Accelerating Access to Innovative Medicines

Opportunities for Australia

Biointelect

Report Authors: Ashleigh Prest, Katrina Lapham, Carolyn Austin

In 2021 Johnson & Johnson released the *Getting Australia to the Front of the Queue* report in partnership with Shawview Consulting. This report explores trends in the global healthcare landscape and identifies opportunities for accelerating access to innovative medicines and medical technologies in Australia as relevant to this global context. Multiple areas for policy reform were identified to ensure Australian patients are among the first in the world to access innovative medicines and technologies. *Getting Australia to the Front of the Queue* outlines five key actions which should be taken to help enable timely access to new medicines in Australia. These include recommendations around reviewing the Quality Adjusted Life Years (QALY) range that is acceptable for cost-effectiveness to ensure that it is aligned with international best practice and requiring the Pharmaceutical Benefits Advisory Committee (PBAC) to apply as comparator the most clinically appropriate therapy.

Building on the findings of *Getting Australia to the Front of the Queue*, Janssen have commissioned Biointelect to investigate opportunities for accelerating access to innovative therapies where high levels of uncertainty create a barrier for reimbursement in Australia. This report focuses on the use of conditional listing arrangements to provide rapid, reimbursed access to medicines that address areas of high unmet need – such as cancer and rare diseases. It makes a series of recommendations around how these arrangements can be strengthened in Australia.

Table of contents

Abbreviations

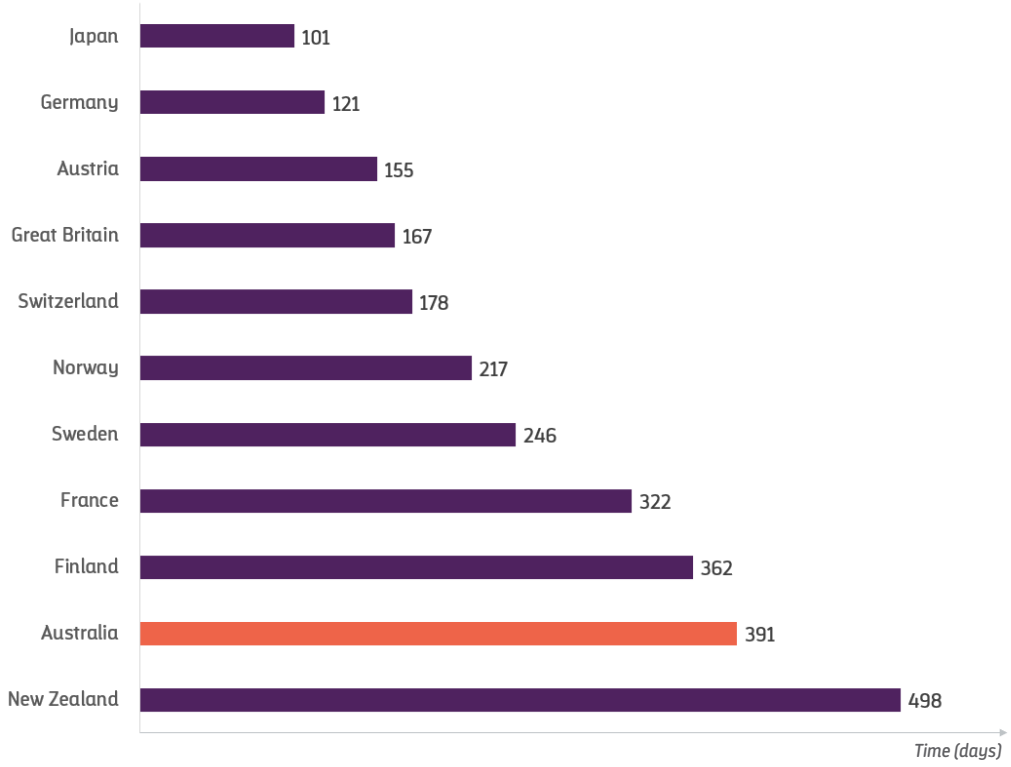
Abbreviation	Meaning
AAC	Autorisation d'acces compassionnel
AAP	Autorisation d'acces precoce
AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz (Pharmaceuticals Market Reorganisation Act)
ARTG	Australian Register of Therapeutic Goods
ATU	Autorisation Temporaire d'Utilisation (Temporary Authorisation for Use)
CAR-T	Chimeric Antigen Receptor T-cell
CDF	Cancer Drugs Fund
CED	Coverage with Evidence Development
CIRS	Centre for Innovation in Regulatory Science
cSCC	Cutaneous Squamous Cell Carcinoma
DCA	Data Collection Arrangement
DoH	Department of Health
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EU	European Union
EUR	Euros
FDA	Food and Drugs Administration
HAS	Haute Autorité de Santé (French National Authority for Health)
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ILAP	Innovative Licensing and Access Pathway
IMF	Innovative Medicines Fund
KPI	Key Performance Indicator
LSDP	Life Saving Drugs Program
MAA	Managed Access Agreement
MAP	Managed Access Program
MBS	Medical Benefits Scheme
MES	Managed Entry Scheme
MM	Multiple Myeloma

Abbreviation	Meaning
MOGA	Medical Oncology Group of Australia
MRDR	Myeloma and Related Diseases Registry
MSAC	Medical Services Advisory Committee
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHRIO	National Institute of Health Research Innovation Observatory
NME	New Molecular Entity
OBR	Outcomes Based Rebates
OECD	Organisation for Economic Co-operation and Development
OS	Overall Survival
PACE	Patient and Clinician Engagement
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCPA	Private Cancer Physicians of Australia
PFS	Progression Free Survival
PICO	Population, Intervention, Comparator, and Outcome
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RoR	Rule of Rescue
RWD	Real World Data
RWE	Real World Evidence
SACT	Systemic Anti-Cancer Therapy
SMC	Scottish Medicines Consortium
TDP	Target Development Profile
TGA	Therapeutic Goods Administration
TKI	Tyrosine Kinase Inhibitor
UK	United Kingdom
US	United States

Executive Summary

Australian patients face longer periods to wait for access to innovative therapies, compared to those in other Organisation for Economic Co-operation and Development (OECD) countries. Time from regulatory approval to funded patient access is approximately two to four times longer in Australia than in Japan, Germany, Austria and Great Britain. Timelines may be even further exacerbated for cancer and rare disease therapies. This may be particularly impactful where there is a high burden of unmet need and patients have few treatment options in the face of life limiting diseases (1).

Figure 1: Time from regulatory approval to funded patient access is longer in Australia than many OECD countries



Source: Medicines Australia (1).

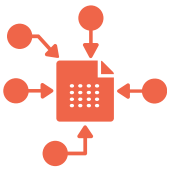
Standard timelines and processes are not only protracted, but are also limited in their capacity to effectively manage potential uncertainties associated with innovative medicines approved based on early or immature clinical trial data. Recent years have seen significant innovation in the development of new therapies for cancers and rare diseases that may extend life and provide a range of other patient-relevant benefits. These offer hope for Australian patients who may have limited treatment options, or time to access treatment.

Recognising the urgency to address such areas of unmet need, Australia's Therapeutic Goods Administration (TGA) has followed international regulators in introducing new pathways that are designed to accelerate patient access to innovative medicines. The Priority Review pathway facilitates the accelerated assessment of important or life-saving medicines, and the Provisional Pathway provides access to promising new therapies where the benefits associated with early access outweigh the risks of providing access while data collection is ongoing.

For Australian patients to benefit from these regulatory pathways, however, timely reimbursement is critical. Current reimbursement processes, which include health technology assessment (HTA), can create delays in patient access. Australia's HTA pathways are particularly unsuited to evaluating products that are approved through the TGA provisional pathway.

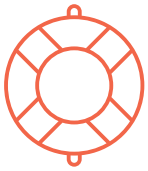
Parallel Submission

The Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process was introduced to enable faster, concurrent processes (2). It is designed to streamline the regulatory and reimbursement processes, with HTA taking place whilst TGA evaluation is ongoing, thereby reducing time to funded access for medicines (2). According to a recent report from the Centre for Innovation in Regulatory Science (CIRS), medicines may be reviewed by the PBAC approximately 138 days prior to TGA approval under a parallel submission. By comparison, those assessed via the standard process typically undergo PBAC evaluation 110 days following TGA approval (on average) (3). TGA approval is still required before a product can receive a positive recommendation from the PBAC. The CIRS found that between 2015-2019, 65% of products were reviewed by the parallel process (3). Despite somewhat streamlining the regulatory and reimbursement processes and notable uptake amongst sponsors, the time to reimbursed access has remained lengthy in Australia compared with many other markets, as illustrated in Figure 1 (1). This is likely attributable to multiple review cycles often being required to obtain a positive recommendation from the PBAC.



Managed Access Program (MAP)

The MAP framework was established within the existing Pharmaceutical Benefits Scheme (PBS) application process to facilitate listing of therapies with uncertain clinical data. Agreements under the MAP include terms that allow for the ongoing resolution of levels of clinical and economic uncertainty, which would otherwise prevent a product from meeting requirements for listing. The MAP has been underutilised and is associated with a number of limitations. Additional data collection may be required under the terms of the MAP, which can place significant burden on patients, clinicians and the healthcare system. The design and execution of observational studies that may be required as part of a MAP can also be challenging in the real world, for example, in instances where additional treatments become available that alter lines of therapy. Products evaluated for access via a MAP must be determined to be cost effective by the PBAC, which requires rigorous assessment of evidence under uncertainty. This may be challenging to resolve when clinical data is immature, as for therapies approved under the TGA's provisional pathway.



Life Saving Drugs Program (LSDP)

The LSDP provides funding for ultra-rare disease therapies which would otherwise fail to meet PBAC requirements for reimbursement. The eligibility criteria are highly restrictive and products must first be rejected by the PBAC on the basis of cost effectiveness which leads to additional access delays.

The introduction of these programs reflects the desire of all stakeholders to accelerate patient access to new therapies, but, ultimately, have failed to meaningfully do so. There is an ongoing need to reform Australian HTA and funding pathways to expedite access to innovative therapies and ensure Australia is positioned among the top OECD nations in timely access to new medicines. New pathways are required to manage the uncertainty associated with innovative products that have been approved by regulators and are seeking reimbursement to enable broad patient access.

Internationally, healthcare systems have acknowledged these urgent needs and have introduced programs and policies to enable early patient access to promising innovative medicines where there is high unmet need. These are summarised in Table 1.

Table 1: Overview of international schemes designed to accelerate patient access to promising innovative medicines

Country	Eligibility Criteria	Interaction with HTA/ subsequent reimbursement	Role of RWE and clinical evidence
Germany: AMNOG & CED / OBR	The AMNOG process provides automatic immediate reimbursed access for all patients while HTA is conducted. In cases of high levels of uncertainty, CED and OBR policies may be implemented to control these risks. Historically these arrangements have been made with insurers while the HTA process is ongoing.	HTA and price negotiation is ongoing while reimbursed access is provided under the AMNOG process.	CED schemes require cohort level longer term data around the safety and efficacy of the therapeutic. OBR schemes require individual patient data on the clinical outcomes of the therapeutic. RWE is typically not influential in HTA/reimbursement decisions but may supplement clinical data.
UK: CDF; and IMF*	Product must be evaluated by NICE and recommended for use within the CDF. Requires plausible potential to satisfy standard NICE evaluation criteria, but with significant uncertainty. Managed access agreement in place.	At the end of the managed access period, product undergoes re-evaluation by NICE. Products may be recommended for listing or de-funded. Role of NICE in listing products on the CDF considered critical to overall operation and efficiency.	Further clinical evidence and RWE generated through the managed access agreement (while the product is funded on the CDF) may be considered in the full NICE evaluation.
France: AAP (formerly ATU)	Exceptional circumstances where no appropriate alternative treatments for patient group, clinical trials suggest efficacy and safety and product considered innovative compared with clinically meaningful comparator.	Separate from HAS reimbursement evaluation. Data collected may inform understanding of how product is used in French clinical practice. No guarantee of reimbursed access.	Real life observational data collected relating to actual conditions of care, but not for clinical research. Observational data may inform but typically does not determine reimbursement outcome. Data used to assess early access renewal.
Italy: 648 List	Must be recognised unmet need and product authorised in other country, OR not yet authorised but clinical trials ongoing (minimum phase II completed) OR off label use. Documented request from patient groups, scientific societies, health facilities/hospitals, clinicians or recommendation from regulator.	Dependent on reason for inclusion on 648 list. For example, where additional clinical data is provided, product may undergo subsequent evaluation. Many products on the list are for rare diseases in which case they may be recommended for inclusion in the 5% AIFA fund (for rare diseases) instead.	Individual patient data collected to support safety and efficacy and to facilitate ongoing access to product .

** The IMF has only recently been introduced but is anticipated to be operated in the same was the CDF, but without being restricted to cancer medicines.*

Understanding the rationale behind establishing these policies and programs, how they operate, as well as the challenges they've encountered and subsequent reforms, provides insights into potential opportunities for accelerating patient access to innovative therapies in Australia.

CED: Coverage with evidence development
OBR: Outcomes based rebates
CDF: Cancer Drugs Fund
IMF: Innovative Medicines Fund
RWE: real world evidence
AAP: autorisation d'accès précoce

Recommendations

1. **Patient access must be the top priority when considering reimbursed access to therapies that are registered on the ARTG. The HTA process itself should not prevent patients from accessing potentially life-saving therapies within critical timeframes.**

> ***Learnings from overseas***
>
> - Germany's AMNOG process provides an example of an approach to reimbursement in which patients are provided immediate access to innovative medicines whilst price negotiations are ongoing.

2. **Decision making should enable reimbursed access to medicines with promising but immature or limited clinical trial data, where there is high unmet need.**

- Risk sharing arrangements should acknowledge that there is uncertainty for both parties in the value of providing patients with access to an innovative therapy with early trial data.
- Conditional listings should take into account any planned trials and data that will become available over time and be provided for a designated period of time only, to allow for the ongoing collection of data. Approval should be limited to the time required to collect the additional data with subsequent re-evaluation at the end of this period.
- Consideration should be given to the legislative requirement that the PBAC consider cost-effectiveness before recommending a therapy, and how this may impact on patient access to ARTG-registered therapies with early trial data only.

> ***Learnings from overseas***
>
> - France's AAP scheme, the CDF and IMF in the UK and the use of OBR in Germany each demonstrate an approach to risk sharing that facilitates early access to medicines, with the potential for rebates to be provided as more mature clinical data becomes available. For products covered by an AAP, reimbursement is automatically granted. The AMNOG process also provides immediate access while reimbursement (including OBR) negotiations remain ongoing.
> - The CDF and IMF include a detailed public data collection arrangement which takes into account ongoing clinical trials. There is a requirement for the medicine to undergo re-evaluation period once this data is available.

3. **Broad stakeholder collaboration, including patients and clinicians, is required to design an appropriate pathway for reimbursement of therapies with early clinical data. Patient and clinician stakeholder engagement is also important to help ensure that the unmet need, as well as patient relevant outcomes, are taken into consideration, and that patients and clinicians understand any conditions associated with early access.**

- This pathway should be complemented in the MSAC pathway where co-dependent technologies are evaluated (for example, biomarker testing for access to precision medicines).

4. **There should be opportunities for impactful patient and clinician consultation or input, planned from the initiation of the reimbursement process. This is an important consideration in determining which therapies would be eligible for early access, on the basis of promising early data and unmet need, both of which should include consideration of patient-relevant outcomes.**

Learnings from overseas

- NICE and the NIHRIO have established multiple opportunities for patients, clinicians and carers to contribute to horizon scanning and HTA processes. This can be particularly important when it comes to defining areas of unmet need and patient defined outcomes.

