

Health Technology Assessment Policy and Methods Review

Emerging health technologies

May 2024

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1 Introduction

1.1 Purpose and structure of paper

The purpose of this paper is to provide an overview of emerging medicines, vaccines and medicine-related health technologies that may require assessment for funding in the foreseeable future. Through its inquiry into approval processes for new drugs and novel medical technologies in Australia (Inquiry), the Standing Committee on Health, Aged Care and Sport (Standing Committee) formed the view that treatments and therapies such as those for rare cancers, antimicrobials, orphan drugs and precision medicines, do not fit neatly into the current system.¹

This paper provides information on the status of regulatory and reimbursement approval for emerging technologies in Australia and internationally that are in the scope of the terms of reference for the Health Technology Assessment (HTA) Policy and Methods Review (HTA Review).

The technologies in scope for the HTA Review identified in the terms of reference are as follows:

1. all medicines and vaccines
2. highly specialised therapies (for example, cell and gene therapies)
3. other health technologies (for example, a pathology test or an imaging technology) that improve health outcomes associated with the technologies defined in points 1 and 2
4. foreseeable changes in health care that may influence the need, accessibility, effectiveness or cost-effectiveness of new health technologies.

This paper has two parts:

1. emerging technologies in scope for the HTA Review, and
2. emerging technologies that are linked to medicines, vaccines and highly specialised therapies.

This paper also seeks to identify any unique characteristics of emerging technologies that may challenge existing health technology assessment, funding or subsidy pathways. This paper does not consider emerging technologies that are in the pre-clinical stage of development.

The goal of this paper is to ensure that consideration of options for reform through the HTA Review is supported by information about the types of emerging technologies that will require assessment for funding or subsidy in the foreseeable future.

1.2 Information sources

The emerging technologies set out in this paper, and the potential challenges they present, have been identified through published horizon scanning studies, and other literature such as academic

¹Standing Committee on Health, Aged Care and Sport, Inquiry into approval processes for new drugs and novel medical technologies in Australia, Chapter 6, Health Technology Assessment, and the Pharmaceutical Benefits Advisory Committee - www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/Newdrugs/Report/section?id=committees%2freportrep%2f024755%2f77593.

papers and reports, and reports from regulatory and HTA bodies in Australia and other countries. These sources include:

- Newcastle University (UK) National Institute of Health Research Innovation Observatory Horizon Scanning Reports
- Patient-Centred Outcomes Research Institute – Horizon Scanning High Potential Disruption Reports
- the World Health Organization report: Emerging trends and technologies: a horizon scan for global public health (2022)
- the American Society of Gene and Cell Therapy – Gene, Cell and RNA Therapy Landscape Report.

Information about the status of regulatory and reimbursement approval was obtained from the websites of the European Medicines Agency (EMA), United States Food and Drug Administration (FDA), Australian Therapeutic Goods Administration (TGA), Australian Pharmaceutical Benefits Scheme (PBS), and the Australian Medical Services Advisory Committee (MSAC).

