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Abstract

The risk of cancer increases with age. In Australia six times as many cancers are diagnosed in people over age 50 as in people under that age. Because of this, Australia’s ageing population is driving a rapid increase in new cases of cancer. Advances in health technology have meant that cancer survival rates have increased significantly in recent years and this is expected to continue as a result of new therapies currently under development.

However, many of these new therapies are very expensive and the incremental cost effectiveness ratio is at, or beyond, the limit of what is considered affordable by health economists and health policymakers. Health consumer advocates have argued that cancer therapies for end-of-life settings should be treated differently from other health technologies and that one year of life at the end of life may be more valuable than one year of healthy life. This has led to the introduction of special rules for advanced cancer therapies by many health technology assessment organisations. Others have argued that advanced cancer receives disproportionate funding relative to its societal burden and that this has a detrimental impact on other, more cost effective, public health initiatives.

In this paper, we outline the actuarial methodology used by health economists to determine the cost effectiveness of health technologies and we examine the decision making process for listing of new therapies on the Pharmaceutical Benefits Scheme (PBS). We use examples from Australia and overseas to highlight the affordability and ethical issues surrounding expensive new therapies for advanced cancers. We explain the role actuaries can play in the health policy debate in the context of our leadership role in the public debate on responses to Australia’s ageing population.

Keywords: Ageing Population, Health Policy, Health Economics, Ethics, Cancer

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Introduction

Cancer is a major cause of death, accounting for 29% of all deaths registered in Australia. The risk of being diagnosed with and of dying from cancer increases markedly with age as shown in Figure 1 and Figure 2. Of the 112,304 diagnoses of cancer in 2008, 86% (97,133) occurred in people over age 50 and 15,171 (14%) in people under that age i.e. there were more than six times as many cancer diagnoses in people over age 50 as in people under that age. Taking into account the size of the population in each age group, the incidence rate of cancer is more than fourteen times higher for those aged over 50 compared with those under 50 (1,464 per 100,000 compared with 103 per 100,000).

Figure 1: Age-Sex Specific Incidence Rates for All Cancers Combined, Australia 2008
One of the most striking features of cancer incidence and mortality is the gender disparity, which widens markedly with age. In the 50 to 54 age group incidence and mortality rates for all cancers combined are similar for men and women. In the 70 to 74 age group men are almost twice as likely to be diagnosed with and more than one and a half times more likely to die from cancer as women.

Advances in health technology have meant that cancer survival rates have increased significantly in recent years. The increase is due partly to advances in treatments, including new drugs, but also in part due to earlier detection through screening programs.

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\(^1\) Cancer incidence in men is very strongly influenced by prostate cancer, which represents about one third of all cases. In turn prostate cancer incidence is known to be strongly correlated to rates of Prostate Specific Antigen (PSA) testing, which is associated with overdiagnosis.

\(^5\) The World Health Organization defines health technology as the application of organised knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives.

\(^*\) Diagnosing cancers earlier can create the appearance of longer survival times. This is the phenomenon of stage migration also sometimes known as the Will Rogers effect.
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As shown in Figure 3, between 1982-1987 and 2006-2010 the five year relative survival for all cancers combined increased from 47% to 66%.³

Figure 3: All Cancers Combined Five Year Relative Survival, Australia 1982-1987 to 2006-2010

The increase in survival rates is expected to continue as a result of many new therapies which are currently under development. A recent analysis by Pharmaceutical Research and Manufacturers of America⁴ revealed that almost 1,000 new cancer medicines and vaccines are currently being tested in the US. Many of these are for advanced cancers.

However, many of the new therapies that have led to the improvement in relative survival are very expensive. In the case of new drugs for advanced (metastatic) cancer, many are at or beyond the limit of what is considered affordable by health economists and health policymakers.
Example: Treatment of Colorectal Cancer

The treatment of colorectal (bowel) cancer provides an example of how the development of new drugs can dramatically increase the cost of care. Until 1996 the only treatment available for patients with metastatic colorectal cancer was 5-fluorouracil plus leucovorin (5FU/ LV) at an average cost per patient of some US$4,000 (measured in 2006 dollars). The median survival for patients with metastatic disease treated with 5FU/ LV is approximately 12 months.