5. **Horizon scanning for therapies that may become registered on the ARTG with early data, and engagement with sponsors at an early stage, is required for a coordinated and effective process.**

Learnings from overseas

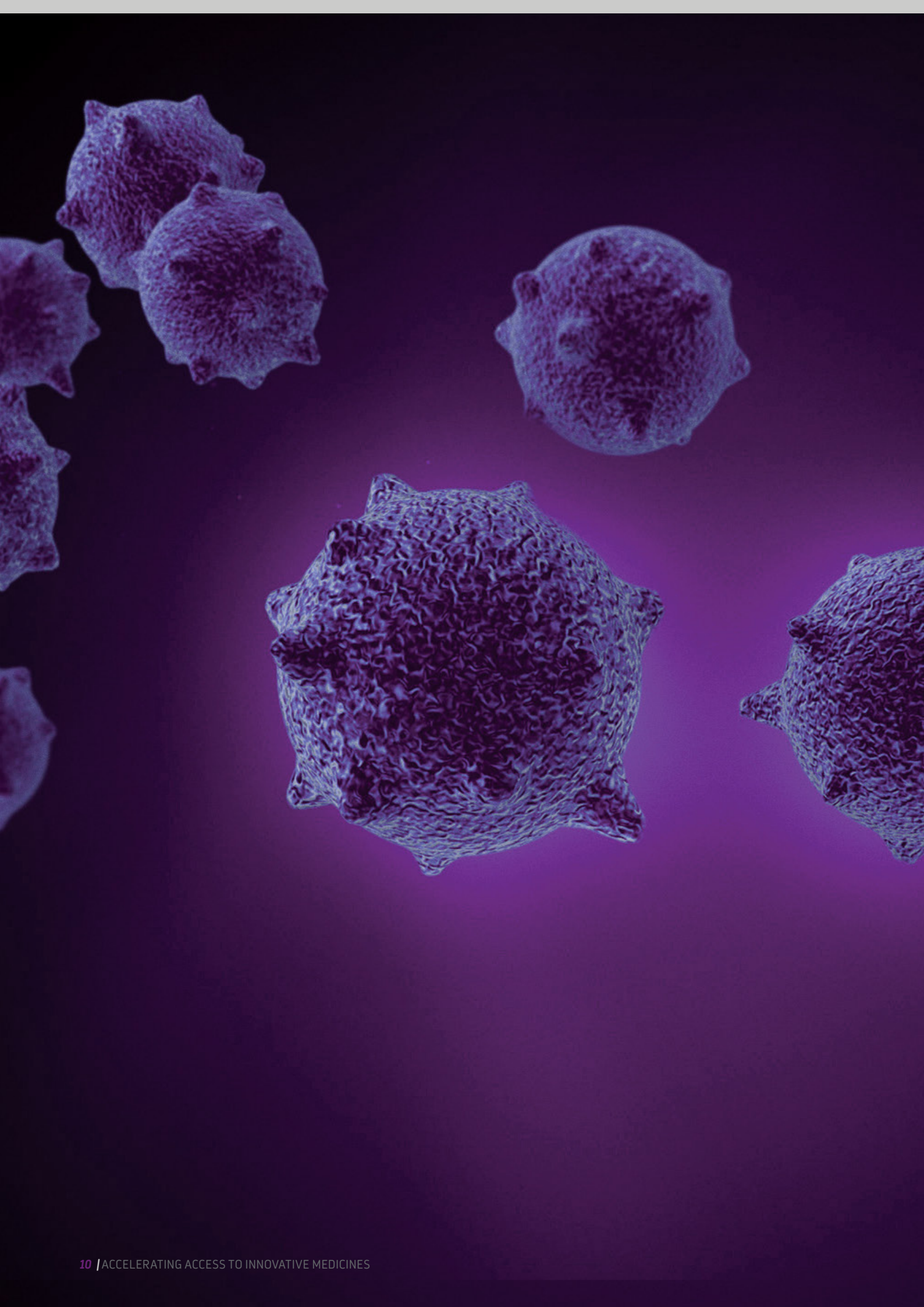
- Horizon scanning is a key first step in the UK's HTA process where it helps identify, filter and prioritise technology for assessment by NICE.

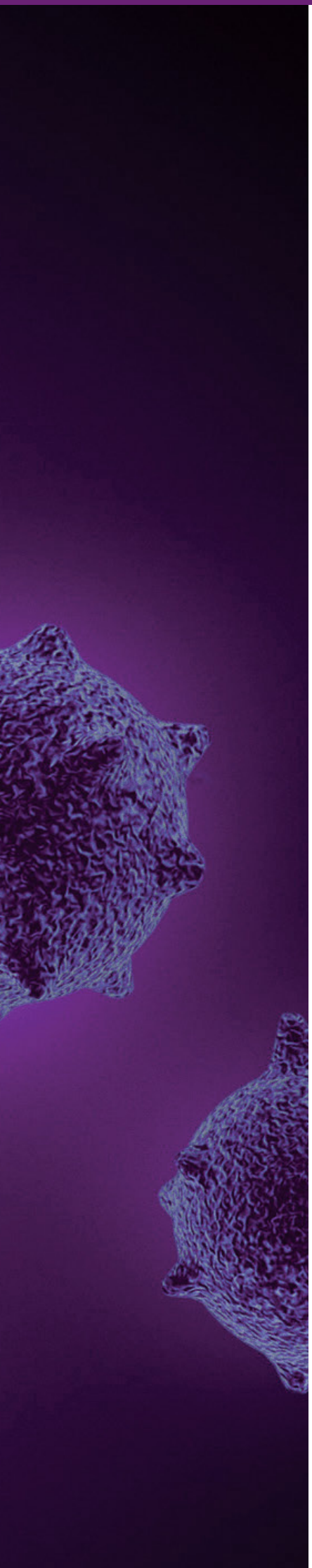
6. **Early access provides an opportunity to generate real world evidence in Australian patients, to understand quality use of the therapy, reduce uncertainty around potential patient numbers and support Australian clinical practice. This may be particularly important for rare diseases where clinical trial data is likely to have limitations.**

Learnings from overseas

- Early access in Italy includes the collection of individual patient data to support safety and efficacy and to facilitate ongoing access to a product.
- The recent NICE Methods Review has specified that real world evidence (RWE) can be important in resolving uncertainties in clinical data, particularly for rare diseases. The draft RWE framework was released for public consultation in March 2022.

7. **Care should be taken to avoid unnecessary burden of authorising access, registering patients, data collection and related activities for all stakeholders (importantly, the healthcare system) in an early access pathway.**





The Evolving Healthcare Landscape

The Australian and global healthcare landscape is rapidly responding to disruptive innovations in the diagnosis, treatment and management of cancer and rare diseases using personalised medicine. Key developments include genomic testing, which facilitates a personalised approach to healthcare, the arrival of immunotherapies capable of utilising a patient's own immune system to fight cancer, and the successful commercialisation of potentially curative cell and gene therapies (4) (5) (6). These innovations provide hope for patients with severe and life-threatening conditions and contribute to better quality of life.

Cancer is a major contributor to disease burden in Australia. In 2019, the number of Australians living with, or having lived with, cancer was estimated to exceed 1 million. This rate is higher amongst Aboriginal and Torres Strait Islander populations and individuals of lower socioeconomic status. Lung cancer is the leading cause of cancer death in Australia and is associated with a 5-year survival rate of only 20% (7) (8). Though survival rates have improved in recent years, 3 in 10 deaths in Australia are still attributed to cancer.

Rare diseases each affect a small number of patients, but together are estimated to affect 8% of the Australian population (approximately 2 million people) (9). Approximately half of all cancer deaths are attributed to rare and less common cancers, like cholangiocarcinoma (bile duct cancer), bone cancer and oesophageal cancer (10) (11).

The application of precision medicine is particularly prominent in the cancer and rare diseases space. Here there is a strong pipeline of innovative therapies, and the progress of recent years shows no sign of slowing in the near future. Food and Drug Administration (FDA) orphan drug designations, which are an indicator of trends in rare disease development, suggest that there has been a steep increase in the number of rare disease therapies in development between 1983 and 2019 (12).

Personalised and precision medicine

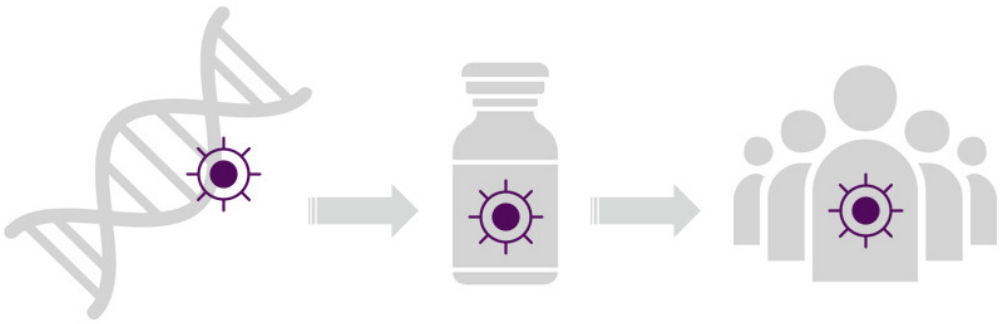
Personalised medicine (also called precision medicine, or targeted therapy) refers to the provision of medical care or treatment that is tailored to the specific genes or proteins of a particular patient. It is an area of medicine that has arisen from the sequencing of the human genome in 2003, and is based on the recognition that, due to variations between patients, a personalised approach to treatment has the potential to improve patient outcomes and potentially minimise side effects, such as those associated with chemotherapy (82).

Personalised medicine can be utilised to treat genetic disorders or to provide a targeted approach to cancer diagnosis and treatment. In recent years, it has been recognised that certain cancers such as breast cancers and lung cancers are inherently diverse and consist of a number of different subtypes – each driven by a different molecular mechanism (83). Therapies that target these molecular mechanisms (signalled by biomarkers) have proved successful in treating a range of different cancers (83).

For example, the discovery of epidermal growth factor receptor (EGFR) mutations in lung cancers and their sensitivity to tyrosine kinase inhibitors (TKIs), has resulted in a significant shift in the treatment paradigm (74) (73). Patients who respond to these personalised therapies may be expected to survive for 3-4 years post diagnosis – a significant improvement when compared with older chemotherapy regimens for which the 5-year survival rate is approximately 20% (75). Although TKIs have improved patient outcomes, more still needs to be done to ensure future therapies advance progression free and overall survival.

Genomic testing is required to detect the presence of any molecular mechanisms, or oncogenic drivers, so the most appropriate treatment can be selected for each individual patient. This includes single gene testing which involves looking for a mutation on a specific gene, as well as multigene panel testing which looks for mutations in multiple genes in a single test. Single gene testing is typically used where there is a known genetic mutation in a patient's family, while multigene panel testing screens for a broader set of potential mutations associated with a condition.

Figure 2: Precision Medicine

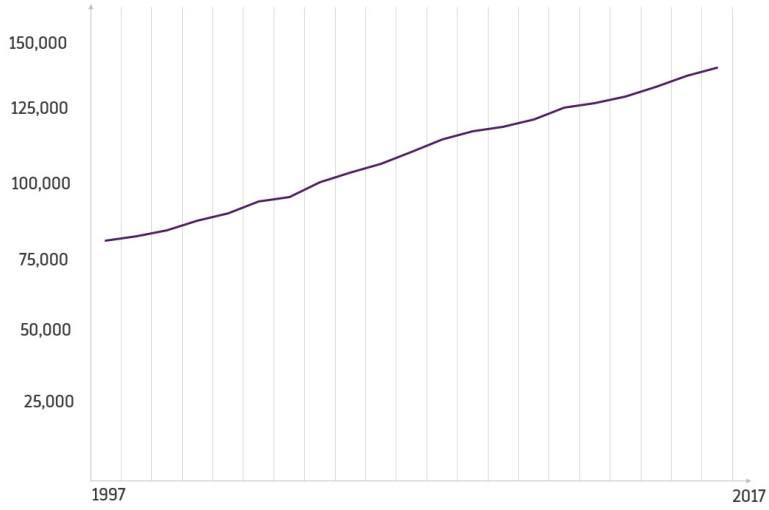


Burden of disease in Australia

Cancer

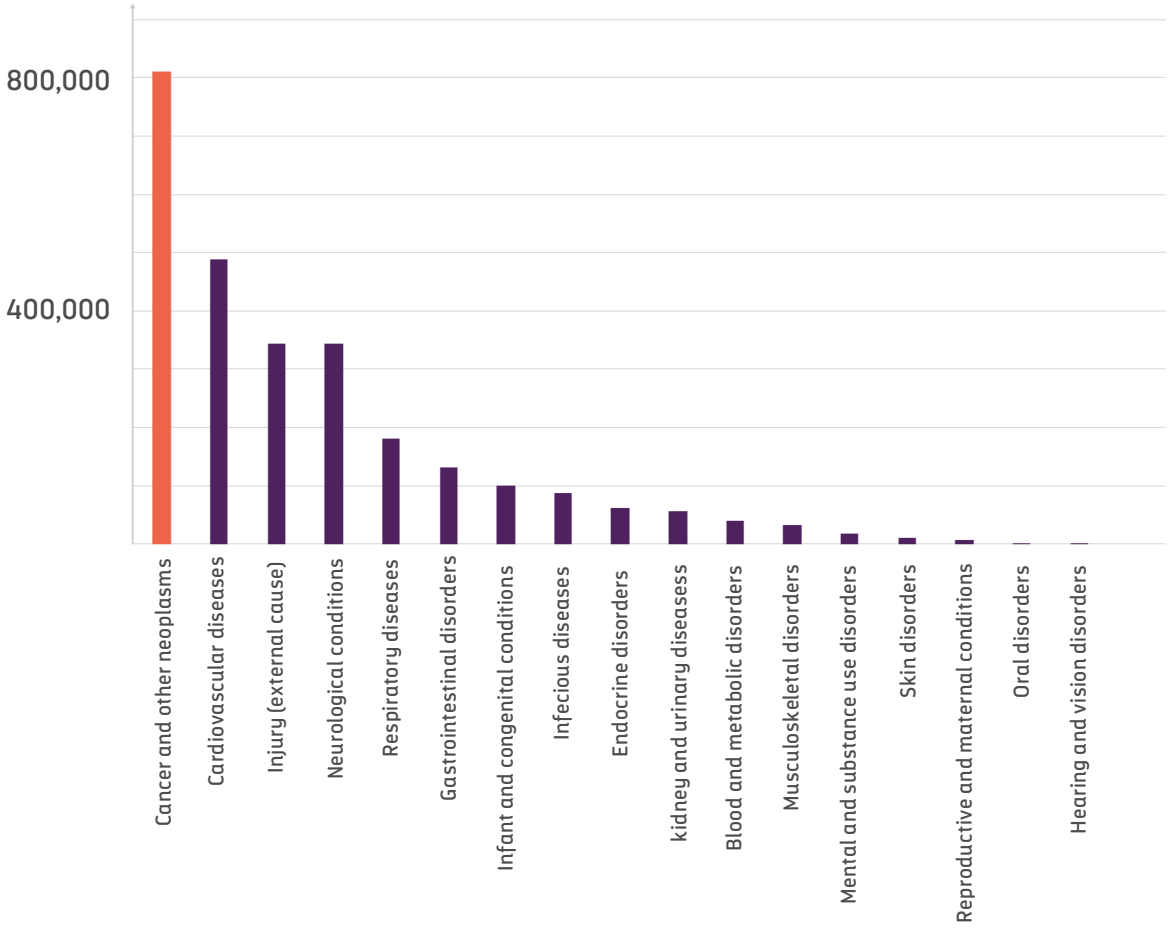
Cancer is associated with high disease burden in Australia. The number of new cancer diagnoses per year has been steadily increasing since 1997, and is associated with high mortality and years of life lost, compared with other diseases. The relative 5-year relative survival rate in Australia, for all cancers combined, is estimated to be 69.7%. Though this reflects recent improvements in survival, 5-year survival rates remain significantly lower for many cancers, including acute myeloid leukaemia (26.3%), lung cancer (20.2%) and mesothelioma (6.4%) (8).

