

Access to cancer medicines in Australia



Medicines Australia Oncology
Industry Taskforce

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Glossary

AACR	Australasian Association of Cancer Registries
ACIM	Australian Cancer Incidence and Mortality (books)
ACPM	Advisory Committee on Prescription Medicines
AIHW	Australian Institute of Health and Welfare
ATC	Anatomical Therapeutic Chemical Classification System
BEACH	Bettering the evaluation and care of health
CAR HSD	Complex Authority Required Highly Specialised Drugs
COSA	Clinical Oncological Society of Australia
CPT	Constant proportional trade-off
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
DALY	Disability adjusted life years
DoHA	Department of Health and Ageing
DVA	Department of Veterans' Affairs
EAPD	Expanded and Accelerated Price Disclosure
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
GDP	Gross domestic product
GP	General practitioner
GNRH	Gonadotropin releasing hormone
HREC	Human Research Ethics Committee
HSANZ	Haematology Society of Australia & New Zealand
MBS	Medicare Benefits Scheme
MSAC	Medicare Services Advisory Committee
MOGA	Medical Oncology Group of Australia
NICE	National Institute for Health and Care Excellence
NHPA	National Health Priority Areas

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NHDC	National Hospital Cost Data Collection
NHHRC	National Health and Hospitals Reform Commission
PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
PBS	Pharmaceutical Benefits Scheme
PhRMA	Pharmaceutical Research and Manufacturers of America
PHI	Private Health Insurance
PHIAC	Private Health Insurance Administrative Council
PLAC	Prostheses List Advisory Committee
QALY	Quality adjusted life years
QOL	Quality of life
RCT	Randomised controlled trials
TGA	Therapeutic Goods Administration
TKI	Tyrosine Kinase Inhibitor
TTO	Time trade-off
UK	United Kingdom
US	United States
YLD	Years lived with disability
YLL	Years of life lost

Executive summary

Cancer is an area of high clinical need in Australia and was first recognised as a National Health Priority Area by the Australian Government in 1996 (AIHW 2013). Past investment in cancer care has resulted in Australia being a world leader in cancer control (Coleman et al 2012). However, cancer will continue to be a major health priority, as cancer incidence is projected to grow significantly over the next twenty years in Australia (AIHW 2012a). As such, balancing the need to provide access to cancer treatment now, and concurrently creating a sustainable system that will support the healthcare needs of cancer patients in the future, remains an important policy focus.

Recently, patients living with cancer, medical professionals caring for patients living with cancer, and the medicines industry have expressed concerns about the increasing challenges in gaining timely, affordable and equitable patient access to new cancer medicines under current regulatory and reimbursement arrangements in Australia (e.g. Kefford 2012; Tillett 2013; Prostate Cancer Foundation of Australia 2013). This report assesses the disease patterns and economics of cancer in Australia and internationally, and canvasses the opinions of various stakeholders on issues pertaining to patient access to cancer medicines. The purpose of this report is to provide a common platform for open and meaningful dialogue among stakeholders, with a view to finding solutions that are mutually agreeable, beneficial to patients and sustainable. It is envisioned that these solutions will ensure Australia continues to remain a world leader in cancer care.

Australia has the highest age-standardised incidence of cancer in the world, resulting in significant disease and economic burden.

On average, one in every two Australians will develop cancer in their lifetime and one in five Australians will die from cancer before the age of 85 years (AIHW 2012b). Cancer accounts for three in every ten deaths in Australia, making cancer one of the leading causes of death (AIHW & AACR 2012). Due to population growth and ageing, the AIHW estimates that cancer cases will increase by almost 40% from 2007, reaching about 150,000 in 2020 in Australia (AIHW 2012a).

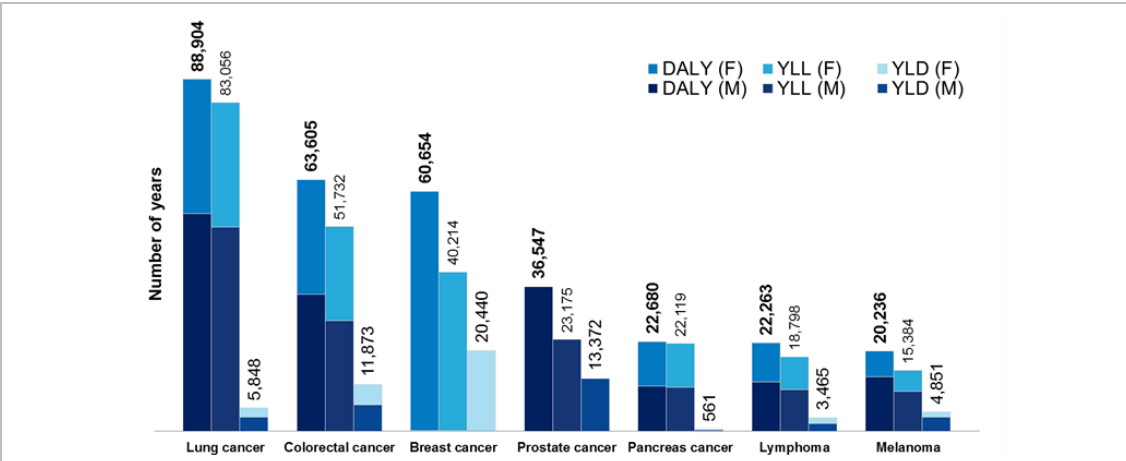
Australia has the highest age-standardised incidence of cancer in the world (Ferlay et al 2010, cited in AIHW & AACR 2012). In particular, Australia has the world's highest incidence of melanoma and prostate cancer, and the third highest rate of breast cancer (AIHW & AACR 2012). Moreover, although poorly recognised, the incidence of rare cancers collectively presents considerable public health challenges. In Europe, five-year relative survival is worse for rare cancers (47%) than common cancers (65%) (Gatta et al 2011)¹. This in part reflects the much lower level of research interest in, and treatment options for, rare cancers.

Cancer accounted for about one-fifth of the total burden of disease (BoD) in Australia in 2003 (Begg et al 2007). Disease burden can be measured using disability adjusted life years (DALYs) – a composite measure of the number of years lost to premature deaths (YLL) and the number of years lived with disability (YLD), compared to living in full health to the

¹ Equivalent statistics for Australia were not available.

average life expectancy of 82.5 years. Most of the DALYs attributable to cancers were related to YLLs rather than YLDs (Chart i): for every 100 cancer related DALYs, 82.5 years were due to premature deaths and 17.5 years were due to cancer related morbidity (Begg et al 2007).

Chart i: Number of disability adjusted life years (DALYs), years of life lost (YLLs) and years lived with disability (YLDs) of cancers with the highest disease burden in 2003

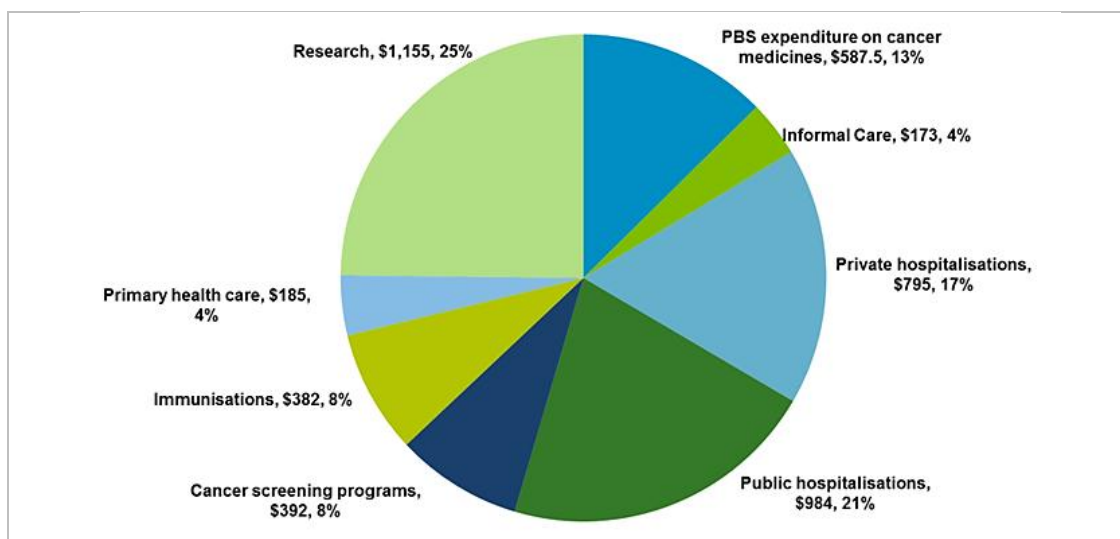


Source: Begg et al (2007)

According to the AIHW’s Cancer in Australia report, about 10% (880,432) of all admissions to Australian hospitals in 2010-11 were related to the management of cancer (AIHW & AACR 2012). The majority of cancer related hospitalisations (75%) were same-day admissions, most likely for chemotherapy administration. Notably, for those patients who stayed overnight, the average length of stay (ALOS) was 7.6 days, compared to a lower ALOS of 5.8 days for all hospitalisations (AIHW & AACR 2012). Innovative technology that may reduce or delay the need for hospital based care (e.g. self-administered treatments) could provide broader benefits to society. These benefits need to be assessed and understood.

This report estimates the total expenditures on cancer in 2012 to be \$4.7 billion. PBS expenditure on cancer medicines constituted 13% of the total expenditure in 2012 (Chart ii). However, total expenditure is a significant underestimate of the real cost of cancer, as the estimation approach is conservative (e.g. it does not fully account for the extent of informal care), and the calculation does not include indirect costs, such as travel and lost productivity due to illness.

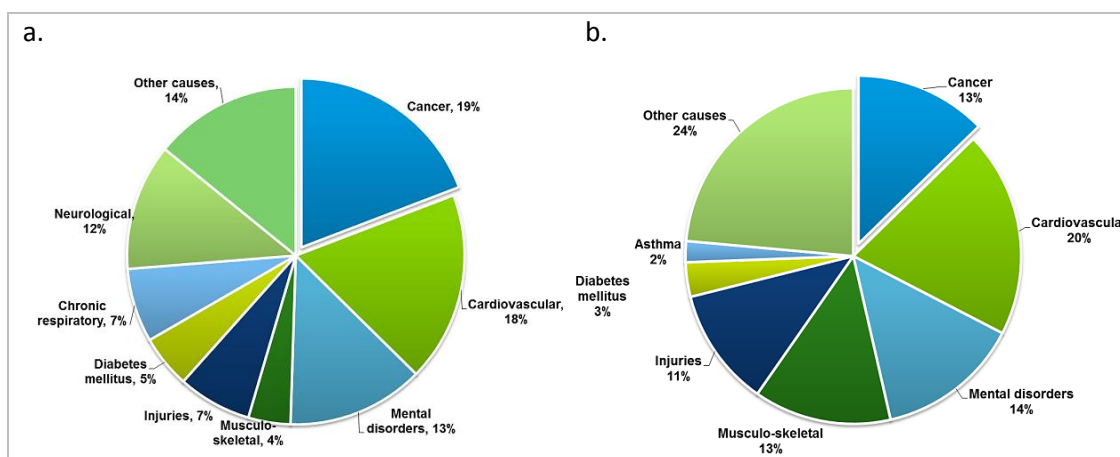
Chart ii: Total expenditures on cancer by sector (\$ Million)



Source: Deloitte Access Economics

There appears to be a misalignment between BoD and healthcare expenditure. For example, in 2003, cancer received 13% of the total health expenditure, but was responsible for nearly one-fifth (19%) of premature death and disability in Australia (Chart iii). In comparison, musculoskeletal diseases also accounted for 13% of health expenditure, but only 4% of the burden of disease. More recent data on BoD and expenditure across all disease areas are not available for comparison. There is a need for further study in this area.

Chart iii: (a) Burden of disease by disease group in 2003; (b) Allocated health expenditure in 2004-05 by disease group



Source: Begg et al (2007) and AIHW (2010)

The process of discovery and development of medicines is complex, time-consuming, and typically high-risk, particularly for cancer medicines.

The development of a new medicine following discovery typically requires a time period of 10 to 15 years. This period is for the collection of scientific evidence to support the quality,

safety and efficacy of the drug, and increasingly, cost effectiveness information to support the reimbursement decision.

It is well recognised that the drug development process has a low rate of success. The probability of a successful drug candidate going through all phases of drug development has been estimated at 1 in every 5,000 molecules, with the successful odds improving to 3 in 5 when a drug candidate enters the Phase III clinical trial program (PhRMA 2008). There has been a paradigm shift towards adopting the principles of rational drug design in drug discovery, with a view to streamlining the number of promising molecules screened at pre-clinical phase, and thus reducing the costs (Mandal et al 2009, Guido et al 2011). There have also been other efforts to achieve greater efficiency in the drug discovery and development processes. These include identifying the causes of trial failure and success factors (e.g. Kola and Landis 2004); using statistical techniques to improve trial design and analysis (e.g. Rawlins and Chalkidou 2011); using adaptive trial design to optimise the assessment of combination therapies (e.g. O’Carragher et al 2012); and reducing the costs of managing clinical trials (e.g. Eisenstein et al 2008). However, overall rates of success remain low and development costs are high.

Some stakeholders noted that new cancer medicines are costly to develop, because cancer is not one disease but made up of many different diseases. The intended patient groups for new cancer medicines are typically smaller because of better differentiation of disease subtypes and the targeted nature of these medicines (discussed further below). Generally, the duration of treatment is much shorter than other types of medicines because in many cases these medicines are used in end-of-life settings. In addition, unlike in more conventional therapeutic areas such as cardiovascular disease, many of these targeted cancer medicines require companion diagnostic tests to identify the patients most likely to benefit, and there are additional costs associated with the development of these co-dependent medicines.

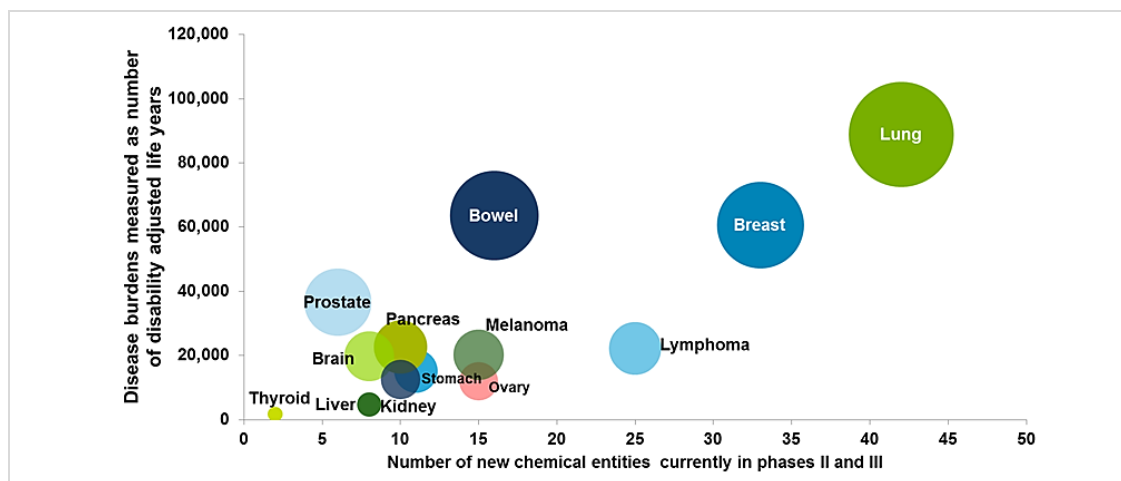
Despite the challenges in medicines discovery and development, advancement in molecular biology has improved the treatment landscape for cancers.

Cytotoxic chemotherapy has been the mainstay of pharmacological treatment for cancer. These medicines do not have a mechanism to distinguish between cancerous or non-cancerous cells, which frequently cause a range of side effects. Recent advances in molecular biology have led to the development of a large number of molecular targets for novel anticancer medicines. These biological and targeted cancer therapies may specifically interfere with cell growth signalling, the regulation of blood vessel development, programmed cell deaths, or may stimulate the immune system to destroy specific cancer cells, or deliver toxic drugs to cancer cells. Through specific molecular mechanisms, these targeted therapies are able to block the growth and spread of cancer, with lesser interference to non-cancerous cells. The advent of these biological and targeted therapies – known as personalised medicine – has greatly expanded cancer treatment options and improved outcomes for patients.

A review of the clinical pipeline shows that there appears to be a focus in aligning R&D efforts to alleviate cancers with the higher disease burden (Chart iv). The pipeline includes medicines for cancers which currently have low 5-year survival rates e.g. cancers of the pancreas, lung and liver. Importantly, the horizon scan identified an emerging trend in developing combination therapy to target cancer biomarkers in the single or multiple

pathways leading to the occurrence of cancer (i.e. oncogenesis). This trend signals a movement towards using targeted therapies in combination, similar to the current ‘cocktail’ approach of combining cytotoxic chemotherapies (see Li et al 2013). This reflects the difficulty of treating cancer using single agents due to the complexity of genetic and bio-molecular pathways of oncogenesis.

Chart iv: Correlation between number of cancer medicines currently in phases II and III clinical trials indicated for the type of cancers and the burden of cancers



Source: Deloitte Access Economics

An analysis by the Pharmaceutical Research and Manufacturers of America (PhRMA) found that 981 cancer medicines and vaccines are currently in all phases of clinical development (i.e. from Phase 0 to Phase 3). Many of these innovations employ the most advanced technology to improve the effectiveness or delivery of cancer medicines (PhRMA 2012). Clinical trials in oncology represent around one-fifth of all interventional trials identified in a recent review (Hirsch et al 2013).

The regulatory and reimbursement system need to anticipate any challenges these technologies would have on the current assessment framework, and be responsive and adaptive in its requirements so as to facilitate access to these medicines.

However, there is a range of issues affecting timely and affordable access to cancer medicines in Australia, particularly for new cancer medicines.

Issues arising from regulatory and reimbursement processes

In Australia, there are time-consuming and complex approval processes prior to a patient gaining subsidised access to a medicine. A medicine must demonstrate that it meets five critical requirements for patients to gain PBS reimbursed access: quality, safety and efficacy (each of which are assessed by the TGA²); clinical and cost effectiveness (as assessed by the PBAC² and the PBPA²); and financial feasibility/acceptability (as assessed by the Minister for Health and the Cabinet). The time period between submission to the TGA for regulatory

² **TGA:** Therapeutic Goods Administration; **PBAC:** Pharmaceutical Benefits Advisory Committee; **PBPA:** Pharmaceutical Benefits Pricing Authority; **MBS:** Medicare Benefits Schedule; **MSAC:** Medical Services Advisory Committee; **PASC:** Protocol Advisory Sub-Committee; **ESC:** Evaluation Sub-Committee of MSAC.

approval and the PBS listing of the medicine is at least 14 months, but some medicines may take several submissions to the PBAC to achieve a successful listing. Recently, for some medicines that have received positive recommendations from the PBAC, there have been a number of deviations from normal processes, including those due to the Government's fiscal considerations, or unsuccessful negotiations between the sponsor and Government in reaching a mutually agreeable price. Either way, these have significantly hindered access to new cancer medicines in the last few years. In developing this report, many stakeholders cited the protracted decision making processes leading to the approvals/rejections of listing cetuximab, vemurafenib and abiraterone as evidence of system inefficiency.

In the event that a medicine achieves approval from the TGA, but fails to gain PBS reimbursement, the medicine may be made available to the public. However, the financial burden is considerable, either to the patient themselves who must pay the full cost of the medicine – a factor that significantly hinders affordable access, or to the sponsors offering compassionate access programs or cost-sharing arrangements to enable patients to gain subsidised access. In 2011-2012, a sample of nine companies provided 4,748 patients with compassionate access (see Table 4.2, p.43). More than half of these supplies (67.9%) were to cover the access gap between TGA registration and PBS reimbursement. Notably, the access was mostly provided free of charge (85.2%). However, these arrangements do not provide sustainable or equitable access because their intent is to provide short-term access while the medicines are in the process of obtaining reimbursement approval. One major cancer treatment centre has estimated that through these programs, the centre provides approximately \$10 million worth of oncology medicines per year that were not TGA-approved or PBS-reimbursed, or both [unpublished data provided by industry stakeholders]. This stakeholder also commented that having to administer such programs to facilitate access to cancer medicines increased the administrative burden for participating hospital pharmacies.

The advent of personalised medicine in cancer also adds an additional layer of complexity to the approval processes. The increasing use of biomarkers in oncology to assess and predict treatment response is a positive step in improving patient health outcomes. However the requirements to fulfil both the PBAC and MSAC processes adds complexity and evaluation time.

The process of evaluating diagnostic tests for reimbursement under the MBS² (as assessed by PASC², ESC², MSAC²) alone takes at least 51 weeks before a listing. On the other hand, the PBAC approval for reimbursement is contingent upon the technology having first been made available via the MBS. While there is an ongoing effort to improve the coordination of processes through the development of a co-dependent technology assessment process, the requirements to fulfil both the PBAC and MSAC processes adds significant burden to what is already a time-consuming and administratively intensive process. Furthermore, coordination between the PBAC and MSAC processes may also impede timely listing of cancer medicines. This is particularly pertinent because the meeting dates of the various committees involved (PASC, ESC, MSAC and PBAC) are fixed. Delay in meeting one milestone date may delay the PBS listing of a medicine by at least four months, because both MSAC and PBAC only meet every four months. While many stakeholders are pleased that some processes have been initiated to improve coordination, they are concerned about the efficiency of the current processes and believe there is scope for considerable improvement.

Several stakeholders also raised concerns about the transparency of the current decision making process for regulatory and reimbursement approval. Many were puzzled by the discrepancies in decisions made by the Australian authorities compared to authorities in other comparable jurisdictions that have equally rigorous assessment processes. One stakeholder felt that the processes are intentionally long to delay listing decisions, reflecting an underlying conservatism in adopting new technology, or an effort to ‘contain’ costs. A number of stakeholders also raised concerns that the current reimbursement process appears to have an increasing overlay of non-transparent political processes.

There were also concerns about a lack of process differentiation for cancer medicine. Unlike regulatory agencies in other comparable countries, cancer medicines, which are to treat serious conditions and often to fill an unmet medical need, do not result in expedited registration or reimbursement timelines. Furthermore, several stakeholders felt that the decision making process appears to have been driven by advocacy: popular cancers received stronger focus, whereas rarer cancers often received much less attention.

There is evidence that the success rate in achieving reimbursement is low, and the timeframe to gain listing on the PBS is lengthening – this is of particular concern for cancer patients, who may only have a short time to live.

Issues arising from evidentiary requirements to support access

Clinical trial design for cancer medicines is providing real challenges to the reimbursement process particularly in the areas of quality of life and surrogate outcomes.

In oncology, overall survival (OS) is often considered to be the most clinically relevant and meaningful end-point, especially for medicines for the treatment of late stage cancer. This is because OS is relatively easy to measure, record, define, and is free of bias. However, it is well recognised that OS as an endpoint is not without limitations and challenges. Most notably, measuring OS substantially prolongs the duration of a trial, increases the number of patients needed to be recruited, and amplifies the cost of completing the trial. The longer timeframe also subjects the trial to a much higher range of factors which may affect confidence in interpreting findings. These factors include the diverse range of disease characteristics as the disease worsens (i.e. progression), and differences in post-progression management (Kelly and Halabi 2010; Kummar et al 2006; Sargent et al 2008). Furthermore, based on ethical considerations, trial committees may terminate a trial when a surrogate end-point such as Progression-Free Survival (PFS) has demonstrated substantial benefits, thereby precluding further collection of OS data.

The ability to demonstrate differences in OS is also challenging for cancer medicines when ‘cross-over’ is allowed. To improve patient recruitment and to mitigate patient concern about not receiving the experimental medicine (perceived by patients as superior), investigators and sponsors have increasingly adopted a design for clinical studies that enables patients who are initially randomised (i.e. assigned by chance) to receive the standard treatment, to later receive the experimental treatment following progression of their disease. This is known as a cross-over trial. This design masks (i.e. ‘confounds’) the ability to measure the OS from the experimental medicine because patients on both treatment arms receive the experimental medicine. Furthermore, there is evidence that oncology trials are more likely to have variations in trial design compared to clinical trials in other disease areas, reflecting the complexity of clinical trials in oncology (Hirsch et al

2013). As such, the preferred evidence from parallel (c.f. cross-over) randomised controlled trials (RCT) may not always be realistic for cancer medicines.

Ethical challenges may also arise when undertaking clinical trials for cancer medicines because Phase III clinical trials are usually conducted following evidence from early studies that have indicated the benefits of the experimental treatment. These benefits include improved quality of life, slower disease progression and sometimes gain in OS. Denying patient access to these experimental treatments that have potential benefits, as indicated from earlier trials, may be ethically challenging³.

For all the above reasons, the preference for evidence based on OS measures or parallel RCTs to support reimbursement decisions may not always be practical. Although surrogate endpoints such as PFS may not always correlate with OS, in certain circumstances, surrogate endpoints may be accepted as the basis of reimbursement decision. One example where a surrogate endpoint is appropriate is when improved PFS has been shown to correlate with improved OS (e.g. in ovarian cancer as demonstrated by Parmar et al 2003; and in non-small-cell lung cancer as demonstrated by Michiels et al 2011). Johnson and colleagues (2006) also demonstrated that PFS may be used in predicting OS in metastatic colorectal cancer and non-small-cell lung cancer, if the anticipated difference in PFS is large enough to exceed estimated surrogate threshold. Finally, regulatory authorities in many jurisdictions, including the TGA in Australia, have granted approvals for cancer medicines on the basis of surrogate endpoints and early clinical trial data. Improving the harmonisation of evidentiary requirements between regulatory and reimbursement agencies may be an important step to facilitate access. On this point, some stakeholders further noted that most companies operate at a global level, and it may not be always possible to meet the unique requirements set down by the Australian authorities: Australia cannot expect to have clinical trials designed to meet the unique requirements of the local environment.

Because of the experimental challenges and the complexity of cancers and cancer medicines outlined above, the evidence base for cancer medicines may have some level of uncertainty. Stakeholders noted that the current system has a low level of acceptance for uncertainty, and has not implemented any processes or practical solutions to address this. This means that the current system is not sufficiently sensitive to assess the complexity of many cancer treatments, particularly for medicines intended to treat small patient populations (i.e. rare cancers).

Notwithstanding the fact that life-extending benefits may exist (but be obscured by current clinical trial designs), measuring the “value” of a clinical benefit is difficult in oncology because other seemingly small benefits may be of great significance to patients, and in a clinical context, especially for advanced cancer. However, the small numerical benefit means that the cost effectiveness calculation may not find it ‘value for money’ from a population perspective. This is particularly the case when the current measurement technique is insensitive to detect improvement in quality of life outcomes in cancer patients (see section 5.2.3). Furthermore, to better reflect perceived societal preferences for funding end-of-life medicines, the assessment of the value of cancer medicines in other international jurisdictions (e.g. the UK) has allowed for downward adjustments (‘weighting’) to the cost-effectiveness ratio (e.g. NICE 2009). However, there is ongoing debate about

³ Albeit the requirement to demonstrate the principle of clinical equipoise as a prerequisite for ethic approval.

the impact and appropriateness of such adjustments (e.g. Chalkidou 2012; Collins and Latimer 2013).

On this note, some stakeholders commented that it is difficult to demonstrate cost-effectiveness of new cancer medicines under the current system in Australia. This is because the price of new cancer medicines is referenced to the price of older cytotoxic chemotherapy, which is typically much lower due to market competition over time; or due to the consequences of PBS reform in reducing the price of medicines that have come off patent (please refer to further discussion on PBS reform next page).

Issues relating to coverage of indications on the PBS

An estimated 80% of all prescription medicines dispensed in Australia received subsidy via the PBS. Patient access to most medicines is significantly reduced if they are not reimbursed under the PBS.

In contrast to the comprehensive Cancer Drugs Fund in the UK (for example), Australia has only one specific-purpose fund for cancer treatment: the Herceptin program for late-stage metastatic breast cancer.

Stakeholders believed that the PBS has inadequate coverage of indications that have a sound evidence base, but are outside of TGA-approved indications. This is because PBS reimbursement requires the medicines having first obtained TGA approval for particular indications, but the list of indications is not always updated in a timely manner in line with the evidence development since the initial approval. A recent study by Mellor et al (2012) found that 29.5% (132) of the 448 protocols of anti-cancer therapy approved for use in a major cancer treatment centre were beyond the TGA's approved use (i.e. 'off-label' use) despite being established evidence-based treatment guidelines. A further 39 protocols were based on findings of Phase II and III clinical trial data.

Several stakeholders identified the reasons why TGA approved indications are not updated in a timely manner when new evidence emerges. First, there are potential time delays due to the complexity of the TGA approval process, and only drug sponsors are permitted to lodge an application for a new indication. Second, there may be a lack of commercial incentives for the sponsor to lodge the application to seek further approval, as off-label prescribing is clinically acceptable insofar as the use is supported by evidence. In some cases, new evidence can be developed by research institutions without the involvement of the original sponsor; this data ownership issue may preclude the sponsor from making an application to broaden the indications. Examples noted by stakeholders include paclitaxel, docetaxel and irinotecan. One stakeholder also noted that the inconsistency between current diagnostic guidelines and the diagnostic criteria specified in the PBS has created a barrier to patient access to evidence-based treatment (see Section 6.2.1 on p.72).

Stakeholders also noted that different coverage of on-label and off-label indications in hospital and PBS formularies may also affect the continuity and affordability of treatment. One clinical stakeholder noted that hospital clinicians sometimes do not choose medicines if they are not PBS listed, even if they are the most appropriate treatment options for a particular patient. This decision is made to avoid the patient having significant out-of-pocket expenses following hospital discharge.

Issues relating to inadequate remuneration for the supply of chemotherapies

Following PBS reform in 2010, the prices of some cytotoxic chemotherapies have decreased substantially. For example, irinotecan has decreased in price by 74.3%, docetaxel by 76.2%, paclitaxel by 86.9% and epirubicin by 89.3% (PBS 2013). While meeting the intended purpose of the reform, such significant reductions in price have resulted in a decrease in remuneration for service providers. Since these 'extra' remunerations have previously been used to cross-subsidise inadequate remunerations for the provision of chemotherapy services in general, the reform may reduce the capacity of some providers to supply certain medicines, particularly for patients in regional areas. Furthermore, two stakeholders were concerned that, in the long run, prices of these cancer medicines would decrease to the extent that sponsors would have insufficient commercial incentives to ensure consistent supply. Indeed, one clinical stakeholder highlighted the dilemma of having to use more expensive alternatives because of supply shortages, and the withdrawal of older medicines. Stakeholders believed that the system should be structured to guarantee the supply of generic cancer medicines.

In contrast, some stakeholders welcomed the initiative because they considered the extra profits made by pharmacists as unjustified, and thought these resources should be used to fund the listing of new cancer medicines. This is especially relevant given that generic medicines in Australia are more costly than in other countries. Industry stakeholders also recognise that these reforms have delivered savings as intended, but are concerned that the savings have not been put back into the PBS via the funding of new medicines.

Issues relating to the value of cancer medicines

A number of stakeholders noted that cancer medicines are expensive, especially for new targeted therapies. Many of these stakeholders qualified their views by stating that they recognised the important role the medicines industry plays in facilitating patient access to medicines. They also recognised the monumental challenges and risks along the discovery and development pathways in bringing one successful medicine to the market. For these reasons, they emphasised the need to maintain a viable medicines industry by providing sufficient commercial incentives, so that the industry can continue to produce new medicines to benefit cancer patients. However, they felt that the prices of some cancer medicines are not justified, and that the medicines industry often has an unrealistic price expectation. Many stakeholders urged sponsors to provide greater transparency regarding how drug prices are set in Australia and globally.

On this note, industry stakeholders noted that almost all companies operating in Australia are affiliates of global companies, and the Australian subsidiaries have limited influence over the development of new cancer medicines, both in terms of trial design and price setting, particularly for those intended to treat a small group of patients. Stakeholders also noted that pricing of medicines should be considered in light of the value the Australian community places on the benefits of these medicines. Various stakeholders noted that the Australian community has limited inputs into the current decision making processes of Government, and there is little provision within the decision-making framework for considering the value these new medicines provide to the broader community. Specifically, there has not been a meaningful debate in Australia about what the community considers to be acceptable levels of funding for caring for palliative patients, including those with advanced cancers. Furthermore, some stakeholders noted that the current system

provides the PBAC with unlimited flexibility in decision making (e.g. by not specifying a threshold to indicate cost-effectiveness). To them, the decision-making framework and principles should be determined by the Australian community, not solely by the PBAC members. As such, engaging with the Australian society, with a view to developing a clear set of decision-making principles that is reflective of the tax-payers' preferences for funding care, would be an important next step forward.

If these issues are not addressed, many stakeholders felt that Australia will fall behind other countries in cancer outcomes in the future.

Without changes to the current system, the challenges facing patient access to cancer medicines will worsen, especially with the abundance of cancer medicines progressing through the clinical development pipeline. A concern is that there are a growing number of Australian oncology patients unable to access cancer medicines compared with their overseas counterparts. Between now and 2015, the industry estimates that almost 50 submissions will come before the PBAC, and a significant proportion of these will involve co-dependent technologies. To some stakeholders, the complexity and lack of responsiveness of the current system have already resulted in Australia falling behind in the adoption of medical technologies that have been well established in other countries.

Some stakeholders also felt that the current environment will disengage the medicines industry from Australia, and some think that the industry may divert their investment to other countries. Industry stakeholders believed that the increasing use of special pricing arrangements is a reflection that the current reimbursement system is not delivering a fair return on innovation. Some stakeholders noted that delays in securing reimbursement has a 'knock-on' effect on clinical trials, as companies may reconsider placing clinical trials and access programs in Australia if there is little or no chance of reimbursement. If this occurred, several stakeholders felt that this would represent a considerable loss to Australia, from both scientific and economic perspectives. Furthermore, confidence in the ability of the Government to manage access to cancer medicines would be eroded. Ultimately, any delays in access have serious impacts for patients, especially for patients nearing the end of life.

Many stakeholders suggest a need to adapt and evolve the registration and reimbursement processes alongside development in technologies for the future.

Some stakeholders noted that the Australian reimbursement system, first implemented 20 years ago for determining the value for money of medicines, has not adapted sufficiently to the changes in the development of medicines and diagnostic technologies, particularly in regard to targeted cancer medicines. Many components of the current process are not fit for purpose to meet the emerging issues associated with cancer medicines.

They noted that while the overarching principles of the system are sound, the system has not kept pace in interpreting and implementing these principles in line with the changing environment. For example, they believed the system needs to use the best methodological practice, and align with the practices and approaches of authorities in other jurisdictions that have implemented a decision making framework based on health technology assessment e.g. evidence requirements, consideration of benefits beyond the healthcare sector and indirect costs.

Many stakeholders felt that access to cancer medicines in Australia is often suboptimal and unsustainable.

Various solutions were suggested as possible ways to address some of the access barriers. Suggestions included:

- Linking the price of a medicine or a test to the health outcomes achieved in actual clinical practice, based on data collected one to two years after listing;
- a review and delisting process to streamline the current formulary, where medicines identified as having little effectiveness could be removed;
- a system whereby individuals are able to contribute towards a health savings account to fund their potential future need for medicines, similar to the Medisave model in Singapore;
- a single set of “federated” requirements to obtain ethics approval for undertaking clinical trials;
- greater level of consumer participation in the decision making process, including extending the current two-week window for consumers to provide comments on upcoming PBAC considerations;
- having a regular audit process to identify medicines utilisation outside of PBS approved indications.

Conclusion

While Australia has performed well in providing affordable and equitable patient access to cancer medicines in the past, the system faces significant challenges from the growing burden of cancer, the emergence of many new cancer treatments and the expectation that that these new advances should be made available to Australian patients in a timely manner.

This report has highlighted many issues and opportunities for all stakeholders to engage in an open dialogue, with the aim being to find mutually agreeable and lasting solutions. To achieve this, all stakeholders must participate in an informed debate, particularly about how Australian society should value the merits of oncology innovations, and how to best facilitate equitable patient access through fair and transparent resource allocation processes.

1 Background

Cancer is a major public health issue in Australia.

There needs to be an ongoing and increased commitment to the prevention and treatment of cancer, including enabling the timely and affordable delivery of innovative cancer medicines. This report considers the issues around access to cancer medicines from the viewpoint of different stakeholders.

Cancer is a major public health issue in Australia. Since 1996, the Australian Government has identified cancer as one of the National Health Priority Areas (NHPA), in recognition of the high social and financial costs it imposes on Australian society. The NHPA initiative recognises that “the strategies for reducing the burden of illness should be pluralistic, encompassing the continuum of care from prevention through to treatment, management and maintenance, and based on appropriate research and data sources” (AIHW 2013). Accordingly, the Australian Government has provided considerable investment in cancer care across the continuum of care. Areas of investment include interventions to prevent cancer risk factors (e.g. tobacco smoking, vaccination against human papilloma virus) to the provision of treatment for individuals with cancer (e.g. cancer medicines, radiotherapy, surgery).

This investment has resulted in Australia becoming a world leader in cancer care. An indication of the effectiveness of the Australian cancer care investment is demonstrated by the significant decrease in the age-standardised mortality rate for all cancers combined, and an increase in 5-year survival rates in the last two decades. A recent study found that Australia ranked highly against other developed countries in patient survival at up to five years following diagnosis of colorectal, lung, breast and ovarian cancers (Coleman et al 2012).

While the effectiveness of Australian efforts in cancer care is encouraging, cancer will remain a major public health issue in Australia now and in years to come. As will be discussed in this report, Australia has the highest age-standardised incidence of cancer in the world (AIHW 2012a). Furthermore, the Australian Institute of Health and Welfare (AIHW) predicts that the number of new cancer cases will increase by almost 40% from 2007, reaching about 150,000 new cases in 2020 (AIHW 2012b). Therefore, ongoing and increased commitment to prevention and treatment, including enabling the timely and affordable delivery of innovative cancer medicines, is strategically important to mitigate the current and future social and economic impacts of cancer.

With regard to medicines, Australia is widely regarded as having a world-class national pharmaceutical reimbursement scheme. The Pharmaceutical Benefits Scheme (PBS) is the primary vehicle for the delivery of subsidised medicines, with a view to ensuring affordable and equitable patient access to medicines. The PBS subsidises a range of cancer medicines for cancer management in private medical facilities, and outpatients or day-admitted patients in public institutions. The PBS also provides a range of other anti-cancer medicines for patients in the community.

Recently, cancer patients, medical professionals caring for cancer patients, and the medicines industry have expressed concerns about the increasing challenges in gaining timely, affordable and equitable patient access to new cancer medicines via the PBS (e.g. Kefford 2012; Tillett 2013; Prostate Cancer Foundation of Australia 2013). These stakeholders have voiced various concerns, including differences in value perception of cancer medicines among stakeholders, stringent evidentiary requirements for reimbursement, and delays due to Federal Government fiscal measures. There is a clear demand for an informed public debate about accessing new medicines generally, and new cancer medicines in particular.

In response, several member companies of Medicines Australia formed the Oncology Industry Taskforce in late 2012. The companies involved are: AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Sanofi Aventis and Takeda. This Taskforce is endorsed by Medicines Australia. Specifically, these companies decided to form the Taskforce against the background of an increasingly difficult reimbursement environment in Australia in relation to cancer medicines:

- 82% of cancer medicines seeking reimbursement on cost-effectiveness grounds were rejected in 2011;
- Up to 50 submissions relating to cancer medicines to the Pharmaceutical Benefits Advisory Committee (PBAC) are expected between now and the end of 2015; and
- There are increasing signs that the Government is looking to further contain spending for medicines.

The Taskforce is keen to work in collaboration with key stakeholders including government, health care professionals and societies, Cancer Australia, and consumer health organisations to improve access to cancer medicines for the benefit of patients.

1.1 Purpose of this report

Deloitte Access Economics has been appointed by the Taskforce to develop a discussion paper on issues pertaining to access to cancer medicines in Australia, and canvass stakeholder perspectives on these issues. This discussion paper is the first project seeking to clarify and communicate the barriers to access to cancer medicines in Australia, and to provide an opportunity for a broad range of stakeholders to participate.

The Taskforce envisages that this discussion paper will provide a common platform for open and meaningful dialogue among stakeholders, with a view to finding solutions that are mutually agreeable, beneficial to patients and sustainable. It is envisioned that these solutions will ensure Australia remains a world leader in cancer care into the future.

