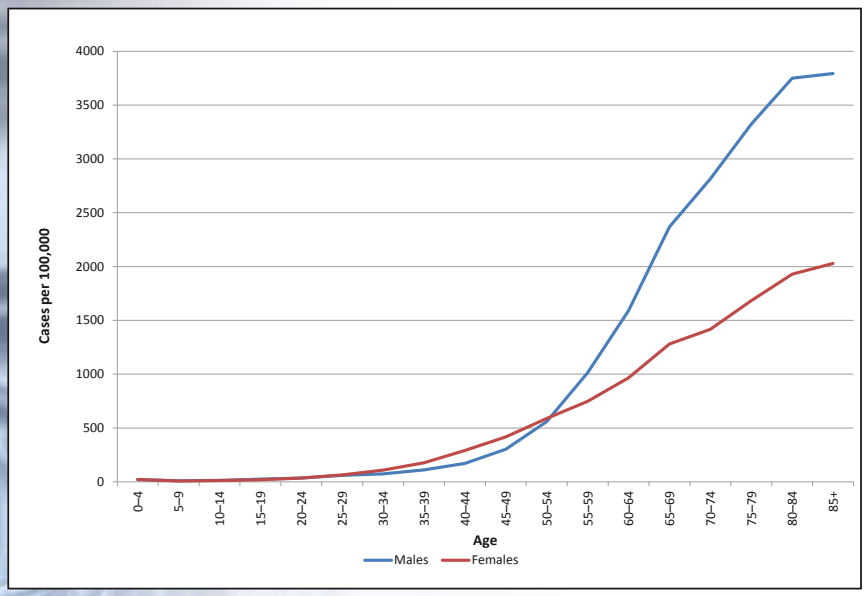
New Therapies for Advanced Cancers

Can our society afford them? Is it ethical to deny patients access to them?

Cancer is a major cause of death, accounting for almost one-third of all deaths in Australia. Although it is not the case for all tumour types, cancer can be regarded as a disease of ageing. As shown in Figure 1, the risk of being diagnosed with cancer increases markedly with age. The latest available figures from the Australian Institute of Health and Welfare (AIHW) show that there are more than six times as many cancer diagnoses in people over age 50 as in people under that age. Depressing news for those of us who are over age 50!

Figure 1: Age-Sex Specific Incidence Rates for All Cancers Combined, Australia 2008



The good news is that 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.

As shown in Figure 2, between 1982-1987 and 2006-2010 the five year relative survival* for all cancers combined increased from 47% to 66%.

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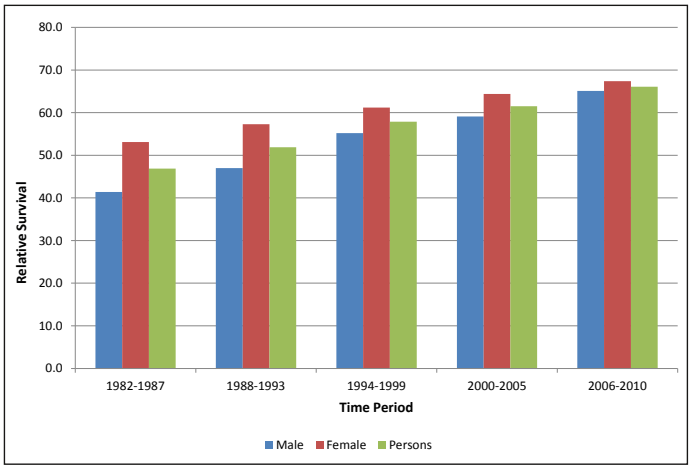
Figure 2: All Cancers Combined Five Year Relative* Survival, Australia 1982-1987 to 2006-2010



** Five-year relative survival rates describe the percentage of patients with a disease that are alive five years after their disease is diagnosed divided by the percentage of the general population of corresponding sex and age that are alive after five years.*

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 America 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 BOWEL CANCER

The treatment of 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 bowel cancer was 5-fluorouracil plus leucovorin (5FU/ LV) at an average cost per patient of some US$4,000. 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 have been developed that show a survival benefit in clinical trials. Wong et al. studied the cost effectiveness of various treatment strategies involving the addition of combinations of new cytotoxins and monoclonal antibodies using a Markov model. The results of the cost effectiveness analysis are shown in Figure 3.

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 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. Health economists make such assessments using a methodology called health technology assessment (HTA), which is based on techniques that will be familiar to actuaries.

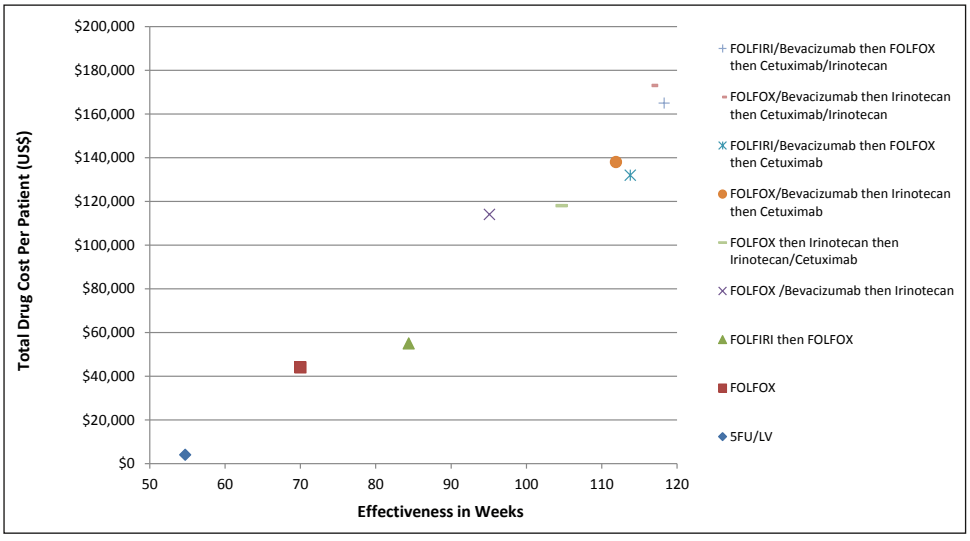
HEALTH TECHNOLOGY ASSESSMENT

HTA is a way of comparing the relative value of health technologies to make decisions about listing and reimbursement. In Australia, HTA is undertaken to list on the Australian Register of Therapeutic Goods and reimbursement under the Pharmaceutical Benefits Scheme (PBS), 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.