Figure 3: New cancer diagnoses per year (1997 – 2017)



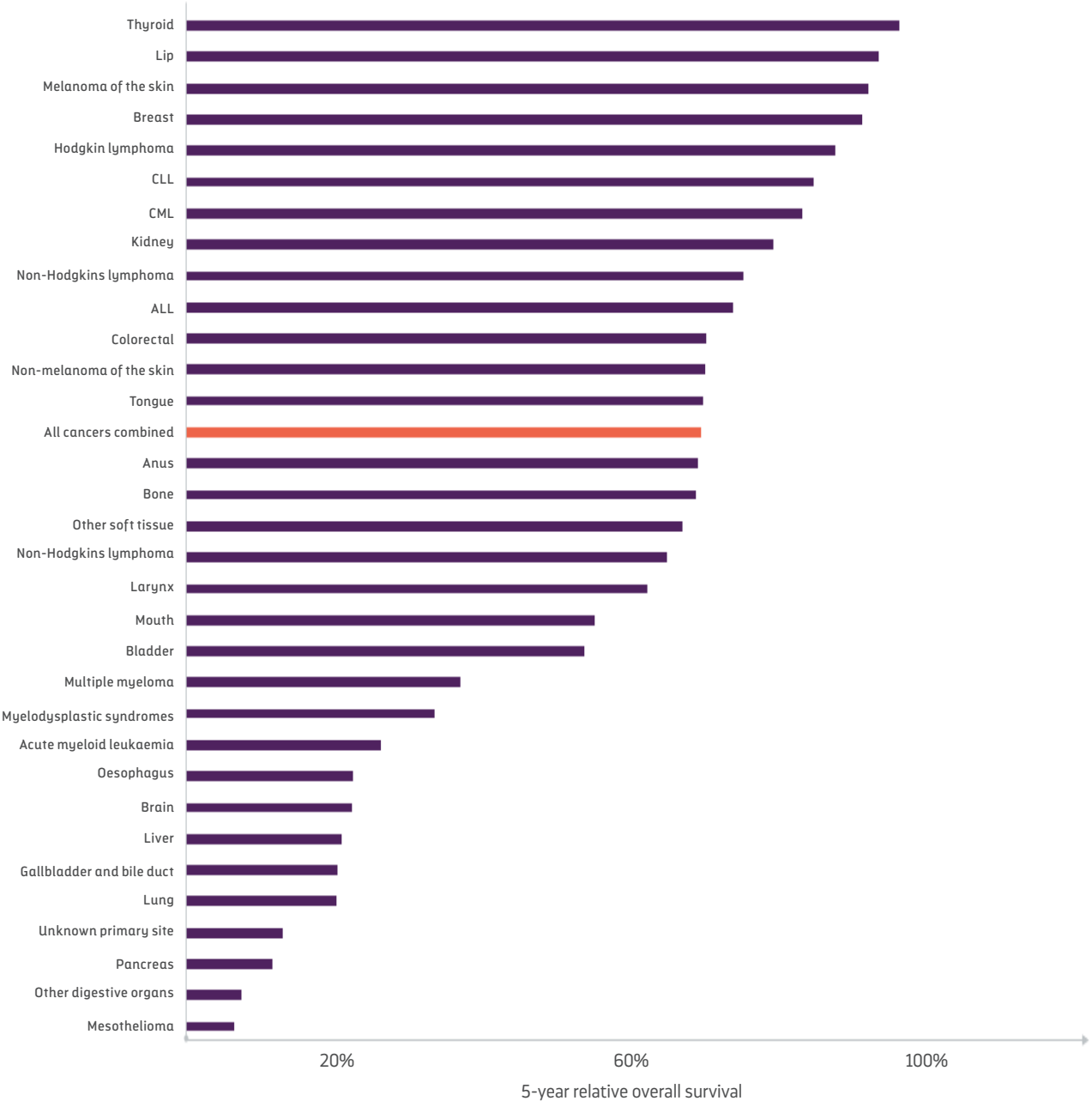
Source: Australian Institute of Health and Welfare (8).

Figure 4: Years life lost due to cancer, compared with other conditions (2018)



Source: Australian Institute of Health and Welfare (8).

Figure 5: Survival rate (5-year relative survival %) for various cancer types

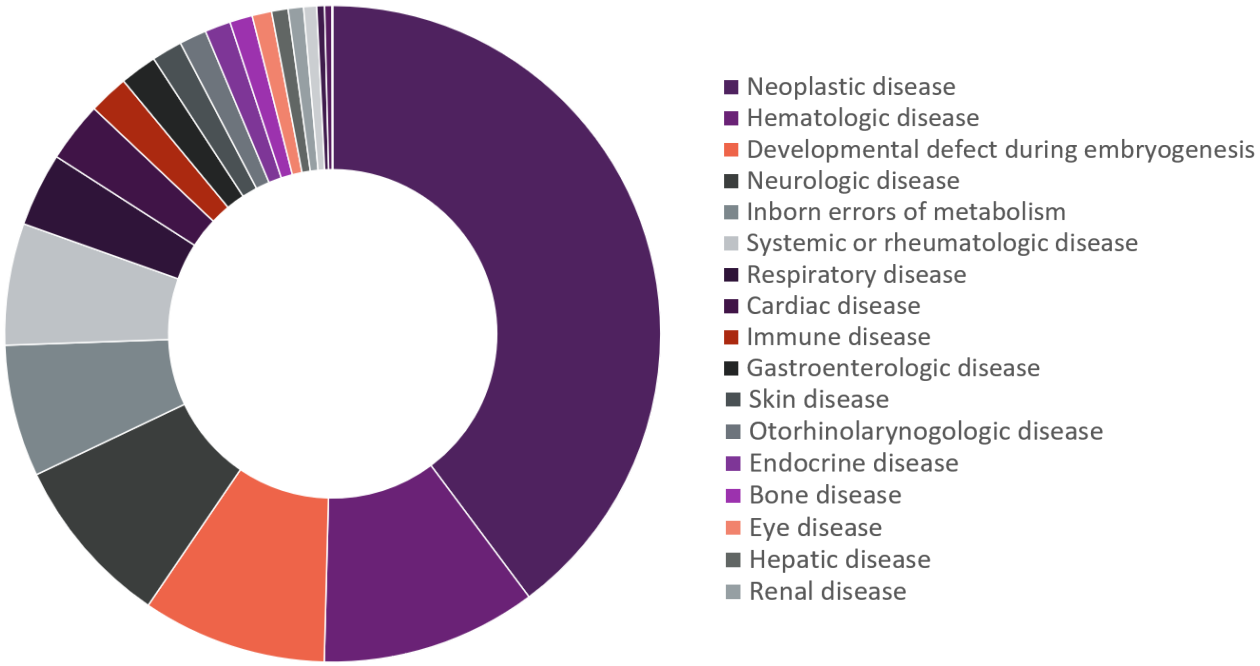


Source: Australian Institute of Health and Welfare (13)

Rare diseases

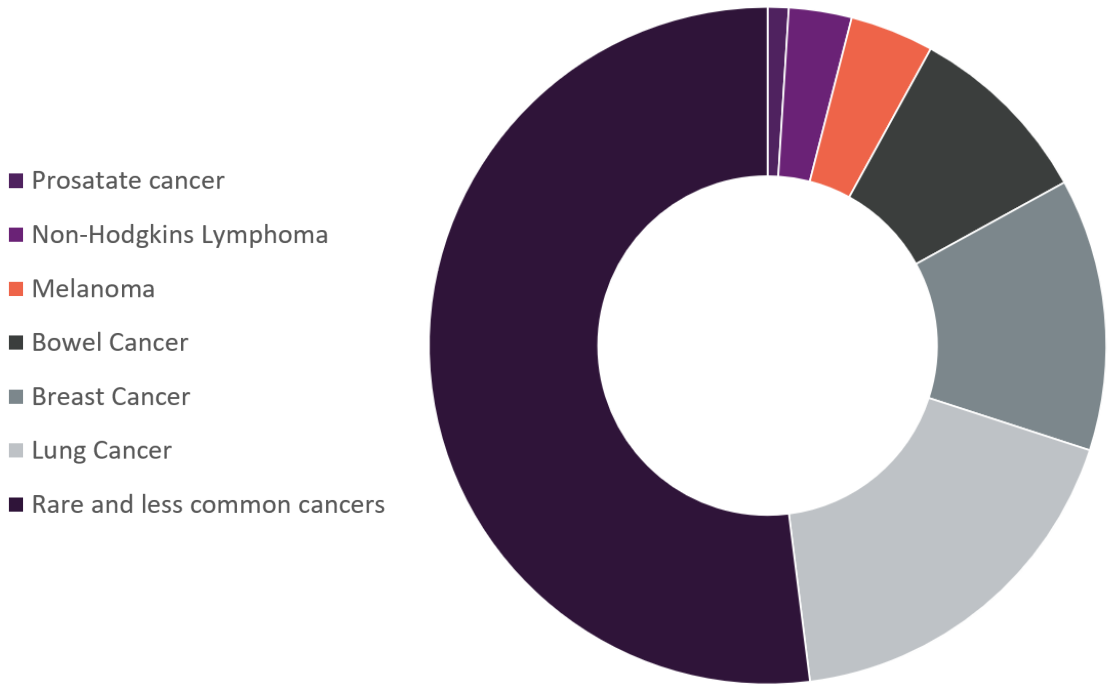
Though rare diseases affect a small number of patients collectively, they impact an estimated 8% of the Australian population (approximately 2 million people) (9). It is estimated that 80% of these conditions have a genetic original which implies the need for a precision medicine approach (14). An analysis of hospital discharges between 1999 and 2010 in Western Australia found that almost 10% of all hospital discharges were related to patients with a rare disease, of which, the majority were identified as having a rare neoplastic disease (15). In addition, of all cancer deaths, rare and less common cancers are associated with more than half of total cancer deaths (16).

Figure 6: Breakdown of rare-disease related hospital discharges



Source: The collective impact of rare diseases in Western Australia: an estimate using a population-based cohort. (15)

Figure 7: Rare and less common cancers versus other cancer types (total cancer deaths in Australians aged 40-59)

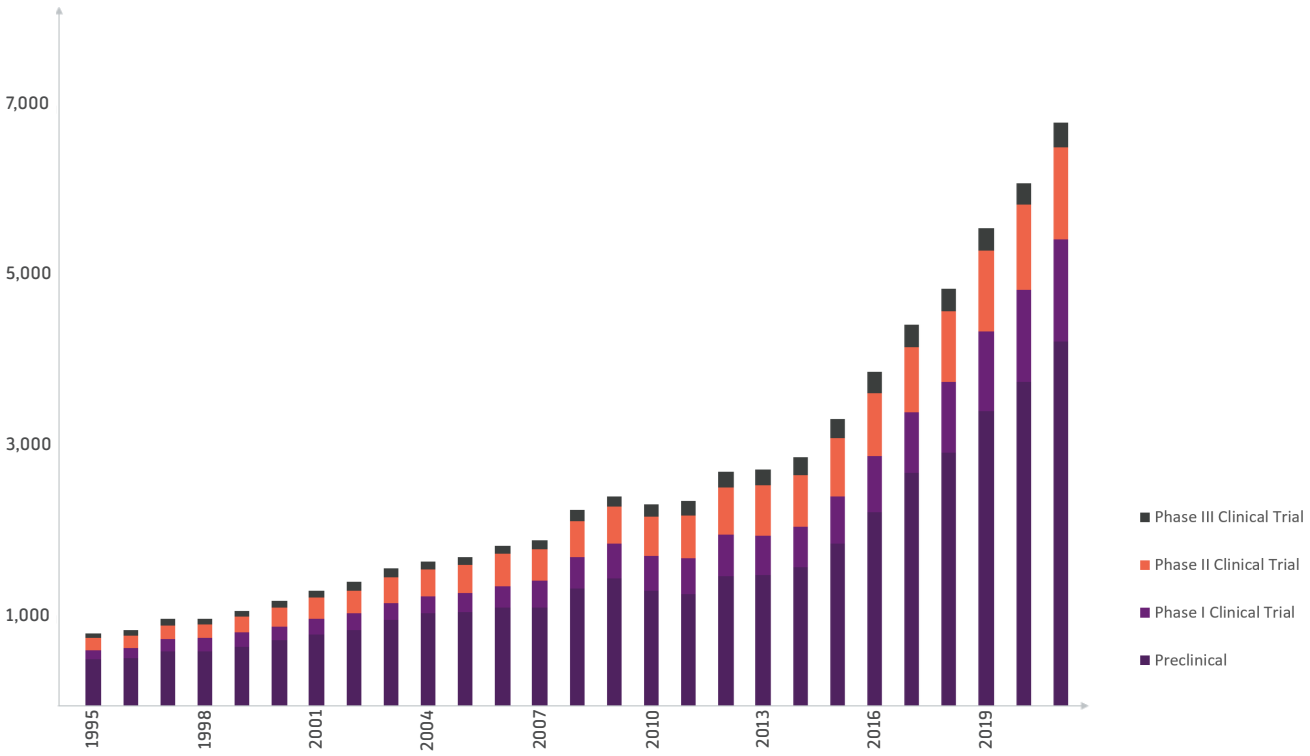


Source: Rare Cancers Australia (16)

The cancer and rare disease pipeline

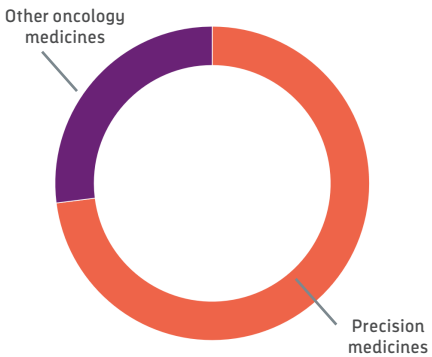
There is a strong and increasing pipeline of innovative therapies in development for the treatment of cancer, and the number in development has continually increased since 1995.

Figure 8: Anti-cancer therapies in development



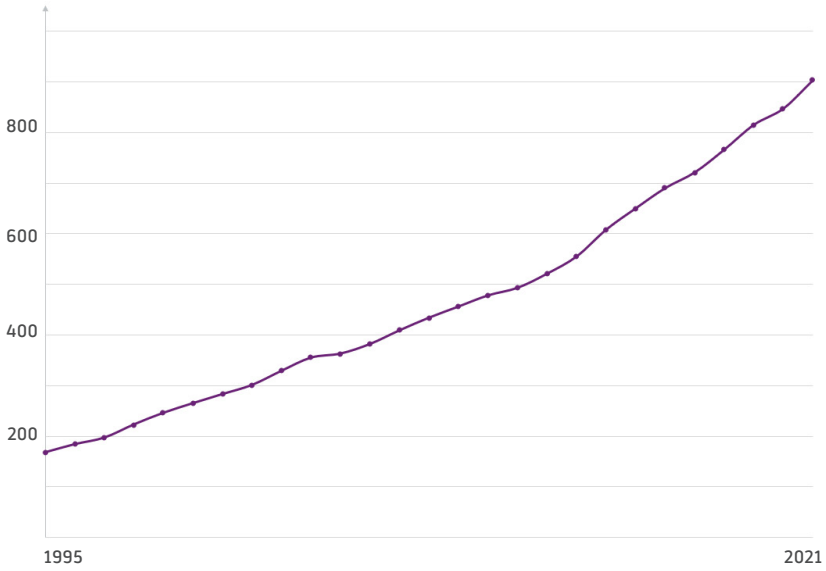
Source: Pharmaprojects® 2021

Similarly, a steep increase in the number of orphan drugs approved for the treatment of rare diseases has been seen over the past few decades. There is also an increasing focus on the development of precision medicines – especially in the oncology space.