1.2 Methods

1.2.1 Targeted literature review and data analysis

A targeted review of literature and databases was undertaken to identify the most relevant information for this report. Specifically, the following websites and databases were explored and data/information was extracted if relevant:

- Australia Institute of Health and Welfare (AIHW) for epidemiological and expenditure data;
- Medicare Australia statistics on PBS and Medicare Benefits Scheme (MBS) expenditure;
- PBS website for pricing information and Pharmaceutical Benefits Advisory Committee (PBAC) recommendations;
- The Australian Public Assessment Reports for prescription medicines by the Therapeutic Goods Administration (TGA);
- The GLOBOCAN 2008 database by the World Health Organisation's International Agency for Research on Cancer;
- US National Library of Medicine's PubMed database;
- Australian Bureau of Statistics; and
- Company websites and company internal data provided by participating sponsors.

The Taskforce identified nine countries for inclusion in a cross-country comparison of cancer prevalence: Australia, Canada, France, Germany, Japan, the Netherlands, Sweden, the United Kingdom (UK), and the United States of America (US). These countries were selected on the basis of the following criteria to capture a contextually representative sample:

- A country that uses health technology assessment to decide if an oncology medicine will be reimbursed, with or without explicitly considering the incremental cost effectiveness ratio;
- Purchase power parity adjusted gross domestic product (GDP) per capita is similar to Australia;
- Comparable treatment outcomes and survival rates to Australia; and
- High level of Influence on the global market (e.g. the US).

Table 1.1 (p.4) provides a high level summary of the health care systems for the selected countries and the overall expenditure on health care and pharmaceuticals. For the selected health care systems in Table 1.1, Chart 1.1 depicts the burden of malignant neoplasm measured in Disability Adjusted Life Years (DALYs) as a proportion of DALYs from all causes for all persons and ages based on the WHO's 2009 estimates for the year 2004. These are the latest estimates available. It is worth noting from the outset that data availability and reporting across all countries is not always consistent. With this caveat in mind, it is not always possible to interpret the data and make inferences with the highest level of confidence. Nevertheless, this report aims to present the published information in ways that will encourage meaningful discussion.

Table 1.1: Summary of health system and expenditure on health care and pharmaceuticals

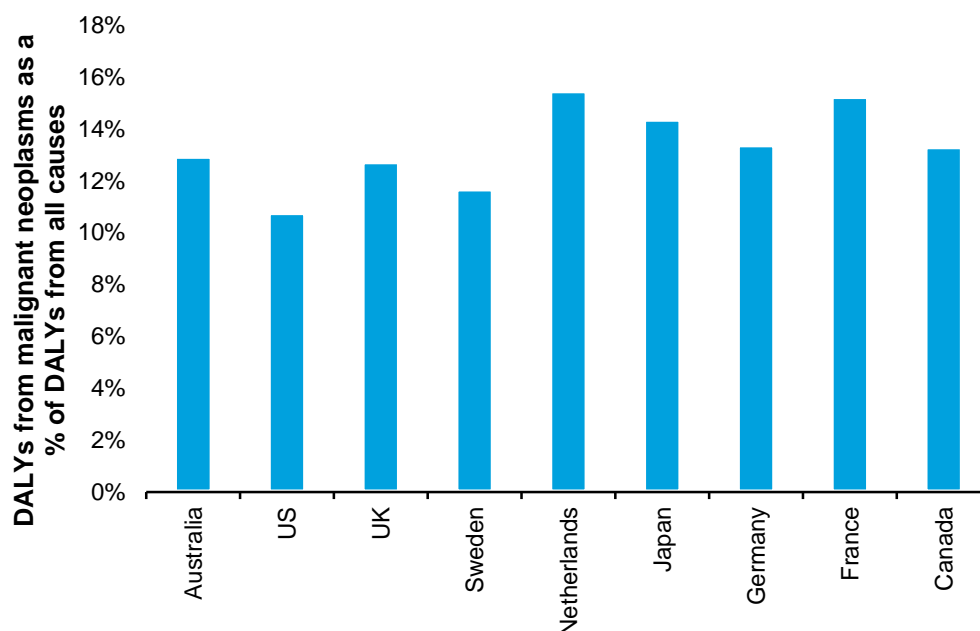
Country	Population in millions in 2011#	Healthcare system description* and eligibility for public coverage	Percentage GDP spent on healthcare	Spending on health care per capita in USD (THE) in 2010	Coverage of pharmaceuticals and eligibility	Spending on pharmaceuticals per capita (% THE)
Australia	22.324	All permanent residents are eligible for Medicare – a tax financed universal public insurance scheme. 46.7% of the Australian population has private hospital insurance and 54.3% had general treatment coverage (includes private hospital and ancillary services).	9.1%	\$3,670	The PBS covers a large proportion of the cost of PBS-listed medicines, with low-income and older people having lower share of the costs. All prescription drugs provided in public hospitals are covered.	\$541 (14.7%)
Canada	34.483	All population is eligible to statutory health insurance coverage for Medicare services – universal coverage for medically necessary hospital, diagnostic, and physician services. 67% of the population buy coverage for non-covered benefits e.g. drugs outside hospital; coverage varies by provinces	11.4%	\$4,445	All prescription drugs provided in hospital settings are covered through Medicare. Provinces have different prescription drug benefit plans, funded primarily through a mixed system of private (e.g. through employment based group plan) and public programs (e.g. for >65 years old or individuals with high drug costs relative to income).	\$741 (16.7%)
France	63.249	Universal Statutory Health Insurance (SHI) system, with all SHI insurers incorporated into single national exchange. Entitlement comes through employment-based scheme (for salaried or self-employed persons and their families), as public coverage for people and their families who have become unemployed, and through being a student or retired person. SHI covers hospital care; rehabilitation or physiotherapy; ambulatory care provided by GPs, specialists, dentists, and midwives; diagnostic services; prescription drugs; medical appliances; some prescribed prostheses; and prescribed transportation.	11.6%	\$3,974	SHI covers prescription drugs in hospital. Coverage of drugs in outpatient settings are defined in a positive list of reimbursement by the Ministry of Health (MoH), following guidance from the National Authority for Health (HAS). For each item, the list specifies both the reimbursement rate and the official tariffs. Patients with a medical condition listed in the list of serious and chronic diseases (affection de longue durée, ALD) are granted 100% reimbursement for all treatment related to that condition, including medicines; cancers are on the ALD list. Medicines for non-ALD diseases are generally reimbursed at 65% or 35% in the outpatient setting with complementary insurance covering the balance for the vast majority of French residents.	\$634 (16.0%)

Country	Population in millions in 2011#	Healthcare system description* and eligibility for public coverage	Percentage GDP spent on healthcare	Spending on health care per capita in USD (THE) in 2010	Coverage of pharmaceuticals and eligibility	Spending on pharmaceuticals per capita (% THE)
Germany	81.798	<p>Universal SHI system, with 154 competing SHI insurers in a national exchange; high income can opt out for private coverage. 10% of the population are covered by PHI; and the remaining 5% (policemen and soldiers) were covered under special programs.</p> <p>SHI covers preventive services, inpatient and outpatient hospital care, physician services, mental health care, dental care, optometry, prescription drugs, medical aids, rehabilitation, hospice and palliative care, and sick leave compensation.</p>	11.6%	\$4,338	<p>All prescription drugs—including newly licensed ones—are covered unless explicitly excluded by law (mainly so-called lifestyle drugs) or pending evaluation.</p> <p>Co-payments include €5 to €10 (US\$6 to \$13) per outpatient prescription (unless the price is at least 30% below the reference price), meaning that over 5,000 drugs are effectively free of charge.</p>	\$640 (14.8%)
Japan	127.799	<p>Universal SHI system, with 3,500 non-competing public, quasi-public and employer-based insurers. There are various compulsory insurance schemes for different populations:</p> <ul style="list-style-type: none"> • Employer-based scheme for employees of large companies and their dependents aged under 75 years; • Coverage by Japan Health Insurance Association for employees of small- or medium-sized companies, and their dependents aged under 75 years; • Municipal-run “Citizens Health Insurance” plans for those aged <u>under</u> 75 years who are unemployed, self-employed, retired, or uninsured for other reasons; • “Health Insurance for the Old-Old” operated by insurers established in each prefecture for individuals aged 75 and over. <p>All plans provide the same national benefits package, which covers hospital care, ambulatory care, mental health care, approved prescription drugs, and most dental care</p> <p>Supplementary private health insurance is held by the majority of the adult population, with benefits provided mainly in the form of lump-sum payments, such as daily amounts for hospitalization.</p>	9.5%	\$3,035	All individuals have to pay coinsurance of 30% for services and goods covered, including prescription drugs, except for children (20%) and people age 70 and over with low incomes (10%).	\$630 (20.8%)

Country	Population in millions in 2011#	Healthcare system description* and eligibility for public coverage	Percentage GDP spent on healthcare	Spending on health care per capita in USD (THE) in 2010	Coverage of pharmaceuticals and eligibility	Spending on pharmaceuticals per capita (% THE)
Netherlands	16.693	<p>SHI system, with universally mandated private insurance in a national exchange. Health insurers are legally required to provide a standard benefits package covering the following:</p> <ul style="list-style-type: none"> • medical care including care provided by general practitioners (GPs), hospitals, specialists, and midwives; • dental care through age 18 (coverage after age 18 is confined to specialist dental care and dentures); • medical aids and devices; • prescription drugs; • ambulance and patient transport services; • paramedical care (limited physical/remedial therapy, speech therapy, occupational therapy, and dietary advice); • ambulatory mental health care (five sessions with a primary care psychologist); and • outpatient and inpatient mental care up to a year. 	12.0%	\$5,056	<p>The system is financed through a nationally defined, income-related contribution and through community-rated premiums set by each insurer (everyone with the same insurer pays the same premium, regardless of age or health status).</p> <p>Although there is no cost-sharing arrangement at the point of service (including pharmaceuticals), every insured person over age 18 must pay a deductible of €220 (US\$282) (as of 2012) for any health care costs in a given year (with some services, such as GP visits, excluded from this general rule).</p>	\$481 (9.5%)
Sweden	9.449	<p>All population is covered by a statutory social health insurance system, financed by local taxes and state grants. ~4% of the population has supplementary private voluntary health insurance</p> <p>The publicly financed health system covers public health and preventive services; primary care; inpatient and outpatient specialized care; emergency care; inpatient and outpatient prescription drugs; mental health care; rehabilitation services; disability support services; patient transport support services; home care and long-term care, including nursing home care; dental care for children and young people; and, with limited subsidies, adult dental care</p>	9.6%	\$3,758	<p>Individuals pay the full cost of prescribed drugs up to SEK1,100 (US\$164), after which the subsidy gradually increases to 100%. There is a national ceiling for out-of-pocket payments that ensures that an adult individual will never pay more than SEK2,200 (US\$329) for prescribed drugs in a 12-month period.</p> <p>A separate annual maximum of SEK2,200 (US\$329) for pharmaceuticals also applies to children belonging to the same family.</p>	\$474 (12.6%)

Country	Population in millions in 2011#	Healthcare system description* and eligibility for public coverage	Percentage GDP spent on healthcare	Spending on health care per capita in USD (THE) in 2010	Coverage of pharmaceuticals and eligibility	Spending on pharmaceuticals per capita (% THE)
UK	61.761	All UK residents are covered by the National Health Service system, financed by general taxation. Most private hospital care—largely for elective conditions — is financed through supplementary private voluntary health insurance.	9.6%	\$3,433	<p>Individuals exempted from prescription drug co-payments include:</p> <ul style="list-style-type: none"> • children under the age of 16 years and • those in full-time education ages 16–18; • people age 60 or older; • people with low income; pregnant women and those who have had a baby in the past 12 months; and • people with cancer and certain long-term conditions and disabilities. <p>Patients who need a large number of prescription drugs on a regular basis can buy pre-payment certificates which limit their cost to £2 (US\$3.20) a week.</p> <p>~ 6% of prescriptions actually incur the full charge at the point of dispensing; the remainder are exempt from charges.</p>	\$369 (10.7%)
US	311.592	<p>Medicare for those aged 65 years and over and some individuals with disability; Medicaid for some of those with low-income. Mostly under 65 years is covered by private health insurance.</p> <p>In 2010, 56% of U.S. residents received primary care coverage from private voluntary health insurance (VHI), with 51% receiving it through their employers and 5% acquiring coverage directly. Public programs covered 27% of residents: 14% under Medicare, 12% under Medicaid, and 1% under military health care programs</p> <p>Benefit packages vary according to type of insurance, but typically include inpatient and outpatient hospital care and physician services.</p>	17.6%	\$8,233	Medicaids and Medicare offers outpatient prescription drug coverage through a supplementary program. Coverage however may vary from state to state within federal eligibility and coverage requirements.	\$983 (11.9%)

*All health systems comprise a mixed of public and privately funded models, but to different extent in the range of services covered and service eligibility.
Source: Thomson et al (2012) Tables 1 and 2; OECD StatExtracts <http://stats.oecd.org/Index.aspx?QueryId=30383> [Accessed Jun 2013]

Chart 1.1: The burden of diseases across selected countries, DALYs (2004)

Source: WHO 2009

1.2.2 Stakeholder consultations

The stakeholder engagement has three specific aims:

- To elicit views from a range of stakeholders for synthesis in this report;
- To facilitate a joint understanding among stakeholders regarding issues relating to patient access to cancer medicines, in order to inform the development of mutually beneficial and enduring solutions; and
- To identify the key issues common to multiple stakeholder groups for desktop research for inclusion in the discussion paper.

In total, 29 stakeholders representing the following interest groups were consulted individually by telephone or face-to-face in semi-structured interviews of up to one hour:

- Health consumer groups, including those representing individuals affected by cancer;
- Relevant Government departments and bodies;
- Clinical groups: oncologists, pharmacists, nurses;
- Health service providers: cancer centres and clinics;
- Other payers: private health insurance; and
- Academics with an interest in medicines access: researchers and research institutes.

Views from the medicines industry were provided by the Oncology Industry Taskforce. Appendix A lists those individuals and organisations who participated in the interviews.

Appendix B lists the interview questions which broadly covered the following topics:

- Patient access to cancer medicines in general;
- Patient access to new cancer medicines;
- The impact of barriers to patient access to cancer medicines on stakeholders and on delivering optimal health outcomes to cancer patients.

1.3 Report structure

The following chapters provide an exposition on various topic areas:

- Chapter 2 – Cancer in Australia and other countries;
- Chapter 3 – Current and future cancer medicines;
- Chapter 4 – Current arrangements to access to cancer medicines in Australia;
- Chapter 5 – Issues on access to cancer medicines in Australia;
- Chapter 6 – Stakeholders views; and
- Chapter 7 – Conclusion.

2 Cancer in Australia and other countries

Cancer is comprised of many different cancers not just one disease. Australia has the highest age-standardised incidence of cancer in the world. In particular, it has the world's highest incidence of melanoma and prostate cancer, and the third highest rate of breast cancer.

Cancer-induced morbidity and mortality impose significant economic losses to our society. There appears to be a misalignment between burden of disease and healthcare expenditure for cancer. Total cost of cancer in 2012 was estimated to be \$4.7 billion.

Innovative technology that may reduce or delay the need for hospital based care could provide broader benefits to society. These benefits need to be assessed and understood.

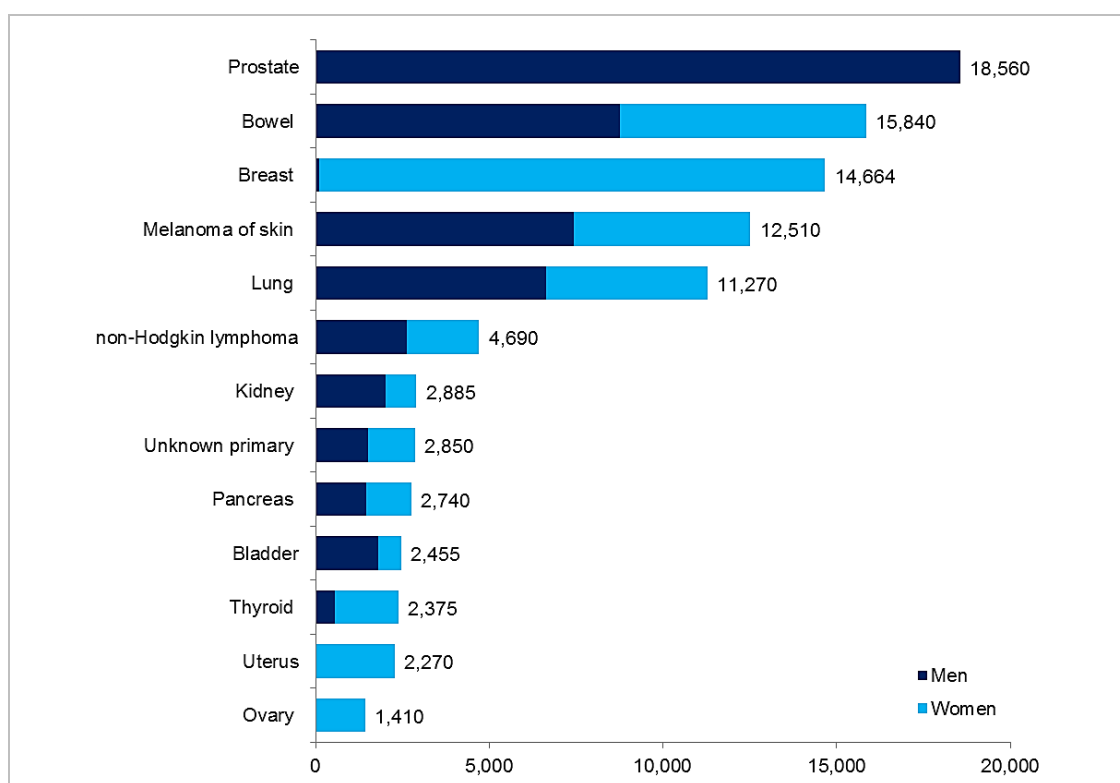
2.1 Population statistics on cancer

2.1.1 Epidemiology of common cancers in Australia

On average, one in every two Australians will develop cancer in their lifetime and one in five Australians will die from cancer before the age of 85 years. In 2012, there were 67,260 and 53,460 cases⁴ of cancer diagnosed in Australian men and women, respectively (AIHW 2012b). This corresponds to 474.4 cases per 100,000 people, with the proportion of newly diagnosed cases significantly higher for men (557.9 per 100,000) than for women (404.5 cases per 100,000) (AIHW 2012b).

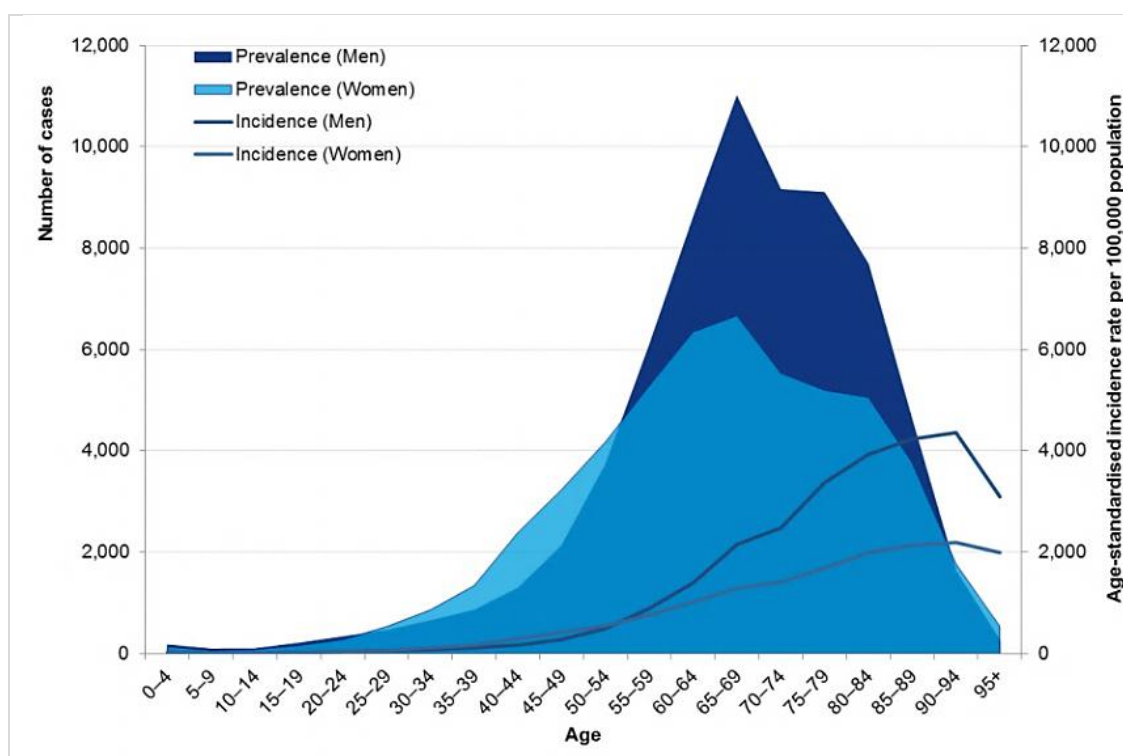
Chart 2.1 shows the ten most common cancers affecting Australian men and women in 2012, with prostate cancer being most common for men, and breast cancer being most common for women.

⁴ Excluding basal and squamous cell carcinoma of the skin.

Chart 2.1: Ten most common cancers affecting Australian men and women in 2012

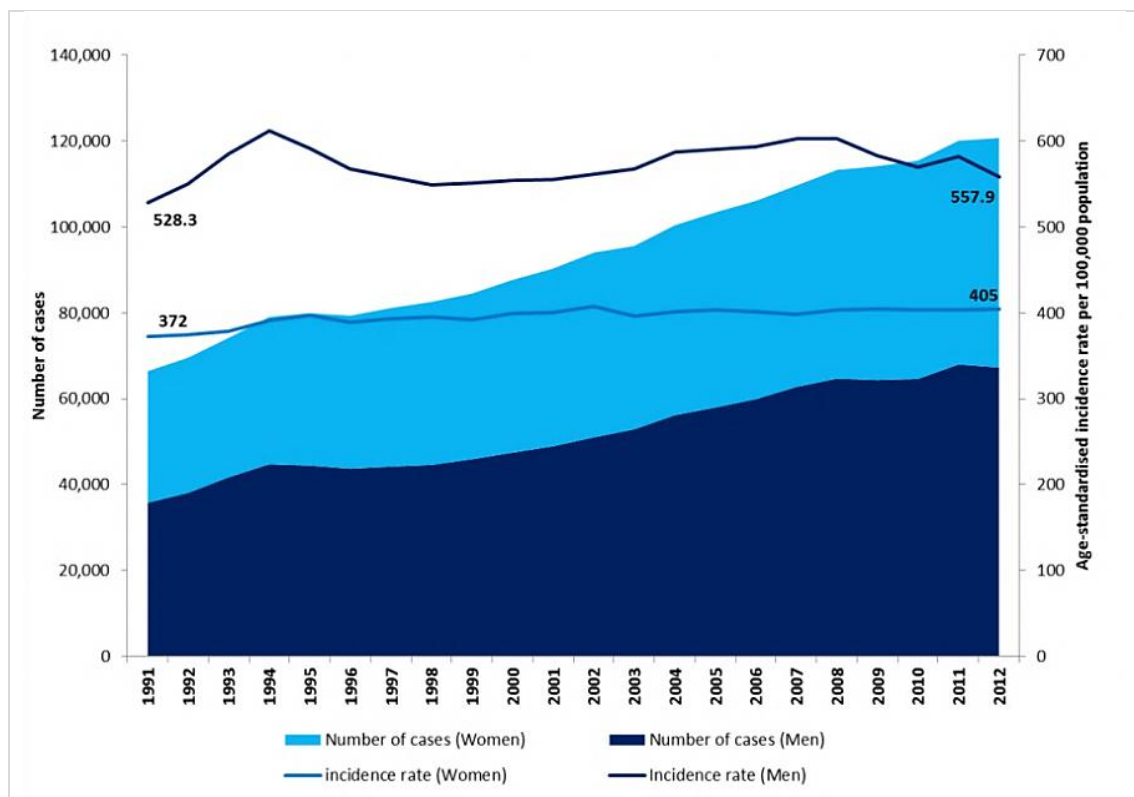
Source: AIHW (2012b) Page.13, Table 2.2; AIHW & AACR (2012) for thyroid cancer in males, and stomach, pancreatic, bladder, and kidney cancers in females, where incidence was used as a proxy for prevalence; AIHW and Cancer Australia (2012) for estimating number of breast cancer cases in men.

The incidence of cancer increases with age. It is estimated that 75% of men and 65% of women who were diagnosed with cancer in 2012 were aged 60 years and over (Chart 2.2). Men have a higher overall age-standardised incidence of cancer for all ages, except in the 25-54 year age group. Women have a higher incidence of cancer in this age group due to the prevalence of breast cancer. Among people aged 55 years and older, men have a higher incidence of cancer due to the increased prevalence of prostate cancer, bowel cancer, melanoma of the skin and lung cancer.

Chart 2.2: Prevalence and incidence rate of all cancers in 2012, by age and gender

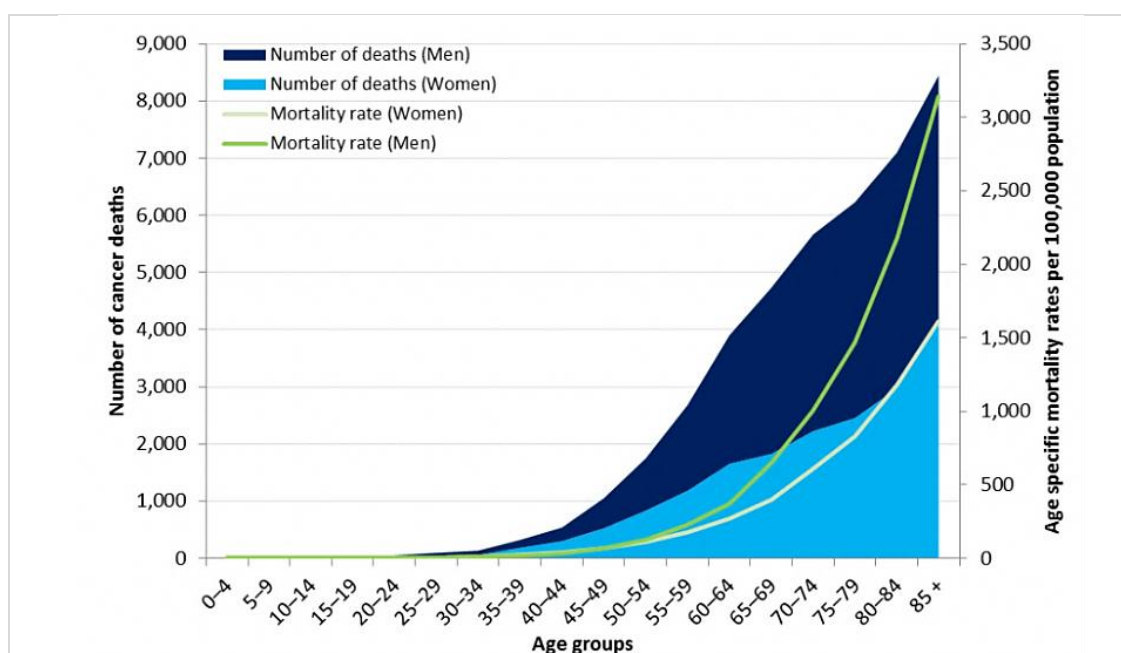
Source: AIHW 2012b

Over the past two decades, the number of cancer cases has increased substantially, from 66,393 cases in 1991 to 120,710 cases in 2012 (Chart 2.3) – an increase of 82%. However, the age-standardised incidence rate only increased by 9.5% from 433.4 cases per 100,000 population in 1991 to 474.4 cases per 100,000 in 2012. This suggests that the increase in the number of cancer cases is due to population growth and ageing over that period of time.

Chart 2.3: Number and rate of cancer incidence between 1991 and 2012

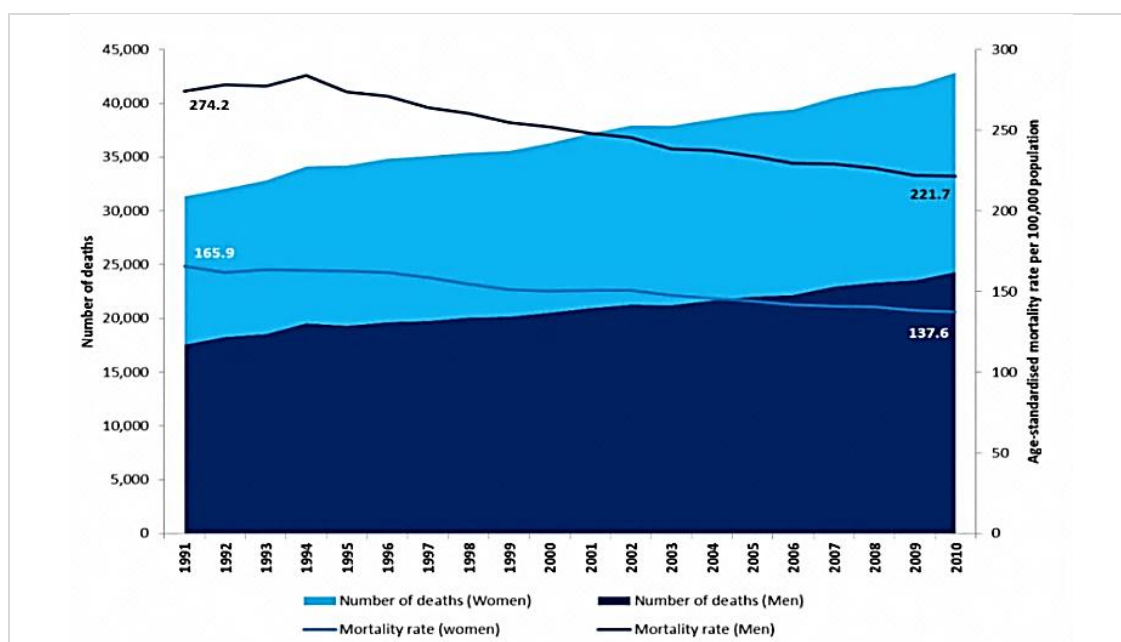
Source: AIHW 2012b

Untreated cancers can cause serious illness and death. Cancer accounts for three in every ten deaths in Australia, making cancer one of the leading causes of death (AIHW 2012b). In 2010, an estimated 42,844 individuals died from cancer, 56.8% of which were men. In line with the age distribution of cancer incidence, the rate of cancer death rose rapidly from 34.6 persons per 100,000 population for people at 40 years of age, to 2141.3 persons per 100,000 population for individuals aged 85 years and over. More than 80% of all cancer deaths occurred in those aged 60 years and over (AIHW 2012b). Overall, Australian men were at much higher risk of cancer related deaths than women in the same age group: the rate was greater than 50% more for those aged 60 years and above (Chart 2.4).

Chart 2.4: Number and rate of cancer related deaths in 2010, by age groups

Source: AIHW (2012b)

Encouragingly, age-standardised mortality rates have fallen over the past two decades (Chart 2.5). This can be attributed to the reduction in mortality rates in a range of cancers, including cancers of the gallbladder (58% reduction), cervix (55% reduction), stomach (50% reduction), bowel (42.6% reduction), breast (30% reduction), and prostate (31% reduction) (AIHW 2012b). Nevertheless, over the same period, mortality rates increased for cancer of the liver (90% increase), thyroid (25% increase), and melanocyte of the skin (10% increase) (AIHW 2012b).

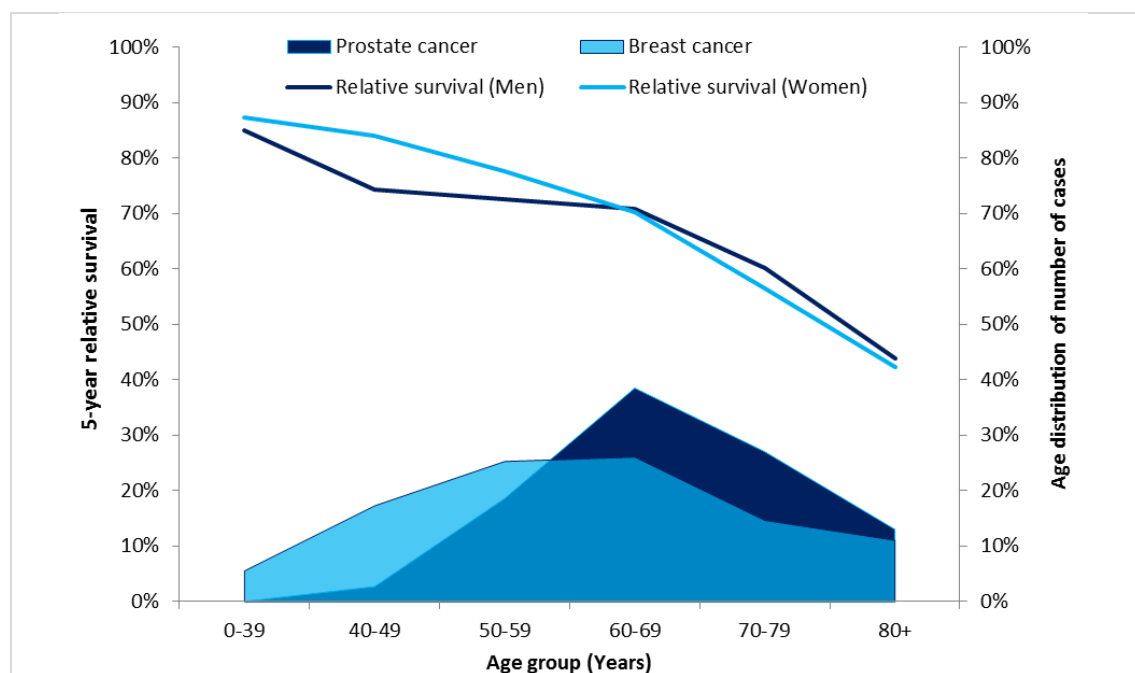
Chart 2.5: Number and rate of cancer related deaths between 1991 and 2010

Source: AIHW (2012b)

Survival following a diagnosis of cancer is dependent upon a range of factors. These factors include patient specific characteristics (e.g. age, gender, co-morbidities), stage and nature of the cancer at the time of diagnosis, and health system factors (e.g. access to cancer treatment and medical care, coordination of care). Cancer survival at the population level is indicative of the effectiveness of cancer control. Standard methodology typically expresses survival data as 'relative survival' – the ratio of the proportion of cancer survivors to the proportion of individuals alive in a comparable general population (i.e. age matched) over the same period of time.

On average, two in every three individuals are alive five years after diagnosis of cancer compared to individuals without cancer of the same age (AIHW 2012b). However, as expected, relative survival is inversely correlated with age (Chart 2.6). This is most probably because of the presence of comorbidities and the more advanced stage of cancer at the time of diagnosis for older individuals. The different profile in survival advantage between men and women younger and older than the 60-69 year age group is most likely to be influenced by the distribution of prostate and breast cancer.

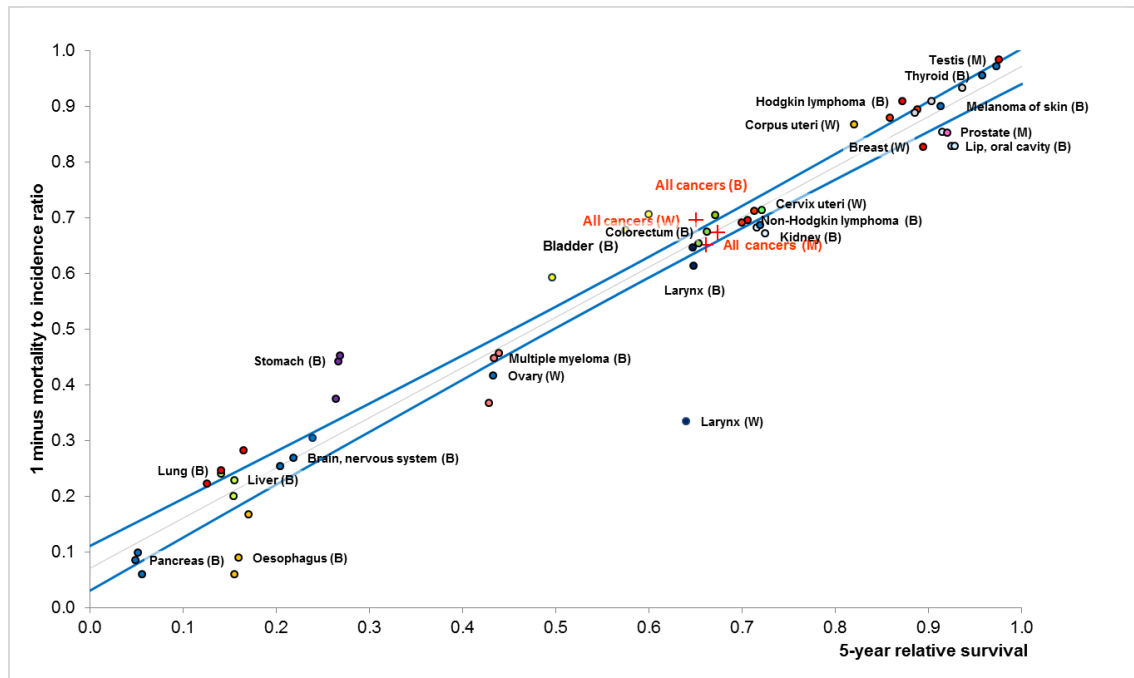
Chart 2.6: Five-year relative survival and age distribution for prostate and breast cancer



Source: AIHW (2012b) and the ACIM book

The likelihood of survival differs for different types of cancer. Chart 2.7 shows the relative survival of Australian patients five years after diagnosis of various cancers. Chart 2.7 also shows the correlation of relative survival with the mortality to incidence ratio, which has been validated as a proxy for site-specific survival for most cancers (Vostakolaei 2010). The chart shows how survival is reduced for all reported cancer types, with survival rates for individuals afflicted by cancers of the pancreas, oesophagus, lung, liver and stomach being substantially lower than among the general population.

Chart 2.7: 5-year relative survival by cancer types, and correlation with mortality-to-incidence ratio



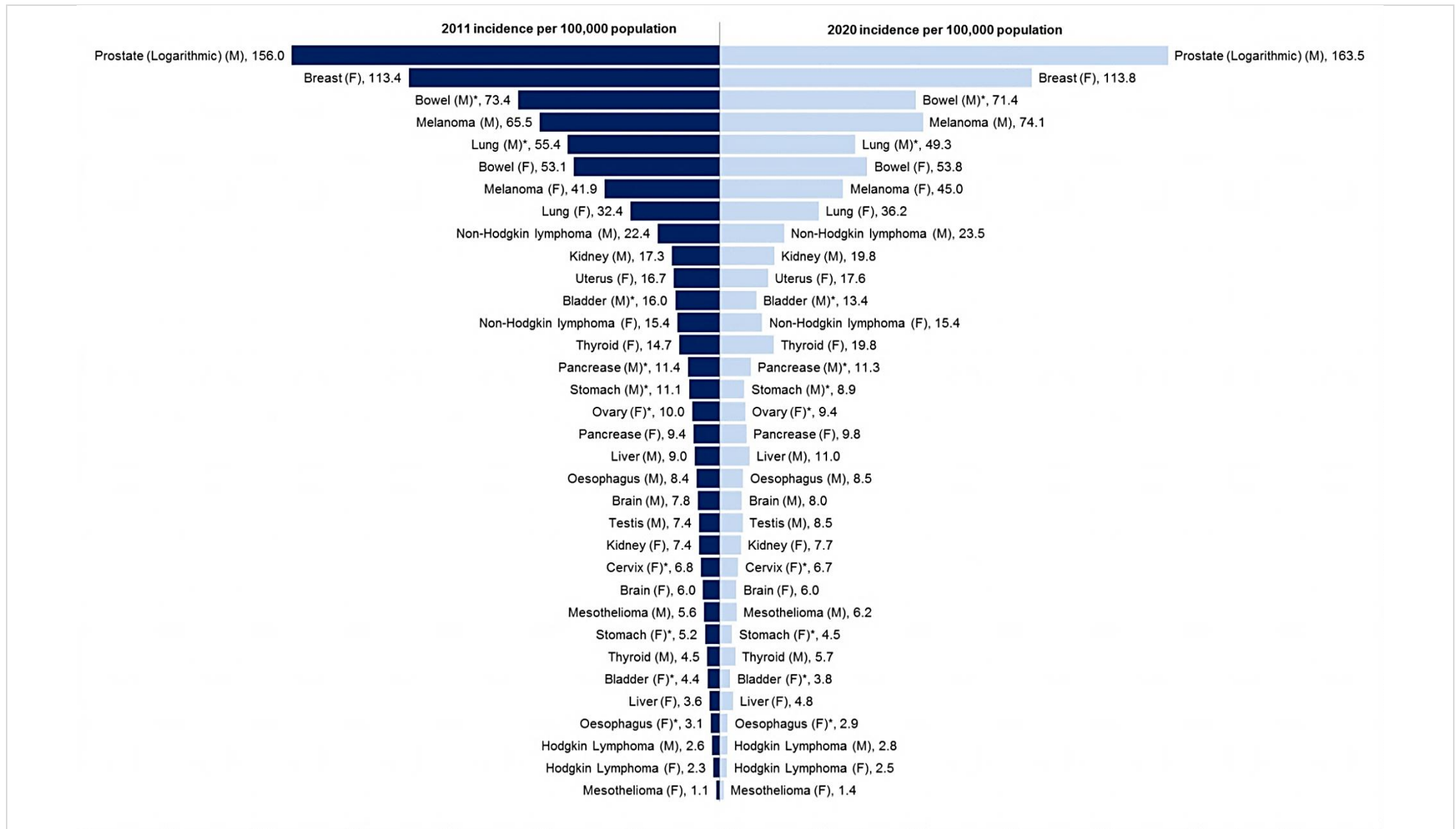
Note: The lines show the regression lines ($r^2=0.902$) and the 95% confidence interval of the correlation analysis.
Source: Deloitte Access Economics analysis of GLOBOCAN 2008 dataset.

