical devices tend to progress with incremental innovations in performance and safety, in a shorter development cycle than for drugs. Devices are more difficult to evaluate because of the shorter development and life cycles, and there is a lack of capital and infrastructure support for level I RCTs. Furthermore, strict adherence to the requirement for RCT-derived evidence of superior efficacy, as is customary in drug development, can be unethical if applied to many medical devices. This is particularly relevant in radiation oncology, where substantial improvement in care can be based on the next version of computer planning software or on enhancement in the accuracy of dose deposition. In the latter case, randomisation of a patient to a known inferior radiation dose distribution resulting in increased irradiation of healthy tissue would be considered unethical by patients and doctors. Nevertheless, some payers, technology assessment agencies, and European and US policy makers have mistakenly applied these methods, such as the sole use of RCTs, to show the validity of new treatment enhancements in radiation oncology.[177] Instead, novel approaches to the assessment of ongoing technological advancement in radiation therapy are warranted.

Research methods for measuring and analysing outcomes

Policy solutions to address rising health-care costs promote innovations that achieve value in cancer care. Porter[178] defines value in health care as health outcomes achieved per dollar spent. In a value-based system, outcomes and costs are comprehensively measured over a full cycle of care. The referenced costs are total costs over a full cycle of care for a designated medical condition (eg, prostate cancer). Achievement of value permits spending more on some services (eg, IMRT) to reduce the need for or expense of other services (eg, avoidance of treatment-related morbidity and morbidity management). Porter further describes a comprehensive, three-tiered hierarchy for outcome measures that values not only the traditional outcome measure of survival, but also endpoints such as recovery time, time to resumption of normal activities, disutility of care, and sustainability of health.

The comprehensive approach to outcomes assessment described by Porter is particularly relevant for advanced radiation therapy technology that might not be intended to solely achieve a survival benefit. Value can also be achieved through technological advances that shorten treatment time (eg, partial breast irradiation or hypofractionation for breast-cancer treatment), result in less toxicity (eg, IMRT for breast, anal, or prostate cancer), result in fewer recurrences or long-term complications (eg, SBRT for lung cancer), or achieve effective palliation. Longitudinal tracking of outcomes using registries and assessment of the associated costs across the continuum of care is mandatory, Porter contends, to assess the true value of medical care delivered.[178]

To make value-based decisions in the evaluation of radiation oncology technology and treatment, a crucial question is what constitutes meaningful evidence. As mentioned above, RCTs have been the traditional assessment method for novel technology. However, RCTs have important limitations, including the issue of generalisability.[179] In this emerging era of personalised medicine and rapid technological advancement, an infinite number of RCTs could be conceived to answer evidentiary questions in radiation oncology. To deal with this dilemma, policy makers and health-services researchers are supplanting the traditional evidence pyramid hierarchy, because of recognition that other forms of medical evidence development often provide more meaningful insight into understanding the effectiveness of new technology.[180]

Policies developed to provide value-based assessment of radiation oncology technology and treatment must create an infrastructure for evidence generation and management. This infrastructure must have the ability to gather evidence in an ongoing manner throughout the relatively short life cycle of radiation oncology technology and to adapt to inevitable incremental changes in the technology. Finally, the infrastructure must provide a path to payment coverage that ensures emerging

technologies provide value and contribute to the advancement of the discipline.

Such policies would ensure that technological advances and novel treatment paradigms that show initial evidence of potential benefit and value are available to patients. Evidence of value for small populations could serve as the basis of initial coverage. Equally important, the mandated collection of outcomes data for reimbursement would guarantee useful post-market information on these innovations. Extension of coverage would occur only if analysis of larger scale evidential studies, including population-based registries such as the SEER-Medicare[181] and EUROCARE-4[182] databases, continued to show value. With the participation of major stakeholders, including manufacturers, payers (private and governmental), and providers, this coverage with evidence development (CED) method is a means to construct and finance the infrastructure for technology assessment.[183,184] The mandating entity will vary depending on the structure of a health-care system, but would likely be the dominant insurer(s). CED policies currently exist for Medicare beneficiaries in the USA; however, implementation has not been robust. The legal and regulatory framework supporting policies such as CED will differ in various health-care systems, but regulatory policies will need to be tailored to enable its use in technology-based treatments.[183]

Registries, supported by increased availability and use of electronic data capture, are a powerful mechanism for generation of meaningful data in the context of radiation oncology technology assessment. Before registry implementation, some factors must be addressed; the objectives and scope of coverage should be defined, including the definition of meaningful endpoints and relevant factors affecting outcomes (ie, needed data fields). This requires prior agreement on taxonomy or later homogenisation of individual data fields. Meaningful endpoints should also include patient self-reported assessments of wellbeing and the effect of care they received. Agreement on methods is important, particularly for collection of data that are difficult and controversial, such as data on cost and utilisation. Various stakeholders should be identified and encouraged to participate (including administrators, physicians, patients, advocacy groups, and policy makers). There could be issues related to identifying financially responsible parties. Regulatory and legal issues need to be clarified, including using informed consent when appropriate, maintaining patient confidentiality through restricted database access and built-in secure methods of data storage and retrieval, and relevant ownership of registry data. Governance of the registry should be clearly defined. Oversight will be needed to authorise and prioritise research and data use. Long-term follow-up of patients at regular intervals is crucial to detect long-term toxicities and late recurrences. Therefore, it is important to create methods to increase participation and the yield of information during long-term longitudinal follow-up. The end result will be the ability to systematically analyse factors affecting relevant quality measures, such as cancer cure rates, toxicities, and associated cost for all patients participating in such registry efforts.

The registry data generated can then be analysed using sophisticated statistical analyses (eg, Bayesian propensity scoring) that account for selection bias inherent in observational data.[185] Statistical analyses, used correctly, can achieve a level of balance in confounding variables that rivals prospective randomised trials. Formal decision analysis and cost-effectiveness methods are alternative mechanisms for data analysis that rely on advanced computer programming to weigh various endpoints (eg, cost, tumour control, and treatment-related toxicities) associated with competing clinical interventions or courses of action.

Beyond advanced statistical analyses and sophisticated computer programming, medical experts can be a powerful resource for data analysis. The research and development/University of California Los Angeles (RAND/UCLA) appropriateness method was developed to combine the best available scientific evidence with the collective judgment of medical experts to yield consensus decisions regarding the appropriateness of medical interventions.[186] The appropriateness method begins with a review and synthesis of the best available medical evidence. A list of indications based on specific clinical scenarios or interventions is then prepared. A multidisciplinary panel of experts is identified, including experts in the specific medical discipline being studied and in related disciplines and health-services research. The panel members initially review and rate the appropriateness of each indication independently, then they meet to discuss and debate the validity of the indications and rephrase or define new indications as appropriate. Panellists subsequently rate the refined indications for appropriateness using a numeric scale. The ratings are analysed statistically to detect agreement. The final product of the exercise classifies the indications as appropriate, uncertain, or inappropriate for the intervention.[187] The best-practices initiative from the

Issues	Possible solutions
Potential cost savings and improved outcomes from technological advances	Value-based assessments of technological advances
Achievement of value through technological advances	Use CED methodology as a means to construct and finance technology assessment infrastructure
Need a new approach and sensibility to the incorporation of technological advances into routine practice	Mandate participation of all major stakeholders in CED development
Differing interpretation of medical evidence for treatment coverage decisions by major stakeholders	Promote creative mechanisms of data generation and analysis
Need novel approaches to the assessment of ongoing technological advancements	End reliance on the RCT as the only means of adequate evidence generation for technology assessment

CED=coverage with evidence development. RCT=randomised controlled trial.

Table 4: **Key issues and policy solutions in assessment of radiation oncology technology and treatment**

American Society for Therapeutic Radiology and Oncology (ASTRO) will use this appropriateness method to evaluate the evidence for use of emerging technologies in radiation oncology.[188]

Over the past decade, radiation oncology technology and treatment have improved in parallel with the unimaginable technological advances in consumer computer and personal media hardware and software. Whereas the comparative value of this technological revolution is obvious with personal computers or high-definition televisions, it is less evident with emerging radiation oncology technologies. However, historical comparison of a modern day linear accelerator equipped to perform IMRT, IGRT, SRS, and SBRT with a 1950s' betatron leaves similarly little doubt as to the progress that has been made.

Conclusion

Rising costs of cancer care and stagnant economies pose a difficult context in which to advance clinical oncology, particularly the technologically intense and complex discipline of radiation oncology. New approaches to the comprehensive measurement of cost and outcomes to assess patient-centred value, and new insight into the appropriate use of clinically derived medical evidence will be a solid foundation for the assessment of radiation oncology technological and treatment advances. Going forward, radiation oncology will use alternative endpoints and research methods to show the comparative effectiveness and value of its ever-advancing modalities. CED addresses the dilemma of limited resources and the need to advance radiation oncology care in a value-based manner. Table 4 provides a summary of these key policy issues and solutions.

Part 6: Affordability of health care—nuclear medicine and imaging perspectives

Recent decades have seen an explosive growth in the availability of new diagnostic imaging technologies and techniques. There have been significant advances in both anatomical and molecular imaging. In particular, recognition of the benefits of combining anatomical and molecular imaging results[189] has led to the development of hybrid scanners. The first commercial versions were devices in which single-photon emission CT (SPECT) systems were combined with a low-dose CT system. This capability was substantially expanded with the development of combined PET-CT scanners.[190] The first commercial installations of such systems occurred in the early 2000s, and the past decade has seen a rapid growth in use of this modality. Long experience with the metabolic probe FDG in neurological and cardiac applications, and encouraging preliminary data regarding its ability to evaluate cancer, paved the way for widespread use in clinical oncology. Building on evidence already available from stand-alone PET in cancer diagnosis,[191,192] PET-CT has been shown to have a markedly improved diagnostic accuracy compared with conventional imaging.[193] Although the diagnostic accuracy of these new technologies is clearly superior, they come at a substantially higher capital and operational costs than conventional imaging techniques. The recent development of hybrid PET-MRI systems will probably further improve diagnostic performance, at an even higher expense.[194]

Thus, multimodal imaging is becoming a focus for the medical community and those responsible for funding health care. On one hand, the attractions of earlier and more accurate diagnosis are obvious to clinicians and dominate their perspectives.[195] On the other hand, governments and health-insurance companies are concerned by the growing cost of health care and are worried by the high potential cost of ever more expensive imaging technologies. The growth of imaging is outstripping all sectors of health-care expenditure in the USA, and much of this is related to new technologies.[196] Various strategies are being adopted to constrain these costs, including limiting self-referral of imaging tests, restricting access to technologies through site licensing, limiting reimbursement to highly defined indications, or reducing reimbursement to provide only marginal costs that require very efficient use of equipment to make it profitable for the operator.

In parallel with the development of imaging techniques, we are at the threshold of a new era of personalised medicine that will involve greater use of molecular-targeted agents.[197] Instead of blockbuster drugs used in a large proportion of patients with cancer, targeted agents will sometimes be suitable only for small subgroups. The costs of developing and validating these agents will need to be amortised over few cases, which could substantially increase the cost unless more efficient methods are developed to bring them to market and to appropriately select patients who are likely to benefit.[198] The pharmaceutical industry is recognising the potential value of molecular imaging in this process; imaging can provide better target identification or more robust monitoring of the modulation of cellular biology by therapeutic intervention. The concept of mapping phenotype and genotype is becoming ever more relevant.

With a growing and ageing population, the cost of novel therapies and a recognition that multiple, more sophisticated, and expensive diagnostic sessions will be mandatory to appropriately select, plan, and assess treatment response poses a major challenge for health-care providers, who are already having to constrain expenditure to meet the budgetary demands set by governments and insurers. Reimbursement for new imaging technologies has become an important issue for the medical profession and for patients, who can face substantial out-of-pocket expenses when these tests are not covered by medical insurance.