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:

Figure 3: Cost Effectiveness* of Treatment Strategies for Bowel Cancer



** Cost per quality adjusted life year gained as a result of treatment.*

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

If the ICER is below a certain threshold (deemed by the assessing agency) it represents a cost-effective treatment.

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:

$$QALY = Length\ of\ Live\ Lived\ in\ Health\ State \times Utility\ for\ Health\ State$$

The utility, or QALY weight, varies between 0 and 1. 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.

Utilities for health states are determined using a number of standard techniques, including time trade off, standard gamble and visual analogue scale.

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.

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.

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 applies a threshold of £30,000 per QALY. However, special guidance applies in circumstances where all of the following criteria apply:

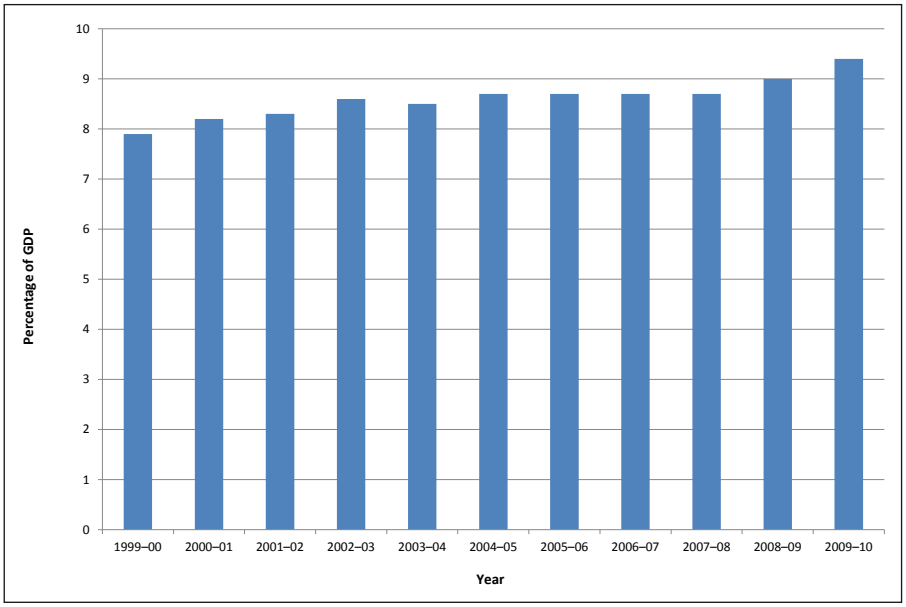
- the treatment is indicated for patients with a short life expectancy, normally less than 24 months;
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current National Health Service treatment; and
- 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

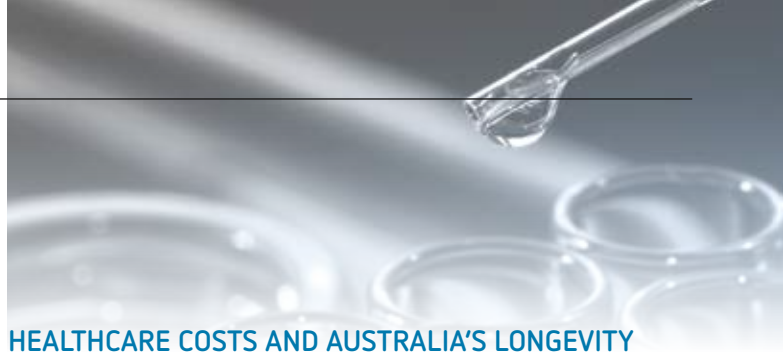
Turning then to the question of the affordability of new treatments for advanced cancers, as shown in Figure 4, annual healthcare spending in Australia increased from 7.9% of GDP in 1999-2000 to 9.4% a decade later. That represents estimated real average growth in healthcare spending of 5.3% p.a. compared with average annual GDP growth of 3.1%.

Figure 4: Annual Healthcare Spending in Australia as a Percentage of GDP



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. It has been 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, ovarian and prostate 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.

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 bowel 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 for free for certain groups of girls and young women under the National Immunisation Program. From 2013 the vaccine will also be available for free to certain groups of boys.

The price agreed between the manufacturer and Pharmaceutical Benefits Advisory Committee 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?

HEALTHCARE COSTS AND AUSTRALIA'S LONGEVITY TSUNAMI

With the rising Australian population and increasing life expectancy, AIHW has estimated that by 2020 the number of diagnoses of cancer will increase by 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. 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?

As noted earlier, the risk of being diagnosed with cancer increases markedly with age. 56% 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) Pharmaceutical Benefits Advisory Committee threshold. Actuaries are ideally placed to analyse and comment upon the additional burden this will place on Australia's retirement incomes system. A

The full version of this paper by Anthony Lowe and Sophie Dyson was presented at the 2013 Actuaries Summit and can be downloaded from http://www.actuaries.asn.au/SUM2013/Program/Media.aspx