2.1.2 Projected cancer incidence in Australia to 2020

Cancer will continue to be a significant challenge in the foreseeable future. Due to population growth and ageing, it has been estimated that cancer cases will increase by almost 40% from 2007, reaching about 150,000 in 2020 in Australia (AIHW 2012b).

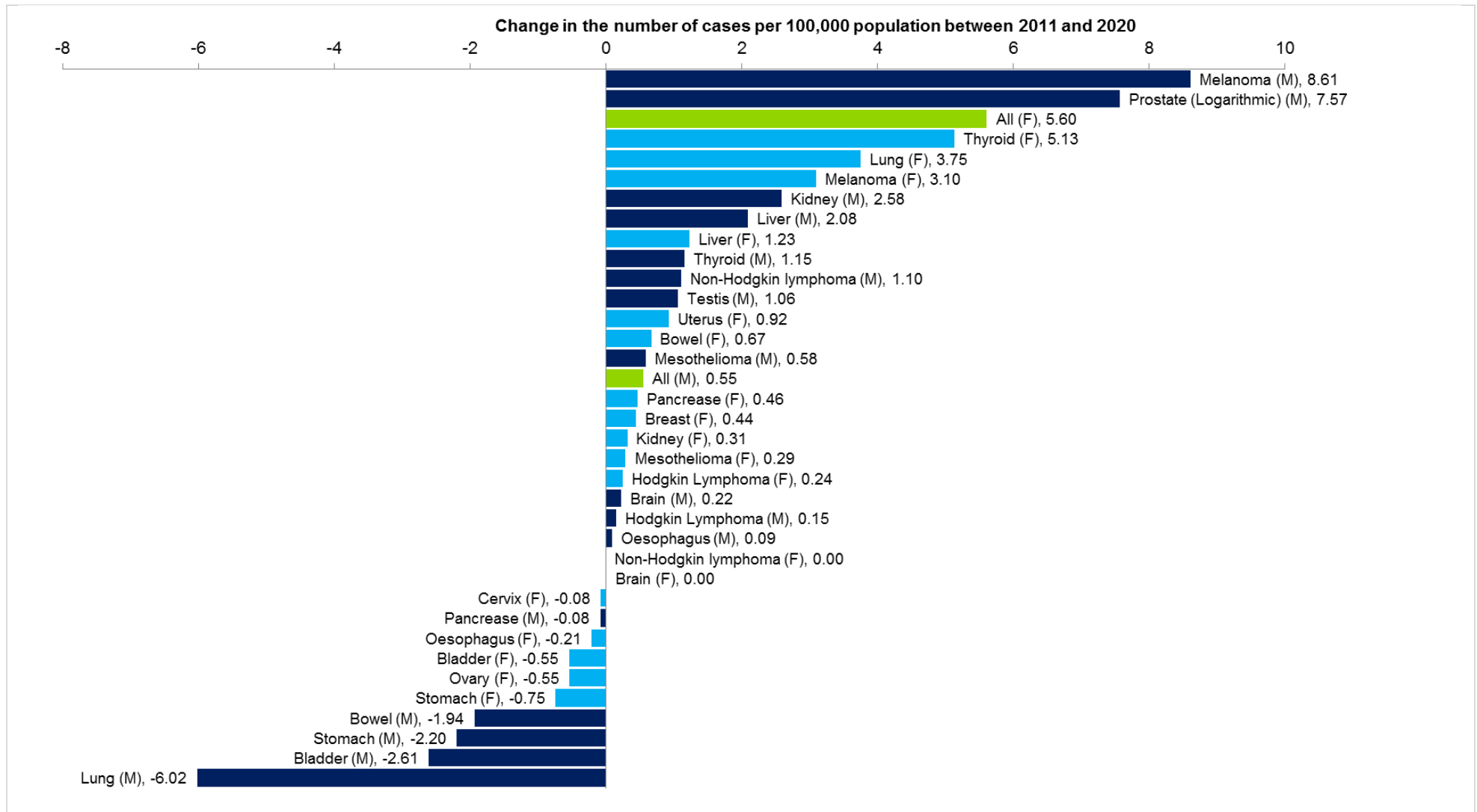
Chart 2.8 (p.17) shows the projected number of new cancer cases by cancer type per 100,000 population between 2011 (left hand chart) and 2020 (right hand chart). Overall, cancers of the breast and prostate will continue to be the most common cancers in Australian women and men in 2020. Melanoma of the skin in men will become the cancer with the third highest incidence followed by bowel cancer in men and women, although at the entire population level bowel cancer will remain the cancer with the second highest incidence.

Chart 2.9 (p.18) shows the predicted changes in the incidence of cancer types for the decade to 2020. Incidence of cancer is predicted to increase substantially in women, with an increase of 5.6 cases per 100,000 population for all cancers. This could be attributable to the predicted increase in cancers of the thyroid, lung and skin melanocyte. Incidence in men will remain reasonably stable over the next 10 years with an average increase of 0.55 cases per 100,000. For men, it is predicted that melanoma of the skin and prostate cancer will increase in the next decade. However, this increase will be counteracted by the predicted reductions in cancers of the lung (15%), bladder (19%), and stomach (25%) (AIHW 2012a).

Chart 2.8: Projected number of new cancer cases per 100,000 population at 2011 and 2020, by cancer type

NOTE: *Cancers projected to have a reduction in incidence

Source: AIHW (2012a)

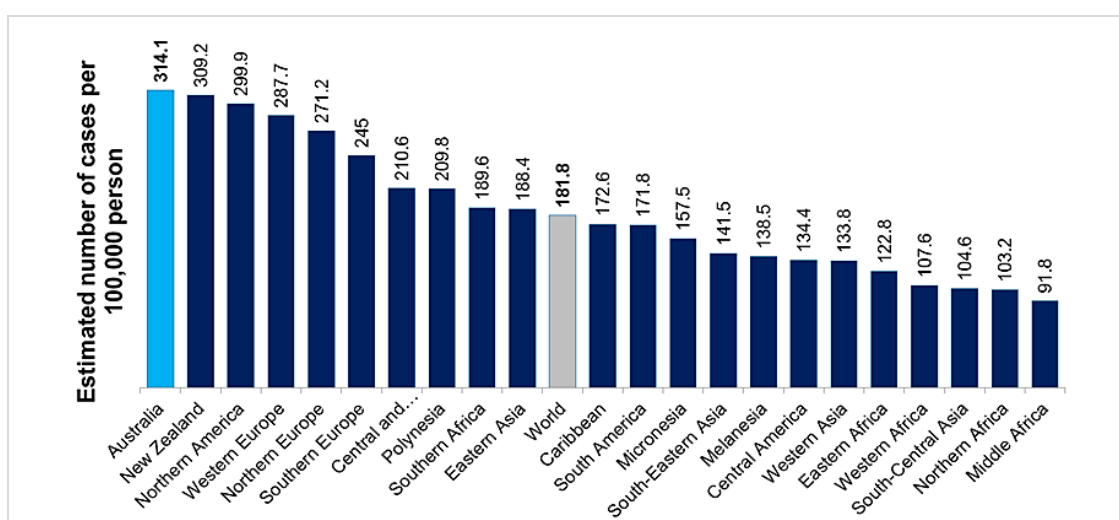
Chart 2.9: Projected change in the number of new cancer cases per 100,000 population between 2011 and 2020 in Australia, by cancer type

Source: AIHW (2012a)

2.1.3 Cross-country comparison of cancer epidemiology

Australia has the highest age-standardised incidence of cancer in the world (Chart 2.10) (Ferlay et al 2010, cited in AIHW & AACR 2012). In particular, Australia has the world's highest incidence of melanoma (37 cases per 100,000 people) and prostate cancer (105 cases per 100,000 males), and the third highest rate of breast cancer (85 cases per 100,000 females) (AIHW 2010). However, it is important to note that the difference in incidence may be due to differences in demographics, cancer detection and screening, types of treatment provided, and cancer coding and registration practices (AIHW 2012b). Cancer data are relatively complete in Australia, because all jurisdictions have legislation that makes cancer a notifiable disease (AIHW 2012b).

Chart 2.10: International comparison of estimated incidence of all cancers, 2008

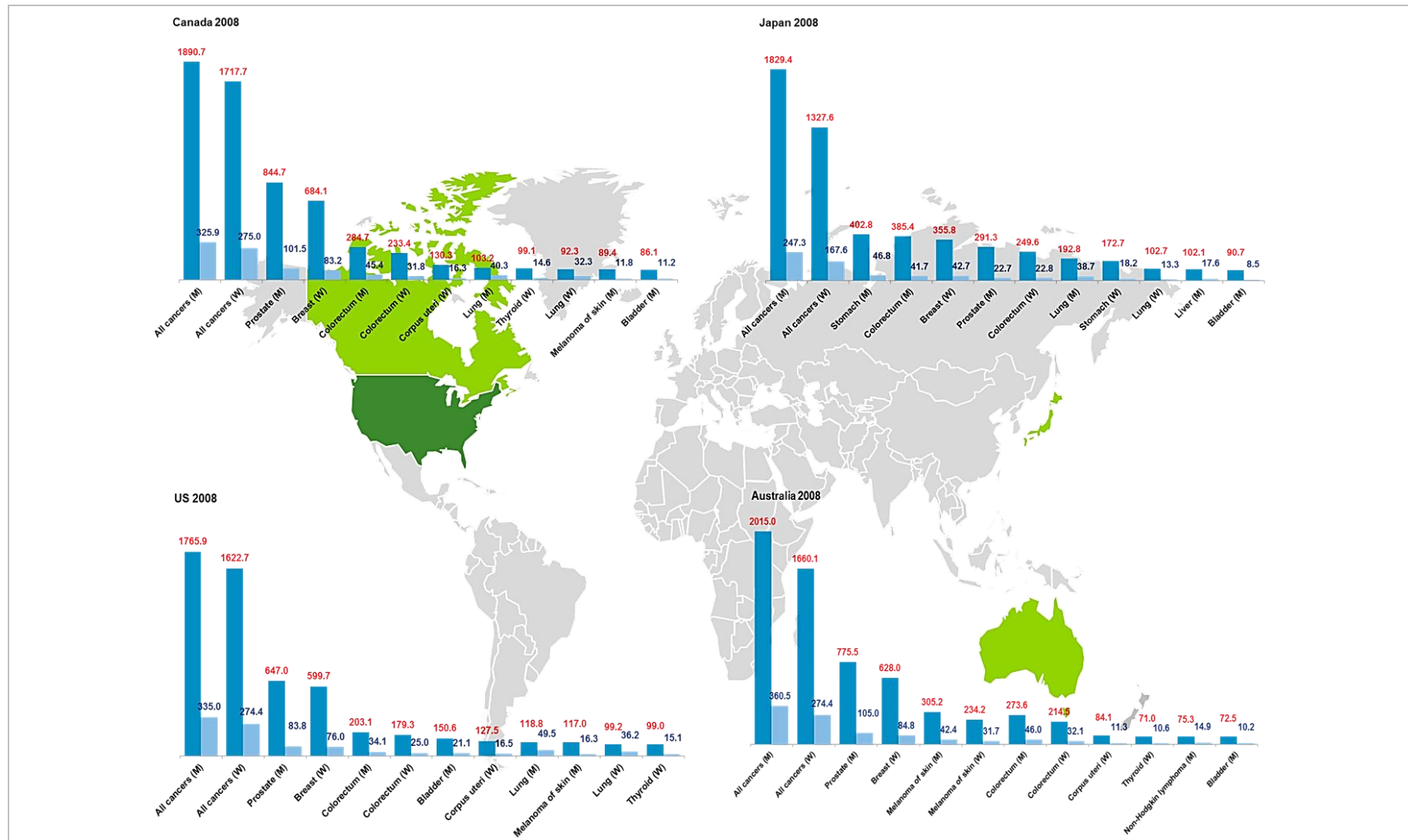


Source: Ferlay et al 2010, cited in AIHW & AACR 2012

To ensure comparability, the following discussion is based on the 2008 cancer epidemiological data extracted from the GLOBOCAN database of the WHO's International Agency for Research on Cancer.

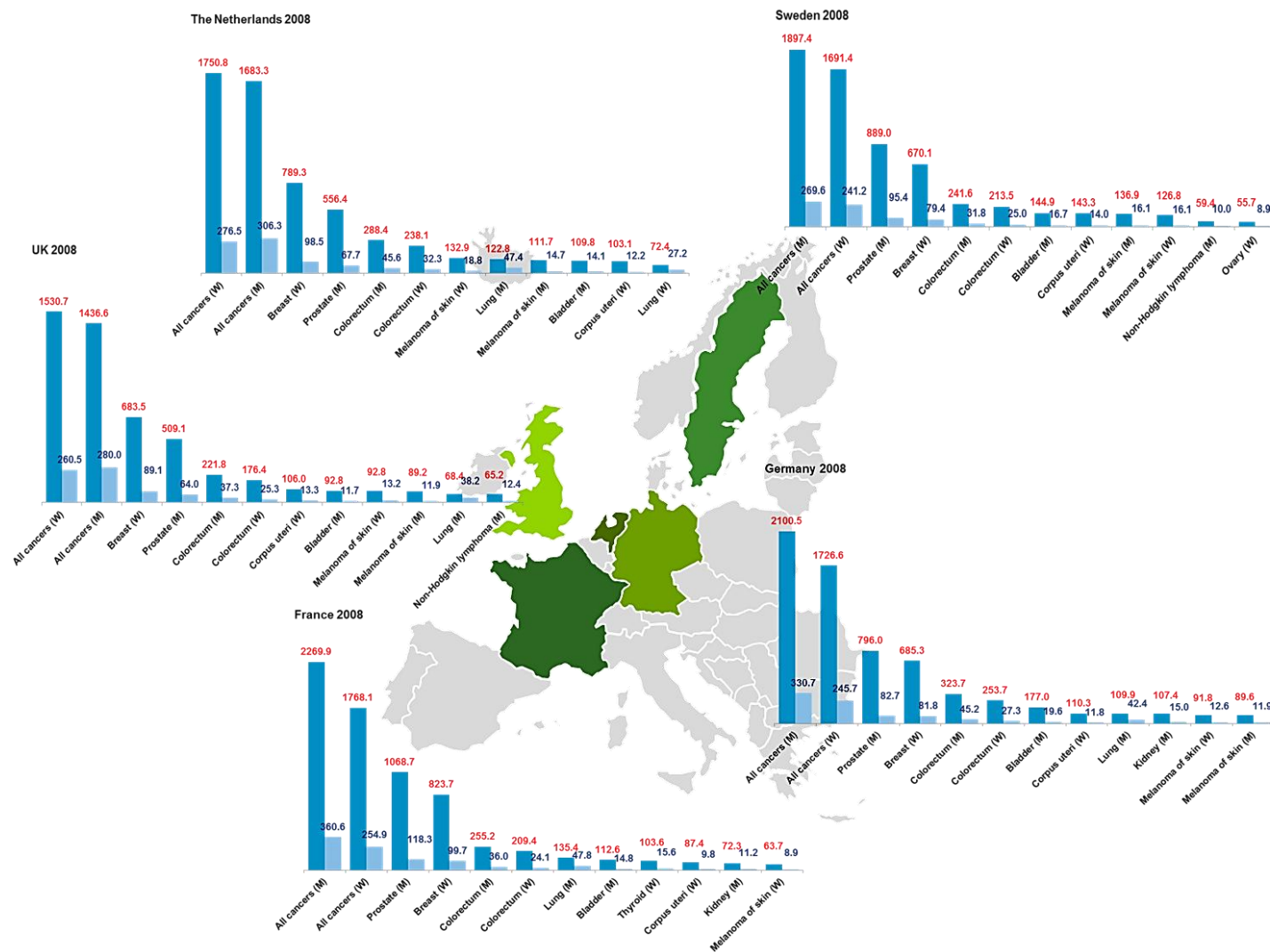
Chart 2.11 and Chart 2.12 show the prevalence and incidence of the ten most common cancers in the countries selected for comparison (see Table 1.1). Except for Japan, all other countries reported the highest 5-year prevalence and annual incidence for breast and prostate cancers; stomach and bowel cancers were the most common cancers in Japan, followed by breast and prostate cancers. As noted above, Australia reported the highest 5-year prevalence and annual incidence of melanoma of the skin compared to other countries. Bowel cancer was also one of the most common cancers reported among the countries selected for comparison.

Chart 2.11: Five-year prevalence and age standardised annual incidence of top 10 cancers in Australia, Canada, Japan and the United States in 2008



Note: Prevalence is indicated by azure, incidence is indicated by aero, and gender in brackets
Source: GLOBOCAN 2008

Chart 2.12: Five-year prevalence and age standardised annual incidence of top 10 cancers in France, the Netherlands, Germany, Sweden, and the United Kingdom in 2008



Note: Prevalence is indicated by azure, incidence is indicated by Aero and gender in brackets

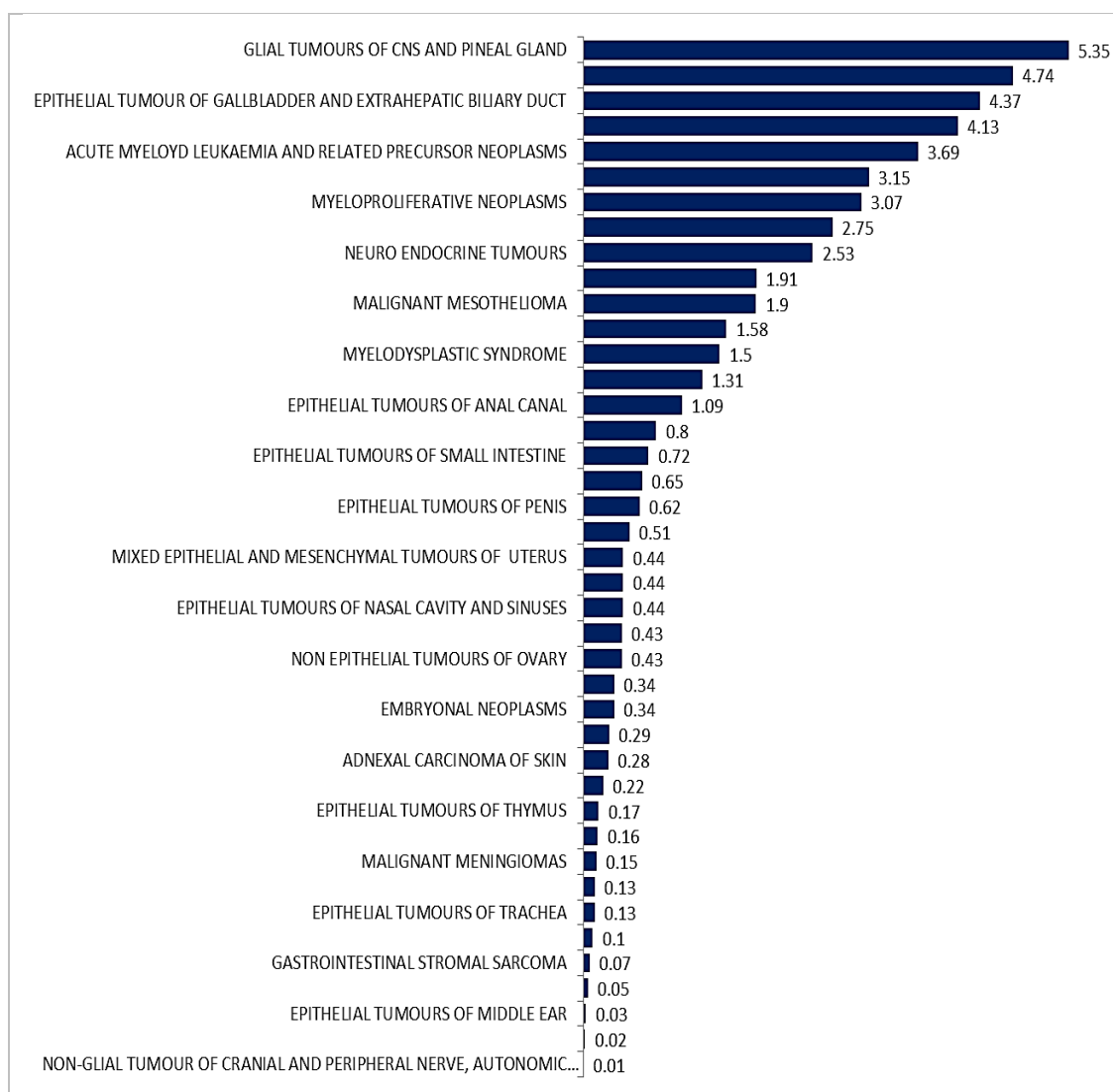
Source: GLOBOCAN 2008

2.1.4 Rare cancers

The discussion above focused on the most common cancers reported globally. However, cancers can develop from other cell types in the body, some of which are infrequent at the population level.

There is now evidence that rare cancers⁵, as a group of diseases, present a considerable public health challenge. A recent study in Europe based on cancer registry data recorded between 1988 and 2002 (Gatta et al 2011) estimated that the annual incidence of all rare cancers in Europe was about 108 per 100,000 population. This corresponds to 22% of all cancer diagnosed over the same period. This study also found that 5-year relative survival was on average worse for rare cancers (47%) than common cancers (65%).

Chart 2.13: Incidence of rare cancers in Europe in 2011, by type per 100,000 population



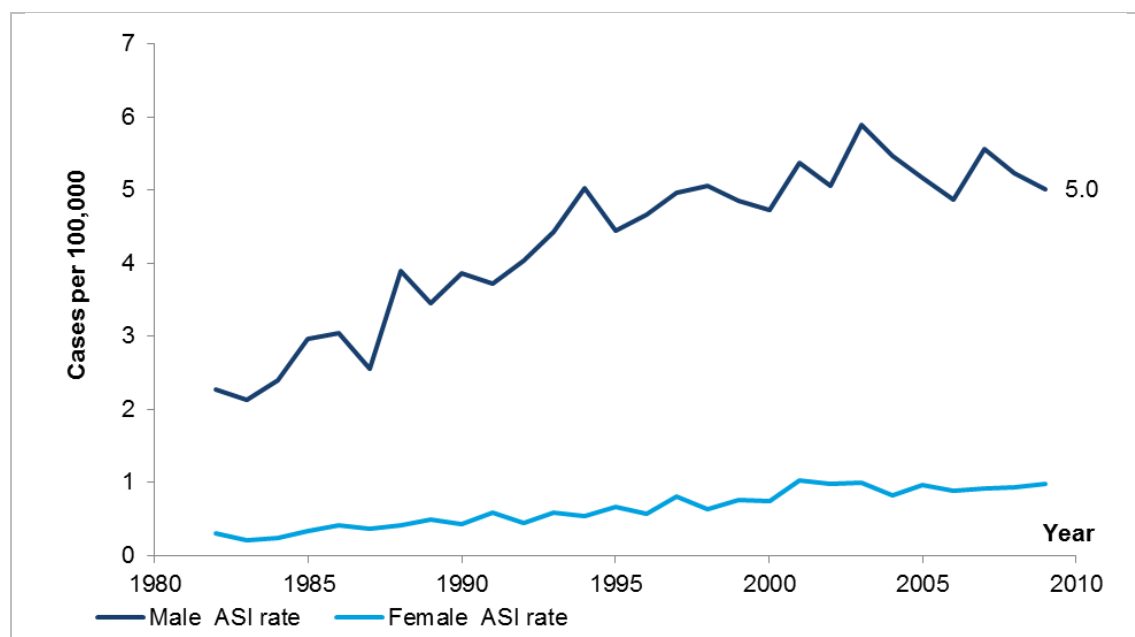
Source: RARECARE 2011

⁵ Defined as cancers with an incidence of less than 6 cases per 100,000 of population per year

In contrast to common cancers, comprehensive estimates for rare cancers are not yet available in Australia. However, there is now a collaborative effort established in Australia – The CART-WHEEL project – to collect information about rare tumours from individuals living with rare cancers, or their proxies. The purpose of this initiative is to collect data to facilitate research on rare cancers. Currently, it collects information for over 400 types of rare cancers (Center for Analysis of Rare Tumors 2013), and will provide useful information for future research.

Some published data are available to indicate the extent of some rarer cancers in Australia. For example, a report by SafeWork Australia estimated the age-standardised incidence of **mesothelioma** in Australia based on data collected by the AIHW to be 2.9 cases per 100,000 population in 2008 (SafeWork Australia 2012). Chart 2.14 presents the trend of age-standardised incidence of mesothelioma between 1982 and 2009. The incidence of mesothelioma is predicted to decline over time because of efforts to prevent workplace exposure to asbestos. However, the incidence of mesothelioma will peak at around 2014 because of the long disease latency following past exposure to asbestos (Clements et al 2007, cited in AIHW 2012a).

Chart 2.14: Age standardised incidence of mesothelioma in Australia, by gender



Source: AIHW – ACIM books 2012

Other reports of statistics for rare cancer in Australia include:

- **Gliomas (astrocytomas and oligodendrogliomas):** In 2007, there were 7 cases per 100,000 population diagnosed with malignant tumour of the central nervous system, 70% of which were gliomas (Cancer Council of Australia 2011).
- **Anal cancer:** Grulich et al (2012) recently highlighted the increased incidence of anal cancer over the last 30 years, especially among HIV-positive men who have sex with men (50–100 per 100,000).

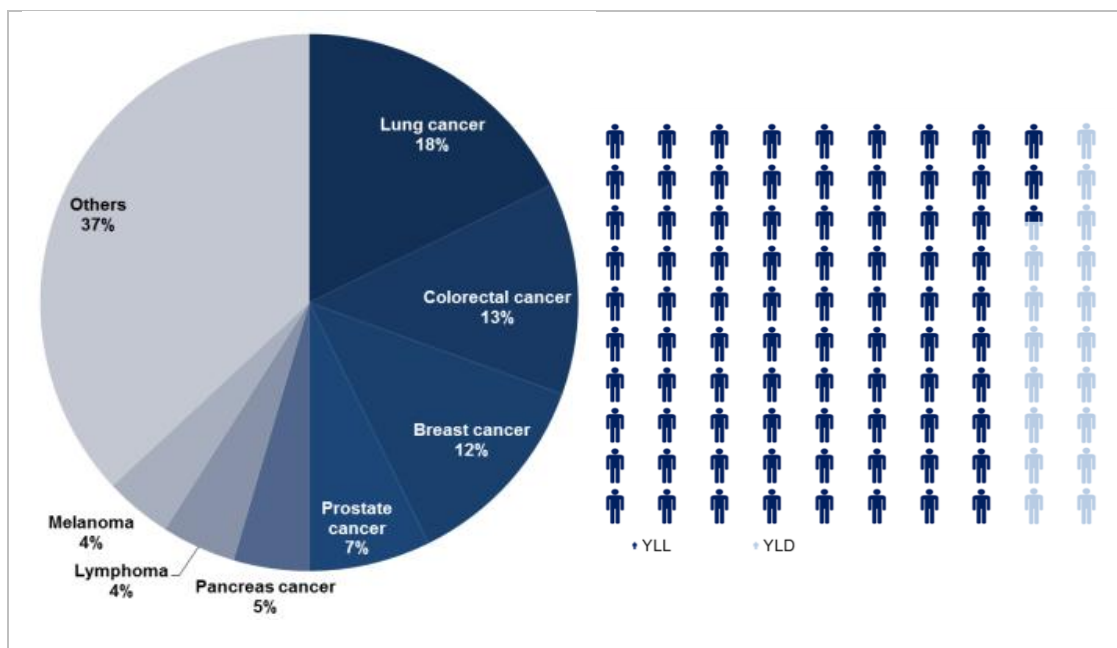
2.2 Population impacts of cancer in Australia

Cancers have imposed economic and social burdens more significant than any other group of illnesses in Australia. The following sections discuss the disease burden of cancers, the proportion of hospital admissions related to the management of cancer, and the financial and economic costs of cancer in Australia.

2.2.1 Disease burden of cancers

Disease burden can be measured using disability adjusted life years (DALYs) – a composite measure of the number of years lost to premature deaths (YLL) and the number of years lived with disability (YLD), compared to living in full health to the average life expectancy of 82.5 years. The AIHW has estimated that cancers resulted in 539,800 DALYs in 2003, which accounted for 19.0% of the total burden of disease. Half of this disease burden was contributed by cancers of the lung, colorectum, breast, and prostate (Chart 2.15a). Most of the DALYs were related to YLLs rather than YLDs: for every 100 cancer related DALYs, 82.5 years were due to premature deaths and 17.5 years were due to cancer related morbidity (Chart 2.15b).

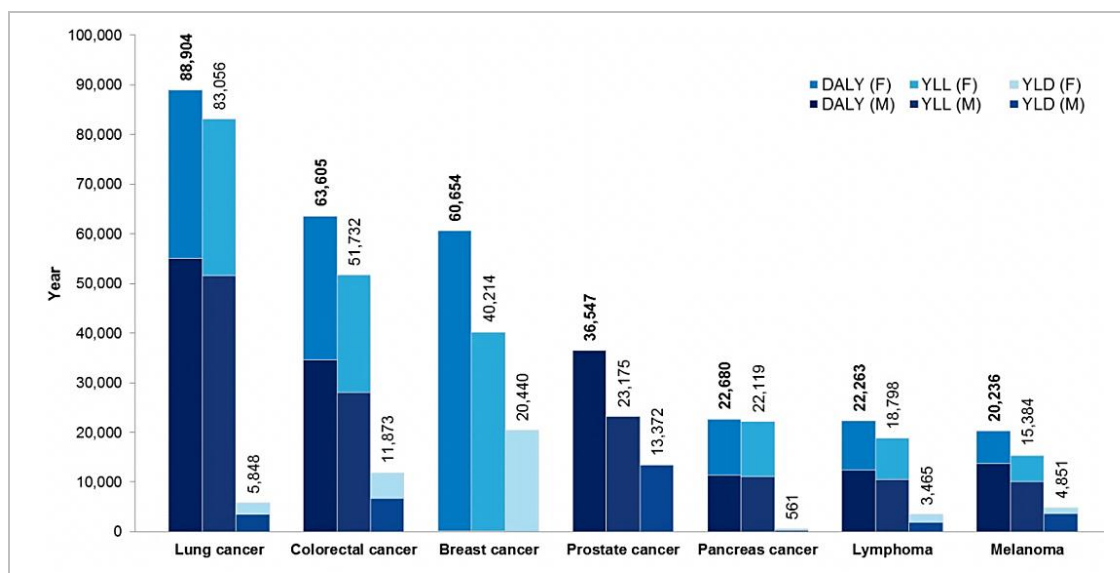
Chart 2.15: Burden of cancer (a) by types (b) by components



Source: Begg et al 2007

Chart 2.16 shows the disease burden by cancer type, gender and DALY components of seven cancers with the highest disease burden in 2003. Similar to the overall observation discussed above, the estimated DALYs were largely a result of YLLs rather than YLDs. For pancreatic cancer, high case fatality due to late-stage diagnosis means that the disease burdens were almost entirely related to YLLs. Except for gender specific cancers, men had a greater share of the estimated disease burdens both in YLLs and YLDs across different types of cancer.

Chart 2.16: Number of disability adjusted life years (DALYs), years of life lost (YLLs) and years lived with disability (YLDs) of cancers with the highest disease burden in 2003



Source: Beggs et al 2007

2.2.2 Hospital admissions

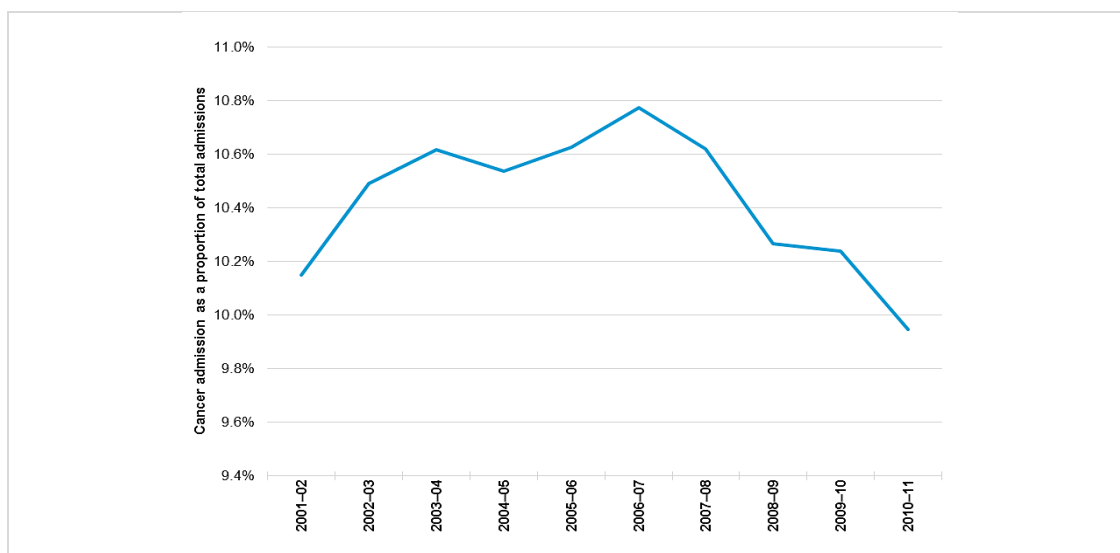
The number of cancer-related hospitalisations within any given year is another indicator of the burden of cancer in Australia. According to the AIHW's Cancer in Australia report, in 2010-11, about 10% (880,432) of all admissions to Australian hospitals were related to the management of cancer⁶ (AIHW & AACR 2012).

There is an increase in the rate of total cancer related hospital admission. Between 2001-02 and 2006-07, total admissions increased on average by 3.8% per annum, increasing to 4.1% on average per annum between 2006-07 and 2010-11 (AIHW & AACR 2012). These changes reflect a multitude of influences, including changes in population demographics and disease burden.

However, cancer related hospital admission as a proportion of total public and private hospital admissions appears to be declining (Chart 2.17, p.26), but the overall magnitude of this change is small: 0.8% absolute change between 2006-07 and 2010-11. This decline could be due to changes in treatment pathways for cancer patients, including increased use of non-admitted hospital services to deliver cancer care (e.g. use of outpatient services, and use of medicines that may reduce or delay the needs for inpatient care). A study in the US found that there was a shift of cancer treatment cost from the inpatient setting to the outpatient setting between 1987 and 2001-2005, similar to the trend in other medical service areas (Tangka et al 2010). The authors attributed this shift to advances in medicine and technology, and other factors such as changing practice of care (e.g. receiving chemotherapy and radiation therapy in the outpatient setting); changing demographics; legislative and policy change; and payers' cost-containment strategies (Tangka et al 2010).

⁶ The AIHW defines a cancer related admission as either: (1) cancer was recorded as the principal diagnosis (ICD-10 AM codes C00-C97, D45, D46, D47.1 and D47.3); or (2) cancer was recorded as an additional diagnosis where the principal diagnosis code related specifically to health services or treatments of patients with cancer (such as Z51.1 Pharmacotherapy session for neoplasm).

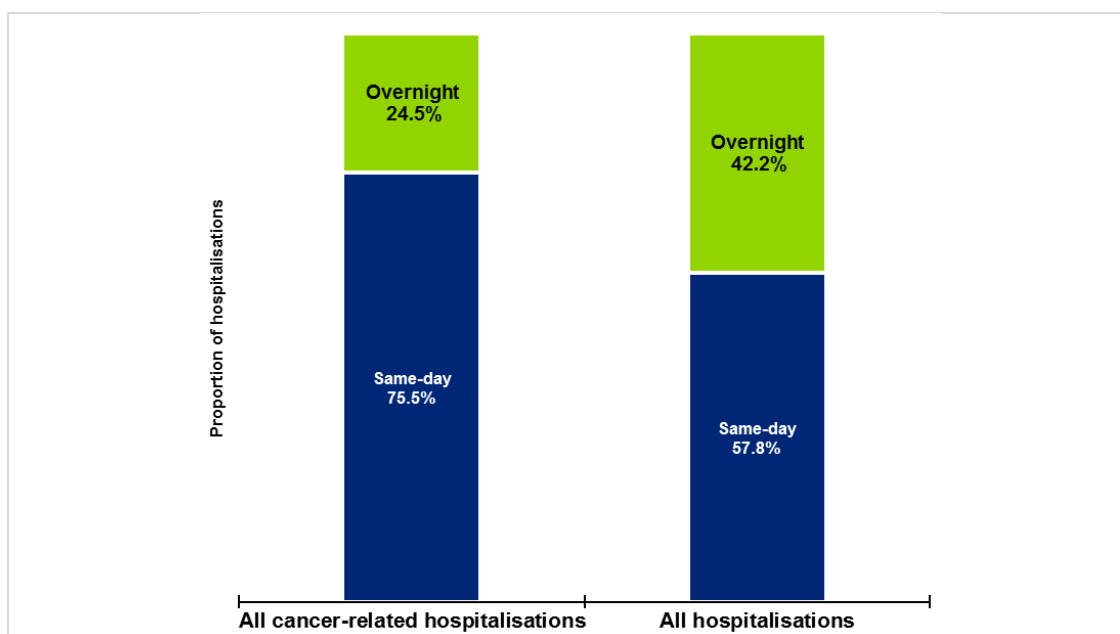
Chart 2.17: Cancer related admission as a proportion of total hospital admissions, 2001-02 to 2010-11



Source: AIHW & AACR 2012: Cancer related admission 2001-02 to 2010-11;
 AIHW 2011b: All admission 2006-07 to 2010-11;
 AIHW 2009: All admissions 2003-04 to 2005-06; and
 AIHW 2007: All admissions 2001-02 to 2002-03.

The majority of cancer related hospitalisations (75%) were same-day admissions (Chart 2.18). For those patients who stayed overnight, the average length of stay (LOS) was 7.6 days, compared to a lower ALOS of 5.8 days for all hospitalisations⁷ (AIHW & AACR 2012).