In the past decade, health technology assessment (HTA) agencies in many countries have been established to assess the usefulness of new medical technologies and to

advise funding bodies on whether the technologies are safe, effective, and provide value for money. Although these groups contend that they promote excellence in health care through performing systematic reviews of new technologies that strictly adhere to principles of evidence-based medicine (EBM) and quality management, they are often institutionalised as part of the policy sector of governments or third-party insurers. Therefore, HTA agencies have often been considered, at least by the medical profession, as being instruments for constraining costs through rationing resources or restricting reimbursement. A counter argument might be that these agencies protect society from the profligate use of technologies that are unproven to benefit patients, and thereby spare the public unjustified expenditure.

These conflicting positions have played out powerfully in the efforts to establish PET as a routine oncological investigation. By chance, the growth in HTAs coincided with the emergence of PET as a clinical imaging modality. The high unit cost of PET studies, particularly in early development when equipment was very expensive and throughput was low, focused attention on the cost-effectiveness. Over time, the perspectives of HTA agencies and clinicians with regard to this modality have become increasingly discordant. Indeed, PET seems to have become an exemplar for bodies wishing to constrain high-cost technologies. For example, the International Network of Agencies of Health Technology Assessment (INAHTA) has stated that HTA findings in general, and linkage between financing of PET and clinical outcomes, empower providers to reduce utilisation and contain cost; they assert that HTA information is essential for managing complex and costly diagnostic technologies.[199] These sentiments reflect the findings of their member agencies, who have published reports with mainly negative or inconclusive judgments about the clinical usefulness and cost-effectiveness of PET. In many jurisdictions, these assessments have resulted in either greatly restricted or delayed patient access to this technology. These judgments seem extraordinary to the nuclear medicine community, in view of more than two decades of research into the clinical applications of PET and the publication of hundreds, if not thousands, of peer-reviewed reports that examine various aspects of its clinical applicability in cancer. The earliest assessments of whole-body PET in oncology, done more than a decade ago, found evidence of high clinical utility and cost effectiveness,[200] and these studies have been supported by evidence of high clinical effect on management, in recent large-scale prospective studies.[201] The perspective of the INAHTA is also in marked contrast to clinical guidelines from major oncological societies, which are increasingly advocating use of PET[202] and PET-CT.[203] This disconnection between HTA agencies and clinical perspectives has profound implications for all imaging and, indeed, all diagnostic tests for patients with cancer. At its crux is a fundamentally different view on how health-care costs should be assessed.

The HTA approach assumes that a better test will always replace or be added to the less accurate one; therefore HTAs seek to ascertain whether this can be justified at a societal scale. In this context, the relative cost of competing modalities is highly relevant, and justification of a more expensive test must rely on other offsets. Many health-economic assessments done by the imaging community have responded to this perspective, by performing decision-tree analysis of diagnostic paradigms using conventional imaging versus a new imaging modality, and comparing the cost-effectiveness of each paradigm to arrive at a predefined outcome. Early studies of whole-body FDG-PET used these methods to suggest that FDG-PET could be cost effective.[204] However, clinicians typically consider the efficiency and accuracy of the diagnostic process ahead of eventual outcome or savings to the community, because they recognise that the outcome and savings depend on many factors on which the diagnostic test can have limited effect. These factors include the availability, cost, and effectiveness of therapies. Biases that are intrinsic and that are deliberately and appropriately engineered in many clinical settings are claimed to be unscientific by groups like INAHTA that criticise so-called instrument pushers, who they see as pursuing a professional agenda to benefit themselves rather than patients or society.[205] In particular, INAHTA has called for more RCTs to validate the benefits of new technologies such as PET. Although this form of trial design is well established in the assessment of therapeutic agents, it presents distinct difficulties when applied to diagnostic imaging technologies.[206]

Focusing on the unit cost of cancer investigations is not logical, since almost every patient will have many investigations to determine the presence of disease and to direct management that is proportionally much more expensive. For example, data from the USA suggest that less than 6% of health expenditure is devoted to the diagnostic processes that are integral to the selection and planning of cancer treatment.[13] At University College London Hospitals NHS Trust, a representative large university teaching organisation with an overall annual budget of £650 million, the total expenditure related to all imaging modalities is less than 7%. Accordingly, accuracy and efficiency in the diagnostic process are potentially key factors in constraining inappropriate health-care expenditure. The cost of imaging tests needs to be more broadly considered in the integrated process of health-care delivery, and we need to include measures that go beyond direct comparison of the unit cost of competing diagnostic strategies, to consider issues such as patient convenience and the ability to more appropriately apply expensive or limited therapeutic resources.[207,208]

Establishing cost-effective use of imaging

Beyond just diagnosis, imaging tests in cancer have many functions. Once disease is identified, a patient and

the care team want to know the extent of disease, since this determines selection and delivery of the most appropriate treatment, and the likely prognosis. In the era of personalised medicine, biological characterisation of disease and identification of therapeutic targets or factors such as hypoxia,[209] which might imply resistance to a particular therapy, will become increasingly important. After treatment has begun, the focus of the diagnostic process changes to evaluating whether treatment is working and the alternatives available if there is an inadequate response. After treatment, the question becomes whether there is a need for salvage therapies and predictions are made regarding the eventual outcome of the disease process. Nevertheless, policy makers often assume that new imaging technologies are only used to assess the presence or absence of disease, whereas clinicians are cognisant that the role of an investigation is highly modified by the clinical scenario. Many more imaging studies are done in the course of monitoring response to treatment, evaluation of ongoing or recurrent symptoms after treatment, or for routine surveillance of patients at a high risk of relapse, than for primary staging of malignancy. For the practical reason that histopathological confirmation of imaging results is more often available for patients undergoing definitive treatment of cancer, much of the evidence for imaging techniques is based on situations that do not represent the only (or most common) application of the technique in question.

There can be no doubt that delayed cancer detection, leading to patients presenting with late-stage disease, is costing lives.[210] Earlier diagnosis is clearly a key objective, but management of advanced cancer remains an important issue and one that consumes considerable health resources. In modern oncology, detection of metastatic disease has important management and prognostic implications. Of the non-invasive imaging investigations, one of the great strengths of FDG-PET is its ability to detect previously occult metastatic disease, particularly in patients with locally advanced disease being considered for potentially curative treatments.[211] Additionally, when there is a possibility of several treatment paths, particularly in the setting of multidisciplinary cancer care, guidance of patients through this therapeutic maze poses substantial difficulties within the current framework of technology assessment. For example, the strengths of MRI in evaluating local relations of a primary tumour to determine surgical technique and prognosis, might only benefit patients in whom metastatic disease has been excluded with a high degree of certainty by another test. Conversely, in patients with distant metastatic disease, the biological characterisation of heterogeneity in target expression can be crucial to outcome, whereas the detailed anatomy of the primary tumour becomes largely irrelevant. Analysing the performance of diagnostic tests in such niche applications, rather than across broad disease and indication categories, is a significant challenge, particularly for individuals without intimate understanding of the nuances of therapeutic options and disease biology. And yet, assessment of new technologies is being institutionalised and taken out of the hands of experts, who are often perceived by policy makers as being conflicted and therefore biased in their assessment of the technologies that they control.[212–215]

Molecular imaging readouts of response are increasingly recognised as important to molecular targeted therapies, particularly in the setting of advanced disease. A well documented example is the presence of a marked reduction in glucose utilisation early after introduction of imatinib for the treatment of GIST. Not only does FDG-PET response occur more rapidly than changes in tumour dimensions,[216] it has also led to recognition of subsequent pseudoprogression on CT.[217] Thus, tumours that are refractory to treatment from the outset, or that subsequently develop resistance, can be identified earlier (figure 7). Despite the obvious clinical benefits of more accurate definition of response and the potential savings, considering the cost of imatinib, a recent HTA review in Australia found no evidence to support the use of FDG-PET in this tumour. This finding emphasises the divergence of clinical and HTA perspectives.

We believe that unique standards should be applied to diagnostic tests in life-threatening diseases. When available treatments are expensive, toxic, and of inconstant efficacy, more accurate characterisation of disease is crucial, particularly if it is key to treatment choice. Avoidance of futile or unnecessary therapy, particularly in patients who are already cured but unable to be deemed so on the basis of a residual mass, has clear advantages for patients in terms of avoiding diminution of quality of life. Avoiding unnecessary treatment also

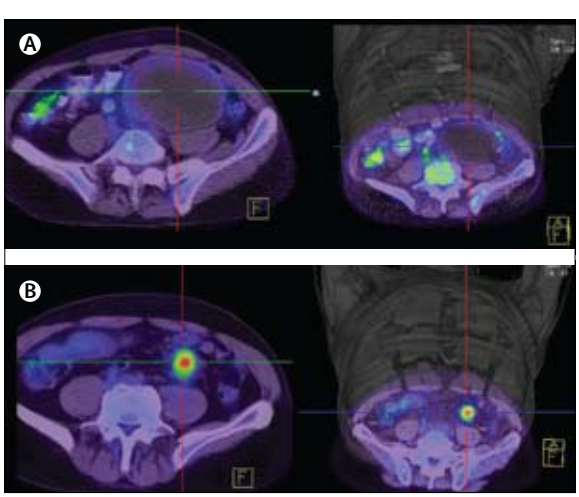

Figure 7: **FDG-PET-CT therapeutic monitoring of GIST**
(A) Initial response assessment. (B) Surveillance at 24 months. Within weeks of starting imatinib (a small molecule inhibitor of the c-Kit oncogene) glucose metabolism, as indicated by uptake of the PET-tracer FDG in the original tumour (A), had markedly decreased despite a large residual mass (B). GIST=gastrointestinal stromal tumour. FDG=^{18}F-fluorodeoxyglucose.

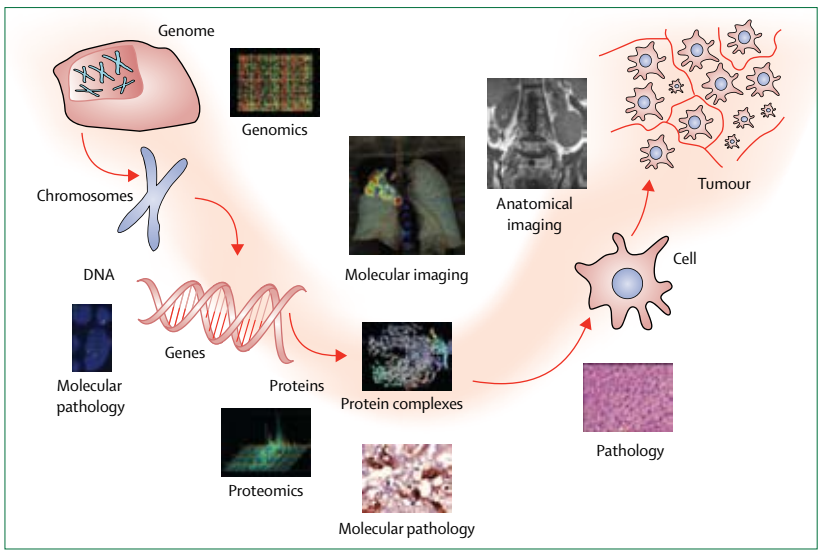

Figure 8: **Molecular medicine recognises that cancer is a disease characterised by alteration in the function of key genes that regulate protein expression**
Genomics and proteomic technologies are making rapid progress in characterising these aspects of tumour biology.

has advantages for society, through direct cost savings related to the differential cost of the therapy versus the diagnostic test, increasing access to rationed therapeutic services for patients who require them, or reduced ongoing costs through managing the morbidity or loss of productivity in the patient or their carers.

Almost all patients and clinicians intuitively understand these principles, yet questions remain as to whether the superior accuracy of new imaging techniques will translate into improved outcomes. Nevertheless, the high cost of cancer treatments, and in many situations, restricted access to timely treatment, demands that we select patients carefully and adapt therapies iteratively as early as possible to optimise survival and minimise morbidity. As identification and modulation of molecular targets become the key to developing, choosing, and validating molecular-targeted therapies, the role of molecular imaging will become even more important. Imaging will be essential in mapping phenotype to genotype.

