Deloitte.
Access Economics

A Collaborative Assessment of Access to Cancer Medicines in Australia

May 2017

Contents

Glossary

AACR	Australasian Association of Cancer Registries
ACIM	Australian Cancer Incidence and Mortality (books)
AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
ASCO	American Society of Clinical Oncology
CDA	Cancer Drugs Alliance
CML	Chronic Myeloid Leukaemia
DALY	Disability-adjusted life years
DUR	Drug Utilization review
EHRs	Electronic health records
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
HTA	Health Technology Assessment
IGR	Intergenerational Report
MAUI	Multi-Attribute Utility Instrument
MAP	Managed Access Programme
MBS	Medicare Benefits Schedule
MES	Managed Entry Scheme
MSAC	Medical Services Advisory Committee
MOGA	Medical Oncology Group of Australia
NHB	Net Health Benefit
NICE	National Institute for Health and Care Excellence, UK
NHPA	National Health Priority Areas
OS	Overall Survival
OIT	Oncology Industry Taskforce
PACE	Patient and Clinician Engagement
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCEHR	Personally Controlled Electronic Health Record
PFS	Progression free survival
PRO	Patient reported outcome
QALY	Quality-adjusted life years
QOL	Quality of life
RCT	Randomised controlled trials
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Therapy
SMC	Scottish Medicines Consortium
TGA	Therapeutic Goods Administration

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Executive summary

Cancer is a major health priority for the community and government.

The Australian Institute of Health and Welfare (AIHW) has reported that one in two men will get cancer by the age of 85 years, and this number is one in three for women. Despite our world leading survival rates, cancer represents the largest disease burden for Australian communities, followed by cardiovascular disease.

As medical technologies have advanced, Australian communities have seen an increasing precision and reduced toxicity in cancer treatments, with improving gains in overall survival (OS) and quality of life (QOL). In the last 20 years, a number of innovative medicines have been made available to Australians with cancer. In the next decade, the number of innovative medicines for cancer is likely to significantly increase, based on an assessment of the approximately 800 cancer medicines currently in industry research pipelines. Traditional models for medicines evaluation are evolving in response to technological change to ensure continued timely and equitable access to quality care.

The Australian government has recognised the need for change and is evolving its policy to meet the challenges presented by cancer medicines. Like its international counterparts, it has announced additional registration pathways to speed up market approval for new medicines, leveraging international data where appropriate.

Changes to the Pharmaceutical Benefits Advisory Committee (PBAC) will see the addition of more clinical expertise and an additional consumer representative. The PBAC now also engages with clinician and patient groups ahead of submissions and has extended the time allowed for patient submissions. Government has also shown an intent to innovate at the reimbursement phase through the increased use of Managed Access Programme (MAP).

A Senate Community Affairs References Committee Inquiry, Availability of new, innovative and specialist cancer drugs in Australia (the 'Senate Inquiry') acknowledged efforts which have been made to improve access to cancer medicines and recommended further review. This included a call for comprehensive review of Australia's regulatory and reimbursement system, a review of the feasibility of establishing a National Cancer Registry and options for improving data collection to enable a modernised Pharmaceutical Benefits Scheme (PBS) to be implemented.

Australia has made positive steps in responding to the complex issues associated with cancer medicines.

A pivotal point is now being reached in acknowledging the significant achievements that have been made, yet there is also a need to consider further opportunities to manage ongoing technological innovations arriving in cancer treatment.

Medicines Australia's Oncology Industry Taskforce (OIT) engaged Deloitte Access Economics to provide a report, which reviewed the progress since the release of its 2013 report Access to Cancer Medicines in Australia. This review identifies factors that influence policy change, explores international policy developments, and calls out potential opportunities for further reform. The review draws together Australian and international research with findings from more than 30 interviews, to provide practical and prioritised considerations for the future public policy approach to cancer medicines.

The review has found Australia has broadly kept pace with its

international peers in policy reforms to meet these challenges—however, opportunities for further improvement still exist. There has been substantial progress in new approaches to the registration of medicines in Australia, and some trialling of provisional access through MAP. The review finds government has taken positive first steps to improve patient and clinician engagement, through clinician engagement via the Medical Oncology Group of Australia (MOGA), as well as engagement with patient groups.

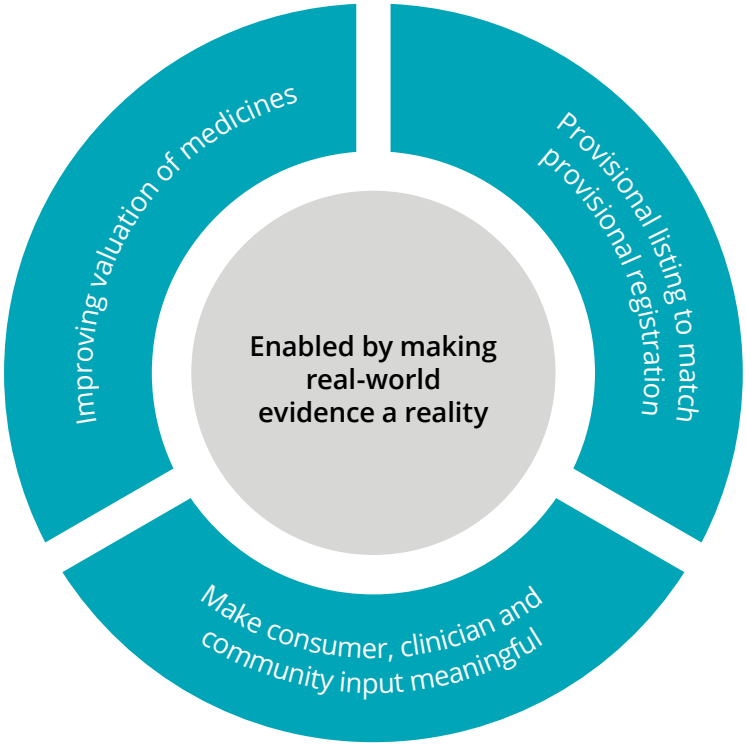
The review uncovers opportunities for change related to investments in real-world evidence, supported by revised evidence requirements for the valuation of cancer medicines; the implementation of provisional listing; and further enhancements to consumer, clinician, and community involvement:

- **Make real-world evidence a reality –** The collection of real-world data to enable the development of real-world evidence is seen as essential in the context of increased uncertainty of medicines valuation. Real-world evidence represents enabling infrastructure, which could potentially support the development of a system for provisional listing, as well as the more systematic and evidence-based valuation of patient outcomes. Over the long-term and if properly implemented, this has the potential to substantially improve the quality use of medicines, and deliver broader health service efficiencies.
- **Agree evidence requirements for cancer medicines –** A review of the PBAC Guidelines has now been completed and has provided industry, government, and other stakeholders with the opportunity to update aspects of the submission process. Given the potential 'long tail' of benefits associated with cancer medicines, and opportunities for more systematic evaluation of patient-important outcomes, which may not be valued by current measures, it is imperative to start considering additional evidence requirements for cancer medicines. This could inform the development of provisional listing arrangements and opportunities for more systematic data collection of patient outcomes through a system for RWE.
- **Implement provisional listing to match provisional registration –** Stakeholders saw an opportunity to match reforms for provisional registration with a policy for provisional listing based on a common set of agreed criteria. Provisional listing would support access to medicines even as evidence was in development, and the use of robust contractual measures based on real-world outcomes would ensure public monies continue to fund medicines, which are cost effective.
- **Make patient, carer, clinician, and community engagement meaningful –** The review also makes recommendations, building on stakeholder feedback, for substantially enhanced consumer, clinician, and community engagement. The major opportunities for improvement, as echoed by the PBAC recommendations for change in its submission to the Senate Inquiry, include increased engagement with patients and clinicians through a Consumer Engagement Group, the use of a Citizens Jury to inform government policy regarding community priorities for medicines, and additional consumer and clinician representation on the PBAC with formal roles for these members. In addition, there may be scope for a specialised expert cancer panel to support evaluation processes and enhance transparency of the value of patient and clinician evidence in PBAC deliberations.

These policy ideas enjoyed strong stakeholder consensus as major priorities for change.

Critically, these policies are not 'cancer specific' initiatives. Rather, these initiatives provide a foundation for the modernisation of the PBS in a way that addresses the challenges, which are acutely felt by cancer patients and their families today.

Ideas for change – priorities



Deloitte Access Economics

Chapter 1:

Why revisit access to cancer medicines?

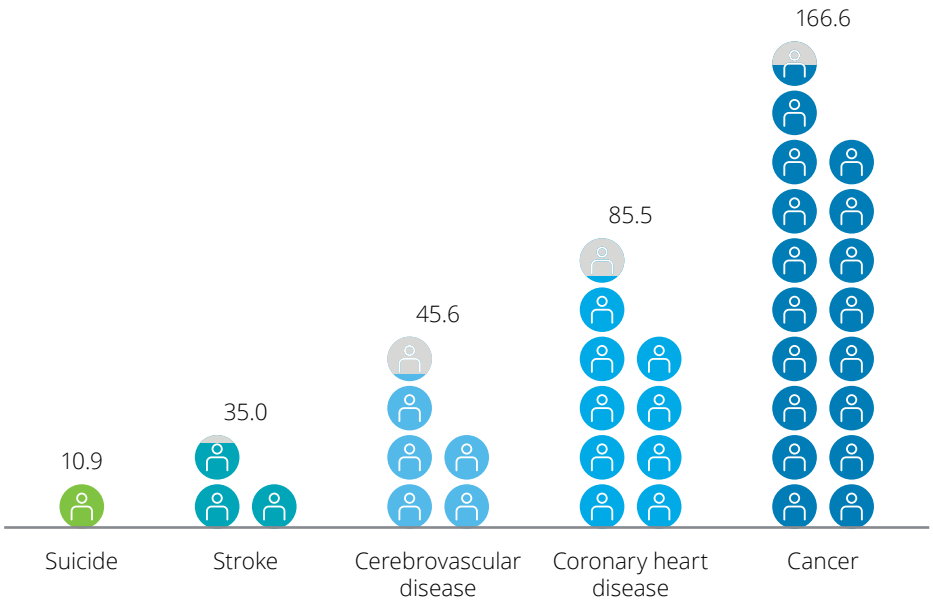
This chapter provides an overview of the disease, technology and policy context, and identifies the objectives of the report given this context as well as the structure for the report.

1.1 Cancer is a significant disease burden for Australian communities...

Australians have among the highest age-standardised incidence of cancer in the world.

Despite our world-leading survival rates, cancer still remains the leading cause of death in Australia. One out of two men will be diagnosed with cancer before the age of 85 years, and the risk for females by this age is one in three.[1] According to the AIHW, the mortality from cancer in Australia in 2013 was 166.6 deaths per 100,000 people (Figure 1.1). Cancer accounts for the greatest proportion of disease burden in Australia (19%), followed by cardiovascular disease at 15%.[2]

Figure 1.1: Mortality from cancer and other health conditions in Australia



Source: Deloitte Access Economics calculated based on data from the AIHW 2016, General Record of Incidence and Mortality (GRIM) books

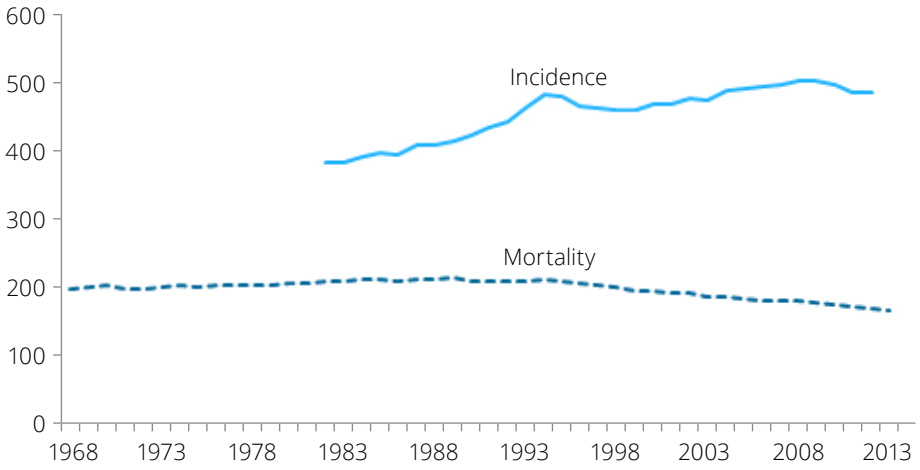
All health conditions are important. The significant burden of cancer means that ensuring equitable access to quality care proportional to its burden is a major priority for Australian communities and governments.

[1]AIHW 2016. Australia's health 2016. Australia's health series no. 15, p.83
[2]AIHW 2016. Australia's health 2016. Australia's health series no. 15, p.54
[3]AIHW, 2016, General Record of Incidence of Mortality (GRIM) books, http://aihw.gov.au/deaths/grim-books/ , [Accessed October 2016]

1.2 ...with significant technology and cost challenges

As medical technologies have advanced, Australian communities have seen an increasing precision and reduced toxicity in cancer treatments, with improving overall survival and QOL.

Figure 1.2: Age-standardised incidence and mortality rates for all cancers combined 1968–2013



Source: Australian Institute of Health and Welfare 2016, Australian Cancer Incidence and Mortality books (ACIM)

The corollary to personalised medicine, however, has been that patient populations become increasingly differentiated and smaller in size, disrupting traditional models for medicines innovation and increasing treatment costs.

As the burden of disease grows and the complexity and cost of treatment rises, it is timely to consider how Australia can continue to sustainably and equitably combat cancer in the future.

1.3 Recent reviews have called for reform to the PBS and enabling infrastructure

Australia has overall performed well in providing affordable and equitable patient access to medicines. Nevertheless, the system faces significant challenges from the growing burden of cancer, the emergence of many new cancer treatments seeking listing on the PBS, increased uncertainty in evidence development for cancer medicines and community expectations that that these new advances should be made available to Australian patients in a timely manner.

The Australian government has taken a number of steps to respond to these challenges, including the recent acceptance of recommendations for additional registration pathways, increased use of MAP and greater consumer and clinician engagement around upcoming submissions.

These have been substantial changes in response to a significant change in medicines development. Even with these changes, however, there remains the potential for further policy reform. Most recently, the Senate Inquiry 'Availability of new, innovative, and specialist cancer drugs in Australia', reported 'there is widespread concern that Australian cancer patients continue to face significant delays and expense in accessing new cancer drugs, or existing drugs that are not available under the PBS for their form of cancer.'

The Senate Inquiry acknowledged effort, which had been made to improve access to cancer medicines, but also clearly articulated that more needed to be done to address persistent challenges and community concerns related to the availability of cancer medicines. Specifically, the Senate Inquiry called for further reforms to medicines policies and infrastructure, to support improved access to cancer medicines, including:

- A comprehensive review of the PBS, including opportunities for greater patient, clinician, sponsor and community involvement; revised health technology assessment (HTA) processes to streamline and fast-track access through the Pharmaceutical Benefits Scheme (PBS); and evidence requirements for cancer medicines
- A review of the feasibility of a National Cancer Registry
- A review of data collection requirements to enable a modernised PBS to be implemented

The government has issued an interim response to the Senate Inquiry and has promised a more comprehensive response will be forthcoming.

In addition, governments in other countries have similarly been trialling new approaches, which could potentially provide insights into potential approaches Australia may pursue.

1.4 Report objectives and method

It is therefore timely to take stock of Australia's policy progress with respect to ensuring timely access to new cancer treatments, and identify further potential policy options to move the cancer agenda forward for the benefit of patients and the community.

Objectives

To this end, the purpose of this report is to:

- Assess the progress that has been made in Australia to improve patient's access to cancer medicines since the Deloitte Access Economics report into Access to Cancer Medicines in 2013
- Identify international approaches and lessons learned, with a view to supporting continued policy progress in Australia
- Engage with stakeholders across government, patient groups, clinicians and academics both within Australia and overseas to ascertain their views on the progress that has been made, factors that influence change and potential further policy reforms
- Identify and discuss proposals for positive change.

Method

Deloitte Access Economics has been commissioned by Medicines Australia OIT to provide an independent, 'point in time' snapshot of stakeholder views on the progress that has been made and the challenges ahead for ensuring positive cancer outcomes for decades to come.

The review draws together Australian and international research with findings from more than 30 interviews to provide practical and prioritised considerations for the future public policy approach to cancer medicines. Interviewees were sampled to represent the stakeholder landscape of government, clinicians, patient groups, industry and academics. International interviewees were also included to provide insights on the approaches, which other jurisdictions have adopted to enhance cancer outcomes. A complete list of interviewees is provided on page 2.

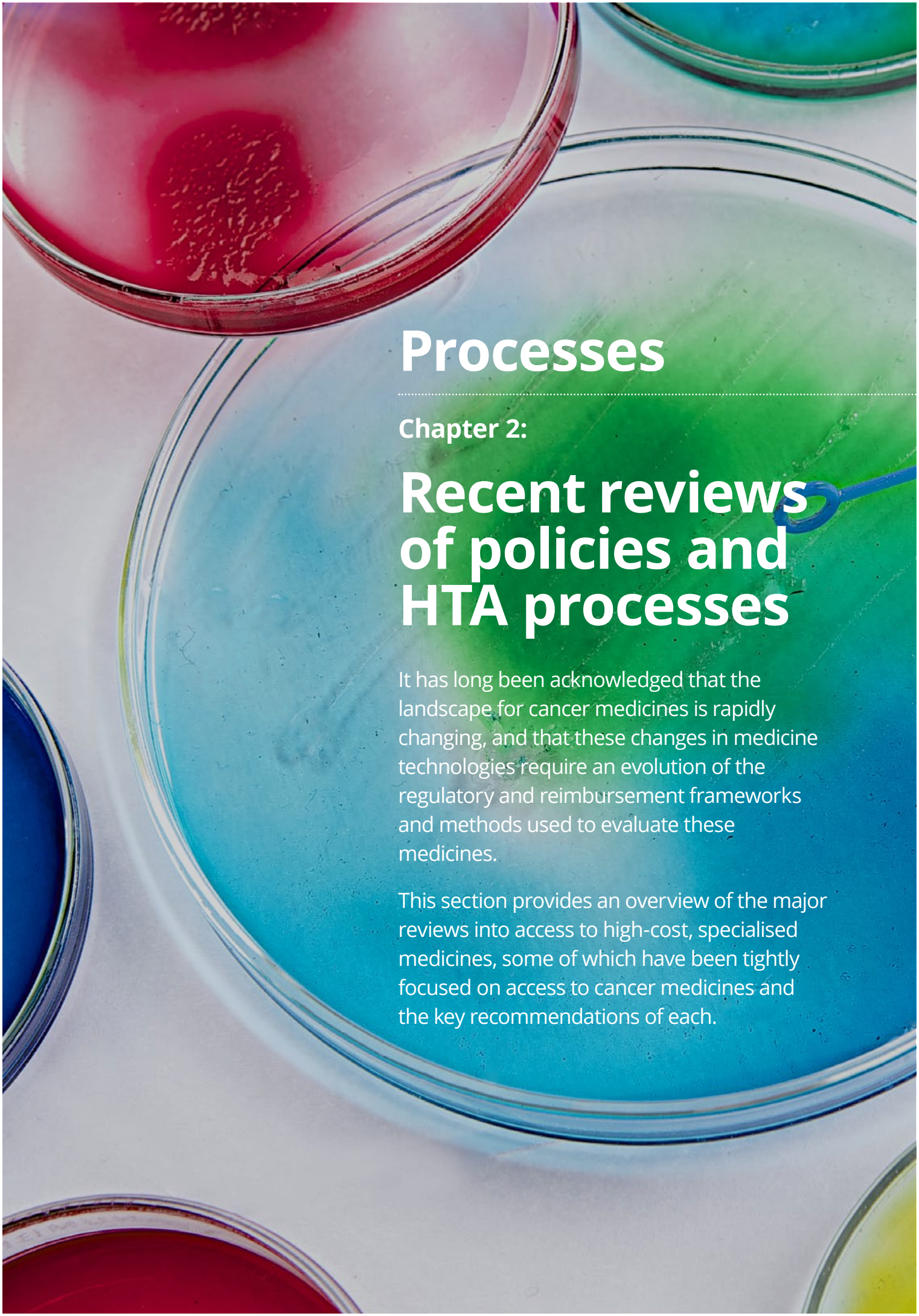
Interviews were conducted in a semi-structured format, broadly following the thematic guide provided in Appendix A. This guide was provided to interviewees ahead of the meeting to allow them to appropriately prepare and engage with the topic areas for discussion.

Report structure

This paper thematically reports on findings across the following four dimensions:

- Registration and listing pathways. The pathways and processes by which medicines are evaluated for marketing authorisation and PBS reimbursement
- The value of cancer medicines. The evidence and perspectives that are considered in determining the value of medicine and its reimbursed price
- Patient, clinician and community involvement. The appropriate role of stakeholders in determining the value of innovations and prioritisation of funding
- Real-world evidence. The incorporation of real-world data, to supplement (or act as a proxy for) randomised controlled trial data, to facilitate decision making.

Findings from this review are presented across three sections: progress; key questions for policy makers and factors requiring change. The paper concludes by putting forward prioritised considerations for policy and systems change in the near, medium and longer term.



Processes

Chapter 2:

Recent reviews of policies and HTA processes

It has long been acknowledged that the landscape for cancer medicines is rapidly changing, and that these changes in medicine technologies require an evolution of the regulatory and reimbursement frameworks and methods used to evaluate these medicines.

This section provides an overview of the major reviews into access to high-cost, specialised medicines, some of which have been tightly focused on access to cancer medicines and the key recommendations of each.

2.1 A brief history of reviews

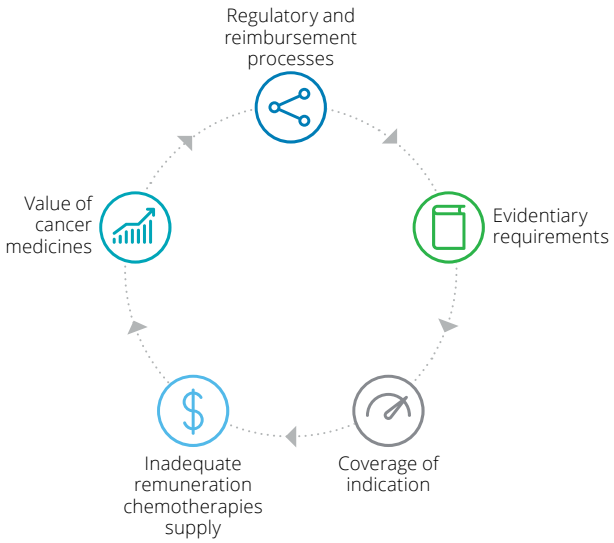
In 2013, Medicines Australia OIT commissioned Deloitte Access Economics to develop a report to assess the disease patterns and economics of cancer in Australia and internationally, and canvas the opinions of various stakeholders on issues pertaining to patient access to cancer medicines.

The report found that while Australia has performed well in providing affordable and equitable patient access to cancer medicines in the past, the system faces 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.

In the three years which followed this Deloitte Access Economics report, a number of subsequent reviews into various aspects of access to cancer medicines have been undertaken. Most notably, it includes the review of the PBAC Submission Guidelines. The revised Guidelines was released in October 2016. Figure 2.1 provides a high-level timeline of key reviews and events considering this topic over the past three years.

Reflecting the need for continued policy reform to address potential inequities or limitations in the system, in 2015 the Senate Inquiry, *Availability of new innovative and specialist cancer drugs in Australia* called for further action to progress the cancer policy agenda.

Figure 2.1 Challenges to Cancer Medicines identified in 2013



Access to cancer medicines in Australia July 2013

Five key issues raised

A key theme that was raised by stakeholders throughout the Senate Inquiry was the need for a fundamental review of the regulatory and reimbursement processes for cancer medicines. Stakeholders raised concerns that the current process is time consuming and complex and is unable to keep up with the pace of change in new medicine applications.

The committee considered the processes for assessing medicines were appropriately rigorous; however, it identified there was an opportunity for improvements in efficiency and reducing uncertainty in the system. The committee noted concerns raised by stakeholders on the significant challenges associated with assessing the cost effectiveness of cancer medicines. This included the calls for the adoption of a more flexible approach to evidentiary requirements in the Australian reimbursement system for medicines.

The findings of the Senate Inquiry echoed those of the 2015 Cancer Drugs Alliance (CDA) White Paper, Improving Access to Cancer Medicines, which also identified the need to modernise the current regulatory and reimbursement system for the future including through greater engagement of consumers in the process.