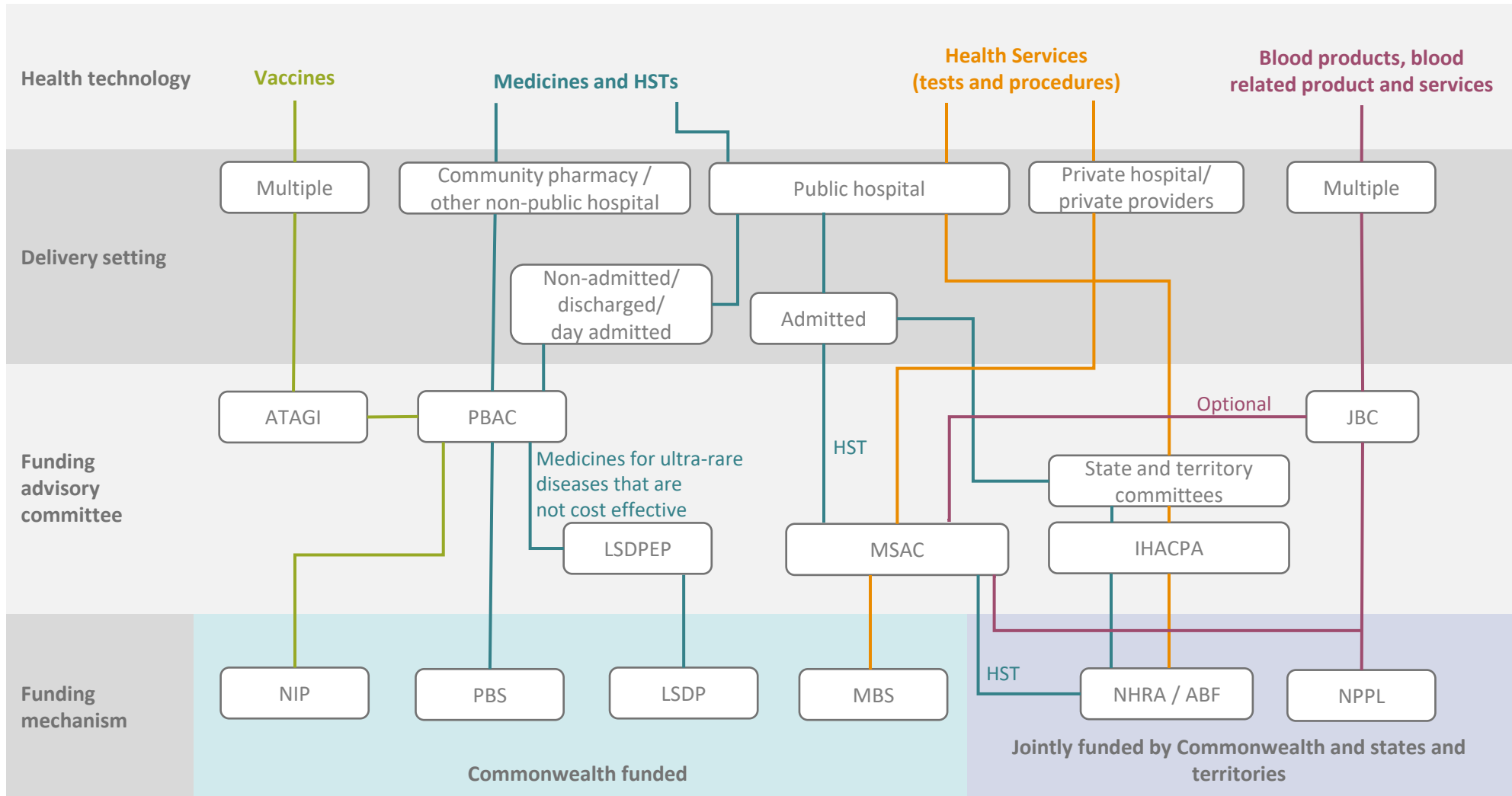
A summary of the technologies identified is provided at Table 1.

1.3 Assessment and funding pathways

Several of the emerging technology types identified in this paper are beginning to be assessed for funding or subsidy in Australia. The funding and assessment pathways, as they have been used for emerging technologies presented in Table 1, are illustrated in the figure below.

More detail about these pathways will be provided in the paper on Australian market approval, funding and assessment pathways and timelines.

Figure 1. Funding pathways for Commonwealth-funded health technologies



Acronyms: ABF = Activity Based Funding; ATAGI = Australian Technical Advisory Group on Immunisation; IHACPA = Independent Health and Aged Care Pricing Authority; JBC = Jurisdictional Blood Committee; LSDPEP = Life Saving Drugs Program Expert Panel; LSDP = Life Saving Drugs Program; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; NIP = National Immunisation Program; PBS = Pharmaceutical Benefits Scheme; NHRA = National Health Reform Agreement; NPPL = National Product Price List.

Table 1 Summary of emerging technologies identified

Category	Examples	EMA (n)	FDA (n)	TGA (n)	Subsidised in Australia	Indications (broad)	Care settings	HTA challenges	Funding and Implementation challenges
Gene therapies	Zolgensma® Luxturna®	Y (6)	Y (8)	Y (3)	Y 1 (PBS) 1 (NHRA-HST)	Genetic disorders or cancers	Mixed settings (public hospital inpatient and outpatient)	- smaller evidence base resulting from trial designs and smaller populations - high uncertainty about long-term health outcomes - high uncertainty about cost-effectiveness - potential for individualised therapy	- high cost - complex and resource- intensive implementation - requires health outcome data collection - requires set up of mechanisms for assessment of health outcome data and price adjustment
Gene silencing oligonucleotides	Spinraza®	Y (8)	Y (16)	Y (4)	Y 1 (PBS)	Genetic disorders	Mixed settings (hospital inpatient and outpatient)	- smaller evidence base resulting from trial designs and smaller populations - long treatment and effect duration - high uncertainty about long-term health outcomes and cost- effectiveness - potential for individualised therapy	- high cost - potential for synthesis of individualised therapeutics using in-house facilities