Obstacles to the introduction of new imaging technologies

One of the most important challenges for the imaging community to overcome is the focus on unit cost of an imaging procedure in the analysis of health expenditure. Although it is understandable for clinicians and funding bodies to be more sceptical of expensive tests such as PET-CT and MRI than less expensive technologies such as CT and ultrasound, the real cost of these procedures often bears little relation to the true economics of imaging or the reimbursement models that operate in many countries. Complex factors affect the apparent cost of an imaging procedure, and these can be divided into three categories: instrumentation, operational, and opportunity costs. Instrumentation costs are related to the purchase price of equipment, its useful life, and the number of patients that can be scanned in usual operating hours. Economies of scale apply for equipment that has a large installed base, allowing for research and development costs to be spread over a high volume of sales and for spare-part inventories and servicing to be efficiently supplied. Operational costs are determined by the cost and use of consumables and the time commitment and expertise of the staff required to perform a scan. Opportunity costs are the offsets provided by achieving a level of diagnostic confidence that allows management to proceed.

In the evolution of new imaging technologies such as MRI and PET, instrumentation and operational costs are strongly biased in favour of established techniques, such as CT. However, both MRI and PET have moved from an environment where small numbers of devices were made and sold and that required huge development and maintenance costs to be offset in the purchase price of scanners and service contracts, to a point where industrial design and manufacture at scale has markedly reduced these costs. This has been partly reflected in reduced purchase prices, but it has also been reinvested in research and development that has substantially improved the technical performance of these devices. A direct result is the improvement in throughput efficiency. High field-strength MRI and time-of-flight PET-CT now perform imaging studies in a fraction of the time required by earlier generation scanners. Higher scan throughput allows greater amortisation of equipment costs, provided that the equipment is used efficiently to scan as many patients as feasible per time period available for use. For extended field imaging used widely in oncology, much of the throughput limitation on these scanners relates to getting patients on and off the imaging bed or positioning them within the scanner.

Higher throughput also has a positive effect on operational costs. Although the cost of manufacture and distribution of MRI contrast agents benefits from economies of scale, the supply of PET isotopes, particularly FDG, has mostly benefited from industrialisation. Instead of expensive cyclotron facilities and the associated engineering, radiochemistry, and quality-assurance resources to service a small number of patients being scanned on a single scanner, as was the traditional academic model of PET practice, the same resources are now applied to supplying multiple cameras in parallel, and commercial supply of FDG has become a business enterprise in many parts of the world. Faster scanning times also mean less radioactive decay and more efficient use of tracers, which has been further improved by synthesis units with increased tracer yields. Shorter scans also mean that more patients can be supervised in a given time interval by the technologist and nursing staff, and that office and clinician time can be used more efficiently rather than simply waiting for scans to finish.

These factors are fairly easily measured and have decreased the cost of providing advanced imaging services. This has been reflected in decreased reimbursement levels in many countries. What is more difficult to quantify is the opportunity cost associated with improved diagnosis. This is highly context dependent. The opportunity cost might relate to the ability to arrive at the appropriate management plan faster, avoiding composite tests, time off work, or time in hospital. It might relate to choosing a treatment strategy that is more likely to achieve a beneficial outcome, and thereby decrease loss of productivity and inefficient use of scarce medical, surgical, or radiotherapy resources. Conversely, improved diagnosis might lead to more expensive therapies being required that in turn need to be judged against the superiority of the outcome that they produce. Herein lies the main obstacle to introduction of new technologies. High cost discourages reimbursement, which impedes efficient use of equipment and staff. This, in turn, limits research opportunities and biases assessments of true costs and benefits, by requiring pooling of data from disparate patient groups, different diagnostic scenarios, and with heterogeneity of validation techniques and treatment approaches.

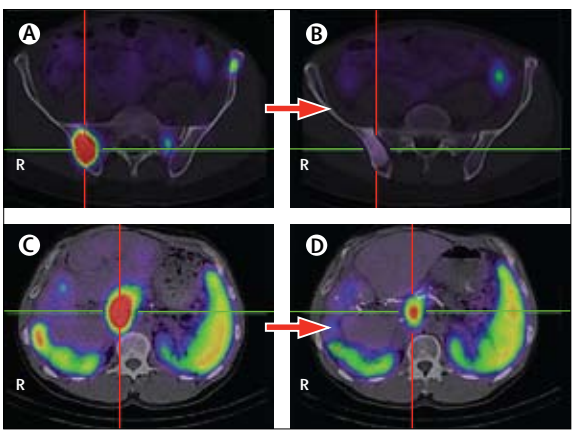

Figure 9: **High somatostatin-receptor expression provides a diagnostic and therapeutic target on well differentiated neuroendocrine tumours**
Lu-177 is a radionuclide with a γ emission suitable for imaging with SPECT-CT and particulate decay leading to therapeutic β irradiation. Post-treatment scans after the first cycle of treatment with Lu-177 DOTA-octreotate (left panels) provide evaluation of the extent and intensity of uptake in bone lesions (A) and soft-tissue deposits (C). Scans done 6 months later after the fourth cycle of treatment (right panels) show resolution of bone lesions accompanied by progressive bone sclerosis (B) and regression of the primary pancreatic lesion (D). Normal physiological uptake in the spleen and kidneys allows relative uptake in tumour deposits to be assessed. SPECT=single-photon emission CT.

What is the way forward?

For new imaging technologies, particularly those associated with nuclear medicine, to remain effective and at the forefront of clinical decision making, they must be supported by a strategy that is all of the following: biology driven, able to link phenotype to genotype, supportive of multidisciplinary collaborative research that encourages interaction between imaging specialists and oncologists, and cognisant of the need to challenge over-regulation.

Recognition that cancer is driven by altered behaviour of specific genes[218] in transformed cells that alter biology, generally through expression of biologically active proteins, has provided a fundamental need to develop techniques, including imaging, that can interrogate these biological processes (figure 8). Cancers can present a wide range of phenotypes, at the cellular level as assessed by histopathology or at the level of individual lesions imaged by molecular probes or functional imaging techniques. Target identification and ascertainment of its relevance to disease behaviour, which can involve complex systems-biology approaches, is a major focus of drug discovery and for the imaging community.

Because of the interconnection of phenotype and genotype, efficient processes for developing, validating, and ensuring availability of imaging probes that can interrogate potential therapeutic targets are key to the future of personalised medicine. Many disciplines need to collaborate to bridge what has become known as the translational gap.[219] Beyond target identification, one of the main challenges with development of imaging probes is to ascertain whether the therapeutic target has sufficient accessibility on cancer cells, such that a high contrast can be achieved between tumours and healthy tissues. In nuclear medicine practice, there are cogent examples of the link between the ability to image a biological target and to use this for therapeutic benefit. These include imaging of the sodium-iodide symporter in thyroid cancer before treatment with iodine-131[220] and imaging of the somatostatin receptor as a target for peptide-receptor radionuclide therapy.[221] In both situations, successful therapy is associated with reduction or loss of the imaging target (figure 9). However, such targets have seldom been used to select or monitor conventional chemotherapy agents. Often, targets that can be considered to be downstream of oncogenic mutations can paradoxically be most useful for disease assessment, hence the proven record of FDG in cancer management.[222] Although FDG uptake is tightly linked to key oncogenes that regulate glycolytic metabolism,[223] it does not always provide the relevant answer to treatment monitoring. For example, recent studies suggest that FDG response might underestimate therapeutic benefits from mTOR inhibitors.[224] It will be important to understand the imaging phenotype in the context of genotype, particularly since tumours of the same type might show genetic variation between patients, but share common pathways at the protein level.[225] Accordingly, it is important that oncology research involves a multidisciplinary approach wherein imaging specialists are engaged in trial design and analysis. As the oncology community is becoming more focused on molecular targeted therapies, the relevance of molecular imaging becomes more obvious. A recent example is the use of radiolabelled monoclonal antibodies to predict and assess the effectiveness of therapeutic antibodies.[226]

Despite these rapid developments, over-regulation is clearly slowing implementation of medical advances, causing frustration in the imaging community[227] and among clinical oncologists.[228] However, as noted by DeVita,[228] anything we put together we can also disassemble, if we are willing to ask whether it is necessary. The medical profession was intimately involved in the establishment of EBM principles and has supported the development of HTAs. However, we have increasingly devolved responsibility for these processes to epidemiologists, statisticians, and clinicians who are not directly involved in oncological practice, and who are increasingly in the employ of bodies that seek to constrain expenditure rather than deliver quality health care. We should take back the HTA agenda,[229] potentially achieving both cost savings and quality care, for the benefit of our patients and society.

Part 7: Genomic testing in oncology—where science and reimbursement meet

Since the publication of the human genome in 2000,[230] genomics has been heralded as the key to personalised medicine, promising to revolutionise the treatment of cancer. Genetic tests are being studied in a variety of settings, from cancer screening in the general population to determining prognosis in patients with newly diagnosed cancer. In view of the breadth of clinical opportunities for genetic testing, we have chosen to focus on the economics of pharmacogenomics, currently one of the most robust areas of research in the field. Pharmacogenomics assesses the effects of genetic variation on response to treatment and can help predict the likelihood of adverse events. According to a recent report from the US Institute of Medicine, six pharmacogenomic tests are included in FDA labelling. At least two of the tests are used in routine clinical practice—*HER2* testing for directing the use of trastuzumab in breast cancer, and *KRAS* testing for directing the use of cetuximab and panitumumab in colorectal cancer.[231] These tests are done in addition to standard assessments, adding cost and complexity to care.[232] The rationale for these tests is that their use will lead to cost savings by limiting care to effective regimens, and decreasing resource use by lowering the frequency of treatment complications. Despite its promise over the past decade, the science has not yet lived up to expectations.

Understanding the economics of pharmacogenomics is challenging because the available evidence is inadequate to truly inform discussions. Uncertainty in the regulatory environment and business model make the market dynamics complex, and reliable cost-effectiveness information and reimbursement algorithms are not available. Ensuring appropriate and reliable evidence generation is the key.

Defining high-quality evidence

It is crucial that high-quality evidence is used to move pharmacogenomic tests from the laboratory to clinical practice. Although only 100 genetic tests were available in 1993, more than 1800 were available by 2009,[233,234] many of which do not have adequate evidence supporting their use. Pharmacogenomics has seen robust evidence generation, leading to changes in FDA labelling and integration into practice.[231]

Several frameworks are used in clinical medicine to judge the quality of evidence that guides treatments. The US Preventive Services Task Force stratifies the quality of scientific evidence for a given topic as being either level I, II, or III. Level I evidence comes from an RCT. Many of the treatments used in clinical practice are based on level I evidence; however, few genetic tests have this level of clinical evidence.

In 1997, the NIH-Department of Energy task force on genetic testing established the standards by which genetic tests are evaluated in the USA.[235] The group outlined three criteria: analytic validity, clinical validity, and clinical utility (panel 4). At a minimum, a test should show analytic validity, consistently predicting the presence of a specific genetic sequence, and establish clinical validity, predicting a clinical outcome of interest. This assessment should be completed before marketing. In the premarket phase, clinical utility is too high a standard to expect all diagnostic tests to achieve; however, it must be the ultimate goal. It is not adequate for a test to predict the presence or absence of a genetic sequence or disease; it must improve a patient's clinical outcome, whether in terms of quality of life, survival, or another endpoint of interest.