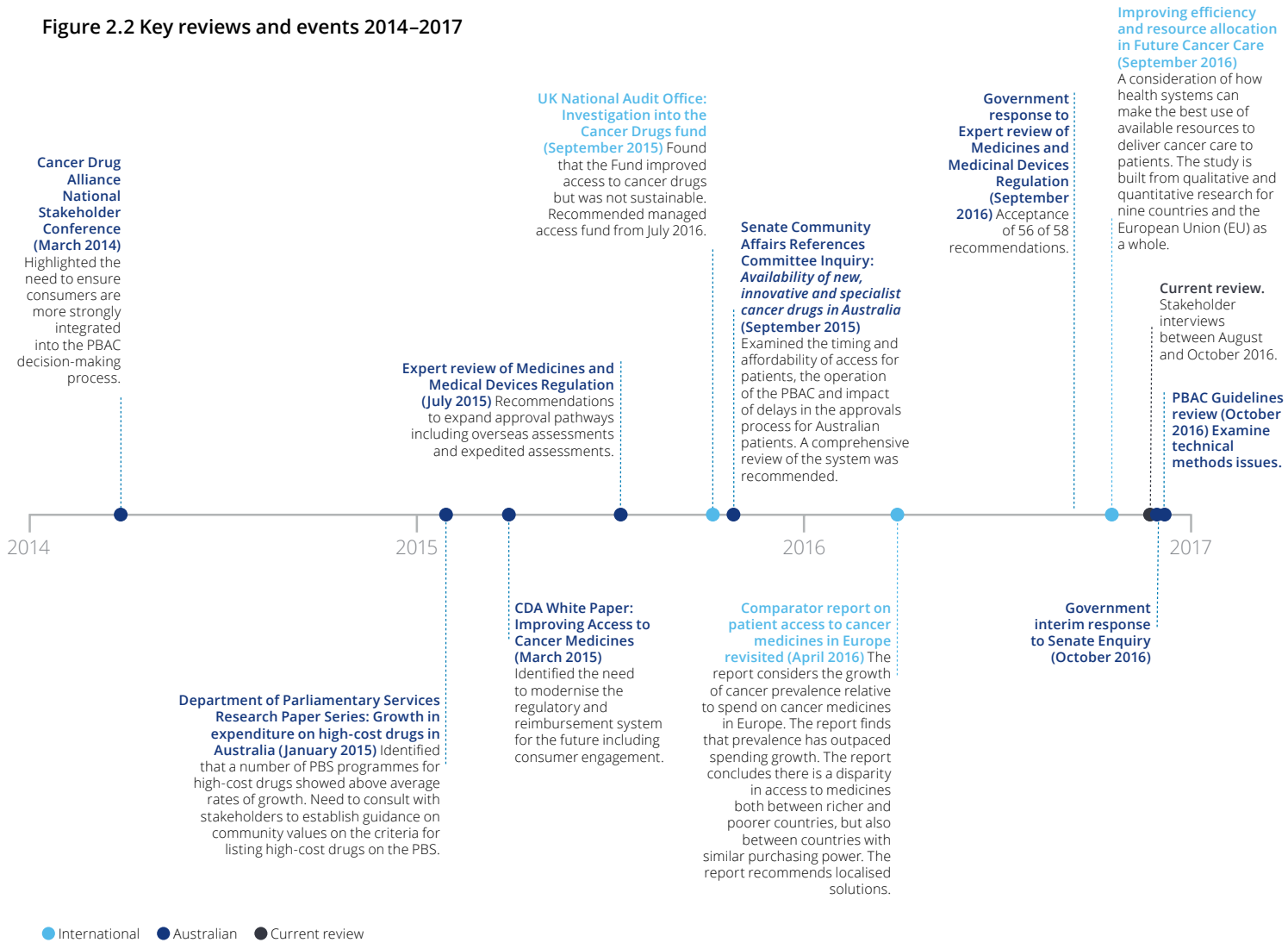
Expert Review

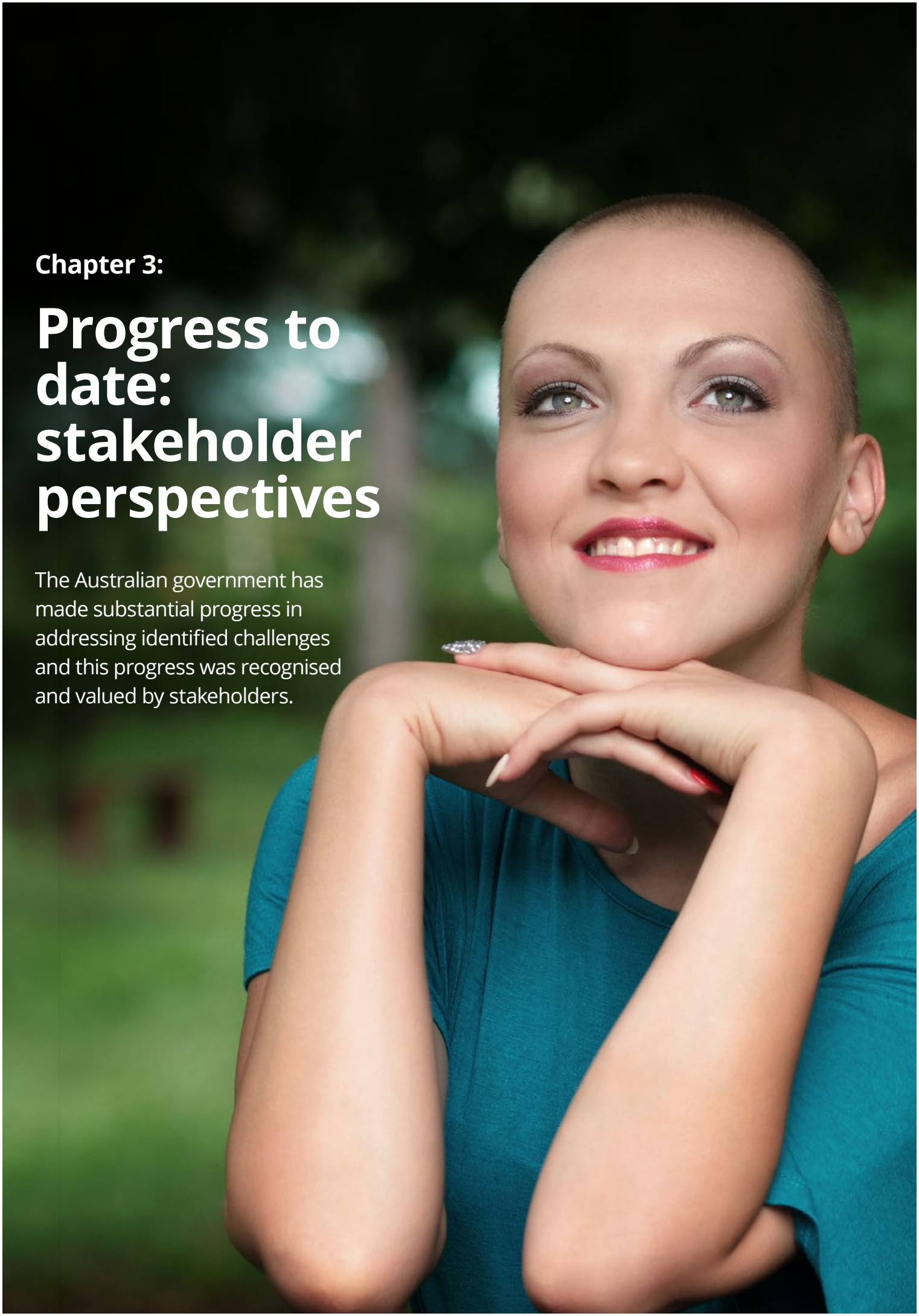
The Expert Review of Medicines and Medical Device Regulation (2015) chaired by Emeritus Professor Lloyd Sansom AO, put forward 58 recommendations pertaining to opportunities to streamline and enhance the registration and listing pathways for therapeutic goods in Australia. Notably, in September 2016, following extensive consultation with stakeholders, the government responded to support 56 of the 58 recommendations. The two rejections were justified on the grounds that their adoption may result in approval delays for new technologies and that their intent may in part be achieved through the implementation of the 56 accepted reforms.

Internationally, governments have also been grappling with the appropriate policy response to evolving cancer medicines technologies: how to balance community expectations for early access with safety and ensuring public funding goes to the highest and best uses. Major international reviews since 2013 focused on highly specialised, high-cost medicines and cancer medicines have included the UK National Audit Office Investigation into the Cancer Drugs Fund, a comparator report on patient access to cancer medicines in Europe and a report into Improving efficiency and resource allocation in future cancer care (see Figure 2.2).

Taken together, the reviews suggest that the challenges pertaining to patient access to cancer medicines are significant, and that Australia has broadly kept pace with its international peers. The reviews highlight governments have taken tentative policy steps to provide for greater tiering in registration and listing pathways and new approaches to HTA processes. The reviews also highlight that policy progress has been a jagged line, with some ideas needing further refinement and some policy solutions more transparent than others. Clearly, there is no single approach to best resolve the challenges presented by cancer medicines, and work continues globally on the appropriate next steps.

Figure 2.2 Key reviews and events 2014–2017





Chapter 3:

Progress to date: stakeholder perspectives

The Australian government has made substantial progress in addressing identified challenges and this progress was recognised and valued by stakeholders.

Some policy ideas have progressed faster and further than others. Accordingly, in some domains, some questions remain regarding whether policy settings might be further refined.

This chapter provides an overview of progress that has been made across the domains of registration and funding pathways; valuing medicines; patient, clinician and community inputs; and RWE. Table 3.1 provides an overview of progress across these four domains.

The chapter then summarises policy progress to date at a high level. Stakeholder perspectives on progress against each domain are also presented.

Table 3.1 Key reviews and events 2014-2017

Registration and reimbursement pathways	
Registration	Introduction of two new pathways to registration on the Australian Register of Therapeutic Goods (ARTG).
Reimbursement	Increased use of MES and redeveloped it to MAP Need to explore systematic provisional listing alongside fast-tracked registration.
HTA processes and the value of cancer medicines	
Valuing medicines	Multiple reviews into cancer medicines have recommended reforms to evidence requirements. Concerns persist regarding a lack of transparency and a lack of considerations for how innovations relating to patient well-being and indirect impacts on carers are valued. A review and revision of the PBAC submission guidelines. Formalising patient, clinician and community involvement.
Formalising patient, clinician and community involvement	
Patient and clinician involvement	Processes for notifying patient groups of upcoming reviews and extensions in time for patients to provide feedback has been positive. Opportunities exist to extend and improve the role of patients and clinicians in decision processes.
Community involvement	Limited progress has been made in the education and involvement of community. Department of Parliamentary Services reported in 2015 that there is little community debate about what should be publically funded.
Real-world evidence	
Real-world evidence	No real change has occurred in the collection of real-world data to inform PBS policy. Data collection in terms of cancer incidence continues to be state based, albeit against national minimum datasets, and fragmented. The Federal Department of Health has appointed Telstra Health to develop and operate the new National Cancer Screening Register. A clinical quality registry has been established for prostate cancer, and significant investment has been made in the Victorian Comprehensive Cancer Centre to support research into best practice. 10% of PBS and Medicare Benefits data have been linked. However, Teague et al (2015) reported that it was possible to decrypt some service provider ID numbers. Following this alert, the Department decided to withdraw the data from the government website. As of May 2017, the government advises that "advised that work is continuing to restore the dataset as soon as possible." No systematic approach is taken to clinical trial data. The Managed Access Programme Sub-Group of the Access to Medicines Working Group prepared the 'Draft Framework for the Managed Access Programme for submissions to the PBAC'. This has been reviewed and amended by PBAC.

3.1 Registration and reimbursement pathways

Table 3.2: Registration and reimbursement

Registration and reimbursement pathways	
Registration	• Government has supported introduction of two new pathways (Pathways Two and Three) to registration on the ARTG. These include permitting the submission of an un-redacted evaluation report from a comparable overseas National Regulatory Authority, along with a copy of the dossier submitted to that National Regulatory Authority, when considered registration applications, as well as fast-tracking 'novel' and lifesaving medicines.
Reimbursement	• Changes in registration pathways do not address challenges at the listing and funding stage or challenges for codependent technologies. • The 2015 Senate Inquiry recommended a comprehensive review of the reimbursement system for the registration and subsidisation of medicines to address issues with access and reduce the timelines for the introduction of new medicines onto the Australian market. • Increased but ad hoc use of 'MES': Ipilimumab (Yervoy) and Pembrolizumab (Keytruda®). Relatively low take-up of MES and dissatisfaction with process reported across stakeholder groups: resource intensive and divert resources away from other PBAC submissions. • Times to registration and listing appears to be longer than other countries (e.g US and Japan) with a number of medicines approved but unfunded. • Stakeholders reported a lag time between when PBAC recommends a listing and eventual listing on the PBS. • Potential for more systematic provisional listing alongside fast-tracked registrations has not been explored; key requirements around development of 'criteria' for registration and listing, supported by new approaches to funding.

As noted in Chapter 2, a comprehensive review of the registration system for medicines was undertaken in 2015 chaired by Professor Lloyd Sansom. The review identified the need for multiple approval pathways in the system that are better tailored to the needs of the application. Specifically:

- Expanding the available approval pathways by utilising overseas evaluation reports (where practicable)
- Introducing expedited approval pathway in certain circumstances
- Enhancing post-market monitoring of medicines and streamlining post-market requirements
- Improving transparency and predictability of processes and decisions, to ensure Australians have timely access to high-quality, safe and efficacious products.

In September 2016, the Australian government responded to this review and accepted these recommendations. Specifically, the government has supported the introduction of two new pathways to support ARTG.

The scope of the review was limited to the registration system and did not examine the reimbursement system for medicines in Australia.

A review commissioned by the OIT found that on an average it takes 22 months for a cancer medicine to be listed on the PBS following registration by TGA. Moreover, the research also found the average time between an initial submission and listing (reimbursement funding) was approximately 20 months (Table 3.3), and that the time between the positive recommendation by PBAC and listing on the PBS was approximately seven months within.

While a number of regulatory and commercial factors contribute to these outcomes, given that most medicines are out of patients' financial reach if not listed (funded) on the PBS, if options for compassionate access, clinical trials or other mechanisms are not available, this suggests that more should be done through collaboration between industry and government to improve the speed to PBS listings as much as possible.

Table 3.3. Number of months to events in the PBS process for 147 'high level' submission for cancer medicines (2010-2016)

Time-to-event analysis	Overall	New cancer medicine	New cancer indication
Period from date of initial PBAC submission to date of PBS listing (months)*	20.5 (49)	20.9 (24)	20.1 (25)
Period from date of initial PBAC submission to date of last PBAC outcome (months)*	11.6 (90)	12.3 (47)	10.9 (43)
Period from date of TGA registration to date of PBS listing (months)	22.2 (49)	18.6 (24)	25.7 (25)
Period from date of PBAC recommendation to date of PBS listing (months)	7.4 (49)	7.6 (24)	7.3 (25)

Source: Wonder Drug Consulting, October 2016, Analysis of PBAC submissions and outcomes for medicines for patients with cancer (2010-2016)

'High level' submissions mean submissions for new medicines (i.e. new listings) and new indications (i.e. new use within a given cancer, irrespective of PBAC major or minor submissions.

Numbers in parentheses are the sample sizes

The 2015 Senate Inquiry recommended a comprehensive review of the reimbursement system for the registration and subsidisation of medicines to address issues with access and reduce the timelines for the introduction of new medicines onto the Australian market. The Senate Inquiry stated the need to identify options for:

- Improving engagement with sponsors and other stakeholders to better tailor applications
- Tiered assessments matching resources to the complexity of applications
- Encouraging greater cooperation between PBAC, TGA and the Medical Services Advisory Committee
- Ensuring greater transparency throughout the assessment process and expanding post-market review of medicines

Some policy progress has been made at the reimbursement stage, with the increasing use of 'rolling data' or 'MES'. These approaches have sought to reduce the time between registration and listing (funding) of the medicine on the PBS. Recent examples include the use of MES for the listing of Ipilimumab and Pembrolizumab; Box 3.1 provides case study summaries of the use of MES for these medicines.

Recent positive recommendations for nivolumab and vorinostat further highlight the progress in fast-tracking innovative cancer medicines and access to medicines for rare cancers. However, it must be noted that vorinostat was TGA registered in December 2009 and first considered for reimbursement in March 2011 for patients with relapsed or refractory T cell lymphoma - a rare cancer that has been estimated to affect about 100 patients per year in Australia. PBAC commentary for the positive recommendation states that "the uncertainty of the cost-effectiveness analysis presented in the previous submission was diminished in the context of a substantial price reduction offered in the resubmission." The 6-year delay in resolving this "uncertainty" between the sponsor and the government is definitely too long for the hundreds of patients with this rare cancer.

Box 3.1: MES case studies – Ipilimumab and Pembrolizumab

Case study 1: Ipilimumab

Ipilimumab is an immunotherapy for the treatment of patients with unresectable[3] or malignant melanoma. TGA approved this medicine for market authorisation in August 2011.[4] PBAC considered two submissions in its meetings in July 2011 and March 2012 before making a positive recommendation for the listing of Ipilimumab on the PBS in November 2012. In making the positive recommendation, PBAC has requested risk-share arrangements for ensuring appropriate use, maintaining cost effectiveness and managing financial risk.

For 'maintaining cost-effectiveness', PBAC has requested implementing 'a mechanism to verify the anticipated overall survival benefits of Ipilimumab in real-world clinical practice in Australia' (PBAC 2012).[5] Under this pay-for-performance arrangement, the sponsor would be expected to rebate the cost of difference in performance between observed versus predicted survival benefits of Ipilimumab in order to maintain the level of cost effectiveness acceptable to PBAC. This was the first time PBAC made a recommendation for listing being subject to collection of RWE.

Ipilimumab was eventually listed (funded) on the PBS in September 2013 after prolonged negotiations. Subsequent study by Alexander et al (2015)[6] found that the efficacy and tolerability of Ipilimumab in an Australian clinical practice setting were similar to those reported in clinical trials.

Case study 2: Pembrolizumab

Pembrolizumab is an immunotherapy for treating unresectable or metastatic melanoma. It was first registered on the ARTG on 16 April 2015[7] and was listed (funded) on the PBS on 1 September 2015, following a positive recommendation from PBAC in the March 2015 meeting.

The registration and PBS listing of Pembrolizumab underwent a parallel process. The process demonstrated a collaborative effort between the sponsor and the Department of Health. For example, the department and the sponsor had five meetings prior to the submission and two meetings after the submissions. Furthermore, 'an extraordinary amount of important additional information was provided throughout the process of evaluation' (p.8, PBAC 2015[8]), including additional trial data, further modelling and analysis. However, the Department noted that 'The provision of extraordinarily large post-submission documents had placed an unreasonable pressure on PBAC's supporting processes, and evaluation capacity, particularly just prior to PBAC meeting.'

The PBS listing was in the context of a MES in recognition of 'clinical need and importance of early access to new medicines for melanoma patients' (p.35) and that treatment effect over the comparator Ipilimumab was uncertain. As part of the MES, PBAC has proposed a plan to review further evidence within two years, to ensure Pembrolizumab was used in line with the best practice and that the cost and cost-effectiveness of Pembrolizumab is acceptable.

Stakeholder perspectives on registration and funding

Stakeholder perspectives on registration and funding centred on the following themes:

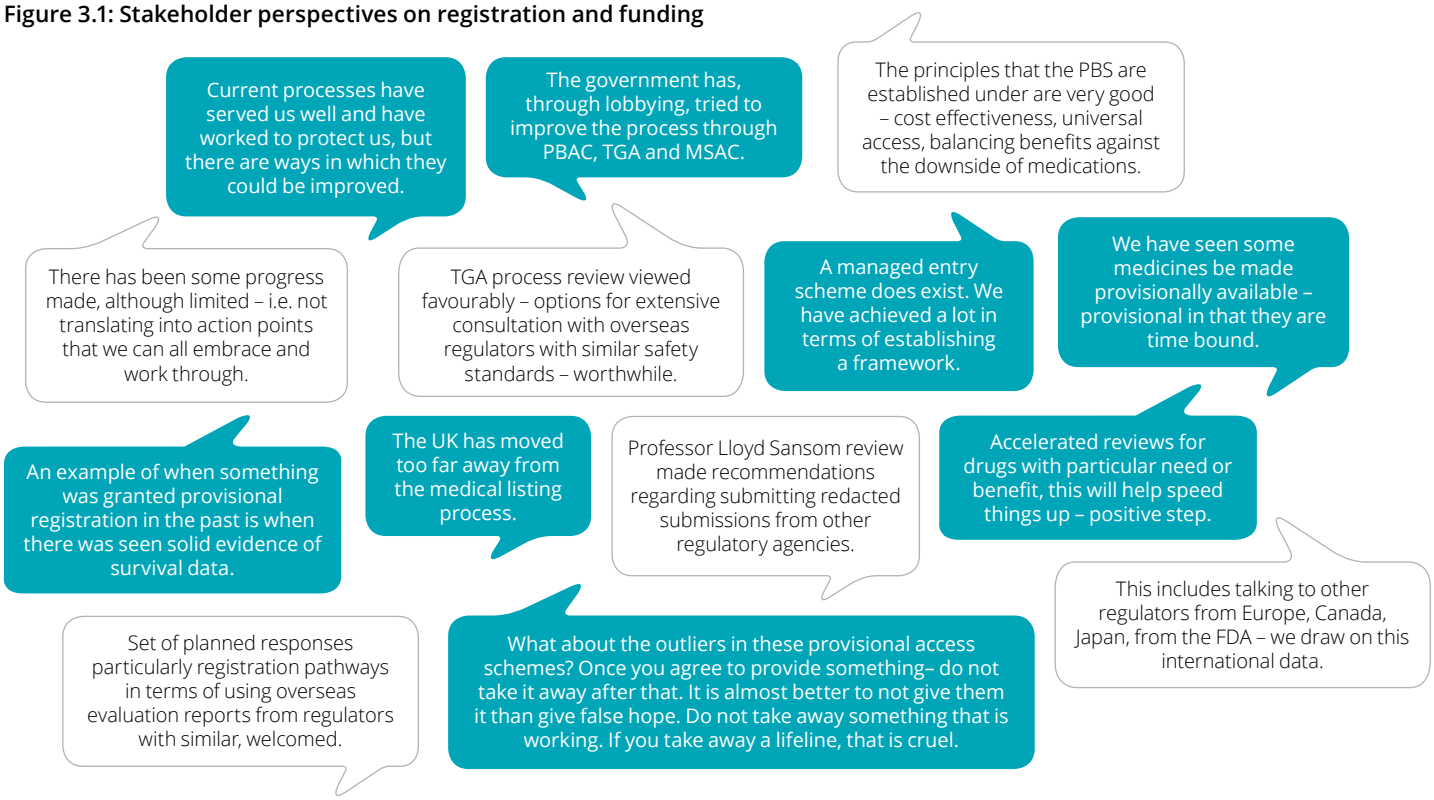
- Strong, positive progress has been made in investigating and modernising registration pathways. Stakeholders viewed the process for modernisation was both considered and consultative. At the same time, some noted that the proposed reforms to registration necessitate equivalent consideration and reforms in reimbursement processes.
- All stakeholders acknowledged the need for data to exist in order for informed decisions to be made. Some viewed that Australia should better leverage global evidence in determining the effectiveness of medicines. This was considered particularly important in the case of rare and less common cancers.
- The increasing personalisation of treatment regimens was seen to increase the rarity of conditions which would in the past have never been

[3]Resectable: Tumours that cannot be removed completely through surgery.
[4]TGA 2011. Australian Public Assessment Report for Ipilimumab. Canberra: Australian Department of Health. www.tga.gov.au/sites/default/files/auspar-yervoy.pdf [Accessed October 2016]
[5]PBAC 2012. Ipilimumab, concentrate solution for I.V. infusion, 50 mg in 10mL, 200 mg in 40 mL, Yervoy® – Public summary document November 2012. Canberra: Department of Health. www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-11/Ipilimumab [Accessed October 2016]
[6]Alexander M, Mellor JD, McArthur G, Kee D 2014. Ipilimumab in pretreated patients with unresectable or metastatic cutaneous, uveal and mucosal melanoma. Med J Aust 201(1):49-53.
[7]TGA 2015. Public summary for ARTG entry 226597 KEYTRUDA Pembrolizumab 50mg powder for injection vial. Canberra: Department of Health. www.tga.gov.au/artg/artg-id-226597 [Accessed October 2016]
[8]PBAC 2015. Pembrolizumab 50 mg vial, 100 mg vial; Keytruda® – Public summary document March 2015. Canberra: Department of Health. www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-03/Files/Pembrolizumab-psd-march-2015.pdf [Accessed October 2016]

considered to be 'rare'. This changing disease classification paradigm was seen to necessitate a review of evidence processes and thresholds to ensure equity of access across conditions.

- Many stakeholders share the view that registration and reimbursement systems need flexibility to reflect the changes happening in medicine – especially the medicines developed in response to a specific genetic defect. There is a need to have targeted therapies registered and available for those with genetic defect rather than just the tumour site/type. However, it should be noted that the effects of medicines for tumours with the same genetic mutation at different organ sites have been variable. Any consideration for flexibility ought to take this into consideration.
- Stakeholders noted that while a managed access programme is desirable, it should be established using agreed criteria. To date MES have been established to provide access to medicines for which a high clinical need exists, with few alternative treatment options available. These medicines have not yet collected sufficient evidence to demonstrate cost-effectiveness. Sponsors receive a provisional price for a drug at the time of initial listing, and are invited to submit a subsequent application for a higher price at the point at which more robust cost-effectiveness data is available. Stakeholders noted that this scheme should not act as a deterrent to either sponsors or government by placing risk unduly on either side. The Managed Access Programme Framework now provides greater clarity regarding the access criteria.
- In relation to managed access, the point was raised that any such scheme should include some mechanism for grandfathering access where a patient is responding to the therapy. If provisional access is granted, there may need to be a compassionate continuation scheme if outlying patients show significant health improvements during the trial period. However, under the current MAP framework, patients "must be informed why a drug is listed through a MAP and of the possibility that the drug may be delisted at the end of the MAP in which case they could elect to pay for the drug privately to continue treatment." One stakeholder, in pointing to individuals affected by population level decisions, commented that there is 'something cruel about denying funding once treatment has showed signs of working'.
- It was reported that there has been relatively low uptake of MES to date. Stakeholders gave the view that this was in part due to frustrations around the process. This has resulted in the redevelopment of MES into MAP. How effective the new MAP framework in mitigating stakeholders' frustrations would be a subject of interest for future investigation.

Figure 3.1: Stakeholder perspectives on registration and funding



3.2 HTA processes and the value of cancer medicines

Table 3.4: HTA processes and valuing cancer medicines

HTA processes and the value of cancer medicines	
Value	• Multiple reviews into cancer medicines have recommended reforms to evidence requirements, including the Senate Inquiry. • An investigation into the growth in expenditure on high costs drugs in Australia was undertaken by the Department of Parliamentary Services in 2015. This investigation identified that there has been little community debate about what should be publicly funded, nor about the price that the community and the government should pay for cancer medicines. • Consistent concerns regarding lack of transparency and/or risks of undervaluing innovations which are highly valued by patients but may not be fully valued using existing quality adjusted life years (QALYs) or multi-attribute utility instrument (MAUI) instruments. • Concerns for assessments on median Overall Survival or median Progression-free survival informing listing and funding submissions ignoring significant benefits for some patients which take time to observe. • PBAC Guidelines review completed and revised Guidelines released October 2016.

Currently, the economic evaluation of a medicine under the PBS process focuses on the direct health system costs and overall survival benefits. In some cases, this tight focus may risk underestimating the full benefit of a medicine to a patient, in terms of impacts on psychosocial wellness, avoided side effectives, potential ability to return to work and impacts on carers. While there are criteria for how these potential benefits might be considered by PBAC (through QALYs), it is increasingly argued that current QALY and MAUI may not fully value innovations which matter to patients and their carers.