Chart 2.18: Proportion of same day hospitalisations in cancer related hospitalisations compared to all hospitalisations, 2010-11

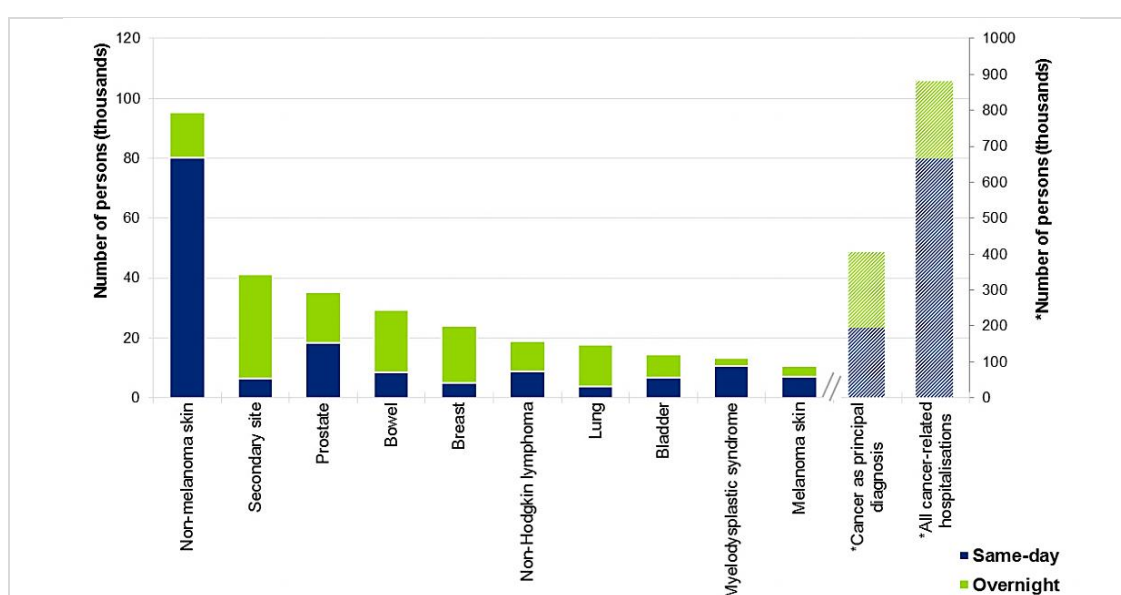


Source: AIHW & AACR 2012

⁷ All hospitalisations refer to all ICD-10-AM codes (A00–Z89)

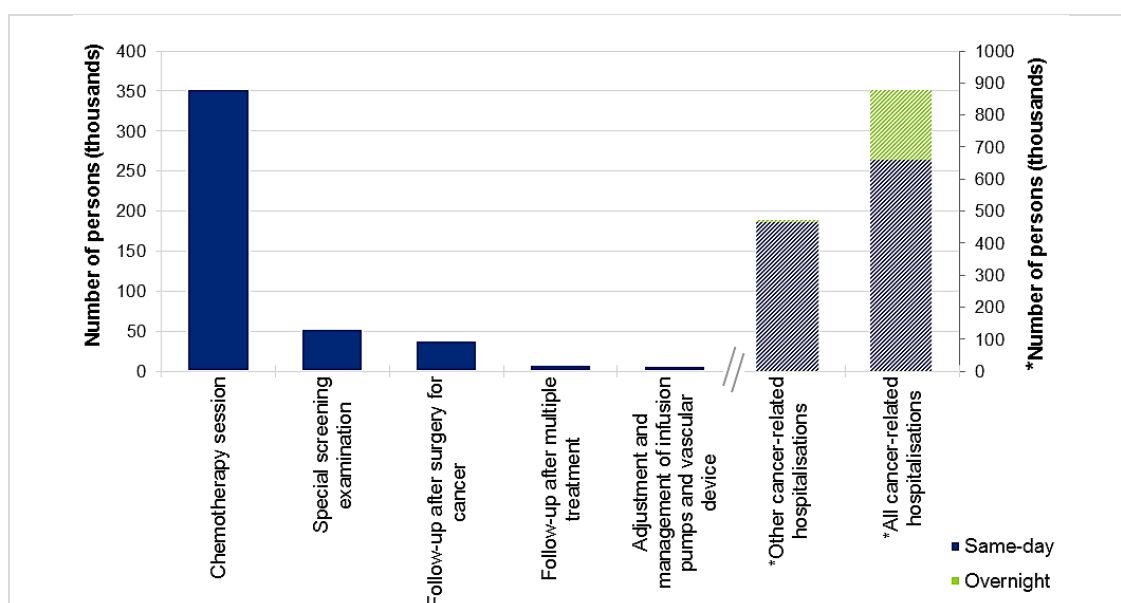
Non-melanoma skin cancer represented the largest number of hospitalised persons in 2010-11 (Chart 2.19), with a considerably higher proportion of same-day hospitalisation compared to the other most common hospitalised cancers (AIHW & AACR 2012). In comparison, secondary site cancers, bowel cancer, breast cancer and lung cancer had higher proportions of overnight hospitalisations, possibly reflecting the severity of conditions. A majority of hospital admissions were day admissions to receive chemotherapy (Chart 2.20).

Chart 2.19: Ten most common hospitalisations with cancer as principal diagnosis, 2010-11



Source: AIHW & AACR 2012

Chart 2.20: Five most common other cancer-related hospitalisations, 2010-11



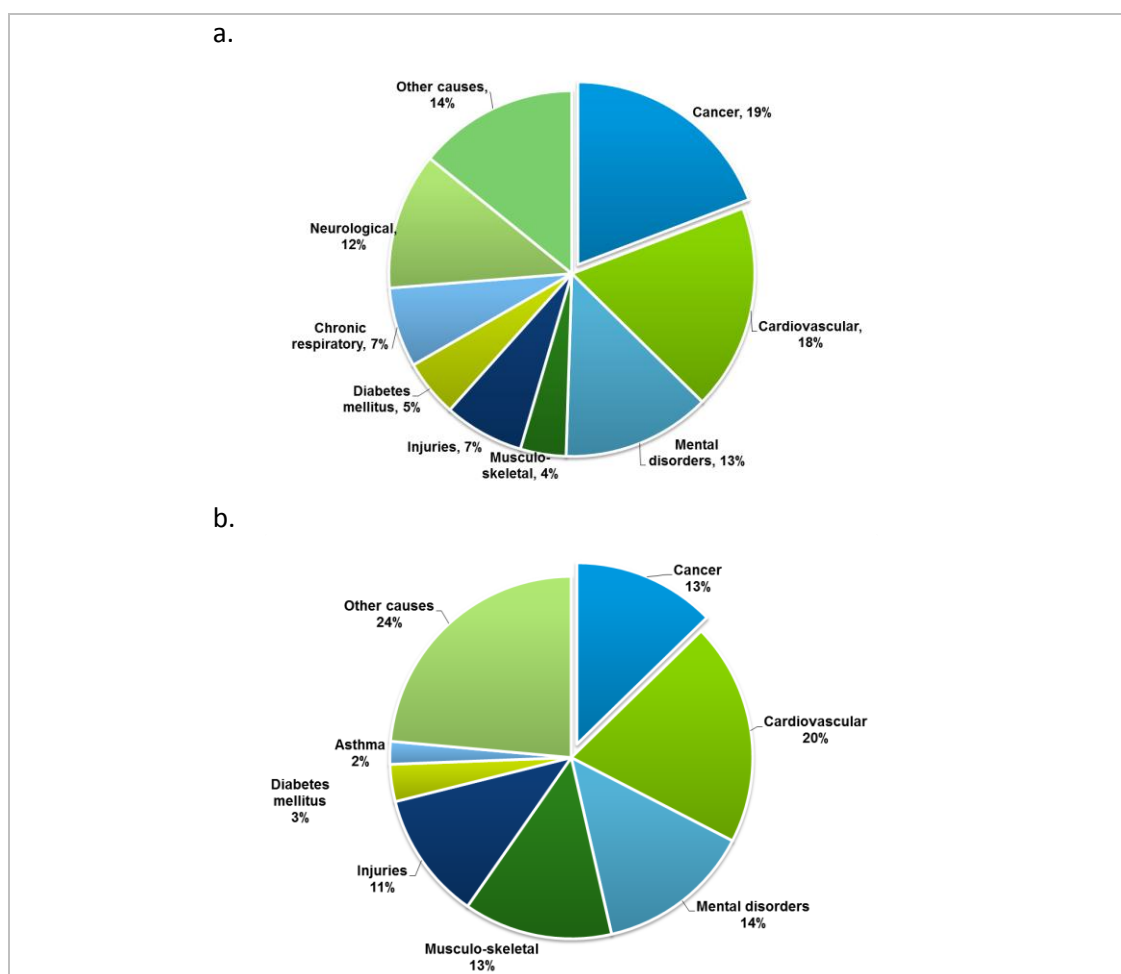
Source: AIHW & AACR 2012

Cancer was the most common (59%) principal diagnosis in palliative care hospitalisations and these hospitalisations accounted for 3.8% of all cancer related hospitalisations (AIHW & AACR 2012). In 2010-11, there were 33,278 palliative care hospitalisations (AIHW & AACR 2012). Secondary site, lung, bowel, pancreatic cancer and prostate cancer represented the most common principal diagnosis for palliative care cancer hospitalisations.

2.2.3 Cancer expenditure and economic cost

Cancer-induced morbidity and mortality impose significant economic losses to our society. There appears to be a misalignment between burden of disease and healthcare expenditure. In 2003, cancer received 13% of the total health expenditure, but was responsible for nearly one-fifth (19%) of premature death and disability in Australia (Chart 2.21a). In comparison, musculoskeletal diseases also accounted for 13% of health expenditure but only 4% of the burden of disease. More recent data on BoD and expenditure across all disease areas are not available for comparison. Given the considerable changes in cancer epidemiology, cancer care (i.e. prevention, diagnosis and treatment) and health system reform over the past decade, there is a need for further study in this area.

Chart 2.21: (a) Burden of disease by disease group in 2003; (b) Allocated health expenditure in 2004-05 by disease group



Source: Begg et al 2007, and AIHW 2010

The following sections identify costs for cancer prevention, management, and treatment. Persons with cancer-induced morbidity and mortality receive care in a number of settings. The most recent published data has been used in each cost category. To ensure consistency, data have been inflated to 2012 prices where required.

2.2.3.2 Expenditure on primary health care

Primary healthcare expenditure was estimated from the data of Bettering the Evaluation and Care of Health (BEACH) program⁸. These data are reflective of the overall GP service items claimed through Medicare (Britt et al 2011). However, the BEACH data is limited by a low participation rate of 21.3% from the sampled general practices (Britt et al 2011). As such, the final sample might not be fully representative of patient demographic and clinical characteristics in Australia, because there may be differences in patient cohort seen by sampled and non-sampled GPs. While there are some limitations to extrapolating the BEACH data, it provides the best means to estimate the use of primary care in the management and treatment of cancer in Australia.

The BEACH data identified episodes of GP care where management of neoplasms was given as a reason for the service encounter (Britt et al 2011). In 2010-11, there were 104.1 million service encounters⁹ attracting at least one MBS or DVA payment. Neoplasm management accounted for 4.3 consultations for every 100 service encounters (95% confidence interval: 4.1, 4.6) between April 2010 and March 2011, corresponding to 4.48 million service encounters. Assuming a cost of \$36.30 per encounter (May 2013 schedule; DoHA 2013a), the provision of primary care for the management of neoplasms incurred expenditure of \$162.5 million to the Australian Government.

It is important to note that this estimate is conservative for several reasons. First, the data did not account for all primary care related to cancer, particularly for diagnostic and preventive procedures such as pathology services and treatments by cancer specialists.¹⁰ GP encounters were costed at \$36.30, with an assumption that the consultations were on average 20 minutes. It is likely that consultation may last longer than 20 minutes or include other procedures, which would attract multiple and higher MBS fees. This estimate also excludes costs related to pathology and imaging services, and specialist treatments.

Patient contributions were costed according to Medicare data on bulk billing rates for the first quarter in 2013 (DOHA 2013b), and information identified in a targeted search of recent literature regarding patient co-payments in 2012. GP visits were bulk billed in 81.5% of patient encounters, with an average co-payment of approximately \$27.25 among patients who were charged (Sahari 2011, inflated to 2012 prices). On this basis, the total costs to individuals for primary care associated with cancer were estimated to be \$22.6 million in 2012, excluding out-of-pocket pathology costs. Together with the Government costs, the total estimated costs for cancer care in the primary setting were \$185.1 million.

⁸ The BEACH program collects data from a random sample of about 1,000 GPs each year, who report details of 100 consecutive patient encounters.

⁹ Estimated based on BEACH 2010-11 data (Britt et al, 2012) the number of MBS items claimed in 2010-11 (118.1 million) and the proportion of encounters which attracted an MBS fee. This calculation also accounts for encounters which have multiple MBS items claimed.

¹⁰ BEACH collects some data on treatments, referrals, pathology, imaging and other investigations by selected disease; however, publically available data was not available on the allocation of these to GP encounters related to cancer. This data is not available for specialists who charge MBS fees.

2.2.3.3 Expenditure on cancer medicines in PBS and RPBS

PBS and RPBS expenditures was estimated from reported expenditures on Sections 85 and 100 items with Anatomical Therapeutic Chemical (ATC) Classification System codes of L01, L02 and L03. In 2012, the PBS reported an expenditure of \$587.5 million for these groups of cancer medicines, representing approximately 6.4% of the total expenditure (\$9,193.7 million) (PBS 2012). This estimate is conservative because it excludes costs under special access schemes such as the Herceptin Program for late stage metastatic breast cancer. It also excludes expenditures on other medicines for the management of symptoms related to cancer (e.g. pain, constipation and other adverse effects). On the other hand, the estimate did not account for special pricing arrangements between the Government and the sponsor, which may result in some levels of rebate.

2.2.3.4 Expenditure on cancer related hospitalisations

Expenditure on public and private hospitalisation was estimated using the National Hospital Cost Data Collection (NHCDC). The NHCDC collects national public and private sector cost weights for Australian Refined Diagnosis Related Group (AR-DRG). The NHCDC collects costs related to the hospital stay of a patient including ward costs (accommodation costs), nursing costs, non-clinical salaries and pathology. The 2009-10 AR-DRG 6.0x Cost Report was used for public sector cost weight and the 2008-09 AR-DRG 5.1 Cost Report (latest available data) for private hospital cost weights.

A conservative approach was taken to identify AR-DRGs with cancer specific diagnosis: only DRGs specifically related to cancer were selected. This approach excludes patients who have a hospital admission related to cancer where they were not grouped into a cancer specific AR-DRG because of other procedures and treatment they received during their hospitalisation.

Private hospitals do not incur the total cost of providing medical services; the costs of medical services are estimated using the MBS. A conservative approach was taken in identifying the MBS items associated with cancer treatment. Total costs of hospitalisation in 2011-12 dollars were estimated at \$984.0 million in public hospitals (DoHA 2012). In private hospitals this was estimated to be \$332.5 million in hospital costs and \$462.8 million in medical fees (DoHA 2011; DoHA 2013a). Total estimated hospitalisation costs attributable to cancer were \$1,779.4 million.

This is a conservative estimate of the costs of cancer because:

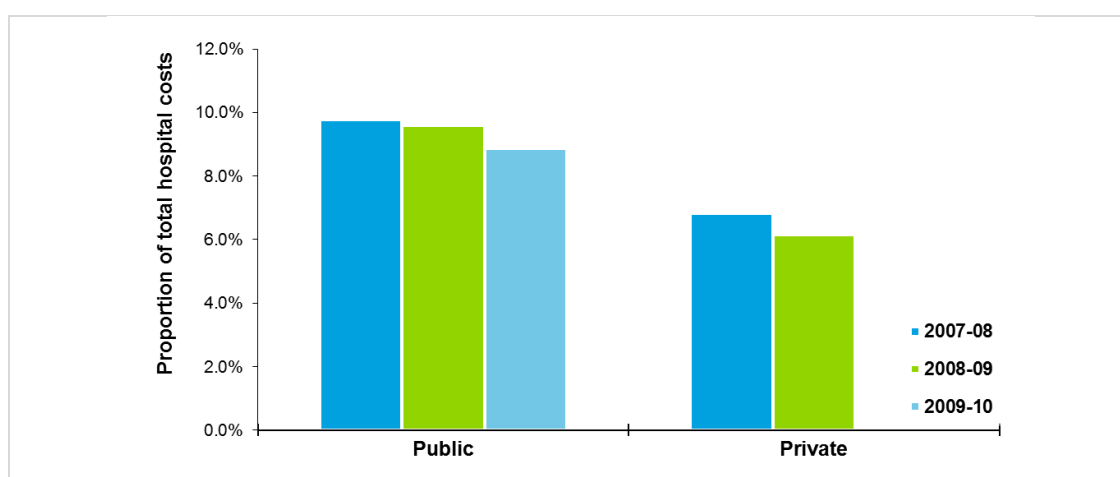
- Only cancer specific AR-DRGs were used, rather than all AR-DRGs where the patient received a principal diagnosis of cancer;
- Anaesthetic costs excluded from private medical fees, as well as other medical fees which could not be fully attributed to cancer;
- Private Health Insurance and patient contributions towards private medical care have not been included; and
- Non-admitted patient care such as outpatients and emergency department attendances have not been included.

Pharmaceuticals in hospitals

Pharmacy cost is one of the components of the costs incurred by hospitals, both in public and private settings. Chart 2.22 depicts pharmacy costs as a proportion of total hospital costs in private and public hospitals. Pharmacy costs as a proportion of total hospital cost for cancer has been decreasing both in public and private hospitals between 2007-08 and 2009-10.

In public hospitals, the absolute pharmacy costs have increased over this period, albeit at a slower rate than the total costs of the cancer hospitalisations. This reflects the fact that the prices of pharmaceuticals remain the same once set, while other costs such as labour (i.e. nursing time) increase over time. However, this is offset to an extent by the expansion of the hospital formulary with the introduction of newer and often more expensive medicines, which have the potential to increase the cost of pharmacy in the hospital setting.

Chart 2.22: Pharmacy costs for cancer related hospitalisation as a proportion of total hospital costs, 2007-08 to 2009-10



Source: NHCDC rounds 2007-08 (DoHA 2010), 2008-09 (DoHA 2011) and 2009-10 (DoHA 2012)

In the private hospital setting, the costs of pharmacy as a proportion of total hospital cost for cancer and the absolute expenditure have decreased between 2007-08 and 2008-09. This is likely to be due to cost shifting between the private hospital setting and the PBS, with more pharmaceutical costs incurred outside of the private hospital setting.

2.2.3.5 Prevention – cancer screening programs and immunisations

Expenditure on cancer screening programs was estimated according to expenditure on screening programs for breast cancer, bowel cancer and cervical cancer in 2008-09 (AIHW 2011a). Using an average annual growth rate of 3.9% per year, the expenditure on screening programs was estimated to be \$392 million in 2012.

Immunisation expenditure was estimated as the total PBS benefits paid for Hepatitis B and Papilloma virus vaccinations in 2012. This does not account for any patient contributions, or the costs of the GP visits to receive the immunisation. In 2012, the PBS paid \$381.9 million for cancer related immunisations (DoHA, 2013c).

2.2.3.6 Research on cancer

Expenditure on research was estimated using the ABS data on total expenditure on R&D for 'Health' in 2008-09 (ABS 2010). Research expenditure was inflated to 2012 prices based on trend growth in Health R&D expenditure. The proportion attributable to neoplasms was estimated using the proportion of research expenditure on neoplasms in 2004-05, which constituted 17% of the total Health R&D expenditure (AIHW, 2010). Based on these assumptions, the expenditure on cancer research was estimated to be \$1,155 million in 2012.

2.2.3.7 Informal care cost

Informal care represents the costs incurred by individuals caring for patients, such as family members and friends. The cost of informal care for patients living with cancer was estimated from the Access Economics (2007) estimate of informal carers per person with 'active' cancer¹¹. Based on average earnings and employment rates reported by the ABS (ABS 2013a and ABS 2013b), the cost of informal care for cancer patients was estimated to be \$173 million.

2.2.3.8 Total cost

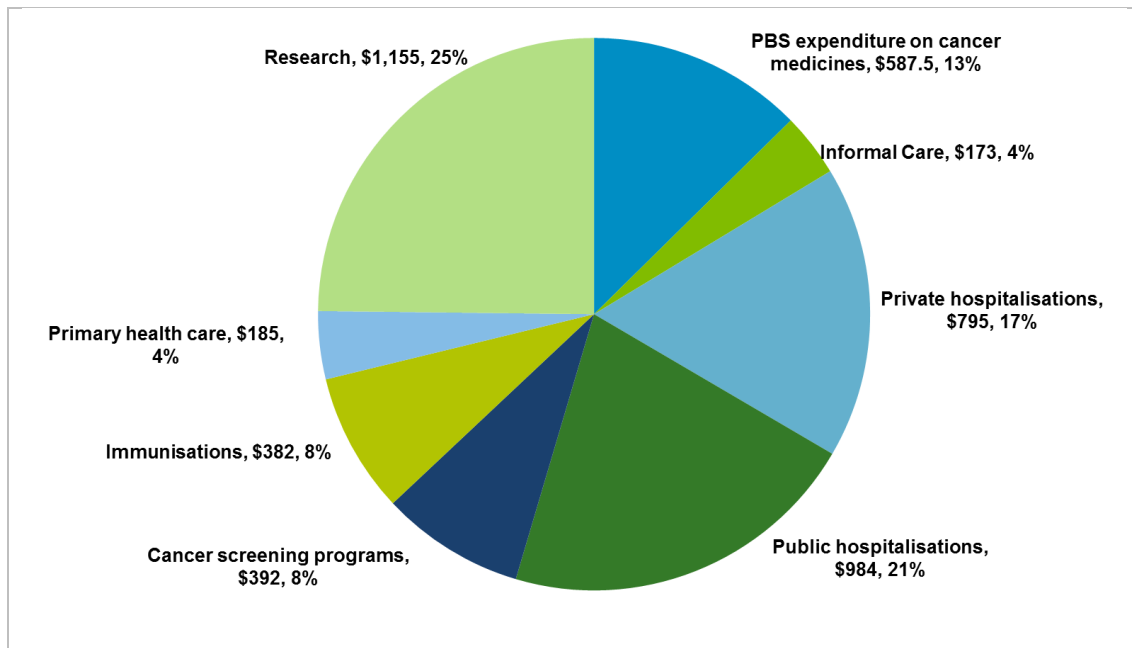
This report estimates the total cost of cancer in 2012 to be \$4.7 billion. PBS expenditure on cancer medicines constituted 13% of the total expenditure in 2012. Table 2.1 and Chart 2.23 detail the cost breakdown of this estimate. It is important to note that this estimate is a significant underestimate of the real cost of cancer, as the estimation approach is conservative (e.g. does not fully account for the extent of informal care), and the calculation does not include indirect costs such as travel and lost productivity due to illness, and expenditure on pharmaceuticals that are not listed on the PBS or hospital formularies.

Table 2.1: Total cost of cancer

Cost category	Estimated expenditure in 2012 dollars (\$ million)
Primary Health Care	\$185.1
PBS expenditure on cancer medicines	\$587.5
Hospitalisations	\$1779.4
Private	\$795.4
Public	\$984.0
Prevention	\$773.9
Cancer screening	\$392.0
Immunisation	\$381.9
Indirect costs	\$1,808.0
Research	\$1,155.0
Informal Care	\$173.0
Total expenditure	\$4,653.9

Source: Deloitte Access Economics

¹¹ This is estimated from the ABS SDAC data in 2003

Chart 2.23: Total cost of cancer by sector

Source: Deloitte Access Economics

2.3 Summary

This chapter reviewed the population statistics on cancer in Australia and other countries. It found that cancer has a high disease and economic burden in Australia, even relative to other comparable countries. While Australia has performed well in achieving better cancer survival than other countries, and has been well regarded for its cancer control effort, cancer will remain a significant challenge in the future. This is because cancer cases will increase by almost 40% from 2007, reaching about 150,000 in 2020 in Australia (AIHW 2012b). This chapter also found that there appears to be a misalignment between burden of disease and healthcare expenditure, although further study is needed to confirm this.

Resource re-allocation according to disease and economic burden, with consideration to the incremental benefits of resources allocated, may be justifiable. Particularly, innovative technology that may reduce or delay the need for hospital based care (e.g. self-administered treatments) could provide broader benefits to society. These benefits need to be assessed and understood.

Finally, the collective burden of rarer cancers deserves attention, particularly regarding the increased incidence of some rare cancers among specific sub-populations.

3 Current and future cancer medicines

The process of medicines discovery and development is complex, lengthy and typically high risk. Whilst overall approval success rates and development costs for cancer medicines are similar to other areas, these medicines generally have smaller patient populations and shorter duration of therapy.

There are more than 250 indications across 114 chemical entities currently in Phase II and III clinical development by 16 major pharmaceutical companies in oncology. Clinical trials in oncology represent around one-fifth of all interventional trials identified in a recent review.

The regulatory and reimbursement system should therefore anticipate any challenges these technologies would have on the current assessment framework, and be responsive and adaptive in its requirements so as to facilitate access to these medicines.

Treatment is one of the cornerstones of cancer control. Effective treatment of cancer often requires several of the following approaches: radiation therapy, surgery, transplantation, chemotherapy, and other pharmacological therapies (e.g. biological therapies, gene therapies, targeted therapies). The choice of cancer treatment is informed by an assessment of the cancer aetiology and the extent to which a cancer has developed (i.e. staging¹²). The following sections provide an overview of the currently available pharmacological treatments, and a horizon scan of cancer medicines currently in mid- to late-stage clinical development.

3.1 Current cancer medicines

3.1.1 Cytotoxic chemotherapy

Pharmacological treatment of cancer largely comprises cytotoxic chemotherapies. Chemotherapeutic agents are typically used in combination according to standardised regimens, and in conjunction with other cancer treatments, such as radiation therapy or surgery. These therapies may aim to cure the cancer especially at an early stage, but most often they are given with a view to prolonging life or to palliating symptoms. Some examples of cytotoxic chemotherapies include:

- **Alkylating agents:** melphalan, ifosfamide, chlorambucil, cyclophosphamide, busulfan, carmustine, fotemustine, temozolomide;
- **Antimetabolites:** methotrexate, raltitrexate, pemetrexed, mercaptopurine, fludarabine, cladribine, thioguanine, gemcitabine, fluorouracil, azacitidine, cytarabine, capecitabine;

¹² The staging systems endorsed by the Union for International Cancer Control are now universally accepted by the clinical and research communities.

- **Plant alkaloids:** vincristine, vinblastine, etoposide, docetaxel, paclitaxel, cabazitaxel;
- **Cytotoxic antibiotics :** doxorubicin, idarubicin, epirubicin, mitozantrone, bleomycin;
- **Platinum compounds:** cisplatin, oxaliplatin, carboplatin; and
- **Other compounds:** hydroxyurea, arsenic, irinotecan, topotecan.

The major disadvantage associated with cytotoxic chemotherapy is that it has non-selective actions against rapidly dividing cells, regardless of whether they are cancerous or non-cancerous. The lack of specificity of chemotherapy is the primary cause of the majority of commonly known haematological, neurological, gastrointestinal and other side effects. These adverse effects may be severe in some cases, including bone marrow suppression (i.e. myelosuppression), toxicity to the gastrointestinal tract, nausea and vomiting, fatigue, pain, alopecia and infertility (Bonaventura 1995). Lenograstim, filgrastim, or pegfilgrastim are often used following myelosuppressive therapy to stimulate the bone marrow to increase production of neutrophils – white blood cells that are critical for defending against infection.

3.1.2 Endocrine therapy

Hormonal treatments of cancer can be either corticosteroids or sex hormones. Corticosteroids such as dexamethasone and prednisolone are often used as part of a combination treatment regimen for haematological cancers, such as leukaemia, multiple myeloma, and lymphoma. They are also often used to reduce swelling around tumours of the brain and spinal cord.

Sex hormones are used to control the growth of tumours that are responsive to hormones: breast, endometrium and prostate. This treatment exerts its effect either by interfering with the level of circulating hormones (e.g. Gonadotropin releasing hormone (GnRH) analogues) or disrupting the interaction between the hormones and the tissues (e.g. receptor antagonists). Examples of hormonal treatments are:

- **Progestogens:** medroxyprogesterone, megestrol;
- **GnRH analogues:** leuporelin, goserelin, triptorelin;
- **Hormones antagonists**
 - Anti-oestrogens: tamoxifene, toremifene;
 - Anti-androgens: flutamide, nilutamide, bicalutamide, cyproterone;
 - Aromatase inhibitors: letrozole, anastrozole, exemestane;
 - Anti-GnRH: degarelix.

3.1.3 Biological and targeted therapies

More recently, advances in the field of molecular biology have led to a large number of molecular targets for novel anticancer medicines. These biological and targeted cancer therapies may specifically interfere with cell growth signalling, the regulation of blood vessel development, programmed cell deaths, or may stimulate the immune system to destroy specific cancer cells, or deliver toxic drugs to cancer cells. Through these specific molecular mechanisms, these targeted therapies are able to block the growth and spread of cancer, with lesser interference to non-cancerous cells. Importantly, some of these targeted therapies have the additional advantage of being associated with known

biomarkers. This characteristic enables use of the therapy in a proportion of patients who express a particular marker and thus are most likely to respond to the therapy. Examples include trastuzumab in breast cancer patients with over-expression of the HER2 protein, cetuximab in patients with colorectal cancer who expressed wild-type KRAS gene, gefitinib for patients with non-small cell lung cancers that express EGFR, and vemurafenib in melanoma patients who expressed mutation of the BRAF gene.

The advent of these biological and targeted therapies has greatly expanded cancer treatment options, particularly for patients with late-stage metastatic disease for whom conventional cytotoxic chemotherapies were ineffective. Some examples include:

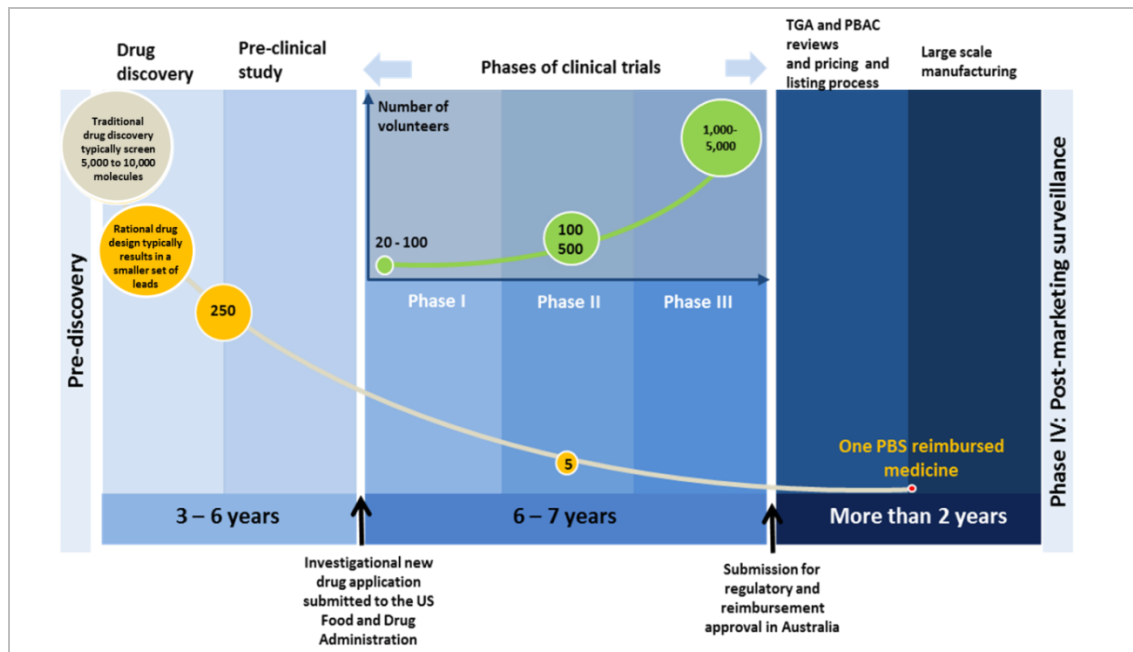
- **Monoclonal antibodies:** rituximab, bevacizumab, cetuximab, trastuzumab, ipilimumab, ramucirumab, brentuximab;
- **Protein kinase inhibitors:** lapatinib, gefitinib, sorafenib, sunitinib, imatinib, erlotinib, nilotinib, dasatinib, pazopanib, vemurafenib; and
- **Others:** thalidomide, lenalidomide.

3.2 A horizon scan of cancer medicines

3.2.1 An overview of the drug development process

The process of medicines discovery and development, leading to the successful marketing of a pharmaceutical, is complex, lengthy and typically high-risk. Although development of medicines can proceed along varied paths for different chemical entities, the process generally comprises pre-clinical and clinical stages, with the latter further divided into three phases of clinical trials (Figure 3.1). The transition from one stage/phase to the next during the development process is a decision for the sponsoring firm and data monitoring committee for the trial, generally with consideration to the evidence of safety and the assessment of potential return on further investment. The safety consideration typically precludes further development for a substantial number of potential candidates, especially at the early stage/phase.

It is worth noting that recent advancement in the understanding of bio-molecular targets has resulted in the adoption of rational drug design in the drug discovery process. In this case, rather than screening large numbers of potential drug candidates in the chemical libraries for possible activity (activation / blocking) of targets as in the traditional paradigm, a smaller set of “leads” is identified on the basis of current knowledge about the bio-molecular targets (Mandal et al 2009, Guido et al 2011). This may result in reduced time and costs in the initial research translation processes from pre-clinical to clinical phases.

Figure 3.1: Process of drug discovery and development

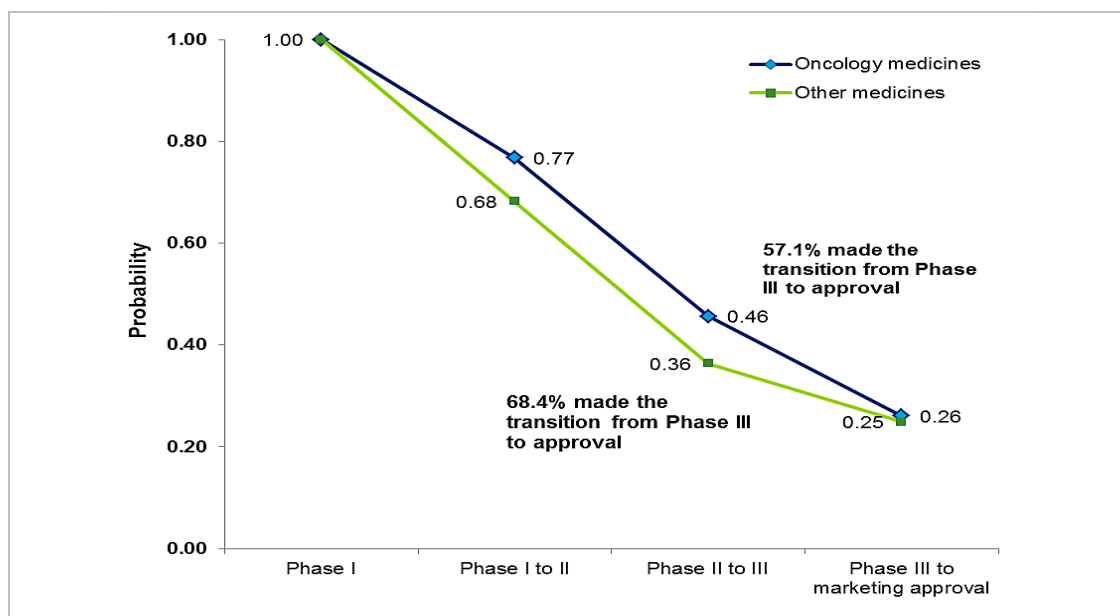
Source: adapted from PhRMA (2008).

The development of a new medicine following discovery typically requires a time period of 10 to 15 years. This period is for the collection of scientific evidence to support the quality, safety and efficacy of the drug, and increasingly, cost effectiveness information to support the reimbursement decision.

It is well recognised that the drug development process has a low rate of success. The probability of a successful drug candidate going through all phases of drug development has been estimated as 1 in every 5,000 molecules, with the successful odds improving to 3 in 5 when a drug candidate enters the Phase III clinical trial program (PhRMA 2008).

A particular challenge for developing cancer medicines is the high rate of failure in demonstrating efficacy and safety after entering the expensive Phase III clinical trials. In an analysis by DiMasi and Grabowski (2007), cancer medicines that had entered Phase III trials had a lower rate of success in gaining an approval compared to other types of medicine (57.1% versus 68.4%). However, the overall approval success rates were similar for oncology and other medicines because of a higher likelihood of progression in early phases for cancer medicines (Chart 3.1). Whilst overall approval success rates and development costs for oncology drugs are similar to other drugs (DiMasi and Grabowski 2007), cancer medicines may be used for smaller patient populations and shorter durations.

Chart 3.1: Transition probabilities between clinical trial phases for oncology and other medicines between 1993 and 2002



Source: DiMasi et al (2007)

There have been efforts to achieve greater efficiency in the drug discovery and development processes, with a view to reducing costs. In addition to using rational drug design approaches mentioned above, other strategies include: identifying the causes of trial failure and success factors (e.g. Kola and Landis 2004); using statistical techniques to improve trial design and analysis (e.g. Rawlins and Chalkidou 2011); using adaptive trial design to optimise assessment of combination therapies (e.g. O’Carragher et al 2012); and reducing the costs of managing clinical trials (e.g. Eisenstein et al 2008). However, the overall rates of success remain low and the development costs are high.

3.2.2 High cost of medicines development

Given the long and complex process, the costs associated with the successful development of a drug are substantial especially during Phase III clinical trials. In a study by DiMasi et al (2003), the total cost associated with the development of a new drug was estimated at US\$802 million in 2000 (Table 3.1), based on financial information provided by 10 companies for 68 new medicines. Direct costs of research and development accounted for about 50% of this estimate; the other 50% was associated with the opportunity cost of committing investment capital for years in research programs of drug candidates that were later proven to be ineffective.

Table 3.1: Estimate of average research and development costs of a new medicine

Category of R&D costs	Total costs (over 11.8 years)	Preclinical phase (over 4.3 years)	Clinical trials and FDA approval (over 7.5 years)
Total cost	\$802 million	\$335 million	\$467 million
Direct cost	\$403 million	\$121 million	\$282 million

Opportunity cost*	\$399 million	\$214 million	\$185 million
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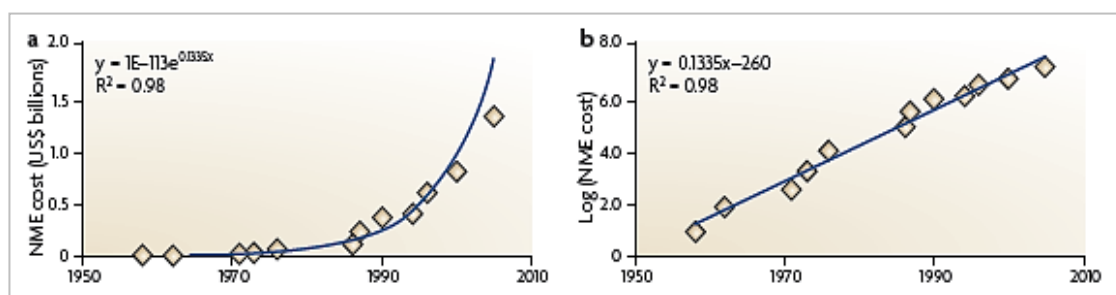
*The potential financial return from alternative investments using the fund otherwise tied up for the development of unsuccessful medicines;

Source: Congressional budget office (2006); DiMasi et al (2003)

The considerable cost of drug development estimated by DiMasi et al (2003) has generated discussion in the literature, especially in relation to its reliability. At least one study has now independently substantiated the robustness of this estimate (Adams and Brantner 2006). Similar to DiMasi et al (2003b), Adams and Brantner (2006) also noted a large variability associated with the estimate: it ranged from \$500 million to \$2 billion, depending on the developing firm and the therapeutic area. In this study, the expected capitalised cost for a new cancer medicine was US\$1,042 million in 2000, second only to the average costs associated with medicines developed for respiratory disorders (US\$1,134 million).

In addition to the substantial capital investment, the pharmaceutical industry faces further challenges in the rising costs of R&D. Based on the costs estimated for drug discovery and development of 12 drugs between 1960 and 2008, Munos (2009) found that the costs of R&D have been growing exponentially at a rate of 13.4% per year over the 48 years in Figure 3.2a. The logarithmic scale shown in Figure 3.2b shows this as a positive linear trend.

Figure 3.2: The rising cost of development of new medicines

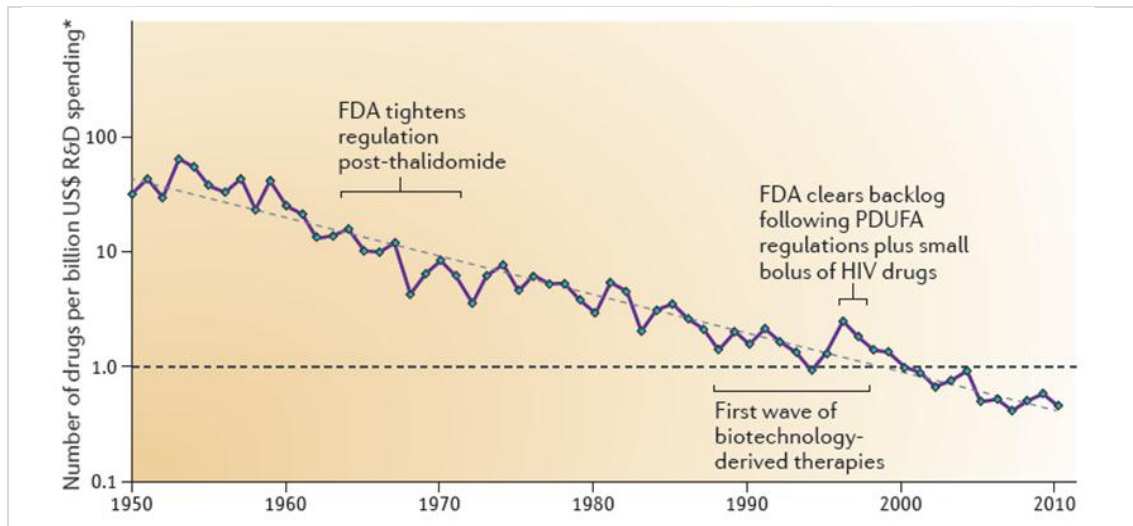


Key: NME – New Chemical Entities;

Source: extracted from Munos (2009) Figures 3a and 3b

Furthermore, Scannell et al (2012) demonstrated that the number of new drugs approved per billion US dollars spent on research and development of medicines has roughly halved every nine years since 1950, falling around 80-fold in inflation-adjusted terms (Figure 3.3).