Current evidence quality

Despite inclusion in FDA labelling, evidence of clinical utility is lacking for most pharmacogenomic tests. Testing for genetic variation in *UGT1A1* before irinotecan use is an excellent example of the strengths and

***Panel 4:* Criteria for evaluating evidence supporting genetic tests**

Analytic validity
Refers to a test's diagnostic sensitivity and specificity, denoting the likelihood of a positive result when a genetic sequence is present and a negative result when it is not

Clinical validity
Refers to a test's ability to predict clinical sensitivity and specificity, or the probability that individuals with a disease (or who will develop the disease) will have a positive test result, whereas those without the disease will have a negative result

Clinical utility
Refers to a test's ability to demonstrate the benefits and risks that accrue from both positive and negative results. If a test result is positive, how likely is the information to improve an outcome of interest?

weaknesses in pharmacogenomics. Irinotecan is widely used in the treatment of colorectal and lung cancers, with up to 30% of patients experiencing diarrhoea and neutropenia as side-effects of treatment.[236] Genetic variation in *UGT1A1* predicts differences in conversion of irinotecan to its active metabolite.[237–240] This variation affects the toxicity profile of the drug. The ability of the test to predict toxicities and guide dosing can help prevent complications from treatment and avoid discontinuation.[237,241] The FDA modified the drug labelling for irinotecan in 2005 to include testing of *UGT1A1*, and an assay is available.[242–244] However, studies have not confirmed an improvement in quality of life or OS from integrating the test into practice, and it is unknown whether lower doses of irinotecan have the same efficacy as the full dose. As a result, the test has not found widespread use in clinical practice.

Although many other pharmacogenomic tests are in development, we do not yet understand the clinical value of those already recommended for use. Analytic validity is an easy place to start. Although it is largely unregulated, most researchers claim that the tests in use today are reliable in predicting the presence of a genetic sequence. Yet, according to Hunter and colleagues,[245] very small error rates per single-nucleotide polymorphism, magnified across the genome, can result in hundreds of misclassified variants for a patient. This problem is magnified in the analysis of somatic genetic alterations in tumours, where the fraction of tumour cells in a biological sample could result in false-negative test results. In view of the ease with which these errors can occur, it is crucial to have adequate quality control for all steps in the testing process. An additional concern is related to test development. Development of an algorithm in a sample leads to overfitting of data and inflated test characteristics.[246] Therefore, test development should include validation in a second sample.

Clinical validity must also be shown. Many of the tests in development explain only a small portion of a patient's risk profile, rate of metabolism for a drug, or other phenotype of interest. Unless it is known that a specific test truly predicts a meaningful difference in the risk of a given outcome or toxicity, is it relevant? Additionally, the patient population from which clinical validity is established is crucial. If test characteristics are assessed from sample populations with high prevalence of a phenotype, the positive and negative predictive values become artificially inflated. Safeguards must be in place to ensure that the test population is appropriate and that the genetic sequence in question is of adequate biological relevance to predict a clinical phenotype.

Establishing clinical validity is particularly important because the number of tests being marketed is increasing rapidly. Many of these tests have great promise, such as the use of *CYP3A4* testing to predict the correct dosing of dasatinib in patients with acute lymphoblastic leukaemia, or the use of *EGFR* testing to predict response to erlotinib and gefitinib in patients with lung cancer.[231] However, some promising early findings have not been substantiated, including recent data from two large studies that found no effect of the *CYP2D6* polymorphism on outcome after tamoxifen therapy.[247] A review of ASCO meeting abstracts from recent years shows numerous pharmacogenomic tests in development looking at a variety of drug–disease combinations, such as temozolomide in patients with glioblastoma multiforme, oxaliplatin in patients with colorectal cancer, bortezomib in patients with multiple myeloma, and gemcitabine in patients with colorectal cancer.[248–251]

Business environment

Despite great strides in the field, the business of pharmacogenomics is evolving slowly. The regulatory environment is in flux, making it difficult for the industry to understand the level of evidence required for premarketing; and patent law is in question, making the profitability of proprietary test development uncertain (table 5). There is also a debate between the device industry and pharmaceutical industry about the relative value of the test and drug in pharmacogenomic clinical strategies.

Issues	Possible solutions
It is often difficult to make informed clinical decisions about when to order genetic tests from the available evidence	Clinicians should require proof of analytic and clinical validity before adopting tests. Clinicians should also be cautious that treatment recommendations based on level I evidence are not altered based on level III evidence about diagnostic tests merely because genomic technologies are involved
Extensive requirements for clinical data generation before marketing will undermine the business model for test development by industry	Coverage with evidence development provides an opportunity to generate data to inform clinical usefulness of tests while enabling earlier financial rewards to test developers, helping to maintain the return on investment
There is inadequate investment in test development because the business model is in flux, particularly with uncertainty regarding the continuing ability to patent genomic tests in the USA	Alternative business models should be developed and encouraged beyond the reliance on proprietary test development. Focusing on high-volume testing and platform-based tools are viable alternatives
Cost-effectiveness data are not robust, making reimbursement decisions difficult	Without data on the clinical usefulness of genetic tests, economic analysis is speculative at best

Table 5: **Possible solutions to key policy issues in the use and commercialisation of pharmacogenomic tests**

Regulation

In the USA, most molecular diagnostic tests are performed by individual laboratories regulated under the Clinical Laboratory Improvement Amendments.[252] This legislation was passed in 1988, before the evolution of genomic testing. It relates to aspects of genetic analysis, such as accuracy and timeliness, but does not address analytic validity, clinical validity, or clinical utility.[253] Marketing via this pathway avoids FDA regulation, but there are initiatives from groups such as ASCO, the Secretary's Advisory Council on Genetics, Health, and Society, and consumer groups to change this practice.[254–256] Europe has similar calls for regulation. In the UK, the NHS evaluates genetic tests before their introduction into routine clinical practice, although not for the private health-care market. Elsewhere in the EU, genetic tests are categorised as low risk and are, therefore, largely immune from premarket evaluation. Without defined regulatory or market expectations, genetic testing will never achieve a higher level of evidence generation.

Hamburg and Collins[257] recently pledged to address the issue of regulatory oversight in the USA, stating that the FDA is coordinating and clarifying the approval requirements and defining the process manufacturers must follow to make specific claims about a test. The FDA plans to define when a companion diagnostic test needs approval before the introduction of a therapy, and to establish a voluntary registry of all genetic tests that indicates whether they have FDA approval. In Europe, efforts are being made to reclassify biomarkers as medium risk so that greater oversight and premarket assessment will be required.[253]

Legal challenge

The business model supporting genetic testing also remains unclear. One of the more interesting and contentious issues is whether genes can be patented. If they cannot, private investment in pharmacogenomics will decrease substantially, because return on investment will not be assured, even if a test makes it to market. The uncertainty derives from a ruling by a US district court in March, 2010.[258] In the decision, a patent for *BRCA1* and *BRCA2* testing held by Myriad Genetics and the University of Utah Foundation was thrown out. The original patent was based on the theory that DNA should be treated no differently than any other chemical compound, and that purification from the body renders it patentable, by using well known techniques to transform it into something distinctly different in character. Many observers consider this as a lawyer's trick to circumvent a ban on the patenting of DNA. The ruling found that isolating DNA does not alter its fundamental quality or the information it encodes.[258] Additionally, comparisons of DNA used to predict risk were found to be abstract mental processes, making them unpatentable under US law. If upheld, this ruling will remake intellectual property law and increase the difficulty in raising capital to pursue biomarker development, because the return on investment from bringing a new test to market will be lower.

Business models

There are several business models for development of genetic tests. Companies like Myriad Genetics have attempted to develop individual proprietary tests, such as their *BRCA* testing, which enable them to pursue an aggressive pricing strategy. Genomic Health has pursued a similar strategy with Oncotype DX, but with research investment to develop the test,[259] whereas Myriad Genetics licensed their intellectual property from the University of Utah where the company's cofounder helped clone the *BRCA1* and *BRCA2* genes.

Alternative business models include that of LabCorp, which relies on high-volume testing to make up for the lower price it charges for its unpatented tests. This approach results in a lower profit margin, but widespread use makes it a viable business model.[260] For example, LabCorp offers testing for the *HLA-B*5701* allele in HIV-positive patients who are initiating treatment with abacavir. Claims data reveal that LabCorp charges only $68 per test, whereas the suggested retail price for Oncotype DX is $3460 per test.[261,262] The *HLA-B*5701* gene predicts hypersensitivity to abacavir and has found widespread acceptance after the FDA, the Department of Health and Human Services, and major infectious disease groups endorsed its testing.[263,264] Companies such as Affymetrix and Illumina take a different approach, providing testing platforms such as bioinformatic devices, gene chips, and sequencing technologies that can be licensed to downstream partners. The Affymetrix GeneChip can be programmed to test a variety of compounds and proteins to gather information about different disease states and treatment targets. By offering technologies that are viable across markets, they are able to avoid reliance on a given test.

If the patent law ruling is upheld, the model of Myriad Genetics might not continue to be viable, particularly if new regulation increases the hurdles to bring a novel test to market. The LabCorp and Affymetrix business models will probably become more relevant. This shift will increase the need for government involvement in funding genetic testing trials, as in the public–private partnerships in Europe. In June, 2010, the NHS announced a partnership with the pharmaceutical and diagnostic industries to test a range of genetic mutations in patients with cancer, basing treatments on the test results. With this approach, fewer tests will be able to develop adequate evidence, but testing could become much more affordable and accessible to the general population.

Economics of biomarkers

Cost-effectiveness

Without data on clinical utility, it is nearly impossible to make informed judgments about the cost-effectiveness

of therapies. Several systematic reviews have assessed economic literature for genetic testing services and interventions, yet few high-quality studies have been reported in oncology that would allow definitive recommendations on the cost-effectiveness of specific tests. A recent review by Wong and colleagues,[265] which examined the economic literature for pharmacogenomics, identified 34 articles that met their inclusion criteria, with seven related to oncology. Only *HER2* was found to have evidence supporting both clinical validity and clinical utility, allowing a true cost-effectiveness analysis. The article found a cost of $125 000 per QALY gained from testing. Other oncology tests had high-quality analyses and were therefore included in the review; however, *UGT1A1* testing in colon cancer and *EGFR* overexpression in lung cancer had unclear clinical utility, whereas Oncotype DX in breast cancer had likely but not definitively proven clinical utility. Thus, the cost-effectiveness analyses of these tests were inconclusive.

The lack of reliable information was reinforced by reviews of genetic services by Djalalov and colleagues[266] and Carlson and colleagues.[267] The former, published in early 2011, found 26 cost-effectiveness analyses that met their inclusion criteria. Of these, six pertained to cancer. Five of the six addressed genetic conditions that increase the risk of cancer (ie, predictive mutations for hereditary non-polyposis colorectal cancer and familial adenomatous polyposis, and *BRCA* mutations as they pertain to breast-cancer prediction), whereas the sixth assessed *HER2* testing.[266] Carlson and colleagues[267] found 63 studies, including 13 related to oncology, but difficulties with study quality and clinical utility data again precluded reliable conclusions. The difficulty in producing definitive analyses stems from the types of trials being done and the evidence generated. As tests continue to be introduced to the market in the years to come without adequate testing of clinical utility, such as *BRAF* testing in melanoma or *ALK* in lung cancer, their economic impact remains difficult to describe.

Reimbursement

Nearly half of the large health-insurance plans in the USA that cover genomic testing do not have a comprehensive policy for how pharmacogenomic tests should be administered, often relying on individual decisions.[268] Several health plans have expressed the need to better understand what they are spending in this area, what they should be covering, and how to manage this with their providers.[268] In the UK, the NHS has approved some tests, such as *EGFR* for patients with lung cancer; however, there are reports that physicians in England have encountered difficulty accessing genetic testing services.[269]

Coverage with evidence development

With all of this uncertainty, CED provides an opportunity to move pharmacogenomics forward. In exchange for reimbursement of a promising technology by insurers such as CMS, test developers would agree to require patients to participate in a clinical trial or registry. This framework was part of an FDA guidance in 2006. Its purpose is to assure that care meets the Medicare standard of being reasonable and necessary, while also providing insight into a test's clinical validity and utility. Subsequent reimbursement decisions are contingent on the trial results.