Source: Krzyszczyk P et al. 2018. (17)

Figure 9: Number of orphan drugs on the market per year

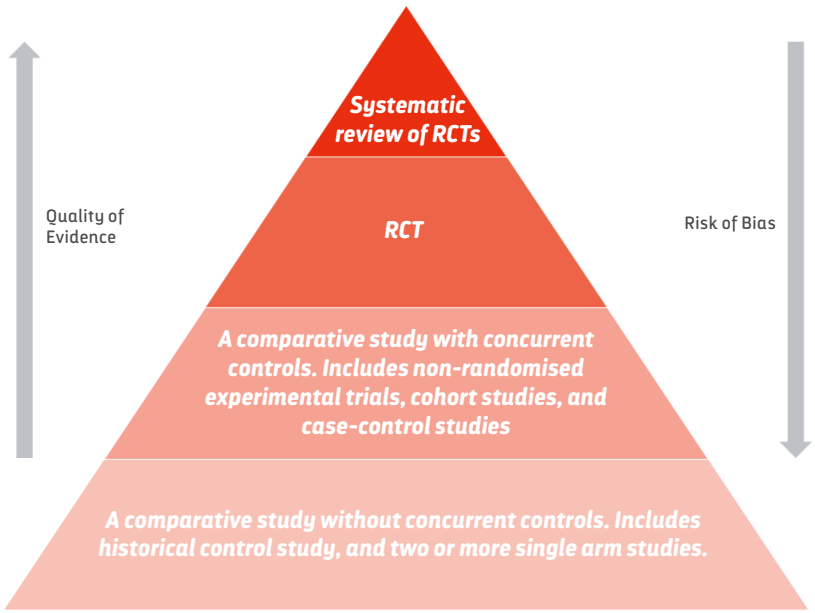


Source: Pharmaprojects® 2021

Demonstrating clinical and cost effectiveness

A phase III randomised controlled trial (RCT) is recognised as the gold standard for demonstrating clinical and cost effectiveness (20). This provides greater certainty around the incremental benefit of a new therapy, vs. existing therapeutic alternatives and the generalisability of results to the patient population. Healthcare systems may be reluctant to commit funds where there is substantial uncertainty in the evidence of clinical benefit and cost-effectiveness. As such, health technology assessment (HTA) agencies have traditionally expressed a preference for evidence generated in RCTs for the purpose of technology appraisal.

Figure 10: Hierarchy of evidence



Source: NHMRC, Yetley E et al. (19), (20)

Clinical Trials

Prescription medicines are typically subject to three main phases of human clinical testing primarily designed to determine safety and efficacy (85) (84).

Phase I

The first time an intervention is tested in humans

Usually involves only small groups of healthy volunteers (approx. 20-80)

Primary aim to determine safe doses of a drug and identify any unexpected safety concerns.

Phase II

Testing of the therapy in a slightly larger group of patients who have the target disease

Designed to begin to evaluate the efficacy and to further monitor safety.

Phase III

Testing in a large group of patients (potentially up to several thousand depending on the disease), for a longer period of time.

Designed to provide a more comprehensive assessment of safety and efficacy.

Phase III trials are commonly conducted as a Randomised Controlled Trial, meaning the therapy will be assessed against a placebo, or current treatment, and patients will be randomly separated into each category, to ensure a robust and high quality study.

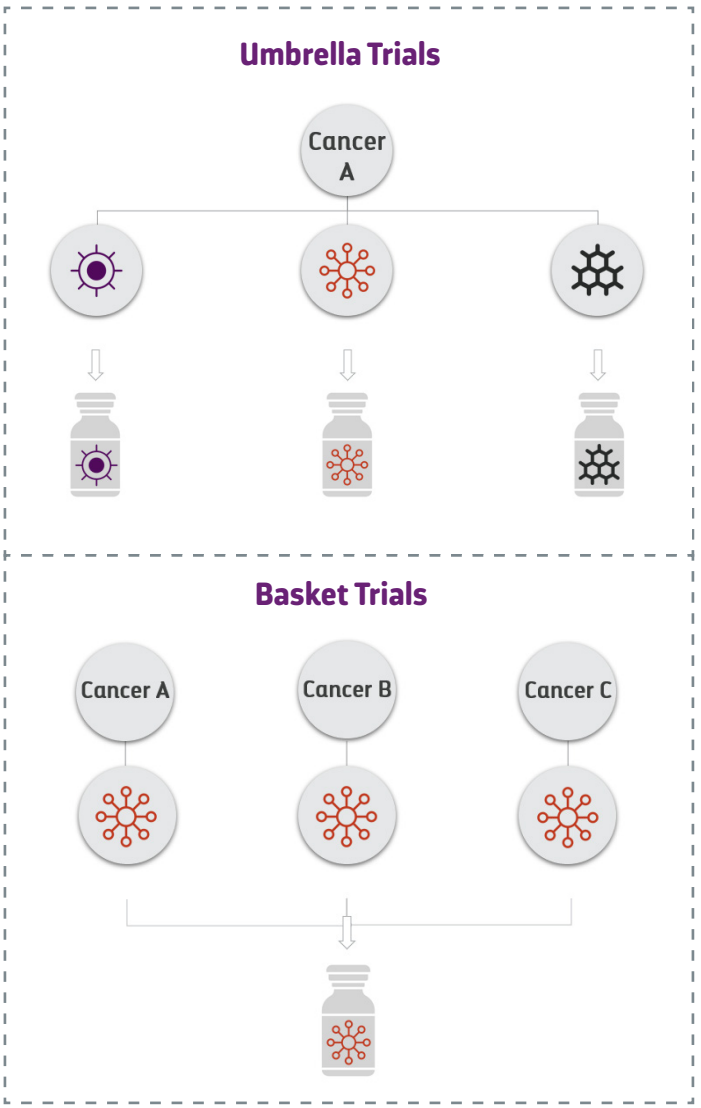
In certain circumstances, a RCT may be neither feasible nor ethical. For example, the small patient numbers associated with rare diseases may limit patient recruitment, while a lack of treatment options for seriously ill cancer patients may necessitate treatment of all patients (20).

Novel clinical trial designs have emerged as a way of evaluating innovative therapies in instances where a RCT may not be practical. These include:

- Basket trials, consisting of multiple tumour types with one common genetic mutation
- Umbrella trials consisting of different genetic mutations within a single histology (20)
- Adaptive designs, which add the flexibility to utilise results collected during the trial to modify the course of the trial moving forward (21).

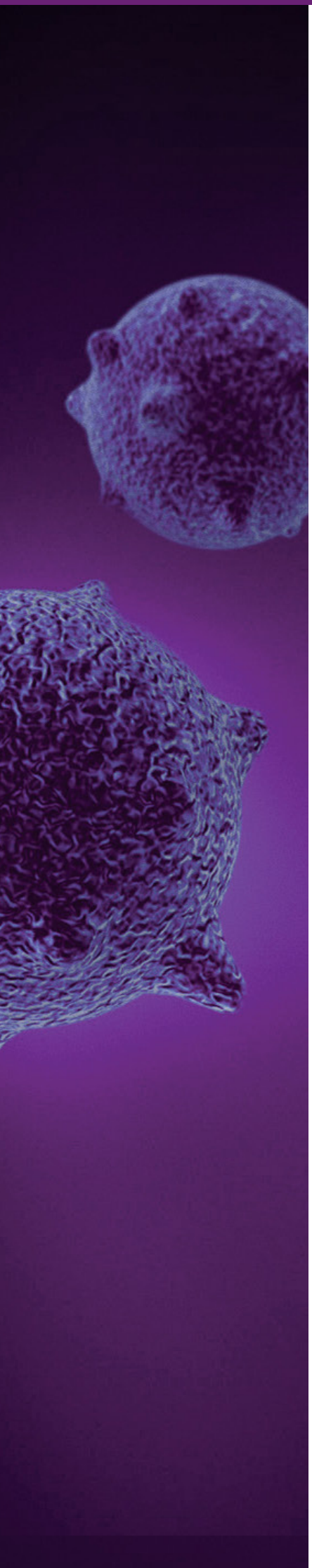
In other circumstances, such as where there is a high unmet need and limited existing treatment options, there may be a strong case for facilitating patient access to promising new therapies, while further data collection is ongoing. Many countries, including Australia, have established processes in recent years that enable conditional, time limited listings, which may be contingent on the subsequent provision of phase III RCT evidence.

Figure 11: Adaptive trial designs, including basket trials and umbrella trials



Source: Verwij J. et al. Pallmann P et al. (20), (21).

Innovative medicines in development have the potential to drastically improve outcomes for Australians with cancers and rare diseases. Given the high burden of disease associated with these conditions, the potential benefit to Australian patients is substantial. Appropriate and rapid pathways that will enable reimbursed patient access, to complement existing regulatory pathways, are required.



Patient Access to Promising, Innovative Therapies

In Australia, fast-track Therapeutic Goods Administration (TGA) pathways such as the provisional pathway and priority review pathway have been implemented to accelerate marketing authorisation for innovative medicines where there is acute unmet need. For this to translate into equitable patient access, however, reimbursement is crucial.

HTA must be conducted prior to listing therapies for reimbursement in Australia. Standard HTA pathways through the Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC) are not well suited to fast-tracking the evaluation of therapies or managing uncertainty in clinical data.

Efforts in recent years to streamline pathways and accelerate patient access indicate broad stakeholder support for these goals; yet, the existing processes and approach to decision making still create delays. As a result, there are significant gaps in the access landscape for therapies that are approved for marketing in Australia, but not accessible to patients because they are not reimbursed. Similar accelerated pathways are required in reimbursement as have been introduced for regulatory processes.

Fast-track regulatory pathways for cancer and rare disease therapies

Fast-track regulatory pathways have been established to enable provisional and priority reviews (20). In Australia, the TGA has developed a provisional approval pathway, and a priority review pathway which are designed to accelerate access to promising new therapies where there is a high unmet need (22) (23). The provisional approval pathway enables conditional registration based on limited clinical trial data with the requirement that additional data is provided within a specified period (22). The priority review pathway facilitates the accelerated assessment of important or life-saving medicines (23).

Table 2: Overview of TGA Fast-track regulatory pathways

Pathway	Provisional pathway	Priority review pathway
Purpose	Provides access to certain promising new medicines where we assess that the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional data are still required.	The priority pathway provides a formal mechanism for faster assessment of vital and life-saving prescription medicines.
Eligibility	Eligible medicines must be indicated for the treatment, prevention or diagnosis of a life threatening or seriously debilitating condition where there are either no existing treatment options, or evidence that the new medicine is likely to provide a significant improvement in efficiency or safety.	New prescription medicine or new indications medicine, serious condition, comparison against registered therapeutic goods, and major therapeutic advance.
Data	Preliminary clinical data: ▪ A non-validated surrogate endpoint ▪ A single arm study ▪ A non-randomised comparison ▪ An interim analysis/duration of study ▪ A small database ▪ Recruitment from a narrow group of patients Must be accompanied by a clinical study plan for the submission of a full clinical data package within a specified timeframe (less than 6 years).	Full data package demonstrating safety, quality and efficacy.
Relevant Timelines	Provisional registration period 2 years. Application for extension or transition to full registration required after 2 years.	150 working days evaluation timeline (up to 3 months shorter than standard review).

Source: TGA (22), (23).

Though the TGA's provisional pathway has the potential to expedite time to patient access for promising therapies (22), equitable access relies on making therapies affordable for all patients via national reimbursement.

Pathways to reimbursement in Australia

Health Technology Assessment in Australia

In Australia, HTA is required to list new technologies for national reimbursement.

PBAC

Medicines listed on the PBS are subsidised by the Australian Government. The PBAC is an independent body that is responsible for evaluating new therapies and recommending these for listing on the PBS. The PBAC considers the **clinical effectiveness, safety** and **cost-effectiveness** of the new medicine, compared with the existing standard of care (78). The National Health Act requires the PBAC to recommend only cost-effective therapies for reimbursement on the PBS. The Parallel Submission pathway was introduced in 2011, allowing sponsors to commence HTA while TGA evaluation is ongoing (2).

MSAC

The MSAC is an independent body that is responsible for appraising technologies, procedures and services for public funding that are not eligible for listing on the PBS. This may include technologies to be listed on the Medicare Benefits Schedule (MBS), as well as a range of other publicly funded programs. The range of technologies that can be considered by the MSAC is broad, and covers medical devices, diagnostics, and medical procedures (86).

Co-dependent technologies

In the context of HTA in Australia, a co-dependent technology is a medical technology or service that relies on another technology to achieve its intended purpose or enhance its effect. Co-dependent technologies are a key component of precision medicine treatments where a diagnostic test is typically required to identify a molecular "biomarker" in order for a medicine targeting that molecular mechanism to be accessed.

Therefore, subsidisation of the medicine through the PBS would also require subsidisation of the diagnostic test through the MBS, resulting in a co-dependent application being lodged to both the PBAC and the MSAC simultaneously (87).

Alternative pathways

Alternative mechanisms exist to evaluate therapies where the clinical data available at the time of appraisal is associated with uncertain cost-effectiveness, but where there is an acute unmet need. These programs aim to facilitate earlier patient access, whilst managing this uncertainty between the "payer" (the PBS) and sponsor. These include the MAP, LSDP and Rule of Rescue (RoR).

MAP

The MAP (formerly Managed Entry Scheme; MES)) was introduced in 2010 as a mechanism by which products may obtain PBS listing on the basis of typically unacceptable clinical or economic uncertainty (79). This pathway is suitable where there is a high unmet clinical need and there is typically a requirement for the ongoing provision of evidence. A MAP is designed to provide (79):

- Earlier patient access to promising therapies
- Sponsors with earlier access to a subsidised market whilst acknowledging that some form of confidential discount may be required in recognition that the initial evidence is less convincing
- Clear articulation of the evidence required to resolve the identified area of uncertainty and the consequences of potential outcomes from the additional evidence

- Agreement by the PBAC to review a submission once the additional evidence becomes available and to reconsider the listing in light of the new evidence
- Appropriate sharing of risk

Either the sponsor, PBAC or Department of Health (DoH) may request the implementation of a MAP. Most MAPs have been pursued following rejection or deferral of an initial PBS submission (80).