Category	Examples	EMA (n)	FDA (n)	TGA (n)	Subsidised in Australia	Indications (broad)	Care settings	HTA challenges	Funding and Implementation challenges
Gene modified cell therapies	Yescarta® Kymriah® Tecartus®	Y (9)	Y (11)	Y (4)	Y 3 (NHRA-HST)	Haematological diseases	Inpatient (to date)	- smaller evidence base resulting from trial designs and smaller populations - high uncertainty about long-term health outcomes - high uncertainty about cost-effectiveness - potential for individualised therapy	- high cost - complex and resource-intensive implementation - requires capital investment to set up specialised facilities - requires health outcome data collection - requires set up of mechanisms for assessment of health outcome data and price adjustment - potential for synthesis of individualised therapeutics using in-house facilities
Tumour/tissue agnostic therapies	Keytruda® Vitrakvi® Rozlytrek®	Y (6)	Y (6)	Y (6)	Y 4 (PBS)	Cancer	Mixed settings (hospital inpatient and outpatient, and others)	- uncertainty about relative benefits in different cancer types. - clinical trials have small, highly heterogeneous populations - accuracy of companion diagnostic test - smaller evidence base resulting from trial designs	- no challenges unique to this group
Antibody drug conjugates	Mylotarg® Adcetris® Besponsa®	Y (10)	Y (12)	Y (8)	Y 5 (PBS)	Haematological malignancies and solid tumours	Mixed settings (hospital inpatient and outpatient, and others)	- no challenges unique to this group	- no challenges unique to this group
Bi-specific antibodies	Blinicyto® Vabysmo® Hemlibra® Glofitamab® (RG6026)	Y (11)	Y (11)	Y (7)	Y 2 (PBS)	Cancer and potentially other diseases	Mixed settings (hospital inpatient and outpatient, and others)	- no challenges unique to this group	- no challenges unique to this group

Category	Examples	EMA (n)	FDA (n)	TGA (n)	Subsidised in Australia	Indications (broad)	Care settings	HTA challenges	Funding and Implementation challenges
Phage therapy	Not yet marketed	N	N	N	N	Treatment of antibiotic-resistant bacterial infections	uncertain	- uncertain	- set up of infrastructure - training of workforce to administer treatment
Faecal microbiota products	Biomictra® Rebyota®	N	Y (2)	Y (1)	N	Treatment of Clostridioides difficile infection	uncertain - potentially hospital inpatient or outpatient setting	- uncertain	- set up of infrastructure - training of workforce to administer treatment
Therapeutic vaccines	Oncotice®	Y (2)	Y (3)	Y (1)	Y (1)	Cancer (other indications being trialled)	Mixed settings (hospital inpatient and outpatient, and others)	- uncertain - potential for individualised therapy	- potential for synthesis of individualised therapeutics using in-house facilities
Single gene tests and panel tests	Companion diagnostics for medicines Panel test for diagnosis of neuromuscular disorders	Y	Y	Y	Numerous subsidised by Commonwealth through the MBS, activity-based funding. States also fund tests outside of ABF in certain circumstances.	Conditions where genetic variations cause disease, predispose carriers to greater risk of a certain disease, or modify effectiveness or safety of a therapy	Mixed settings (hospital inpatient and outpatient)	- accuracy of companion diagnostic tests - potential broader use of test than sponsor seeks in application for subsidy - increasing stratification of disease leading to smaller evidence base. - smaller evidence base resulting from trial designs - tests can have prognostic value in addition to clinical utility - algorithm for calculating risk in some panel tests not known	- alignment of funding decisions for test and linked therapy - large number of tests already in use across Australia - existing tests are highly heterogenous, includes in-house facilities and commercial products - ownership of data - potential to supersede existing diagnostic methods, and change treatment algorithms that form criteria for subsidy
Gene expression tests	EndoPredict® Oncotype DX®	NA	Y	Y	Y 1 (MBS)	Prediction of diseases such as recurrence of breast cancer, or transplant rejection	Uncertain	- poor evidence of clinical utility - high cost - algorithms for calculating risk in some tests not known	- high cost - need for individual quality assurance for different tests

Category	Examples	EMA (n)	FDA (n)	TGA (n)	Subsidised in Australia	Indications (broad)	Care settings	HTA challenges	Funding and Implementation challenges
Polygenic Risk Scores	None	N	N	N	None	Conditions where genetic variations cause disease, predispose carriers to greater risk of a certain disease, or modify effectiveness or safety of a therapy	Uncertain	- potential utility in a broad range of clinical settings (multiple comparators, and health outcomes depending on genes analysed) - variable and opaque methodologies for calculating risk	- incidental findings may result in additional interactions with the health system - potential to supersede existing diagnostic methods, and change treatment algorithms that form criteria for subsidy - ownership of genomic data
Radiotheranostics (Radioligand therapy & companion radioactive diagnostic agents)	Lutathera® Pluvicto® 177Lu PSMA i&t	Y	Y	Y	Not supported (MSAC)	Solid tumours	Delivered by nuclear medicine specialists in specialist outpatient facilities	- none identified	- complex and resource intensive implementation - requires capital investment and use of specialised facilities - requires arrangements for appropriate disposal
Digital health technologies	Medication adherence applications Clinical decision support systems Health monitoring devices Algorithms for disease risk profiling			Y (as medical devices)	Y	Many	All	- variability, quality, and generalisability of data - algorithms for calculating risk in some tests not known	- potential to supersede existing diagnostic methods, and change treatment algorithms that form criteria for subsidy

Y = there are technologies of the specified category that have market authorisation from the EMA, FDA, or TGA or are subsidised in Australia; (n) = the number of health technologies of the specified categories identified that have market authorisation from the EMA, FDA, or TGA or are subsidised in Australia; N = there are no examples of the technologies of the specified category that have market authorisation in relevant jurisdictions.