CED remains an underdeveloped means for genetic test development, partly because the specifics are unclear regarding the threshold for coverage initiation, the mechanisms that will be used to cover the increased costs of evidence generation, and concerns about conflicts of interest. CED was applied to off-label treatments for colorectal cancer and PET scans in 2005; however, there has been little use of this pathway in oncology since then. The largest stumbling block is that the NIH, CMS, and private payers have not developed mechanisms to cover the additional costs of gathering clinical information, analysing the data, and publishing the results.[270] CED could address many complexities by generating adequate evidence, improving access for patients, addressing regulatory concerns, simplifying reimbursement decisions, and improving the likelihood and timing of financial gains.[270–272]

Conclusion

Although advances have not occurred as quickly as anticipated, genetics represents a cornerstone of personalised medicine. The economic proposition for the technology remains uncertain, because researchers are struggling to understand basic concepts of validity and utility of pharmacogenomic discoveries. Clinicians should temper enthusiasm for the spectacular science in this area while research continues to understand its role in clinical practice. Creating a pathway to expedite these efforts will accelerate the development of personalised medicine in oncology.

Part 8: Pricing and affordability of new anticancer medicines—an industry perspective

Cancer care accounts for about 10% of health spending in Organization for Economic Co-operation and Development (OECD) nations. Within this, medicine costs represent about a tenth. But the pricing and affordability of new anticancer drugs are controversial. Relevant trends include increasingly complex research and the growing use of cost-effectiveness analysis coupled with the challenges of anticancer medicines assessment. The value of therapeutic innovations for relatively small numbers of individuals is being questioned. But investing in better cancer treatments is consistent with both patient and long-term public interests. Methods of assessing the value of new medicines should reflect this. The effects of regulatory regimens and intellectual property provisions on oncology research should also be reviewed.

Panel 5: Cost of pharmaceutical innovation

A recent study by the Tufts Centre for the Study of Drug Development in the USA estimated that the average cost of a new medicine (including clinical trial outlays, spending on failed molecules, and interest payable on research and development investments, but excluding other costs and all profit contributions) is roughly US$1·3 billion.[275] Anticancer drug development costs are likely to be more because of high failure rates and above average premarket development periods.[276]

Some commentators argue that the prices of anticancer medicines, which in extreme instances approach $100 000 for a course of treatment, are excessive, and that governments should take direct responsibility for funding relevant research. However, such views ignore the reality that in most OECD countries other than the USA, medicine prices are directly or indirectly controlled. One guide to whether or not private pharmaceutical companies are making undue profits is the value of their shares. Between 2001 and the end of 2009, the market capitalisation (aggregated share value) of the ten largest pharmaceutical companies fell, despite mergers, by over $600 billion, or approaching 50%.[276]

Such data are not consistent with excessive corporate income or security. Experience also suggests that increased state expenditure on anticancer medicines research will not replace private corporate outlays. Public funding is often linked to expectations of industrial development. The research-based pharmaceutical industry is characterised by high fixed costs, such as those of research and development, often counterbalanced by lower marginal costs of production. These factors help explain why patented medicines are typically much more expensive than generic copies, and why the true price of pharmaceutical products is often disputed by those not exposed to the financial risks of medicines research and development.

OECD=Organization for Economic Co-operation and Development.

A wide range of new medicines for previously poorly treated common conditions were introduced during the second half of the 20th century, as a result of the combined efforts of pharmaceutical companies, universities, and other private and publicly funded settings. Notwithstanding continuing inequities, such treatments are now affordably accessible not only in Europe, North America, and wealthier Pacific nations, but also to billions living in less affluent regions. Measuring the value to humanity of such progress is methodologically challenging. But available research suggests that the overall benefits of the medicines developed up to the start of the current century have exceeded the amounts paid for them by an order of magnitude.[273,274] Many of these treatments will, as low-cost generic products, continue to contribute health gains throughout the foreseeable future.

However, as demographic and epidemiological changes have progressed, challenges facing the research-based pharmaceutical industry and other sections of the medicines research community have increased. The growing significance of later-in-life conditions such as cancer and dementia necessitates more complex research questions than were necessary previously. This is driving up costs at a time when—perhaps transiently—the rate of new product introduction is lower than investors have previously been able to expect. At the same time, regulatory and associated hurdles in areas such as pricing and reimbursement have continued to rise.

A reduced flow of new blockbuster drugs will probably continue, and there are still important opportunities for improving the prevention and treatment of infectious diseases in undeveloped countries. But the mainstream of new medicines research has moved on to areas where the clinical benefits of new drugs (often in combination with others) can take decades to assess fully. Additionally, the number of patients likely to require any one near-personalised treatment is relatively low. Such trends are economically important. The combination of high research and development costs (panel 5) and limited patient populations largely explains why the pricing and cost of new anticancer medicines is controversial in many countries, particularly those in which the allocation of health resources is most strongly affected by short-term utilitarianism (ie, greatest good for the greatest present number). It is against this background that we consider issues relating to the supply of cancer medicines to patients, and the future funding of oncological research and innovation.

The challenge of measuring value

The subdiscipline of health economics underpins the work of publicly funded HTA agencies such as NICE in the UK, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) in Germany, the Swedish Council on Health Technology Assessment (SBU), and PBAC in Australia. Health economics is also closely linked to the mission of the more recently established PCORI in the USA. PCORI will initially focus on comparative effectiveness, yet some American commentators believe it will lead to a wider application of cost-effectiveness based criteria for determining treatment entitlements in the USA.[38,40]

Health economics developed in parallel with the therapeutic revolution of the second half of the 20th century, and the growth in public and private medicines and wider health spending in developed countries. Its early pioneers in America included authors such as Selma Mushkin and Nobel Prize winner Kenneth Arrow. It was also during the 1960s that the Centre for Health Economics at York University was formed under the leadership of Alan Williams. In Europe, the agenda of publicly funded health economists has become largely focused on rationing the introduction of

potentially costly changes in medical care. In the UK, this led to the establishment of NICE and the subsequent assessment of whether or not products such as new anticancer medicines should be considered affordable in NHS patient care.

In the past decade, many other organisations across Europe have begun using similar methods. Their approaches vary in detail. For example, in Sweden, measurement of value includes societal gains, such as patients being able to return to work (Jonsson B, Karolinska Institut, personal communication). But all the methods involve estimating the duration of additional life with a new medicine, compared with that offered by standard therapy, combined with an assessment of the quality of the life gained. This approach allows the cost of each extra QALY delivered to be identified and judged against a maximum affordability threshold. In the case of NICE, this threshold is usually taken to be about £30 000. In the USA, proponents of incremental cost-effectiveness based care entitlement have suggested a threshold of $129 000 per QALY (related to the cost of kidney dialysis),[38] although research suggests that the average US citizen would be willing to pay more for an additional life-year.[277] The quality of public and political debate surrounding this cost–benefit analysis is limited. For example, it is difficult even for senior clinicians and managers to understand that although a drug or intervention might have an ICER of $50 000 per QALY, its actual cost might be less than $5000 or as much as $100 000. Differences between mean and incremental QALY costs can be similar in scale.

Some health economists believe passionately in the validity of this type of cost-effectiveness estimation and the appropriateness of using it to set new (patented) medicine prices via value-based pricing. Others argue that, as currently applied, such techniques have substantial weaknesses. These weaknesses relate to several factors. For example, some question the reliability of quality-of-life estimations, and the moral validity of judging one state of human existence to be inherently less (or more) valuable than another.[278] Another perceived weakness is the use of fixed, essentially arbitrary, incremental affordability thresholds, which ignore the fact that communities might attach a premium value not only to treatment of exceptionally severe or late-stage conditions, but also the relief of orphan illnesses. The fact that medicines for rare illnesses often cost as much or more to develop than those for common disorders, and that supplying different volumes of a drug typically has less of an effect on total costs than is often understood, arguably makes using the cost per QALY gained an inherently unfair method of setting permitted prices or reimbursement levels. Finally, the cost-effectiveness approach has been criticised because in the context of oncology and other specialties, even pharmacologically unrelated innovations are linked steps in an ongoing process of development that is of much greater long-term value to society than the aggregated incremental usefulness of personal episodes of care occurring over limited time periods.

Most of the new, targeted, anticancer treatments that have become available recently, or are due to enter the market in the next few years, are as single agents unlikely to cure late-stage disease, and might confer only limited life-expectancy gains. Yet this does not imply that they will not have important value for some patients, particularly if they can be more effectively used in combination with other drugs or in contexts such as early-stage cancer treatment. This is illustrated by improving staged survival rates in areas ranging from breast to colorectal cancer,[279] and by the effect of medicines such as imatinib in chronic myeloid leukaemia. It has been estimated that from 1980–2010, anticancer medicines increased life expectancy of the average patient with cancer by nearly 1 year, at a mean cost in the USA of $6500.[280]

Although some critics question the value of a gain of this magnitude, it is both cost effective and, at a population level, epidemiologically significant. Such progress implies that if financial investment and research efforts can be continued over the next few decades, medical and allied professionals will ultimately be able to prevent, cure, or effectively contain many more cases of cancer. It is strongly in the global public's long-term interest that research into better forms of cancer care continue to be funded via the private, voluntary, and public sectors. Policy makers should therefore seek to assure the continuing viability of pharmaceutical research and development in oncology.

Protecting patient and public interests in better cancer treatment

It would be unrealistic to think that many (if any) governments are likely to simultaneously permit free, competitively based pricing of new anticancer medicines and guarantee universal access to the best possible therapies. In less affluent nations, cancer care is already emerging as a growing problem, for which it will be very challenging to match demand and capacity. But in regions such as North America and the EU, it should be possible to achieve a balance between medicines pricing and access policies that will sustainably combine robust incentives for innovating for the future with good standards of care delivery in the present. This balance is possible because evidence does not show an immediate crisis in these regions. In the USA and France, treatment of all types of cancer accounts for about 5% of total health-care spending. Within that proportion, cancer drug costs, although rising, still account for roughly a tenth.[281] Hence, in nations with the highest volume of cancer medicine usage (in France patients are effectively guaranteed access once an official price has been set, whereas the USA has free pricing within a competition-driven health market) the proportion of GDP spent on oncology drugs is 0·1–0·2%. Even if the introduction and use of new

Issues	Possible solutions
Ensure stratified and targeted cancer medicines are equitably available to patients	Recognise that these medicines require an appropriately funded approach to fair reimbursement and pricing
Identify cancer-service related savings for use on cancer medicines and other cost-effective interventions	Re-engineer chemotherapy suites to assure optimised and efficient usage, and purchase high-quality off-patent medicines efficiently
Ensure continued inward investment into countries by life-sciences companies	Develop life-sciences strategies with strong promotion of low-bureaucracy clinical trials
Where possible, move cancer care out of hospital to lower cost and safer settings	Optimise use of oral and other cancer medicines that allow patients to be treated safely at home or in other community settings
Reduce limitations and uncertainties in cancer-medicines evidence-base	Investigate use of risk share and flexible pricing arrangements with payers

Table 6: **Possible solutions to key issues in delivering affordable cancer care from a pharmaceutical industry perspective**

cancer treatments were to cause substantial cost increases in the coming decade, these statistics do not suggest a dilemma of unaffordability.

The availability of previous generations of proprietary medicines as generic versions—including some widely used anticancer drugs—means that overall pharmaceutical spending has recently fallen as a proportion of total health costs in several OECD countries.[282] In the UK, there is evidence that past levels of spending on new anticancer medicines have been much lower than those recorded in other nations of similar wealth. This might have undermined public trust in the NHS and is perhaps why the British Government plans to introduce value-based pricing by 2014.[97] Since pricing in about a quarter of the world's overall pharmaceutical market is linked to UK drug prices, this development has wider significance than might first be appreciated. It could also encourage regulators in other major markets to introduce their own forms of value-based pricing, which unless appropriately structured will discriminate against the provision of low-volume treatments for people with less common therapeutic needs.[283]

Safeguards against such unwanted outcomes could build on the current Swedish value-based pricing approach, by adjusting the affordability thresholds to take into account orphan drugs and allied equity concerns, as well as long-term societal interests in industrial and scientific development. New forms of medicines licensing might also be included. Public and private health-care funders in the USA, the EU, and elsewhere could be required to fund conditionally licensed treatments as normal care entitlements while evidence of their value continues to be gathered.[40]

However, awareness of issues such as the strengths and weaknesses of QALY-based measures in determining fair prices for medicines should not obscure the importance of variables such as the willingness of health-care funders to meet the costs of high-quality care. Nor should it draw attention away from other matters of shared concern to pharmaceutical companies and other stakeholders in better cancer treatment (table 6).