Figure 3.3: Number of drugs approved by the US Food and Drug Administration per billion US dollar spent on drug research and development, 1950-2010



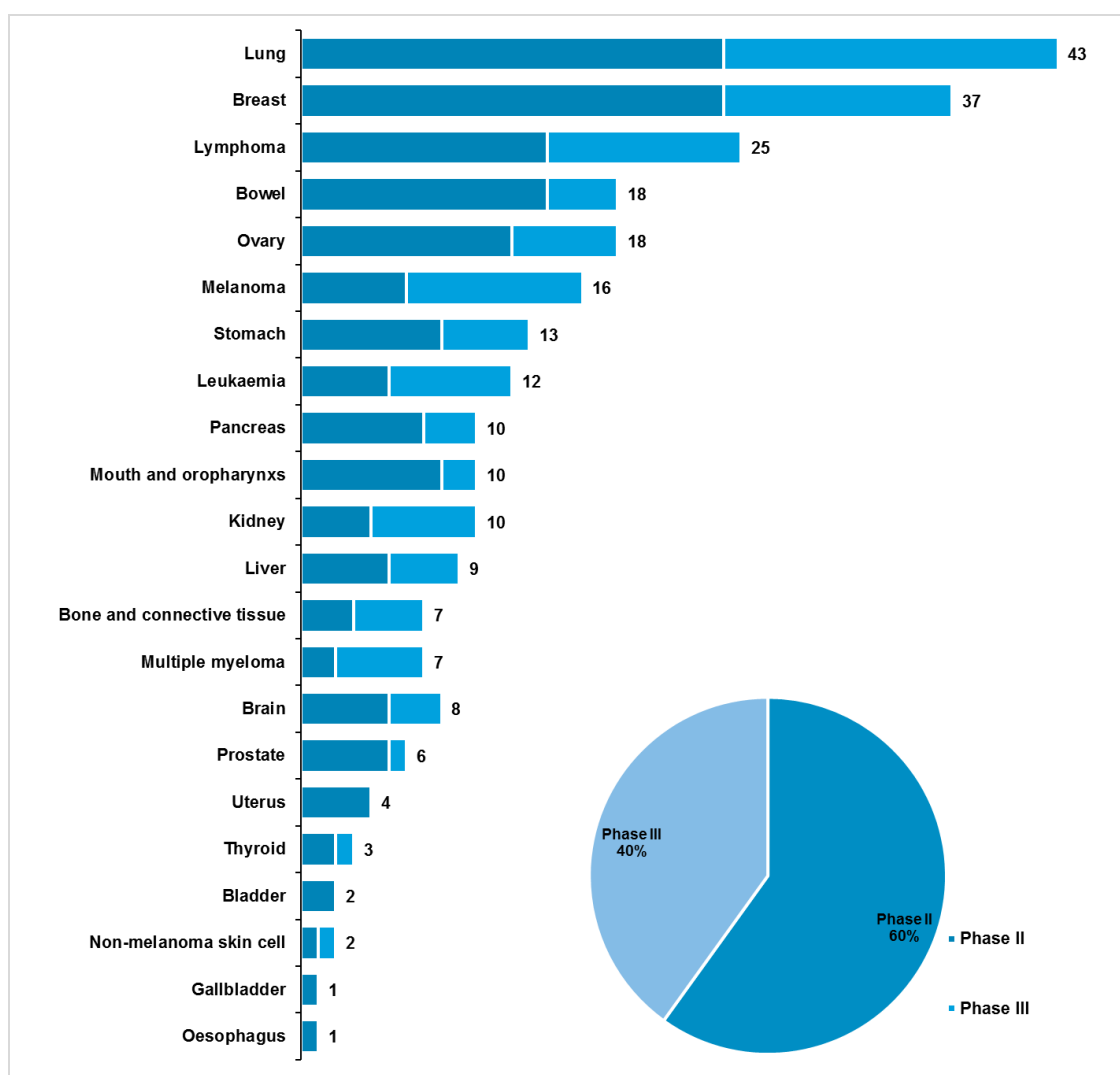
Source: Scannell et al 2012

3.2.3 Cancer medicines in the clinical trial pipeline

Advances in the field of molecular biology have been, and will be, a strong catalyst for the development of novel anti-cancer medicines. Despite the significant improvement in cancer survival over the past decades, the medicines industry and cancer research institutions continue to commit substantial human and financial resources to develop anti-cancer medicines, with a view to meeting high unmet clinical need. In a recent review of all clinical studies registered on ClinicalTrials.gov between October 2007 and September 2010, the authors found a total of 8,942 oncology trials, which corresponds to about one-fifth of all interventional trials identified (n=40,970) (Hirsch et al 2013).

This report undertook a review of cancer medicines currently in clinical development by collating information from company websites, ClinicalTrials.gov, the EU clinical trials register, and members of the Oncology Taskforce. This horizon scan identified a strong pipeline of cancer medicines that would potentially be available to cancer patients and oncologists within the next decade. There are more than 250 indications across 114 chemical entities currently in Phase II and III clinical development by 16 major pharmaceutical companies in oncology¹³. As expected, more medicines are in Phase II development than in Phase III. If successful in undergoing clinical trials, it is likely that a large proportion of these medicines would be submitted to the TGA and PBAC for regulatory and reimbursement consideration. The system should therefore anticipate any challenges these technologies would have on the current assessment framework, and be responsive and adaptive in its requirements so as to facilitate access to these medicines.

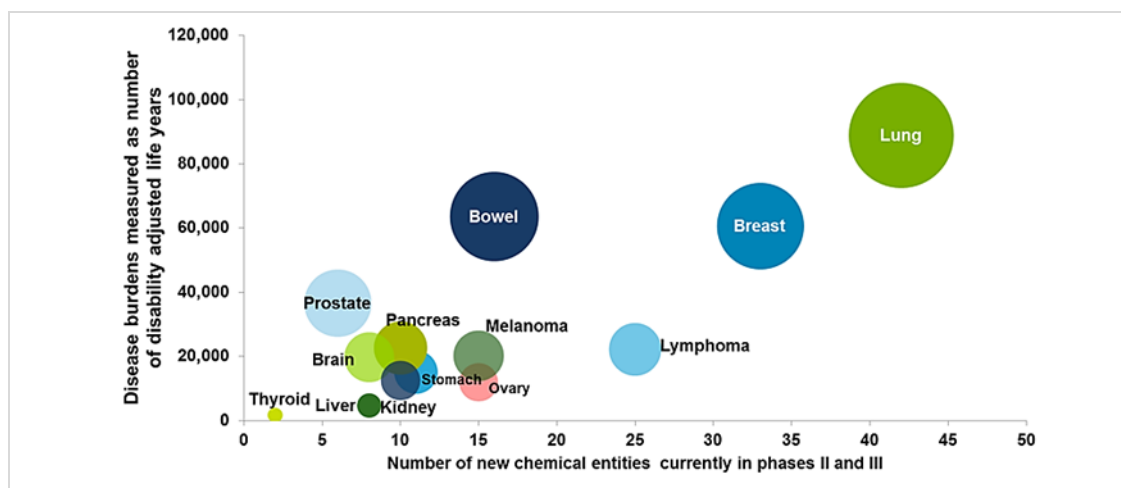
¹³ AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Merck, Merck Serono, Novartis, Pfizer, Roche/Genentech, Sanofi, Takeda. It is important to note that a number of innovative cancer medicines in the developmental pipeline of smaller firms, such as AVEO pharmaceuticals, GPC Biotech/Agennix, the Enzon Pharmaceuticals, The EntreMed, and Curis; these are not included in the horizon scan.

Chart 3.2: Number of molecules in Phase II and III clinical development, by cancer type

Source: Company websites, ClinicalTrials.gov, EU clinical trials register; and members of the oncology Taskforce.

As shown in Chart 3.3, the number of cancer medicines currently in Phase II and III development is approximately correlated to the disease burden of cancer types. That is, there are more molecules in development for cancers that are of higher disease burdens, rather than incidence. For example, there are proportionally fewer molecules developed for prostate cancer because it has a relatively lower disease burden compared to other types of cancer, even though prostate cancer is predicted to have the highest incidence. As expected, the horizon scan identified few molecules intended for the treatment of rare cancers (e.g. anal cancer). Overall, this indicates a focus in aligning R&D efforts to alleviate cancers with the higher disease burden from a population perspective. Encouragingly, the pipeline includes medicines for cancers with low 5-year survival rates e.g. cancers of the pancreas, lung and liver (see Chart 2.7).

Chart 3.3: Correlation between number of cancer medicines currently in phases II and III clinical trial indicated for the type of cancers and the burden of cancers



Source: Deloitte Access Economics

It is important to note that approximately 4 in every 5 molecules in Phase II or III clinical development are new chemical entities. Many of these molecules have direct actions on new molecular targets, indicating an ongoing effort to innovate in line with advancements in the bio-molecular understanding of cancer.

Importantly, the horizon scan identified an emerging trend in developing combination therapy to target cancer biomarkers in the single or multiple pathways of oncogenesis. Some examples include:

- Treatment for metastatic melanoma by inhibiting both mitogen-activated protein kinase and the BRAF gene; and
- Treatment for non-Hodgkin Lymphoma by inhibiting both phosphoinositide 3-kinase and mammalian target of rapamycin (mTOR) on the PI3K/AKT/mTOR intracellular pathway relating to cancer cell death.

This trend signals a movement towards using targeted therapies in combination, similar to the current 'cocktail' approach of combining cytotoxic chemotherapies. This reflects the difficulty of treating cancer due to the complexity of genetic and bio-molecular pathways of oncogenesis. This complexity means that single agents typically have relatively low efficacy, and are susceptible to relapse and recurrence of cancerous cells due to drug resistance.

3.3 Summary

This chapter reviewed the current and future landscape of cancer medicines. Cytotoxic chemotherapy has been the mainstay of pharmacological treatment for cancer. With the advancement in molecular biology, the treatment landscape will continue to evolve towards greater use of targeted and biological therapies. There is an emerging trend in developing combination therapy to target cancer biomarkers in the single or multiple pathways of oncogenesis. Regulatory and reimbursement approval processes must anticipate the challenges of the changing landscape, and evolve in parallel.

4 Current arrangements to access to cancer medicines in Australia

An estimated 80% of all prescription medicines dispensed in Australia received subsidy via the PBS; this means that patient access to most medicines is significantly reduced, if not reimbursed under the PBS. In cancer, a 2012 review found that 42.2% of the total treatment protocols approved for use in a specialist oncology centre were off-label and were unfunded by the PBS.

A considerable number of patients receive access via sponsor compassionate access schemes. However, these arrangements do not provide sustainable access because their intent is to facilitate short-term access while the medicines are in the process of obtaining reimbursement approval.

Australia has one specific-purpose fund for cancer: the Herceptin program for late-stage metastatic breast cancer. This is in contrast to the comprehensive Cancer Drugs Fund in the UK.

In summary, access arrangements for cancer medicines are dependent on where a patient lives, who their physician is, their access to specialised cancer treatment and their level of private health insurance. The interplay of these factors means that access can be inequitable.

In Australia, a medicine must first receive regulatory approval from the TGA before it is available to patients. Patients may access medicines that have not received TGA approval only under specific circumstances (see sections 4.7.2 and 4.7.3). For regulatory approval, the sponsor needs to provide evidence of quality, safety and efficacy of the medicine.

The following sections discuss policies underpinning access to subsidised cancer medicines in Australia, and four pathways for patients to receive these medicines:

- **The PBS:** for community-dwelling patients, and for patients in private medical facilities, and outpatients or day-admitted patients in public institutions when accessing PBS-funded cancer chemotherapy;
- **Public hospital formulary:** for individuals who are admitted to public hospitals as public patients for care and treatment;
- **Private health insurance:** for individuals who enter a private contract with an insurer to access non-PBS reimbursed medicines; and
- **Other pathways:** access to medicines within a clinical trial setting, or via medicines sponsor's Compassionate Access Programs.

4.1 The PBS

Australia is widely regarded as having a world-class national pharmaceutical reimbursement scheme that plays an important role in ensuring access to medicines – the PBS. The initial scheme established in 1948 was limited in its capacity: it provided medicines free-of-charge to pensioners, and had a list of 139 ‘life-saving and disease preventing’ medicines for others in the community. Over the decades since its inception, the scope and structure of the PBS has evolved, alongside the changing landscape of population health and healthcare in Australia. Today, there are more than 740 medicines listed on the PBS. An estimated 80% of all prescription medicines dispensed in Australia received subsidy via the PBS.

With regard to oncology, there are about 170 PBS-reimbursed medicines (in various dosages and forms). Similar to medicines in other therapeutic areas, the PBS provides a range of anti-cancer drugs for community-dwelling patients. It also provides access to chemotherapy for cancer management, as specified under the Australian Health Care Agreement (AHCA 2003-08) between the Commonwealth and jurisdiction Governments. Under this arrangement, *participating public hospitals* would be able to supply PBS-reimbursed medicines under the following conditions:

- Access to the PBS for all public admitted patients *on discharge* and *non-admitted* patients. Patients will be able to get up to one-month's supply (or clinically appropriate supply of up to one month) of medication; and
- Access to a list of *chemotherapy drugs* subsidised by the Commonwealth Government. These chemotherapy drugs will be available to *day patients*.

4.1.1 PBS reimbursement policy and processes

The PBS is governed by the National Health Act 1953 (the Act). The Act specifies the establishment of a statutory independent expert committee – the Pharmaceutical Benefits Advisory Committee (PBAC) – to be responsible for assessing the evidentiary basis of the proposed listing presented in a submission by the requesting sponsor. On the basis of a positive recommendation from the PBAC, the sponsor makes a pricing application to the Pharmaceutical Benefits Pricing Authority (PBPA). Upon reaching a pricing agreement, the Minister makes the final decision with consideration to the PBAC and PBPA's recommendations, but these recommendations do not bind the Government to give effect to those recommendations.

As part of the routine PBS listing process, if the increased annual net cost to the Government associated with listing a medicine is projected to be more than \$10 million in any of the first four years of listing, the Cabinet must consider the proposed listing before the Minister may declare a listing on the PBS. Rarely, the Cabinet would intervene to reject a PBAC recommendation. However, in February 2011, the Government suspended the listing of eight medicines and vaccines that received positive PBAC recommendations, quoting financial difficulty as the reason, even though some of the listings would have no overall fiscal impact (e.g. they were recommended on cost minimisation grounds). Seven of these medicines eventually gained listing on the PBS after prolonged negotiation and considerable advocacy from health consumers. Although none of these medicines was for the treatment of cancer, the significant deviation from the routine process signalled a policy shift towards fiscal control rather than patient access.

Indeed, the Government's position in not observing the '\$10 million rule' was made clear in its response to the recommendations of the Senate Finance and Public Administration References Committee ('the Committee') on the Government's administration of the PBS (DoHA 2011). In August 2011, members of the Committee recommended the Government "reinstate the '\$10 million rule' so that medicines that have a financial impact of less than \$10 million in each year over the forward estimates can be listed on the PBS Schedule by the minister without waiting for Cabinet approval" (p. xi, Senate Finance and Public Administration References Committee 2011). However, the Government did not support this recommendation and stated (DoHA 2011):

It is appropriate for the Government to apply responsible fiscal scrutiny to proposed new PBS listings, as it does for all new expenditure. It has always been the Government's role to consider where finite resources would be best directed in the health portfolio and to weigh competing pressure on the budget across the health and other areas of government responsibility. (p.5)

In this response, the Government also stated that it "undertook to not defer any drugs that cost under \$10 million a year for a period of 12 months while the Government works with all parties to achieve longer term PBS sustainability" (p.5). In September 2012, the Government communicated a commitment to further extend the moratorium on Cabinet deferrals of listing to June 2014. However, the requirement for the Cabinet to consider all new listings with a net cost to the Government remains, and the Government has not ruled out the possibility of re-introducing deferrals beyond June 2014 (Medicines Australia, 2012). Many stakeholders (see chapters 5 and 6) view this extra step of having to negotiate approval from the Cabinet following the rigorous PBAC process as another hurdle to gain reimbursed access.

4.1.2 Cost effectiveness requirements

Similar to other pharmaceutical reimbursement schemes worldwide, increased healthcare expenditure in the past decades has been an important factor influencing the PBS. In 1987, an amendment was made to the Act to explicitly require the PBAC to take into consideration in its listing recommendation, both the effectiveness and cost of a medicine, compared with an appropriate drug or non-drug therapy. In the early 1990s, the PBS became the first national pharmaceutical reimbursement scheme to formally adopt an explicit "value for money" criterion for the listing recommendation. Since then, economic and financial evaluations have been critical parts of submissions to the PBAC.

Cost effectiveness is a critical consideration when a submission claims superior clinical effectiveness and safety for the proposed listing, compared to the treatment that is most likely to be replaced in clinical practice (i.e. the comparator). This is known as a "major" submission. The sponsor must present a case for favourable cost-effectiveness by assessing the differences in costs and effects between the proposed treatment and the comparator, known as an incremental or marginal analysis. The cost-effectiveness is typically summarised in a measure known as an incremental cost-effectiveness ratio (ICER) which is the additional cost for a unit of health outcomes achieved. An ICER can be expressed in different forms depending on how the health outcomes are quantified e.g. cost per hospitalisation avoided, cost per Quality Adjusted Life Year (QALY) gained, and so on. As noted in the guideline for preparing submissions to the PBAC, the composite measure of a QALY is the preferred metric, if there is a claim of incremental life-years gained and if

relevant randomised trials report quality-of-life results. In fact, the incremental cost per QALY gained is almost always used as the measure of cost effectiveness¹⁴.

On the basis of economic considerations, the government would not fund a medicine that has an ICER higher than its willingness-to-pay (WTP) for a unit of health outcome. In other words, the proposed listing would only be funded if the net benefit (i.e. the difference between WTP per unit of health outcomes and ICER) is greater than zero. The PBAC has not explicitly set a fixed threshold to indicate the government's WTP for a QALY gained. The PBAC's WTP is related to:

- the characteristics of the clinical condition;
- perceived confidence in the evidence of efficacy;
- safety and the total financial implications; and
- politically determined acceptable expenditure.

Nevertheless, a former PBAC chair noted on record that an ICER greater than \$50,000 per QALY gained would be considered "on the high side" (Lopert 2009); this implied an average WTP threshold of below \$50,000 per QALY gained. Indeed, a retrospective analysis of PBAC decisions made between 1994 and 2004 using a statistical model indicated that the probability of receiving positive recommendations from the PBAC would be less than 5% if the ICER is greater than \$75,000 per QALY gained. The probability increases if the medical condition is life threatening, or when there is greater confidence in the evidence presented (Harris et al 2008). There is no suggestion that the WTP threshold is any different for cancer compared to non-cancer therapies.

4.1.3 Financing the PBS

Australia has national public health insurance in the form of Medicare for the provision of subsidised medical services listed on the Medical Benefits Schedule (MBS), and the PBS for the provision of subsidised pharmaceuticals. The primary financial source for Medicare is general taxation revenue and a statutory insurance levy of 1.5% on taxable income for those with a taxable income above the low-income thresholds¹⁵.

In 2010 and 2011, the Australian Commonwealth Government provided \$55.6 billion to fund health expenditure, a large part of which directly contributed to the delivery of the MBS and the PBS (\$32.8 billion, or 58.9%). In the year ending 30 June 2010, Australian tax payers contributed \$8.4 billion for the delivery of the PBS, which represented a 9.3% increase in expenditure from the previous financial year. Unlike other countries such as the UK, the PBS does not provide specific funding arrangements for cancer medicines (see Section 4.4).

Appendix A provides a diagram that illustrates the overall flow of funds in the Australian healthcare system and key stakeholders of health financing.

¹⁴ Infrequently, the PBAC recommended on the basis of "life years gained": examples include arsenic trioxide for treating promyelocytic leukaemia, and sorafenib for treating advanced hepatocellular carcinoma.

¹⁵ The thresholds vary according to family or individual, seniors and pensioners, and number of dependants.

4.2 Public hospital formulary

Access to subsidised medicines for admitted public patients in public hospitals is dependent on the formulary of individual hospitals and in Queensland, the state-based formulary. The decision to list pharmaceuticals on the formulary of Australian hospitals is currently governed by the drug committees of individual hospitals or states and territories. For high cost drugs (including many cancer medicines), an evaluation committee makes an assessment and provides advice to the jurisdictional advisory body (Table 4.1). The advisory body makes a recommendation to the hospital or jurisdictional government, who makes the final decision.

Table 4.1: Advisory body for the listing of (high-cost) medicines on hospital formularies

Jurisdiction	Advisory body
New South Wales	New South Wales Therapeutic Advisory Group
Victoria	Victorian Medicines Advisory Committee
Queensland	Queensland Health Medicines Advisory Committee
Western Australia	Western Australian Drug Evaluation Panel
South Australia	South Australian Medicines Advisory Committee
Tasmania	State-wide Therapeutic Drug Committee
Australian Capital Territory	Hospital-based Drug and Therapeutics Committees
Northern Territory	Hospital-based Drug and Therapeutics Committees

There is no single streamlined process across institutions/jurisdictions to assess proposed formulary listing of a medicine and the timeframe of the listing process is variable. A proposal to the National Health and Hospital Reform Commission in 2008 to establish joint Australian Therapeutics Advisory Groups across Australian jurisdictions was not adopted (Denaro 2008; NHHCR 2009).

Nevertheless, requests for listing on hospital formularies generally require evidence of safety, efficacy, cost-effectiveness, and financial feasibility from the perspective of individual institutions/jurisdictions. These requirements are similar to those of the PBS but to a much lesser degree in terms of the amount of information presented. Another key point of difference in process is the requirement for a lead clinician to present the listing request, rather than the drug sponsor as in the PBS.

Overall, the coverage of medicines in hospital formularies is broader than that listed on the PBS, especially for medicines used in indication, patient group, dosage or form not approved by the TGA or PBS, but with a sound clinical evidence base to support usage. This use is known as 'off-label' and the indication referred to as 'accepted' in the Australian Medicines Handbook. Many cancer medicines are used for 'off-label' indications in the hospital setting e.g. docetaxel, gemcitabine. A review by Mellor and colleagues (2012) found that 189 (42.2%) of the total 448 treatment protocols approved for use in a specialist oncology centre were off-label and were un-funded by the PBS (see section 5.3 for further discussion).

Financing public hospitals

Public hospitals in Australia are largely funded¹⁶ by the State and Territory Governments and the Australian Commonwealth Government through the five yearly Australian Health Ministers' Conferences. The funding covers the care and treatment individuals receive while in public hospitals as a public patient¹⁷, including the use of medicines. The Commonwealth Government uses the tax revenue for specific purpose payments to the jurisdictional governments as a contribution towards public hospital services (\$14.2 billion or 25.6% of the total funding for jurisdictional Governments) (AIHW 2012). Historically, hospital have received global budgets from jurisdictions, with individual hospitals setting the pharmacy budget. The introduction of Activity Based Funding will modify these arrangements, with pharmacy costs included in the efficient price paid to hospital.

4.3 Private health insurance

Australians may choose to purchase private health insurance (PHI) to receive insurance cover for medical services (e.g. dental services) and pharmaceuticals that are not subsidised by government (i.e. non-reimbursed medicines). The PHI industry is regulated by an independent statutory authority called the PHI Administration Council. PHI policy is set by the Australian Government Department of Health and Ageing and the Minister must approve any increase in fees. As at June 2012, 46.7% of the Australian population had coverage for private hospital insurance, and 54.3% had general treatment coverage which includes both private hospital and ancillary services coverage (PHIAC 2012).

Private health insurers provide financial coverage for TGA-approved, non-PBS listed medicines, or the use of PBS-listed medicines for non-PBS listed indications, for hospitalised or non-hospitalised individuals. Medicines access under most insurance policies, particularly for medicines that are considered high cost, is typically restrictive in the range and the total amount that can be claimed. Access is typically at the discretion of the individual insurers or occasionally negotiated on a member-by-member basis. As such, the coverage is typically limited under most insurance policies.

To date, there has not been a systematic effort to gauge health funds' ability and willingness to fund non-listed PBS items and the payments appear predominately to be *ex gratia*. The legislative requirements surrounding the coverage of non-PBS listed medicines are also unclear. In contrast, PHI is required under the Private Health Insurance Act 2007 and the Private Health Insurance (Prostheses) Rules to pay benefits for a list of medical prostheses specified by the Minister for Health and Ageing, as recommended by the Prostheses List Advisory Committee (PLAC).

¹⁶ Public hospitals also received funding from treating private patients and patients' contributions

¹⁷ Patients may choose to be treated as a private patient in a hospital (public or private). In this case, Medicare will cover 75% of the Medicare Benefits Schedule (MBS) fee for the associated medical costs.

4.4 Specific purpose fund – the Herceptin program for late-stage metastatic breast cancer

In 2001, the Australian Government set up a special programme independent of the PBS to fund trastuzumab (Herceptin) for patients with late stage metastatic breast cancer. Prior to the Government decision to establish this program, the PBAC had thrice rejected the submissions from the sponsor to have trastuzumab listed on the PBS because it was not considered cost-effective. However, after hearing community concerns about the lack of access to trastuzumab, the Government of the day decided to set up a special program to fund the drug. As at June 2011, 4,309 patients have accessed Herceptin for the treatment of late-stage metastatic breast cancer; 445 of these patients were patients newly registered on the program (Medicare Australia 2013).

4.5 Specific purpose fund – the UK

It is worth noting that the UK has established a specific purpose fund for cancer medicines. The UK Government committed an initial £50 million to the Cancer Drugs Fund for the period October 2010 to April 2011, and a further £200 million for each year between 2011 and 2013 (UK Government Department of Health 2011). This fund was to subsidise drug treatments, including radiopharmaceuticals, for patients who have been unable to access a drug recommended by their oncologist, including:

- Drug-indication combinations appraised by the National Institute for Health and Care Excellence (NICE) and not recommended on the basis of cost effectiveness, or where the recommendations materially restrict access to the treatment to a smaller group of patients than the specifications set out in the marketing authorisation (an ‘optimised’ recommendation);
- Drug-indication combinations on which NICE has not, or not yet, issued appraisal guidance (this may include off-label use where the clinician considers such a treatment to be the most appropriate based on clinical need).

Currently, some stakeholders have raised concerns about the access to cancer medicines when the Cancer Drug Funds expires in 2014 (Cancer Research UK, 2013).

4.6 Patient contributions

Similar to other national medicine reimbursement programs, Australian patients are required to contribute towards the costs of prescribed medicines under the PBS. Patient contributions were introduced to reduce moral hazard¹⁸ and to increase funding to the system without resorting to higher levels of taxation.

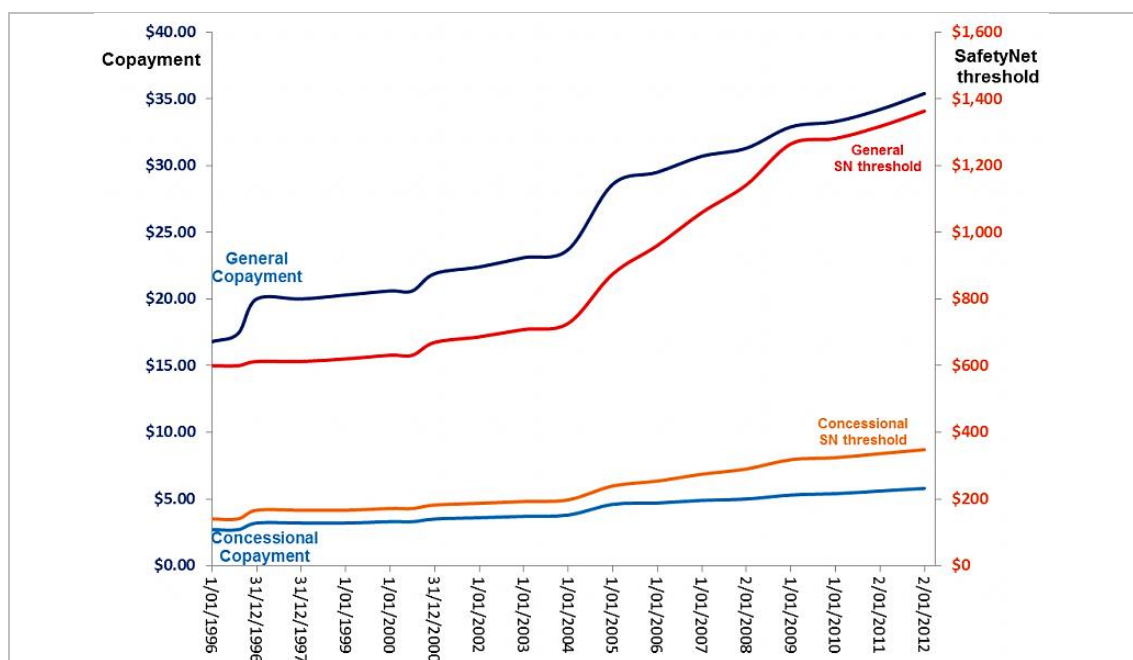
In Australia, the level of patient contribution (also known as ‘co-payment’) is fixed according to whether the individuals hold a concession card, or whether the patients have

¹⁸ A tendency towards taking risks or over consumption of medical care because of the costs that could be incurred, will not be felt by the party taking the risk.

reached the 'safety net' threshold. Concession card holders are typically individuals who receive income or social support payments or low-income earners, whereas the Safety Net is an arrangement to have a reduced level of co-payment upon reaching the threshold so that individuals or their families are safe-guarded from having large expenses on pharmaceuticals. This arrangement is 'means tested' i.e. subject to income thresholds.

The amount of co-payment has changed significantly over the last decades. In 2013, patients with concession cards pay \$5.90 per prescription and, upon reaching the safety net threshold of \$354.00 in a calendar year, the co-payment is waived. For other patients (i.e 'general patients'), the co-payment is \$36.10 and reduced to \$5.90 when the safety net of \$1,390.60 has been reached. Chart 4.1 shows the increase in the amount of PBS co-payments for non-concessional (i.e. general) and concessional patients in Australia (DoHA 2012). The increase in co-payment in general patients, but not patients with concession entitlements, correlated with the growth in GDP per capita (ABS 2012).

Chart 4.1: Changes in the amount of PBS co-payment and safety net (SN) thresholds for general and concession patients between 1996 and 2012



Source: DoHA (2012)

4.7 Other access pathways

4.7.1 Compassionate or early access programs

Compassionate or early access programs to cancer medicines typically involve TGA registered medicines that are not yet reimbursed under the PBS for the following reasons:

- Submission to the PBAC is in preparation;
- Submission to the PBAC is being considered;
- Decision to list has been deferred by the PBAC or delayed due to pricing negotiation; and

- Submission to the PBAC has been rejected.

These programs are initiated by the medicines sponsors, and approved by the drugs or therapeutics committees of the participating hospitals. Most of these programs are intended to provide access for a limited time or to a pre-specified financial commitment. The medicines are typically provided free of charge to patients. However, some early access programs involve a cost-sharing arrangement between the patients and the sponsor whereby the patients share a part of the cost. Table 4.2 (p.51) presents the extent of access to cancer medicines via the compassionate or early access programs in 2011 and 2012. A sample of nine companies provided 4,748 patients with compassionate access in 2011-2012. More than half of these supplies (67.9%) were to cover the access gap between TGA registration and PBS reimbursement. Notably, the access was mostly provided free of charge (85.2%). A major specialist cancer centre provides approximately \$10 million of cancer medicines per year through these programs for cancer medicines that were not PBS-reimbursed or TGA-approved (see section 4.7.2), or both [unpublished data, personal communication].

Table 4.2: Access to cancer medicines through compassionate or early access programs

Sponsor	Nr products	Nr patients (2011-2012)	TGA registration status		Access arrangement	
			On-label	Off-label	Fully funded	Cost-sharing
1	6	1,994	55.5%	44.5%	81.9%	19.1%
2	4	842	93%	7%	83%	27%
3	6	693	67.1%	32.9%	99.3%	0.7%
4	2	132	12.8%	87.2%	87.2%	12.8%
5	1	150	-	100%	100%	-
6	1	405	100%	-	100%	-
7	5	273	78.4%	21.6%	35.2%	64.8%
8	2	233	100%	-	100%	-
9	1	26	-	100%	100%	-
Total	28	4,748	67.9%	32.1%	85.2%	14.8%

Source: Data provided by sponsors

4.7.2 Special Access Scheme for TGA unapproved therapeutics

Individuals may access medicines that have not been approved by the TGA via the Special Access Scheme. This scheme refers to “arrangements which provide for the import and/or supply of an unapproved therapeutic good for a single patient, on a case by case basis” (TGA 2013). For accessing unapproved medicines via this scheme, patients must be defined as “persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment”. Patients who do not satisfy this definition may also access TGA unapproved therapeutics if the TGA accepts the clinical justification and circumstances of use.

4.7.3 Medicines access in clinical trials setting

Australians may also access TGA unapproved medicines under the Clinical Trial Exemption (CTX) and the Clinical Trial Notification (CTN) Schemes. Access under the CTN Scheme is subject to the trial receiving approval from the Human Research Ethics Committee (HREC) who is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine and the ethical acceptability of the trial process, and for approval of the trial protocol. In some institutions, a scientific review or drug subcommittee may review the proposal before consideration by the HREC. The TGA is not involved in the review process, but the approving authority must notify the TGA prior to trial commencement.

Under the CTX Scheme, the TGA reviews the information about the medicines provided by the sponsor, including the overseas status of the medicine, proposed Usage Guidelines, a pharmaceutical data sheet, a summary of the preclinical data and clinical data. The TGA Delegate decides whether or not to object to the proposed Usage Guidelines for the product. The HREC in each host institution/organisation is responsible for approving the proposed trial protocol after reviewing any additional comments from the TGA Delegate, and the summary information received from the sponsor. The institution or organisation concerned gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.

4.8 Summary

This chapter reviewed the common pathways to access to subsidised cancer medicines in Australia: PBS, Public hospital, Private health insurance, access through clinical trial or via Compassionate Access Programs, access through Special Access Scheme for TGA unapproved therapeutics, and medicines access in clinical trial settings.

The PBS is the primary vehicle for the delivery of subsidised medicines, including cancer medicines. An estimated 80% of all prescription medicines dispensed in Australia received subsidy via the PBS; this means that patient access to most medicines is significantly reduced, if not reimbursed under the PBS. A medicine must demonstrate its merits in fulfilling five critical requirements for patients to gain PBS reimbursed access: quality, safety and efficacy (as assessed by the TGA), clinical and cost effectiveness (as assessed by the PBAC and the PBPA), and financial feasibility/acceptability (as assessed by the Minister for Health and the Cabinet). Government intervention in the listing processes in recent years, and the challenges in reaching reimbursement agreement with the authorities, signal a policy shift towards fiscal control rather than patient access. Although the government has confirmed in 2012 that PBS listings with less than \$10 million per year will not have to be approved by the Cabinet prior to listing until June 2014, the Government has not ruled out the future possibility of re-introducing the Cabinet approval process for all PBS listings with a net cost to the Government.

Access to subsidised medicines for admitted public patients in public hospitals is dependent on the formulary of individual hospitals and in Queensland, the state-based formulary. The coverage of indications in a hospital formulary is typically more comprehensive than in the PBS because it supports the use of some indications that have a sound evidence base but

has not yet been updated on the TGA-approved list – a prerequisite for PBS-listing. Examples include the use of docetaxel and gemcitabine for a range of cancer indications.

Private health insurers play a minimal role in providing financial coverage for TGA-approved, non-PBS listed cancer medicines, or the use of PBS-listed cancer medicines for non-PBS listed indications, for hospitalised or non-hospitalised individuals. The range of medicines and the total amount that can be claimed are typically restrictive. Access is typically at the discretion of the individual insurers or occasionally negotiated on a member-by-member basis.

Australia has one specific purpose fund for cancer: the Herceptin program for late-stage metastatic breast cancer. This is in contrast to the comprehensive Cancer Drugs Fund in the UK, which provides £200 million for each year between 2011 and 2013 (UK Government Department of Health 2011). However, there are concerns about access to cancer medicines in UK when the Cancer Drug Funds expires in 2014.

Australian patients are required to contribute towards the costs of prescribed medicines under the PBS. The level of patient contribution is fixed according to whether the individuals hold a concession card, or whether the patients have reached the 'safety net' threshold. The level of patient contribution does not vary by the therapies i.e. patients living with cancer pay the same level of 'co-payment' as patients without cancer.

Patients may gain subsidised access via sponsors' compassionate access programs or cost-sharing arrangements. A considerable number of patients have benefited from such programs. More than half of the supplies in 2011-2012 (62.5%) were to cover the access gap between TGA registration and PBS reimbursement. The access was mostly provided free of charge (85.7%). However, these arrangements do not provide sustainable access because their intent is to facilitate short-term access while the medicines are in the process of obtaining reimbursement approval.

In summary, access arrangements are dependent on where a patient lives, who their physician is, their access to specialised cancer treatment, their level of private health insurance – all of which mean that access to cancer medicines can be inequitable.

5 Issues on access to cancer medicines in Australia

There is evidence that the success rate in achieving reimbursement is low, and the timeframe to gain listing on the PBS is lengthening – this is of particular concern for cancer patients, who are at an increased mortality risk.

The increasing use of biomarkers in oncology to assess and predict treatment response is a positive step in improving patient health outcomes. However, the requirements to fulfil both the PBAC and MSAC processes add complexity and evaluation time.

Clinical trial design for cancer medicines is providing real challenges to the reimbursement process particularly in the areas of quality of life and surrogate outcomes

In the reimbursement area, it is exceedingly difficult for the newer cancer agents to prove cost effectiveness against the older cytotoxic agents.

This chapter outlines issues affecting timely and affordable access to cancer medicines in Australia arising from:

- Regulatory and reimbursement processes;
- Evidentiary requirements to support reimbursement decisions;
- Coverage of indications on the PBS; and
- Level of remuneration for the supply of cytotoxic medicines.

5.1 Regulatory and reimbursement processes

5.1.1 Time-consuming approval processes prior to access

As discussed in Chapter 4, a medicine must demonstrate that it meets five critical requirements for patients to gain PBS reimbursed access: quality, safety and efficacy (all of which are assessed by the TGA); clinical and cost effectiveness (as assessed by the PBAC and PBPA); and financial feasibility/acceptability (as assessed by the Minister for Health and the Cabinet). The time period between submission to the TGA for regulatory approval and the PBS listing of the medicine is at least 14 months¹⁹. Some medicines may take several submissions to the PBAC to achieve a successful listing. An extreme example is the process leading to the eventual PBS listing of cetuximab for the treatment of colorectal cancer. In this case, there was a significant gap of six years between TGA approval (4 February 2005)

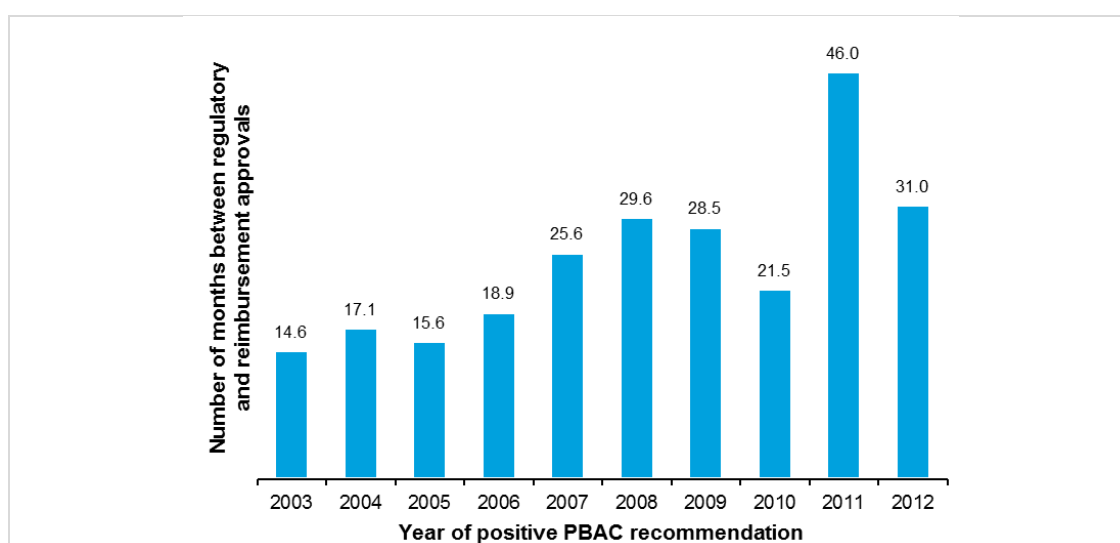
¹⁹ For a TGA submission in February, June and October, and then a submission for consideration by the PBAC in November, March (the following year), and July (the following year); if successful, the earliest listing would be in April, August and December the following year from the initial TGA submission.

and listing on the PBS for reimbursement (1 February 2011), after seven unsuccessful (major and minor) submissions to the PBAC. While there are many reasons underlying this protracted process, the delay must be better understood to improve medicines access.