LSDP

The LSDP provides funding for medicines that treat patients with rare and life-threatening diseases. Through the LSDP, eligible patients are provided access to very expensive medicines at no expense. In order to be listed on the LSDP, a medicine must first be rejected for PBS listing based on a failure to meet the required cost effectiveness criteria. The medicine must also be indicated for the treatment of a rare disease. Here it should be noted that this does not include genetic subtypes of more common diseases such as cancer. Criteria that must be met for funding via the LSDP include:

- Rare but clinically definable disease for which the drug has proven therapeutic modality (e.g. approved TGA indication)
- Disease is identifiable with reasonable diagnostic precision
- Epidemiological and other studies provide evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease
- There is evidence to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug
- The drug must be accepted as clinically effective, but rejected for PBS listing because it fails to meet the required cost effectiveness criteria
- There is no alternative drug listed on the PBS or available for public hospital in-patients which can be used as lifesaving treatment for the disease.
- There is no alternative non-drug therapeutic modality which is recognised by medical authorities as a suitable and cost-effective treatment for this condition
- The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a one-year period for the patient, would constitute an unreasonable financial burden to the patient (32)

Rule of Rescue (RoR)

The RoR is not a formalised scheme or process but rather supplementary factors for consideration to recommend a product for listing in instances where the PBAC would typically reject a submission due to a lack of cost effectiveness. For the RoR to apply, the following must be met:

- No alternative treatment exists (both nonpharmacological and pharmacological interventions) for these patients in Australia
- The indication is severe, progressive, and expected to lead to premature death
- The indication applies to only a small number of patients
- The proposed therapeutic provides worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition

Reimbursement timelines in Australia

In Australia, the time between regulatory approval and reimbursement can result in substantial delays to patient access, and is often associated with numerous resubmissions before a positive recommendation is received (24). An analysis of PBAC submissions and outcomes between 2010 and 2018 found that the average time from initial PBAC submission to PBS listing ranged from 357 days in 2011, to 644 days in 2014 with an overall upward trend in the time taken to list on the PBS during this period (24). For cancer medicines, it has been reported that the median time from TGA registration to PBS listing was as long as 608 days between 2010 and 2017 while the median time to PBS listing for orphan drugs during the same period was reportedly 552 days (1).

These timelines are considerably longer than many comparable countries. For example, an analysis of the time to HTA decision in selected European jurisdictions found that the median time was 405 days in England, 384 days in Scotland, 209 days in Germany and 118 days in France (25).

Reforms have been made in an attempt to address these protracted timelines, including the introduction of a parallel regulatory and reimbursement process, however, concerns remain that Australian patients may be unable to access new therapies within a similar timeframe as their overseas counterparts. This concern was widely captured in stakeholder input in the recent parliamentary inquiry into the approval process for new drugs and novel medical technologies in Australia.

"There are increasing instances of access delays in Australia compared with other countries above all with respect to what is recommended in United States (US) and European evidence-based cancer treatment guidelines. This impacts negatively on the quality and availability of the cancer care and therapies for Australian patients." Medical Oncology Group of Australia (MOGA), parliamentary inquiry submission (26).

Limitations of existing pathways in Australia

As outlined above, the time taken to achieve reimbursement in Australia is excessive, particularly when compared with other countries, and can be especially protracted for oncology or rare disease medicines. Though various pathways have been introduced in an attempt to facilitate patient access to innovative therapies, these are associated with a number of limitations.

Parallel Pathway

In 2011, the Department of Health introduced the TGA and PBAC Parallel Process, which permits simultaneous TGA and PBAC evaluation (2). Under a parallel submission, medicines may be reviewed by the PBAC approximately 138-days prior to TGA approval. By comparison, those assessed via the standard process typically undergo PBAC evaluation 110 days following TGA approval (on average) (3). A report by the Centre for Innovation in Regulatory Science, found that between 2015-2019, 65% of products took advantage of the parallel review process (3). Despite somewhat streamlining the regulatory and reimbursement processes and notable uptake amongst sponsors, the time to reimbursement has remained lengthy – suggesting the process has failed to significantly accelerate patient access. This process also contains no mechanism to manage the level of uncertainty that may be associated with promising new oncology and rare disease medicines.

Managed Access Program

The MAP was introduced to facilitate the evaluation of products with early or uncertain clinical data through risk sharing arrangements between the payer (PBS) and sponsor. Within the legislative framework of the PBS (the National Health Act) the PBAC may only recommend products that are determined to be cost-effective

(27). Therefore, reimbursement via a MAP still requires the product to meet the PBAC's requirements for cost effectiveness. This means that, assuming remaining uncertainties can be resolved, heavy price discounting is typically required to meet cost-effectiveness requirements. This is often not practical from a sponsor point of view – particularly if there is limited opportunity to obtain a higher price, where justified, following the resolution of uncertainty. This high level of risk borne by sponsors acts as a disincentive to pursue a MAP and has contributed to the underutilisation of the scheme. The framework for the MAP is not enshrined in legislation (28). As a result, the scheme is associated with a lack of transparency for patients, clinicians and sponsors (29) (30). For patients and clinicians, this can create confusion around how funding decisions are made (29) which may be especially frustrating in cases where it directly impacts ongoing access to a particular medicine. For sponsors, it creates significant uncertainty around the potential long-term implications for their product from a pricing perspective – particularly in light of maturing clinical evidence (31). These issues have been acknowledged by the PBAC who noted:

"The PBAC would be more comfortable in its decision making if there was a specific legislative basis for conditional recommendations and managed access programs. This would also enhance transparency to about how and when such conditions could be applied. It would make it clearer to clinicians and patients that continued listing may depend on their participation in additional data collection." PBAC (28).

A MAP can also be challenging to implement in cases requiring the collection of observational or real world data (RWD). When new products become available, this can impact treatment paradigms and lines of therapy. As a result, it may no longer be feasible to measure outcomes associated with the product in question as they cannot be differentiated from the new therapy. In addition, MAPs have the potential to be highly resource intensive for the sponsor, the DoH and clinicians, due to additional data collection requirements (29). Considering the strong pipeline of cancer and rare disease products, this may also undermine the long-term sustainability of MAPs for stakeholders involved in their implementation. Together, these factors may act as a disincentive for sponsors to seek reimbursement via a MAP.

Life Saving Drugs Program

A medicine must first be reviewed and rejected by the PBAC before an application to the LSDP can be made (32). As a result, patients face protracted delays in accessing these life-saving medicines. Ultimately the LSDP is designed to provide a last resort for a very limited number of medicines. Eligibility criteria for the LSDP are constrained. The therapy must be indicated to treat a condition with prevalence of less than 1:50,000, which is more restrictive than the TGA's definition of an orphan drug (1:10,000). Patients with a specific genetic subtype of more common umbrella conditions such as cancer are not eligible for the LSDP, even where they otherwise meet the criteria for consideration as a rare disease (32). This limits the utility of the scheme for facilitating patient access to precision medicines, where cancer is a major condition.

Rule of Rescue

As the RoR is not a formal or standardised pathway, its ability to routinely accelerate the path to market for promising new therapies is limited. While the RoR may provide a means of obtaining reimbursement in exceptional circumstances, it is unlikely to support timely access to the large pipeline of oncology and rare disease medicines expected to reach the market in coming years – particularly those with provisional approval.

Perspectives of patients and patient advocacy organisations

A gap in current reimbursement pathways to effectively manage uncertainty while providing patients with

access to promising, innovative therapies, and the subsequent impact this has on patient outcomes, is well recognised amongst patients and patient advocacy organisations in Australia.

The 2020 Parliamentary Inquiry into the Approval Process for New Drugs and Novel Medical Technologies in Australia shone a light on many of the frustrations experienced by patients when it comes to accessing new therapies. Key concerns expressed by multiple organisations include:

1. Length of time required for PBS listing, particularly in the case of rare or life-threatening diseases
2. Availability of treatment options for Australian patients versus their overseas counterparts
3. Number of submissions often required to achieve PBS listing
4. Suitability of existing HTA processes for the evaluation of innovative therapeutics
5. Challenges in meeting cost-effectiveness requirements for rare / innovative medicines and subsequent impact on patient access

Many organisations have long advocated for change in these areas, including prior to the parliamentary inquiry. For example, a 2018 report by the Lung Foundation Australia captured the impact that waiting for PBS reimbursement can have on patients:

"Regulatory and reimbursement processes also need to keep pace with the rapid advances in scientific research in lung cancer. Lung cancer is emerging as a model of precision, or personalised, medicine, in which treatment decisions are individually tailored to the patient. Precision medicine is particularly relevant to choices about use of innovative new medicines for lung cancer; however, most patients cannot afford to wait and the quality of their care is negatively impacted when the appropriate course of treatment for their situation is either not yet available or is not subsidised by the Pharmaceutical Benefits Scheme in Australia." (35).

Parlimentary Inquiry Submissions

Fabry Australia:

"The length of time from clinical trial outcomes to actually listing the medicine/therapy on the PBS is too long and needs shortening. This is too long when living with a rare, chronic, life-threatening progressive disease ... Adopting process to approve and list new novel therapies such as gene therapy is critical as there are many global studies now enrolling Fabry patients including Australia ... it is important that the timelines for regulatory processes and reimbursement is shortened and delays are minimised to ensure patients with such chronic progressive conditions who have already suffered leading into their diagnosis, access and benefit from such novel therapies without delay. Fabry disease is rare, fatal, and progressive condition with a poor prognosis. The current policies, legislation and funding mechanisms are not equipped to address the urgency and the severity of this condition. The pathways to fund and reimburse companies brining novel therapeutic approaches for rare diseases need to be clear, transparent with appropriate timelines." (28)

MOGA:

"The evidence base for cancer medicines may have some levels of uncertainty. The current system has a low level of acceptance for uncertainty, and has not implemented any process or practical solutions to address this. Hence, the current system may not be sufficiently sensitive to assess the complexity of many cancer treatments, particularly those intended to treat small patient populations with rare cancers. MOGA and Private Cancer Physicians of Physicians (PCPA) are of the view that publicly reimbursed access to oncology drugs is

significantly delayed in Australia compared to other Organisation for Economic Co-operation and Development (OECD) countries. There are increasing instances of access delays in Australia compared with other countries above all with respect to what is recommended in US and European evidence-based cancer treatment guidelines. This impacts negatively on the quality and availability of the cancer care and therapies for Australian patients." (26)

Ovarian Cancer Australia:

"Ovarian Cancer Australia acknowledges that Australia's drug approval process must be based on evidence and rigour and that the Australian Government should secure the best possible price for the drugs listed on the PBS. However, to the 5,000 women with few treatment options for their ovarian cancer, the current drug listing processes seem lengthy and bureaucratic. It is a long and complex process to secure approval and listing and in the meantime women with ovarian cancer die. These women are our mothers, grandmothers, daughters, spouse or friends."(28)

Rare Voices Australia:

"Australian HTA processes utilise models that are designed primarily for more common diseases. This presents challenges for reimbursement decisions for medicines/technologies for rare diseases. Smaller patient numbers impact cost effectiveness, and there is often less clinical evidence available due to the challenges of conducting large-scale clinical trials. This highlights the importance of fit-for-purpose approaches to both research and HTA models for rare diseases." (33)

Rare Cancers Australia:

"It is important that Australia maintains a system that ensures we pay for treatments in alignment with their levels of comparative effectiveness and assessed innovation. We contend however, that this could be achieved whilst still granting access to treatments once they are assessed as effective and then using real world patient experience to assess pricing after the fact. Cost-effectiveness or pricing should NEVER deny the right of patients to access lifesaving medicines." (34)

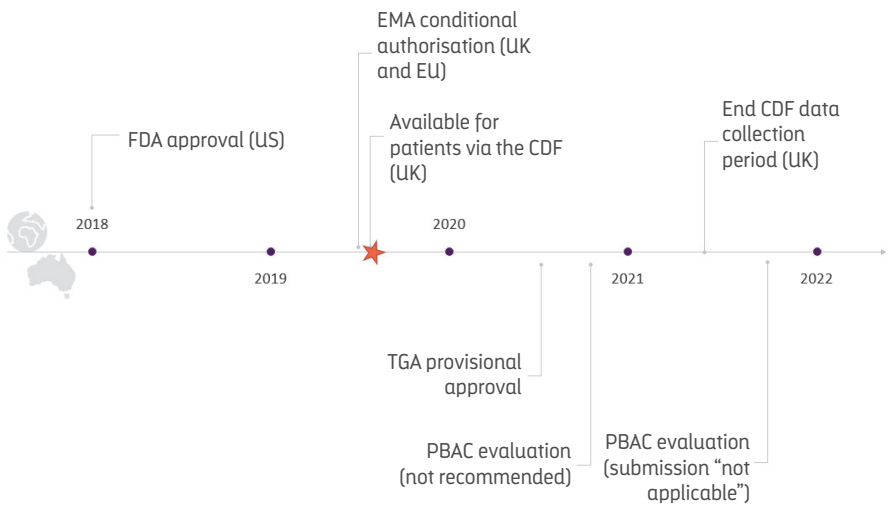
Case study: Cemiplimab for the treatment of cutaneous squamous cell carcinoma

Australia has some of the highest rates of skin cancer in the world, of which non-melanoma skin cancers, such as cutaneous squamous cell carcinoma (cSCC), are particularly prevalent (36). In fact, the incidence of cSCC in Australia is approximately 100 times greater than northern European countries. For patients with advanced or metastatic disease there are limited treatment options available with patients typically receiving a combination of surgery and radiation therapy (37). For patients who are unsuitable for surgery or radiation, their only remaining option is the use of systemic chemotherapy. In Australia, it is estimated that around 80% of patients with advanced cSCC receive best supportive care (consisting of surgery, radiotherapy and symptom management) and approximately 20% receive chemotherapy (38).

In 2018, cemiplimab (Libtayo®) became the first immunotherapy approved by the US FDA for the treatment of selected forms of advanced cSCC (37). This was followed by conditional authorisation by the European Medicines Agency (EMA) in June 2019 (39). In the United Kingdom (UK), cemiplimab was recommended for inclusion in the Cancer Drugs Fund (CDF) in at the beginning of July 2019 with supply subsequently made available from 30th July 2019 (40). In approving cemiplimab for listing on the CDF, the committee noted that trial data was immature and associated with a number of uncertainties, however the overall response rate appeared to be very promising and experts agreed that cemiplimab was likely to be considerably more effective than chemotherapy (41). A data collection period extending to July 2021 was agreed to during which time long term overall survival and progression free survival data for all 3 cohorts of phase II trials was to be collected (41).

In Australia, cemiplimab received TGA provisional approval in July 2020 (42) and was evaluated for PBS reimbursement in November of the same year (38). This submission was rejected with the PBAC indicating that a larger data set would be required, including additional phase II clinical data, with additional Australian epidemiological data also recommended to reduce uncertainty in financial estimates (38). This decision was made despite strong support from the MOGA who categorised cemiplimab as one of the therapies of highest priority for PBS listing (38).

Figure 12: Overview of cemiplimab path to market in Australia versus the US and UK.



Source: (37), (38), (39), (40), (41), (42), (43), (44)

Cemiplimab was resubmitted as part of the November 2021 PBAC meeting, the outcome of which was that it is to be considered at a future PBAC meeting (43). It has since been added to the agenda of the March 2022 PBAC meeting (44). It remains to be seen when, or if, cemiplimab will be listed on the PBS. Without PBS listing, the majority of Australian patients are unlikely to be able to afford cemiplimab. This is particularly striking, considering the disease burden of cSCC in Australia compared with the UK, where cemiplimab is now readily available.

Early Funded Access

A number of mechanisms or policies in place internationally are designed to facilitate accelerated access to promising new therapies (where there is a high a high unmet need), despite immature or incomplete clinical evidence. These offer insights into balancing patient access to new therapies in areas of high unmet medical need whilst managing budget constraints in Australia. Table 3 provides an overview of international approaches to supporting early, funded access to innovative therapies.