Additional variables in the sustainability equation for cancer medicines research include the extent of fiscal incentives available to investors, and the degree to which regulatory requirements impose avoidable costs and restrictions on innovators' freedoms to offer their products. The duration of patent terms or other exclusive supply rights is another key determinant of a society's capacity to permit returns sufficient to motivate investors to accept the risks of continuing to fund medicines research.

Conclusion

Anticancer medicines research and development and the technologies derived from it will ultimately confer major benefits for the global society. But the challenges now facing research-based companies are greater than those that existed in the second half of the 20th century. Failure to constructively address this situation threatens to undermine the capacity of the pharmaceutical industry and its public and voluntary sector partners to deliver more effective future therapies.

To this end, the cost-effectiveness appraisal techniques used by HTA agencies across the world should be reviewed to ensure that the permitted prices of beneficial new products adequately reflect societal preferences. They should take into account the severity and prevalence of conditions being treated, and long-term benefits associated with the development of enhanced understanding and new technologies in areas such as genetics.

But fair pricing alone cannot guarantee fair patient access to treatment. As the French example highlights, patients with cancer might need explicit entitlements to appropriately priced medicines if public interests in both care standards and ongoing innovation are to be protected. Additional necessary reforms might include the re-engineering of regulatory requirements[284] and a review of intellectual property law as it affects cancer drug development. It could prove necessary to extend periods of supply exclusivity to encourage further research investment, while also permitting prices low enough to fall within health-economics defined value-for-money thresholds.

Part 9: Patient perspective on the cost of cancer care in Europe and the USA

The cost of cancer care represents a significant burden in Europe and the USA. How those costs are covered varies widely from one region to another, but patients with cancer

in Europe and the USA often bear a disproportionate amount of the financial burden of their own cancer care. We provide a patient advocate perspective on the cost of care to patients with cancer in Europe and the USA.

European perspective

Every year, 3·2 million Europeans are diagnosed with cancer, a figure that is expected to rise because of the ageing population.[285] Cancer accounts for about a third of deaths in Europe and is the second most common cause of death,[286] with almost every family being affected in some way by cancer. Without a therapeutic breakthrough for most cancers, particularly rarer forms, cancer remains a key public-health concern and a leading cause of disability and death in Europe.

The rise of cancer incidence and its effect on increasing health-care costs is a key concern for European citizens. With 23 official languages and 27 different national health-care systems, complemented by financial barriers to accessing health-care services across country borders, inequalities in cancer care have increased across EU member states. According to the EUROCARE-4 study, survival of the four most common cancers was best in Nordic countries and central Europe, intermediate in southern Europe, lower in the UK and Ireland, and lowest in eastern Europe.[287] The reasons behind these differences involve a wide range of factors, including percentage of GDP spent on health care, reimbursement procedures, average income and education levels, living and working conditions, health behaviours, and access to health-care services. From a patient's perspective, cancer care across Europe is a patchwork of mixed equity and coverage.

Although assessment and approval of new cancer therapies is now done largely via a centralised European procedure, reimbursement of health-care services is still the remit of EU member states.[288] Health expenditure per capita and the share of cancer care in total health expenditure vary greatly between countries; for example, Germany spends 7·2% of its health budget on cancer, the UK 5·6%, and Bulgaria only 4%.[289] In view of growing financial demands because of an ageing population, countries such as the UK and Sweden have introduced HTA methods to contain costs and set priorities. As a result, in some countries, patients cannot access therapies that have shown to be effective for their cancer but have exceeded an arbitrary economic threshold.[96] With HTA institutions now emerging in member states, accelerated by the budgetary pressure of the financial crisis, disparities based on financial capabilities and insurance status of individual patients are expected to further increase across Europe. The EU seems to be losing its leadership status in health innovation in favour of other regions, particularly North America and Asia.[290] With legislative fragmentation and bureaucratic burden leading to cancer research moving out of Europe, European patients suffer from challenges accessing clinical trials and innovative therapies.

Beyond the direct costs of cancer to individuals and health-care budgets, the economic and societal effect of cancer on family income and overall productivity is large, though not widely acknowledged in economic discussions of health-care budgets. Cancer affects the individual financially, and often a whole family. The effect is largest when the principal earner has cancer, but can also be substantial if close relatives must provide care and cannot continue employment. On average, the salary of European patients with cancer falls by 25% in the first year after diagnosis.[291] In Europe, cancer represents a major exclusion factor from the labour market because of the nature of cancer pathologies, where patients have moments of perfect ability and then of absolute inability to work. The indirect cost of cancer in terms of lost productivity is estimated to be around 30% higher than the direct cost of health spending on cancer treatments.[292] For example, Germany is losing 490 working life-years every year on cancer alone.[293] Employment integration of chronically ill patients, as well as sickness benefits, vary largely between EU countries. Nordic countries lead with a 30% reintegration rate, and the lowest rates are found in southern countries such as Greece, Malta, Italy, and Spain (9–13%).[291] Many EU countries have employment discrimination laws and employment regulation to support disabled people, but not chronically sick people. Therefore, many patients with cancer are permanently lost to the labour market, who could return to their jobs if given a chance and the time to overcome their disease. The financial effect of cancer in terms of social costs and reduced productivity is apparent. Furthermore, vulnerable groups—ie, people in poverty, migrants, ethnic minority groups, and disabled or elderly people—are often more affected economically and socially by cancer because their environment is less capable of compensating the strains of a cancer diagnosis.[294]

Future outlook

In the past decade, patients with cancer have strived to have a voice in health-policy decisions made on their behalf. In the 1990s and early 2000s, patient protection measures such as the EU clinical trials directive and EU regulation of information on medicinal products were introduced without prior patient consultation. Indeed it is now clear that these regulations have had the very opposite effect on patient protection to that intended, by reducing the variety and number of cancer clinical trials that actually inform clinical management. Today, patient advocacy groups are more accepted as equal stakeholders, providing expertise that cannot be provided by health-care professionals, consumer groups, and regulators alone. Following the motto nothing about us without us, these groups are prepared to join a rational debate on research priorities, cost containment, increasing

efficiency, and social inclusion to achieve affordable cancer care and to meet the societal challenges.

With an ageing population leading to an increasing burden of cancer, difficult decisions on priorities in health-care budgets will have to be made in the next decade. Patient advocacy organisations have a crucial role when society, researchers, and authorities need to agree on priorities. By focusing on drug pricing rather than the effect of end-to-end cancer care on survival, quality of life, health-care costs, and ability to work, current value-appraisal mechanisms of health technologies have major shortcomings. The contribution of patient groups on the assessment of priorities, quality of life, and the value of new therapies is crucial. Furthermore, patient groups have a key role in making cancer care more targeted, efficient, and effective, with their contribution to research design and conduct, patient information and informed consent, and disseminating information on best medical practice to patients and oncologists. Patients are much more than just the subjects of health care. Patient contribution to the debate on health-care costs and budget priorities is not just a measure of empowerment, but an important responsibility of patient advocacy groups as a partner and ally.

US perspective

Cancer care in the USA is fast becoming unaffordable except for the well insured and most affluent. As health-care costs rise,[295,296] patients with cancer and their families are bearing a greater burden of cost as a result of decreasing coverage of health insurance policies and resulting increase in copays and deductibles. For the 46 million uninsured individuals in the USA, the picture is even more grim.

How does the cost of cancer care (in particular, that borne by the patient) affect the individual and society? To start, individuals with private insurance pay out-of-pocket health-care costs: premiums, copays, and deductibles. Costs vary greatly depending on the insurance plan, but it is not uncommon for an individual to pay 20% of costs.[297] Until recently, almost all health-insurance plans had annual or lifetime caps (or both), which cancer-care expenses can easily exceed, adding to the cost burden for the individual. In addition to direct health-care expenses such as copays, patients encounter unexpected expenses when undergoing cancer treatment. These out-of-pocket costs include transportation or travel expenses, childcare, and incidentals. Employed individuals might have to work reduced hours or take unpaid leave to have treatment or care for a family member going through treatment.

The median age at cancer diagnosis is 67 years, and most individuals in the USA who are older than 65 years have public health insurance through Medicare. However, outpatient services are at the individual's expense, and prescription drug coverage has annual limits, which do not fully cover the cost of many oral cancer drugs. The cost of a cancer diagnosis does not necessarily end with active treatment. Elderly patients with a prior cancer diagnosis pay 20% more in out-of-pocket expenses than individuals with no history of cancer.[298]

Uninsured patients face a more precarious situation, since they are forced to navigate through a maze of public-assistance and charitable programmes and services. For example, the Breast and Cervical Cancer Prevention and Treatment Act provides access to Medicaid-funded treatment for women diagnosed through a cancer screening programme offered by the Centers for Disease Control and Prevention. Substantial underfunding of the screening programme, however, means only 14% of otherwise-eligible women are served. Uninsured individuals are more likely to receive a delayed diagnosis, and are more likely to die prematurely than those with insurance, largely because of this delay.[299]

High financial costs have other ramifications for patients and their families. According to a recent study by the Cancer Support Community,[300] 81% of patients and 72% of caregivers experienced moderate to severe stress levels due to the costs of cancer care, even though the vast majority (91%) of those surveyed had health-care insurance. Mounting medical expenses can lead individuals and families to bankruptcy; almost half (46·2%) of personal bankruptcy filings in 2001 were due, at least in part, to medical causes,[301] and by 2007 the proportion had grown to 62·1%.[302]

In addition to mental and emotional distress, medical costs and insurance status can lead to undertreatment and lack of appropriate follow-up care for cancer survivors. A recent study showed that a higher prescription copayment was associated with early discontinuation and non-adherence to treatment with aromatase inhibitors. Most at risk are elderly women, who were a third more likely to discontinue their prescription if they had high copays.[303] Another study showed that survivors of breast cancer do not receive appropriate mammography surveillance, with the uninsured least likely to do so; 54% of uninsured individuals had surveillance compared with 79% of privately insured survivors.[304] Yet another study showed that Medicaid or uninsured patients with lung cancer were less likely to receive surgery or chemotherapy and more likely to die than patients on Medicare or who were privately insured.[305]

Solutions

The passage of health-care reform in 2010 is beginning to address some of the challenges related to the personal burden of cancer care. Millions of people who are currently uninsured will have access to coverage for cancer treatment through an expanded Medicaid programme and through insurance options offered through new state exchanges. Those who are currently insured are already seeing valuable new patient protections, such as elimination of annual and lifetime

caps, that should help minimise the risk of financial hardship. Many of the most valuable features, however, will not reach individual patients until 2014. Even after these benefits are phased in, gaps will remain. For example, although there will be limits on out-of-pocket expenses, patients fighting lengthy battles with an expensive disease like cancer will still be exposed to crippling costs.

Some health-care expenditures are unwarranted and contribute to the high cost of cancer care. These expenditures come in many forms—such as inefficiencies, unnecessary medical tests, and overtreatment. Patients themselves can contribute to excess costs, perhaps because they believe more treatment or newer treatments are better, or that they are not empowered to question their care. Improved patient education of evidence-based practices is important, and patient advocacy organisations have an important role in disseminating current and accurate information.

The public and private sectors must continue to protect and foster clinical research and development of new cancer therapies. We need better predictive and prognostic markers to realise the real potential for targeted therapies. This would not necessarily lead to lower treatment costs, but to better patient outcomes and more appropriate allocation of treatment costs.

Summary

Patient advocacy groups can, and must, have a valuable role in the identification and implementation of strategies to contain costs without sacrificing quality of care. Though the health-care payer systems vary substantially between Europe and the USA, patients carry much of the financial, physical, and emotional burden regardless of where they live. Patient advocates are best equipped to speak on behalf of those who have been diagnosed with cancer.