Over the ensuing decade a number of new drugs were developed that show a survival benefit in clinical trials. Wong et al.5 have studied the cost effectiveness of various treatment strategies involving the addition of combinations of two new cytotoxins; irinotecan and oxaplatin; and two new monoclonal antibodies; bevacizumab and cetuximab; using a Markov model. The results of the cost effectiveness analysis are shown in Figure 4.

Figure 4: Cost Effectiveness of Treatment Strategies for Colorectal Cancer

The analysis clearly demonstrates that treatment strategies involving the addition of combinations of the new drugs are effective and can extend life expectancy by just over one year. However, the effectiveness is strongly positively correlated with cost. The most effective strategy, FOLFIRI/ Bevacizumab then FOLFOX then Cetuximab/ Irinotecan, extends life expectancy by 64 weeks compared to 5FU/ LV at an additional cost of US$161,000.
This raises the question of how we assess whether treatments are “worth” the cost, and how we as a society make decisions about the allocation of health resources. To do this, we now consider health technology assessment (HTA), carried out by health economists, but based on techniques that will be familiar to actuaries.

Health Technology Assessment

Health Technology Assessment (HTA) is a way of comparing the relative value of health technologies (such as procedures, pharmaceuticals or devices) to make decisions about listing and reimbursement. In Australia, HTA is undertaken in relation to listing on the Australian Register of Therapeutic Goods and reimbursement under the Pharmaceutical Benefits Scheme, National Immunisation Program, Medicare Benefits Schedule and Prostheses List.

In pharmaceutical submissions, the main focus of an economic evaluation is on how much a new therapy costs to achieve additional health outcomes compared with therapies that would be replaced. By way of example, consider an advanced cancer clinical setting where there is currently no treatment available other than best supportive care. A pharmaceutical company develops a new drug which is shown through a phase III clinical trial to be both safe and to give a survival advantage i.e. on average patients taking the drug live longer than those who do not. In this case the evaluation would compare best supportive care with the new drug. A more complicated assessment is required in a clinical setting, such as the colorectal cancer example, in which a number of treatment options or strategies are available.

In evaluating drugs we calculate a quantity known as the incremental cost effectiveness ratio (ICER) to compare incremental cost with incremental outcomes. If the outcome being assessed is overall quality and length of life (cost-utility analysis), the ICER is simply the expected additional cost of the new therapy divided by the expected increase in Quality-Adjusted Life Years, or QALYs:

\[
ICER = \frac{E[\text{discounted cost of treatment } 2 - \text{discounted cost of treatment } 1]}{E[\text{discounted QALYs for treatment } 2 - \text{discounted QALYs for treatment } 1]}
\]

If the ICER is below a certain threshold, it represents a cost-effective treatment.

†† A particular point to note here is that very commonly with new therapies for advanced cancers, including the colorectal cancer example discussed above, the median survival advantage is measured in weeks or months not years.
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The QALY is a measure which combines length of life lived in a given health state with quality of life in that health state into a single index:

\[ \text{QALY} = \text{Length of Life Lived in Health State} \times \text{Utility for Health State} \]

The utility, or QALY weight, varies between zero and one. A year lived in perfect health has a utility of 1, whereas death has a utility of 0. Health states which are worse than death (utility < 0) are permissible.

Although in a formal sense the utility cannot be greater than 1, health consumer advocates have argued that cancer therapies for end-of-life settings should be treated differently from other health technologies, and that one year of life at the end of life may be more valuable than one year of healthy life. This has led to the introduction of special rules for advanced cancer therapies by many health technology assessment organisations, which effectively acknowledge that utilities greater than 1 are in some sense permissible. From an ICER perspective, the implication of using utilities greater than 1 is that the denominator is increased which can make more costly treatments appear cost-effective.

Utilities for health states are determined using a number of standard techniques, including:

- **Time trade off** in which respondents are asked to choose between remaining in a state of ill health for a period of time, or being restored to perfect health but having a shorter life expectancy

- **Standard gamble** in which respondents are asked to choose between remaining in a state of ill health for a period of time, or choosing a medical intervention which has a chance of either restoring them to perfect health, or killing them

- **Visual analogue scale** in which respondents are asked to rate a state of ill health on a scale from 0 to 100, with 0 representing being dead and 100 representing perfect health.

Another way of determining the utility for a given health state is to use a standard instrument such as the EQ-5D‡‡ questionnaire, which categorises health states according to a number of dimensions.