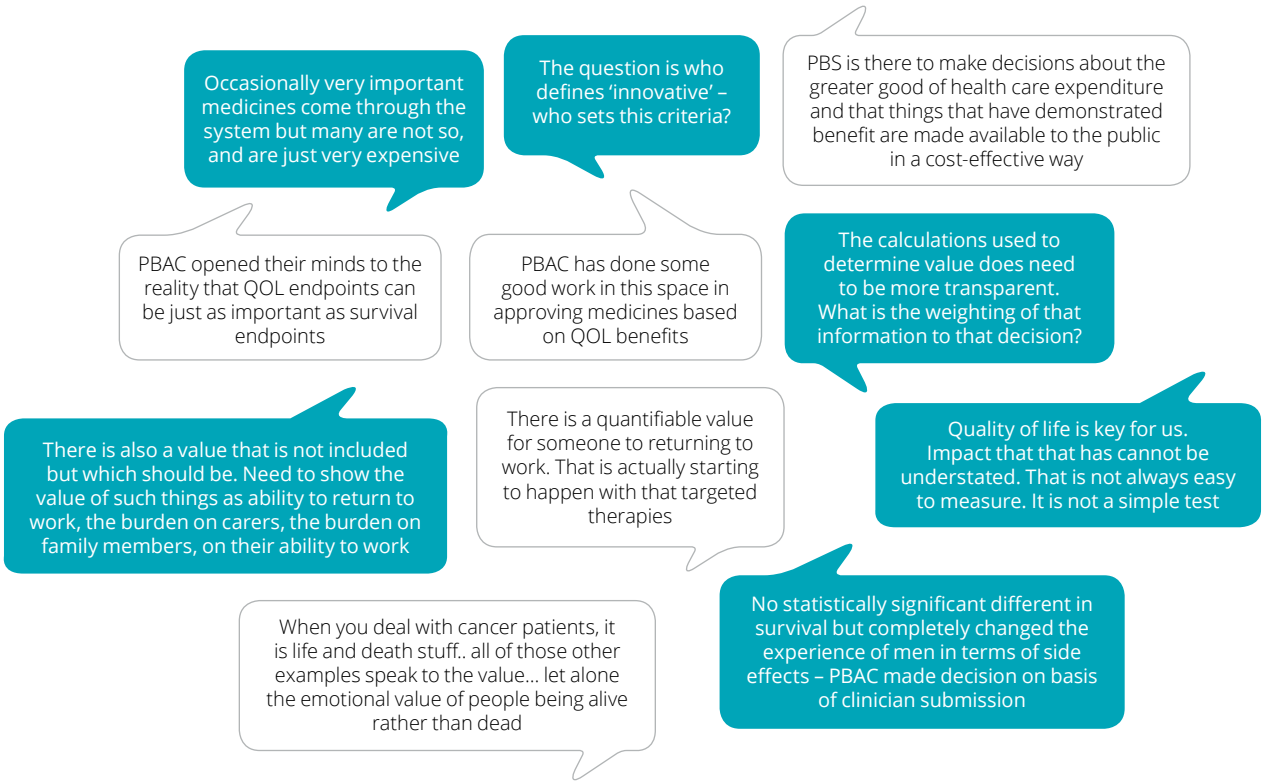
A review of PBAC guidelines examined technical methods issues within the PBAC submission process. This provided industry, government and other stakeholders with the opportunity to update and replace outdated aspects of the submission process. However, it did not address or provide the impetus for the fundamental system reform that was identified and recommended by either the Senate Inquiry or the CDA White Paper. This is because policy, process and values were out of scope for the PBAC guidelines review.

Stakeholder perspectives on value of cancer medicines

Stakeholders collectively questioned the concept of 'value' with discord emerging in relation to what this term means:

- Many stakeholders acknowledged the challenges associated with balancing innovation, stakeholder values and fiscal austerity, 'even though the budget is constrained, it is essential that innovation continues'.
- All stakeholders placed value on innovation in medicines – however, it was at this point that opinions diverged. The definition of innovation was not uniformly agreed upon. Some stakeholders suggested that genuine 'breakthroughs' were not common and questioned whether research and development (R&D) was valued highly enough by funders, whereas some others suggested that overstating these costs may cause sponsors to seek inflated prices.
- Several stakeholders questioned whether determination of value ignored important data. Two clinicians commented that a primary focus on median overall survival and median progression free survival risked ignoring benefits realised for some patients. The 'long tail' of survival seen in some trial data was argued to be 'unique to cancer', meaning that drugs were being undervalued for a substantial population segment.
- Many stakeholders questioned what is 'valued' when making reimbursement decisions. The majority of cancer advocacy groups pointed to quality of life adding significant value to individual lives. It was unclear to them how this value was taken into consideration when funding decisions were being made.
- Uniformly, stakeholders agreed that without transparent criteria being accessible to all stakeholders, it would be difficult to understand how various values were considered during the HTA process.

Figure 3.2: Stakeholder perspectives on valuation of cancer medicines



3.3 Formalising consumer, clinician and community involvement

Table 3.5: Patient, clinician and community involvement

Formalising consumer, clinician and community involvement	
Patient and clinician involvement	• In Australia, increased consideration for stakeholder input to PBAC process has been given in the form of formal 'hearings' with patient groups and greater engagement with clinicians regarding product appraisal (e.g., through MOGA) and an intention to appoint an additional consumer representative to take the total to two • Processes for notifying patient groups of upcoming reviews and extensions in the time for patients to provide feedback has been positive • Some patient groups were reported to be more informative and understand PBAC processes, others were reported to have greater uncertainty around what information was needed to inform decision making. Surveys were reported to be distributed by some patient groups to inform consumer submissions • Patient submissions are essential and can be influential, but sometimes criticised as lacking rigour to support evidence-based decisions • Some patient groups expressed concern that the Code of Conduct was limiting patient group understanding of potential product benefits, and general lack of knowledge (and health literacy) about listing processes continued to impede meaningful patient and community involvement.
Community	• Department of Parliamentary Services reported in 2015 that there is little community debate about what should be publically funded • Limited progress has been made in the education and involvement of community • Concerns about not allowing PBS to grow, or using offsets/caps to slow access, without some community input into prioritisation.

Continuing advances in medical technologies have created new opportunities to 'individualise' care. However, this capacity to deliver more personalised care has contributed to growing expectations for greater consumer involvement in policy and purchasing decisions. At the same time a strong consumer voice has become established as good regulatory practice.

In Australia, increased consideration for stakeholder input to PBAC process has been given in the form of formal 'hearings' with patient groups and an intention to appoint an additional representative. Recent forums and reviews have, however, recommended that there is scope to make this input more 'meaningful'.

The 2014 CDA Stakeholder Forum highlighted the consumer view that consumers should be at the forefront of funding decisions. It also added to the view that patient and consumer organisations should be more strongly integrated into the PBAC decision-making process. The consumer groups represented at the Forum called for four priority actions, including:

- A greater representation of patients within the decision-making process
- Increased community/patient education to increase active participation of patients in the process
- Investment by patient groups and all relevant stakeholders to work together to improve the system
- Greater transparency of discussions and decisions.

The 2015 Senate Inquiry also recommended enhancing and formalising mechanisms for consumers and clinicians to play a more central and substantial role in the evaluation of new medicines and new indications. This includes expanding consumer and clinician representation on PBAC; enhancing existing avenues for stakeholder input, including the use of consumer and patient hearings; and incorporating public perspectives on overarching moral, ethical and opportunity cost considerations into PBAC decision making processes, including consideration of models employed by comparable overseas regulators.

The government has a stated aspiration to build on its platform for consumer and clinician engagement. The PBAC submission to the Senate Inquiry indicated PBAC would like to expand to include earlier engagement with consumer (patient and carer) and clinician groups ahead of submissions but that this would require additional resources to implement.

More broadly, stakeholders indicated that the community could be engaged to a greater extent on priority setting and funding levels. An investigation into the growth in expenditure on high costs drugs in Australia was undertaken by the Department of Parliamentary Services in 2015. This investigation identified that there has been little community debate about what should be publicly funded, nor about the price that the community and the government should pay for cancer medicines. The report also recommended a review be undertaken of the processes and criteria for the funding of high cost medicines. This was echoed by PBAC in its submission to the Senate Inquiry, which called for wider community consultation, particularly with respect to the community's willingness to pay for small changes in overall survival.

The government is yet to respond to the recommendations of this report or implement processes which would see a substantive role for community in defining the parameters of public value judgments.

Stakeholder perspectives on formalising consumer, clinician and community involvement

All stakeholders felt that consumer involvement had made some progress, yet could still be further enhanced. In particular, the lack of a formal feedback mechanism was viewed as problematic. Views included:

- While many acknowledged progress made by having one PBAC consumer representative, there was unequivocally support for further enhancement. The possibility of adding additional consumer representation was raised in multiple interviews.
- All of the consumer groups said that while the opportunity to provide submissions was appreciated, each used the word 'token' to describe the current process. These groups gave examples of providing submissions that supported unsuccessful applications. It was unclear to them how this perspective had played into the final decision.
- Several groups discussed the lack of progress incorporating clinical perspectives in decisions. Two stakeholders noted the ever growing complexity in cancer medicines, stating that to understand this, deep clinical expertise is required. It was unclear to them whether this expertise was sought appropriately and/or valued by PBAC.
- Stakeholders also questioned how clinical submissions were contributing to decisions. An example was given for an application that was supported by Peter MacCallum Cancer Centre in Victoria, which was ultimately rejected. The stakeholder questioned how this clinical opinion had failed to sway the outcome, given the subject matter expertise from where it originated.
- It was identified by many stakeholder groups that community perspectives have not been given a voice in the HTA process. Several groups were aware of the Citizens Council in the UK and suggested that a similar forum may be worthy of consideration in Australia.

Figure 3.3: Stakeholder perspectives on patient, clinician and community involvement

3.4 Real-world evidence

Table 3.6: Real-world evidence

Real-world evidence	
Real-world evidence	• No real change has occurred in the collection of real-world data for the purposes of informing PBS policies. • Data collection in terms of cancer incidence continues to be state-based, albeit against national minimum datasets, and fragmented. • No systematic approach is taken to assess clinical trial data or managed access schemes. • A clinical quality registry has been established for prostate cancer, and significant investment has been made in the Victorian Comprehensive Cancer Centre to support research into best practice. • The Senate Inquiry recommended that the Australian government commission a review of current data collection mechanisms for cancer medicines. • PBS and MBS data has been linked for the first time in 2015 to support research. However, the Department of Health removed this particular dataset from the public domain following privacy concerns that some service provider ID numbers could be decrypted from the dataset.

www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr16-dept-dept005.html

Real-world data refers to observational health care data that is collected outside of randomised controlled trials.[9] Real-world data can come from registries, electronic health records, and administrative data sets. Real-world evidence (RWE) can be generated from these data sources and used to inform regulatory and potentially reimbursement decision making.[10]

RWE is an important part of addressing some of the current challenges posed by innovative medicines. It has the potential to support life cycle product development and monitoring and to improve regulatory and reimbursement decision making.[11] This includes monitoring of authorised products post listing, as well as providing additional support for new medicines approved under managed entry and conditional registration and reimbursement pathways.

There are challenges to utilising RWE, including ensuring the quality and integration of health care data from different sources. Sophisticated data analysis capabilities to interpret and apply the information appropriately will be essential to realising the full potential of RWE.

Challenges in generating long-term outcome data for oncology clinical trials has led to considerations around how best to utilise data collected once medicines enter the market and are used in the 'real-world'. Data collected on medicine use, such as administrative claims data, linked health data or registry data, has the potential to be used to inform ongoing decisions in health care.

The CDA White Paper (March 2015) identified the need to modernise the current regulatory and reimbursement system for the future, noting that this will take time and resource investment. Specific recommendations for system reform included establishment of a national data collection system on treatment outcomes to inform ongoing decision on regulation and reimbursement. The report also recommended the establishment of a National Chemotherapy Registry that can be used to continually improve the quality of chemotherapy treatment in Australia.

The Senate Inquiry also recommended that the Australian government commission a review of current data collection mechanisms for cancer medicines.

It is noted that the government made a commitment in 2015-16 Budget to the establishment of a new national registry of cancer screening. In May 2016, a contract was awarded to Telstra Health to assist the government in implementing this initiative.

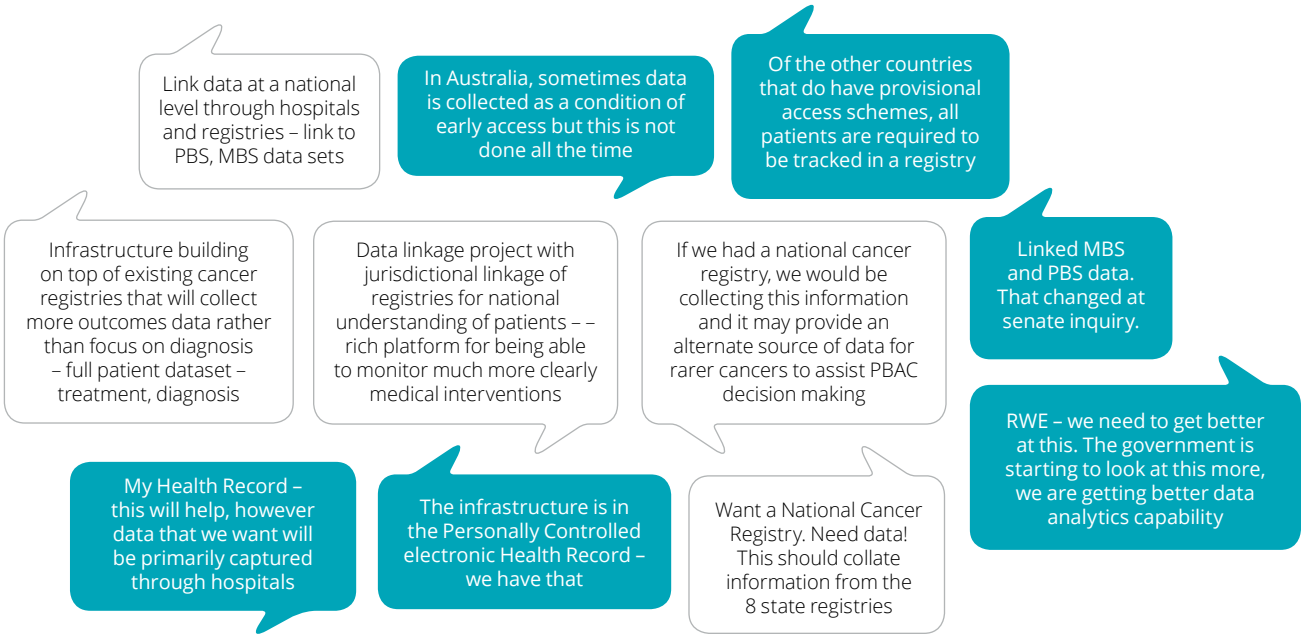
Stakeholder perspectives on RWE

All stakeholder groups identified the need for data to inform decisions. Yet there has been little progress to date on this point. There was discord around how and when data should be collected, with progress further limited by a lack of clarity around responsibilities for progressing this. Stakeholders discussed that:

- RWE has been raised by various stakeholders groups for many years. Major barriers to progress include questions regarding data governance, such as who would be responsible for funding data collection and who would have ownership of the data. Stakeholders discussed that getting this right would serve all groups well, yet no one had stood up to drive this in a collaborative way.
- Linking PBS and MBS data was acknowledged to be a positive first step, but stakeholders also stressed the importance of defining the questions to be answered by the data, otherwise 'lots of data would be collected but no evidence developed'. As noted, due to breach of privacy, the 10% linked PBS-MBS dataset remains unavailable as at May 2017.
- Real-world evidence presented challenges in quality control and the management of 'messy data' would need to be addressed; theoretically, RWE holds the promise of substantially improving quality use of medicines and health system efficiency.
- There have been steps taken toward better data through the introduction of the Personally Controlled Electronic Health Record (PCEHR) and data linkage of the PBS and MBS, but neither of these have been directly designed to address the challenges of high cost medicines.
- The infrastructure exists, although it is piecemeal and in its infancy. The infrastructure for the PCEHR exists, the National Cancer Register has an agreed minimum data set and there is integration of the PBS and MBS data. Stakeholders stated that this progress was desirable, yet still had a ways to go.

[9]http://ec.europa.eu/health/files/committee/stamp/2016-03_stamp4/4_real_world_evidence_background_paper.pdf
[10]http://ec.europa.eu/health/files/committee/stamp/2016-03_stamp4/4_real_world_evidence_background_paper.pdf
[11]http://ec.europa.eu/health/files/committee/stamp/2016-03_stamp4/4_real_world_evidence_background_paper.pdf

Figure 3.4: Stakeholder perspectives on RWE



Chapter 4:

Key questions for policy makers

Notwithstanding the efforts that have been made to address stakeholder concerns for the availability of cancer medicines, there remains continued concern that more could be done to improve access to cancer medicines.

Implementing reform, however, relies on a common understanding of the problem to be solved. Stakeholder consultations indicated greater clarity of the policy problems to be resolved was needed to inform an appropriate policy response.

Key questions which may shape government's approach to resolving the challenges in accessing cancer medicines identified by stakeholders included:

- Is cancer different?
- What does 'equity of access' mean to the community?
- How can patient and clinician perspectives be incorporated in a way that aligns with PBS principles for evidence development?
- How can we sustainably value innovation in the context of uncertainty?

Greater clarity to the answers to these questions can support a more meaningful dialogue on the best next steps for patients and the community.

This chapter presents stakeholder perspectives and key data to inform the discussion of these issues, in order to build platform for meaningful dialogue and policy progress.

4.1 Is cancer different?

In order to determine an appropriate policy response, it is important to fully explore the extent to which the challenges associated with accessing cancer medicines are 'unique to cancer'. To the extent that cancer medicines faced truly unique challenges compared with other types of medicines, this would potentially merit a differentiated policy approach. For example, truly rare diseases are covered by the Life Saving Drugs (LSD) Programme.

The rationale for the LSD programme is that there may be a lack of commercial incentives or available evidence to support the listing of these medicines on the PBS, and without a specialised programme, these patients would be disadvantaged.

Stakeholder perspectives on the issue of 'is cancer different' were highly divided. Figure 4.1 highlights some of the different perspectives identified through the consultation period.

Figure 4.1: Stakeholder perspectives on 'is cancer different?'

The range of answers (Figure 4.1) demonstrates the question is far more complex than it appears on face value. It is worthwhile thinking through these different perspectives and the evidence to support these arguments. Key factors which stakeholders identified as potentially differentiating cancer included:

- The high burden of disease
- Cancer as a life-threatening disease
- The number of cancer subtypes and smaller patient populations
- Uncertainty in evidence
- The pace of innovation and technology change

By contrast, stakeholders which identified that cancer is 'not different' pointed to significant risks of unintended consequences or perverse incentives from differentiated policy responses.

These issues are considered in turn.

Burden of disease: Does the prevalence of cancer merit a differentiated response?

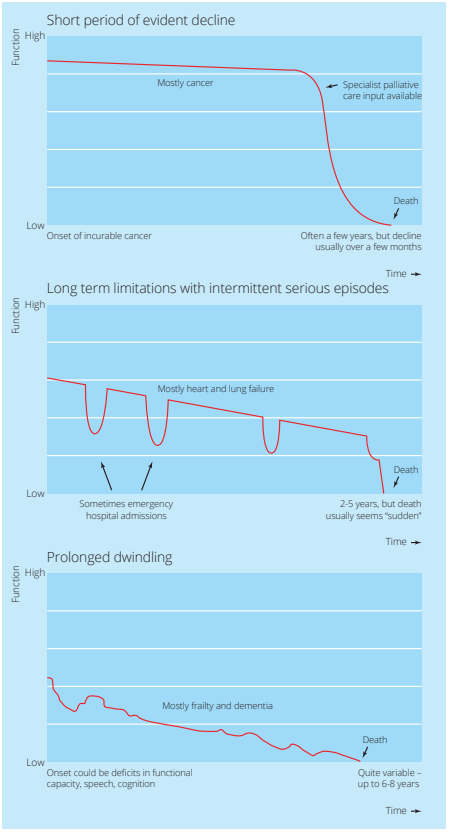
The Australian Institute of Health and Welfare, in the recent Australian's Health 2016 report, found that cancer has the greatest burden of disease across both females and males in Australia.[12] The burden of cancer was driven by people dying earlier than expected, as opposed to living with disability which is the case for some disease, such as mental illness or musculoskeletal disorders. As shown in Figure 1.1 in Chapter 1, cancer is the leading cause of mortality in Australia. The Department of Health submission to the Senate Inquiry noted that one in two Australians will be diagnosed with cancer in their lifetime and one in five will die from cancer before the age of 85. From a public health perspective, it is estimated that over 800,000 disability-adjusted life years (DALYs) were lost due to cancer in 2011.[13]

Cancer prevalence is trending upwards, due to improved detection, an ageing population, and improved cancer management and treatment, which increases rates of survival.

These data suggest that cancer is a priority for the community and merits government funding commensurate with its impact on the community.

In terms of PBS funding, one in every $6 dollars spent on the PBS is directed toward cancer treatments.[14] This equates to over $600 million per year. This is up from one in every $8 estimated in 2013. Cancer is one of nine National Health Priority Areas (NHPA), along with asthma, cardiovascular health, diabetes, injury prevention and control, mental health, arthritis, musculoskeletal conditions and dementia. The establishment of Cancer Australia also reflects the priority status of cancer as a condition by the community.

While cancer is a significant disease for the community, the burden of disease alone is unlikely to be a sufficient rationale for a highly differentiated policy response, given the range of challenges and health priorities facing government.



Source: Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. BMJ : British Medical Journal. 2005;330(7498):1007-1011.

[12]Australia's health 2016: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129555788, p.51
[13]Australia's health 2016: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129555788, p.58
[14]Department of Health, 2015, http://www.health.gov.au/internet/ministers/publishing.nsf/Content/health-mediarel-yr2015-ley048.htm

Cancer as a life-threatening disease: Does the need for a rapid response merit a differentiated response?

Cancer patients face particular challenges related to the urgency of their treatment needs. Unlike some conditions, for which there is time to determine an optimal treatment path, cancer patients with terminal illness require immediate treatment.

It was estimated by Munich RE that more than 90% of terminal illness claims related to a cancer diagnosis. Other end-of-life diseases, including congestive heart failure, stroke and dementia face different disease development profiles and treatment options, which arguably change the experience of the disease. As noted by a number of stakeholders: 'cancer causes fear'. Research by Murray et al (2005) demonstrates that the decline associated with cancer can be steeper, versus heart or lung failure, or dementia.

In the UK, a Citizens Council was asked to review whether 'end of life' diseases should be treated differently than other conditions. The Citizens Council recommended a differentiated approach to the valuation of end-of-life medicines.

Cancer is not the only terminal illness present in the community and so may not be differentiated on this basis. But the experience of the disease, however, may be different, and given this experience and available treatment options, it would be potentially valuable to consider community perspectives for whether this merits a standard or varied policy approach.

Subtypes and evidence development: Are there challenges in evaluating cancer medicines which potentially merit a differentiated response?

A significant challenge with cancer is that it is not 'one disease,' but many. It was reported that there were more than 200 subtypes of cancer diagnosed in 2014. In its submission to the Senate Inquiry, the Department of Health estimated five most commonly diagnosed cancers in 2014 were:

- Prostate cancers – 17,050 persons
- Bowel cancer – 16,640 persons
- Breast cancer – 15,410 persons
- Melanoma – 12,640 persons
- Lung – 11,580 persons.

Together, these cancers account for approximately 60% of all cancers diagnosed in a year. Beyond this, there is a long tail of different cancer subtypes, and in 2014, it was estimated that 42,000 people would be diagnosed with some form of 'rare' or 'less common' cancer. This suggests that approximately one-third of all cancers diagnosed are 'less common' or 'rare'.

This is different from the treatment of other diseases and stands in significant contrast to conditions which have been treated with so-called 'blockbuster drugs,' such as statins for cardiovascular drugs.

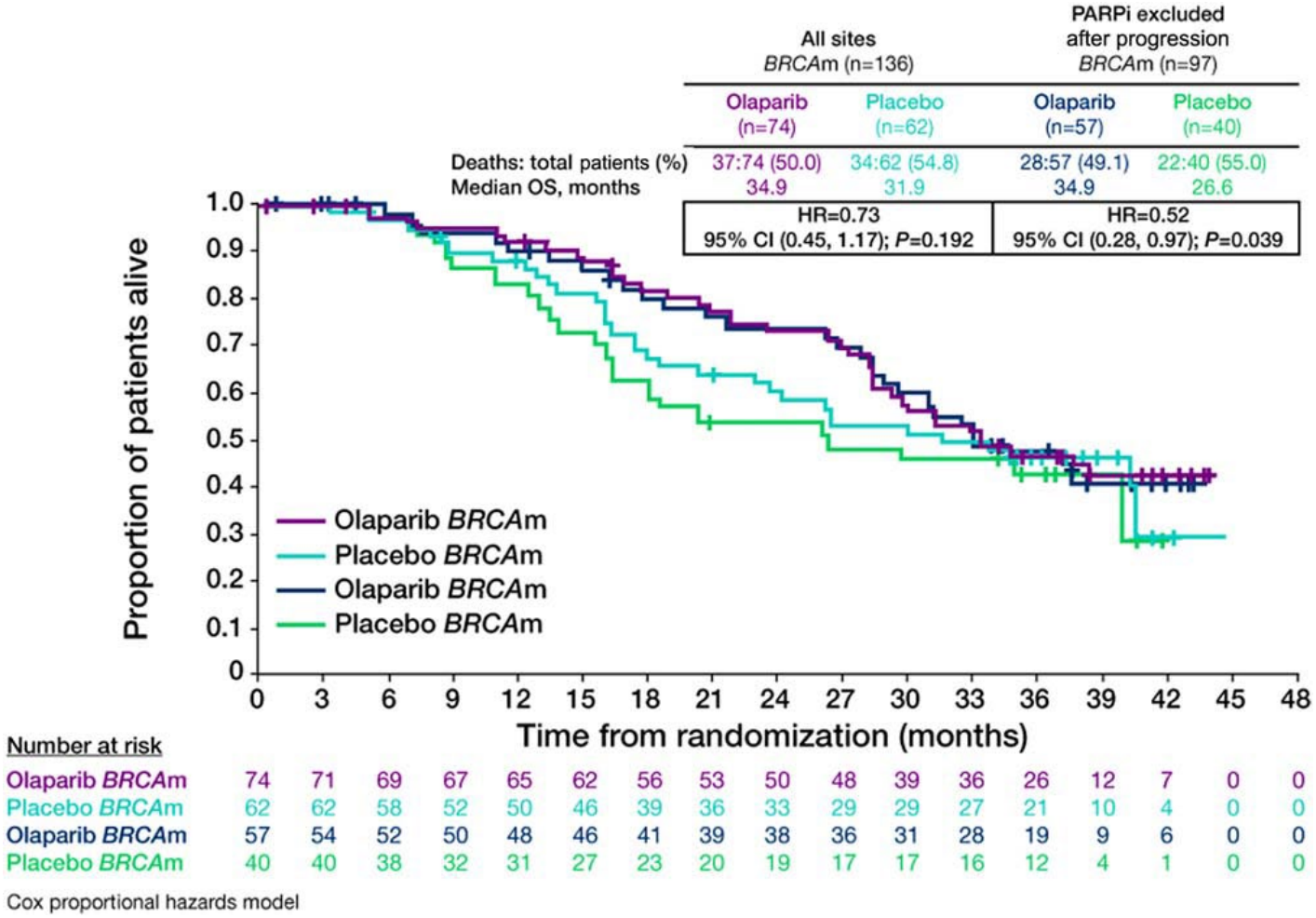
The increasing differentiation in patient populations for cancer creates challenges for manufacturers, regulators, clinicians and patients alike:

- From a manufacturer's perspective, the challenge of shrinking patient populations has substantially changed the economics of drug development, with the costs of drug development now spread across a smaller potential market.
- From a regulator's perspective, the smaller patient sizes present new statistical uncertainty.
- From a clinician and patient perspective, where there is a lack of commercial incentive or available evidence to demonstrate clinical benefit, there is a risk that medicines are not listed or are substantially delayed.