Part 10: Can we deliver affordable cancer care for high-income countries? Concluding comments

We are at a crossroads for affordable cancer care, where our choices—or refusal to make choices—will affect the lives of millions of people. Do we bury our heads in the sand, keep our fingers crossed, and hope that it turns out fine, or do we have difficult debates and make hard choices within a socially responsible, cost-effective, and sustainable framework? The figures for the economic burden of cancer care reported in Part 1 of this Commission should worry everyone, not just those in developed countries; for example, the annual cost of systemic therapy relative to GDP doubled from 1995 to 2009. The costs associated with new cancer cases alone in 2009 were estimated to be around US$286 billion, of which medical care makes up more than half, and lost productivity costs account for about a quarter of the total. Estimates of the global economic impact of cancer (ie, the cost of years lost from ill health, disability, or early death) are even more staggering; at nearly $900 billion cancer outstrips all other conditions (figure 10). From a purely economic standpoint, cancer is the most significant disease in developed countries. Expenditure on cancer care has risen considerably in all high-income countries. The are many drivers for this increase, including overutilisation, disincentivisation driven by reimbursement rules and defensive medical practice, consumer driven over-demand, high-cost innovation, and futile disease-directed care.

The remarks in Part 1 recommended that we reduce use and lower the costs of cancer services and interventions through a suite of macroeconomic and behavioural approaches. Policy debates must establish how to integrate and drive these approaches, although the challenges are powerful and dynamic. An ageing and increasing population means that the future cancer burden will quickly overwhelm high-middle-income countries such as Brazil, India, China, and Russia, and then progress to low-income and middle-income countries. Cost–benefit studies from developed countries where study populations have a median age of 60 years are of limited use. Research specific to populations in low and middle-income countries is needed for treatment and resource allocation. Capacity building and global initiatives look good on paper, but have yet to be translated into better outcomes. The reality is that for developing countries, delivering affordable cancer care is currently a distant vision.[306] Radically different approaches are going to be needed to bend the cost curve in developed and developing countries (figure 11).

All contributors to this report identified substantial increases in the rate of technological innovation in their respective specialties, coupled with shorter life-cycles for each cancer technology (whether these were cancer medicines, imaging, or surgical procedures) as new versions, upgrades, or class shifts emerge. The

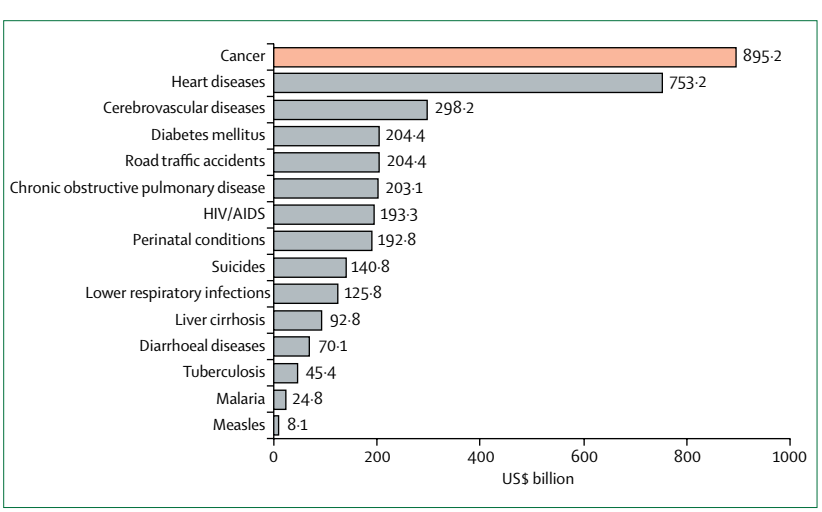

Figure 10: **Global economic value of disability-adjusted life years lost in 2008, by disease or event**
Reproduced with permission from the American Cancer Society.

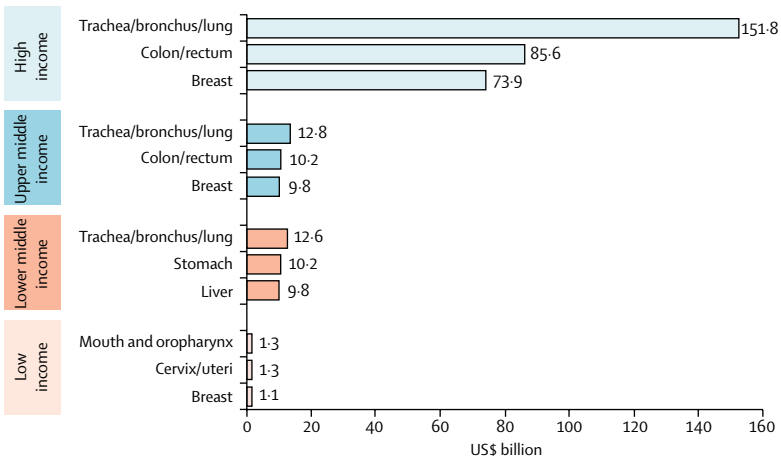

Figure 11: **Estimated economic value of disability-adjusted life years lost in 2008, according to cancer type and national income level**
Reproduced with permission from the American Cancer Society.

paradox is that this type of innovation can also reduce costs and improve outcomes; however, none of the contributors advocated unrestricted spending on cancer care and new technologies. Instead, they agreed that we need to consider how much we are spending on cancer treatment and prevention, whether it is reasonable compared with other priorities, and whether resources are allocated efficiently.

Indeed, with a growing list of effective cancer interventions, it becomes even more crucial to scrutinise carefully what we spend to ensure funding for the most effective interventions, and to give potential innovators the confidence that funding will be available to support and reward the discovery and delivery of effective technologies as they are developed. Resistance to this ethos should not be underestimated, however, since earlier and earlier adoption of novel technologies, often with low evidence and cost-effectiveness bases, is being promoted.[307]

Nuclear medicine, imaging, and radiotherapy

As noted in Part 6, debate around affordability has been at the heart of nuclear medicine and imaging developments for some time, despite the fact that their application in prognostic and predictive stratification promises cost reductions in the medium term. But these technologies are also expensive and increasingly under scrutiny by HTA agencies. However, the fast evolution times and quick take up of technologies such as PET have presented HTA authorities with data from small-scale clinical trials rather than large-scale phase 3 and 4 studies. With only 6% of cancer health-care expenditure devoted to diagnosis (this figure includes all diagnostic procedures), the overfocus on affordability of these technologies was considered in Part 6 to be a distraction. That section suggests that we should be asking why so little is being spent, and why, from a health economics standpoint, these technologies have not been appreciated as integral to the entire patient pathway and not just the upfront diagnosis. A focus on affordability as a subjective judgment needs mutuality (full disclosure) and education of how and when imaging technologies are used, to understand the trade-offs with funding research and development of a particular imaging technology. Furthermore, accurate diagnostic techniques paired with appropriate evaluations of treatment could reduce costs by avoiding surgery in metastatic disease, radiation in radioresistant tumours, and the misapplication of many cancer drugs in settings where they cannot possibly provide significant clinical benefit.

Part 5 reflected on the fact that more than 60% of patients receive some form of radiotherapy during their treatment or in the palliative setting. Again, this modality has seen huge innovation, from the days of cobalt machines to image-guided IMRT and the now increasing use of radiotherapy in combination with molecularly targeted agents. But all this has come at a cost, one that many providers and insurers seem increasingly reluctant to pay. Paradoxically, there has also been resistance to pay for less costly approaches such as perioperative radiation for breast cancer, a technique that is, within certain limits, accepted by experts. Cost cutting around radiotherapy has led directly to serious breaches in safety and quality. Despite potential savings from integrating radiotherapy in a more rational way into patient pathways, the large capital and revenue costs associated with this modality have been systematically opposed. Part of the issue, as Part 5 highlighted, is not simply a lack of willingness to pay, but the lack of coherent regulatory guidance on cost-effectiveness and few health-economic studies in this area. The conclusion is that there is an urgent need to move to value-based radiotherapy and to create the infrastructure to generate the necessary clinical and macroeconomic evidence. The firm policy solution is to follow CED methods to construct and manage the future development of radiotherapy technologies.

Voice of patients and the research community

In the debate about affordable cancer care, the voice of patients is central to delivering acceptable sociopolitical solutions. The viewpoint of patient advocates expressed in Part 9 presented affordability as a public policy issue, derived from national health-care systems; with 23 languages in Europe and more than 30 national health-care systems in the western world, each with their own sociopolitical priorities, fragmentation is inevitable in addressing the cost of cancer care. However, the globalisation of media means that disparities in access to care and outcomes are quickly exposed and disseminated among patient groups, adding to a sense of unfairness and injustice. Affordability is also about social justice and inclusion, in a world where disparities between the affluent and deprived are becoming more acute.[308]

Part 9 highlighted the considerable social effects of cancer care, including losses from the labour market and an approximate 25% fall in income during the first year of a cancer diagnosis. It is clear that affordability of cancer care is a problem for families, not just for patients. Disparities in employment law also mean that many patients are permanently lost to the labour market as a result of a cancer diagnosis. The situation is particularly acute for the non-insured and underinsured. For example, around 46 million people are uninsured in the USA, and these individuals are more likely to die because of delayed diagnosis. The cost of cancer is effectively pricing many people out of the health-care market.

How we define value remains a divisive area. As discussed in Part 2, even when research delivers new treatments, it might not meet cost-effectiveness criteria. Value-based pricing, where technologies are approved only at prices that ensure that their expected health benefits exceed those that might be obtained by applying the same resources to other health strategies, might lead to more affordable cancer care. However, problems remain: statistical rather than clinical significance in research results (a point echoed in Part 3 with respect to marginal benefit), inaccurate ICER estimates due to the misuse of surrogate endpoints, and recruitment of selective populations for clinical trials leading to poor applicability in the real world. The solutions proposed in Part 2 focused on a radical improvement in the methodological rigour of clinical trials of cancer technologies, coupled with greater integration of health economic studies. Although there might be substantial sociopolitical resistance to constraining off-label use of technologies for patients with cancer, research offers the only tangible solution to preventing marginal, expensive technologies from entering health-care systems in the first place. How and whether we can promote and educate health-care professionals and patients to be cost conscious remains to be investigated.[309] Furthermore, there is a fine line between using cost sharing to persuade patients not to overutilise, and placing so much fiscal burden on patients that they underutilise or non-utilise.[310]

A tale of two professions: cancer surgery and medical oncology

The lack of high-quality data on cost for many areas of cancer care is particularly lamentable for cancer surgery, which provides the bulk of control and cure for solid cancers. Part 4 highlighted the scant data to support evidence-based policy making and only recent integration of health economics into clinical studies of cancer surgery. Cancer surgery has seen radical changes in technology over the past two decades, including increasing use of robotics and more complex procedures. The volume of surgeries has also increased substantially with the ageing demographics.

Part 4 identified four causes for decreasing affordability of cancer surgery: a culture of medical excess (more is better); a failure to understand trade-offs (ie, benefit, no matter how small, is acceptable no matter what the costs); inability of patients to afford cancer surgery; and over-compliance, the costly medical disease of bureaucracy. The section also called for greater debate, education of stakeholders, and a radical change to fully integrate health economics into all cancer surgery research.

Expenditure on cancer therapy has risen substantially; in Europe, between 1993 and 2004, total sales for cancer drugs alone increased from €840 million to €6·2 billion.[48] Focusing on the experiences of three high-income countries—UK, Australia, and the USA—Part 3 discussed the variety of cost-sharing schemes that have evolved to cope with the increasing price of cancer medicines, from patient-access schemes in the UK to the federally mandated pharmaceutical benefits scheme in Australia. Unlike in high-income countries with mainly social and central health-care systems, the USA has seen a huge increase in off-label use of cancer medicines. This practice is so widespread that prescribing habits have quickly found their way into treatment guidelines and have driven up costs without an evidence base. The lack of health-economic studies and a failure to include key patient populations (ie, elderly patients with cancer) in these studies contributes to an unsustainable future for medical oncology. Furthermore, Part 3 identifies the increasing problem of accepting marginal benefits in early clinical development of drugs that, unsurprisingly, translate to marginal benefits in the clinic. One solution offered is to tailor novel therapies using biomarkers and increase the use of imaging to select responders (and non-responders). A second solution is to cut out medicines with marginal benefits during the clinical development process, and to change off-label usage.