‡‡ EQ-5D is a standardised measure of health status developed by the EuroQol Group (a network of European researchers) in order to provide a simple, generic measure of health for clinical and economic appraisal. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys.
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As shown in the ICER definition above, discount rates are commonly applied to costs and to QALYs. Whilst initially it may seem strange that a discount rate is applied to QALYs, the concept is that a year of life lived in the future is in some sense worth less than a year of life lived now. Whilst we do not discuss discount rates in this paper, it should be noted that there has been much debate amongst health economists about whether the discount rates for costs and QALYs should be the same or different; see for example Claxton et al.6

Returning to the colorectal cancer example, the ICER for FOLFIRI/Bevacizumab then FOLFOX then Cetuximab/Irinotecan compared to 5FU/LV is:

$$\text{ICER} = \frac{161,000}{64} = 2,500 \text{ per week}$$

Figure 5 and Figure 6 show the ICER for each treatment strategy plotted against the marginal effectiveness and marginal total drug cost per patient compared with 5FU/LV, respectively. The more complex treatment strategies such as FOLFIRI/Bevacizumab then FOLFOX then Cetuximab/Irinotecan extend life expectancy, but at an ever increasing ICER and total drug cost per patient. Even the treatment strategy with the lowest ICER (FOLFIRI then FOLFOX) has an ICER of US$1,700 per week (US$90,000 per year).

Figure 5: ICER vs. Marginal Effectiveness Compared to 5FU/LV
In this paper we do not discuss the modeling techniques used in health technology assessments other than to note that the most common approaches are decision trees and Markov Models. Monte Carlo simulation is also commonly used in sensitivity analysis.

Figure 7 shows a simplified decision tree for evaluating the Faecal Occult Blood Test (FOBT) for colorectal cancer, which forms the basis of the National Bowel Cancer Screening Program for Australians over age 50\textsuperscript{55}.

The decision tree comprises a number of nodes, branches and outcomes. The first node is the decision node (square) which describes the issue i.e. the decision to screen with FOBT or not. There is only one decision node in a tree. Next we have chance nodes (circles) which represent all possible events and their probabilities e.g. that a person who is screened either does have cancer, which has a probability of 0.5%, or does not, which has a probability of 99.5%. The final type of node is a terminal node (triangle) which represents the end of the tree and is where we attach the outcomes (payoffs), e.g. costs of treating cancer if present and QALYs. The cost attached to each chance node is the weighted average cost of subsequent possible outcomes.

\textsuperscript{55} As well as quantifying the cost effectiveness of treatments, HTAs are also used to assess the cost effectiveness of screening programs.
Health Technology Assessment and Reimbursement

In addition to looking at safety and efficacy, many countries, including Australia, use HTA when deciding whether to reimburse patients for the costs of new therapies. As indicated above, the ICER is compared to a threshold. If the ICER is less than the threshold then the new therapy will be recommended for reimbursement. If it is more the therapy will be rejected. In the case of the Pharmaceutical Benefits Advisory Committee (PBAC), there is no single threshold, but PBAC also takes into account “less quantifiable” issues such as the severity of the disease, availability of alternatives and social values in making its recommendations. However, PBAC decisions in the past have shown that the ICER is of the order of $50,000.

The argument by health consumer advocates that cancer therapies for end-of-life settings should be treated differently from other health technologies has led to the introduction of special rules for advanced cancer therapies by many health technology assessment organisations. For example in the UK, the National Institute for Clinical Excellence (NICE) applies a threshold of £30,000 per QALY. However, special guidance applies in circumstances where all of the following criteria apply:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current National Health Service (NHS) treatment
- The treatment is licensed, or otherwise indicated, for small patient populations.
If these conditions are met, appraisal committees may take into account an extra QALY weight for the end-of-life health state. For example, if the ICER for the treatment is £60,000 per QALY, with QALYs being valued in the conventional way, but the appraisal committee agrees that the QALYs experienced by the patients concerned are worth twice the norm, then the appraisal committee is permitted to recommend use of the therapy as it would fall within the £30,000 cost per QALY.