Table 3: Overview of international schemes designed to accelerate patient access to promising innovative medicines

Country	Eligibility Criteria	Interaction with HTA/ subsequent reimbursement	Role of RWE and clinical evidence
Germany: AMNOG & CED / OBR	The AMNOG process provides automatic immediate reimbursed access for all patients while HTA is conducted. In cases of high levels of uncertainty, CED and OBR policies may be implemented to control these risks. Historically these arrangements have been made with insurers while the HTA process is ongoing.	HTA and price negotiation is ongoing while reimbursed access is provided under the AMNOG process.	CED schemes require cohort level longer term data around the safety and efficacy of the therapeutic. OBR schemes require individual patient data on the clinical outcomes of the therapeutic. RWE is typically not influential in HTA/reimbursement decisions but may supplement clinical data.
UK: CDF; and IMF	Product must be evaluated by NICE and recommended for use within the CDF. Requires plausible potential to satisfy standard NICE evaluation criteria, but with significant uncertainty. Managed access agreement in place.	At the end of the managed access period, product undergoes re-evaluation by NICE. Products may be recommended for listing or de-funded. Role of NICE in listing products on the CDF considered critical to overall operation and efficiency.	Further clinical evidence and RWE generated through the managed access agreement (while the product is funded on the CDF) may be considered in the full NICE evaluation.
France: AAP (former ATU)	Exceptional circumstances where no appropriate alternative treatments for patient group, clinical trials suggest efficacy and safety and product innovative compared with clinically meaningful comparator.	Separate from HAS reimbursement evaluation. Data collected may inform understanding of how product is used in French clinical practice. No guarantee of reimbursed access.	Real life observational data collected relating to actual conditions of care, but not for clinical research. Observational data may inform but typically does not determine reimbursement outcome. Data used to assess early access renewal.

Italy: 648 List	Must be recognised unmet need and product authorised in other country, OR not yet authorised but clinical trials ongoing (minimum phase II completed) OR off label use. Documented request from patient groups, scientific societies, health facilities/hospital, clinicians or recommendation from regulator.	Dependent on reason for inclusion on 648 list. For example, where additional clinical data is provided, product may undergo subsequent evaluation. Many products on the list are for rare diseases in which case they may be recommended for inclusion in the 5% AIFA fund (for rare diseases) instead	Individual patient data collected to support safety and efficacy and to facilitate ongoing access to product

Germany

In Germany, the *Arzneimittelmarkt-Neuordnungsgesetz* (AMNOG) (Pharmaceuticals Market Reorganisation Act) scheme introduced in 2011 provides free pricing at launch and for the subsequent 12 months. During this period, sponsors are required to negotiate price based on the product's added therapeutic benefit compared with current standard of care (45). This negotiated price will apply from year 2 onwards. In the case of orphan drugs, added therapeutic benefit is assumed without reference to an appropriate comparator provided the overall expenditure for the entire patient population does not exceed 50M Euros (EUR) (45). This process applies to all new patented medicines with annual expenditure greater than 1M EUR (45). As a result, German patients are afforded rapid, reimbursed access to medicines post marketing authorisation.

Novel approaches to pricing, such as outcomes-based rebate (OBR) schemes, have historically seen little use in Germany, however, the arrival of innovative medicines (such as CAR-T cell therapies) that are inherently associated with higher levels of uncertainty, have driven developments in this area (46). For example, both Kymriah® and Yescarta® were subject to OBRs during the 12-month free pricing period (46). Under these agreements, the sponsors are required to provide a rebate where patients die within a specified period (thought to be 12 months) (46). Various coverage with evidence development (CED) schemes have also been applied to address uncertainties associated with cell and gene therapies (47).

France

France has a long history of regulations that allow patients to obtain access to potentially beneficial new medicines in cases where there are no other satisfactory treatment options (48). This approach emerged in response to the Human Immunodeficiency Virus (HIV) epidemic and evolved into six separate mechanisms with similar objectives of facilitating patient access to innovative therapies, but different entry criteria (48). As of July 2021, these pathways have been consolidated into two distinct mechanisms – the *Autorisation d'acces precoce* (AAP) and the *Autorisation d'acces compassionnel* (AAC) (48). The AAP is designed to provide temporary authorisation and financial coverage for a new medicine or indication prior to marketing authorisation, reimbursement or an agreement on price. Pricing within the AAP is set by the applicant who is responsible for reporting sales annually. A rebate is subsequently applied annually where the rebate is calculated based on the turnover and number of patients treated within the AAP. By comparison, the former *Autorisation Temporaire d'Utilisation* (ATU) (Temporary Authorisation for Use), while also permitting free pricing, relied on a clawback mechanism to recoup funds where the final reimbursable price is less than the original ATU price (48).

A *Therapeutic Use Protocol* accompanies AAP authorisation and outlines how the product can be used as well as safety and efficacy monitoring requirements. This governs the collection of additional data for the duration of the authorisation. The therapeutic use protocol strengthens data collection requirements compared with its predecessor, the ATU. This has resulted in some concerns raised over the impact this will have on hospitals and

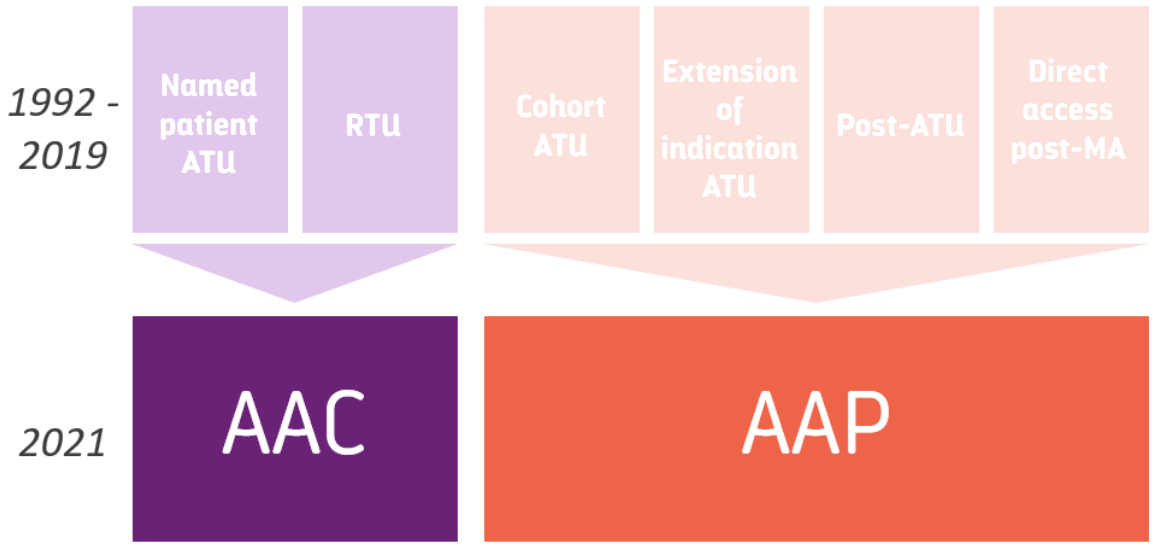
physicians from a resource perspective.

Limitations and reforms

The current AAP and AAC were launched to consolidate the 6 separate schemes which had been introduced between 1992 and 2019 to address various areas of unmet need. The previous framework was criticised for being overly complicated and for placing increasing economic pressure on healthcare expenditure. This restructuring was ultimately intended to simplify and harmonise France's early access pathways, thereby facilitating timely access to new medicines in a way that is sustainable to the broader health system (48). It is also designed to improve transparency around relevant timelines by imposing timeframes within which application decisions must be made and sponsor companies must make medicines available (49).

These reforms also included the removal of a clawback mechanism which was used to control budget expenditure under the previous ATU scheme. Within the ATU, a clawback was activated once sponsors had agreed to a reimbursable price following the free pricing period (49). This was found to be overly complicated and challenging to administer and so was replaced with an annual rebate scheme in the new AAP (48).

Figure 13: Overview of French Early Access Schemes



Source: Motte P. et al. (48), Beley L., Van Vooren B., Bogaert P (49)

UK

Cancer Drugs Fund and Innovative Medicines Fund

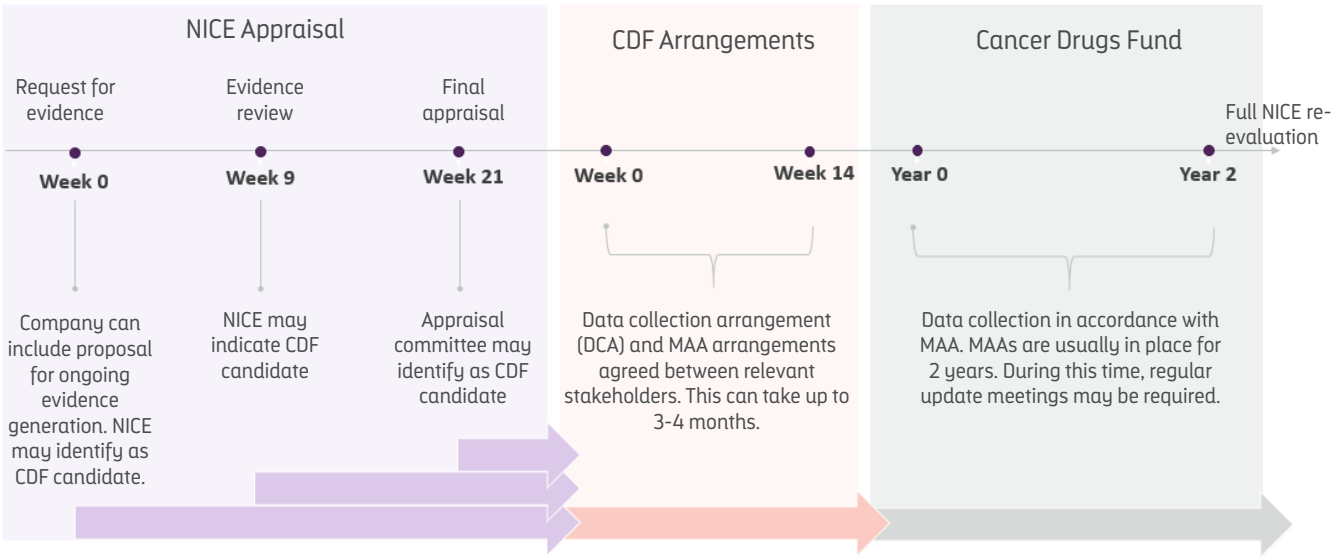
The CDF is designed to accelerate patient access to promising, innovative therapies in circumstances where the available evidence is associated with unacceptable levels of uncertainty and therefore unable to sufficiently demonstrate cost effectiveness (50). For medicines recommended for use within the CDF, interim funding is provided for a specified period of time while additional evidence is collected to address the key areas of clinical uncertainty (51). Once this additional evidence has been collected, the medicine undergoes full re-evaluation and subsequently receives either a yes or no recommendation for funding (51).

All drugs listed within the CDF are subject to a **Managed Access Agreement** (MAA) which consists of a data collection arrangement (DCA) and a commercial agreement (52). The DCA will define what data is to be collected

in order to address the identified uncertainties in clinical outcomes (53). Acceptable sources of additional data include RWD and clinical studies (either ongoing clinical trials or a new) (53). The price is stipulated in a confidential commercial agreement.

In July 2021, National Health Service (NHS) England announced the establishment of a new Innovative Medicines Fund (IMF) off the back of the success of the CDF (54). The IMF is intended to accelerate access to promising innovative medicines for patients with any condition, including rare and genetic diseases (54). It is expected to operate in much the same way as the CDF.

Figure 14: Overview of CDF Process



Source: Motte P. et al. (48), Beley L., Van Vooren B., Bogaert P (49)

Limitations and reforms

The original CDF introduced in 2010 received extensive and ongoing criticism. This largely revolved around its justification, sustainability and decision-making process (55). The CDF was intended to provide temporary access to cancer drugs unable to be recommended by NICE on the basis of cost-effectiveness, or for cancer drugs not yet appraised by NICE (56). With the fund sitting outside of NICE, it was suggested that it created a perverse incentive for sponsors to by-pass NICE and the need to either collect further evidence to demonstrate cost-effectiveness or to reduce prices accordingly (56) (57).

In a 2015 forum, then chair of the CDF, Dr Peter Clark, acknowledged that the existing system had provided companies a get out of jail card, with the CDF ultimately undermining NICE and their approach to HTA (58). The original CDF also quickly exceeded its allocated budget, with 2014-2015 expenditure reportedly amounting to a 48% overspend (56). Concerns were also voiced around the prioritisation of cancer over other diseases or conditions given the opportunity cost this represents (57). These criticisms ultimately lead to a number of reforms and a restructure CDF introduced in 2016.

Key changes to the reformed CDF included allocating ownership of the CDF to National Institute for Health and Care Excellence (NICE) and introducing clear MAA requirements for all drugs listed. As outlined above, these MAA arrangements consist of strict data collection requirements agreed to by both sponsors and NICE prior to listing on the CDF (59). Expenditure control mechanisms have also been introduced to ensure the overall CDF budget is controlled (59). Under this new arrangement, sponsors are required to pay rebates based in a pro-rata

calculation of the company's drugs.

Though these reforms address many of the shortfalls associated with the original CDF, criticism has remained around ring fencing of funds for cancer indications only – including from patients and oncologist who have reportedly expressed guilt and concern around the prioritisation of cancer above other indications (60). This is expected to be addressed by the introduction of the IMF which, as outlined above, will be constructed similarly to the CDF but is not restricted to oncology indications.

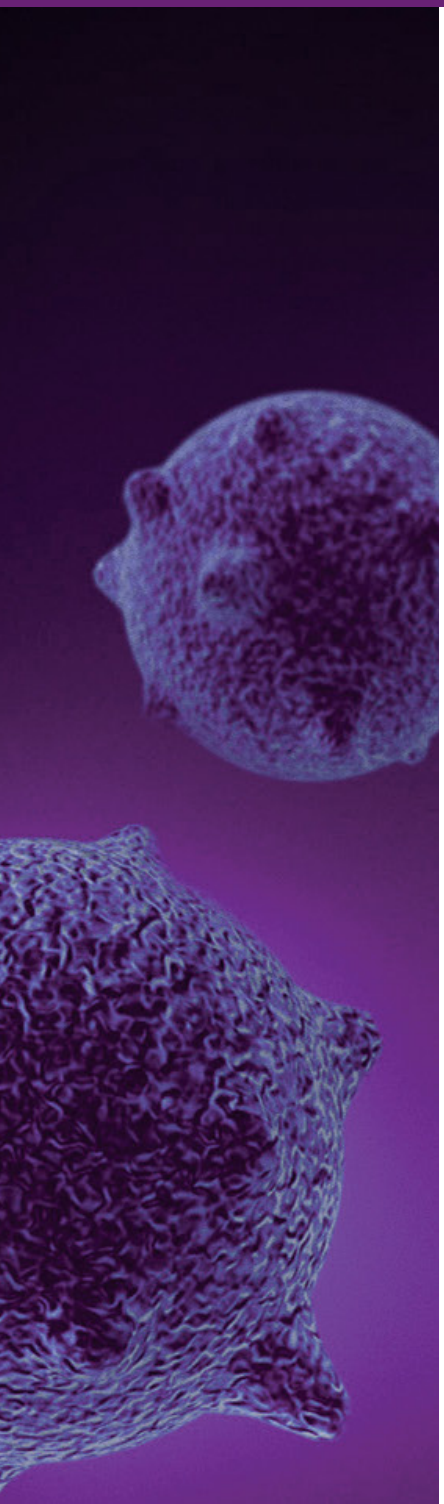
Innovative Licensing and Access Pathway (ILAP)

In 2021, the UK government also announced the implementation of the Innovative Licensing and Access Pathway (ILAP). The ILAP is designed to facilitate safe, timely and efficient development of medicines, improving patient access in the process (61). The ILAP is designed to provide medicine developers (both commercial and non-commercial) with input from key stakeholders, such as regulatory and reimbursement bodies, throughout the drug development process.