Medicines and biomarkers: industry and academic perspectives

Part 8 reflected on an industry perspective to cost drivers, and discussed the increasing complexity of research needed to develop medicines, or any other technology, for an ageing population with a variety of comorbidities. With the demise of the blockbuster drug and increasing research and development costs, industry finds itself with huge costs and increasing stratification of the cancer-patient population. Adding to the theme of measurement of value, comments in Part 8 noted that a real understanding of health economics and the associated complexities around underlying assumptions and trade-offs eludes most of the health-care profession and public, thus considerably hindering the affordability debate. Provocatively, Part 8 questioned the assertion that cancer costs have reached crisis levels, with cancer treatment costs accounting for only 10% of total health care in even the most high-usage countries (USA and France). In a similar vein to Part 9, Part 8 also advocated CED; however, it went further, with calls for acceptance of willingness to pay,

Issues	Solutions: immediate action	Solutions: more research to understand why and how
Increase in absolute amount and rate of cancer-care expenditure	• Drive innovation in low-cost technologies, including use of off-patent products, and re-engineer patient pathways to provide high-quality, cost-effective, and value-based care • Support research agendas for delivering societal objectives, particularly health-economic studies, non-commercial head-to-heads, research into non-pharmaceutical technologies (eg, surgery), and prognostic and predictive biomarker studies	• Develop new business models for financing cancer care and fair renumeration of providers • Rethink how pharmaceuticals and other high-cost technologies are priced, including development of new price-value models • Implement CED as standard practice, particularly in modalities such as radiotherapy • Define what a balanced scorecard might look like between national interest in cost control and industry requirement to service shareholders, avoiding one group benefiting at the expense of another
Ageing demographics	• Mandate the inclusion of elderly patients in clinical research, taking into account frailty and the effect of comorbidities	• Model the effect on cancer care and solutions for these demographic trends in LMICs
Rapid technological innovation	• Increase the rigour with which new technologies are developed, and reduce the number of marginal benefit technologies being taken to phase 3 through more intelligent early phase trial design and more rigorous evidential standards	• Value-based pricing, where both outcomes and costs are comprehensively measured over a full cycle of care compared with other approaches and modalities
Failure in equity: increasing numbers of patients lost to affordable cancer care	• Ascertain out-of-pocket expenditures, and provide complete coverage plans for high-value treatments for all patients irrespective of ethnic background, income, age, or sex • Provide new ways of delivering care for rare cancers in a more centralised manner	• Develop and test new value-based models using real-world patients and taking into account indirect costs, effect on family, etc • Develop new approaches to integrating social justice to tackle exclusion and discrimination in affordable cancer care and implement practical solutions
Overutilisation of care by health-care professionals and patients (culture of excess)	• Reduce culture of futile care • Radically control and reduce off-label prescribing; drive evidence-based prescribing • Public education of the evaluation and validation of cancer technologies • Education that value-based care is not poor care	• Promote increased education of health-care professionals, including discussions with patients on use of less intensive treatment options • Constrain medicolegal litigation • Develop cost-sharing models for care to manager consumer demand in low value care
Disconnection of regulatory and health-technology processes from each other and society	• Align or merge often conflicting regulatory and health-technology appraisal processes • Radically reduce regulatory bureaucracy on cancer research	• Bring stronger understanding of clinical development to regulatory authorities and provide stable guidance for predictive biomarker testing
Poor intelligence for evidence-based policy making, and overfocus on benefits (often minimal)	• Promote complex multimodal clinical trials particularly for high-cost technologies such as imaging and novel radiotherapy (eg, IGRT) • Mandate integrated health economic studies in all cancer clinical trials to accepted international guidelines (eg, ISPOR) • More research and integrated health economic studies in cancer surgery • Stop accepting statistical benefit as equivalent to clinical benefit; use valid outcome measures (eg, overall survival)	• Re-evaluate the methodological basis of economic decision-making in cancer care, particularly the systematic evaluation of patient values and what constitutes meaningful benefit (or harm) • More complex high-value early phase studies; rethink the traditional evidence-based pyramid hierarchy in favour of intelligence-dense clinical trials
Fragmentation and heterogeneity of political prioritisation for cancer across high-income countries	..	• Develop new models for delivering transnational access and treatment for cancer • Hold nation states to an agreed international cancer control plan, setting out broad standards including fiscal support

CED=coverage with evidence development. LMICs=low-income and middle-income countries. IGRT=image-guided radiotherapy. ISPOR=International Society for Pharmacoeconomics and Outcomes Research.

***Table 7*: Barriers and solutions to affordable cancer care in high-income countries**

exclusivity, and additional fiscal incentives to stimulate and sustain the cancer-medicine pipeline.

The era of personalised cancer therapy and novel targeted therapies have been intimately associated with the co-development of biomarkers for many types of cancer. As pointed out in Part 7, the expectation is that these tests will lead to cost savings by selecting patients for the most effective treatment and lessening complications, but the science has not lived up to this promise. At the core of this problem is the lack of rigorous assessment, including few health-economic studies, of the ever increasing number of tests entering the market (by 2008, for example, there were 1800 pharmacogenomic tests).

Furthermore, clinical utility is often at odds with the perceived benefit of a test. Even the supposedly easier assessment of analytical validity can be a minefield of misclassifications, making any health-economic assessment invalid. Although there are many predictive tests in development for a wide range of novel and current cancer medicines, the regulatory requirements are in a constant state of flux. These shifting goalposts, along with poor scientific and clinical development, are major barriers to the realisation of biomarkers as technologies for cost savings in medicines and other therapeutic modalities.

Summary

Are we to simply let the train of affordable cancer care crash off the tracks? The consensus from all groups concerned is that policy makers, politicians, patients, and health-care professionals need to address the issue now. It is too late for many patients to access affordable cancer care. But solutions require vision, and to

paraphrase Theodore Roosevelt, we need an ideal and we need to live up to it. Although this report has focused on cancer care, prevention is also essential and this too demands political will, ample funding, and a substantial change in mindset as well as personal and political engagement and willpower.[311]

Some of the barriers and proposed solutions to affordable cancer care (table 7) are obvious and need immediate action. Others are far more challenging and reflect the fact that cancer is a complex disease embedded in equally complex and heterogeneous sociopolitical health-care systems. Creative solutions that cross disease boundaries, such as the approach to care integration through bundled payments in the Netherlands, will need to be found and tested.[312] How we re-engineer deeply held sociomedical cultural practices to deliver affordable cancer care is another challenge. Value, for example, can be irrational when set within the context of our deeply rooted faith in medicines.[313] In addition to the policy solutions proposed (table 7), it is time to establish high-level working groups to explore and develop value-based cancer care. This can only go hand-in-hand with open and accessible publication of cancer outcomes across a broad range of indicators.

We believe that value and affordable cancer care can be introduced into the cancer policy lexicon without detracting from quality, and that the management tools, evidence, and methods are available to affect this transformation across all developed countries.

Contributors

Introduction: written by RS. Part 1: Lead author was JP (correspondence to jeffrey.peppercorn@duke.edu). KS, JZ, NJM participated in the concept development, writing, and editing of the manuscript, and approved the final version. Part 2: Lead author was IFT (correspondence to ian.tannock@uhn.on.ca). EA and IFT were responsible for the concept and writing. DKh, PB, and PA contributed to reviewing the manuscript and author revisions. Part 3: Lead author was JGM (correspondence to gordon.mcvie@ieo.it). TF wrote the section on cost of cancer care in the USA. JS wrote the section on cost of cancer care in Australia. SW wrote the section on cost of cancer care in the UK. SC contributed to the structure of the report and writing of the section on cost of cancer care tomorrow. JGM provided ideas and structured the report, and wrote sections on lessons from the past and cost of cancer care tomorrow. Part 4: Lead author was ADP (correspondence to claire.arnold@kcl.ac.uk). ADP, PN, AE, and MFB contributed equally to the manuscript. Part 5: Lead author was MLS (correspondence msteinberg@mednet.ucla.edu). MLS, MDR, SAM, DV, TR, and GS wrote the manuscript. Part 6: Lead author was RJH (correspondence to rod.hicks@petermac.org). RJH and PJE contributed equally to the manuscript. Part 7: Lead author was KAS (correspondence to kevin.schulman@duke.edu). BRH wrote the original draft. BRH, DPC, and KAS conceived and revised the manuscript. Part 8: Lead author was DT (correspondence to david.taylor@pharmacy.co.uk). DT wrote the first draft, and DT and PC reviewed and amended the manuscript. Part 9: Lead author was NGB (correspondence nbrinker@komen.org). JG, NGB contributed equally to the manuscript. Part 10: Lead author was RS (correspondence to richard.sullivan@kcl.ac.uk). RS, DM, DKe, and MA contributed equally to the manuscript.

Conflicts of interest

RS has received research funding from Pfizer and Novartis, and has received payment for lectures by Celgene. MA has received consultancy and honoraria fees from Amgen, Sandoz, Helsinn, Johnson & Johnson, Norvartis, Roche, Merck, Pierre Fabre, Hospira and Pfizer, and honoraria from Baxter. JP has received consultancy fees from Aveo Pharmaceuticals, Bayer, Celgene, Genentech, Novartis, and Heathwell Foundation. He has received honoraria from Genentech, and Novartis and research support from Novartis. JZ has acted as a consultant for Amgen, ARIAD, Novartis, Pfizer, Roche, Sanofi-Aventis, Abraxis, Abbott, Patrys, MSD, Imclone, Bayer, and Abbott and has received research funding from Amgen, MerckSerono, Novartis, Pfizer, Roche, and Sanofi. NB is employed by Susan G Komen for the Cure. NJM has received consultancy fees from AstraZeneca, Genomic Health, Saladax, Sanofi-Aventis, Helsinn, Pfizer, Veridex, Genentech, and Amgen and honoraria from Biogen. KAS has received research support from Actelion Pharmaceuticals, Allergan, Alnylam Pharmaceuticals, Amgen, Amylin Pharmaceuticals, Astellas Pharma, Bristol-Myers Squibb, Inspire Pharmaceuticals, Johnson & Johnson, Kureha Corporation, Medtronic, Merck & Co, Nabi Biopharmaceuticals, NovaCardia, Novartis, OSI Eyetech, Sanofi-Aventis US, Scios, Tengion, Theravance, Thomson Healthcare, and Vertex Pharmaceuticals. He has received consulting fees from Advanced Health Media, the Certified Medical Representatives Institute, the Commonwealth Fund, EnablEd, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, LifeMasters Supported SelfCare, McKinsey & Company, Medical Decisions Network Medtronic, Merck & Co, National Pharmaceutical Council, Novartis, Novo Nordisk, Orexigen Therapeutics, Quintiles Transnational Corp, Social and Scientific Systems, Wallen and Associates, and WebMD. He holds equity in Alnylam Pharmaceuticals, Cancer Consultants Inc, Faculty Connection, General Electric Company, the Manufacturers Life Insurance Company, PepsiCo Inc, the Physician Education Leadership Institute, Procter & Gamble, and Tellus. PC is employed by the ABPI, which is a trade association for the UK pharmaceutical industry, and until March, 2010, was employed by Roche UK. DT has received research funding from a range of public and private bodies, including NICE, the Department of Health, Alliance Boots, Pfizer, and the Pharmaceutical Research and Manufacturers of America. JG has received consultancy fees from Bristol-Myers Squibb, Novartis and Pfizer. SW has received honoraria from Amgen, ISIS Pharma, and payment for educational presentation from Roche. DKh has received consultancy fees from Roche, AstraZeneca, and Sanofi-Aventis. All other authors declared that they have no conflicts of interest.

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