Related to the challenges of the number of subtypes are the challenges in evidence development. It has been argued by stakeholders and in the literature that cancer medicines are characterised by greater statistical uncertainty than other medicines; this is due, in part, to smaller patient sizes[15], but also unique challenges around survival outcomes over time. Currently, the preferred primary endpoint used to evaluate clinical benefit by PBAC is median overall survival. But as identified by a number of clinicians, academics and regulatory stakeholders, cancer medicines can often exhibit a 'long tail of survival' for a substantial cohort of patients (See for example, Figure 4.2).

[15]Rare Cancers Australia's submission identified a trial which took three years to identify 50 patients with a target mutation. See http://m.jco.ascopubs.org/content/early/2015/02/03/JCO.2014.59.8334.full

Figure 4.2: Challenges with cancer medicines evaluations – the long tail of survival



Source: Ledermann et al. 2014, The Lancet Oncology, Volume 15, Issue 8, Pages 852-861,

These challenges are a function of advances in genomics which has led to more targeted therapies for cancer patients. Over time, these challenges may be seen across other conditions. Therefore, these issues possibly merit a differentiated response, but ideally one which could be extended over time to other classes of medicines as new technologies emerge.

The pace of innovation and technology change: Does the number of new cancer medicines seeking listing merit a differentiated response?

Australia's challenges with access to expensive new medicines, including cancer medicines, are not an isolated experience. Expenditure on cancer medicines has increased worldwide (up to an estimated $91 billion in 2013) and the pipeline for new medicines is strong (Department of Health, 2015).

Notwithstanding the significant increases in the costs to develop medicines, investment in cancer treatment remains considerable. Research by Professor Michael Drummond (health economist, York University, UK) found that over 10,000 clinical trials are focusing on non-small cell lung cancer lung, breast and prostate cancer alone and the number of oncology compounds in development within the top 10 pharmaceutical companies is substantial in all three major phases of development. Currently, there are approximately 75 oncology products in phase 1, 52 in phase 2 and 52 in phase three, indicating that a substantial number of new cancer treatments are expected to be submitted for regulatory approval and reimbursement in the near future.[16] The Australian Department of Health has similarly reported that it has estimated almost 1,000 anti-cancer medicines are currently in various phases of preapproval testing; more than the number for heart disease, stroke, and mental illness combined (Department of Health, 2015).

[16]McGuire, A., Drummond, M., Martin, M. & Justo, N., 2016, Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes? Expert review of Pharmacoeconomics & Outcomes Research, 15(4):599-605.

There is a risk that innovation in the treatment of cancer is exceeding the current regulatory systems' ability to review these new technologies. Reflecting the time criticality of patient needs, this may justify a need to support appropriate resourcing to meet this higher demand on the regulatory system. The additional resourcing may not need to be 'cancer specific,' but reflecting the full impact of likely submissions which may impact on PBAC workloads. These workload increases are anticipated owing to the fact that, due to the expanding nature of the value footprint for oncology medicines, 'value' may be unable to be clearly assessed at the time of first regulatory approval. Thus, subsequent evaluations may be required, resulting in PBAC incurring an additional time and resource cost.

Policy risk: What do the risks associated with a potential differentiated response mean for policy makers?

The clear risk of a differentiated policy approach for cancer is the risk of unequal access to medicines or unintended consequences arising from a differentiated approach. A number of stakeholders highlighted this risk and the potential for perverse incentives or a lack of value for public money in the event of a differentiated policy.

In the United Kingdom, the Cancer Drugs Fund represents a highly differentiated approach to cancer medicines[17] to cope with medicines systematically failing to meet traditional evidence requirements of the National Institute for Health and Care Excellence, UK (NICE). However, an audit criticised the fund for a lack of price controls for these cancer medicines. Another review of the Fund by Aggarwal et al (2017) found that the Fund "has not delivered meaningful value to patients or society. There is no empirical evidence to support a 'drug only' ring fenced cancer fund relative to concomitant investments in other cancer domains such as surgery and radiotherapy, or other noncancer medicines. Reimbursement decisions for all drugs and interventions within cancer care should be made through appropriate health technology appraisal processes"

Similarly, a recent analysis of fast-tracked registrations by the Food and Drug Administration (US) was undertaken and published in JAMA.[18] In total, 36 drugs were analysed, 19 of which were approved based on rate of response, 17 based on progression-free or disease-free survival (PFS or DFS). Based on a median follow-up of 4.4 years, the research found only five drugs had demonstrated improvement in overall survival in randomised clinical trials, which was less than half the rate demonstrated through traditional HTA processes.

This highlights the risks for policy makers related to policy innovation and potentially departing from traditional methods for HTA evaluation. The negative lens for reviewing the above data would be that an accelerated registration and listing pathway may result in medicines receiving funding, which would have been rejected using traditional methods (31 of the 36 medicines). Alternatively, one could also see that patients had earlier access to medicines (five of the 36 medicines) which were shown to improve their overall survival outcomes over available therapies.

In statistical terms, this is a classic 'Type I' versus 'Type II' error[19] question: which risk would one rather bear as a policy maker:

- The risk of denying access to medicines which may potentially offer benefit (acknowledging that due to the terminal nature of the condition, timeliness is a real consideration).
- The risk of funding medicines which later prove to be not cost effective or less cost effective than expected.

For policy makers, the sequitur is 'which risk can be most readily mitigated'? While the risk of funding medicines that are not cost-effective (or not as cost effective as one thought or hoped) can be managed through contractual arrangements, such as pay for performance, risk sharing, or rebate arrangements, the risk of delays or unequal access is not so readily reduced.

The experience of the US clearly points to a need to learn from experience. For example the research authors argue that the FDA should determine a timeline for drug approvals on the basis of a surrogate endpoint to prove their effectiveness.

These are hard questions, and not easily resolved. The risks of a differentiated approach are real, and government is not inappropriate in its caution for seeking to adopt methods which are robust and evidence based.

[17]UK National Audit CDF
[18]Kim C, Prasad V. JAMA Intern Med. Online: October 19, 2015. doi:10.1001/jamainternmed.2015.5868
[19]In statistical hypothesis testing, a type I error is the incorrect rejection of a true null hypothesis (a 'false positive'), while a type II error is incorrectly retaining a false null hypothesis (a 'false negative').
Aggarwal A, Fojo T, Chamberlain C, Davis C, Sullivan R. Do patient access schemes for high-cost cancer drugs deliver value to society?-lessons from the NHS Cancer Drugs Fund. Ann Oncol. 2017 doi: 10.1093/annonc/mdx110.

4.2 What do we mean by 'equity of access'?

Australia's PBS is built on the foundations of the National Medicines Policy. This policy, launched in 1999, has guided the evolution of the PBS, particularly through recent PBS reforms which have, in principle, sought to balance improved affordability from off-patent medicines with sustained access to innovation. The National Medicines Policy has four key pillars:

- Timely access to the medicines that Australians need at a cost individuals and the community can afford
- Medicines meeting appropriate standards of quality, safety and efficacy
- Quality use of medicines
- Maintaining a responsible and viable medicines industry

The concept of 'equity of access' is similar to Australian principles for 'universal access' to health care, which differentiates Australian policy approaches from other systems which tolerate a greater variation of outcome based on private ability to pay.

The challenges of cancer medicines, however, can begin to test perceptions of what 'equity of access' means in practice:

- Does it purely mean 'fairness of process'? or
- Does it mean 'equal access to care'?

This is not to say that Australia should fund all medicines which are developed; stakeholders did not suggest PBAC depart from an evidence-based approach. Rather the question centred on how new evidence could be considered as it emerges.
One stakeholder, who had recently lost a spouse to cancer, highlighted this challenge for patients and their families:

> "A single dose was funded by the PBS, but a double dose was not funded, even though data in the US showed it would double the chance of survival. So we faced the question of 'do we self-fund?', which would have been more than $50,000? It took time... and in the end we were able to get on a clinical trial. But it took me time to figure this out. What if we had known sooner? What about the people who don't know how to navigate the system? ...Most people cannot afford these medicines if they are not funded by the PBS."

Another example highlighted by stakeholders included the listing of nivolumab (monoclonal PD-1 antibody):

While this is now available on the PBS for Melanoma patients, and will be available for patients with certain types of lung cancers, there is the potential for this same drug to treat diffuse large B-cell lymphoma, follicular lymphoma, B-cell non-Hodgkin lymphoma and chronic myeloid leukaemia, but under our current system it may be many years (if ever) before the treatment is readily available to blood cancer patients.

Similarly, one stakeholder shared the view that 'Rare diseases continue to be a question without an answer'.

Registration and listing decisions must rely on evidence, taking into account safety considerations, evidence of clinical benefit and assessments of affordability. The current system works well in instances where sponsors have collected sufficient evidence to justify a registration or investment decision. In this instance, the decision maker has had 'sufficient' data to make an informed decision. But in cases of small patient sizes, this becomes more problematic, in terms of ability to recruit patients. For cancers that are less common, it is difficult to produce robust clinical data.[20]

Moreover, the impact of patient cross-overs into other therapies also confounds evidence development.

The definition of 'rare' cancer was also challenged, with one person questioning 'So are we going to say there are 42,000 people with 'rare' cancers now?' One stakeholder discussed that as new evidence emerges related to genetic causes of cancer, patient populations with 'rare' disease categories could increase. The reason expressed for this view was that as the specific genetic fault become better understood, subcategories of cancers were being created.

[20]Edward L. Korn, Lisa M. McShane,* Boris Freidlin, 2013 Statistical Challenges in the Evaluation of Treatments for Small Patient Populations, Science Translational Medicine, 7:178.

Figure 4.3: Stakeholder perspectives – what does the community expect of 'equity of access'?

Increasingly, while traditional evidence-based approaches have delivered equity of access, in the context of less certain evidence, there may be 'fairness of process,' but risks of a reduced 'equity to care'.

4.3 How can we sustainably value innovation?

Cancer medicines are more expensive than any class of medicine previously seen. Stakeholders also grappled with the trends in these costs and what it means for the long-term sustainability of the system.

The drivers for the growth in cost are many and complex. It can be agreed that the mapping of the genome and the growing knowledge of genomics has influenced cancer medicines first and has seen the first tentative steps toward more 'personalised' care. Cancer is not 'one disease' but many; tests can identify the genetic mutation effecting a cancer and determine whether a medicine will be effective in controlling the cancer. Unlike the 'blockbuster' drugs launched in the 1980s and 1990s, like statins, the population sizes for cancer medicines are small. This has fundamentally disrupted pharmaceutical manufacturers models for R&D and upended the economics of drug development.

A recent article by by Professor Michael Drummond (health economist, York University, UK) summarised meta-analysis which presented estimates of the cost of general drug development obtained from a number of published studies. This study demonstrated that between 1975 and 2013 development costs had increased nearly ninefold and reached $1.447 billion.[21] Similarly, the article reported that according to a recent publication by Tufts Centre for the Study of Drug Development, only 30% of compounds in the marketed portfolio of pharmaceutical companies are generating revenues equal to or greater than the average cost of development of a new drug. To increase the pressure on new products in this area even further, a growing number of oncology treatments come off patent after 2015.

Research productivity for new medicines technologies declined substantially and triggered substantial global industry consolidation through the 2000s.

[21]McGuire, A., Drummond, M., Martin, M. & Justo, N., 2016, Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes? Expert review of Pharmacoeconomics & Outcomes Research, 15(4):599-605.

As reported by Drummond, a recent article investigated the success rates of drug development between 2003 and 2011 and found that the likelihood of gaining approval, through phase 1 to FDA approval was 12.1% across all indications, but only 6.7% in oncology.[22]

In addition to these complexities, which increase the financial investment required to establish evidence of clinical benefit, there is evidence that the time to market has also increased.[23] The average time from synthesis of a self-originated new chemical entity to approval by the US FDA has been found to have increased from 7.9 years in the 1960s to 12.8 years in the 1990s in the United States, due to the increases in the length of clinical trials.[24] Similarly, according to Tufts Centre for the Study of Drug Development, the time to develop oncology products increased to an average of 8.2 years over the period 2006-11, compared to 7.6 years over the period 2000-2005.[25]

Adding to this, the costs in cancer are compounded in some cases through the use of combination therapies, which clinicians use to try to combat a cancer that mutates in response to therapies.

Taken together, these multiple factors have contributed to the growth in prices for cancer medicines.

Notwithstanding the new complexity and rising uncertainty of R&D for medicines development may explain to a great extent the rising cost of cancer drugs, there was concern among stakeholders that the growth in prices was not sustainable and questions about how the community can continue to realise the best value for money. As noted by PBAC in its submission to the Senate Inquiry, rising R&D and manufacturing costs do not explain the total growth in prices. Manufacturers operate in a competitive market and are required by shareholders to maximise returns on their investments.

In this complex market dynamic, governments and regulatory agencies are the levers the community has available to realise the best value for money. Government must allocate scarce health dollars to the highest and best use.

Understandably, HTA and reimbursement authorities are finding this increasingly challenging and seeking new approaches to realise value for money. While wanting to grant access to medicines as early as possible, these authorities must apply high safety standards and ensure that any new approaches to evidence, such as departing from median overall survival standards to other surrogate measures of benefit, such as PFS (or DFS) or time to treat, are a robust evidence base to justify the expenditure of scarce taxpayer and health dollars.

Data has shown that over time, however, R&D is contributing to a progressive increase in overall survival and quality of life. For example:

- A recent ASCO publication reported incremental innovation over 15 years had extended overall survival for breast cancer patients from 20 months to more than 50 months[26].
- Cancer Drugs Alliance reported that the one-year overall survival for patients with advanced stage or metastatic melanoma was 30% to 35%, but is not greater than 70% to 80% in clinical trials of targeted and immune drug therapies[27].
- A recent study published in Health Affairs reported that new cancer treatments in routine clinical practice for patients with metastatic breast, lung, or kidney cancer, or chronic myeloid leukaemia (CML) for the period from 1996 to 2000 and the period from 2007 to 2011 and found that although there were large increases in medical costs, there were also large gains in life expectancy.[28]

This highlights the significant challenge for regulators, payers, the community and manufacturers: Valuing medicines on the basis of changes to median overall survival at the conclusion of a clinical trial lasting only one year ignores the 'long tail of survival' and the incremental benefits which are developed over time.

Increasingly, studies have shown the use of PFS to be a robust measure for granting early, provisional access,[29] supported by appropriate mechanisms for reviewing evidence and prices over time. PBAC has recognised that PFS can be a patient-relevant endpoint in itself where extending remission is associated with better quality of life. PBAC decision for Gazyva (obinutuzumab) in chronic lymphocytic leukaemia made this point, given the slow, chronic nature of this cancer.

In addition, there was concern that holding to traditional evidence requirements would limit the growth of the PBS to a level that is below what the community may find acceptable. Stakeholders were also concerned that innovations in cancer medicines which patients value may not be valued by the system, and this, over the longer term may have unintended consequences for patients and their carers (Figure 4.4).

[22]Hay, M., Thomas, D., Craighead, J., et al., 2014, Clinical development success rates for investigational drugs, Nature Biotechnology, 32, 40-51
[23]McGuire, A., Drummond, M., Martin, M. & Justo, N., 2016, Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes? Expert review of Pharmacoeconomics & Outcomes Research, 15(4):599-605.
[24]Dickson, M. and Gagnon, J-P, 2009, The cost of new drug discovery and development, Discovery Medicine, February 2015
[25]McGuire, A., Drummond, M., Martin, M. & Justo, N., 2016, Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes? Expert review of Pharmacoeconomics & Outcomes Research, 15(4):599-605.
[26]Nixon N. & Verma S., 2016, A Value-Based Approach to Treatment of HER2-Positive Breast Cancer: Examining the Evidence, American Society of Clinical Oncology Education Book: American Society of Clinical Oncology: 35, 56-63.
[27]CDA Submission
[28]David H. Howard, Michael E. Chernew, Tamer Abdelgawad, Gregory L. Smith Josephine Sollano and David C. Grabowski New Anticancer Drugs Associated With Large Increases In Costs And Life Expectancy Health Affairs 35, no.9 (2016):1581-1587
[29]McGuire, A., Drummond, M., Martin, M. & Justo, N., 2016, Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes? Expert review of Pharmacoeconomics & Outcomes Research, 15(4):599-605.

Figure 4.4: Stakeholder perspectives – how do we value cancer medicines?

It is within this context that government must make policy choices which deliver the best value for money to the community it represents. This means understanding:

- **Priority setting –** What is the community willing to pay for medicines? Is the overall funding level for the PBS appropriate?
- **Valuing innovation –** Does the system achieve value for money and value the things that patients and their families value?
- **Procedural fairness –** Is the process fair and transparent?

Overall PBS funding – does this reflect community values and priorities?

Starting in 2002, the government committed to the release of an Intergenerational Report (IGR) every five years. The goal of the IGR is to assess the long-term sustainability of government policies over 40 years, including the financial implications of demographic change.

The maiden IGR, released in 2002, had significant and ongoing consequences for the operation of the PBS. At the time of the 2002 IGR's release, the PBS was the fastest growing area of health expenditure, with government expenditure increasing by 9.9% over the previous year. Moreover, this had followed a decade of double digit growth of around 14%. Over time, it became clear that as prescription volumes were increasing, Australia was not realising value for money for off-patent medicines due to the way that reference pricing worked at that time.

Consequently, the 2002 IGR catalysed a number of reforms to the PBS, with the goal of realising better value for money from off-patent medicines, without compromising access to new, innovative medicines. The initial reforms implemented in 2006 resulted in the creation of two formularies, the F1 and the F2, which would be used to drive savings from off patent medicines to control the growth in expenditure while sustaining access to innovative medicines.

These and subsequent reforms, including most recently the PBS access and sustainability package (PASP), have delivered large savings to government and the community it serves.

Today, however, the PBS is one of the with well managed growth programmes within the health portfolio. Several stakeholders questioned whether the amount set aside to subsidise drugs each year in Australia

through the PBS reflected community values. There was discussion around what the community expectation is in terms of government spending and whether this amount reflects the value that medicines hold in the community more broadly. Stakeholders questioned whether $10 billion dollars in funding for the PBS, in the context of approximately $450 billion of government expenditure on health services per annum, reflected community expectations appropriately. For example, as shown in Figure 4.4 above, the following stakeholder comments were made:

- PBS was last seriously reviewed in 1989; we need to have a conversation about this without freaking out citizens.
- There is a broader issue here about government priorities. Should we increase health spend [to support increased access to the PBS]? We would like to see a broader debate about health priorities and health spending.
- Why are we keeping PBS funding at this level? There needs to be a balancing act between the taxpayer expectations and what government actually does.

It is important to state that stakeholders did not want blanket access at any cost to unproven technologies. Even among stakeholders who were questioning the total growth of the PBS, there was a strong emphasis that medicines should be safe and the principles of the PBS were sound. For example, one person stating that: 'We want to protect the PBS. It needs to be evidence based. It just needs to evolve.' Similarly, other stakeholders shared that:

- We should not fund technologies where there is no evidence, but if the biology is understood, even for small patient groups, and there is a hold up in the process... these patients will not be around.
- We accept that money is not infinite. It is a balancing act. We do want to ensure that our money is spent on treatment that is safe and also effective.

Supporting this, PBAC in its submission to the Senate Inquiry indicated that community engagement with regard to willingness to pay for potentially small gains in survival needed to be undertaken.

Does the current process value and reward innovation that matters to patients and the community?

For the PBS to continue to deliver on its reputation for delivering great outcomes for Australia, the outcomes of the regulatory and reimbursement processes must reflect the values of patients and the broader community. If innovations valued by patients and the community are not valued by the listing and reimbursement processes, then the community would be concerned for risks of regulatory failure. However, this point was contentious in the minds of some stakeholders, as there were competing views on what is considered to be 'breakthrough'. As one stakeholder questioned: 'Who and what determines that a medicine meets the criteria of a significant advance in treatment? We need a set of criteria to take this discussion forward and caution should be applied to using these words.'

The concept of innovation in cancer has become a challenging topic for patients, clinicians, regulators and industry. Traditionally, improvements in health outcomes have been measured through the use of quality-adjusted life years (QALYs) and incremental cost effectiveness ratios.[30] The validity of QALYs as the sole measure for benefit have been coming under increasing scrutiny in recent years, however, there have been substantial concerns that current QALY measures are based on societal perceptions of 'quality of life' changes, whereas patients may value such changes quite differently.[31]

Within the context of cancer medicines specifically, these issues often become more significant. For example, for patients with (advanced) disease, the balance between quality versus quantity of life is a much more personal determination than for early breast cancer, where the goal is to cure. It also does not take into account the benefit of time-off treatment or symptom improvement. Some medicines may provide significant improvements in patient wellness or an ability to return to work, which are not directly valued in QALY measures. For example, a 2016 study involving a systematic review of the literature identified cases in which patients had been involved in the HTA process. Patients were found to prioritise 'individual impact and benefit', and/or offering 'relief or prevention of symptoms or complications of disease ("quality of life")'. The focus of the valuation was generally based on 'individual need'.[32]

Devlin and Lorgelly (2016) identified that QALYs may need to evolve as a measure of value in relation to cancer. In particular, the review found that cancer-specific patient-reported outcomes (PROs) assessments are increasingly becoming available. These new tools may more appropriately reflect the health-related quality of life enhancements that some new medicines provide. Further, the review found that current QALY calculations do not take into account 'process of care' preferences. That is, some patients may prefer treatment that is available in their home versus a hospital. The paper also reflected comments expressed by numerous stakeholders, indicating that QALYs do not account for the wider economic benefit of treating cancer. This may include the patients or carers being able to return to work earlier or be able to contribute to society in other ways as a result of accessing a particular treatment (e.g. volunteering).[33]

Many stakeholders shared the view that the population perspective occurs at the expense of the patient or clinician perspective, with one stakeholder positing that 'consumers were not spoken of during the value discussion'. The issue around 'quality of life' not being accounted for during decisions was mentioned by 14 separate stakeholders. One stakeholder said that 'if quality is improved markedly, this is a win for cancer patients, because everyone wants to participate in society'. Another comment included 'but there is a quantifiable value for someone to return to work. That is actually starting to happen with that targeted therapies, the side effects are minimal and they are once again becoming productive members of society.'

Government has increased its engagement with clinicians and patients through engagement with MOGA and consumer groups, inviting public submissions and extending the time for those submissions. It may be that more transparency is needed for government as well, to be able to better communicate the weight and value of this input. The concept of greater transparency and new approaches for communicating decisions was also supported by PBAC in its submission to the Senate Inquiry.

While payers must ensure overall value for money on behalf of the community, it is also important that all patient-important outcomes are considered. If innovations valued by patients and the community are not valued in the same way by decision makers, then the community may become concerned about this misalignment.

Greater evidence development is needed to support this discussion of value. It is understandable that PBAC seeks as much evidence as possible to build a robust, statistically valid dataset from which to make decisions. Supporting PBAC with systematic evidence development, such as through RWE development would support greater allocative and dynamic efficiency over time, and the ability to fully value all patient-important outcomes.

Is there adequate transparency in HTA processes?

Stakeholders considered that the calculations used to determine value need to be more transparent, including how supplementary inputs are weighted and how this considered in PBAC decisions. Several stakeholders expressed that 'the calculations used to determine value does need to be more transparent. What is the weighting of that information to that decision?'

PBAC and government have pointed to consultation with a range of stakeholders and evidence consideration as part of its decision making (Table 4.1) and have stated that patient and clinician views are taken into consideration. PBAC's expanded engagement with MOGA, as well as engagement with patient groups, indicates an intent to gather all relevant evidence. It might be that greater transparency in the valuation of evidence would further support PBAC's engagement with the community.

In its submission to the Senate Inquiry, PBAC reported that it would welcome greater transparency, in partnership with the industry.