1.4 Issues raised in relation to emerging technologies

Several challenges posed by emerging technologies were identified in submissions to the Inquiry, the horizon scanning studies and other documents considered in this paper. These are briefly summarised below and will be considered in greater depth in later papers to support the HTA Review.

1.4.1 Assessment and funding pathways

Industry stakeholders that made submissions to the Inquiry considered there was lack of clarity for sponsors about pathways for assessment of certain health technologies such as gene and gene-modified cell therapies. Industry stakeholders also expressed concern about different assessment procedures, assessment timings, and funding mechanisms for medicine and diagnostic test components of co-dependent technologies.

The Standing Committee and state and territory stakeholders also raised concern about existing funding arrangements causing potential gaps in continuity of care for patients who receive some of their treatment as inpatients and some of their treatment as outpatients.²

Concerns have also been raised about potential for treatments currently delivered in the inpatient setting (such as CAR T cell therapy) to become outpatient treatment and how they might be funded should this occur.

1.4.2 HTA Challenges

The challenges to HTA vary depending on the technology. Therapies that target specific gene variants, or gene expression profiles, have been identified as posing the greatest challenge to evaluation methods.³ These include gene therapies, gene-silencing oligonucleotides, gene-modified cell therapies, tumour-agnostic cancer drugs, and use of drugs based on gene expression assays.

The lack of high-quality data and high uncertainty associated with the design of clinical trials used to determine safety and effectiveness have been identified as the main challenges in assessing these therapies.⁴ Trials for these therapies are often far shorter than the claimed duration of effectiveness, leading to significant uncertainty about long-term effectiveness.

These therapies are also being developed for progressively smaller populations, particularly as new pathogenic gene variants are discovered, leading to the creation of sub-populations within existing disease categories. This has led to progressively smaller patient numbers in traditional phased clinical trials and development of basket trials, also contributing to uncertainty. In smaller disease populations, Phase 2 trials that demonstrate substantial improvement in safety and efficacy have been considered sufficient to enable provisional market authorisation without progression to a

² Standing Committee on Health, Aged Care and Sport, Inquiry into approval processes for new drugs and novel medical technologies in Australia, Chapter 1, Introduction - www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/Newdrugs/Report/section?id=committees%2freportrep%2f024755%2f77593.

³ Milou A. Hogervorst, Rick A. Vreman, Aukje K. Mantel-Teeuwisse, Wim G. Goettsch, Reported Challenges in Health Technology Assessment of Complex Health Technologies - www.sciencedirect.com/science/article/pii/S1098301521031879?via%3Dihub.

⁴ Trapani D, Tay-Teo K, Tesch ME, Roitberg F, Sengar M, Altuna SC, Hassett MJ, Genazzani AA, Kesselheim AS, Curigliano G. Implications of Oncology Trial Design and Uncertainties in Efficacy-Safety Data on Health Technology Assessments. *Curr Oncol*. 2022 Aug 16;29(8):5774-5791 - <https://pubmed.ncbi.nlm.nih.gov/36005193/>.

Phase 3 trial in the same disease stage, with confirmatory data collected from a different disease stage.

Models of treatment are also being developed where in-house facilities manufacture therapies (for instance, gene therapies and gene-silencing oligonucleotides) that are designed to target specific genes in individual patients. It is unlikely that the safety and effectiveness of each individualised therapy could be established through clinical trials.

1.4.3 Funding and implementation

Several of the emerging therapies identified have a very high cost. These costs create opportunity costs for funders at the federal and state level.

Several of the emerging therapies identified also require more resource intensive implementation than previous new therapies. These challenges arise from greater uncertainty about safety and effectiveness over the longer term, and more severe adverse effects. This, in turn, necessitates data collection via registries, and increases the likelihood of complex administrative requirements requiring admission of patients to hospitals or attendance at other specialised care settings, and potentially very high costs (on a per-patient basis or in terms of total costs, or both).

Additional arrangements to enable implementation of decisions to fund some of the identified emerging therapies have included establishing specialised facilities and data collection arrangements. They have also included contractual arrangements between suppliers and funders to manage risks associated with underperformance of the therapy, use outside of the intended population, or greater numbers of patients than estimated in the HTA.⁵

⁵ PBAC Public Summary, September 2021, Onasemnogene Apeparvovec (Zolgensma) - www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-09/onasemnogene-abeparvovec-solution-for-injection-customise;

MSAC Public Summary, August and November 2019, Tisagenlecleucel (CTL019) for treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (Kymriah) -

www.msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public

MSAC Public Summary, July and November 2020, Luxturna (voretigene neparvovec) for the treatment of biallelic RPE-65-mediated Inherited Retinal Dystrophies -

www.msac.gov.au/internet/msac/publishing.nsf/Content/1623-public.