Affordability and Ethical Considerations

Turning then to the question of the affordability of new treatments for advanced cancers, as shown in Figure 8, annual healthcare spending in Australia increased from 7.9% of GDP in 1999-2000 to 9.4% a decade later.\footnote{That represents estimated real average growth in healthcare spending of 5.3% p.a. compared with average annual GDP growth of 3.1%***} That represents estimated real average growth in healthcare spending of 5.3% p.a. compared with average annual GDP growth of 3.1%***

Figure 8: Annual Healthcare Spending in Australia as a Percentage of GDP

*** Compared to other OECD countries healthcare spending in Australia is relatively modest as a percentage of GDP. For example, in 2009 the United States and France spent 17.4% and 11.8% of GDP respectively on healthcare. The OECD median expenditure in that year was 9.6% compared to Australia’s spending of 9.1%
Two questions which arise in this context are how sustainable is the rate of increase; and what percentage of GDP is it reasonable to spend on healthcare compared to housing, education, social security and other essential services? These questions come into sharp focus when we consider the high cost of developing new cancer drugs and the modest survival benefit, often measured in weeks or months, which they offer.

The older chemotherapy treatments, such as the taxanes†††, are relatively blunt instruments, but are effective treatments for many common cancers. Many of the newer therapies, such as monoclonal antibodies, are targeted to specific molecules or signalling pathways, and are much more expensive per patient than the older medicines. In part this is because the patient population for whom they are effective, and over which the drug development cost has to be spread, is often small. The costs of drug development are very high. Adams and Brantner‡‡‡ have estimated that the average cost of bringing a new cancer drug to market, including preclinical and clinical trials, is of the order of US$1 billion. †††

This leads us to the great promise of modern medical science, personalised medicine, and its potential to drive a dramatic increase in healthcare spending. It is known that the risk of developing cancer is influenced by genetic as well as environmental and lifestyle factors. For example, the BRCA1 and BRCA2 gene mutations are known risk factors for breast and ovarian cancer. §§§ The concept behind personalised medicine is to use our knowledge of genetics to predict disease development, to influence decisions about lifestyle choices, and to tailor medical treatment to the individual.

The new science of pharmacogenomics aims to match the best available drug to the patient based on their genetic makeup. The ultimate hope is that it may be possible to tailor a drug to a specific individual and their illness.

††† The first taxane, paclitaxel (Taxol), is an extract from the bark of the Pacific Yew tree Taxus brevifolia. Paclitaxel was discovered in 1967 through a plant screening program at the Cancer Chemotherapy National Service Center in the US. However, its mechanism of action was not understood until 1979.

‡‡‡ Costs for cancer drugs are higher than for other therapeutics because of the length of time required to conduct phase III clinical trials. Pharmaceutical companies will often seek initial approval for cancer drugs in an advanced clinical setting. The eligible patient population is usually small, hence the length of time needed to conduct the phase III clinical trial, but the chances of demonstrating a statistically significant survival benefit are greatest.

§§§ Both mutations, but especially BRCA2, are also known risk factors for prostate cancer.
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But what if we could tailor a drug to a specific individual? How many people could afford to pay US$1 billion, or even a fraction of that amount, for a drug specifically tailored to their condition? Many of the new therapies for advanced cancer are simply not affordable to everyday Australians without reimbursement through PBS or health insurance. How much could you afford to pay to extend the life of a loved one suffering from metastatic colorectal cancer? Is US$161,000 an affordable price to pay to extend their life by a median of 64 weeks? Perhaps you and your family would find US$161,000 in the hope that your loved one was one of the lucky ones for whom the treatment extended their life by much more than 64 weeks? How would you feel if you knew that treatment which you simply could not afford was available, but that PBS and health insurers would not reimburse the cost?

Consumption of healthcare is typically different from consumption of other goods and services because consumers are largely shielded from the costs by the public system and health insurance. Hence there is a moral hazard that consumers will make different choices than they would if they and their families were paying the full cost of treatment. As a taxpayer, how much do you think it is reasonable for the public system or health insurer to pay to extend someone else’s loved one’s life for a median of 64 weeks? Is US$161,000 simply too high a cost for PBS or a health insurer to bear?

Whilst health consumer advocates have argued that cancer therapies for end-of-life settings should be treated differently from other health technologies, others have argued that advanced cancer receives disproportionate funding relative to its societal burden and that this has a detrimental impact on other, more cost effective, public health initiatives.

Take for example a preventative health intervention such as vaccination with Gardasil®, which protects against four strains of the human papillomavirus (HPV) that are sexually transmitted and can cause genital warts or cervical cancer. The vaccine is currently available free for certain groups of girls and young women under the National Immunisation Program. From 2013 the vaccine will also be available free to certain groups of boys.