[30]A treatment with a low cost per QALY is more cost effective than one with high cost per QALY. An ICER is simply the ratio between the difference in cost and the difference in benefit of two interventions. In cost-effectiveness analyses, ICER are commonly expressed as incremental cost per QALY.
[31]McGuire, A., Drummond, M., Martin, M. & Justo, N., 2016, Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes? Expert review of Pharmacoeconomics & Outcomes Research, 15(4):599-605.
[32]Tatjana E. MacLeod, Anthony H. Harris, and Ajay Mahal, 2016, Stated and Revealed Preferences for Funding New High-Cost Cancer Drugs: A Critical review of the Evidence from Patients, the Public and Payers, Patient, 9:p. 201–222
[33]Devlin, N & Lorgelly, P, 2016, QALYs as a measure of value in cancer, Journal of Cancer Policy, 76: 1-7

Table 4.1: What does PBAC consider in its assessment

Domain	Topics	PBAC's position	Examples using public summary documents of cancer medicines or further descriptions
Clinical needs	Unmet needs	Within consideration	Ipilimumab – 'PBAC noted the high unmet clinical need for treatments for metastatic melanoma with proven survival advantage' http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2012-11/Ipilimumab.pdf
	Rare disease	Within consideration	Sunitinib: 'PBAC acknowledged there was a high clinical need for treatment for this rare type of tumour' http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2011-07/Sunitinib_SUTENT_Pfizer_PSD_6-8_2011-07_FINAL.pdf
	Equivalent therapy	Within consideration through cost-minimisation analysis	Ponatinib = dasatinib, nilotinib http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-11/files/ponatinib-psd-11-2014.pdf
Comparative effectiveness	Mortality impact	Overall survival (OS) within consideration	Olaparib: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/olaparib-psd-march-2016.pdf
		PFS considered secondary to OS	Pazopanib – 'PBAC accepted the claim of superior efficacy in PFS for pazopanib vs. BSC; however, considered the claim of superior efficacy in OS for pazopanib vs. BSC inappropriate as there was no statistically significant improvement on the OS depicted in the VEG110727 trial.' http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2013-07/pazopanib-psd-07-2013.pdf
	Individual impact	Considered within utility values derived from MAUI Disutility from adverse events are also considered	Draft revised PBAC guidelines: 'Ideally, report MAUI results as the difference (with 95% confidence interval) in the integrals between the mean utility weights obtained over time up to the median period of follow-up in the trial for the proposed medicine and its main comparator. This directly estimates the incremental QALYs gained. Also report the results analysed as specified in the trial protocol, particularly if the difference between integrals cannot be generated directly. If the scoring algorithm has not been derived from the general population in Australia, consider presenting sensitivity analyses using alternative scoring algorithms. If more than one MAUI has been used in the included study, compare the results from the two MAUIs. Discuss the interpretation of these QALY results. Assess the results against other outcomes measured in the trial. In particular, discuss the consistency or inconsistency with any concomitantly assessed disease-specific PRO measure and/or generic PRO measure.'

Domain	Topics	PBAC's position	Examples using public summary documents of cancer medicines or further descriptions
Comparative safety	Adverse events	Consider short and long term	Vismodegib: 'vismodegib is a toxic drug and several adverse drug reactions were reported to be very common (≥10%) in the clinical studies. Additionally, sonic hedgehog pathway inhibitors such as vismodegib have been demonstrated to be embryotoxic and/or teratogenic. Teratogenic effects include severe midline defects, missing digits, and other irreversible malformations. Vismodegib exposure through semen can also be embryotoxic and/or teratogenic.' http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/vismodegib-psd-march-2016.pdf
Comparative cost effectiveness	ICER	Within consideration	All submissions.
Budgetary impacts	Financial impacts projected over five years	Within consideration	Research suggests that financial impact was a significant predictor of the recommendation for reimbursement. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3582189/
Quality use of medicines	E.g. administration, reduced pill burden	Within Consideration	Blinatumomab: 'The current mechanisms and/or framework for provision of high cost PBS reimbursed chemotherapy through the outpatient setting would not be practical with blinatumomab nor would it provide quality use of medicine. According to the submission, monitoring for toxicities over the initial treatment periods should be conducted continuously' https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-11/files/blinatumomab-psd-november-2015.docx
Innovation	First in class	Not within consideration	
	Breakthrough	Only if considerable advantage in health outcomes	Nivolumab Pembrolizumab
Theoretical benefits	Logical deduction	Not considered unless supported by evidence	Everolimus – 'PBAC noted that the submission proposed that, based on the response rate of tumour volume and skin lesions seen in M2301, PBS listing of everolimus would decrease the frequency of MRIs, surgery and skin lesion treatments required and also lead to fewer inpatient and outpatient hospital visits for patients, therefore reducing the overall burden of TS on State and Territory health budgets. PBAC considered that these cost savings may have been overestimated in the submission and were not well supported. Also the submission did not allow for the costs associated with the occurrence of adverse events.' http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2013-04/everolimus-psd-04-2013.pdf;jsessionid=kon95ccgxtmk11uqjsi8cvyly/

Domain	Topics	PBAC's position	Examples using public summary documents of cancer medicines or further descriptions
Broader societal impacts	Productivity gains	No or limited (unless supported by evidence)	Pulmonary arterial hypertension (PAH) agents – 'PBAC noted the advice received from Pulmonary Hypertension Australia clarifying the burden of the discontinuation rules for PAH agents. PBAC specifically noted the advice that requirement for 6 monthly assessments is a burden on patients and results in a cost to the health system and lost productivity in the workplace. PBAC noted that this advice was supportive of the evidence provided in the submission.' http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-07/files/bosentan-epoprostenol-macitentan-july-2015.pdf

4.4 How can we make patient, clinician and community involvement more meaningful?

There was acknowledgement of the progress that has occurred to date in relation to involving consumers and clinicians in the HTA process. Many consumer groups noted that a consumer representative has been added to PBAC (although this occurred prior to 2014). This representative now makes contact with health consumer organisations and proactively engages them. Consumers noted that it is desirable for them to continue to make submissions to inform listing decisions.

One stakeholder praised PBAC for informing consumers groups about applications that were due for consideration at the next meeting, albeit with some frustration: ...but patients don't know to submit those personal stories, and therefore, they do not submit submissions when needed, they do not know they have the opportunity, although PBAC has been sending out information to consumer groups to let them know what is due to be considered. This is very much appreciated. All stakeholders, including government, acknowledged that while progress has been made, there is more to be done.

There are three groups of stakeholders, namely:

- Consumers (patients and their carers)
- Clinicians
- Community

While these groups do input into the process at points, it is unclear how this 'evidence' influences the eventual decision. The key challenge is making patient and clinician input evidence based and systematic, with clear roles with respect to priority setting as well as specific product appraisals.

Consumer involvement

Every consumer group used the word 'tokenistic' to describe current patient involvement. While the opportunity to participate in the process is appreciated, stakeholders want to better understand how this contributes to the outcome. Many stakeholders stated that they had made submissions in the past and were unsure how this evidence had contributed to the eventual decision. This was particularly perplexing in the cases were the decisions had been unfavourable. Consumers reported spending time and effort preparing submissions, yet they were uncertain of what content to include. It was reported that there is no standard template for submissions, meaning consumers were not sure what points to emphasise. One stakeholder said 'when consumers have been engaged as part of the submission process, they felt that they were not listened too. The consumers felt they did not have enough information about what information they were required to produce. Consumer involvement needs to be formally included in PBAC process, with clear descriptions of how this involvement is considered and what exactly this involvement entails.'

Many stakeholders recognised the complexity of the process, a process through which consumers navigate at vulnerable points in their lives. One stakeholder said that 'while there is a formal process for consumer submissions, the process can be overwhelming/daunting. Consumers need support to participate fully'. Consumers stated that they had never considered PBAC process prior to their illness. The registration and listing process requires stakeholders to understand scientific evidence, which at times can be beyond a laypersons understanding. Herein lies the challenge, in that the HTA process is evidence driven, with many consumers unsure how to present submissions that are appropriately informed by evidence. A further challenge was pointed out by several stakeholders, in that while anecdotal evidence is informative, it is not rigorous. Finding the balance between evidentiary requirements and case-by-case examples was a challenge that no group was able to recommend a solution for.

Patient input on disease and current treatments occurs to some degree and is more methodological on the part of some consumer groups versus others. One consumer group reported sending out patient surveys as a way of gathering data. Another stakeholder stated that 'you are unlikely to win unless your patient group is mobilised'.

To make consumer input more meaningful, a more systematic approach could be explored, potentially through a consumer liaison forum or engagement group to support patients, carers and survivor groups. This was recommended by PBAC, which indicated it would expand early engagement with patients and clinicians, but was currently resource constrained.

In addition, greater data collection for patient-reported outcomes on all patient-important outcomes through a system for RWE would also likely improve PBAC's ability to fully value patient and carer perspectives.

Clinician involvement

Several countries involve clinicians in the HTA process. On this point, one stakeholder identified that 'in Australia, no industry leaders or key opinion leader (KOL) clinicians are involved in the HTA process. NICE has its process – it does not go to a KOL, but industry in the United Kingdom involves KOLs in its economic submissions.' Four stakeholders also expressed a desire to enhance clinical involvement. One consumer group gave an example of a submission made by Peter MacCallum Cancer Centre during an unfavourable application process. It was unclear to that group how the Peter MacCallum Cancer Centre perspective was taken into consideration by PBAC, given their eminence in treating cancer. On the role of stakeholders in the process, one stakeholder stated that 'clinicians are caught between individual and population perspective. Clinicians want to be engaged, as long as we have the right mechanism. My view is that there are three important elements of the decision-making process: these are independence, data-driven and clinician led'.

Several stakeholders also suggested that notwithstanding the clinical expertise of PBAC members, it might be helpful given the complexity of the submissions and uncertainty of the evidence to increase the resourcing of cancer specialists to support PBAC. Given the evolving field of customised medicine and genomics, it was shared that some medicines require a particular specialisation when assessing efficacy. One stakeholder stated that 'it is extremely difficult to understand how PBAC committee can make a decision on highly complex drugs that act on a specific molecular target that people have spent 15 years working on'.

There may be increasing opportunities to engage with clinician panels more systematically, building on current engagement through MOGA. Increased transparency of the value of clinician input may also go a considerable way to supporting enhanced dialogue between PBAC and clinicians.

Community involvement

Currently, there is no formal mechanism for taking the broader community perspective into account. And one stakeholder questioned whether this was appropriate; 'as a community, do we want to fund these things? If you ask people they will probably say yes. The department knows that, and doesn't want to ask people for that reason.' The perception that communities tend to favour increased investment in cancer treatment is supported in research published by MacLeod, Harris and Mahal (2016), which found that the community prioritised cancer treatments, as long as these were 'effective', 'life-saving or improved quality of life'. The community were found to take a much broader perspective than individual patients, valuing 'significant innovation' and 'wider social benefit'.

Many stakeholder groups were aware of the Citizens Council that has been established in the United Kingdom and were receptive to establishing a similar mechanism in Australia. The importance of capturing societal perspectives was something that was endorsed by stakeholder groups and sponsors. Research by Linley and Hughes (2013) warned against policy based on assumptions of societal preferences. The research identified that inappropriate allocation of resource can result from assuming, rather than requesting, societal perspectives. For example, research found that society was more willing to pay for higher price medicines than policy makers have suspected[34]. Devlin and Lorgelly (2016) suggest that community involvement is essential in order to weight QALYs to reflect societal values.[35]

Given the substantial trade-offs involved, more systematic processes for engaging with the community are likely merited, to inform and justify policy directions.

4.5 Implications for policy

These key questions facing policy makers underscore the significant challenges facing government in navigating the challenges of cancer medicines. It highlights the government has made efforts in seeking to address the various concerns, though each policy provides an opportunity for learning and further policy developments.

There was a strong interest among the stakeholders engaged through this research that while the challenges of cancer need to be met, ideally policies could be designed in such a way that they could be readily extended to other medicines.

At the same time, while policy approaches could, optimally, be designed to meet a range of challenges, there are a number of aspects of cancer which merit an expeditious policy response: New mechanisms to cope with uncertainty in evidence and new approaches to valuing patient-important outcomes which may be undervalued by current QALY and MAUI instruments.

Critically, answering these questions and developing the next steps in policy response will require consultation with consumers, clinicians and the community at large: How much as a community we are willing to spend on cancer medicines, what innovations matter to patients and their carers. It will also require further investments in mechanisms, such as RWE, to begin to address some of the uncertainty inherent in cancer medicines valuation.

[34]Warren Linley and Dyfrig Hughes, 2013, Societal Views on NICE, Cancer Drugs Fund and Value Based Pricing Criteria for Prioritising Medicines: A Cross Sectional Survey of 4118 Adults in Great Britain, Health Economics, 22: 948–964
[35]Devlin, N & Lorgelly, P, 2016, QALYs as a measure of value in cancer, Journal of Cancer Policy, 76: 1-7

Chapter 5:

Constraints and common ground – stakeholder perspectives

In discussing the key challenges relating to access to cancer medicines in Australia, stakeholders discussed the constraints and perceived barriers which have limited progress in each of the four policy domains.

Major constraints to change consistently identified by stakeholders included a challenging budget context, a lack of data and system complexity, as well as competing policy priorities among stakeholders and a lack of consensus around the priorities for change. To this end, the report seeks to build that consensus by identifying the areas of common ground for policy change identified by stakeholders.

This chapter details the key barriers identified as well as the major areas of agreement.

5.1 Key constraints and perceived barriers to change

Broader fiscal challenges

While stakeholders debated potential policy opportunities, they uniformly acknowledged that the current fiscal environment is constrained and that public funds will be spread more thinly as the population grows and ages. The health portfolio in particular was identified as an area of concern for government. While reforms to other areas of the health portfolio are complex and difficult to implement, stakeholders noted that the PBS represents a programme where it is relatively easier to constrain expenditure growth.

A number of stakeholders explicitly commented that policy solutions will necessarily be informed by the overall financial sustainability of government. At the same time, there was a concern that decisions regarding the overall growth of the PBS relative to other programmes, in the context of fiscal austerity, be evidence based and supported by community engagement.

Within the context of funding constraints, several stakeholders further commented that the constraints not only applied to funding of the PBS in total, but also the funding of HTA processes and the Department of Health specifically. Multiple stakeholders noted the Department of Health budget was under pressure more broadly, and questioned how policy ideas, which proposed additional resourcing would be perceived and supported by government.

At least seven different stakeholders made comment that while it would be ideal to review PBAC processes, the funds to support a completely flexible process were also limited.

Cost was also mentioned by a number of stakeholders as a barrier to systems for RWE. A number of interviewees pointed to market failures that would prevent such a system being initiated without public funding and coordination. Others noted, however, that there was scope to recover some costs from industry over time and properly developed a system for RWE had the potential to substantially improve quality use of medicines and value for money over time.

System complexity and data constraints

A further challenge to progress was the complexity of the system and the numbers of stakeholders which must be engaged. Complexity challenges encompassed themes of data governance and a lack of data to support evaluations, as well as multiple and intersecting regulatory and reimbursement systems (TGA, PBAC and Medicare Services Advisory Committee (MSAC).

Competing priorities and lack of consensus, health literacy

Given the different perspectives held by various groups, other stakeholders highlighted the complexity of different patient, clinician and community priorities as a challenge in itself. One stakeholder summarised the challenge that discordance creates, being that: 'stakeholders are not on the same page and this presents a barrier for change. Different stakeholders put out that 'we need this' or that, and it sounds like 'we need everything'. We need to be more defined in terms of our key priorities across all stakeholders'.

Other stakeholders also highlighted that a lack of health literacy represented a significant barrier to change, particularly in the context of a highly technical set of challenges and a highly complex system. It was reported to be difficult to engage with the broader community on these issues as a result of this complexity, which represented a challenge to identifying clear priorities for the community and for government.

5.2 Finding the common ground

While numerous challenges were identified through consultation, there was also recognition that stakeholders shared common ground.

There was unequivocal consensus that there is a strong need for more RWE. All consumers groups recognised that without evidence, government decisions are impaired. The view was shared that this would not be able to fully resolve uncertainty and evidence challenges, but enhanced RWE would go a long way and enable all other change.

There was also strong consensus on the need for enhanced and more transparent patient and clinician input. This view was shared by consumers and government alike. A point of similarity here was that a lack of transparency was leading to distrust or scepticism between parties.

Finally, there was also consistent concern that registration and listing (reimbursement funding) should not rely on commercial forces alone, innovation in listing and funding approaches needs to address potential market failures. While there was strong consensus on the point of RWE and a need to make stakeholder participation more meaningful, as part of this solution, there was less consensus around what a new approach would look like.

The majority of stakeholders agreed that separate funding mechanisms for cancer medicines, such as the Cancer Drugs Fund in the United Kingdom, were undesirable in the Australian context.

The shared, theoretical ideal was for a system which could accelerate access in an evidence-based way, albeit expanding the evidence currently evaluated through current HTA processes, based on agreed criteria for what can be fast-tracked and robust mechanisms for data collection and evaluation.

Opportunities

Chapter 6:

International approaches: Insights and lessons for Australia

The challenges of high cost, specialised cancer medicines are not unique to Australia. All developed countries have been similarly engaging on these issues and seeking to develop appropriate policy responses which balance potential benefits, risks and costs with the goal of optimising sustainable access to care. There are ideas which can be adapted from the approaches which other countries have adopted in response to similar challenges.

This chapter highlights some new approaches which have been trialled overseas, which may provide insights for Australia.

6.1 International policy innovations: Overview

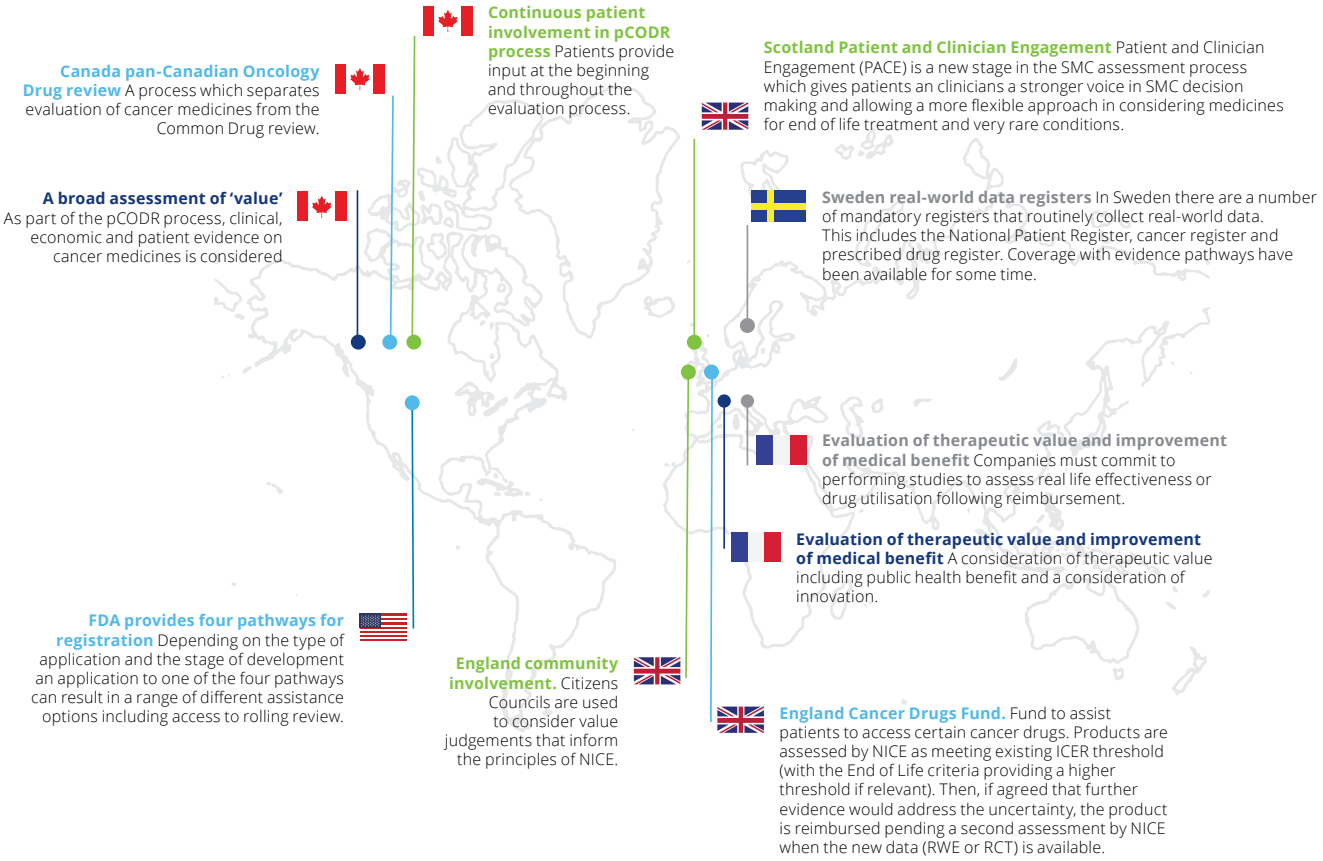
Figure 6.1 illustrates approaches which other governments have adopted that could potentially provide insights into further opportunities for Australia to pursue. Insights are categorised across the four domains of registration and reimbursement pathways; valuing cancer medicines; patient, clinician and community involvement; and, RWE.

Overall, the review of international approaches to funding cancer medicines highlighted that:

- **Governments are trialling new approaches for provisional registration and reimbursement pathways.** Most Organisation for Economic Co-operation and Development (OECD) governments have trialled an approach to fast-tracked registration and/or funding in response to the challenges presented by cancer medicines.
  - **Governments are dedicating resources to ensure procedural fairness.** A number of governments have introduced dedicated resources to enable more timely and effective evaluation of (cancer) medicines.
  - **Governments are implementing agreed criteria for fast tracking.** Internationally, governments have introduced criteria to balance the risks and benefits of early access (both registration and reimbursement) to medicines. In some instances, these expedited pathways are explicitly tied to cancer; in others, they are defined by criteria that are commonly met by cancer medicines though not explicitly limited to cancer medicines.
  - **Alternative submission processes, such as clinician-led submissions** or reviews can be viable mechanisms for dealing with market failures.
- **Governments are trialling new approaches to valuing patient and clinician perspectives.** The question of value has been considered in a number of countries. Different approaches have been adopted to integrating the consumer, community and clinician perspective of value into reimbursement decisions. Some countries have adopted novel, systematic approaches to define and value innovation in medicine.
- **Real World Evidence is essential.** A number of countries have implemented measures to systematically collect real-world data and processes to develop this data into evidence to support the decision-making life cycle. Commonly, where this has been successful, the effort is centralised and data is linked across a number of sources.

The following sections present key case studies into international policy innovations and key insights which Australia can derive from these reforms.

Figure 6.1: Major international policy innovations



6.2 International themes: New pathways for registration and reimbursement are needed

A number of governments have trialled approaches to fast-tracked registration and/or reimbursement. Two case studies are provided below to illustrate both the application and importance of criteria in facilitating separate registration/ reimbursement pathways.

United Kingdom

In 2010, the NHS England established the Cancer Drugs Fund to assist patients to access certain drugs before they receive approval from NICE. The fund subsidises drug treatments, including radiopharmaceuticals, for patients who have been unable to access a drug recommended by their oncologist.

The CDA noted in its submission that the fund continues to cover approximately 59 cancer drugs and during the five years it has been in existence has allowed more than 60,000 cancer patients to receive treatment they would have not have otherwise had access to.

From 26 July 2016, the fund has operated under renewed parameters that were put in place to ensure longer-term sustainability following higher than anticipated expenditure in its first years of operation. Indeed, in the two years to March 2015, the cost of the fund increased by 138%. The drivers of this cost increase were the number of patients supported by the fund and the increases in average cost of medication per patient.

Now, the fund operates on a fixed budget, under an expenditure control mechanism. It essentially operates as a 'managed access fund'. This mechanism aims to ensure that it never closes to new entrants and affords similar opportunities for off-label drugs to gain access to CDF. This is dependent on the drugs showing clinical promise and being assessed as likely to meet existing cost-effectiveness requirements (when further evidence is made available).

Canada

In 2007, Canada established the pan-Canadian Oncology Drug review (pCODR) process to separate the evaluation of cancer medicines from the common drug review (CDR) process. The pCODR makes recommendations to provincial cancer agencies and governments to guide cancer medicine funding decisions. In April 2014, pCODR was integrated into the Canadian Agency for Drug Technologies and Health (CADTH).

The purpose of the pCODR process is to bring consistency and clarity to the assessment of cancer drugs. Following approval by the national regulator, Health Canada, pCODR makes recommendations on the reimbursement of cancer medicines. Similar to Australia, a parallel regulatory and reimbursement submission process is available to sponsors to shorten the time between decisions.

Interestingly, Canada has also established a systematic approach to clinician-led submissions in addition to manufacturer-led submissions. This is a novel approach to the challenge of market failures arising from the challenges of data collection for less common cancers. For example, recently, a group of clinicians at Sunnybrook Medical Centre in Toronto prepared a submission for aldesleukin for in-transit metastases from melanoma. Reflecting their roles as clinicians, Cancer Care Ontario provided assistance to the submitters in the economic analysis and the application was approved by pCODR. This increased public funding for patients which would have otherwise not received subsidisation.

United States

The US FDA regulates the use of prescription medications in the United States. The FDA provides pharmaceutical companies with four pathways that 'get important new drugs to the patient earlier' to 'treat serious conditions[36] and fill an unmet medical need[37]'. These are aimed at:

- Expediting product development through:
  - Fast track designation
  - Breakthrough therapy designation
- Expediting registration through:
  - Accelerated approval
  - Priority review

Table 6.1: FDA criteria for expedited programmes for serious conditions[38]

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority review
	Designation	**Designation**	**Approval Pathway**	**Designation**
Qualifying criteria	• A drug that is intended to treat a serious condition AND non-clinical or clinical data demonstrate the potential to address unmet medical need. OR • A drug that has been designated as a qualified infectious.	• A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies.	• A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint).	• An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness. OR • Any supplement that proposes a labelling change pursuant to a report on a paediatric study under 505Ab. OR • An application for a drug that has been designated as a qualified infectious disease product. OR • Any application or supplement for a drug submitted with a priority review voucher.

Fast track designation works by facilitating the development and expediting the review of medications. A pharmaceutical company applies for fast track consideration when there is no therapy available or if 'a therapy may be potentially better than available therapy'.

The breakthrough therapy designation has been described as 'unique in that the FDA invests significant resources and time in numerous discussions with the sponsor and close co-operation in the development of the clinical programme'.

Depending on the type of application and the stage of development, an application to one of the four pathways can result in a range of different assistance options, including access to rolling review, access between pathways and increased access to FDA advice during the approvals process.