Emerging Health Technologies

2 Advanced therapies

The terms “advanced therapies”, or “advanced therapy medicinal products (ATMPs)” have been defined as medicines for human use that are based on genes, tissues, or cells.⁶ Different definitions and classifications are used by academia, industry, and governing bodies.

There is no definition for advanced therapies under the *Therapeutic Goods Act 1989* or the *Therapeutic Goods Regulations 1990*. However the TGA uses the following definition for advanced therapies on its website:

- a) Gene therapies
 - i) the substance is used in or administered to human beings to regulate, repair, replace, add, or delete a genetic sequence
AND
 - ii) the substance is involved in the therapeutic, prophylactic, or diagnostic effect of the product
- b) Gene modified cell therapies
- c) Cell and tissue therapies that:
 - i) are not devices
 - ii) have been classified as class 3 or 4 biologicals.
- d) Either a or b in combination with a device⁷.

2.1 Gene therapies

Gene therapies are used in or administered to humans to regulate, repair, replace, add, or delete a genetic sequence (in vivo) for therapeutic, prophylactic, or diagnostic effect, and are regulated by the TGA as prescription medicines.⁷ The FDA provides the following examples of gene therapy products:

Plasmid DNA: Circular DNA molecules can be genetically engineered to carry therapeutic genes into human cells.

⁶ EMA, Advanced therapy medicinal products - www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview.

⁷ TGA, Advanced Therapies - www.tga.gov.au/advanced-therapies.

Viral vectors: Viruses have a natural ability to deliver genetic material into cells, and therefore some gene therapy products are derived from viruses. Once viruses have been modified to remove their ability to cause infectious disease, these modified viruses can be used as vectors (vehicles) to carry therapeutic genes into human cells.

Bacterial vectors: Bacteria can be modified to prevent them from causing infectious disease and then used as vectors (vehicles) to carry therapeutic genes into human tissues.

Human gene editing technology: The goals of gene editing are to disrupt harmful genes or to repair mutated genes.

Patient-derived cellular gene therapy products: Cells are removed from the patient, genetically modified (often using a viral vector) and then returned to the patient.⁸

2.1.1 Development, market approval, and Australian funding status

This analysis identified nine gene therapies that have market authorisation across Europe, the US and Australia. They are used to treat certain familial diseases or cancers. Currently two gene therapies are registered in Australia and are subsidised. There are several more gene therapies in development.

Table 2 Gene therapies

Drug name (Brand name)	Registered Indication	EMA	FDA	TGA	Australian Subsidy
Voretigene neparvovec-rzyl (Luxturna®)	Biallelic RPE65 mutation-associated retinal dystrophy.	Y	Y	Y	Y NHRA (HST)
Onasemnogene abeparvovec-xioi (Zolgensma®)	Treatment of Spinal Muscular Atrophy (Type I)	Y	Y	Y	Y (PBS)
Etranacogene dezaparvovec (Hemgenix®)	Haemophilia B (congenital Factor IX deficiency)	Y (O)	Y	Y	N (Submission received for National Blood Agreement funding)
Talimogene laherparepvec (Imlygic®)	Unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.	Y	Y	N (cancelled in 2021)	N (Not registered)
ASC618	Haemophilia A	N (O)	N	N	N (Not registered)
Giroctocogene fitelparvovec (PF-07055480/ SB-525)	Haemophilia A	N (O)	N	N	N (Not registered)

⁸ FDA, What is Gene Therapy, www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy.

Drug name (Brand name)	Registered Indication	EMA	FDA	TGA	Australian Subsidy
Valoctocogene roxaparvovec (Roctavian®)	Severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5)	Y	Y	N*	N (Submission received for National Blood Agreement funding)
Eladocogene exuparvovec (Upstaza®)	Severe aromatic L-amino acid decarboxylase (AADC) deficiency	Y (O)	N	N	N (Not registered)
Nadofaragene firadenovec (Adstiladrin®)	High-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours	N	Y	N	N (Not registered)
Delandistrogene moxeparvovec-rokl (Elevidys)	Treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.	N	Y	N	N (Not registered)
Beremagene geperpavec-svdt (Vyjuvek)	Dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene	N (O)	Y	N	N (Not registered)

Y= registered or funded. N = not registered (including not approved for registration). O = Orphan medicine (EMA): A medicine for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs.⁹ * = submission currently under evaluation with regulator.