A team of experts define a target development profile (TDP) for the product in question which outlines how developers can work with key stakeholders throughout the product development process to ensure a coordinated and efficient approach to evidence generation. This includes establishing a road map for early patient access and a plan to address commercial and managed access considerations (61).

Italy

In Italy, a number of mechanisms are in place to support early access to medicines. These include Law 648/96, which allows eligible products to be reimbursed via the 648 List (62). Under Law 648/96 drugs may be reimbursed by the National Health Service prior to full marketing authorisation or whilst clinical trials are ongoing (63). A request for inclusion in the 648 List can be made by a patient organisation, scientific societies, healthcare and hospital authorities, universities or clinicians but not a pharmaceutical company (63). Medicines included in the list are subject to price negotiation between the pharmaceutical company and Agenzia Italiana del Farmaco (AIFA) (Italian Medicines Agency) (62).



Considerations for Implementation in Australia Building on Learnings from Overseas

Australia has the opportunity to learn from other countries to develop appropriate policies for early reimbursed access to innovative medicines, while avoiding some of the setbacks encountered elsewhere. The following key considerations should be taken into account when designing an appropriate pathway for the Australian system.

Stakeholder collaboration

Australia's healthcare ecosystem is diverse and consists of a broad range of stakeholders who will be impacted in different ways by any changes in this area.

Figure 15: Australia's Healthcare Ecosystem

As such, broad stakeholder collaboration when designing a suitable pathway for early reimbursement has the potential to help ensure subsequent policy is designed to meet the needs and practicalities of all relevant stakeholders.

Similarly, greater collaboration between key stakeholders during the implementation and operation of the program has the potential to further expedite access. This includes collaboration between regulatory and HTA bodies where early alignment on evidence requirements and key areas of uncertainty can help streamline evidence collection and subsequent review. This collaborative approach is a key component of the UK's new ILAP process which provides a pathway for medicine developers to actively engage with both regulatory and

reimbursement bodies in the early stages of development.

It's worth noting that, though broadly recognised as an important component of accelerated access to innovative medicines, this approach has proven challenging to implement in European nations where regulatory processes are carried out at the European level whereas HTA is the responsibility of individual countries (64). Given that both regulatory and reimbursement processes are carried out at the Federal level in Australia, this suggests there is an opportunity for Australia to strengthen alignment and collaboration between the relevant agencies to help streamline the path to market. This has the potential to be particularly impactful in areas of high unmet need.

Patient and clinician engagement

To effectively address areas of unmet need, meaningful input from both patients and clinicians is vital to ensure the delivery of truly patient centred care. This input may be valuable at an early stage, to ensure that meaningful patient outcomes are taken into consideration during the evaluation of new technologies.

England's NICE HTA process includes a dedicated scoping phase, prior to HTA, during which clinicians and patients are provided the opportunity to help define the key criteria such as relevant comparators, population and patient outcomes. It is acknowledged that clinical outcomes, such as those captured in clinical trials, may not align with patient expectations or perspectives around relevant outcomes (65).

Patient and clinician engagement has a particularly important role to play in the evaluation of rare diseases. This includes characterising disease burden and unmet need, as well as aiding in the understanding of the potential impact of a new therapy. Both NICE and the Scottish Medicines Consortium have established processes that give patients and clinicians a voice in decision making processes, particularly for rare diseases (66) (67).

NICE have created separate guidance for the evaluation of highly specialised technologies (HST) which may be utilised for the consideration of technologies indicated for the treatment of "ultra-rare conditions" (68). HSTs are typically accompanied by some form of MAA, similar to therapies funded via the CDF. Key criteria of the MAA, such as the rationale for the agreement and its duration, are reviewed in advance by relevant stakeholders, including patient groups (66). The HST process includes multiple opportunities for patients and other relevant stakeholders to provide input. For example, commenting on current approaches to disease management and patient experience, and participation in the Evaluation Committee that provides recommendations to NICE around benefits and costs (66).

Ultimately, while the Committee must still consider value for money of the technology, their recommendation is also influenced by the input provided by patients, clinical experts and other consultees during the evaluation process (66). The input provided by patients within this process has been shown to be impactful in multiple ways, most notably around providing context to support the interpretation of evidence (69).

Horizon scanning

Horizon scanning in the healthcare space refers to the process of systematically identifying and evaluating new or emerging health technologies to ascertain their potential impact on healthcare systems and subsequently expedite access to these technologies (70). This process is typically undertaken to help policymakers, payers and healthcare providers prepare for the arrival of disruptive, emerging technologies (70).

When it comes to addressing areas of high unmet need and providing early or expedited access to innovative therapies, comprehensive and effective horizon scanning is considered an important first step in the process. Through horizon scanning it is possible to identify areas of high unmet need as well as the pipeline of new therapies capable of addressing these. This creates an opportunity to proactively determine evidence requirements for new medicines and how clinical studies or RWE can be used to address areas of uncertainty. It can also inform the prioritisation of new therapies for inclusion in an early access program.

In addition, horizon scanning creates an opportunity for payers and healthcare providers to effectively budget for the arrival of innovative therapies which are typically associated with high costs. This can also facilitate the management of financial risk associated with the provision of an early access scheme – for example informing the development of an appropriate budget cap for the scheme. It can also help to identify system issues which may act as a barrier to the arrival of disruptive technologies – creating an opportunity to proactively address these such that delays to patient access are avoided.

In the UK, horizon scanning has long been established as the first step in the technology appraisal process for new therapeutic products (71). The National Institute of Health Research Innovation Observatory (NIHRIO) is responsible for horizon scanning and provides information on emerging health technology with significant impact potential for patients or health services (71). The results of this horizon scanning feed into the subsequent HTA process conducted by the NICE (71). The outputs are also utilised by the NHS (70). The role of NIHRIO is to identify activities and relevant technologies and subsequently filter them in accordance with the relevant criteria. The NICE then undertake additional filtration and subsequent prioritisation for HTA based on criteria such as significance of health benefit, variation in use and added value.

Data collection and evidence requirements

Ongoing data collection is a key component of policies designed to facilitate early reimbursed access to medicines. Consideration should be given as to the type of evidence that can effectively support early reimbursement and subsequently how this can be collected. Data collected via ongoing clinical trials remains preferrable and is a key component of programs like the CDF and IMF. Here it's worth noting that the oncology space is well understood with widespread alignment on key endpoints and surrogate endpoints, such as overall survival (OS) and progression free survival (PFS). By comparison, rare diseases are inherently more challenging to investigate. Not only are patient numbers very small, but rare diseases are typically chronic and may be associated with a dearth of information around their natural history. As a result, it can be both challenging to collect extensive clinical trial data, but also to determine what evidence is required to address areas of uncertainty. Consequently, RWE and patient registries are likely to play a more important role in the ongoing evaluation of medicines in the rare diseases space. It is therefore important to establish flexible data collection requirements and timeframes tailored to a specific medicine, the unmet need and areas of uncertainty.

Data collection has the potential to be highly resource intensive for all involved, including clinicians, patients, sponsors and the government. Robust data collection systems and infrastructure that is integrated into the broader healthcare system can facilitate access to relevant data while reducing the burden on clinicians and other key stakeholders. For example, the Systemic Anti-Cancer Therapy (SACT) dataset in the UK systematically collects data in relation to anti-cancer therapy activity from NHS England providers (72). SACT data is a key source of RWD for products listed on the CDF.

In Italy, an internationally recognised web-based registry has long been in place to collect patient and treatment data to help monitor the provision of high priced medicines (73). The registry system is funded by pharmaceutical companies but governed by the AIFA which is responsible for the regulation, pricing, and reimbursement of medicines (73). The registry may be utilised as part of standard pharmaceutical funding and access pathways or to monitor use of therapies that have been granted early access via the 648 List (73). Clinicians and pharmacists are responsible for data collection and entry. This could include details such as patient demographics, clinical data and eligibility, dispensing, and follow up data (73). This data collection may be strictly linked to the provision of the medicine to ensure clinicians and pharmacists are incentivised to meet collection requirements. The registry system is designed to allow patient data to be linked across different product registries and data collection is standardised by disease (altered for a specific drug or indication), which facilitates the reporting and analysis of data (73).

The collection of healthcare data in Australia at present is highly fragmented and existing data sources (such as the PBS, MBS and hospital data) are not linked to relevant clinical information such as patient outcomes. This means that where the collection of RWD is required to support a MAP or risk sharing arrangement for a

particular medicine, there is a need to establish a registry or bespoke data collection system. This creates a multitude of disease specific registries which vary in terms of structure, governance and ownership. Challenges in the collection and utilisation or RWD are compounded by differences between States and Territories in terms of their infrastructure and approach to data management, as well as a lack of collaboration and interaction between jurisdictions. Additional challenges are encountered in the rare disease space where the small number of patients may create the potential to re-identify patients from available data.

There is a need to strengthen the collection of RWD in Australia, including amongst rare disease patients, to support the role of RWD in HTA. There is also an opportunity to improve and streamline the collection of RWE via international data sharing across comparable jurisdictions. This may be particularly important in the rare disease space where patient populations in an individual country may be too small to support meaningful data collection.

It is important to note that the collection and use of RWD requires careful and thorough consideration of data ownership, data privacy, and consent of data use, especially when considering international sharing, and jurisdictional differences that may apply.

Appropriate risk sharing

The sharing of risk between sponsors and the government is an important component of any managed access or early reimbursed access scheme. This needs to be balanced and appropriate to minimise the burden of the scheme on the healthcare system whilst also ensuring sponsors remain incentivised to utilise the relevant pathway. A range of mechanisms have been utilised internationally including rebates, clawbacks or pay for performance schemes, each with varying degrees of success.

As outlined in above, clawback mechanisms were a fixture of processes such as the ATU in France. Under this scheme, sponsors were permitted to set the price of their medicine, however, once a price was negotiated, they were required to pay back retrospectively the difference between the final negotiated price and the initial list price (48). This was challenging for sponsors to determine ahead of time how much they were likely to be required to pay back. As part of the new AAP scheme introduced in 2021 an annual rebate system has been implemented in place of ATU's clawback (48). As part of this process, companies are still permitted to set their own price and are then subject to rebates which are calculated in accordance with a predictable scale comprising the turnover and number of patients treated. Rebate rates increase according to a series of defined turnover tiers (48).

The NHS in the UK also utilise a range of financial control mechanisms, including the use of rebates, in order to control CDF expenditure. Here the CDF budged is fixed with the amount agreed annually. This budget not only covers the any drugs supplied via the CDF, but also associated administrative costs. If the CDF budget is exceeded, then sponsors with a product listed in the CDF will be required to pay a rebate to the NHS (52).

Entry and exit to program (eligibility)

Clearly defined entry and exit criteria can help to ensure the integrity of existing HTA process is not undermined whist helping provide transparency for patients and clinicians. These could include consideration of relevant eligibility criteria for the scheme, how long the conditional funding is provided, and what happens at the end of the conditional funding period.

As outlined above, strict criteria around unmet need and disease severity are typically a key requirement for entry into an early reimbursement program. These are comparable to the TGA's eligibility requirements for the provisional pathway.

The UK's revised CDF and new IMF schemes both clearly outline how long the conditional funding will be provided as well as the requirements following this period. Here the duration of funding via the CDF or IMF is intended to facilitate the collection of additional data during a 2-year period with the specific requirements for

each product captured within its MAA and DCA. Following this period, the product undergoes full re-evaluation after which it may be either be approved for listing or delisted. If a product is delisted, it is important to take into consideration the implications this may have for patients who are currently using the product. For drugs that fail to receive reimbursement following listing on the CDF there is a requirement for the pharmaceutical company to fund the ongoing provision of the product in question for existing patients until the treating physician considers it appropriate to stop.

Conclusion

Disruptive innovations in healthcare, like precision medicines, are rapidly shifting the way we diagnose, treat and manage life threatening conditions such as cancer and rare diseases. These have led to a robust pipeline of innovative cancer and rare disease medicines which provide hope for those patients with severe or life-limiting conditions.

If Australian patients are to benefit from these innovations, timely reimbursement is crucial, yet the time from regulatory approval to funded patient access is approximately two to four times longer in Australia than comparable OECD countries. This can be particularly impactful where there is a high unmet need and limited existing treatment options.

As a result, reform is needed in order to expedite access to innovative therapies and see Australia ranked as a world leader in timely access to new medicines. This includes ensuring there are suitable pathways or mechanisms to manage the uncertainty associated with innovative products that are reaching the HTA process off the back of immature clinical data. Australia can learn from other countries to develop appropriate policies for early reimbursed access to innovative medicines, while avoiding some of the setbacks encountered elsewhere. The upcoming HTA Review outlined in the Medicines Australia 2022-2027 Strategic Agreement with the Australian Government provides an opportunity to reform Australia's approach to HTA, thereby ensuring Australian patients receive access to innovative medicines as soon as possible.

References

1. Medicines Australia. Medicine's Matter: Australia's Access to Medicines 2014-2019. [Online] 2020. [Cited: 11 05 2022.] http://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2020/11/Medicines-Matter-Access-Report.pdf

2. Australian Government, Department of Health. Memorandum of Understanding with Medicines Australia . The Pharmaceutical Benefits Scheme. [Online] 28 September 2010. [Cited: 21 02 2022.] https://www.pbs.gov.au/info/industry/useful-resources/memorandum.

3. Centre for Innovation in Regulatory Science. Review of HTA outcomes and timlines in Australia, Canada and Europe 2015 - 2019. s.l. : Centre for Innovation in Regulatory Science, 2020. R&D Briefing 78.

4. Optimizing Precision Medicine for Public Health . Bilkey G., Burns B., et al. . s.l. : Frontiers in Public Health , 2019. https://doi.org/10.3389/fpubh.2019.00042.

5. Hillel A., Haderi A., Steele R. Curative cell and gene therapies and healthcare system disruption . European Pharmaceutical Review. [Online] 20 May 2021. [Cited: 25 November 2021.] https://www.europeanpharmaceuticalreview.com/article/154305/curative-cell-and-gene-therapies-and-healthcare-system-disruption/.

6. Delivering cellular and gene therpaies to patients: solutions for realizing the potential of the next generation of medicine. Elverum K., Whitman M. 27, s.l. : Gene Therapy, 2020, Vols. 537–544.

7. Australian Institute of Health and Welfare. Lung cancer in Australia: an overview . s.l. : Australian Government, 04 November 2011.

8. Australian Institute of Health and Welfare . Australian Burden of Disease Study 2018: Interactive data on disease burden . Australian Institute of Health and Welfare . [Online] 24 November 2021. https://www.aihw.gov.au/reports/burden-of-disease/abds-2018-interactive-data-disease-burden/data.

9. Department of Health. What we're doing about rare diseases. Australian Government Department of Health . [Online] 11 March 2020. [Cited: 21 December 2021.] https://www.health.gov.au/health-topics/chronic-conditions/what-were-doing-about-chronic-conditions/what-were-doing-about-rare-diseases.

10. Australian Institute of Health and Welfare. Cancer in Australia 2019. s.l. : Australian Government , 2019.

11. NORD. Rare Disease Database. Rare diseases. org. [Online] NORD, 2021. [Cited: 17 02 2022.] https://rarediseases.org/for-patients-and-families/information-resources/rare-disease-information/.

12. Using four decase of FDA orophan drug designations to describe treands in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. Miller K., Fermaglich L., Maynard J. . s.l. : Orphanet Journal of Rare Diseases, 2021, Vol. 16:265.

13. Australian Institute of Health and Welfare. Cancer in Australia 2021. Australian Institute of Health and Welfare. [Online] 01 December 2021. [Cited: 20 01 2022.] https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2021/data.