[36]A serious condition is defined by the FDA as '. . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one', FDA, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

[37]An unmet medical needs is defined by the FDA as '...an unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).', FDA, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

[38]http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Box 6.1: Key insights for Australia

The approach in these jurisdictions provides examples of how other countries have responded to emerging challenges presented by cancer medicines by developing tailored, differentiated pathways for access.

Clinician-led submissions and clinical panel reviews can provide a robust alternative to manufacturer-led submissions and address 'market failures' – that is, where there is minimal private incentive to pursue access pathways.

Findings in these jurisdictions suggest that there needs to be robust and transparent criteria to support provisional registration and listing to ensure the sustainability of dual/multi pathways.

6.3 International themes: different perspectives of 'value' can be combined with traditional evidence

As innovation becomes more nuanced, the modes for defining and valuing innovation have also evolved. A number of developed countries have moved to increasingly involve patient, carer and community evidence in both the development of national medicines policies as well as the appraisal of new products.

The approaches adopted in the United States, England, Scotland, Canada, Sweden and the United Kingdom are outlined briefly below.

United States

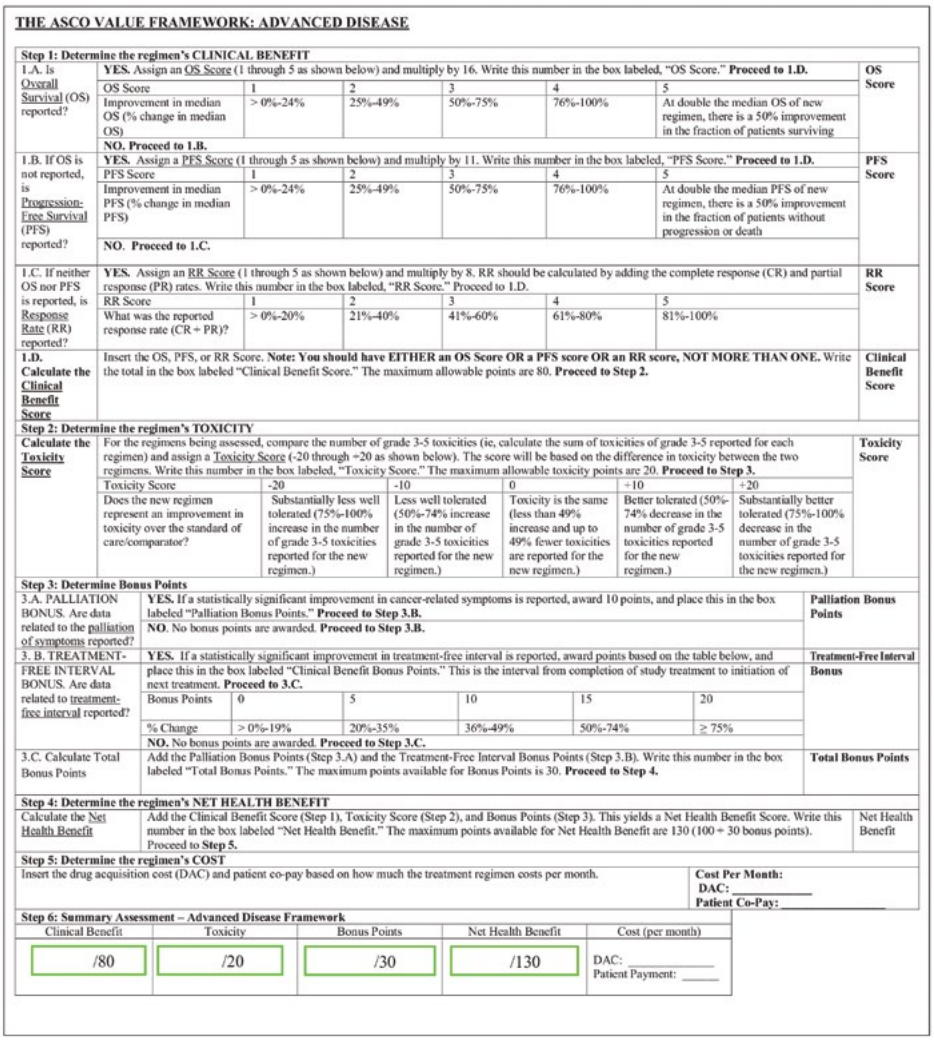
In 2013, the American Society of Clinical Oncology (ASCO) Board of Directors charged the Value in Cancer Care Task Force with developing a framework for comparing the relative clinical benefit, toxicity and cost of treatment in the medical oncology setting. At the clinical level, the goal of the ASCO Framework is to provide a standardised approach to assist physicians and patients in assessing the value of a new drug treatment for cancer as compared with one or several prevailing standards of care.[39]

The Institute of Medicine has identified six elements of quality health care delivery: safety, effectiveness, patient centeredness, timeliness, efficiency and equity. In 2015, ASCO created a scorecard of value in cancer care placing emphasis on the elements of clinical benefit (efficacy), toxicity (safety) and cost (efficiency). The ASCO Value Framework is a conceptual model that incorporates elements of clinical benefit, toxicity and symptom palliation as derived from a comparative clinical trial and combines these elements into a score termed the 'net health benefit' (NHB). The patient and clinician are able to modify the weight of any of the elements included in the value framework depending on personal preference/circumstances (for example, balancing benefits against toxicity). The final NHB therefore reflects the priorities that are most important to the patient and are arrived upon through guidance from the physician.

ASCO noted that while patient centeredness, timeliness of therapy and equity in access to cancer care are important, these are hard to objectively measure. In feedback received on the conceptual value framework, a substantial number of respondents commented on the lack of patient-reported outcomes in the value framework. The taskforce acknowledged the limitations associated with this omission, but noted that this reflects the absence of this data in many clinical trials. ASCO further noted that in its framework, clinical trials that demonstrate an improvement in the duration of treatment-free interval, Quality of Life or symptom palliation are eligible for 'bonus points' that add to the NHB.[40] ASCO recently acknowledged that the assessment of value of a cancer medicine should be dynamic and adapt to new medical information that may better inform its use. It further stated that this information cannot be regarded as definitive at the point of first regulatory approval.[41]

[39]Schipper, L.E. et al (2015) American Society of Clinical Oncology Statement: A conceptual Framework to Assess the Value of Cancer Treatment Options, Journal of Clinical Oncology
[40]Schipper, L.E. et al (2015) American Society of Clinical Oncology Statement: A conceptual Framework to Assess the Value of Cancer Treatment Options, Journal of Clinical Oncology; Schipper L.E. et al (2016) Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received, Journal of Clinical Oncology
[41]Schipper, L.E. et al (2015) American Society of Clinical Oncology Statement: A conceptual Framework to Assess the Value of Cancer Treatment Options, Journal of Clinical Oncology; Schipper L.E. et al (2016) Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received, Journal of Clinical Oncology

Figure 6.2: ASCO Value Framework



THE ASCO VALUE FRAMEWORK: ADVANCED DISEASE

Step 1: Determine the regimen's CLINICAL BENEFIT

1.A. Is Overall Survival (OS) reported?	**YES.** Assign an OS Score (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." **Proceed to 1.D.**						**OS Score**
	OS Score	1	2	3	4	5	
	Improvement in median OS (% change in median OS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median OS of new regimen, there is a 50% improvement in the fraction of patients surviving	
	NO. Proceed to 1.B.						
1.B. If OS is not reported, is Progression-Free Survival (PFS) reported?	**YES.** Assign a PFS Score (1 through 5 as shown below) and multiply by 11. Write this number in the box labeled, "PFS Score." **Proceed to 1.D.**						**PFS Score**
	PFS Score	1	2	3	4	5	
	Improvement in median PFS (% change in median PFS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median PFS of new regimen, there is a 50% improvement in the fraction of patients without progression or death	
	NO. Proceed to 1.C.						
1.C. If neither OS nor PFS is reported, is Response Rate (RR) reported?	**YES.** Assign an RR Score (1 through 5 as shown below) and multiply by 8. RR should be calculated by adding the complete response (CR) and partial response (PR) rates. Write this number in the box labeled, "RR Score." Proceed to 1.D.						**RR Score**
	RR Score	1	2	3	4	5	
	What was the reported response rate (CR + PR)?	> 0%-20%	21%-40%	41%-60%	61%-80%	81%-100%	
1.D. Calculate the Clinical Benefit Score	Insert the OS, PFS, or RR Score. **Note: You should have EITHER an OS Score OR a PFS score OR an RR score, NOT MORE THAN ONE.** Write the total in the box labeled "Clinical Benefit Score." The maximum allowable points are 80. **Proceed to Step 2.**						**Clinical Benefit Score**

Step 2: Determine the regimen's TOXICITY

Calculate the Toxicity Score	For the regimens being assessed, compare the number of grade 3-5 toxicities (ie, calculate the sum of toxicities of grade 3-5 reported for each regimen) and assign a Toxicity Score (-20 through +20 as shown below). The score will be based on the difference in toxicity between the two regimens. Write this number in the box labeled, "Toxicity Score." The maximum allowable toxicity points are 20. **Proceed to Step 3.**						**Toxicity Score**
	Toxicity Score	-20	-10	0	+10	+20	
	Does the new regimen represent an improvement in toxicity over the standard of care/comparator?	Substantially less well tolerated (75%-100% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Less well tolerated (50%-74% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Toxicity is the same (less than 49% increase and up to 49% fewer toxicities are reported for the new regimen.)	Better tolerated (50%-74% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	Substantially better tolerated (75%-100% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	

Step 3: Determine Bonus Points

3.A. PALLIATION BONUS. Are data related to the palliation of symptoms reported?	**YES.** If a statistically significant improvement in cancer-related symptoms is reported, award 10 points, and place this in the box labeled "Palliation Bonus Points." **Proceed to Step 3.B.**						**Palliation Bonus Points**
	NO. No bonus points are awarded. **Proceed to Step 3.B.**						
3. B. TREATMENT-FREE INTERVAL BONUS. Are data related to treatment-free interval reported?	**YES.** If a statistically significant improvement in treatment-free interval is reported, award points based on the table below, and place this in the box labeled "Clinical Benefit Bonus Points." This is the interval from completion of study treatment to initiation of next treatment. **Proceed to 3.C.**						**Treatment-Free Interval Bonus**
	Bonus Points	0	5	10	15	20	
	% Change	> 0%-19%	20%-35%	36%-49%	50%-74%	≥ 75%	
	NO. No bonus points are awarded. **Proceed to Step 3.C.**						
3.C. Calculate Total Bonus Points	Add the Palliation Bonus Points (Step 3.A) and the Treatment-Free Interval Bonus Points (Step 3.B). Write this number in the box labeled "Total Bonus Points." The maximum points available for Bonus Points is 30. **Proceed to Step 4.**						**Total Bonus Points**

Step 4: Determine the regimen's NET HEALTH BENEFIT

Calculate the Net Health Benefit	Add the Clinical Benefit Score (Step 1), Toxicity Score (Step 2), and Bonus Points (Step 3). This yields a Net Health Benefit Score. Write this number in the box labeled "Net Health Benefit." The maximum points available for Net Health Benefit are 130 (100 + 30 bonus points). Proceed to **Step 5.**	Net Health Benefit

Step 5: Determine the regimen's COST

Insert the drug acquisition cost (DAC) and patient co-pay based on how much the treatment regimen costs per month.	**Cost Per Month:** DAC: _____ Patient Co-Pay: _____

Step 6: Summary Assessment – Advanced Disease Framework

Clinical Benefit	Toxicity	Bonus Points	Net Health Benefit	Cost (per month)
/80	/20	/30	/130	DAC: _____ Patient Payment: _____

Canada

As part of the pCODR process, clinical advice on cancer medicines is comprehensively considered. The pCODR takes into account evidence from a number of sources, including patient groups, drug manufacturers, clinician-based tumour groups, and the pCODR Provincial Advisory Group. These groups are required to register with pCODR in order to submit and contribute to the drug submission[42]. The process has been developed over time to ensure transparent and rigorous engagement of stakeholders throughout the assessment.

Clinical guidance panels and an economic guidance panel are established with membership that varies depending on the type of cancer treated by the drug under review.

Clinical guidance panels include clinicians from across Canada who are experts in managing specific cancers. Members of these panels describe in detail, for the expert review committee, the disease and the context for the disease – treatment options, symptomatology, and usual standard of care. This creates the context in which the evaluation of evidence from clinical trials is made. The panel provides a recommendation regarding benefits and harms – this includes consideration of outcomes broader than overall survival (OS) – including PFS and ease of symptom burden. A recent example of a medicine that was recommended for reimbursement by pCODR on patient outcome improvement alone is ruxolitinib, which was shown to have a profound impact on disease symptom – shrinkage of splenomegaly, of reduction in pain but there was limited available evidence on OS or PFS.

Guidance for providing clinician input, including a clinician input template is available. Registered clinician information is collected by CADTH and becomes input to the pCODR review. A clinical guidance report is prepared for consideration by the pCODR expert review committee. After the

initial recommendation is made available, stakeholders have a further opportunity to provide feedback.

A pilot initiative to increase opportunities for clinicians to provide input and feedback and participate in the pCODR process is currently underway. The expanded initiative will enhance opportunities for clinicians to provide value-added information, not only for the pCODR programme but also for the larger discussion of drug funding decisions in Canada.

pCODR provides two opportunities for patients to participate in the review process. Registered patient advocacy groups (or individuals in the absence of an advocacy group existing) can provide written comments at the following two points:

- Early in the process for use in preparation of reports used by the pCODR expert review committee (pERC) to develop its recommendations;
- Later in the review after pERC makes its initial recommendation – providing feedback on this initial recommendation. Feedback on the initial recommendation can only be made if the stakeholder first provided input in the early stages of the review.[43]

England

The system in England has invested significant resources to help patients and has a wide range of means for interacting with patient advocates. This includes having a 12-person team whose sole – purpose is to work with patient advocacy organisations.

In addition, NICE has an established Citizen's Council, whereby patient advocates are represented on their appraisal committee and involved in the appraisal process.

An example of the deliberations of the Citizen's Council was reviewed as part of this report. The Citizen's Council[44] was asked to respond to the following question:

Is there a preference to save the life of people in imminent danger of dying instead of:

a. Improving the life of other people whose lives are not in immediate danger? or
b. Saving the lives of many people in the future through disease prevention programmes (such as treating high blood pressure or lowering blood cholesterol levels)?

The 2006 decision was that the phrase Rule of Rescue should be changed to 'exceptional case'. The majority of the group held the view that saving those in imminent danger of dying was preferable to saving lives of those not in imminent danger (i.e. preventative or in non-life-threatening circumstances).

Scotland

Patient and Clinician Engagement (PACE) is a new stage in the Scottish Medicines Consortium (SMC) assessment process. This stage gives patients and clinicians a stronger voice in SMC decision making and allows for a more flexible approach in considering medicines for end-of-life treatment and very rare conditions.[45]

The PACE process involves a meeting between patient representatives and health care professionals. The aim of this meeting is to facilitate discussion on the benefits of a medicine, with a focus on how it impacts the patient's quality of life. The view is that this information is not aptly captured in the conventional assessment process. The SMC has emphasised this systematic engagement of consumers and clinician groups is aimed at ensuring procedural fairness and equity across diseases and tumour types.

Invitees to the PACE meeting include:

1. Representatives of the patient and carer voice (nominated by Scottish Cancer Coalition, Rare Diseases UK or Genetic Alliance – up to three representatives per meeting)
2. Clinical experts (nominated by clinical networks – up to three representatives per meeting)
3. SMC Patient and Public Involvement Group member
4. SMC Public Involvement Team member
5. SMC New Drugs Committee member

Sweden

In Sweden, the Board of Pharmaceutical Benefits (TLV) is an autonomous national authority that evaluates drugs for reimbursement and inclusion in the Pharmacy Benefit Scheme. The assessment of drugs is initiated by the manufacturer, who provides a submission to the TLV. Drugs are assessed based on their cost effectiveness, using a cost-per-QALY threshold of approximately between SEK 700,000 and SEK 1 million. As part of the evaluation, a societal perspective is also taken which takes into account productivity costs. The principle of solidarity and equity is also incorporated into value assessments, and the threshold varies with, for example, disease severity. Since 2009, the New Treatment Council, a working group within the Swedish Association of Local Authorities, was introduced to make access to drugs across the country more equal. Using a societal perspective, in theory, means that Sweden may value certain health care interventions more highly than other countries, if, for example, they lead to productivity gains.[46]

[42]https://www.cadth.ca/pcodr/registration#clinician
[43]https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-patient-engagement-guide.pdf
[44]NICE Citizens Council Report, Rule of Rescue, January 2006
[45]https://www.scottishmedicines.org.uk/files/PACE/PACE_factsheet_FINAL.pdf
[46]OHE and IHE Consulting Report, Improving Efficiency and Resource Allocation in Future Cancer Care, September 2016

Box 6.2: Key insights for Australia

Defining the value of cancer medicines – particularly the dimensions of patient centric value, timeliness and equity – is difficult . The inclusion of patient, clinician and community perspectives can support reimbursement authorities in arriving at appropriate value judgments.

A dedicated clinical panel (and a similar patient panel) can ensure cancer submissions do not disadvantage normal HTA reviews, such as those undertaken by PBAC and can – at least in part – address challenges in evaluating uncertain evidence.

Increasingly, the assessment of medications requires intricate value judgments and trade-offs which should – where funded by the public purse – be informed by public values. Well-designed community forums can be used to elicit these values, and greater evidence for patient-important outcomes and wider economic benefits are considered in some circumstances.

6.4 International themes: Real-world evidence as enabling infrastructure for change

A number of countries have implemented measures to systematically collect real-world data to inform evidence development and processes to integrate this data into decision making. Commonly, where this has been successful, the effort is centralised and data is linked across a number of sources. Michael Drummond in 2015 highlighted that the need for, and successful implementation of, systems for RWE will rely on:

- Uncertainty about the clinical or economic benefits of the technology, and where this uncertainty can be reduced by further investigation
- Outcomes (clinical or economic) can be suitably defined and measured
- Convincing evidence on effectiveness can be generated from observational studies
- Data collection timelines are sufficiently lengthy to generate the relevant information but of defined duration to inform the ongoing reimbursement and value decision
- The data collection and analysis requirements can be easily implemented and are affordable
- The potential reimbursement outcomes that could result from the data collection and analysis are clearly defined.

Funding schemes, such as risk-sharing arrangements and coverage with evidence development are contingent upon robust RWE collection. These schemes operate on the basis that access is conditional on comprehensive, post-market evidence collection. The rate of reimbursement is based on the results of this data collection.

Several examples of countries that have successfully implemented real-world evidence in medicine access programmes are provided below.

Sweden

All Nordic countries have had national and population-based health registers that collect mandatory patient-level information in place since the 1950s. There are a number of mandatory registers in Sweden that routinely collect 'real-world' data[47]. This includes the National Patient (hospital discharge) Register, cancer registry and prescribed drug register as well as specific disease registers. The Nordic region has also universally adopted electronic medical records in its health care systems providing a strong source for Real World Evidence.

Coverage with evidence development pathways have been available in Sweden for some time. Medicines sponsors are often required to collect real-world observational data to inform these decisions. During recent years, the Swedish reimbursement agency has increasingly used conditional approvals. In general, these require post-approval evidence to be presented to the authority within a two-to three-year time frame after the reimbursement approval.[48] Most commonly, these conditional approvals are implemented to inform uncertainty around appropriate usage of the medicine in terms of the patient population or uncertainties around the cost-effectiveness estimates presented at initial reimbursement .[49]

The Swedish reimbursement agency also routinely conducts cost-effectiveness reviews of medicines to assess the ongoing reimbursement status of the medicine. This includes evaluating post-market evidence generated on the medicine as it is used at a population level.

[47]Office of Health Economics 2015, 'Data Governance Arrangements foo Real-World Evidence', London.

France

France introduced cost effectiveness into its HTA process in January 2014. This was initiated in response to increasing health care expenditure, a perceived mismatch between prices and clinical outcomes and increasing medicine prices resulting from personalised medicines and increased R&D costs.[50] Outcomes of both the clinical and cost-effectiveness evaluations are used to negotiate prices of medicines with manufacturers.

Access to the French drug market is increasingly being driven by data on the comparative effectiveness and cost effectiveness of medicines, and there is an increased role for post-marketing studies. These can include safety and efficacy studies, or specific follow-up of potential risks via a patient registry.[51] Other post-marketing studies that could be required include monitoring of the real use of the medicines. Financial penalties are in some instances imposed on pharmaceutical companies if they do not report information that could impact the benefit risk assessment of the medicine.

There are two main databases in France — one of reimbursed care in the outpatient setting (SNIIRAM) and the other on stays in public and private hospitals (PMSI) — these databases were linked in 2006.[52] These databases are utilised to facilitate systematic collection of post-market evidence.

United Kingdom

NHS England has established the Systemic Anti-Cancer Therapy (SACT) dataset. This mandatory system collects data about anti-cancer therapy activity from all NHS England chemotherapy providers. The database relates to all cancer patients, both adult and paediatric, in acute inpatient, day-case and outpatient settings and delivery in the community. Notably, the database captures information related to treatment for all solid and haematological malignancies, including patients in clinical trials.

SACT aims to:

- Develop a view of patterns of systemic anti-cancer therapy, including chemotherapy, administered across England.
- Assist patients and their clinical teams in choosing appropriate treatments and care.
- Improve patient care by helping supporting rational clinical decision making to improve patient care.[53]

United States

The US FDA also has a recent history of using real-world data to support post-market surveillance initiatives.[54] In 2007, the FDA developed a system for post-market risk identification and analysis of medicines, the Sentinel Initiative. A pilot, the Mini-Sentinel, was launched in 2009 to test the feasibility of analysing health care information from a variety of sources and using this to inform and improve decision-making. An evaluation of this pilot showed that the programme resulted in two medicine label changes, three safety communications and no product withdrawals or recalls.[55] However, the pilot concluded that there was still considerable opportunity to leverage real-world evidence further and clinical trial evidence remains the predominant method to support drug approval.

The Medicaid Drug Utilization review (DUR) Program also utilises RWE to monitor patient safety, appropriate medicine use and expenditure. This is enabled through state-administered utilization management tools and systems that interface with CMS' medicaid management information systems.[56] Annually, States are required to report on their prescribing habits, cost savings generated from their DUR programmes and their programme's operations, including adoption of new innovative DUR practices.

A national cancer register exists in the United States and is driven by the National Cancer Institute. The Surveillance, Epidemiology, and End Results Program aims to produce information on cancer statistics, with the intention to reduce the burden of cancer among the US Population. Data is collected from various locations and sources throughout the United States. This includes drawing on information from population-based cancer registries[57].

Box 6.3: Key insights for Australia

Surveyed countries have typically devised Real World Evidence by linking existing registries.

Realising the theoretical potential of real-world data requires a clear definition of the questions to be answered, supported by appropriate systems for data collection and governance.

[48]http://www.ispor.org/news/articles/Sept-Oct2013/IC_Vol19-5_Payers_and_Regulators_Raise_the_Bar_in_Europe_Consequences_for_Using_Research_in_Real_World_Evidence.pdf
[49]http://www.ispor.org/news/articles/Sept-Oct2013/IC_Vol19-5_Payers_and_Regulators_Raise_the_Bar_in_Europe_Consequences_for_Using_Research_in_Real_World_Evidence.pdf
[50]http://social.eyeforpharma.com/evidence/new-era-reimbursement-france
[51]Remuzat et al. 2013, 'New drug regulations in France: what are the impacts on market access?', Journal for Market Access and Health Policy, vol. 1, p. 1-9.
[52]https://www.imshealth.com/files/web/Global/Services/P&MA_2015.pdf
[53]http://www.chemodataset.nhs.uk/home
[54]http://cdn.bipartisanpolicy.org/wp-content/uploads/2016/06/BPC-Health-Innovation-Safe-Effective-Cures.pdf
[55]http://cdn.bipartisanpolicy.org/wp-content/uploads/2016/06/BPC-Health-Innovation-Safe-Effective-Cures.pdf
[56]https://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/drug-utilization-review.html
[57]http://seer.cancer.gov/registries/list.html

Chapter 7:

Positive ideas for change

Australian patients, clinicians, communities and governments all share a common goal to sustainably improve timely access to medicines. There was strong support for the PBS and the principles on which it was developed, and a consistent concern that government take the steps needed to strengthen the PBS as medicine technologies continue to evolve.

This chapter presents policy opportunities identified by stakeholders across the four policy domains. It briefly describes the policy, the rationale for its implementation, potential questions or unintended consequences that would need to be addressed, stakeholder consensus, and potential next steps.

The major opportunities for government and the community, on which stakeholders to this report were in strong agreement, include:

- Making Real World Evidence a reality
- Making patient, clinician and consumer involvement meaningful through formalised evidence requirements, enhanced engagement and systematic evidence development through RWE systems
- Implementing a system for provisional listing on the PBS to match recent government recommendations for provisional registration.