It has been reported that there are many gene therapies in the development pipeline. In 2019 the FDA predicted that it would approve 10-20 new cell and gene therapies a year by 2025.¹⁰

2.1.2 Assessment for funding of gene therapies in Australia

The assessment and funding pathways for gene therapies so far have varied depending on treatment setting and cost. The gene therapies funded to date have required the creation of complex implementation arrangements to manage risks associated with uncertain clinical effectiveness and associated cost-effectiveness particularly over the long term.

Zolgensma

Zolgensma was considered by the PBAC for listing on the PBS at its November 2020, May 2021, and September 2021 meetings. It was recommended for listing on the PBS under the Section 100 Highly Specialised Drugs Program on a cost-minimisation basis to risdiplam. The PBAC agreed to the proposal for an outcomes-based risk sharing arrangement to address uncertainties with the clinical evidence and associated cost effectiveness.¹¹

⁹ European Medicines Association, Orphan medicine - www.ema.europa.eu/en/glossary/orphan-medicine.

¹⁰ Timothy Hunt, The Cell And Gene Therapy Sector In 2023: A Wave Is Coming – Are We Ready?, In Vivo Pharma Intelligence – [invivo.pharmaintelligence.informa.com/IV146781/The-Cell-And-Gene-Therapy-Sector-In-2023-A-Wave-Is-Coming--Are-We-Ready](https://www.invivo.pharmaintelligence.informa.com/IV146781/The-Cell-And-Gene-Therapy-Sector-In-2023-A-Wave-Is-Coming--Are-We-Ready).

Luxturna

Luxturna was considered by the MSAC at its July 2020 and November 2020 meetings. At the November 2020 meeting the MSAC supported joint Commonwealth and State/Territory funding through the Highly Specialised Funding arrangements under the National Health Reform Agreement. MSAC considered that several measures should be implemented to contain risks associated with public funding which included treatment centres meeting eligibility criteria, pay for performance arrangements, provision of biannual reports to the Department of Health and Aged Care on numbers of patients treated and treatment results, and a full review of clinical effectiveness, cost effectiveness and budget impact no later than 3 years post the commencement of public subsidy.¹²

Hemgenix

The sponsor for Hemgenix has applied for public funding through National Blood Arrangements. Hemgenix is currently being considered by MSAC.¹³

2.2 Gene silencing oligonucleotides

Gene silencing oligonucleotides are used to inhibit disease-associated genes. Their effectiveness is dependent on identification of specific genetic alterations. There are two main commercial types that have received market authorisation to date: antisense oligonucleotides and small interfering RNAs.¹¹ The majority that have gained market authorisation to date are used to treat rare genetic diseases however they are also being trialled in the treatment of cancer, viral diseases, and as individualised therapies.

2.2.1 Development, market approval and Australian funding status

This analysis identified 17 gene silencing oligonucleotides that have market authorisation across Europe, the US and Australia. One of these, nusinersen, is subsidised in Australia.

Table 3 Gene silencing oligonucleotides

Drug name (Brand name)	Registered Indication	EMA	FDA	TGA	Australian Subsidy
Nusinersen (Spinraza®)	Spinal muscular atrophy	Y	Y	Y	Y
Inclisiran (Leqvio®)	Hypercholesterolemia or mixed dyslipidaemia	Y	Y	Y	N (Not Recommended by PBAC March 2023)
Patisiran (Onpattro®)	Hereditary transthyretin amyloidosis	Y	Y	Y (O)	N (No submission)
Givosiran (Givlaari®)	Acute hepatic porphyria	Y	Y	Y	N

¹¹ PBAC Public Summary, September 2021, Onasemnogene Apeparvovec (Zolgensma) - <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-09/onasemnogene-apeparvovec-solution-for-injection-customise-w>

¹² MSAC Public Summary, July and November 2020, Luxturna (voretigene neparvovec) for the treatment of biallelic RPE-65-mediated Inherited Retinal Dystrophies - www.msac.gov.au/internet/msac/publishing.nsf/Content/1623-public

¹³ MSAC Application page, Etranacogene dezaparvovec for the treatment of Haemophilia B - www.msac.gov.au/internet/msac/publishing.nsf/Content/1728-public

¹¹ Mounné L, Marie AC, Crouvezier N. Oligonucleotide Therapeutics: From Discovery and Development to Patentability. *Pharmaceutics*. 2022 Jan 22;14(2):260 - www.ncbi.nlm.nih.gov/pmc/articles/PMC8876811.