Overall, there is evidence that the overall success rate in achieving reimbursement is inadequate, and the timeframe to gain listing on the PBS is lengthening, especially in recent years. Research by Pearce et al (2012) found that 113 requests for PBS listing were made for 63 new medicines that have gained marketing approval from TGA in 2004. As at August 2010, only 66 (58%) of these submissions were successful in gaining PBS listings, with an average of 2.8 submissions to the PBAC (median 2, range 1-7).

Another analysis found that the average time for PBS listing of anti-neoplastic and immune-modulating agents (i.e. medicines in ATC category L) from the date of TGA approval, increased markedly between 2003 and 2013 from 14.6 months to 31.0 months (Pretium, 2013) (Chart 5.1, page 55). This analysis also found that the average number of submissions to achieve a positive PBAC recommendation in 2012 is slightly higher for medicines in ATC category L compared to medicines in other ATC categories (Table 5.1).

Chart 5.1: Average time from positive regulatory recommendation to PBS listing, antineoplastic and immune-modulating agents (major ATC category L submissions)



Source: Pretium 2013

Table 5.1 shows that the overall success rate of major cost-effectiveness submissions²⁰ in achieving a positive PBAC recommendation appears to be comparable between medicines in ATC category L (36%) and medicines in other ATC categories (37%). However, for all submissions between 2003 and 2012, a lower proportion of medicines in ATC category L (67%) successfully achieved a positive PBAC recommendation, compared to medicines in other ATC categories (76%). Furthermore, there was a reduction in the proportion of positive PBAC recommendations from July 2011 onwards (37% and 36%) compared to the preceding period (51% and 58%) (Pretium 2013), suggesting an increasingly challenging reimbursement environment in Australia.

²⁰ Submissions that claim superior clinical effectiveness and safety for the proposed listing, compared to the comparator.

Table 5.1: Number of major submissions to achieve a positive PBAC recommendation and success rates, medicines with ATC category L and other categories

	Medicines with ATC category L	Medicines in all other categories
Average number of major PBAC submissions until a positive recommendation, 2012	1.61	1.48
Positive recommendations, 2003 -2012, all submissions	67%	76%
Positive recommendations, 2003 -2012, all major submissions	49%	54%
Positive recommendations, 2003 -2012, major cost-effectiveness submissions	36%	37%
Positive recommendations, 2003 to March 2011, all submissions	51%	58%
Positive recommendations, July 2011 onwards, all submissions	37%	36%

Source: Pretium 2013

A more detailed analysis of reimbursement success for oncology drugs shows that around 80% of medicines undergoing a cost effectiveness review by the PBAC require multiple submissions before achieving reimbursement. Specifically, in a review of public summary documents for oncology medicines reviewed by the PBAC between 2005 and 2011, O’Leary et al²¹ demonstrated that only 20% of first time submissions received a positive recommendation. The success rates for subsequent submissions were higher than for first submissions (32% for second submissions; 46% for third submissions, and 67% for fourth submissions), but also demonstrate the significant access gap between TGA approval and eventual PBS listing within the Australian system.

In the event that a medicine achieves approval from the TGA, but fails to gain PBS reimbursement, the medicine may be made available to the public. However, the financial burden is considerable to the patient themselves who must pay the full cost of the medicine – a factor that significantly hinders affordable access.

Alternatively, patients may gain subsidised access via access pathways such as sponsors’ compassionate access programs or cost-sharing arrangements. As discussed in Section 4.7, these programs are at substantial cost to the program sponsor and participating institutions. These arrangements do not provide sustainable access because their intent is to facilitate short-term access while the medicines are in the process of obtaining reimbursement approval. There is also a possibility that the sponsor may withdraw these arrangements if the medicines eventually fail to gain reimbursement approval, resulting in problems with treatment continuity for participating patients. Furthermore, these arrangements are often negotiated by clinicians or specialist institutions with the sponsor. As such, it may not be available to all patients, resulting in inequity of access among patient populations. Another potential issue with these access programs is when the indication eventually approved by the PBAC is more restrictive than that permitted under the programs. In this event, some patients may not meet the more restrictive criteria and are therefore not eligible for the subsidised access. Furthermore, treatment received prior to

²¹ [http://www.valueinhealthjournal.com/article/S1098-3015\(12\)03896-X/abstract](http://www.valueinhealthjournal.com/article/S1098-3015(12)03896-X/abstract)

PBS listing may have modified their disease state to the extent that the patient's condition may no longer meet the PBS eligibility criteria. While the PBAC may approve 'grand-fathering' arrangements to continue supply of reimbursed medicines, access is considered on a case-by-case basis which creates substantial uncertainty for patients.

5.1.2 Complex and time-consuming assessment of co-dependent technology for reimbursement under the MBS

The increasing use of biomarkers in oncology to assess and predict treatment response is a positive step in improving patient health outcomes. Patients with a known cancer biomarker may be more likely to respond to therapy than patients who do not express the biomarker. As outlined in Section 3.1.3, a number of current cancer medicines target specific biomarkers of cancer cells to hinder their growth and spread, with lesser interference to non-cancerous cells. Furthermore, the horizon scan of cancer medicines currently in phases II and III of clinical development shows that targeted therapies will continue to be a key driver in the oncology treatment landscape in the coming decades, including the emerging trend in combination targeted therapies (Section 3.2).

Despite their benefits, biomarkers add an additional layer of complexity to the reimbursement of new cancer medicines. In Australia, approved biomarkers must have an associated diagnostic test (co-dependent technology) and this test must be available on the MBS if the presence of a biomarker is one of the criteria to determine eligibility for PBS reimbursement. In this case, the PBAC approval is contingent upon the technology for measuring the biomarker to be available via the MBS, following consideration by the Medicare Services Advisory Committee (MSAC).

The application to the MSAC is complex and involves seven stages, as outlined in Table 5.2 (p.57). Overall, the pre-assessment processes to the point of publishing the Decision Analytic Protocol (DAP) for public consultation take at least 21 weeks; and the submission process following finalisation of the DAP takes at least a further 30 weeks before a listing on the MBS. While there is ongoing effort to improve the process through the development of a co-dependent technology assessment process (e.g. having a HTA access point), the requirements to fulfil both the PBAC and MSAC processes adds complexity and evaluation time.

Coordination between the PBAC and MSAC processes, which has been developing, may also impede timely listing of cancer medicines. This is particularly pertinent because the meeting dates of the various committees involved (PASC, ESC, MSAC and PBAC) are fixed. Delay in meeting one milestone date may delay the PBS listing of a medicine by at least four months because both MSAC and PBAC only meet every four months.

Table 5.2: Steps involved in seeking approval for the provision of medical services on MBS

Process step	Description
Proposal for public funding	Applicant can be any individual/institution/ organisation; however, the proposal requires support from the relevant craft group.
Assessment/ policy suitability	The applicant is asked to submit preliminary information to ensure the proposal meets the requirements for consideration for public funding, including the provision of evidence from relevant peak bodies. The Department assigns an

Process step	Description
	‘application manager’ to support the applicant through the process. The Department also commences identification (or recruitment) of particular expertise to the MSAC Expert Standing Panel (MESP) to provide advice on the proposal, and to the Protocol Advisory Sub-Committee (PASC).
Defining the assessment approach	PASC proposes a Decision Analytic Protocol (DAP). An external evaluation group develops the DAP to set out the clinical management algorithm that specifies the clinical and economic evidence required to inform MSAC’s appraisal. PASC then considers and amends (if required) the draft DAP. The draft DAP is then published on the MSAC website for public consultation providing an opportunity for all interested parties to comment on the proposed assessment approach. The MSAC secretariat will also approach relevant professional bodies for comment during public consultation. PASC to review the outcomes of the public consultation and determine the final DAP. After finalisation of the DAP, the applicant can choose whether to proceed with the application or not.
Preparing assessment report	Applicant may choose to proceed via two assessment pathways: contracted assessment (CA) or a submission based assessment (SBA). A CA is when an applicant agrees to the Department contracting an assessment group with expertise in health technology assessment. An SBA is when an applicant gathers the evidence which addresses and supports the questions for public funding as outlined in the final DAP. The Department will then undertake a contracted critique of the SBA. An applicant may choose to go down the path of an SBA as it is likely to expedite the process.
Evaluation of evidence	For SBA, the department will contract an evaluator to provide a critique of the report. For CA, the applicant is provided an opportunity to prepare a critique. MSAC’s Evaluation Sub-Committee (ESC) reviews the assessment report and critique, and provides a written report to the applicant for comment and to MSAC.
MSAC appraisal	MSAC appraises the assessment report, ESC report and the critiques and comments, and determines its advice to government.
Listing decision	Government consider the recommendations of MSAC for listing approval

Source: DoHA

5.1.3 Increasing process uncertainty

In November 2010, the TGA implemented a business process reform, with a view to streamlining the submission process for prescription medicine applications that require the evaluation of non-clinical, clinical and/or bioequivalence information. Part of the reform is implementation of a pre-submission planning phase and the requirement to submit a complete dossier prior to the initiation of the standardised evaluation process. While such reform aims to improve process efficiency, there were occasions whereby the reform processes have delayed the regulatory approval because of a lack of resources in meeting the planned evaluation timeframe.

The reimbursement approval process also has an increasing level of process uncertainty. As outlined in section 4.1.1, the Minister for Health makes the final decision to list a medicine on the PBS with consideration to the PBAC and PBPA’s recommendations. If the increased annual net cost to the Government associated with PBS listing is projected to be more than \$10 million in any of the first four years of listing, the Cabinet must consider the proposed

listing before the Minister may declare a listing on the PBS. Prior to 2011, the Cabinet mostly followed the independent advice provided by the PBAC, recognising the rigorous evaluation process followed by this statutory body of leading experts in medicines policy. However, since February 2011, for some medicines that have received positive recommendations from the PBAC, there have been a number of deviations from normal processes, including those due to the Government's fiscal considerations, or unsuccessful negotiations between the sponsor and Government in reaching a mutually agreeable price. Either way, these have significantly hindered access to new cancer medicines in the last few years.

5.1.4 Lack of process differentiation for cancer medicines

Another pertinent issue relates to a lack of process differentiation for cancer medicines. Unlike regulatory agencies in other comparable countries, cancer medicines, which are to treat serious conditions and often to fill an unmet medical need, do not result in expedited registration or reimbursement timelines. This is in contrast to the FDA multi-tiered system whereby therapeutically important medicines are made available via the Fast Track, Accelerated Approval and Priority Review, on the condition that the sponsor conducts additional studies to further define the degree of clinical benefit. FDA's approval of imatinib for the treatment of chronic myeloid leukaemia in 2001 only took four months under the priority review process, when the standard review process would have taken approximately 15.7 months (FDA 2012). This example demonstrates how an appropriate system structure can improve access to cancer medicines.

5.2 Evidentiary requirements to support access

5.2.1 Study design requirements

Parallel randomised²² controlled trials (RCT) are considered to be the "gold standard" for the provision of the rigorous, high quality evidence for determining whether a cause-effect relation exists between treatment (versus a comparator therapy or placebo) and outcome (Sibbald 1998). This view is endorsed by the *Guidelines for preparing submissions to the PBAC (version 4.3)*. However, for the reasons outlined below, the requirement for providing evidence from parallel RCT may not be always realistic, particularly for cancer medicines.

Recruitment of patients to participate in oncology trials has been increasingly difficult, particularly for subtypes of cancer with small patient populations, and in advanced stages of disease when patients have already undergone multiple treatments that may preclude them from participation. The lack of participation is also related to the patient's perception that the experimental medicine is more promising than the comparator, and their reluctance to face the possibility of being randomly assigned to a ('inferior') comparator medicine in a RCT. To mitigate this issue and with ethical considerations, investigators and sponsors who conduct clinical trials in oncology have increasingly allowed "cross-over", whereby patients randomly assigned to the comparison arm are given access to the experimental medicine when their cancer worsens (i.e. progression).

²² Patients are assigned by chance to the experimental medicine or the comparator.

Ethical challenges may also arise when undertaking clinical trials for cancer medicines because Phase III clinical trials are usually conducted following evidence from early studies that have indicated the benefits of the experimental treatment. These benefits include improved quality of life, slower disease progression and sometimes gain in OS. Denying patients access to these experimental treatments that have potential benefits, as indicated from earlier trials, may be ethically challenging²³.

There is evidence that oncology trials are more likely to have variations in trial design compared to clinical trials in other disease areas. A recent review of oncology trials registered at ClinicalTrials.gov by Hirsch et al (2013) found that oncology trials were more likely to be single arm (62.3% vs 23.8%; $p < 0.001$), open label (87.8% vs 47.3%; $p < 0.001$), and nonrandomized (63.9% vs 22.7%; $p < 0.001$), compared with other specialties. There remains uncertainty whether such variations can be fully explained by the differences in clinical areas or whether it is in part due to poorly considered/implemented design.

If there is a good reason why an RCT design has not been undertaken (e.g. for the treatment of a rare cancer), regulatory and reimbursement bodies may consider accepting the evidence from the 'next best' possible trial design (e.g. a single arm design) and provide guidance for facilitating patient access. Some stakeholders believe that the reimbursement body has been reluctant to deviate from the requirement for evidence from parallel RCT design when making decisions.

5.2.2 Clinical trial efficacy endpoints

A range of parameters have been used to evaluate the clinical efficacy of cancer treatment. These include objective tumour response measures (e.g. tumour size), response rate, time to tumour progression, time to treatment failure, progression-free survival (PFS) and overall survival (OS).

OS is the time from patient's enrolment in a trial to the time of death due to any cause. In oncology, OS is often considered as the most clinically relevant and meaningful end-point, especially for medicines for the treatment of late stage cancer. This is because OS is relatively easy to measure, record, define, and is free of bias. For these reasons, the PBAC has also expressed preference for a demonstration of OS over other measures, such as PFS – the duration of time alive without disease progression. However, it is well recognised that OS as an endpoint is not without limitations and challenges. Most notably, measuring OS substantially prolongs the duration of a trial, increases the number of patients needed to be recruited, and amplifies the cost of completing the trial. The longer timeframe also subjects the trial to a much higher range of confounding factors which may affect the confidence in interpreting findings. These factors include patients receiving further treatment when the disease worsens, the diverse nature of disease characteristics upon progression, and differences in post-progression management (Kelly and Halabi 2010; Kummar et al 2006; Sargent et al 2008).

Furthermore, based on ethical considerations, trial committees may terminate a trial when a surrogate end-point such as PFS has demonstrated substantial benefits, thereby precluding further collection of OS data within the trial. The ability to demonstrate differences in OS is also challenging for cancer medicines when cross-over is allowed (see

²³ albeit the requirement to demonstrate the principle of clinical equipoise.

previous section). This masks (i.e. ‘confounds’) the ability to measure the OS from the experimental medicine because patients on both treatment arms receive the experimental medicine. For these reasons, the preference for evidence based on OS measures to support reimbursement decisions may not always be practicable.

Intermediate or surrogate endpoints are substitutes for the definitive endpoints predictive of the clinical efficacy. In cancer clinical research, surrogate endpoints such as PFS are relevant in earlier stage cancers and, as explained above, when the assessment of OS is considered to take too long (e.g. in longer-term disease such as prostate cancer), or in trials of earlier lines of therapy for advanced cancer where subsequent therapy following progression cannot be ethically denied. By definition, a surrogate endpoint may be associated with higher levels of uncertainty compared to OS because it is only intended for ‘predicting’ the clinical benefits (or harm). An improvement in surrogate endpoints, or the lack thereof, does not always translate into relevant clinical outcomes. It is therefore important to demonstrate a strong and consistent correlation between the surrogate and definitive endpoints. An example is the strong correlation between PFS and OS in the setting of first-line treatment of advanced colorectal cancer with fluorouracil-based chemotherapy (Tang et al 2007, cited in Amir et al 2012). Tumour shrinkage (response) was shown not to be an acceptable surrogate end point for overall survival in advanced colorectal cancer (DiFiore 2008). Conversely, a lack of tumour shrinkage following treatment with cancer medicines that aim to stabilise cancer cells (i.e. cytostatic, rather than killing cancer cells) such as tyrosine kinase inhibitors does not necessarily imply a lack of efficacy because these agents may in fact elicit significant clinical benefit in stabilising and improving progression-free survival (Kelly and Halabi 2010; Kummar et al 2006).

On the other hand, surrogate endpoints may be considered more reliable because their measurements are closer to the time point when the intervention is applied than for hard endpoints such as OS, and therefore less likely to be confounded by secondary therapies. In fact, regulatory authorities have granted approvals for oncology drugs on the basis of surrogate endpoints. In reviewing the endpoints used by the FDA to approve new cancer drug applications between 1990 and 2002, Johnson and colleagues (2003) found that the FDA approved 39 out of 57 cancer medicines on the basis of endpoints other than survival. Although this study is dated, it is probable that surrogate endpoints continue to be considered as reasonable by the regulatory agencies for marketing approval, including the TGA in Australia.

Another pertinent issue is the different perception of clinical benefits between patients, clinicians and decision makers. For example, to many patients with advanced disease and their treating clinicians, surrogate endpoints such as PFS may be a meaningful personal and clinical goal when receiving a particular treatment, particularly when this treatment is associated with improvements in cancer symptom control. A seemingly small clinical benefit may be of great significance to patients who have exhausted all other treatment options, or have significant symptoms from their cancers. However, such extent of clinical benefits often does not meet the criteria of value assessment by reimbursement authorities, which may affect the decision to provide affordable access to these medicines. This means that patients, clinicians and clinical trial sponsors often feel dispirited by the reimbursement processes. A discussion is needed to clarify the assessment of clinical benefits, especially with a view to reconciling the different value perceptions among stakeholders. In other jurisdictions (e.g. the UK), the assessment of end-of-life medicines, including cancer medicines, has allowed for downward adjustments (“weighting”) to the

cost-effectiveness ratio (e.g. NICE 2009), to better reflect perceived societal preferences for funding end-of-life medicines. However, there is debate about the impact and appropriateness of such adjustments (e.g. Chalkidou 2012; Collins and Latimer 2013).

In summary, it is important to recognise the merits of surrogate endpoints when making reimbursement decisions. The lack of hard endpoints such as OS should not be a major barrier to access to cancer medicines if there are reasonable justifications as to why such measures were not collected in the clinical trial. Although surrogate endpoints such as PFS may not always correlate with OS, in certain circumstances, surrogate endpoints may be accepted as the basis of the reimbursement decision. One example where a surrogate endpoint is appropriate is when improved PFS has been shown to correlate with improved OS (e.g. in ovarian cancer as demonstrated by Parmar et al 2003; and in non-small-cell lung cancer as demonstrated by Michiels et al 2011). Johnson and colleagues (2006) also demonstrated that PFS may be used in predicting OS in metastatic colorectal cancer and non-small-cell lung cancer, if the anticipated difference in PFS is large enough to exceed estimated surrogate threshold. Finally, further discussions are needed to ensure reasonable harmonisation of evidentiary requirements between regulatory and reimbursement authorities in Australia, and how best to prioritise healthcare resources in view of the different value perceptions of clinical benefits.

5.2.3 Quality of life outcomes

As discussed in Section 4.1.2, there is an increasing focus on quality of life (QoL) outcomes when making reimbursement decisions in Australia, if there is a claim of life-years gained, and if relevant clinical trials report quality-of-life results. This is especially relevant for cancer treatment because many cancer medicines (e.g. cytotoxic chemotherapy) are associated with adverse effects that may negatively affect a patient's quality of life. Measuring the value of an oncology medicine by the composite measure of a QALY would capture both quality and quantity of life years gained, with a view to allowing consistent comparisons. However, there are several well recognised challenges in measuring quality of life in patients with cancers, using existing methods and survey instruments to measure 'utility' – the preferences for goods or services as a proxy for measuring quality of life.

First, using a generic utility instrument to measure the QoL benefits of cancer medicines may undervalue the actual benefits experienced by cancer patients. In reviewing 110 economic evaluations of cancer treatments, Tengs et al (2004) found that adjusting for health-related QoL yielded resource allocation decisions that were not different from outcomes if no adjustment had been made. This led Garau et al (2010) to hypothesise that the QALY construction methodology may not capture any QoL improvement amongst patients receiving cancer treatments. In their review, Garau et al (2010) found that the limited number of dimensions and levels in the descriptive systems specified in existing standardised utility instruments, such as the EQ-5D, are too non-specific to elicit the nuances of cancer patients' day to day living.

A second methodological issue with the assessment of QoL improvement is the potential misalignment in preferences between cancer patients, health professionals, and the general population. The preferences of members of the general public have been recommended for economic evaluation when making health policy decisions. This is because society's resources are allocated to maximise health at a population level, rather

than at an individual level. However, there is now evidence to suggest that patients with cancer generally assign a higher utility value for a given health state. This utility level is slightly lower amongst health professionals, and lower again amongst the general public. A comprehensive review by de Witt et al (2000) found that the majority of evidence indicates that on average patients tend to value a given health state more highly than do individuals without the condition. This may be because members of the general public are not fully informed about a particular illness based on the description used in eliciting their preferences. For example, if a dimension such as vitality plays an important part in determining quality of life of cancer patients, the general population would not provide an accurate valuation if the descriptive system in the utility survey instrument omits this dimension. Another possible explanation is that cancer patients with impaired functioning may perceive a slight functional improvement more positively than those without these impairments. As such, using the preferences of the general public as the basis for allocating resources undervalues the potential QoL benefits of cancer treatments, and discriminates against people affected by cancers (Blinman et al 2012).

In constructing the QALY, many utility instruments used the 'time trade-off' (TTO) technique to elicit preferences regarding a particular health state (i.e. living with a specific cancer). The TTO method involves asking participants to make hypothetical trade-offs between living a shorter life in full health, and living a longer life in poorer health. The respondent's indifference point is found by varying the time of different scenarios. One of the key assumptions with the TTO method is that individuals make trade-offs without considering the number of remaining life-years i.e. 'constant proportional trade-off' (CPT). In developing the utility weights for the EQ-5D utility instrument, a sample from the general population were given a 10-year TTO framework. The CPT assumption of TTO is erroneous when trying to elicit preferences for cancer conditions because the life expectancy of cancer patients is usually much shorter than 10 years, particularly in late-stage cancer (Garau et al 2010). Another reason why the CPT assumption is not applicable to cancer patients is that when the remaining life-expectancy is very short (less than one year), individuals were unwilling to sacrifice any of that time to improve their quality of life (Miyamoto and Eraker cited in Garau et al 2010).

Another methodological issue relates to the capacity of cancer patients to improve their QoL. Because of the severity of their illness, the scope for improvement in QoL may not be adequately large, even if patients experienced a meaningful increase in survival. Nevertheless, cancer patients may place a high value on an increased probability of surviving, even in the absence of a QoL improvement.

5.2.4 Choice of comparators to demonstrate cost effectiveness

As discussed in Section 4.1.2, one of the key reimbursement criteria is the requirement to demonstrate cost effectiveness against the comparator, defined as the treatment that is most likely to be replaced in clinical practice. With the rapid emergence of new cancer medicines, the treatment landscape is rapidly evolving and as such, the appropriate comparator for the purposes of evaluating cost-effectiveness may not be known at the time the trial is designed for the assessment of safety and efficacy. This poses a problem because it is quite likely – and most often the case – that the appropriate 'main comparator' nominated within a reimbursement submission is not the comparator(s) of the Phase III clinical trials. In this case, the therapeutic efficacy and safety of the new medicine

relative to the appropriate comparator has to be estimated indirectly from clinical trials with a common third comparator. This is less methodologically rigorous than the direct comparison method. In fact, the PBAC has a low acceptance of using indirect comparisons to substantiate claims of clinical superiority and cost effectiveness.

A second related issue is variations in standards of care in different countries. Clinical trials in oncology (and in other clinical areas) are mostly international. The comparator chosen for the assessment of efficacy and safety in Phase III clinical trials is most likely to be in line with the requirements of larger jurisdictions, such as the EU or the US. Because of variations in standards of care in different countries, the chosen comparator may not necessarily align with clinical practice in Australia. Similarly, a comparator may not be reimbursed in Australia whereas reimbursements overseas have made this a widely used and appropriate comparator. Such differences again results in the need for an indirect comparison.

In Australia, the price of a new medicine is set with reference to the price of the chosen comparator, and with appropriate adjustments regarding therapeutic relativity and pack sizes. In oncology, most of the established treatment options for patients are older cytotoxic chemotherapies²⁴ that have been available for many years. Some of these medicines are subject to generic competition following the expiry of their patent, and as such have relatively lower prices. The prices of these older cytotoxic medicines are also lower because of the consequences of PBS reform in reducing the price of generic medicines. In some cases, reference pricing methods have resulted in a price that is not possible to demonstrate cost-effectiveness of the new medicine to the PBAC, or is viable for the innovative company to list the new medicine on the PBS. Therefore, the practice of setting reimbursed prices for new medicines with reference to older comparators may sometimes be an obstacle to patient access to innovative cancer medicines.

5.3 International comparisons

While it is difficult to make international comparisons, there are a growing number of examples of Australian cancer patients being unable to access oncology medicines or experiencing delays in access compared with their overseas counterparts, and compared with what is recommended in US and European evidence-based cancer treatment guidelines.

Some of these examples are highlighted in Table 5.3, as a starting point for discussion. These examples do not take into account that the market authorisation may have been granted earlier in other countries compared to Australia. However, since Australia has a parallel submission process (reimbursement applications can be filed before market authorisation has been granted by the TGA), any differences in market authorisation dates between Australia and other countries are likely to have minimal impact on the preliminary hypothesis that publicly-reimbursed access to oncology drugs is significantly delayed in Australia compared to other OECD countries. A more formal and rigorous international comparison study needs to be undertaken.

²⁴ With the exception of radiotherapy and surgery

Table 5.3 Comparison of the PBS reimbursement status of oncology medicines against other OECD jurisdictions: some examples

Cancer type/ Medicine	PBS listing date	No. of PBS- listing submissions	Dates accepted by public- funded drug-subsidy programs in other countries
Malignant melanoma			
• ipilimumab	1 Aug 2013	3	Apr 2012 (Germany ^a); May 2012 (Canada ^b); Dec 2012 (UK ^c), Apr 2013 (Scotland ^d)
• vemurafenib	Not listed	2	Jul 2013 (Germany ^a); Jun 2012 (Canada ^b); Dec 2012 (UK ^c)
Advanced colorectal cancer			
• cetuximab	1 Sep 2011	6	Jan 2010 (Netherlands ^a); Jul 2004 (Germany ^a); Aug 2009 (UK ^a); May 2005 (France ^a)
• panitumumab	Not listed	2	Dec 2007 (Germany ^a) April 2008 (France ^e) October 2008 (Netherlands ^a)
• bevacizumab	1 July 2009	2	Jan 2006 (Canada ^b); Sep 2005 (France ^f); Dec 2010 (UK ^c)
Advanced non-small cell lung cancer			
• pemetrexed –first line	Not listed	3	Jan 2008 (UK ^c)
• erlotinib-first line	Not listed	2	Jun 2012 (UK ^c); Aug 2011 (Germany ^a)
• gefitinib-first line	Not listed	2	Jul 2010 (UK ^c)
HER2-positive metastatic breast cancer*			
• trastuzumab	Not listed*	3	Apr 2000 (Canada ^b); May 2001 (France ^e); Mar 2002 (UK ^c)

Source: (a) Data on file from sponsor²⁵, (b) Pcodr (2013)²⁶, (c) nice.(2013)²⁷, (d) www.scottishmedicines²⁸, (e) www.has-snte.fr²⁹ *Herceptin for metastatic breast cancer is funded by a specific-purpose Medicare program.

²⁵ measured by IQWiG / GBA positive recommendation (data on file), indicates that the pricing discussions for drug-subsidy programs will typically begin within one month with the GKV-SV, the Federal Association of Statutory Health Insurance Funds. Since January 2011, review under the AMNOG process may result in price adjustment following reimbursement.

²⁶ Measured by pCODR notification to implement as posted at www.pcodr.ca. Lag time to listing implementation in each province varies, for example first provincial implementation for ipilimumab occurred July 2012, with other provinces staggered thereafter, see: www.pcodr.ca/idc/groups/pcodr/documents/webcontent/pcodr-provfund_yervoy-advme1.pdf. Trastuzumab and bevacizumab were accepted prior to the creation of the pCODR program; public-subsidy program acceptance is based on sponsor's data on file.

²⁷ Measured by NICE positive recommendation as posted at www.nice.org.uk. Ipilimumab, vemurafenib and erlotinib are available through the NHS via a patient access scheme. Bevacizumab is an exception, as it was rejected by NICE; this drug was subsequently supplied through the Cancer Drug Fund (CDF).

²⁸ Measured by SMC positive recommendations as posted at www.scottishmedicines.org.uk, which typically signals agreement between company and sponsor on terms of initial listing and swift implementation of listing thereafter

²⁹ Measured by HAS positive recommendation as posted in English. This signals agreement between the public-subsidy program and sponsor and imminent listing and availability to patients under the program. Available at http://www.has-sante.fr/portail/jcms/c_6056/en/recherche-avancee?portlet=c_39085&search_antidot=&lang=en&typesf=opinions.

In addition to delays in access, Australia has been found to be one of the five worst countries in terms of 'indication coverage' for oncology medicines that do achieve reimbursement. An international comparison of the degree of reimbursement-coverage for 10 oncology medicines published by Cheema and co-authors in 2012 showed that reimbursement agencies in Finland, Sweden, and the United States reimbursed 100% of the total cancer indications approved by their respective licensing authorities. Germany reimbursed 92% of all indications licensed by the European Medicines Agency (EMA). France and Italy respectively reimbursed 95% and 91% of the licensed EMA cancer indications. The Netherlands reimbursed 84% of EMA-licensed cancer indications. The five countries that reimbursed the fewest of the total indications licensed by their respective market authorisation authorities were Canada at 54% (n = 26), Australia at 46%, Scotland at 40%, England at 38%, and New Zealand at 25%.

Furthermore, cancer drug utilisation in Australia is low when compared with France, Spain, Germany, Austria, Denmark, Switzerland and the United States over the period 2008 and 2009. Of the 14 countries studied in the 2010 report on "Extent and Causes of International Variations in Drug Utilisation", Australia ranked 12th (Richards 2010). Only Canada and New Zealand had lower utilisation rates for cancer medicines. For drugs launched within the last five years, Australia ranked 11th out of the 14 countries. As the study was conducted prior to the formation of the UK's Cancer Drugs Fund, it is likely that cancer drug utilisation would have increased in the UK since then; however this is unlikely to materially alter the conclusion that cancer drug utilisation in Australia is low compared to other countries.

5.4 Coverage of indications on the PBS- TGA and PBAC issues

A prerequisite for PBS reimbursement of a medicine is having first obtained TGA approval for particular indications. Often, PBS reimbursement is restricted to a subset of the TGA-approved indications, where the use of a medicine has been demonstrated to be cost-effective for that indication in a specific patient population under specific clinical circumstances (e.g. by a trained specialist). To gain reimbursed access to these medicines, patients must satisfy the restriction criteria specified in the PBS schedule.

However, the TGA-approved list of indications is not always in line with the evidence development since the initial approval, resulting in a disparity between PBS reimbursed access and clinical evidence-based guidelines. A recent study by Mellor et al (2012) found that 29.5% (132) of the 448 protocols of anti-cancer therapy approved for use in a major cancer treatment centre were beyond the TGA's approved use (i.e. 'off-label' use) despite being established evidence-based treatment guidelines. A further 39 protocols were based on findings of Phase II and III clinical trial data. This is not surprising in an area of high research intensity. This lack of consistency between clinical practice and approved indications has affordability implications because, as noted above, the PBAC only considers requests for reimbursement if the indication sought is consistent with TGA approval. As such, patients who require these evidence-based treatments outside of TGA-approved indications are reliant on other means of access, potentially posing financial burdens.

There are many reasons why TGA approved indications are not updated in a timely manner when new evidence emerges. First, there are potential time delays due to the complexity

of the TGA approval process, and only medicine sponsors are permitted to lodge an application for a new indication. Second, there may be a lack of commercial incentives for the sponsor to lodge the application to seek further approval, as off-label prescribing is clinically acceptable insofar as the use is supported by evidence. In some cases, new evidence can be developed by research institutions without the involvement of the original sponsor; this data ownership issue may preclude the sponsor from making an application to broaden the indication. Addressing these issues may improve the responsiveness of the TGA registration status to changes in the clinical landscape.

For PBS reimbursement, the PBS listing process may mitigate this issue by moving a restricted listing to a general listing (i.e. listing without restriction). This may be particularly suitable for medicines that have had a significant price reduction following loss of market exclusivity (e.g. docetaxel). Although some cancer medicines have been 'de-restricted' (e.g. gemcitabine), there is currently no guidance on the process requirements.

5.5 Level of remuneration for the supply of cytotoxic chemotherapies

Since August 2007, the Australian Government has implemented a PBS reform package to ensure the "long-term sustainability of PBS". Part of this reform package includes a measure known as Price Disclosure. This measure aims to progressively reduce the price of some PBS medicines which are subject to competition³⁰, with a view to aligning the price that the Australian Government pays closer to the market price at which the medicines are supplied. On 1 December 2010, the Australian Government undertook further PBS reform and extended the price disclosure arrangements to include all non-exempted medicines on the F2 formulary, known as the Expanded and Accelerated Price Disclosure (EAPD). The implementation of the EAPD has significantly lowered the price of a number of medicines, especially some cytotoxic chemotherapies. For example, since 1st April 2012, irinotecan has decreased in price by 74.3%, docetaxel by 76.2%, paclitaxel by 86.9% and epirubicin by 89.3% (PBS 2013).

While meeting the intended purpose of the initiative, such significant reductions in price have resulted in a decrease in remuneration for supplying these medicines. Since these 'extra' remunerations have previously been used to cross-subsidise inadequate remuneration for the provision of chemotherapy services in general, EAPD may reduce the capacity of providers to supply certain medicines, thus negatively impacting a patient's ability to access chemotherapy services.

These issues were discussed at a Senate Inquiry on "Supply of chemotherapy drugs such as docetaxel". This Inquiry was prompted by a chorus of disapproval from stakeholders following the implementation of price reductions for docetaxel (Community Affairs References Committee 2013). At this inquiry, the Senate Committee heard evidence from private providers of chemotherapy services regarding the sustainability of the current level of funding for the provision of chemotherapy drugs under the PBS. Key concerns raised at this inquiry include:

³⁰ Mostly medicines that have lost market exclusivity. These medicines are categorised in the 'F2 formulary'.

- Increased costs, due to the reduction in remuneration, would likely reduce service capabilities because it would decrease the providers' capacity to invest in staff training and to purchase the latest technology required to maintain high standards of care. This would in turn result in a shift in cancer care to the already highly constrained public health system;
- In particular, rural cancer services would be most at risk by the funding decreases because of the higher average cost per service unit provided at these centres. Many of these pharmacies have also incurred cost due to unplanned last-minute changes to the dose or treatment, and the initially ordered preparation cannot be returned to the third party compounder.
- There was consensus about the need to determine the appropriate source of remuneration to pharmacists to reflect the costs of supplying chemotherapy infusions. However, there was disagreement between the Pharmacy Guild and the Department as to whether the shortfall in revenue arising from the implementation of EAPD should be funded through the Efficient Funding of Chemotherapy (EFC) arrangement, or through dividends of savings from EAPD.

Following the inquiry, the Minister for Health announced a review to determine the correct subsidy for chemotherapy infusions, to be completed by October 2013. As an interim measure, the government allocated \$29.7 million to pay providers an additional \$60 for each chemotherapy infusion for six months between July and December 2013.

5.6 Summary

This chapter reviewed issues on access to cancer medicines in Australia. A range of issues have been identified for further discussion and action. These include:

- Time consuming and complex regulatory and reimbursement processes prior to access;
- New process uncertainty in achieving PBS listing approval;
- The practice of setting reimbursed prices for new drugs with reference to older comparators, may ultimately prevent patient access to innovative cancer medicines.
- A range of evidentiary requirements that do not adequately reflect the context of cancer medicines;
- Coverage of indications on the PBS do not always reflect the standard of cancer care and treatment recommendations; and
- Level of remuneration for the supply of cytotoxic chemotherapies may be inadequate for continued supply of those medicines.

6 Stakeholders views

Many stakeholders felt that access to cancer medicines in Australia is often suboptimal and unsustainable.

Stakeholders noted that many components of the current process are not fit for purpose to meet the emerging issues associated with cancer medicines.

Many stakeholders commented on the significant time lag between the TGA approval and the PBS listing processes, due to PBAC rejection or deferral, or fiscal consideration by the Government. Often, this means that some patients are not receiving the best available care.

There has not been a meaningful debate in Australia about what the Australian community considers an acceptable level of funding for caring for patients nearing their end of life, including those with advanced cancers.

This section presents the findings from semi-structured interviews with relevant stakeholders with a view to gaining an in-depth understanding of their experience and perceptions about access to cancer medicines in Australia. The purpose of these consultations was to facilitate a multi-faceted understanding of issues relating to patient access to cancer medicines based on different stakeholder perspectives. It is hoped that this understanding will inform the development of mutually beneficial and enduring solutions.

Invitations to participate were extended to 43 stakeholders. Twenty nine stakeholders participated in the consultations between 15 April 2013 and 2 June 2013 (Appendix A). The remaining stakeholders either declined or did not respond to the invitations. At least two representatives from each of the following groups participated in the consultations:

- Health consumer organisations;
- Government and payers;
- Clinicians: oncologists, haematologists, pharmacists, nurses;
- Pathologists: cancer centres and clinics;
- Other stakeholders: private health insurers; academics with an interest in medicines access; and
- The medicines industry.

The following sections summarise the views of interview participants by thematic categories rather than by stakeholder groups so as to maintain participants' anonymity. Many of these themes are shared by different stakeholder groups.

6.1 Access to cancer medicines

The majority of interview participants considered the pharmaceutical access system that has been in place in Australia has performed well in the past in providing affordable and equitable patient access to cancer medicines, compared to other countries with similar socioeconomic contexts. This view was supported by the favourable statistics to date on cancer health outcomes in Australia relative to other comparable countries. Some interview participants said they were pleased with the Australian healthcare system achievement in providing access not on the basis of a patient's ability to pay, as in other healthcare systems dominated by private providers (e.g. the US).

However, many interview participants placed significant caveats around this positive view, because there are many circumstances in which access to cancer medicines in Australia is suboptimal and unsustainable. These include: access to new cancer medicines; lack of coverage for off-label indications; administrative burden to fulfil access requirements; the discrepancy between medicines access via the hospital and the PBS; and access to medicines for rare cancers. These issues are discussed further in the sections below.

6.1.1 Increasing challenges to access to new cancer medicines

Many interview participants noted increasing challenges in accessing new cancer medicines in a timely and affordable manner. They noted that most cancer medicines eventually become available in Australia, but Australian patients and clinicians typically have to wait much longer than their counterparts in the US and Europe.

Several stakeholders attributed this delay to a range of factors. Firstly, stakeholders believed that medicine sponsors often postpone applications to the authorities in Australia, possibly because Australia has a much smaller market compared to other jurisdictions. Secondly, stakeholders believed that the assessment process for regulatory approval following the sponsor's eventual application to the TGA is unnecessarily "cumbersome" and duplicates the rigorous processes that have already been undertaken by the FDA and EMA based on the same laboratory and clinical evidence. Thirdly, stakeholders believed that the processes leading to the reimbursement of new cancer medicines on the PBS have become increasingly uncertain in recent years. Many participants cited the protracted decision making processes leading to the approvals/rejections of listing cetuximab, vemurafenib and abiraterone as evidence of system inefficiency. Section 6.2 further discusses barriers to access arising from current processes.