7.1 Policy opportunities: overview

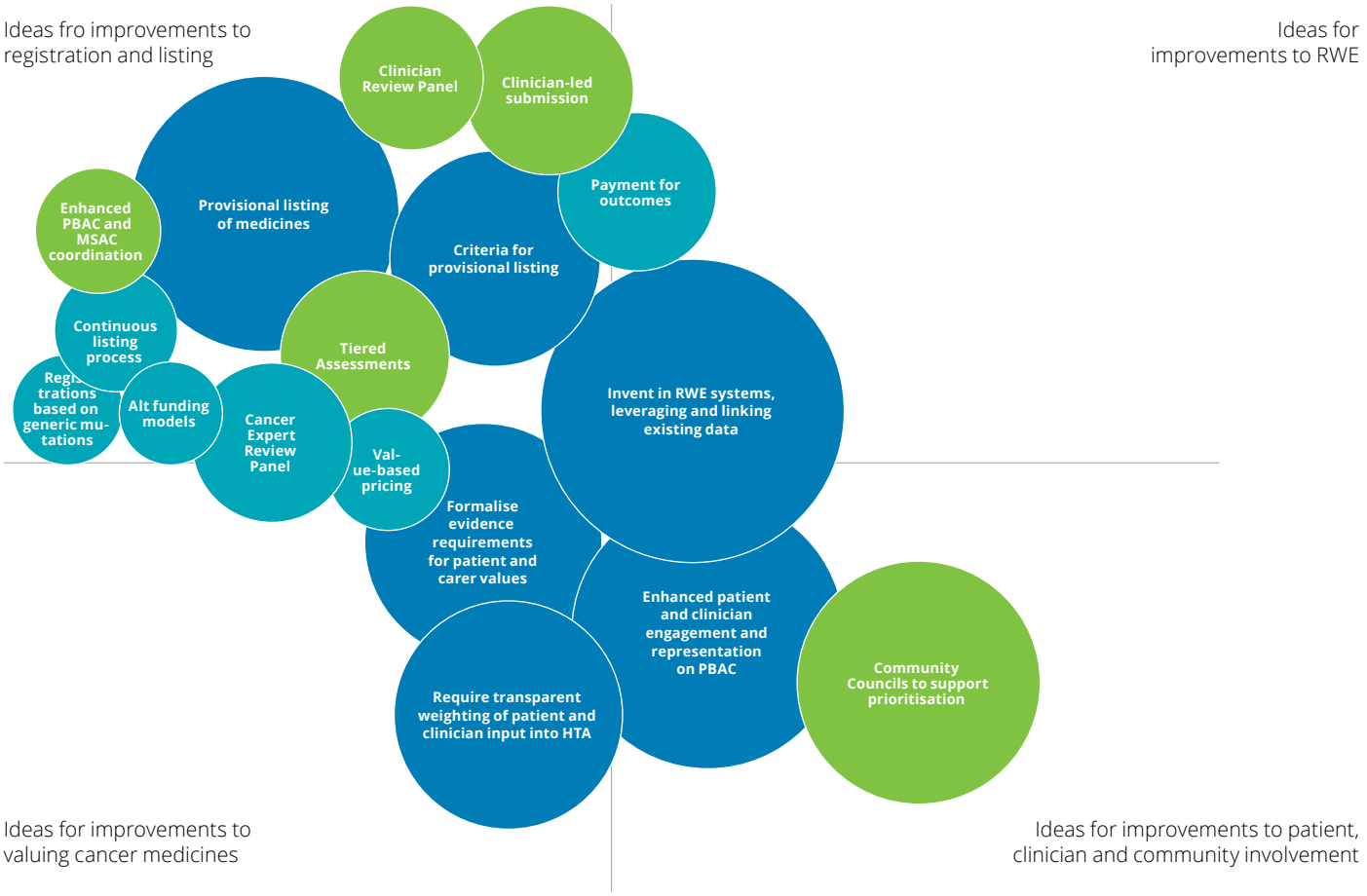
Building on the recommendations of the Senate Inquiry for a comprehensive review of the PBS, the feasibility of a National Cancer Registry and other data collection mechanisms, a wide range of potential policy ideas were identified through stakeholder consultations which have the potential to address continued challenges to timely and equitable access to medicines. Figure 7.1 shows the range of options identified and the level of consensus of stakeholders around the priority.

As can be seen in Figure 7.1, effectively all stakeholders identified investments in Real World Evidence as a major priority for government, directly addressing challenges arising from uncertainty and enabling a range of subsequent policy changes to be implemented more effectively.

Similarly, while acknowledging the efforts of government to expand the input of patients and clinicians into HTA processes, there was a consistent call for additional policy changes to make patient, clinician and community input more meaningful and transparent. This included expanded patient and clinician representation on PBAC and enhanced engagement through a Consumer Engagement Group. It also included community input into priority setting and transparent weighting of clinician and patient input into HTA processes.

Other major ideas centred around options for improving early access through the PBS without compromising on the evidence-based principles on which the PBS is based. Real-world evidence was seen as a significant enabler for many policy reforms to be effectively implemented. There was consistent support for the concept of clear criteria for provisional listing, as part of potentially a wider scheme for supporting early access.

Figure 7.1: Ideas for change



Note: The larger the circle the greater the number of stakeholders who identified a policy or initiative as a priority for government. Circles which are smaller indicate the idea was identified less often. Circles which are turquoise rather than green indicate there was a significant difference of opinion of the best policy option. Blue circles indicate the highest priorities by domain.

7.2 Ideas to improve RWE

There was unequivocal consensus that there is a strong need for more RWE. All consumers groups recognised that without evidence, government decisions are impaired. Moreover, RWE has the potential to enable innovative new approaches to regulation and reimbursement to be implemented over time.

Real-world data come in a range of forms, including electronic health records, disease registries, clinical quality registries, pharmacy data, observational data and patient-level surveys.

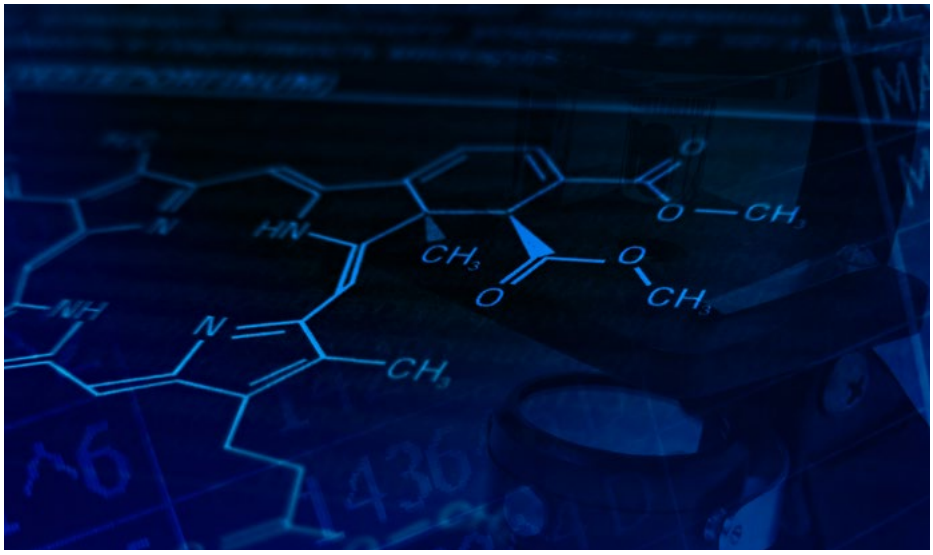
To date, evidence of real-world outcomes has been collected on an ad hoc basis, required at times through MES, but not always. The ad hoc and duplicative approach to data collection was reported by stakeholders as a deterrent to using the MES, and resulted in efficiency losses through lack of a coordinated approach.

Academic and clinician stakeholders provided guidance with regard to the information that would need to be collected and reported to support the development of system of RWE able to support HTA processes; these data included:

- Disease stage and progression, including overall survival, progression free survival, disease-free survival, response rates and time to treat outcomes
- Treatment history and care plans
- Genetics, biomarkers, and family history
- Patient reported quality of life and wellness, including ability to return to work and the impact on carers.

Critically, much of the data that is needed to enable a more dynamic PBS system is already collected:

- Every state has a cancer registry, which collects information according to the national minimum dataset
- Every hospital in Australia must report a patient's cancer diagnosis to the relevant state-based registry, including disease stage
- Clinical quality registries have been developed in a number of states
- Clinicians document a patient's genetic profile and family history, treatment plan, and disease progression. Genetic profiling is increasing to support models of care and better patient outcomes.



The key challenges (Figure 7.2) are that:

- The data sits on multiple systems that are not fully connected
- Outcomes data is not systematically collected
- Current approaches fail to 'follow the patient' across the 'continuum of care' and 'continuum of life' journeys.

Therefore, what is needed is investment in the systems to link these datasets and improve the systematic reporting of patient health outcomes (Figure 7.3). There are some state-based and health services data linkage but it is patchy across state-based and individual health services.

Figure 7.2: Current data collection – disconnected and incomplete

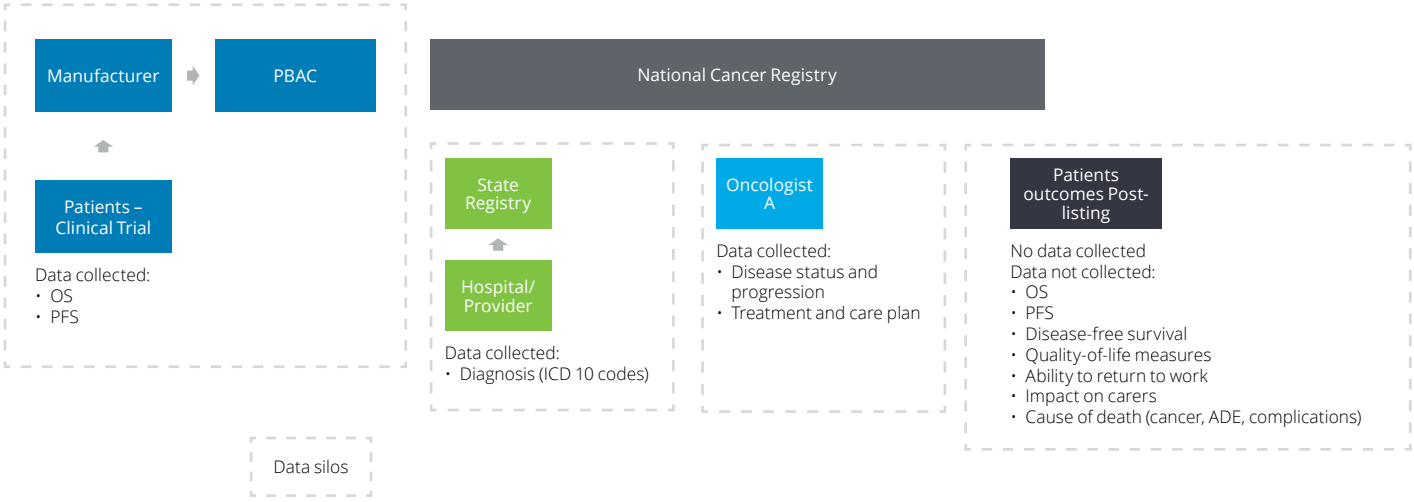
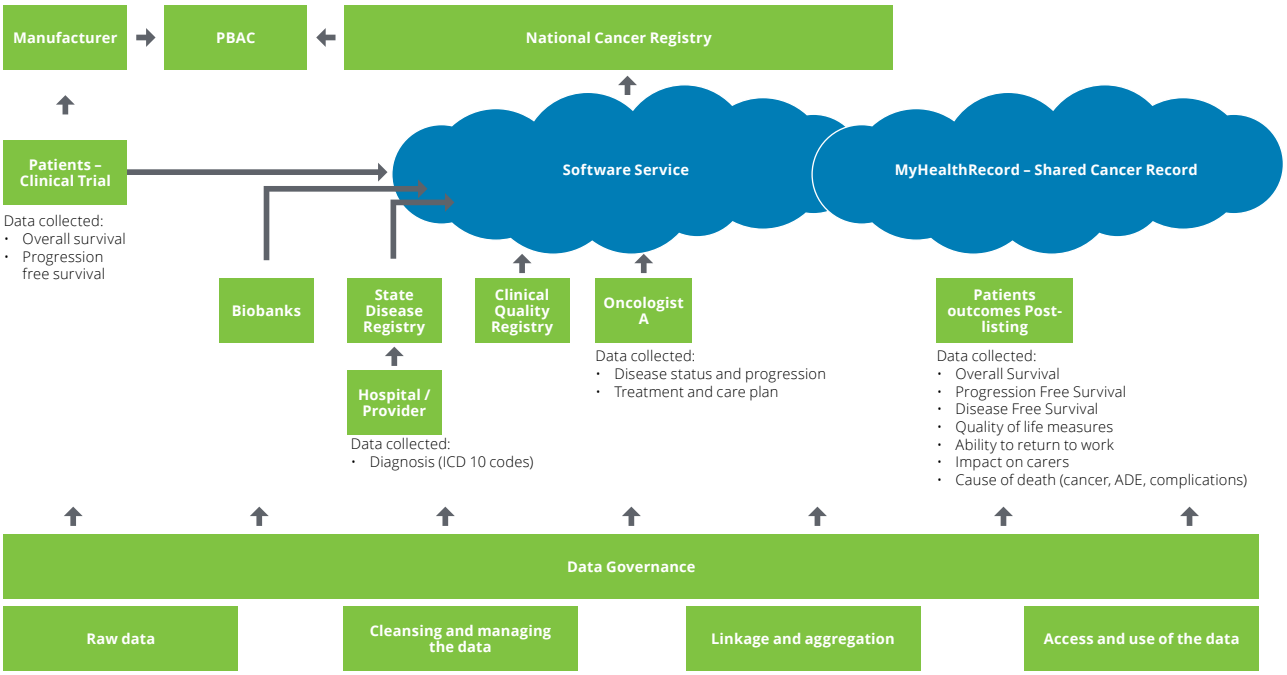


Figure 7.3: A system for RWE: linking datasets and reporting patient outcomes



Historically, this would require significant investment in infrastructure to achieve linkage to all data sets and enable a unified clinical record.

Today, however, new ICT technologies have the potential to virtually connect these systems through software service layers. Technologies like clinical and research information exchange platforms will allow clinicians and researchers to share de-identified data to enable clinical and evidence-based research to support better patient care outcomes. Moreover, the MyHealth Record provides the foundational infrastructure to follow the patient from diagnosis through clinical trials, hospitals and specialist care settings.

A system for RWE will support government to allocate scarce funding to the highest and best use, making the PBS more sustainable over the longer term and improving outcomes for patients and their families.

Developing a system for RWE to support PBAC listing and reimbursement decisions would involve:

- The development of a shared cancer record for cancer patients, potentially leveraging the MyHealth Record functionality
- A software service to link source systems and report data into a National Cancer Registry
- A clinician portal for clinical staff involved in delivery of care to cancer patients
- Tools to enhance the delivery of multi-disciplinary meetings by tumour streams
- A research portal for cancer researchers to access research information and gain access to collaboration tools
- A data governance model and data profile to enable implementation of a cancer research information exchange.

Technically, these solutions are available and able to be implemented. There are solutions available and in use in Australia, such as for the Prostate Clinical Quality Registry, and overseas, such as in the international examples cited in Chapter 6. If government wanted to invest in RWE, it would not need to develop these solutions; rather government would need to 'shop around' for these solutions. For example, the Moffitt Centre in the United States has implemented a system for RWE development; Box 7.1 provides a summary of international approaches which have been implemented.

Box 7.1: Solutions to support a system for Real World Evidence – Moffitt Cancer Center

The complexities of modern oncology care require a team-based approach to deliver quality management. Having a shared record of patient reported outcomes, which is quantitative, validated, easily captured and standardized, has been recognised as having the potential to add huge value.

Multiple electronic patient reported outcome systems, often using electronic tablets, have been created and are beginning to be widely deployed (ASCO 2016). The Patient Care Monitor is one example of a system that has evolved into a comprehensive patient engagement platform, with a complete review of systems survey and capabilities for mobile health usage. Recent clinical trials have established electronic patient reported outcome systems as an effective method of providing information, which aids improved patient outcomes, including reduced health resource utilization and longer time on therapy. Electronic patient reported outcomes are also increasingly incorporated into clinical trials, where they can provide more thorough reporting of adverse events than can be captured by alternative methods.

Tampa, Fla.-based Moffitt Cancer Center has deployed its own private enterprise network across its hospital network to link medical imaging, electronic health records (EHRs) and molecular medicine to facilitate collaboration between physicians, researchers and clinicians.

Moffitt Cancer Center served nearly 350,000 outpatient visits in 2015 and employs more than 5,000 people. The organization is deploying the private network in order to support data-intensive applications such as advanced medical imaging, electronic health records and molecular medicine. The network will also improve efficiency and help eliminate costs associated with multiple, disparate networks.

By deploying this platform, Moffitt aims to provide its medical staff assured access to patients' updated EHRs and the ability to collaborate on the various cancer research work being conducted.

Financially, the cost of the technical systems does not represent a significant barrier. Stakeholder consultations indicated the software services could be expected to cost in the order of $10 million, and the cost of operating the Prostate Cancer Registry was indicated to cost in the order of $1 million per annum. Other stakeholders estimated the total cost to establish a system for data collection and reporting might cost in the order of $20 million. These are high-level estimates, which would require a full feasibility study and business case to properly cost; nevertheless, in the context of the PBS, which involves funding of $10 billion per annum, the investment to bring these capabilities online represents a modest investment, with the potential to enable significant efficiency gains to be realised.

It is important to acknowledge that implementing a system such as this will pose several challenges that will need to be overcome. Three of the biggest challenges to implementing RWE as is being proposed here will be stakeholder management and alignment, privacy and security and gaining agreement on a set of data standards underpinning the solution.

The undertaking of a feasibility review to flesh out issues like these and to understand what technology solutions and databases could be leveraged would appear to be a sensible next step.

A well-defined system would be expected to deliver returns on investment through improved quality use of medicines and broader health system efficiency gains.

The major challenges relate to agreeing a model for data governance, which would provide for the ethical use of personal data to support the broader public interest, and covers:

- Raw data collection
- Cleansing and managing the data
- Linkage and aggregation
- Access and use of the data.

This challenge is not unique to Australia, however, and a number of countries are tackling this issue as a priority to realise significant gains in efficiency and effectiveness of health care investments. A recent report in the UK for the Office for Health Economics developed a number of principles for the implementation of good RWE data governance, including recommendations for optimal ownership and funding arrangements.

In implementing a system for real-world health outcomes, government could also leverage this initiative to develop a more robust evidence base with respect to the value of innovations in cancer medicines which are not directly measured by existing QALY tools, including overall patient values, wellness and ability to return to work.

Table 7.1: Summary – policy ideas for RWE

Policy idea	Description	Rationale	Key questions or unintended consequences
Invest in system for Real World Evidence	Invest in software systems to enable linkage of existing databases and more systematic reporting of patient outcomes as part of the development of a National Cancer Registry which reports to PBAC.	RWE would substantially improve outcomes against National Medicines Policy (NMP) objectives including better Quality Use of Medicines (QUM), affordability through improved allocative efficiency and supporting more timely access to medicines.	How can data governance challenges be resolved effectively?
Develop criteria and data fields for patient-reported health outcomes to inform PBAC valuations of medicines innovations	Invest in tool to gather RWE and patient reported outcomes, including information regarding patient values and wellness and broader societal impacts.	Would improve on systematic collection of information, which would support current individual patient perspectives.	What options exist to leverage the MyHealthRecord as a system for data collection?

7.3 Ideas to improve registration and funding processes

Registration and funding was an area where good progress has been made, particularly given the recent adoption of the Sansom review recommendations for additional registration pathways. To this end, the policy opportunities for government identified by stakeholders were more strongly centred around potential ideas to improve (reduce) the time to achieve listing. Several stakeholders noted that accelerated registration may in fact have the unintended consequence of increasing bottlenecks at the listing phase without some sort of policy response at the listing phase.

A range of policy options were canvassed by stakeholders, with the most significant proposed changes being:

- Introduce provisional listing to match provisional registration, including
  - Agree criteria for provisional listing to support earlier access which balances concerns for safety and evidence with accelerated access and
  - Formalise and systematically collect patient, clinician and community RWE requirements
- Introduce and support opportunities for clinician-led-submissions and/or clinician review panels to address potential market failures
- Create an expert review panel for cancer medicines
- Require transparent weighting of criteria considered, including patient, clinician and community input
- Implement a tiered and/or continuous listing review process
- New approaches to funding.

Implement a policy for provisional listing of medicines on the PBS

This recommendation builds on the existing managed access scheme, with the potential to broaden the remit of such a scheme. There is a clear desire for a revised approach to the current processes for supporting accelerated listing on the PBS. Stakeholders were strongly in consensus that the revised approach should not accelerate medicines in a way that compromised PBS principles for safety or evidence, but that allowed for provisional funding with evidence development. This reflected concerns that if a medicine was not listed on the PBS it was effectively out of reach for most Australians.

A system for provisional listing would be based on:

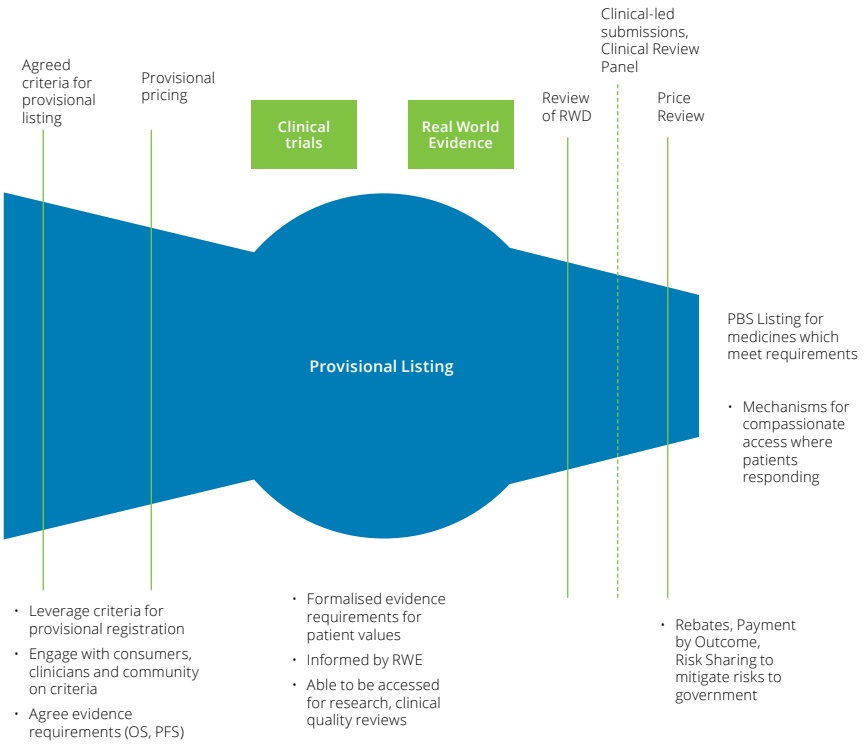
- Agreed criteria for which medicines would be eligible for provisional listing, ideally building on the criteria developed for provisional registration
- Agreed indications and restrictions based on tumour type or genetic mutations to allow for evidence development without compromising patient safety

- Agreed requirements for evidence development, including ongoing clinical trials as well as RWE (see Figure 7.3 above) reporting by patients, clinicians and sponsors – this includes the use of RWE and ongoing RCT data as it becomes available
- Agreed processes for price reviews and/or rebates based on patient outcomes
- Some form of mechanisms for grandfathering access for patients that are found to be responding to the therapy in the event that the medicine does not prove to be efficacious on a population basis. It is acknowledged that this may be problematic under the direction of the National Health Act, but there may be alternative funding mechanisms to support continued access which could be explored if this is not able to be addressed, such as a compassionate access programme or supporting programme.

In designing a policy for provisional listing, all stakeholders were concerned that speed of access not compromise defined thresholds for risk and safety. Some stakeholders noted that minimum standards of acceptable risk need to be clearly articulated.

The potential benefits of a provisional listing approach would be greater transparency and predictability of process for provisional listing, and most importantly, the potential for patients to access medicines earlier. This would directly address patient concerns for delays in access due to challenges of uncertainty in evidence development and could be used as a formal mechanism to support clinician-led submissions or clinical reviews of medicines for rare or less common cancers.

Figure 7.4: Related policy ideas to support provisional listing



The key challenge to the implementation of such a scheme would be the definition of criteria for provisional listing, which would likely require community, consumer and clinician engagement. Clearly, government would have a concern that the scheme would not be used such that everyone could 'jump the queue', and some discussion would be needed to determine how narrow the scope of the system might be in the first instance, building on the recent experience of MES for some medicines.

Support opportunities for clinician led-submissions to address potential market failures

This policy would build on the approach implemented in Canada where in addition to manufacturer-led submissions to PBAC there would be the expanded option for clinician or patient groups to bring forward submissions to PBAC. This would serve to address patient, clinician and community concerns around cancer sub-types which may see substantially delayed access or no submissions to PBAC based on a lack of commercial incentives.

Currently, clinicians and patients generally lack access to data in order to bring these submissions to government. There have been some instances of patient groups bringing submissions, such as Rare Cancers Australia putting forward submissions for vorinostat and romidepsin with funding support from manufacturers. Depending on the implementation of a provisional listing scheme and associated data reporting requirements, there may be opportunities for clinicians or patient groups to access these data more frequently and prepare a submission.

Key challenges to this model, however, relate to legislative and regulatory requirements. For example, one stakeholder indicated there were potential legal barriers to implementing this change, including indemnity requirements that must be fulfilled by manufacturers and requirements for guarantee of supply by manufacturers. Other stakeholders

questioned whether this was the best use of clinicians' time; ideally, the model would be developed in such a way as to support clinician groups through a panel of suppliers, similar to the pCODR experience. To this end, the government could establish a panel of providers which would be able to support clinician and/or patient groups to analyse the data in support of a submission. These providers could be engaged on a 'low bono' or public interest basis as part of supporting the broader community.

Implement clinician review panel

Similar to the above idea, it may also be possible for PBAC to establish a clinical review panel, similar to the mechanisms hospitals have in place to review whether scarce hospital funding should be allocated to a high cost patient therapy. In this model, as RWE was developed, it could be possible that a submission was not made; rather, as evidence was developed through provisional listing the clinician panel would be asked to review the evidence and recommend a potential extension to a new indication.

A dedicated clinical panel can ensure cancer submissions do not distract from normal drug reviews and can – at least in part – address challenges in evaluating uncertain evidence.

Implement an expert cancer review committee

Since its establishment in 1953, government has relied on independent advice from PBAC to evaluate new medicines for listing on the PBS. PBAC brings together the highest levels of clinical, health economic and pharmacological expertise.

It was noted in the stakeholder consultations, however, that the review of complex cancer submissions are 'resource intensive and time consuming', which divert resources from other PBAC submissions. This is similar to overseas experience; in Canada, for example, the challenges of cancer medicines in terms of the volume and complexity of applications, had led its regulatory authority to implement a dedicated expert cancer review committee, distinct from its normal CDR processes. Canadian stakeholders indicated this supported a more effective review of complex and uncertain evidence, and ensured both cancer medicines and other drug reviews were not disadvantaged. Australia could seek to introduce a similar approach, which may be reviewed over time as technologies evolve, to determine its ongoing need.