Drug name (Brand name)	Registered Indication	EMA	FDA	TGA	Australian Subsidy
				(O)	(No submission)
Inotersen (Tegsedi®)	Homozygous familial hypercholesterolemia	Y (O)	Y	N	N (Not registered)
Lumasiran (Oxlumo®)	Primary hyperoxaluria type 1	Y	Y	N*	N (Not registered)
Volanesorsen (Waylivra®)	Familial chylomicronaemia syndrome	Y	N	N	N (Not registered)
Vutisiran (Amvuttra®)	Hereditary transthyretin amyloidosis	Y	Y	N	N (Not registered)
Casimersen (Amondys 45®)	Duchenne muscular dystrophy	N	Y	N	N (Not registered)
Eteplirsen (Exondys 51®)	Duchenne muscular dystrophy	N	Y	N	N (Not registered)
Fomivirsen (Vitravene®)	Cytomegalovirus retinitis in immunocompromised AIDS patients	W	Y	N	N (Not registered)
Golodirsen (Vyondys 53®)	Duchenne muscular dystrophy	N	Y	N	N (Not registered)
Mipomersen (Kynamro®)	Homozygous familial hypercholesterolemia	N	Y	N	N (Not registered)
Vitolarsen (Viltepso®)	Duchenne muscular dystrophy	N	Y	N	N (Not registered)
Eplontersen (Wainua)	Hereditary transthyretin-mediated amyloidosis	N	Y	N	N (Not registered)
Tofersen (Qalsody)	Amyotrophic lateral sclerosis	N	Y	N	N (Not registered)
Nedosiran (Rivfloza)	Primary hyperoxaluria type 1 (PH1)	N	Y	N	N (Not registered)

Y= registered or funded. N = not registered or funded. W = withdrawn. O = Orphan medicine (EMA): A medicine for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs. O = Orphan medicine (TGA): Sponsors receive a fee waiver to help bring medicines for a small population to market¹². * = submission currently under evaluation with regulator.

A 2021 scan of oligonucleotide drugs in clinical development found 130 phase II or phase III clinical trials involving 80 oligonucleotides. They were being tested in 102 different indications targeting 66 different genes. The study found use in metabolic disorders, ophthalmology, gastrointestinal, dermatology, hormonal disorders, oncology, cardiovascular, infectious disease, haematology, immunology, neurology, muscular diseases, genitourinary disease, and respiratory diseases.¹¹ A 2023 scan of RNAi, mRNA and antisense oligonucleotides found 897 therapies in the pipeline (from preclinical to pre-registration).¹³ This analysis found the most common therapeutic area targeted was rare diseases.

¹² Therapeutic Goods Administration, Orphan drug designation - <https://www.tga.gov.au/resources/resource/guidance/orphan-drug-designation>

¹³ American Society of Gene and Cell Therapy, Gene, Cell and RNA Therapy Landscape Report, 2023, <https://asgct.org/publications/landscape-report>.

2.2.2 Assessment for funding of gene silencing oligonucleotide drugs in Australia

To date, one gene silencing oligonucleotide has been subsidised in Australia. Spinraza¹⁴ (nusinersen), was assessed by the PBAC and is subsidised through the PBS.

Spinraza

Spinraza (nusinersen) is registered in Australia for the treatment of 5q spinal muscular atrophy (SMA). The PBAC considered submissions to list nusinersen on the PBS for the first time at its November 2017 and March 2018 meetings. At its November 2017 meeting the PBAC did not recommend the listing of nusinersen for the treatment of patients with infantile onset (type 1) and childhood onset (types II and III) based on uncertainty about clinical effectiveness in terms of the extent and durability of response across the spectrum of SMA for which subsidy was sought. The primary evidence presented was two head-to-head randomised trials comparing nusinersen to sham controls. The PBAC noted that both trials were of short duration (13 months and 15 months respectively) in the context of a lifelong condition.

At its March 2018 meeting the PBAC considered a resubmission from the sponsor requesting listing of nusinersen for the treatment of paediatric patients with infantile-onset or childhood onset SMA with onset of symptoms prior to 3 years of age. The submission provided updated results from an open label extension trial which appeared to confirm that treatment with nusinersen in patients with type 1 SMA increases life expectancy. The PBAC recommended listing.

2.3 Gene modified cell therapies

Cell therapies are a form of treatment where live cells are transferred into a patient to treat a disease. Cellular therapy products include cellular immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells for certain therapeutic indications, including hematopoietic stem cells and adult and embryonic stem cells.¹⁵ Emerging cell therapies involve manipulation of cells before they are transferred into a patient. This manipulation may or may not involve genetic manipulation.

Gene-modified cell therapy or cell-based gene therapy involves the incorporation of a functional gene into a cell-based therapy.¹⁶ It involves the removal of specific cells from the body, *ex vivo* genetic modification, and administration back into the patient to help the patient fight a disease. There are multiple types of gene modified cell therapies in development including:¹⁷

- Chimeric antigen receptor (CAR) T-cell therapies
- T-cell receptor (TCR) therapies
- Tumour infiltrating lymphocytes (TILs)
- Natural killer (NK) cell therapies
- Marrow derived lymphocytes (MILs)

¹⁴ PBAC Public Summary, March 2018, Nusinersen (Spinraza) - www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-03/Nusinersen-psd-march-2018.