14. Genomics England. Rare disease genomics. Genomics England. [Online] 2022. [Cited: 25 02 2022.] https://www.genomicsengland.co.uk/genomic-medicine/understanding-genomics/rare-disease-genomics#:~:text=Most%20rare%20diseases%20have%20a,of%20the%20disease%20is%20identified..

15. The collective impact of rare diseases in Western Australia: an estimate using a population-based cohort. Walker C., Mahede T., et al. . 5, s.l. : Genetics in Medicine, 2016, Vol. 19.

16. Rare Cancers Australia . What is Rare Cancer. Rare Cancers Australia . [Online] [Cited: 20 January 2022.] https://www.rarecancers.org.au/page/131/what-is-a-rare-cancer#:~:text=In%20Australia%20each%20year%2052%2C000,common%20cancer%3B%2025%2C000%20wont%20survive..

17. The growing role of precision and personalized medicine for cancer treatment. Krzyszczyk P et al. s.l. : Technology, 2018, Vol. 6. 10.1142/S2339547818300020.

18. National Health and Medical Research Council . NHMRC levels of evidence and grades for recommendations for developers of guidelines . s.l. : Australian Government , 2009.

19. Options for basing dietary reference intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group. Yetley E et al. . s.l. : Am J Clin Nutr. , 2016, Vol. 105(1).

20. Innovation in oncology clincial trial design. Verweij J., Hendriks H., Zwierzina H. . s.l. : Cancer Treat Rev., 2019, Vols. 74:15-20. 10.1016/j.ctrv.2019.01.001.

21. Adaptive designs in clinical trials: why use them, and how to run and report them. Pallmann P., et al. . 29, s.l. : BMC Medicine , 2018.

22. Therapeutic Goods Administration. Provisional approval pathway: prescription medicines . Therapeutic Goods Administration . [Online] 20 March 2018. [Cited: 30 November 2021.] https://www.tga.gov.au/provisional-approval-pathway-prescription-medicines.

23. —. Priority reivew pathway: prescription medicines . Therapeutic Goods Administration . [Online] 2 August 2018. [Cited: 21 December 2021.] https://www.tga.gov.au/priority-review-pathway-prescription-medicines.

24. Analysis of PBAC submissions and outcomes for medicines (2010-2018). Lybrand S., Wonder M. 224-231, s.l. : International Journal of Technology Assessment in Health Care, 2020, Vol. 36(3). doi:10.1017/S026646232000029X.

25. ESMO. Huge variations between countries in time for reimbursement decisions on new cancer drugs . ESMO. [Online] 19 October 2018. [Cited: 21 December 2021.] https://www.esmo.org/newsroom/press-office/mcbs-hta-cancer-drugs-approval-hwang.

26. Medical Oncology Group of Australia . Oncology groups call for creation of a single decision-making body. MOGA. [Online] 30 October 2020. [Cited: 21 December 2021.] https://www.moga.org.au/all-news/oncology-groups-call-for-creation-of-a-single-decision-making-body.

27. Office of Parlimentary Counsel. National Health Act 1953. Canberra : Australian Government , 2017. Act No. 59, 2017.

28. Department of Health . House of representatives standing committee inquiry into access to medicines. Pharmaceutical Benefits Advisory Committee public hearing summary of issues. s.l. : Australian Government , 2020.

29. A real world example of coverage with evidence development in Australia - ipilimumab for the treatment of metastatic melanoma . Kim H., Comey S, Hausler K., Cook G. s.l. : Journal of Pharmaceutical Policy and Practice, 2018, Vol. 11:4. DOI 10.1186/s40545-018-0131-4.

30. Wenzl M., Chapman S. . Performance-based managed entry agreements for new medicines in OECD countries and EU member states: how they work and possible improvements going forward. OECD : s.n., 2019.

31. Gould T. Is it possible to manage PBS managed entry schemes? . s.l. : Commercial Eyes , 2015.

32. Department of Health. Procedure guidance for medicines funded through the Life Saving Drugs Program (LSDP). s.l. : Department of Health , 2018.

33. Rare Voices Australia . Submission 86. Rare Voices Australia submission: Parliamentary Inquiry into approval processess for new drugs and novel medical technologies in Australia . s.l. : Parliament of Australia , 2020.

34. Rare Cancers Australia . Submission 166. Rare Cancers Australia submission to the standing committee on the Health, Aged Care and Sport: Inquiry into approval processes for new drugs and novel medical technologies in Australia . s.l. : Parliment of Australia , 2020.

35. Lung Foundation Australia . Improving outcomes for Australians with lung cancer. A call to action . s.l. : Lung Foundation Australia , 2018.

36. American Institute for Cancer Research. Skin cancer statistics. World cancer research fund. [Online] 2018. [Cited: 16 December 2021.] https://www.wcrf.org/dietandcancer/skin-cancer-statistics/.

37. Skin Cancer Foundation. Advanced Squamous Cell Carcinoma Treatment . Skin Cancer Foundation . [Online] February 2020. [Cited: 16 December 2021.] https://www.skincancer.org/skin-cancer-information/squamous-cell-carcinoma/advanced-scc/#immunotherapy.

38. PBAC. Public summary document - November 2020 PBAC meeting. 5.03 cemiplimab. s.l. : PBAC, 2020.

39. European Medicines Agency. Libtayo. European Medicines Agency . [Online] 27 October 2021. [Cited: 16 December 2021.] https://www.ema.europa.eu/en/medicines/human/EPAR/libtayo.

40. NHS England. National Cancer Drugs Fund List. s.l. : NHS England , 03 December 2021.

41. National Institute for Health and Care Excellence. Final appraisal document. Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma. s.l. : NICE, May 2019.

42. Therapeutic Goods Administration. Libtayo: Australian prescription medicine decision summary. TGA. [Online] 29 July 2020. [Cited: 12 December 2021.] https://www.tga.gov.au/apm-summary/libtayo.

43. Pharmaceutical Benefits Advisory Committee . November 2021 PBAC Meeting Outcomes . s.l. : PBAC, 2021.

44. —. March 2022 PBAC Meeting Agenda . s.l. : PBAC, 2022.

45. OECD. Pharmaceutical reimbursement and pricing in Germany . s.l. : OECD, 2018.

46. Outcomes-based reimbrusement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries . Jorgensen J., Hanna E., Kfalas P. 1715536, s.l. : Journal of Market Access and Health Policy , 2020, Vol. 8.

47. The use of innovative payment mechanisms for gene therapies in Europes and USA. Joregensen J., Kefalas P. s.l. : Regenerative Medicine, 2021, Vols. 16(4), 405 - 422.

48. France implements major changes in its early access framework. Motte P. et al. 11, s.l. : Regulatory Rapporteur, 2021, Vol. 18.

49. Beley L., Van Vooren B., Bogaert P. New Early Access and Off-Label Use Rule in France. Inside EU Life Sciences: updates on legal developments in the EU life sciences industry. [Online] 6 July 2021. [Cited: 13 December 2021.] https://www.insideeulifesciences.com/2021/07/06/new-early-access-and-off-label-use-rules-in-france/.

50. Does the reformed cancer drug fund generate evidence on effectiveness? A cross-sectional analysis of publicly accessible documentation . Macdonals H., Goldacre B. s.l. : Medrxiv, 2020. https://doi.org/10.1101/2020.03.06.19014944.

51. National Institue for Health and Care Excellence . Cancer Drugs Fund. NICE. [Online] [Cited: 19 December 2021.] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund.

52. NHS England. Appraisal and funding of cancer drugs from july 2016 (including the new Cancer Drugs Fund). s.l. : NHS England, 2016.

53. Centre for health Technology Evaluation . Specification for Cancer Drugs Fund data collection arrangements . s.l. : National Institute for Health and Care Excellence.

54. NHS. NHS Engalnd announces new Innovative Medicines Fund to fast-track promising new drugs . [Online] 21 July 2021. [Cited: 9 December 2021.] https://www.england.nhs.uk/2021/07/nhs-england-announces-new-innovative-medicines-fund-to-fast-track-promising-new-drugs/.

55. Will the reformed Cancer Drugs Fund address the most common types of uncertainty? An analysis of NICE cancer drug appraisals . Morell L. et al. s.l. : BMC Health Services Research, 2018, Vols. 18, 393.

56. Did it matter that the cancer drugs fund was not NICE? A retrospecitve review. DPhil P. D., Chamberlain C., Wollingworth W. . 6, s.l. : Value in Health , 2016, Vol. 19.

57. Appleby J. The Cancer Drugs Fund: inequitable and inefficient? TheKing'sFund. [Online] 23 09 2014. [Cited: 13 12 2021.] https://www.kingsfund.org.uk/blog/2014/09/cancer-drugs-fund-inequitable-and-inefficient.

58. Lawrence J. . Cancer Drugs Fund has undermined NICE, its chair admits. s.l. : The Pharmaceutical Journal, 2015.

59. Bailey S. Remap consultaing . Remap comsulting . [Online] 6th June 2018. [Cited: 13 December 2021.] https://remapconsulting.com/recent-changes-to-nices-sta-appraisal-process-and-the-cdf-what-does-this-mean-for-manufacturers/.

60. What's fair to an individual is not always fair to a population: a qualitative study of patients and their health professionals using the Cancer Drugs Fund . Chamberlain C. et al. . 8, s.l. : Health Policy, 2019, Vol. 123. https://doi.org/10.1016/j.healthpol.2019.05.022.

61. Medicines and Healthcare products Regulatory Agency. Guidance: Innovative licensing and access pathway. Gov.uk. [Online] 5 October 2021. [Cited: 9 December 2021.] https://www.gov.uk/guidance/innovative-licensing-and-access-pathway.

62. Garimerti C. Reimbursed early access to unauthorised medicinal products or therapeutic indications in Italy: Udates on the procedure as per law 648/96. Regulatory Pharma Net. [Online] 26 April 2021. [Cited: 10 December 2021.] https://www.regulatorypharmanet.com/reimbursed-early-access-to-unauthorised-medicinal-products-or-therapeutic-indications-in-italy-updates-on-the-procedure-as-per-law-648-96/.

63. AIFA Italian Medicines Agency. AIFA Italian Medicines Agency. Law 648/1996. [Online] [Cited: 10 December 2021.] https://www.aifa.gov.it/en/legge-648-96.

64. Deloitte . Patient access to innovative medicines in Europe. A collaborative and value based approach. s.l. : Deloitte Centre for Health Solutions , January 2019.

65. Public Involvement Programme. Scoping technology appraisals: a factsheet for patient and carer organisations . s.l. : Natioinal Institute for Health and Care Excellence, November 2015.

66. National Institute for Health and Care Excellence. Interim Process and Methods for the Highly Specialised Technologies Programme Updated to reflect 2017 changes. s.l. : National Institute for Health and Care Excellence, 2017.

67. Scottish Medicines Consortium. Patient and Clinician Engagement (PACE) process . Healthcare Improvement Scotland . [Online] [Cited: 16 December 2021.] https://www.scottishmedicines.org.uk/how-we-decide/pace/.

68. National Institute for Health and Care Excellence. Highly specialised technologies guidance . National Institute for Health and Care Excellence. [Online] 2022. [Cited: 13 April 2022.] https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-highly-specialised-technologies-guidance.

69. Evaluation of the impact of patient input in health technology assessments at NICE. Livingstone H., Verdiel V., Crosbie H., Upadhyay S., Harris K., Thomas L. 1, s.l. : Technology Assessment in Health Care, 2021, Vol. 37. DOI: https://doi.org/10.1017/S0266462320002214.

70. Facing the dynamics of future innovation: the role of HTA, industry and health system in scanning the horizon. Oortwijn W . 2018, HTAi Policy Forum Scientific Secretary 2017.

71. NIHR Innovation Observatory. Who we are and what we do. NIHR Innovation Observatory. [Online] 2021. [Cited: 25 November 2021.] https://www.io.nihr.ac.uk/what-we-do/.

72. NHS. SACT systemic anti-cancer therapy chemotherapy dataset. [Online] [Cited: 17 December 2021.] http://www.chemodataset.nhs.uk/home.

73. The Evolution of AIFA Registries to Support Managed Entry Agreements for Orphan Medicinal Products in Italy. Xoxi, E., Facey, K. M., Cicchetti, A. s.l. : Frontiers in Pharmacology, 2021.

74. OECD. Pharmaceutical Innovation and Access to Medicines . 2018.

75. Imprecision in the Era of Precision Medicine in Non-Small Cell Lung Cancer. Sundar R., Chenard-Poirier M., et al. . s.l. : Fronteirs in Medicine, Precision Medicine, 2017. https://doi.org/10.3389/fmed.2017.00039.

76. Lung Cancer in the Era of Precision Medicine. Politi K., Herbst RS. s.l. : Clin Cancer Res, 2015. 10.1158/1078-0432.CCR-14-2748.

77. Eisenstein M. New lung-cancer drugs extend survival times . s.l. : Nature, 2020.

78. American Society of Gene and Cell Therapy. Gene, Cell, & RNA Therapy Landscape. Q2, 2021.

79. Therapeutic Goods Administration . Provisional determination eligibility criteria . Therapeutic Goods Administration . [Online] 26 August 2021. [Cited: 30 November 2021 .] https://www.tga.gov.au/publication/provisional-determination-eligibility-criteria.

80. Australian Government Department of Health. The Pharmaceutical Benefits Scheme . [Online] 2021. [Cited: 30 November 2021.] https://www.pbs.gov.au.

81. Australian Government Department of Health . PBAC Minutes for the Managed Access Program Framework - March 2015. The Pharmaceutical Benefits Scheme. [Online] 24 July 2015. [Cited: 30 November 2021.] pbs.gov.au/info/news/2015/07/pbac-minutes-for-the-managed-access-program-framework/.

82. The Australian Managed Entry Scheme: Are We Getting it Right? . Tuffaha H., Scuffham P. s.l. : Pharmacoeconomics, 2018, Vols. 36(5):555-565. 10.1007/s40273-018-0633-6.

83. Evohealth. Cell and Gene Therapies: Rising to the Challenge. s.l. : Evohealth, 2021.

84. Personalized Medicine. Vogenberg, F. R., Barash, C. I., Pursel, M. 10, s.l. : Pharmacy and Therapeutics,

2010, Vol. 35.

85. Australian Government. Targeted therapy. Cancer Austrealia. [Online] [Cited:] https://www.canceraustralia.gov.au/impacted-by-cancer/treatment/targeted-therapy.

86. The Royal Melbourne Hospital. Phases of clinical trials. The Royal Melbourne Hospital. [Online] https://www.thermh.org.au/research/patients-families/phases-clinical-trials.

87. Australian Government, National Health and Medical Research Council, Department of Industry, Innovation and Science. Phases of clinical trials. Australian Clincal Trials. [Online] 19 February 2015. https://www.australianclinicaltrials.gov.au/what-clinical-trial/phases-clinical-trials.

88. Australian Government, Department of Health. About MSAC. Medical Services Advisory Committee. [Online] 15 September 2020. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/about-msac.

89. —. What is Co-dependent Technology? Medical Services Advisory Committee. [Online] 6 June 2018. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/Factsheet-09.

90. MSAC. Medical Services Advisory Committee (MSAC) Reform Implementation, Process Framework . s.l. : Department of Health, 2016.

91. Horizon scanning of new and emerging medical technology in Australia: its relevant to Medical Services Advisory Committee health technology assessments and public funding. O'Malley S., Jordan E. s.l. : International Journal of Technology Assessment in Health Care, 2009, Vol. 25:3. doi:10.1017/S0266462309990031

Biointelect

Suite 5.02, Level 5, 139
Macquarie Street, Sydney NSW
Australia 2000

T 1300 800 984

E info@biointelect.com