Tiered, continuous and coordinated assessment processes

Currently PBAC accepts 'major' and 'minor' submissions, as well as submissions to list general equivalents and resubmissions. Major submissions were reported in the Senate Inquiry to take between four and six months to prepare.

Similar to submissions to the Senate Inquiry, stakeholders indicated that alternative processes should be explored to expedite the submission process. This would be in addition to provisional listing processes, by creating further tiering of submissions to better allocate scarce resources across HTA processes. This would potentially allow for far reduced reviews of less complex submissions such that resources could be redirected to more complex, high-risk medicines, or those with a higher clinical need.

Greater tiering of evidence has been implemented by most of Australia's international peers.[58]

A redirection of resources could support the introduction of a provisional listing process or a dedicated cancer review panel, and moreover may be needed regardless due to the pace of innovation and potential number of submissions.

In addition, as part of a move to implement new approaches to HTA processes, PBAC and MSAC could move to adopt a continuous listing process rather than meeting three and four times per year, respectively. This could support a more dynamic listing process and evidence review between the two bodies and reduce the time between registration and listing, particularly for complex submissions with a high clinical need. This would require a full review of the operations of both PBAC and MSAC to design a more coordinated approach.

Transparent weighting of patient, clinician and community evidence alongside clinical considerations

Public summary documents have been recognised as an important step forward in supporting increased access.

Improving transparency by making the majority of the documents publically available and allowing an effective discussion in the community of the real benefits, harms and cost of the products, as well as reducing the number of resubmissions, is in everyone's interest.

A number of patient groups and clinicians reported they were uncertain about the extent to which PBAC valued their input. For example, one stakeholder said, 'There is one line in the PSD saying 'Patient input was valued'. What does that mean?' Government stakeholders similarly indicated more systematic evidence was needed, and that while engagement with patients and clinicians was occurring, it could be helpful if it were more transparent.

[58]OHE/IHE, Improving Efficiency and Resource Allocation in Future Cancer Care

PBAC could implement 'scorecards' to illustrate the types of evidence which were considered and taken into consideration with respect to listing and funding considerations. This includes increased explanation of the usefulness of inputs from patients and clinicians. Importantly, formal weighting would not necessarily need to be implemented, which might impair PBAC's judgment; rather, the scorecard could be used to report the ways in which different evidence was considered as part of the overall decision.

This was consistent with the recommendations of PBAC to the Senate Inquiry; namely that 'processes should be developed to generate plain language presentations for lay and professional audiences in the benefits, harms and costs of new drugs'.

New funding models

Overall, new funding models were not tabled as a significant priority by stakeholders, such as reforms for value-based pricing or more systematic pricing by outcomes. There may be merit in these ideas, but these policies could be implemented over time, as enabling infrastructure is established.

Summary of registration and listing policy ideas

Table 7.2: Summary – policy ideas for registration and listing processes

Policy idea	Description	Rationale	Key questions or unintended consequences
Criteria for provisional listing	This policy would see the development of clear criteria for the provisional listing of medicines on the PBS, mirroring provisional registration.	This would provide transparent guidance to patients, clinicians, the community and sponsors regarding the conditions under which accelerated access would be considered.	What would be the appropriate role of patients, clinicians and the community to inform these criteria?
Provisional listing of cancer medicines	For medicines that met the provisional listing criteria, PBAC could seek to fast-track access to these medicines by patients. Depending on the level of uncertainty in evidence which would be tolerated, real-world data collection could be established through an umbrella trial or a shared cancer record as part of a system for RWE collection. A system for provisional listing would need mechanisms for price revisions and potentially rebates if the medicine was not as effective as expected, or if it was more effective than expected. There would also need to be mechanisms in place to agree whether a patient could continue to receive treatment if they had been shown to respond to the therapy.	The development of provisional listing would improve timely access to medicines, with mechanisms built in place to ensure continued sustainability of the system and strong cost controls by government.	How would the government deal with medicines which proved not cost effective?
Clinician-led submissions	Similar to international approaches, this model would allow for designated groups to bring forward submissions in addition to manufacturer-led submissions	This would address potential market failures where a lack of commercial incentives delays evidence development and/or submissions by the private sector for smaller patient populations. This would improve timeliness and equity of access to medicines.	What legislative or regulatory changes might need to be effected to implement clinician-led submissions? What processes would need to be implemented or agreed with manufacturers to guarantee supply?

Policy idea	Description	Rationale	Key questions or unintended consequences
Establish a clinician review panel for new indications based on RWE	The clinical review panel would review RWE collected through provisional listing to determine whether restrictions should be relaxed or indications extended without a sponsor submission.	This would address potential market failures where a lack of commercial incentives delays evidence development and/or submissions by the private sector for smaller patient populations. This would improve timeliness and equity of access to medicines.	What legislative or regulatory changes might need to be effected to implement an extension of indications? What processes would need to be implemented or agreed with manufacturers to guarantee supply?
Implement a dedicated cancer expert review panel to support cancer medicines review	Similar to the approach adopted in Canada, this would involve a panel of experts dedicated to the review of cancer medicines, including challenges related to uncertainty in evidence and the valuation of innovations and impact on patient and carer wellness.	While this is a 'cancer specific' policy, the goal would be to lessen the resource burden on PBAC and enable more timely evaluation of all medicines. This reflects stakeholder feedback that the evaluation of cancer medicines for MES was resource intensive and time consuming relative to other submissions.	How would this be resourced and how would the recommendations of cancer expert review be integrated into wider HTA processes?
Implement tiered assessment processes	Introduce greater tiering of submissions to reduce the complexity of applications for less complex submissions and increase the availability of resources for higher complexity and clinical need applications, including potentially provisional listings.	This could improve the timeliness of access to cancer medicines, and implemented appropriately, reduce regulatory red tape and improve overall system efficiency.	How could PBAC mitigate any risks associated with lower complexity applications to ensure the community was not exposed to unacceptable risks?
Allow for continuous listing processes	Allow for continuous submission and listing processes for PBAC and MSAC rather than periodic applications per year (3p.a. for PBAC, 4p.a. for MSAC)	This could improve the timeliness of access to cancer medicines, and implemented appropriately, reduce regulatory red tape and improve overall system efficiency.	Are there efficiencies to be realised through a redesigned regulatory approach? Would a continuous listing process have adverse impacts on the total administrative cost to government?
Require transparent valuation of patient, clinician and consumer input in HTA processes	At the conclusion of each PSD, there could be a standard scorecard of the full range of evidence considered with an indication of the extent to which the evidence influenced listing and funding decisions.	This would improve patient, clinician and community confidence in PSD and help consumers to understand the trade-offs being considered by government in the listing of new medicines	Should weighting of input also be transparent, and if so, does this dilute the ability for regulators to exercise judgement?

7.4 Ideas to improve approaches to the valuation of cancer medicines

Over the past decade, there has been rapid growth in the cost of cancer care as a whole. At the same time, there have been substantial incremental improvements in cancer outcomes, with cancer potentially transitioning from a terminal to a chronic illness.

Policy makers, regulators, payers and clinicians are tasked everyday with evaluating the trade-offs between alternative therapies, and ensuring patients have access to treatments with meaningful health benefits in a resource-limited environment.

Ideally, HTA processes would value all patient-important outcomes. The limits of current tools to measure patient values have been discussed and were a significant concern for stakeholders, particularly clinicians and patient groups.

Stakeholders expressed an interest in formalising requirements for patient-reported outcomes, to better measure aspects of patient wellness, including psychological impacts, and an ability to return to work. Collecting patient reported outcomes would allow clinicians and funders to longitudinally monitor a patient's tolerance of therapy, response to therapy, and symptoms that result from the underlying disease or treatment. This would allow for a more comprehensive evaluation of the interplay between treatment and a more comprehensive 'global' quality of life.

Empowering and requiring patients to self-report through the development of a shared cancer record as part of a system for RWE would provide for more systematic evidence development.

In addition to formalising evidence requirements for patient values of innovations, a dedicated expert cancer medicines review committee could support the valuation of cancer medicines which are subject to greater uncertainty.

Summary of valuing medicines policy ideas

Table 7.3: Summary – policy ideas for valuing cancer medicines

Policy idea	Description	Rationale	Key questions or unintended consequences
Formalise and systematise, using RWE, evidence development for individual quality of life, symptom burden and wellness and broader societal/ productivity impacts	Develop agreed evidence requirements and support the data collection for patient-important innovations	This policy idea acknowledges the limitations of some QALY and MAUI tools, and would seek to develop additional systematic data to improve allocative and dynamic efficiency of the PBS, ensuring innovations which patients value are appropriately valued by HTA processes	How can this data be cost effectively collected and analysed? Who bears the responsibility for data collection and/or analysis?
Implement a dedicated cancer expert review panel to support cancer medicines review	Similar to the approach adopted in Canada, this would involve a panel of experts dedicated to the review of cancer medicines, including challenges related to uncertainty in evidence and the valuation of innovations and impact on patient and carer wellness.	While this is a 'cancer specific' policy, the goal would be to lessen the resource burden on PBAC and enable more timely evaluation of all medicines. This reflects stakeholder feedback that the evaluation of cancer medicines for MES was resource intensive and time consuming relative to other submissions.	How would this be resourced and how would the recommendations of cancer expert review be integrated into wider HTA processes?

7.5 Ideas to improve approaches to patient, clinician and consumer involvement

Good progress has been made in better understanding the important role that patients and clinicians have to play in HTA processes. Important steps with respect to consumer representation, increasing time for engagement with consumers and greater engagement with clinicians through groups such as MOGA have been important steps by PBAC and the government to more fully engage with patients and clinicians. All stakeholders acknowledged this provided a sound platform for further policy reforms; key opportunities for increasing patient, clinician and community involvement include:

- Introduce a community council or citizens' jury to inform priority setting
- Introduce a consumer engagement group
- Expand patient, clinician and community representation on PBAC
- Require transparent valuation of patient, clinician and consumer input in HTA processes
- Clinician-led submissions
- Formalise and systematise, using RWE, evidence development for individual quality of life, symptom burden and wellness and broader societal/ productivity impacts
- Invest in education on PBAC processes and health literacy
- Expand opportunities for sponsors/ submitting group to meet with PBAC ahead of submissions to agree evidence.

Introduce a Community Council or Citizens' Jury

Increasingly, the assessment of medications requires intricate value judgments and trade-offs which should – where funded by the public purse – be informed by public values. Well-designed community forums can be used to elicit these values.

These decision-making frameworks have been considered in other countries, including the UK, Canada and the Netherlands. Community Councils can be used to determine overall willingness to pay, inform criteria for provisional listing on the PBS and approaches to the valuation of innovations.

Indeed, PBAC, in its submission to the Senate Inquiry recommended community consultation regarding the value placed by society on very small improvements in survival or progression free survival for patients with cancer.

Introduce a Consumer Engagement Group

The need for HTA processes arises from information asymmetries which make it difficult for manufacturers and patients to interact in the way they might normally do, in a 'perfectly functioning' market. Because information regarding the costs and benefits of medicines are highly technical, HTA processes support consumers by engaging with manufacturers on these issues and aggregating public demand to arrive at a better outcome for patients and the community.

Increasingly, however, as technologies become more personalised and regulatory systems evolve, best practice regulation involves a strong consumer voice and meaningful engagement in regulatory processes by consumers.

With respect to medicines HTA, a number of governments have instituted some form of community support for engagement in HTA processes, including notably Canada and Scotland. These processes have been implemented to improve equity and meaningfulness of engagement across patient conditions with the explicit goal of ensuring less-resourced consumers are not disadvantaged.

The need to support patient and consumer input into HTA processes is particularly important in medicines policy. This was noted by a significant number of stakeholders, who reflected there are 'more mature' and 'more mobilised' patient groups, which are able to engage with PBAC processes and 'see greater rates of success' and 'less mature' or 'less resourced' groups, often with cancers that experience lower rates of survival, which do not know how to engage the system and/or what data PBAC is seeking.

This idea is in line with PBAC's proposal to the Senate Inquiry for 'increased resources to PBAC and Secretariat' to allow additional stakeholder consultation during evaluation. PBAC noted that currently stakeholder meetings are generally held after an initial consideration due in the main to lack of time and resources, and that 'early consultation on defining the clinical place of new treatments as well as defining patient-relevant outcomes would assist both PBAC … and the sponsors.'

The Consumer Engagement Group would engage with consumers, clinicians and sponsors ahead of submissions to understand the potential benefits of the medicine and agree evidence requirements by all stakeholders. This would then support a comprehensive value assessment of the proposed medicine in a way that all stakeholders could understand. The chief challenge to implementing this recommendation is the need for additional resources, which given broader budget constraints may be difficult to implement. An alternative 'leaner' approach, to investment in additional FTE would be a 'liaison forum' approach which could provide for greater information sharing across community groups. This would likely not fully address concerns among consumers for engagement with PBAC on products ahead of PBAC's initial assessment.

Expand patient, carer, clinician and community perspectives on PBAC

All stakeholders uniformly acknowledged that the current PBAC consumer representative was a 'good start' to patient involvement, and that building on the lessons for this, more could be done to formalise the roles of the patient, carer, clinician and community perspectives on PBAC.

PBAC could provide for at least two representatives of consumer (patient and clinician) perspectives, and a broader community representative to provide broader guidance with respect to product appraisals, supported by evidence from Community Councils. This would serve to formalise perspectives on patient and carer perspectives on product appraisal as distinct from broader community priorities.

In addition, there is an opportunity to build on current engagement with clinicians to more formally, systematically and transparently gather clinician evidence and report the impact of that evidence on PBAC recommendations through more transparent valuation of patient, clinician and community perspectives. This could be done through earlier engagement, as suggested by PBAC in its Senate Inquiry submission, which is not currently undertaken due to resource constraints. A more transparent feedback mechanism would also likely support robust clinician engagement.

Support health literacy campaigns

A number of stakeholders highlighted that government could also invest in media to help consumers better engage in the debate, which might go some way to improving community understanding and expectations for what can be delivered and why government has made a decision. This would support a policy to improve transparency in PBAC decisions.

Table 7.4: Summary – policy ideas for increasing patient, clinician and community involvement

Policy idea	Description	Rationale	Key questions or unintended consequences
Introduce Community Council to inform priority setting	Establish a Community Council to advise PBAC and government on priority setting, evidence requirements for patient values and systematic policy reforms, building on UK, Canada and Netherlands experience.	A Community Council would provide for an evidence-based approach to priority setting, and willingness to pay for different types of innovations, helping to shape specific policies with respect to 'what the community and individuals can afford' and 'what equity of access' means to the community.	How can the government ensure a fully balanced perspective across competing budget priorities?
Introduce a Consumer Engagement Group	Establish a liaison forum or small support group, which supports patients and patient groups to more meaningfully engage with PBAC.	There is currently variable understanding of PBAC processes and requirements among patients and patient groups, which risks inequitable and variable levels of engagement with PBAC by patients and patient groups.	What would be the most appropriate model for a consumer engagement group: a liaison forum or dedicated resources? Would equity risks be sufficiently managed in a liaison forum?
Expand patient, clinician and community representation on PBAC	Increase the number of patient, clinician and community representatives on PBAC with formalised roles regarding the different perspectives needed to inform decision making (product appraisal and priority setting).	There is currently one consumer representation. This single person is intended to bring the full views of the community and patients to PBAC discussion. An increase in the representation of patients and community on PBAC, informed by Community Councils, would provide for a more formalised set of perspectives to HTA processes.	What would be the best way to formally define the roles and responsibilities of each representative? How could the community be confident the consumer and community perspectives are appropriately valued?
Require transparent valuation of patient, clinician and consumer input in HTA processes	At the conclusion of each PSD, there could be a standard scorecard of the full range of evidence considered with an indication of the extent to which the evidence influenced listing and funding decisions.	This would improve patient, clinician and community confidence in PSD and help consumers to understand the trade-offs being considered by government in the listing of new medicines.	Should weighting of input also be transparent, and if so, does this dilute the ability for regulators to exercise judgment?

Policy idea	Description	Rationale	Key questions or unintended consequences
Clinician-led submissions	Similar to international approaches, this model would allow for designated groups to bring forward submissions in addition to manufacturer-led submissions.	This would address potential market failures where a lack of commercial incentives delays evidence development and/or submissions by the private sector for smaller patient populations. This would improve timeliness and equity of access to medicines.	What legislative or regulatory changes might need to be effected to implement clinician-led submissions? What processes would need to be implemented or agreed with manufacturers to guarantee supply?
Formalise and systematise, using RWE, evidence development for individual quality of life, symptom burden and wellness and broader societal/ productivity impacts	Develop agreed evidence requirements and support the data collection for patient-important innovations.	This policy idea acknowledges the limitations of some QALY and MAUI tools, and would seek to develop additional systematic data to improve allocative and dynamic efficiency of the PBS, ensuring innovations, which patients value, are appropriately valued by HTA processes.	How can this data be cost effectively collected and analysed? Who bears the responsibility for data collection and/or analysis?
Invest in education on PBAC processes and health literacy	Engage with patient, clinician and community groups on HTA processes and reforms, including the types of evidence to be considered and how to engage with the HTA process.	Improved equity of access and quality use of medicines through improved engagement with HTA processes.	How can an information campaign be systematically delivered?
Expand opportunities for sponsors/submitting group to meet with PBAC ahead of submissions to agree evidence	Engage with patient, clinician and industry sponsors to agree the evidence needed to support an appropriate valuation of the innovations with each medicine.	Improved equity of access and quality use of medicines through improved engagement with HTA processes.	How can independence and conflicts of interest be managed? How can government engage with patients on the clinical benefits and trade-offs of a technology?

7.6 Moving forward: Key priorities for government

On balance, the range of opportunities identified suggests there are feasible policy solutions, which strongly align to the principles of the National Medicines Policy and government statements for reducing regulatory red tape.

Critically, these policies are not 'cancer specific' initiatives. Rather, these initiatives provide a foundation for the modernisation of the PBS in a way that addresses the challenges, which are acutely felt by cancer patients and their families today, but which could be extended to other classes of medicines as needed.

Major opportunities exist to invest in the enabling infrastructure to bring RWE into common practice. What is needed is investment in the data linkage layer to bring multiple and disparate systems together, and to leverage precedent investments in the MyHealth Record into a tool for more systematically gathering patient-reported outcomes.

A system for RWE could go some way to addressing uncertainties in evidence development for cancer medicines. Combined with formalised approaches for systematic evidence development of patient-important outcomes, this could support the appropriate valuation of new medicines and ensure that the innovations, which patients and the community value, are valued by the HTA system.

Leveraging this enabling infrastructure, there is strong consensus for a policy for provisional listing, based on:

- Agreed criteria for provisional listing
- Agreed processes for the review of provisionally listed medicines prices based on RWE and/or anticipated forthcoming RCT data
- Some mechanisms for enabling continued access where patients have been shown to respond and meet agreed criteria, if possible under current legislation or supporting programmes

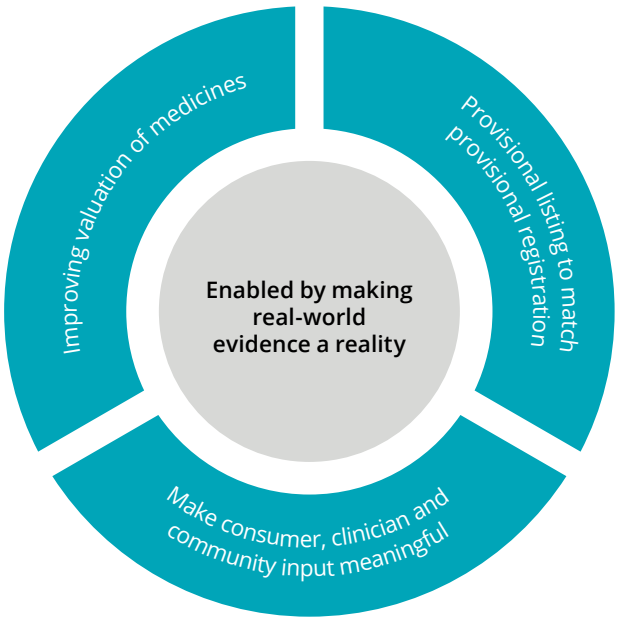
To inform the implementation of systems for RWE and provisional listing, government could review current evidence requirements for cancer medicines. This would be focused on approaches to best value the potential 'long tail' of benefits associated with cancer medicines, as well as the systematic collection and evidence requirements for patient-important outcomes to be considered by the HTA processes.

Complementing this, government should also consider options for a systematic reform to patient, clinician and community involvement, including key actions for:

- Mechanisms for systematic evidence development regarding community priorities for PBS funding and policy settings, such as a Community Council
- A consumer engagement group to support equitable engagement with HTA processes
- Formalisation and enhanced transparency of patient and community values in HTA processes
- Opportunities for clinician-led submissions and/or a clinician review panel to address lack of commercial incentives for submissions for less common cancers

These policy ideas enjoyed strong stakeholder consensus as major priorities for change.

Ideas for change – priorities



Appendix A: Consultation brief

Deloitte.
Access Economics

Access to cancer medicines in Australia

Consultation brief

Consultation Brief

Thank you for agreeing to meet with us to discuss our work considering the future state of access to cancer medicines in Australia. This consultation brief provides an overview of topics we would like to discuss.

Access to cancer medicines: The challenges

Australia has one of the world's highest age-standardised incidence of cancer. Australia, however, also enjoys cancer survival outcomes that are on par with the best in the world. That said, cancer patients and clinicians have expressed concern that they experience delays and expenses in accessing new cancer drugs or existing drugs that are not covered by the Pharmaceutical Benefits Scheme.

The environment in which access and funding decisions are made has been changing. Tightening budget constraints and the increasing average cost of new cancer medicines place financial pressure on the public purse. At the same time, some stakeholders have expressed concern that traditional methods of appraisal may undervalue innovation and improvements to patients and their carers, risking delays in access. The voice of the patient and the public has gained increasing significance as the trade-offs become both more expensive and less tangible.

Calls for reform and recommendations for change

These challenges have been acknowledged and analysed across several recent pieces of work.

In 2015, the Senate Community Affairs Reference Committee released a report on the availability of new, innovative and specialist cancer drugs in Australia. The report called for further action to progress the cancer policy agenda, including a comprehensive review of:

- Registration and listing pathways for medicines in Australia, as well as HTA processes, including evidence requirements and patient, clinician and community involvement
- Options for real-world data collection, including linking existing databases, post-market surveillance and capturing off-label use
- The feasibility of a National Cancer Registry.

There has also been recommendations for reforms to registration and listing pathways by the Sansom Review in 2015. Patient groups have also called for reform to the use of managed entry schemes and greater patient and clinician involvement in HTA processes.

Objectives of this report

Given the recommendations of the Senate Inquiry and other recent reviews, it is timely to take stock of Australia's progress, and identify policy options to move the cancer agenda forward, for the benefit of patients, their families and the wider community.

Deloitte Access Economics has been engaged by the Medicines Australia Oncology Industry Taskforce to:

- Examine the recommendations of the Senate Inquiry, in light recent policy developments in Australia and overseas
- Identify and discuss proposals for further system reforms.

The work will be informed by consultation with stakeholders from health consumer organisations, government and payers, peak public health and clinical bodies, peak industry bodies and international experts.

Issues for consideration

The project seeks to explore the key issues identified by the 2015 Senate Inquiry for further policy reform:

- **Registration and funding pathways**: what reforms are needed to the pathways and processes by which medicines are evaluated and funded?
- **Value of cancer medicines**: what evidence and perspectives should be considered in determining the value of a medicine and its reimbursed price?
- **Formalising consumer, clinician, community and sponsor involvement**: what is the appropriate role of these stakeholders in determining the value of innovations and prioritsation of funding?
- **Real world evidence**: what options exist for incorporating real world evidence in enabling decision making, and what is needed to make these options happen?

In our consultation we would like to understand your perspectives with respect to:

- **Progress** in policy development
- **Barriers** to change
- **Options** for reform.

Consultation themes and key questions

1 Registration and funding pathways

Registration

Registration of medicines

- Q **What changes to the current registration pathways would you suggest for improving timely access to new cancer medicines that are considered innovative or 'breakthrough', or for existing medicines seeking expansion of indications?**
- Q **What have been the barriers to implementation of the recommended reforms?**

Listing / funding

Listing and funding decisions

- Q **What options exist for tiering listing/funding decisions?**
- Q **What progress has been made?**
- Q **International examples?**
- Q **What are the major barriers to change?**

2 Real world evidence

Real world evidence

Use of real world evidence (RWE) of safety, efficacy and cost-effectiveness derived from analysis of data collected outside of clinical trials

- Q **What progress has been made to increase the use of RWE in Australia and overseas?**
- Q **How could RWE be used to improve access?**
- Q **What are the barriers to incorporating this?**

Enabling Infrastructure

Data collection mechanisms, establishing a National Registry of Cancer Medicines, technical and administrative support

- Q **What are the other enablers which need to be set in place to enable change?**
- Q **Are there any international examples of best practice to be considered?**
- Q **What are the barriers to change?**

3 Value of cancer medicines

Valuing innovation

Valuing and incentivising innovative research

- Q **In addition to effectiveness, safety, cost effectiveness and budgetary impact, what other considerations/criteria should be considered in assessing the value of cancer medicines?**
- Q **Should there be any reforms to the HTA processes for different types of listings? If so, how?**

Sustainability

Ensuring the long-term sustainability of the PBS

- Q **How will the system ensure that decisions take into account financial sustainability (as well as community preferences)?**

4 Formalising patient, community, sponsor and clinician involvement

Prioritisation

Consumer and community input into the prioritisation in of funding decisions

- Q **How should consumers, clinicians and the community be involved in setting priorities?**

Community expectations

To inform thresholds, overall decision making directions and priorities

- Q **How could the community's preferences be incorporated into decision making?**

Product appraisal

Incorporation of patient and clinician preferences for specific attributes of the technology

- Q **Is there scope and reason to enhance patient and clinician involvement in decision making processes? If so, how?**

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Limitation of our work

General use restriction

This report is prepared solely for the internal use of Medicines Australia. This report is not intended to, and should not, be used or relied upon by anyone else and we accept no duty of care to any other person or entity. The report has been prepared for the purpose of assisting the Medicines Australia OIT to assess the progress that has been made in Australia to improve patient's access to cancer medicines. You should not refer to or use our name or the advice for any other purpose.

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