6.1.2 Coverage of indications and reimbursement restrictions

Many clinicians noted that the lack of coverage for indications which are supported by well-established evidence but not registered on the ARTG (i.e. off-label indications) was a barrier to access, because many patients could not afford these medicines without the PBS subsidy. They noted that the current system does not quickly respond to new evidentiary developments. As discussed in Section 5.3, this is largely because the approved list of indications on the ARTG is rarely updated in parallel with the development of evidence, and PBS listed indications must concord with the list of indications on the ARTG. Often this may be because the TGA approval for additional indications is process-laden and time consuming, because the evidence does not meet the requirements of the TGA, or because

there is insufficient commercial incentive for the sponsor to pursue the listing – especially when the medicine has lost market exclusivity following the expiry of its patent. Furthermore, new evidence can be developed by research institutions without involvement of the original sponsor; this data ownership issue may preclude the sponsor from making an application to broaden the indications in the ARTG.

An example noted in the consultation is a lack of PBS coverage for using paclitaxel (together with carboplatin) to treat endometrial cancer, even though it is recommended in the officially endorsed guidelines by Cancer Australia and Cancer Council Australia 2013. Another example is when gemcitabine had a restricted listing on the PBS – it was not reimbursed for cancer of the biliary tract because it was not TGA listed. Other examples include docetaxel and irinotecan for a range of indications that are outside TGA approved indications, but have a sound clinical basis.

One stakeholder also highlighted the inconsistency between current diagnostic guidelines and the diagnostic criteria specified in the PBS. This stakeholder noted an example that, to be eligible for PBS-reimbursed dasatinib (and all other Tyrosine Kinase Inhibitors, TKIs)³¹, a patient living with chronic myeloid leukaemia must fulfil criteria based on cytogenetic and morphological changes, rather than molecular changes – the current recommended standard of diagnosis. As such, some patients could not access dasatinib (and all other TKIs) even though current guidelines recommended the initiation of treatment.

Different coverage of on-label and off-label indications in hospital and PBS formularies may also affect the continuity and affordability of treatment. One clinical stakeholder noted that hospital clinicians sometimes do not choose non-PBS reimbursed medicines, even if they are the most appropriate treatment, to avoid significant out-of-pocket expenses for patients following hospital discharge.

6.1.3 Complex administrative requirements for reimbursement

Many clinical stakeholders said they faced significant challenges in navigating the complex administrative requirements to fulfil reimbursement criteria specified in the Schedule of Pharmaceutical Benefits. This complexity is due to many different approval processes for access, including the types of approval (e.g. Complex Authority Required Highly Specialised Drugs (CAR HSD) for trastuzumab, streamlined authority, phone and written authority prescriptions), and application forms to access different drugs (e.g. TKIs, multiple forms of imatinib, trastuzumab via the Herceptin Program). While acknowledging the importance of defining access criteria to ensure medicines are used for patients most likely to benefit or for use by clinicians with the most appropriate clinical expertise, many stakeholders felt that current administrative processes impose unnecessary demands on resources and could be further streamlined.

6.1.4 Barriers arising from state/federal funding arrangements

Several stakeholders noted that current funding arrangements between the States and the Commonwealth had negative impacts on access to cancer medicines. Under the current

³¹ Please note that **ALL** Tyrosine Kinase Inhibitors for chronic myeloid leukaemia, including nilotinib and imatinib, are affected by this access issue because these medicines have identical reimbursement criteria.

arrangements, a patient receiving inpatient care at a public hospital cannot access PBS-funded medicines, despite being admitted for a legitimate reason. Even though the patient could have received an oncology treatment while in hospital, the patient would need to present again as a non-admitted patient so that the hospital pharmacy can supply PBS-funded medicines in accordance to the PBS requirements (e.g. rituximab infusion). This is often inconvenient for patients, and these administrative hurdles may result in an inefficient use of resources.

6.1.5 Access to medicines for rare cancers

Four clinical stakeholders noted that medicines for rare malignancies are far fewer than medicines for common cancers. They believed that this obviously relates to the research priority and commercial imperative for more common cancers. Furthermore, they believed that the decision making process appears to be driven by advocacy: popular cancers received a disproportionate amount of attention whereas rarer cancers are often ignored.

Another factor is the challenges in undertaking clinical trials for rare cancers because of difficult patient recruitment. One stakeholder noted that clinical trials for rare cancers are often conducted through collaborative trial groups for rare cancers such as the European Organisation for Research and Treatment for Cancer because these groups have established networks to access patients with rare cancers. However, these trials were often undertaken with much less support from the industry and the data collected may be less suited to registration and reimbursement requirements. Stakeholders emphasised that, unless the systems for research and development, medicines regulation and reimbursement are supportive of medicine development for rare cancers, patients with these diseases will continue to be excluded from the benefits of advancements in oncology science. Furthermore, as personalised medicines continue to improve disease characterisation, problems of access would be particularly pertinent for rare subtypes of common cancers.

6.2 Regulatory and reimbursement approval

All stakeholders concurred that a rigorous regulatory and reimbursement approval process is fundamental to ensuring the quality, safety, efficacy and cost-effectiveness of medicines used in Australia. However, stakeholders noted that many components of the current process are not conducive to meeting these aims. These components are discussed below.

6.2.1 Assessment and listing process and timeframe

As noted in Section 6.1.1, several stakeholders considered the extent of assessment for regulatory approval by the TGA is an unnecessary duplication of effort, if regulatory agencies in other jurisdictions have already undertaken assessments based on the same laboratory and clinical evidence. Furthermore, the regulatory approval process in Australia does not provide an expedited route for medicines that represent a major advancement in treatment, or for medicines used to treat serious or life-threatening conditions with significant unmet clinical needs. Processes in Australia take a 'one-size-fits-all' approach, which is not appropriate for every application. This is in contrast to the FDA multi-tiered

system whereby therapeutically important medicines are made available via the Fast Track, Accelerated Approval and Priority Review (see Section 5.1.4).

Many stakeholders commented on the significant time lag between the TGA approval and the PBS listing processes, due to PBAC rejection or deferral, or fiscal consideration by the Government. Often, this means that some patients are not receiving the best available care. An example noted in the interview was the listing process leading to the eventual listing of azacitidine for the treatment of myelodysplastic syndrome – a rare group of disorders³² affecting the formations of blood cells which can progress to leukaemia. In September 2009, the PBAC provided a positive recommendation to the Minister for the listing of azacitidine on Section 100 Highly Specialised Drug Scheme of the PBS. Despite PBAC's recommendation, azacitidine was not made available to patients until February 2011 – a 14-month delay from the usual listing process. Other examples include recent failures to reach an agreement between sponsors and the PBAC for the listings of vemurafenib and abiraterone. Another stakeholder highlighted that the PBAC has recently requested post-marketing evidence and commitment as a condition for reimbursement approval for ipilimumab and eculizumab. The stakeholder believed that this signals a potential 'fifth hurdle' in the process that may challenge access to cancer and other medicines.

In contrast to the above views, other stakeholders highlighted the challenges in measuring and comparing time to access in different countries because of a multitude of factors influencing the decision making process, from medicines regulation to reimbursement. They noted that some sponsors have found parallel processing of submissions between the TGA and the PBAC helpful, whereas others found it difficult to provide the PBAC with informative submissions while the TGA is conducting its evaluation. If the TGA Delegate makes a negative recommendation, the sponsor will withdraw the submission for consideration at the PBAC meeting, but must incur the expense of having had the PBAC submission reviewed by the various subcommittees.

The stakeholders also highlighted that time to regulatory approval for cancer medicines is of average length compared to other jurisdictions and some studies suggest it is declining (reference not provided). Notwithstanding the significant variance in time to reimbursement for cancer medicines in Australia, the average timeframe of about two years in Australia is similar to that of authorities in other comparable countries (e.g. NICE in the UK).

6.2.2 Complexity and lack of coordination of listing processes

Several stakeholders noted the apparent disconnect in processes between the TGA, PBS and MBS listing processes. They noted a lack of continuity in process management between different Government authorities to facilitate the entire access pathway from regulatory registration, to PBS reimbursement of pharmaceuticals and MBS reimbursement of medical services to provide the associated tests. Many stakeholders acknowledged that the Government has endeavoured to provide better coordination of processes by putting in place initiatives such as parallel processing for submissions to the Advisory Committee on Prescription Medicines (ACPM) and PBAC, and assessment for co-dependent and hybrid

³² Within Australia, there were 972 cases of myelodysplastic syndrome reported in 2004, with an estimated incidence of 4.6 persons per 100,000 population.

technologies. While many stakeholders are pleased that some processes have been initiated to improve coordination, they are concerned about the efficiency of the current processes and believe there is scope for considerable improvements.

In part, this is because the current process requirements are so complex that it is difficult to synchronise processes from a pragmatic point of view. One example relates to the difficulty associated with managing processes if there are two different sponsors, for the oncology medicine and the pathology test required to identify patients with certain disease characteristics. In this case, timely access is highly dependent on both sponsors submitting the applications concurrently. This may be an increasing problem because of the ongoing focus on developing personalised medicines.

6.2.3 Evidentiary requirements

In recognition of the fact that most clinical trials are undertaken globally, several stakeholders emphasised the ongoing need to harmonise evidentiary requirements among authorities in Australia and those overseas so that clinical trials can be run more efficiently. On this point, some stakeholders further noted that most companies now operate at a global level, and it may not be always possible to meet the unique evidentiary requirements set down by the Australian authorities: Australia cannot expect to have clinical trials designed to meet the unique requirements of the local environment.

Several stakeholders said that the current high burden of proof in Australia to gain regulatory and reimbursement approval can impede patient access to useful medicines. In their view, for diseases with significant unmet clinical need and for technologies that have proven to be efficacious and safe, making decisions based on a surrogate endpoints may be appropriate, on the condition that the sponsor has the obligation to undertake Phase IV post-marketing evaluation. In fact, many stakeholders considered the current deficiencies in gathering post-marketing real-world evidence as a significant gap in the overall process in assessing the merits of medicines in Australia. However, other stakeholders said that they would “defend” the PBAC’s decision to reject some listings, because they thought the clinical evidence based on surrogate endpoints was not compelling, did not warrant the resource, and might give patients false hope.

For the assessment of co-dependent technologies, several stakeholders felt that the bar to meet the requirements set out in the current Government guidelines is very high, and in many cases unrealistic. For example, several stakeholders considered the expectation of having RCT-based evidence for pathology tests as impractical. Furthermore, because the proposed evaluation protocols (see Table 5.2) are not always developed by individuals with the necessary expertise in the relevant topic area, these protocols often “miss the crux of the issue” and present lengthy information to the extent of being “indigestible”. One stakeholder also notes that these protocols also often specify requirements that are impossible to achieve. For example, the protocol would ask to review the sensitivity and specificity of the test in the real-world population in Australia; as these are new technologies, real-world data are unsurprisingly not available. Furthermore, one stakeholder believed that the longer evaluation process for medicines with co-dependent diagnostic tests could pose issues in equity of access. One stakeholder notes that the cost of the molecular test is often much lesser than the cost of medicines. Withholding

reimbursement for medicines because of tests seems unreasonable because most patients would be able to fund such once-off costs.

Several stakeholders also commented on problems pertaining to quantifying the quality of life (QoL) in cancer patients. Specifically, the QoL measure was considered too generic to capture the nuances of individual preferences for fatal and non-fatal diseases. To illustrate this point, one stakeholder gave an example whereby a one year extension of life at 0.5 QoL for a patient with late-stage cancer would be considered equal to a 0.5 QoL improvement arising from symptomatic relief for patients with a non-fatal disease. In the view of this stakeholder, survival is not the same as symptomatic improvement.

As discussed in section 5.2, the evidence base for cancer medicines may have some levels of uncertainty because of the experimental challenges and the complexity of cancers and cancer medicines. Stakeholders noted that the current system has a low level of acceptance for uncertainty, and has not implemented any process or practical solutions to address this. This means that the current system is not sufficiently sensitive to assess the complexity of many cancer treatments, particularly for medicines intended to treat small patient populations (i.e. rare cancers).

6.2.4 Process transparency

Several stakeholders raised concerns about the transparency of the current decision making process for regulatory and reimbursement approval. Many were puzzled by the discrepancies in decisions made by the Australian authorities compared to authorities in other comparable jurisdictions that have equally rigorous assessment processes. One example used to highlight this discrepancy was the use of crizotinib to treat ALK-positive non-small cell lung cancer, which has received approvals from both the FDA and EMA, but not the TGA. One stakeholder felt that the processes are intentionally long to delay listing decisions, reflecting an underlying conservatism in adopting new technology.

In terms of reimbursement, a number of stakeholders raised concerns that the current process appears to have an increasing overlay of non-transparent political processes. Several stakeholders shared the disappointment about the recent PBAC rejection of a listing request for vemurafenib for the treatment of metastatic melanoma because this medicine has been approved by authorities in other countries that are equally concerned about the cost-effectiveness of medicines. This rejection is particularly pertinent in Australia, given its relatively high incidence of melanoma.

While acknowledging the need to consider the budgetary impact of listings, several stakeholders were dispirited by the Government's decision to not fund effective treatments for rare cancers, for which the overall impact on the health budget would have been minimal. Two examples were noted to highlight this issue: the lack of reimbursement for sunitinib and everolimus to treat pancreatic neuroendocrine tumour and metastatic carcinoid tumours respectively, for which there is currently no alternative treatment option. Stakeholders would like more transparency regarding the decision making process, and for this process to have a higher level of patient involvement.

6.3 Value of cancer medicines

A number of stakeholders noted that cancer medicines are expensive, especially for new targeted therapies. Many of these stakeholders qualified their views by stating that they recognised the important role the medicines industry plays in facilitating patient access to medicines. They also recognised the monumental challenges and risks along the discovery and development pathways in bringing one successful medicine to the market. For these reasons, they emphasised the need to maintain a viable medicines industry by providing sufficient commercial incentives, so that the industry can continue to bring new medicines to benefit cancer patients. However, they felt that the prices of some cancer medicines are not justified, and the medicines industry often has an unrealistic price expectation. Many stakeholders urged sponsors to provide greater transparency regarding how drug prices are set in Australia and globally.

One example mentioned by several stakeholders was the 50% price reduction for aflibercept in 2012 in the US, after the Memorial Sloan-Kettering Cancer Center in New York made a decision to not approve the medicine, on the basis that the price was not in line with the benefits, and ignoring the cost of cancer treatment was “not tenable” (Bach et al 2012; Grisham 2012). Other stakeholders brought attention to a recent article published by a group of more than 100 experts in chronic myeloid leukaemia, in which these experts highlighted the fact that 11 of the 12 medicines approved by FDA in 2012 for various cancer indications were priced above \$100,000 per year. These experts argued that the prices of these medicines are “(1) too high, (2) are unsustainable, (3) may compromise access of needy patients to highly effective therapy, and (4) are harmful to the sustainability of our national health care systems” (p. 4439) (Experts in Chronic Myeloid Leukaemia, 2013).

Some stakeholders were critical of the medicine industry’s justification for high prices, namely, to recoup their investment in developing the medicines and to build capacity for future innovations. They cited imatinib as an example, for which the cost of research and development would have been recouped within the first two years of marketing, and additional earnings over subsequent years of the patent would provide generous profits to the sponsor. Another stakeholder noted that the initial phases of drug discovery and development are often undertaken at academic and research institutions under the auspices of tax-payer funds. Many sponsors only incurred the costs for undertaking Phase III trials, which is highly unlikely to be the oft-cited figure of \$1 billion (see Adams and Brantner 2006). As such, it is unreasonable for sponsors to justify a price as necessary to recoup the cost of all phases of drug development, when the cost of research and development has already been funded partially by tax payers.

Many stakeholders urged sponsors to provide greater transparency regarding how medicines prices are set in Australia and globally. One stakeholder noted that the price of cancer medicines does not seem to reflect the cost of manufacturing; small molecules are priced at the same level as complex biological products that have more complicated manufacturing and quality assurance processes. On transparency of pricing, one stakeholder also sought better transparency for special pricing arrangements, in which the PBS-listed price differs from the agreed price between the sponsor and the Commonwealth Government. On this note, industry stakeholders commented that almost all companies operating in Australia are affiliates of global companies, and the Australian subsidiaries have limited, and generally low level of influence over the development of new cancer

medicines, both in terms of trial design and the setting of the price, particularly for those intended to treat a small group of patients.

Many stakeholders were concerned about the unsustainable nature of the prices for cancer medicines, similar to the views expressed by the experts in Chronic Myeloid Leukaemia (2013) and Bach and colleagues (2012). Many stakeholders understood why the PBAC and the government had to carefully consider the affordability of these medicines from a health system perspective, especially when there are many competing priorities from other disease areas. One stakeholder brought attention to the conclusion of the oft-cited article on delivering affordable cancer care in high-income countries (Sullivan et al 2011): “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” (p.933).

There is consensus that most patients are not able to afford new cancer medicines if a medicine is not listed on the PBS. Several stakeholders observed that high prices of medicines limited these treatment options to the very wealthy: “very few [patients with cancer] have up to \$120,000 of discretionary funds per year to access the treatment”.

On the other hand, industry stakeholders noted that new cancer medicines are costly to develop, because cancer is not one disease but made up of many different diseases. The intended patient groups for new cancer medicines are typically smaller because of better differentiation of disease subtypes and the targeted nature of these medicines (discussed further below). Generally, the duration of treatment is much shorter than other types of medicines because in many cases these medicines are used in end-of-life setting. In addition, unlike in more conventional therapeutic areas such as cardiovascular disease, many of these targeted cancer medicines require companion diagnostic tests to identify the patients most likely to benefit, and there are costs associated with the development of these tests.

Industry stakeholders also noted that pricing of medicines should be considered in light of the value the Australian community place on the benefits of these medicines. Indeed, various stakeholders noted that the Australian community has limited inputs into the current decision making processes of Government, and there is little provision within the decision-making framework for considering the values these new medicines provide to the broader community. Specifically, there has not been a meaningful debate in Australia about what the Australian community considers an acceptable level of funding for caring for patients nearing their end of life, including those with advanced cancers. Furthermore, industry stakeholders noted that the current system provides the PBAC with unlimited flexibility in decision making (e.g. by not specifying a threshold to indicate cost-effectiveness). To them, the decision-making framework and principles should be determined by the Australian community, not solely by the PBAC members. As such, engaging with the Australian society with a view to developing a clear set of decision-making principles that is reflective of the taxpayers’ preferences for funding care would be an important next step forward.

Finally, many stakeholders commented on the relatively minimal contribution from the private health insurance sector in improving access to cancer medicines. There is little transparency to patients and clinicians regarding what medicines are covered by an insurance policy. When a medicine is covered, the rebate is usually capped at an amount

far below the cost of the medicine. Furthermore, there is no mechanism for individuals to insure themselves to fund personal use of high cost medicines in the future. Individuals may have paid top-level insurance coverage for many years without making claims, only to find out that reimbursement is minimal when they need it.

6.4 Other concerns

Stakeholders raised a range of other issues in the consultations. Several stakeholders perceived the governance culture in various government departments as “disappointing”. Stakeholders believed the departments focused on financial accountability rather than patient access to medicines. One stakeholder said the Government has a ‘nay-saying’ culture, with a focus on “why should we do this?” rather than, “how can we do this?”. Two stakeholders said the Government delayed the adoption of new technology, either because of conservatism or as a cost-containment measure: “you know that it will be funded eventually but it’s a matter of when”. Many stakeholders felt that the silo structure of different authorities and government departments should be removed, as patient access to cancer medicines is often beyond the remit of one particular authority. One stakeholder suggested a joint committee between MSAC and PBAC to achieve greater process efficiency.

Issues pertaining to price reductions of cancer medicines arising from the EAPD initiative (see Section 5.5) also generated some views. Some stakeholders welcomed the initiative because they considered the extra profits made by pharmacists as excessive and unjustifiable, and thought these resources should be used to fund the listing of new cancer medicines. This is especially relevant given that generic medicines in Australia are more costly than in other countries. Conversely, other stakeholders felt that in the absence of reasonable reimbursement to reflect the costs of supplying cytotoxic chemotherapies, the EAPD initiative will negatively impact the supply of these medicines. In a long run, prices of these cancer medicines would decrease to the extent that sponsors would have insufficient commercial incentives to ensure consistency of supply. Indeed, one clinical stakeholder highlighted the dilemma of having to use more expensive alternatives because of supply shortages, and the withdrawal of cyclophosphamide and mitomycin C. Stakeholders believed that the system should be structured to guarantee the supply of generic cancer medicines.

In discussing the costs of cancer medicines and research, several stakeholders stressed the importance of making Australia an attractive place to undertake clinical research. These stakeholders felt that undertaking clinical trials in Australia has become very expensive, especially considering the high cost of meeting system requirements. In their view, clinical trials and research expertise would move off-shore without system improvement and investment. Patients would also be deprived of access to investigational medicines. Two issues highlighted are the cumbersome and duplicated process of obtaining ethics approval from individual institutions, and a lack of administrative support for research organisations to navigate the system requirements. In their view, there should be a single set of “federated” requirements. Other stakeholders noted that the cumbersome processes and costs had already had an impact on clinical trial activity, with figures from the TGA showing that the number of clinical trials undertaken in Australia has fallen for the fourth time in five years. Clinical trial numbers are down 30% from their 2007 high of 865 (Medicines Australia 2013b).

Other issues highlighted included:

- The timeframe for consumers to contribute to the PBAC decision making process is insufficient. This should be extended beyond the two-week window because patients are often too fragile to be able to meet that timeframe;
- Current rules/guidelines of the Patient Assisted Travel Schemes (PATS) specifically exclude rural and regional patients for the purpose of participating in clinical trials. This may limit participation by some rural and regional patients in clinical trials, thereby restricting their access to investigational cancer medicines. The stakeholder believed that this is inconsistent with the policy intent of the Clinical Trials Action Group Report endorsed by the Government (CTAG 2011), in which clinical trials should be made more accessible to patients to improve recruitment to trials;
- The medicines industry has significant expenditure on marketing activities. Resources for these activities should be diverted to investment in research and working with the regulators to facilitate patient access to medicines;
- As many cancers have now become chronic conditions, patients' persistence in using cancer medicines becomes even more pertinent. Access to medicines that offer simpler dose administration and fewer side effects would have a positive impact on the health outcomes of patients, especially for those living in non-metropolitan areas; and
- The Government does not appear to have a regular audit process to identify utilisation outside of PBS approved indications. This usage increases government expenditure and is not an efficient use of resources because expensive medicines may be used to treat conditions for which there is much less evidence.

6.5 Impacts arising from current barriers to access cancer medicines

Many stakeholders representing clinical and consumer groups commented on the impact on patients when a cancer medicine is not reimbursed. The financial burden of these medicines is significant – some patients mortgage their assets to fund treatment. This situation is also distressing for clinicians, especially when their professional judgement recognises that the patient would likely benefit from a certain treatment, if cost concerns were not a barrier.

Several stakeholders believed that delayed access to reimbursed cancer medicines means that the system is more reliant on compassionate and early access programs. In addition to the potential issues associated with these programs (see section 4.7.1), their operation places undue demand on hospital resources. One clinical stakeholder from a major cancer treatment centre commented that the centre has to employ a full time pharmacist to manage 40 to 50 compassionate or early access programs, to ensure timely access to new medicines while the TGA or the PBAC are considering the listing decisions. This is an extremely resource intensive process because of different inventory and financial management processes. Hospital pharmacy funding does not recognise the resources required to administer these programs. Furthermore, the private sector will not be able to provide such access; this presents an equity issue because not all cancer patients (e.g. those from regional and rural areas) receive treatment at a major treatment centre where such programs are more commonly available.

Without changes to the current system, stakeholders believe that the challenges facing patient access to cancer medicines will worsen, especially with the abundance of cancer medicines progressing through the clinical development pipeline (see Section 3.2). Between now and 2015, the industry estimates that almost 50 submissions will come before the PBAC, and a significant proportion of these will involve co-dependent technologies. To some stakeholders, the complexity and lack of responsiveness of the current system have already resulted in Australia falling behind in the adoption of medical technologies that have been well established in other countries³³.

Some stakeholders also felt that the current environment will disengage the medicines industry from Australia, and some think that the industry may divert their investment to other countries. Industry stakeholders believed that the increasing use of special pricing arrangements is a reflection that the current reimbursement system is not delivering a fair return on innovation that should be considered from a global perspective. Some stakeholders noted that delay in securing, or lack of, reimbursement has a “knock-on” effect on clinical trials, as companies may reconsider placing clinical trials and access programs in Australia if there is little or no chance of reimbursement. If this occurred, several stakeholders felt that this would represent a considerable loss to Australia, from both scientific and economic perspectives. Furthermore, confidence in the ability of the Government to manage access to cancer medicines would be eroded. Ultimately, any delays in access have real patient impact in the area of cancer treatment, especially when cancer treatments are typically provided to patients nearing the end of life.

6.6 Resource allocation

Regarding equitable access, most stakeholders agreed that resource allocation decisions should be made with consideration to all therapeutic areas, and cancer medicines should not be treated differently. However, many felt that the principle of equity should be implemented with consideration to the following factors:

- Population burden of disease;
- Severity of disease, including consideration for end-of-life needs;
- Unmet clinical need, especially for diseases where there is no alternative treatment;
- Wider perspective when assessing economic merits, including the impact of:
 - Costs for families and carers; and
 - Patient’s productivity if a drug improves functionality.

Several stakeholders noted that the current decision making framework already encompasses many of the above points. However, the evidence presented to support the claim is often not methodologically rigorous and compelling (e.g. societal benefits, using surrogate endpoints).

The discussion on whether to include societal preference for cancer care and end-of-life care in the decision making process was contentious. In the view of many stakeholders, debate on this topic would be ethically challenging and inevitably emotive from the

³³ For example, Japan and France have a population coverage of more than 90% for EGFR testing, whereas Australia has taken eight years to achieve a coverage of about 25%.

viewpoints of individual patients and family. Some considered that decision making at the population level ought to be made on the basis of 'average' which may not commensurate with individual preferences. Several stakeholders noted the fund specifically for cancer care in the UK, but were not certain that would be a necessary solution for the Australian context.

In considering the ICER threshold (see section 4.1.2) to determine economic merit of a medicine, one stakeholder commented that cost-effectiveness thresholds appear to be much higher in other sectors than that considered by the PBAC. A cross-sectoral view (i.e. in health and non-health sectors) in determining economic merit of an investment is therefore needed. Another stakeholder noted that the implicit ICER threshold of \$50,000 per QALY gained has not reflected indexation over time. Finally, one stakeholder suggested a link between the ICER threshold and per capita GDP similar to the recommendations of the World Bank, as a potential way forward.

6.7 Suggestions for further consideration

Many stakeholders suggest a need to adapt and evolve the registration and reimbursement processes alongside development in technologies for the future. Some stakeholders noted that the Australian reimbursement system first implemented 20 years ago for determining the value for money of medicines has not adapted sufficiently to the changes in the development of medicines and diagnostic technologies, particularly in regard to targeted cancer medicines. Many components of the current process are not fit for purpose to meet the emerging issues associated with cancer medicines.

They noted that while the overarching principles of the system are sound, the system has not kept pace in interpreting and implementing these principles in line with the changing environment. For example, they believe the system needs to use the best methodological practice, and align with the practices and approaches of authorities in other jurisdictions that have implemented a decision making framework based on health technology assessment e.g. evidence requirements, consideration for benefits beyond the healthcare sector and indirect costs.

One of the themes that emerged from the consultations with stakeholders is the possible use of more real-world evidence as part of the value- or performance-based funding process. Several stakeholders noted that the price of a medicine or a test should be linked to the health outcomes achieved in actual clinical practice, based on data collected one to two years after listing. They highlighted the absence of monitoring in the current process as a deficiency of the current system, and emphasised the need to examine whether the medicine/test is achieving the health outcomes and value for money as claimed in the submission, often based on 'imperfect' clinical trial and modelling evidence. One stakeholder believed that because the burden of proof is lower at the time of listing, this proposed system may facilitate a more rapid decision making process, and therefore increase timely patient access. Furthermore, this proposed process may also facilitate access in the absence of 'perfect' data collected from clinical trials, and may provide certainty for decision making through real-world observations.

The stakeholders noted several provisos. First, the processes should be operated on the basis of an agreed set of overarching principles, and should not be administratively

burdensome and complicated. Second, the prices may be set at a lower level during the data collection period given the medicines would have unrestricted reimbursement (but in line with the TGA registered indication). In other words, there would need to be a change in medicines industry expectations from “profit maximising” to “profit making”. Third, if the post-approval evaluation found evidence of inadequacy, some rejections are reasonable. The starting and stopping rules must be clearly pre-specified. At a practical level, a key step for the implementation of such a process would be to establish data collection processes in Australia (e.g. a registry), with a view to minimising selection, measurement and reporting biases.

Three stakeholders also suggested streamlining the current formulary, possibly by including a review and delisting process, where medicines identified as having little effectiveness may be removed.

Another possible model suggested by stakeholders is a system whereby individuals are able to contribute towards a health savings account to fund their potential future need for medicines, similar to the Medisave model in Singapore.

Finally, many stakeholders stressed the importance of recognising a joint responsibility between the government, industry, clinical community, cancer patients, and indeed the broader society to finding mutually agreeable solutions. To achieve this, the first step is to have a public discussion about how Australia can fund the rising costs of healthcare in general, and pharmaceuticals specifically.

6.8 Summary

This chapter described the views of stakeholders consulted. Many stakeholders confirmed the issues highlighted in the previous chapter and have provided examples to support their view. Stakeholders also identified a range of other issues which will compromise cancer outcomes in Australia if not addressed. These include:

- Barriers to access cancer medicines due to state/federal funding arrangements;
- Inadequate access to medicines for rare cancers;
- Expensive drug discovery and development for cancer medicines;
- Australian medicine sponsors have limited, and generally low level of influence over the development of new cancer medicines, both in terms of trial design and the setting of the price, because Australia has a relatively small market on a global scale;
- Unrealistic price expectation by the medicines sponsors, and a lack of transparency regarding how medicines prices are set in Australia and globally;
- A governance culture focusing on financial accountability rather than patient access to medicines in Government departments;
- A need to identify appropriate remuneration for generic cancer medicines to ensure consistency of supply;
- A need to ensure Australia’s attractiveness for undertaking clinical research.

A number of suggestions have been put forth for further debate and consideration.

7 Conclusion

This report has highlighted many issues and opportunities for all stakeholders to engage in an open dialogue for finding mutually beneficial and lasting solutions. To achieve this, all stakeholders should first recognise their joint responsibility in supporting patient access to cancer medicines. All stakeholders should participate in an informed debate, particularly about how Australian society should value the merits of oncology innovations, and how to best facilitate equitable patient access through fair and transparent resource allocation processes.

Although the primary focus of this report is on access to cancer medicines in Australia, the issues outlined in this report are certainly not exclusive to the Australian context (see Sullivan et al 2011; Turner and Associates 2008; Wilking and Jönsson 2005). As such, a study into how other health systems address these issues is needed.

All stakeholders should work towards:

- Procedural improvements by streamlining the complex and lengthy regulatory and reimbursement processes, particularly for medicines with co-dependent diagnostic tests;
- Ensuring that medicines that have gone through rigorous regulatory and reimbursement assessments are listed without undue political interference;
- Ensuring there is adequate investment into the treatment for rare cancers;
- Ensuring that medicines are priced at a level that is affordable and sustainable to the system;
- Recognising that incremental innovations in cancer research, as in other therapeutic areas, are fundamental to the eventual breakthrough discovery.

In considering the strategies to mitigate future challenges, it is important to reflect upon the monumental achievements in bettering cancer outcomes over the past 200 years (see DeVita and Rosenberg 2012). Such achievement requires strong commitment from all stakeholders in providing an environment conducive to innovative research and facilitative to cancer care.

References

- Adams CP, and Brantner VV, 2006. Estimating the cost of new drug development: Is it really \$802 Million? *Health Affairs* 25(2):420-428.
- Australian Bureau of Statistics, 2013a. Employee Earnings, Benefits and Trade Union Membership, Australia. Cat no. 6310.0. Canberra: ABS.
- 2013b. Wage Price Index, Australia. Cat no. 6310.0. Canberra: ABS.
2012. Australian Labour Market Statistics. Cat no. 6105.0. Canberra: ABS.
2010. Research and Experimental Development – All sector summary. Cat no. 8112.0. Canberra: ABS.
- Access Economics, 2007. Cost of Cancer in NSW – Report for Cancer Council NSW. Canberra: Access Economics.
2008. The economic value of cancer R&D – Report for Cancer Institute NSW. Canberra: Access Economics.
- Australian Institute of Health and Welfare, 2013. National Health Priority Areas. www.aihw.gov.au/national-health-priority-areas [Accessed Jun 2013].
- 2012a. Cancer incidence projections: Australia, 2011 to 2020. Cancer Series no. 66. Cat. No. CAN 62. Canberra: AIHW.
- 2012b. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer Series no. 69. Cat. no. CAN 65. Canberra: AIHW.
- 2012c. Health expenditure Australia 2010–11. Health and welfare expenditure series no. 47. Cat. no. HWE 56. Canberra: AIHW.
- 2011a. Public health expenditure in Australia 2008–09. Health and welfare expenditure series no. 43. Cat. no. HWE 52. Canberra: AIHW.
- 2011b. Australian hospital statistics 2010-11. Health and welfare expenditure series no. 43. Cat. no. HWE 52. Canberra: AIHW.
2010. Health system expenditure on disease and injury in Australia, 2004-05. Health and welfare expenditure series no. 36. Cat. no. HSE 87. Canberra: AIHW.
2009. Australian hospital statistics 2007-08. Health and welfare expenditure series no. 30. Cat. no. HSE 50. Canberra: AIHW.
2007. Australian hospital statistics 2005-06. Health and welfare expenditure series no. 33. Cat. no. HSE 71. Canberra: AIHW.

- Australian Institute of Health and Welfare & Australasian Association of Cancer Registries, 2012. Cancer in Australia: an overview, 2012. Cancer series no. 74. Cat. no. CAN 70. Canberra: AIHW.
- Australian Institute of Health and Welfare & Cancer Australia 2012. Breast cancer in Australia: an overview. Cancer series no. 71. Cat. no. CAN 67. Canberra: AIHW.
- Bach PB, Saltz LB, Wittes RE, 2012. In Cancer Care, Cost Matters. The Opinion Pages in New York Times. Published: October 14, 2012.
www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html [Accessed: May 2013]
- Begg S, Vos T, Barker B, Stevenson C, Stanley L, Lopez AD, 2007. The burden of disease and injury in Australia 2003. PHE 82. Canberra: AIHW.
- Blinman P, King M, Norman R, Viney R, Stockler MR, 2012. Preferences for cancer treatments: an overview of methods and applications in oncology. Ann Oncol. 23(5): 1104-10.
- Bonaventura A, 1995. Complications of cytotoxic therapy. Austr Prescr 18:65-67.
- Britt H, Miller GC, Charles J, Henderson J, Bayram C, Valenti L, Harrison C, Pan Y, O'Halloran J, Zhang C, Fahridin S, 2011. General practice activity in Australia 2010–11. General Practice Series: No. 29. Sydney: Sydney University Press.
- Cancer Australia and Cancer Council Australia, 2013. Management of apparent early stage low and high risk endometrial cancer. Canberra: Commonwealth Government of Australia.
- Cancer Council Australia, 2011. Adult gliomas (Astrocytomas and oligodendrogliomas): a guide for patients, their families and carers. Sydney: Cancer Council Australia/Clinical Oncological Society of Australia.
- Cancer Research UK, 2013. Cancer News – 4 April 2013– Clarity over Cancer Drugs Fund should be 'a priority'. www.cancerresearchuk.org/cancer-info/news/archive/cancernews/2013-04-04-clarity-over-cancer-drugs-fund-should-be-a-priority [Accessed June 2013].
- Center for Analysis of Rare Tumors, 2013. CART-WHEEL project. www.cart-wheel.org/gui/Info/AllTumourTypes.aspx [accessed Jun 2013].
- Chalkidou K, 2012. Evidence and values: paying for end-of life drugs in the British NHS. Health Econ Policy Law. 7(4): 393-409.
- Clements M, Berry G, Shi J, Ware S, Yates D & Johnson A 2007. Projected mesothelioma incidence in men in New South Wales. Occupational and Environmental Medicine 64: 747-52.
- Coleman MP, Forman D, Bryant H et al, 2011. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer

- Benchmarking partnership): an analysis of population-based cancer registry data. *Lancet* 377: 127-138.
- Collins M, Latimer N, 2013. NICE's end of life decision-making scheme: impact on population health. *BMJ* 346: 1363.
- Community Affairs References Committee, 2013. Supply of chemotherapy drugs such as Docetaxel. Canberra: Commonwealth of Australia.
- Congressional Budget Office, 2006. Research and development in the pharmaceutical industry. Washington DC: Congress of the United States.
- Clinical Trials Action Group, 2011. Clinically competitive: Boosting the business of clinical trials in Australia. Canberra: Commonwealth Government of Australia.
- D'Agostino RB Sr, 2011. Changing end points in breast-cancer drug approval--the Avastin story. *N Engl J Med*. 14;365 (2): e2.
- Denaro C, 2008. Joint Australian Therapeutics Advisory Groups – submission to NHHRC. www.catag.org.au/wp-content/uploads/2012/09/joint-tags-nhhrc-submission-2008.pdf. [Accessed June 2013].
- Department of Health and Ageing, 2011. Response to the recommendations of the Finance and Public Administration References Committee report on the Government's administration of the Pharmaceutical Benefits Scheme. Canberra: DoHA. [www.health.gov.au/internet/main/publishing.nsf/Content/08FD4E7D7C382F3DCA257A3600177B1F/\\$File/Govt-response-deferrals.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/08FD4E7D7C382F3DCA257A3600177B1F/$File/Govt-response-deferrals.pdf) [Accessed June 2013]
- DiMasi JA, Hansen R, and Grabowski HG, 2003. The Price of Innovation: New Estimates of Drug Development Costs. *J Health Economics* 22: 151–85.
- DiMasi JA, and Grabowski HG, 2007. Economics of new oncology drug development. *J Clin Oncol* 25(2): 209-216.
- DeVita, VJ, Rosenberg S 2012. Two hundred years of cancer research. *New England Journal of Medicine* 366(23):2207-2214.
- de Witt GA, Busschbach JJV, de Charro F, 2000. Sensitivity and perspective in the valuation of health status: whose values count? *Health Econ* 9: 109-26
- Department of Health and Ageing (DOHA) 2013a. Medicare Benefits Schedule Book: Operating from 1 May 2013. [http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/72A85B0A56219B2DCA257B3B007ED3A4/\\$File/201305-MBS.pdf](http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/72A85B0A56219B2DCA257B3B007ED3A4/$File/201305-MBS.pdf) [accessed 20 May 2013].
- 2013b. Monthly and quarterly standard reports: quarter 2 2012, https://www.medicareaustralia.gov.au/statistics/mth_qtr_std_report.shtml, [Accessed May 2013]
- 2013c. PBS statistics. <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>, [Accessed May 2013]

- 2012, National Hospital Cost Data Collection. Cost Report Round 14 2009-10". Canberra: Department of Health and Ageing.
- 2011, "National Hospital Cost Data Collection. Cost Report Round 13 2008-09". Canberra: Department of Health and Ageing.
- 2010, "National Hospital Cost Data Collection. Cost Report Round 12 2007-08". Canberra: Department of Health and Ageing.
- Eisenstein EL, Collins R, Cracknell BS, Podesta O, Reid ED, Sandercock P, Shakhov Y, Terrin ML, Sellers MA, Califf RM, Granger CB, Diaz R, 2008, Sensible approaches for reducing clinical trial costs. *Clin Trials*. 5:75–84
- Experts in chronic myeloid leukemia 2013. Price of drugs for chronic myeloid leukemia (CML), reflection of the unsustainable cancer drug prices: perspective of CML Experts. *Blood* 121:4439-4442.
- Ferlay J, Shin H, Bary F, Forman D, Mathers C & Parkin D 2010. GLOBOCAN 2008 version 1.2. Cancer incidence and mortality worldwide. International Agency for Research on Cancer (IARC) CancerBase No. 10. Lyon: IARC.
- Food and Drug Administration 2007. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Rockville: U.S. Department of Health and Human Services.
- Food and Drug Administration 2012. Fast Track, Accelerated Approval and Priority Review. www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm#compare [Accessed May 2013]
- Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, Otter R, Licitra L, Mallone S, Tavilla A, Trama A, Capocaccia R; RARECARE working group, 2011. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 47(17): 2493-511.
- Garau M, Shah KK, Mason A, Wang Q, Towse A, and Drummond M, 2011. Using QALYs in cancer: A review of the methodological limitations, *Pharmacoeconomics* 29(8): 673-685.
- Guido RV, Glaucius O, Andricopulo AD, 2011. Modern drug discovery technologies: opportunities and challenges in lead discovery. *Combinatorial Chemistry & High Throughput Screening* 14: 830-839.
- Grisham J, 2012. The New York Times commends Memorial Sloan-Kettering's stance on a costly cancer drug. New York: Memorial Sloan Kettering Cancer Center. <http://www.mskcc.org/blog/new-york-times-commends-msk-s-stance-costly-drug> [Accessed May 2013]
- Harris AH, Hill SR, Chin G, Li JJ, Walkom E, 2008. The role of value for money in public insurance coverage decisions for drugs in Australia: a retrospective analysis 1994-2004. *Med Decis Making* 28 (5): 713-22.