The price agreed between the manufacturer and PBAC is not publicly available information. However, the course of three injections over a period of seven months costs $450 to obtain through a doctor. How then should we as a society weigh up the relative merits of vaccinating more than 360 girls and boys against HPV and extending a metastatic colorectal cancer patient’s life for a median of 64 weeks?

**** Note that applying discounting to QALYs could be argued to disadvantage preventative health strategies over interventions such as extending an advanced cancer patient’s life because the QALYs gained are many years into the future.
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The application of prospect theory to cancer patients suggests that patients and their families weigh the risks and benefits of treatments differently to health policymakers. Cancer patients, faced with an uncertain prognosis, may appear to be risk seeking in making treatment choices. In other words, the definition of what is affordable to the public health system or insurer depends on whether you are a cancer patient, or a health policymaker or physician.

Healthcare Costs and Australia’s Longevity Tsunami

With the rising Australian population and increasing life expectancy, the Australian Institute of Health and Welfare (AIHW) has estimated that the number of diagnoses of cancer will increase from 112,304 in 2008 to about 150,000 by 2020, an increase of almost 35%. The increase in the number of cases diagnosed is expected to be most evident in older populations.

These estimates are based on preliminary 2007 Census-based estimated resident populations and projected using the cohort-component method which may underestimate future increases in life expectancy. Hence, future incidence of cancer may be higher than estimated.

Advances in medical science have resulted in significant improvements in cancer survival rates and this trend is expected to accelerate in future through developments such as personalised medicine and pharmacogenomics. Many cancers, such as breast and prostate cancer, now have many of the characteristics of chronic disease with a high proportion of survivors expected to live a decade or more after diagnosis.

The costs of primary treatment, such as surgery and radiotherapy, are increasing, as are the costs of managing the effects of cancer as a chronic disease, the costs of therapies for advanced cancers, and the costs of end-of-life care. With the dependency ratio predicted to approximately double from 20% in 2007 to between 38% and 42% in 2057 how will our society afford these accelerating healthcare costs?

AIHW estimated that in 2004-05, the costs of treating cancer were $3.8bn, which represented 5% of Australia’s total current expenditure on health. In 2010-11, total recurrent expenditure on health was $123.7bn. Estimating expenditure on cancer to be a similar proportion, $6.3bn was spent on treating cancer in 2010-11.
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There were an estimated 43,000 deaths from cancer in 2010. In the bowel cancer example above, the cost of extending life by 64 weeks was $161,000 per person. Over all cancer deaths, the potential impact of increasing the cost of end of life treatment by (say) $50,000 to $100,000 would be $2bn to $4bn. Not all cancers would potentially cost this much to treat, and in some cases the period from diagnosis to death would be under a year, but it illustrates the impact that high cost end of life treatments could have on healthcare costs (and this is before considering cost increases at earlier stages of cancer treatment).

It is expected that in future the public system and health insurers will not meet the full cost of treatments for advanced cancers and that patients and their families will be required to bear an increased proportion of costs. Recent changes to the approvals process for new drugs to be listed on PBS suggest that this may already be starting to occur. It should also be noted that many cancer patients face substantial out of pocket expenses.

As noted earlier, the risk of being diagnosed with cancer increases markedly with age. Fifty-six per cent of all cancers diagnosed in Australia in 2008 occurred in people over age 65. Therefore, the projected increase in cancer treatment costs is likely to place a huge additional burden on Australia’s retirement incomes system.

Conclusion

Actuaries have a great deal to contribute to the health policy debate on the costs of treatment for advanced cancers. Methods familiar to actuaries are used by health economists to determine the cost effectiveness of health technologies. In particular, the simplifying assumption of a single discount rate for costs and QALYs has been much debated and may benefit from further thinking.

Actuaries can also contribute to sensitivity analysis of the projected increase in cancer incidence based on the cohort-component method. As previously noted, this may underestimate future increases in life expectancy and hence future incidence of cancer.

Finally, advances in medical technology are driving dramatic increases in cancer survival, but at very high incremental cost effectiveness ratios. Many of the new therapies for advanced cancer have ICERs at or above the (approximate) PBAC threshold of $50,000 per QALY. Actuaries are ideally placed to analyse and comment upon the additional burden this will place on Australia’s retirement incomes system.
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