- Hirsch BR, Califf RM, Cheng SK, Tasneem A, Horton J, Chiswell K, Schulman KA, Dilts DM, Abernethy AP 2013. Characteristics of Oncology Clinical Trials: Insights From a Systematic Analysis of ClinicalTrials.gov. *JAMA Intern Med*:1-8. doi: 10.1001/jamainternmed.2013.637
- Johnson JR, Williams G, Pazdur R, 2003. End points and United States Food and Drug Administration approval of oncology drugs. *J Clin Oncol* 21:1404-1411.
- Johnson KR, Ringland C, Stokes BJ, Anthony DM, Freemantle N, Irs A, Hill SR and Ward RL, 2006. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. *Lancet* 7: 741-746.
- Kelly W and Halabi S 2010. *Oncology Clinical Trials: Successful Design Conduct and Analysis*. New York: Demos Medical Publishing.
- Kefford RF, 2012. Drug treatment for melanoma: progress, but who pays? *Med J Aust* [Online first 12/07/12 doi: 10.5694/mja12.10955].
- Kummar S, Gutierrez M, Doroshow JH, Murgo AJ, 2006. Drug development in oncology: classical cytotoxics and molecularly targeted agents. *Br J Clin Pharmacol* 62(1): 15-26.
- Li F, Zhao C, and Wang L, 2013. Molecular Targeted Agents (MTA) combination therapy for cancer: developments and potentials. *Int J Cancer* (accepted article) doi: 10.1002/ijc.28261.
- Lopert R, 2009. Evidence-based decision-making within Australia's Pharmaceutical Benefits Scheme. *The Commonwealth Fund Pub* 1297(60): 1-13.
- Mandal S, Moudgil M, Mandal SK, 2009. Rational drug design. *Eu J Pharmacol* 625: 90-100.
- Medicines Australia, 2012. Media release: One step forward, one step back on deferral of PBS listing – 28 September 2012. <http://medicinesaustralia.com.au/2012/09/28/one-step-forward-one-step-back-on-deferral-of-pbs-listings/> [Accessed June 2013]
- Medicare Australia, 2013a. Late stage metastatic breast cancer. www.medicareaustralia.gov.au/provider/patients/late-breast-cancer.jsp [Accessed May 2013]
- 2013b. Number of new clinical trials continues to fall - 8 April 2013. <http://medicinesaustralia.com.au/2013/04/08/number-of-new-clinical-trials-continues-to-fall/>. [Accessed July 2013]
- Mellor JD, Van Koeeverden P, Yip SW, Thakerar A, Kirsas SW, Michael M, 2012. Access to anticancer drugs: many evidence-based treatments are off-label and unfunded by the Pharmaceutical Benefits Scheme. *Intern Med J*. 42(11): 1224-1229.
- Michiels S, Mauguen A, Fisher D, Burdett S, Paulus R, Mandrekas SJ, Belani CP, Shepherd FA, Eisen T, Pang H, Collette L, Le Pechoux C, Pignon J, 2011. Evaluation of disease-free survival as surrogate endpoint for overall survival using two individual patient data

- meta-analyses of adjuvant chemotherapy in operable non-small cell lung cancer. *J Clin Oncol* 29: (suppl; abstr 7004).
- Munos B, 2009. Lessons from 60 years of pharmaceutical innovation. *Nature Reviews* 8:959-968.
- National institute for Health and Clinical Excellence, 2009. Appraising life-extending, end of life treatments. London: NICE.
- National Health and Hospitals Reform Commission, 2009. A healthier future for all Australians – Final report June 2009. Canberra: NHHRC.
- O’Carragher N, Unciti-Broceta A, and Cameron DA, 2012. Advancing cancer drug discovery towards more agile development of targeted combination therapies. *Future Med Chem* 4(1): 87-105.
- Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB, Wheeler S, Swart AM, Qian W, Torri V, Floriani I, Jayson G, Lamont A, Tropé C; ICON and AGO Collaborators, 2003. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet*. 361(9375): 2099-106.
- Pearce A, van Gool K, Haywood P, Haas M, 2012. Delays in access to affordable medicines: putting policy into perspective. *Australian Health Review*, 36(4): 412-418.
- Pharmaceutical Benefits Scheme, 2013. www.pbs.gov.au/info/industry/pricing/eapd [Accessed May 2013]
- Pharmaceutical Benefits Scheme, 2013. Expenditure and prescriptions twelve months to 30 June 2012. Canberra: Department of Health and Ageing.
- Pharmaceutical Research and Manufacturers of America, 2012. Medicines in Development-Cancer. Washington, DC: PhRMA.
- Pharmaceutical Research and Manufacturers of America, 2008. Pharmaceutical Industry Profile 2008. Washington, DC: PhRMA.
- Pretium Pty Ltd, 2013. Roche Products Australia Pty Ltd, A drug Tracker report. 06 May 2013. Sydney.
- Prostate Cancer Foundation of Australia, 2013. One Man’s plight to help support the listing of abiraterone on the Pharmaceutical Benefits Scheme. www.prostate.org.au/articleLive/pages/One-Man%E2%80%99s-plight-to-help-support-the-listing-of-abiraterone-on-the-Pharmaceutical-Benefits-Scheme.html [Accessed Jun 2013].
- Private Health Insurance Administrative Council, 2012. Privately Insured People with hospital Treatment Cover – Annual analysis. Kingston: PHIAC.
- Productivity Commission, 2013. Report on Government Services 2013. Canberra: Commonwealth of Australia.

- Rawlins MD, and Chalkidou K, 2011. The opportunity cost of cancer care: a statement from NICE. *Lancet* 12: 931-932.
- Richards M, 2010. Extent and cause of international variations in drug usage: a report for the secretary of State for Health. Department of Health England.
- Sargent DJ, Hayes DF. 2008. Assessing the measure of a new drug: is survival the only thing that matters? *Journal of Clinical Oncology*: 26(12):1922–1923.
- SafeWork Australia, 2012. Mesothelioma in Australia – Incidence 1982 to 2008; Deaths 1997 to 2007. Canberra: Commonwealth of Australia.
- Sahari S 2011, 'GP co-payments at highest level ever', *Australian Doctor*, 17 June 2011, <http://www.australiandoctor.com.au/news/latest-news/gp-co-payments-at-highest-level-ever>. [Accessed 20 May 2013]
- Senate Finance and Public Administration References Committee, 2011. The Government's administration of the Pharmaceutical Benefits Scheme. Canberra: The Senate.
- Scannell JW, Blanckley A, Boldon H, Warrington B, 2012. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov* 11(3): 191-200.
- Sullivan R, Peppercorn J, Sikora K, et al 2011. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 12: 933–80.
- Tang PA, Bentzen SM, Chen EX, Siu LL, 2007. Surrogate end points for median overall survival in metastatic colorectal cancer: literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. *J Clin Oncol* 25(29): 4562-4568.
- Tangka FK, Trogon JG, Richardson LC, Howard D, Sabatino SA, Finkelstein EA, 2010. Cancer treatment cost in the United States: Has the burden shifted over time? *Cancer* 116(14): 3477-84.
- Tengs TO 2004. Cost–effectiveness versus cost–utility analysis of interventions for cancer: does adjusting for health-related quality of life really matter? *Value Health* 7(1), 70–78.
- Thomson S, Osborn R, Squires D, and Jun M, 2012. International Profiles of Health Care Systems. New York: The Commonwealth Fund.
- Tillett A, 2013. Patients urge subsidy for cancer drugs. *The West Australian* article: 29 March 2013.
- Turner and Associates, 2008. Issues of access to cancer drugs in Canada – a report for the Canadian Cancer Action Network. Toronto.
- United Kingdom Government Department of Health, 2011. Cancer Drugs Fund. Letter to Medical Directors in Strategic Health Authorities in England. www.gov.uk/government/uploads/system/uploads/attachment_data/file/147429/dh_124792.pdf [Accessed May 2013]

Wilking N, Jönsson B, 2005. A pan-European comparison regarding patient access to cancer drugs. Stockholm: Karolinska Institutet and Stockholm School of Economics.

World Health Organisation (WHO) 2009, Disease and injury country estimates persons, all ages, accessed at http://www.who.int/healthinfo/global_burden_disease/estimates_country/en/.

Appendix A: Stakeholders who participated in interviews

Group	Role	Representative groups/individuals
Government/ Payer	Government decision makers	1. PBAC – Dr Suzanne Hill
		2. MSAC – Professor Robyn Ward
		3. TGA – Anthony Hobbs
		4. Treasury and Finance – Nick Hunt
Health Consumer organisation	Government and non-government cancer control agencies including consumer organisations	5. Cancer Council – Professor Ian Olver
		6. CanSpeak – Dr John Stubbs
		7. Leukaemia Foundation – Dr Anna Williamson
		8. Breast Cancer Network Australia – Kathy Wells
		9. Lung Foundation Australia and Global Lung Cancer Coalition – Professor Matthew Peters
		10. Bowel Cancer Australia – Julien Wiggins
Clinical	Professionals caring for people with cancer	Oncology nurses
		11. CNSA - President Elect - Sandy McKiernan
		12. Keith Cox
		Pharmacists
		13. Peter MacCallum and COSA – Dan Mellor
		14. Austin Health – Jim Siderov
		15. The Society of Hospital Pharmacists of Australia and Peter MacCallum Cancer Institute – Sue Kirska
		16. Private Pharmacists - Stuart Giles
		Oncologists and Haematologists
		17. Associate Professor Gary Richardson- MOGA and PCPA
		18. Professor John Zalberg – Cancer Drugs Alliance, Australasian Gastro-Intestinal Trials Group (AGITG)
		19. Professor Michael Millward – Australian Lung Cancer Trials Group (ALTG)
		20. Dr Steve Begbie – oncologists in rural practice
		21. Dr Michael Boyer – Chief Clinical Officer at the Sydney Cancer Centre
		Pathologists
		22. Professor Stephen Fox

Group	Role	Representative groups/individuals
Other	Private Health Insurance Clinical evaluators	23. Professor Paul Waring
		24. Dr Keith Byron
		25. Dr Adrienne Morey
		26. Dr Stan Goldstein
		27. Ms Liliana Bulfone – Shoten Consulting and Deakin University
		28. Professor Rob Carter – Deakin University
		29. Richard De Abreu Lourenco – University of Technology Sydney

Appendix B: Interview questions

Telephone interviews were undertaken with 29 stakeholders to understand their views about the challenges to access cancer medicines. The stakeholders were identified by the Taskforce to represent all groups with an interest in access to cancer medicines.

The questions below were intended to be a guide only, and were tailored for the audience e.g. questions directed to evaluators focused on valuing medicines, and questions to clinicians focused on the treatment of patients. The calls were conversational in nature. The interview scripts were modified to enable more in-depth exploration of any themes that emerged from the interviews.

1. What is your view on patients access to cancer medicines under the current arrangements in relation to the following topics (*as relevant to the stakeholder in question*):

- range of cancer medicines and their indications, including discussion about applying reimbursement criteria (PBS or hospital formulary requirements);
- affordability of cancer medicines, including costs to the Government and individual organisations (e.g. hospital, insurance companies), and patient's out-of-pocket cost;
- processes to gain patient access (e.g. approval process for supply, including evidence from pathology);
- evidentiary requirements to gain regulatory and reimbursement approval; and
- cost of drug development for cancer medicines;
- clinical trials and the time gap between patients accessing medicines in trials and then via PBS access;
- the role of access programs after TGA approval;
- patients treated in the **private** setting versus **public** settings;
- timing of access; and
- equity of access.

2. Please describe how any issues raised in relation to the above impact upon the role you play related to cancer medicines?

Responsibilities may include caring for patients, prescribing therapies, making recommendation to the Minister for Health, representing the interests of your members, and responsibilities to current and future populations affected by cancer

3. In relation to Question 1, are there any issues specific to your State and institution (if relevant)

4. If you have raised issues in relation to Question 1, have they affected or will they affect the health outcomes of patients and their carers?

Health outcomes encompass survival, quality of life, and convenience (e.g. easier dosing, less monitoring, less attendance to health services, and so on).

- Give examples of medicines where this worked or didn't work if possible

5. In your opinion, should cancer medicines be valued differently to treatments for conditions other than cancer, why or why not?

6. **If you answered yes to the above, what are the factors and how should they be considered differently?** Some examples include:
- level of innovation;
 - clinical needs;
 - benefits;
 - costs;
 - cost effectiveness;
 - societal preference for cancer treatment;
 - affordability to the PBS; or
 - a combination of all or some of the above criteria, but with different emphasis on different criterion.
7. **In your opinion, what will the impact be to the following groups if access to new cancer medicines continues to be dependent upon the existing determinants of value under the current arrangements?**
- individual patients;
 - carers;
 - government;
 - industry;
 - oncologists; and
 - the Australian population.

Appendix C: Oncology pipeline in Phase II and Phase III clinical trials

Molecule	Mechanism of action	Indications
Afatinib	Novel irreversible ErbB Family blocker	NSCLC
Afatinib	Novel irreversible ErbB Family blocker	Breast cancer
Afatinib	Novel irreversible ErbB Family blocker	Head and neck cancer
alisertib	Aurora A kinase inhibitor	Relapsed or refractory peripheral T-cell lymphoma
alisertib	Aurora A kinase inhibitor	Diffuse large B-cell lymphoma
alisertib	Aurora A kinase inhibitor	NSCLC and SCLC
alisertib	Aurora A kinase inhibitor	Gastro-oesophageal cancers
alisertib	Aurora A kinase inhibitor	Head & neck cancer
alisertib	Aurora A kinase inhibitor	Ovarian cancer
alisertib	Aurora A kinase inhibitor	Breast cancer
AUY922	HSP90 inhibitor	NSCLC
Axitinib	VEGF tyrosine kinase inhibitor	RCC Adjuvant
axitinib	VEGFR, PDGFR, cKIT inhibitor	Hepatocellular carcinoma
azacitidine	DNA methyltransferase inhibitor	Myelodysplastic syndromes
AZD4547	FGFR tyrosine kinase inhibitor	Gastric Adenocarcinoma
BAY80-6944	PI3K-Inhibitor	Non-Hodgkin Lymphoma
BAY86-9765	MEK-Inhibitor	Hepatocellular carcinoma
BAY86-9766	MEK-Inhibitor	Pancreatic Neoplasms
bevacizumab	Anti-VEGF	relapsed platinum-resistant ovarian cancer
bevacizumab	Anti-VEGF	Glioblastoma multiforme
bevacizumab	Anti-VEGF	metastatic ovarian cancer
bevacizumab	Anti-VEGF	adjuvant HER2-negative breast cancer
bevacizumab	Anti-VEGF	adjuvant HER2-positive breast cancer
bevacizumab	Anti-VEGF	high-risk carcinoid
bevacizumab	Anti-VEGF	adjuvant NSCLC
Blinatumomab	anti-CD19 x anti-CD3 (BiTE®) bispecific antibody	Acute lymphoblastic leukemia
Blinatumomab	anti-CD19 x anti-CD3 (BiTE®) bispecific antibody	Non-Hodgkin Lymphoma
Bosutinib	Abl and src-family kinase inhibitor	Chronic Myelogenous Leukemia
brentuximab vedotin	CD30 directed antibody-drug conjugate	relapsed cutaneous T-cell lymphoma
brentuximab vedotin	CD30 directed antibody-drug conjugate	Post-ASCT Hodgkin lymphoma
brentuximab vedotin	CD30 directed antibody-drug conjugate	mature T-cell lymphoma
brentuximab vedotin	CD30 directed antibody-drug conjugate	Hodgkin lymphoma
brentuximab vedotin	CD30 directed antibody-drug conjugate	relapsed or refractory hodgkin lymphoma

Molecule	Mechanism of action	Indications
brentuximab vedotin	CD30 directed antibody-drug conjugate	relapsed or refractory systemic anaplastic large cell lymphoma
Buparlisib	PI3 Kinase inhibitor	NSCLC
Buparlisib	PI3 Kinase inhibitor	Breast cancer
BYL719	PI3 Kinase inhibitor	Breast cancer
CC-223	dual mTOR inhibitors	Multiple myeloma
CC-223	dual mTOR inhibitors	diffuse large B-cell lymphoma
CC-223	dual mTOR inhibitors	Glioblastoma multiforme
CC-223	dual mTOR inhibitors	Hepatocellular carcinoma
CC-223	dual mTOR inhibitors	NSCLC
CC-223	dual mTOR inhibitors	Hormone receptor-positive breast cancer
Cixutumumab	IGF-1R antibody	NSCLC
Crizotinib	c-MET-ALK Inhibitor	ALK-Positive NSCLC
dabrafenib	BRAF protein kinase inhibitor	Metastatic melanoma
dabrafenib	BRAF protein kinase inhibitor	NSCLC
Dacomitinib	pan-HER inhibitor	NSCLC
Dacomitinib	EGFR tyrosine kinase inhibitor	advanced NSCLC
dalotuzumab	IGFR1 mAb	Rectal cancer
Dalotuzumab, ridaforolimus	IGFR1 mAb, mTOR inhibitor	Breast cancer
Denosumab	anti-RANKL monoclonal antibody	Giant cell tumour of the bone
Denosumab	anti-RANKL monoclonal antibody	Hypercalcaemia of malignancy
DI17E6	Anti-integrin mAb	Metastatic colorectal cancer
DI17E6	Anti-integrin mAb	Metastatic castration-resistant prostate cancer
dinaciclib	CDK inhibitor	Refractory chronic lymphocytic leukaemia
Dovitinib	FGFR tyrosine kinase inhibitor	RCC
Elotuzumab	anti-CS1 Mab	Multiple myeloma
Elotuzumab	anti-CS1 Mab	Multiple myeloma - front line
eltrombopag	thrombopoietin receptor agonist	Acute myeloid leukaemia
eltrombopag	thrombopoietin receptor agonist	Myelodysplastic syndromes
Enzastaurin	PKCB and PI3K/AKT Inhibitor	Diffuse large B-Cell lymphoma
erlotinib	EGFR inhibitor	adjuvant NSCLC
Everolimus	M-TOR inhibitor	Breast cancer
Everolimus	M-TOR inhibitor	Hepatocellular carcinoma
foretinib	Mesenchymal-epithelial transition factor (C-met) kinase inhibitor	Squamous Cell Cancer of the Head and Neck
foretinib	Mesenchymal-epithelial transition factor (C-met) kinase inhibitor	Metastatic gastric cancer
foretinib	Mesenchymal-epithelial transition factor (C-met) kinase inhibitor	NSCLC
foretinib	Mesenchymal-epithelial transition factor (C-met) kinase inhibitor	Breast cancer
foretinib	Mesenchymal-epithelial transition factor (C-met) kinase inhibitor	RCC
fostamatinib	spleen tyrosine kinase (SYK) inhibitor	Large B-Cell lymphoma
fostamatinib	spleen tyrosine kinase (SYK) inhibitor	T-cell lymphoma
fostamatinib	spleen tyrosine kinase (SYK) inhibitor	Head and Neck Neoplasms

Molecule	Mechanism of action	Indications
fostamatinib	spleen tyrosine kinase (SYK) inhibitor	Pheochromocytoma
fostamatinib	spleen tyrosine kinase (SYK) inhibitor	Colorectal Neoplasms
fostamatinib	spleen tyrosine kinase (SYK) inhibitor	NSCLC
fostamatinib	spleen tyrosine kinase (SYK) inhibitor	RCC
Fulvestrant	oestrogen receptor antagonist	Breast cancer
ganitumab	Anti-IGF-1R Mab	Pancreatic cancer
Gefitinib	EGFR tyrosine kinase inhibitor	NSCLC
GSK-2110183	AKT protein kinase inhibitor	Ovarian cancer
Icrucumab	TGFbR1	Colorectal Cancer
Icrucumab	TGFbR1	Breast cancer
Icrucumab	TGFbR1	Bladder, urethra, ureter and renal pelvis carcinoma
Icrucumab	TGFbR1	Bladder, urethra, ureter and renal pelvis carcinoma
Iniparib	gamma-H2AX inducer	NSCLC
Iniparib	gamma-H2AX inducer	Squamous Non-Small-Cell Lung Cancer
Iniparib	gamma-H2AX inducer	Treat Triple Negative Breast Cancer Brain Metastasis
Iniparib	gamma-H2AX inducer	Advanced, Persistent, or Recurrent Uterine Carcinosarcoma
Iniparib	gamma-H2AX inducer	Ovarian Cancer
Iniparib	gamma-H2AX inducer	Triple Negative Metastatic Breast Cancer
inotuzumab ozogamicin	CD22 mAb	Acute lymphoblastic leukemia
inotuzumab ozogamicin	CD22 mAb	Non-Hodgkin Lymphoma
Ipilimumab	immunotherapy	Gastric cancer
Ipilimumab	immunotherapy	NSCLC
Ipilimumab	immunotherapy	SCLC
Ipilimumab	immunotherapy	Metastatic melanoma - adjuvant
Ipilimumab	immunotherapy	Prostate cancer
Ipilimumab	immunotherapy	Ovarian cancer
Ixazomib	Proteasome inhibitor	Multiple myeloma
Ixazomib	Proteasome inhibitor	Relapsed or refractory primary amyloidosis
lambrolizumab (MK-3475)	PD-1 inhibitor	Melanoma
lapatinib	HER2 and EGFR dual kinase inhibitor	Breast cancer
lapatinib	HER2 and EGFR dual kinase inhibitor	Gastric cancer
lapatinib	HER2 and EGFR dual kinase inhibitor	Head & neck squamous cell carcinoma (resectable disease)
lapatinib	HER2 and EGFR dual kinase inhibitor	metastatic breast cancer
L-BLP25	MUC1 antigen-specific cancer immunotherapy	NSCLC
LDE225	Smo receptor inhibitor	Medulloblastoma
LDE225	Smo receptor inhibitor	Basal cell carcinoma
LDK378	ALK inhibitor	ALK-Positive NSCLC
LEE011	CDK 4/6 inhibitor	Breast cancer
lenalidomide	anti-angiogenic	Myelodysplastic syndromes
lenalidomide	anti-angiogenic	B cell chronic lymphocytic leukaemia
lenalidomide	anti-angiogenic	Non-Hodgkin Lymphoma
LGX818	BRAF kinase inhibitor	Metastatic melanoma
Litrinesib	Eg5 inhibitor	SCLC

Molecule	Mechanism of action	Indications
Litronesib	Eg5 inhibitor	Ovarian cancer
Litronesib	Eg5 inhibitor	Prostate cancer
Litronesib	Eg5 inhibitor	NSCLC
Litronesib	Eg5 inhibitor	Colorectal Cancer
Litronesib	Eg5 inhibitor	Gastroesophageal cancers
Litronesib	Eg5 inhibitor	SCCHN
Litronesib	Eg5 inhibitor	Breast cancer
LY2090314	GSK3B Inhibitor	Acute leukaemia
LY2090314	GSK3B Inhibitor	Pancreatic cancer
LY2495655	JAK2 Inhibitor	Essential thrombocythemia
LY2495655	JAK2 Inhibitor	Polycythemia Vera
LY2495655	JAK2 Inhibitor	Primary Myelofibrosis
LY2495655	Myostatin antibody	Cancer-related cachexia
LY2603618	CHK1 Inhibitor 1	Pancreatic cancer
LY2603618	CHK1 Inhibitor 2	NSCLC
MEDI-550	anti-CD19 MAb	diffuse large B-cell lymphoma(DLBCL)
MEDI-550	anti-CD19 MAb	chronic lymphocytic leukemia
MEDI-573	anti-IGF MAb	MBC
MEDI-575	anti-PDGFR-alpha MAb	NSCLC
MEK162	MEK inhibitor	Metastatic melanoma
Midostaurin	FLT-3 inhibitor	Aggressive systemic mastocytosis
Midostaurin	FLT-3 inhibitor	Acute Myeloid Leukaemia
MK-1775	Wee1 inhibitor	p53 Mutant Ovarian Cancer
MK-2206	Akt inhibitor	Lymphoblastic leukaemia
MK-2206	Akt inhibitor	Solid tumours
motesanib	VEGFR1-3 PDGFR C-Kit inhibitor	advanced non-squamous NSCLC
Necitumumab	EGFR antibody	NSCLC
Nintedanib	Triple angiokinase inhibitor, simultaneously blocks VEGFR, FGFR, PDGFR	NSCLC
Nintedanib	Triple angiokinase inhibitor, simultaneously blocks VEGFR, FGFR, PDGFR	Ovarian cancer
Nintedanib	Anti-fibrotic kinase inhibitor	Idiopathic pulmonary fibrosis (IPF)
Nivolumab	anti-PD1	NSCLC
Nivolumab	anti-PD1	Melanoma
Nivolumab	anti-PD1	RCC
obinutuzumab	anti-CD20 Mab	diffuse large b-cell lymphoma
obinutuzumab	anti-CD20 Mab	front-line indolent non-hodgkin's lymphoma
obinutuzumab	anti-CD20 Mab	refractory indolent non-hodgkin's lymphoma
obinutuzumab	anti-CD20 Mab	front-line chronic lymphocytic leukemia
olaparib	PARP inhibitor	Gastric cancer
olaparib	PARP inhibitor	Pancreatic cancer
olaparib	PARP inhibitor	Advanced Ovarian Cancer
olaparib	PARP inhibitor	gBRCAm breast cancer

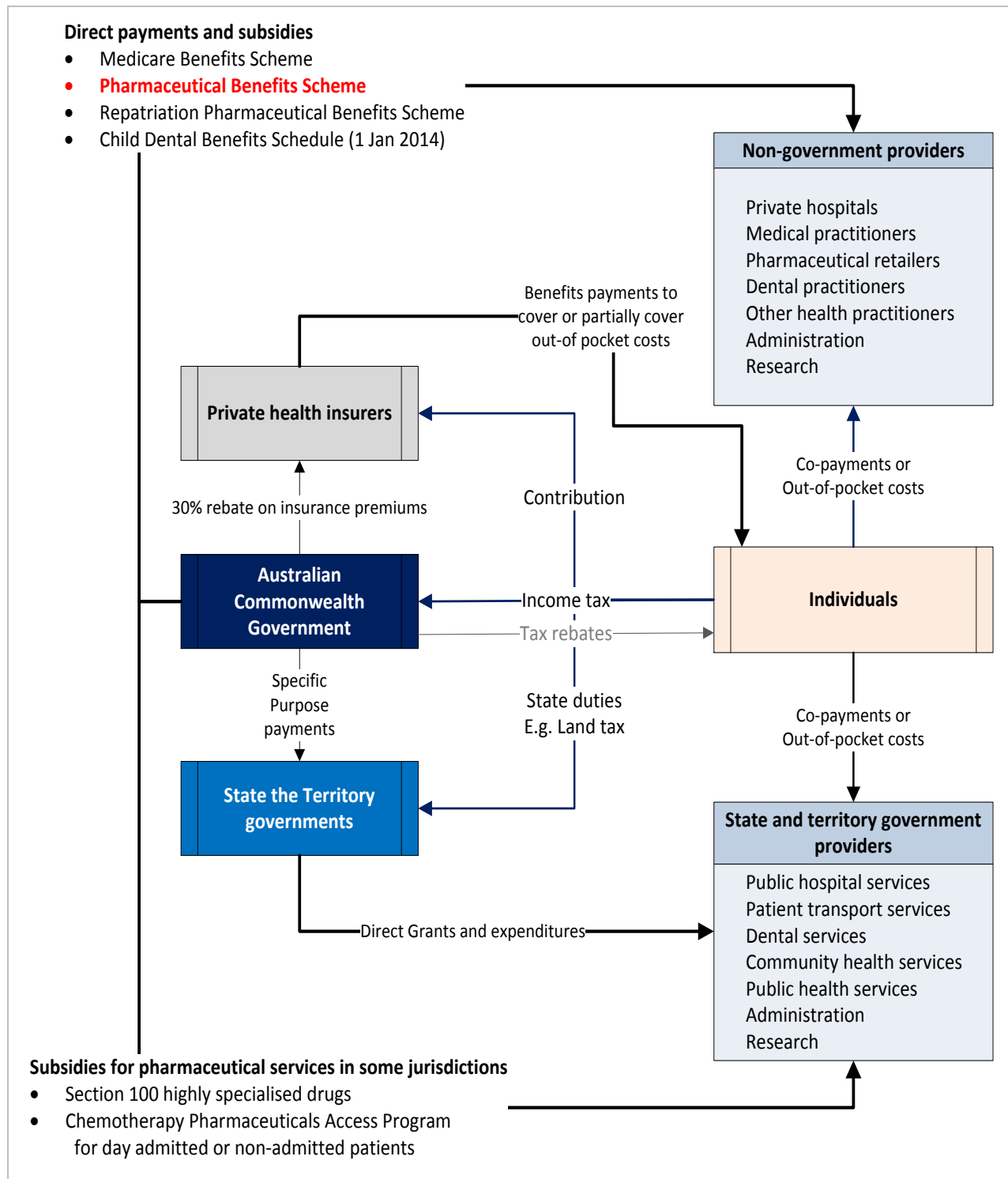
Molecule	Mechanism of action	Indications
olaparib	PARP inhibitor	colorectal cancer
Olaratumab	PDGFRa antibody	NSCLC
Olaratumab	PDGFRa antibody	Soft tissue Sarcoma
Olaratumab	PDGFRa antibody	Prostate cancer
Ombrabulin	tubulin-binding agent	Sarcoma
Ombrabulin	tubulin-binding agent	Advanced-stage Soft Tissue Sarcoma
Ombrabulin	tubulin-binding agent	recurrent ovarian cancer
Ombrabulin	tubulin-binding agent	NSCLC
onartuzumab	Anti-Met MAb	metastatic NSCLC
onartuzumab	Anti-Met MAb	Metastatic HER2-negative gastric cancer
onartuzumab	Met MAb	non-squamous NSCLC
onartuzumab	Met MAb	squamous NSCLC
onartuzumab	Met MAb	Glioblastoma multiforme
onartuzumab	Met MAb	Colorectal Cancer
onartuzumab	Met MAb	Tripple negative metastatic breast cancer
onartuzumab	Anti-Met MAb	metastatic colorectal cancer
onartuzumab	Anti-Met MAb	Avastin-naïve recurrent glioblastoma
onartuzumab	Anti-Met MAb	non-squamous NSCLC
onartuzumab	Anti-Met MAb	squamous NSCLC
onartuzumab	Anti-Met MAb	triple negative metastatic breast cancer
Palbociclib	CDK 4,6 Kinase Inhibitor	Advanced Breast Cancer
Panitumumab	Antibody antagonist of the epidermal growth factor receptor (EGFr)	Colorectal Cancer
Panitumumab	Antibody antagonist of the epidermal growth factor receptor (EGFr)	Squamous cell head and neck cancer
Panobinostat	Pan DAC inhibitor	Multiple myeloma
Pasireotide	Somatostatin receptor agonist	Acromegaly
Pazopanib	Multi-kinase angiogenesis inhibitor	Ovarian cancer
Pazopanib	Multi-kinase angiogenesis inhibitor	RCC
Pazopanib	Multi-kinase angiogenesis inhibitor	Sarcoma
pertuzumab	Anti-HER2 Mab	early HER2 Breast cancer
pertuzumab	Anti-HER2 Mab	HER2 -positive gastric cancer
pertuzumab	Anti-HER2 Mab	2nd line HER2-positive metastatic breast cancer
PF-05212384	dual inhibitor of PI3K and mTOR	endometrial cancer
Pimasertib	MEK inhibitor	Pancreatic cancer
Pimasertib	MEK inhibitor	Malignant melanoma
pomalidomide	anti-angiogenic	Myelofibrosis
pomalidomide	anti-angiogenic	Multiple myeloma
protein-bound paclitaxel	tubulin-binding agent	metastatic pancreatic cancer
protein-bound paclitaxel	tubulin-binding agent	metastatic melanoma
protein-bound paclitaxel	tubulin-binding agent	first line metastatic breast cancer
protein-bound	tubulin-binding agent	bladder cancer

Molecule	Mechanism of action	Indications
paclitaxel		
protein-bound paclitaxel	tubulin-binding agent	Ovarian Cancer
Radium-223-Dichloride	radiopharmaceutical	Prostate Cancer Patients With Bone Metastases
Ramucirumab	VEGFR2 Antibody	Breast cancer
Ramucirumab	VEGFR2 Antibody	Gastric cancer
Ramucirumab	VEGFR2 Antibody	Hepatocellular carcinoma
Ramucirumab	VEGFR2 Antibody	NSCLC
Ramucirumab	VEGFR2 Antibody	Colorectal Cancer
Ramucirumab	VEGFR2 antibody	Colorectal Cancer
Ramucirumab	VEGFR2 antibody	NSCLC
Ramucirumab	VEGFR2 antibody	Gastric cancer
Ramucirumab	VEGFR2 antibody	Hepatocellular carcinoma
Ramucirumab	VEGFR2 antibody	Ovarian cancer
Ramucirumab	VEGFR2 antibody	Glioblastoma multiforme
Ramucirumab	VEGFR2 antibody	Breast cancer
Ramucirumab	VEGFR2 antibody	Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Carcinoma
Regorafenib	Multiple Tyrosine Kinase Inhibitor	gastrointestinal stromal tumour
Regorafenib	Multiple Tyrosine Kinase Inhibitor	Colorectal Cancer
RG7160	Dual-acting humanised, immunoglobulin G1 monoclonal antibody against epidermal growth factor receptor (EGFR)	solid tumours
RG7321 (GDC-0941)	PI3 Kinase inhibitor	ER+ metastatic breast cancer
RG7321 (GDC-0941)	PI3 Kinase inhibitor	metastatic HER2-/HR+ breast cancer
RG7321 (GDC-0941)	PI3 Kinase inhibitor	metastatic NSCLC
RG7414	Anti-EGFL7	metastatic colorectal cancer
RG7414	Anti-EGFL7	non-squamous NSCLC
RG7421 + RG7204	MAPKK inhibitor+BRAF inhibitor	Metastatic melanoma BRAF positive
RG7422 + GDC 0980	Dual inhibitor of PI3 Kinase and mTOR Kinase	ER+ metastatic breast cancer
RG7422+ GDC 0980	Dual inhibitor of PI3 Kinase and mTOR Kinase	endometrial cancer
RG7422 + GDC 0980	Dual inhibitor of PI3 Kinase and mTOR Kinase	RCC
RG7593	Anti-CD22	Non-Hodgkin Lymphoma
RG7596	anti-CD79b	Non-Hodgkin Lymphoma
RG7597	Anti-HER3/EGFR	Head and neck cancer
RG7597	Anti-HER3/EGFR	Colorectal Cancer
RG7686	anti-glypican 3 Mab	Metastatic liver cancer
Rilotumumab	anti-hepatocyte growth factor/scatter factor	Gastric cancer
romidepsin	Zn-dependent histone deacetylase inhibitor	pancreatic cancer
romidepsin	Zn-dependent histone deacetylase inhibitor	ovarian cancer
romidepsin	Zn-dependent histone deacetylase inhibitor	Breast cancer

Molecule	Mechanism of action	Indications
Ruxolitinib	JAK1 and JAK2 Inhibitor	Polycythemia Vera
SAR245408	pan-PI3K inhibitor	advanced endometrial cancer
SAR245409	inhibitor of PI3K and mTOR	CLL
SAR245409	inhibitor of PI3K and mTOR	NHL
SAR256212	Anit-ErbB3 Mab	Breast cancer
SAR302503	JAK2 Inhibitor	intermediate-2 or high-risk myelofibrosis
SAR302504	JAK2 Inhibitor	Polycythemia Vera, or essential thrombocythemia, and in patients with ruxolitinib-resistant or intolerant myelofibrosis
SAR3419	anti-CD19 antibody-drug conjugate	DLBCL
selumetinib	MEK inhibitor	Colorectal Cancer
selumetinib	MEK inhibitor	Locally Advanced or Metastatic NSCLC Stage IIIb - IV
selumetinib	MEK inhibitor	Biliary cancer
selumetinib	MEK inhibitor	Soft tissue Sarcoma
selumetinib	MEK inhibitor	Melanoma
selumetinib	MEK inhibitor	Pancreatic cancer
selumetinib	MEK inhibitor	Recurrent Adult Diffuse Large Cell Lymphoma
Sorafenib	Multiple Tyrosine Kinase Inhibitor	Thyroid Cancer
Sorafenib	Multiple Tyrosine Kinase Inhibitor	Breast Cancer
Sorafenib	Multiple Tyrosine Kinase Inhibitor	Adjuvant HCC
Sorafenib	Multiple Tyrosine Kinase Inhibitor	Adjuvant RCC
Sunitinib	Multiple Tyrosine Kinase Inhibitor	RCC Adjuvant
Sym004	anti-eGFR mAbs	Squamous Cell Cancer of the Head and Neck
Tabalumab	BAFF antibody	Multiple myeloma
TAK-385	LHRH antagonist	Prostate cancer
Talimogene Laherparepvec	Oncolytic immunotherapy	Melanoma
TH-302	Hypoxia-targeted drug	Soft tissue sarcoma
TH-302	Hypoxia-targeted drug	Pancreatic cancer
Trametinib	MEK1/2 inhibitor	Metastatic melanoma
Trametinib	MEK1/2 inhibitor	NSCLC
Trametinib	MEK1/2 inhibitor + AKT protein kinase inhibitor	Thyroid cancer
Trametinib	MEK1/2 inhibitor + AKT protein kinase inhibitor	Oral Cavity Squamous Cell Cancer
Trametinib	MEK1/2 inhibitor + AKT protein kinase inhibitor	Colorectal Cancer
Trametinib + 2141795	MEK1/2 inhibitor + AKT protein kinase inhibitor	Melanoma
Trametinib + dabrafenib	MEK1/2 inhibitor + BRAF protein kinase inhibitor	Metastatic melanoma
Trametinib + dabrafenib	MEK1/2 inhibitor + BRAF protein kinase inhibitor	Metastatic melanoma
Trametinib + dabrafenib	MEK1/2 inhibitor + BRAF protein kinase inhibitor	Colorectal Cancer
trastuzumab emtansine	Anti-HER2 Mab	Breast cancer
trastuzumab emtansine	Anti-HER2 Mab	HER2-positive gastric cancer
trastuzumab emtansine	Anti-HER2 Mab	HER2 Breast cancer
trastuzumab emtansine	Anti-HER2 Mab	HER2-positive gastric cancer

Molecule	Mechanism of action	Indications
trastuzumab emtansine	Anti-HER2 Mab	HER2-positive tumour
Trebananib	Tie2 and Ang1 Ang2 inhibitor	Ovarian cancer
tremelimumab	anti-CTLA4 MAb	Malignant Mesothelioma
tremelimumab	anti-CTLA4 MAb	Colorectal Cancer
tremelimumab	anti-CTLA4 MAb	Hepatocellular Carcinoma
tremelimumab	anti-CTLA4 MAb	Melanoma
Veliparib	PARP inhibitor	BRCA-Deficient Breast Cancer
vemurafenib	BRAF kinase inhibitor	Thyroid cancer
vintafolide	Folic acid drug conjugate	Platinum-resistant ovarian cancer
vintafolide	Folic acid drug conjugate	NSCLC
vismodegib	cyclopamine-competitive antagonist of smoothened receptor	operable basal cell carcinoma
Volasertib	PLK-1 antagonist	Myeloid leukaemia
Volasertib	PLK-1 antagonist	Ovarian cancer

Appendix D: Financial structure in the Australian Healthcare system



Source: Adapted from AIHW (2012), Figure 1.1 (p.3)

Limitation of our work

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