¹⁵ FDA, cellular gene therapy products - www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products.

¹⁶ Drug Development and Delivery, Genetic modification therapies – clinical applications and technology platforms - drug-dev.com/genetic-modification-therapies-clinical-applications-technology-platforms.

¹⁷ Foundation for Cell and Gene Medicine – Healing Genes Program, Gene Modified Cell Therapy – healinggenes.org/gene-modified-cell-therapy/.

- Listeria-based therapies
- Dendritic cell vaccine therapies

The majority of these do not have market approval. Chimeric antigen receptor (CAR) T cell therapies represent the largest category of gene modified cell therapies that have obtained market approval. They are made by collecting T cells from the patient and genetically modifying them in a laboratory to produce proteins on their surface called chimeric antigen receptors, or CARs that recognize and bind to specific proteins, or antigens, on the surface of cancer cells. The CAR T cells are then expanded for clinical use and infused back into the patient.¹⁸

They can be generated by either viral transduction leading to a permanent CAR expression, or by using mRNA as well as transposon technology for transient CAR expression.¹⁹

2.3.1 Development, market approval and Australian funding status

This analysis identified eleven gene-modified cell therapies approved by the FDA, nine approved by the EMA, and four approved by the TGA. Three are approved for subsidy in Australia.

Table 4 Gene-modified cell therapies

Drug name (Brand name)	Registered Indication	EMA	FDA	TGA	Australian Subsidy
Axicabtagene ciloleucel (Yescarta®)	Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	Y	Y	Y	Y (NHRA HST)
Tisagenlecleucel (Kymriah®)	B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse. Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.	Y	Y	Y	Y (NHRA HST)
Brexucabtagene autoleucel (Tecartus®)	Relapsed or refractory mantle cell lymphoma (MCL), who have received two or more lines of therapy, including a BTK inhibitor, unless ineligible or intolerant to treatment with a BTK inhibitor. Relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (B-ALL).	Y	Y	Y	N (MSAC supported public funding in July 2021, but not yet implemented)
Lisocabtagene maraleucel (Breyanzi®)	Large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B	Y	Y	N	N (Not registered)

¹⁸ Feins, S., Kong, W., Williams, E. F., Milone, M. C., & Fraietta, J. A. (2019). An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. *American Journal of Hematology*, 94(S1), S3–S9 - doi.org/10.1002/ajh.25418.

¹⁹ Vucinic V, Quaiser A, Lückemeier P, Fricke S, Platzbecker U and Koehl U (2021). Production and Application of CAR T Cells: Current and Future Role of Europe. *Frontiers in Medicine*. 8:713401 - www.frontiersin.org/articles/10.3389/fmed.2021.713401/full.

Drug name (Brand name)	Registered Indication	EMA	FDA	TGA	Australian Subsidy
Ciltacabtagene autoleucl (Carvykti®)	Relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody	Y	Y	Y	N Not supported for public funding by MSAC (July 2022)
Idecabtagene vicleucl (Abecma®)	Relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.	Y	Y	N	N (Not registered)
Betibeglogene autotemcel (Zynteglo®)	Beta-thalassemia who require regular red blood cell transfusions	W	Y	N	N (Not registered)
Elivaldogene autotemcel (Skysona®)	Cerebral adrenoleukodystrophy (CALD)	W	Y	N	N (Not registered)
Atidarsagene autotemcel (Libmeldy®)	Metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity	Y	N	N	N (Not registered)
FT536	Treatment of multiple solid tumour indications	N	N	N	N (Not registered)
Afamitresgene autoleucl	Treatment of solid tumours	N	N	N	N (Not registered)
Invossa (TissueGene-C)	Treatment of symptomatic and persistent knee osteoarthritis (OA)	N	N	N	N (Not registered)
Autologous CD34+ enriched cell fraction (Strimvelis®)	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID).	Y (O)	N	N	N (Not registered)
Nalotimagene carmaleucl (Zalmoxis®)	Adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies	W	N	N	N (Not registered)
Motixafortide (Aphexda)	In combination with filgrastim (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma	N	Y	N	N (Not registered)
Exagamglogene autotemcel (Casgevy)	Treatment of sickle cell disease (SCD)	Y (C, O)	Y	N	N (Not registered)
omidubicel-olnv (Omisirge)	For use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection	N	Y	N	N (Not registered)

Y= registered or funded. N = not registered or funded. W = withdrawn. C = Conditional marketing authorisation (EMA): A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. The marketing authorisation holder is expected to provide comprehensive clinical data at a later stage²⁰. O = Orphan medicine (EMA): A medicine for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs.

As of 2021, there are approximately 900 studies worldwide with the use of CAR T cells as investigational drugs in different tumour entities.

2.3.2 Assessment for funding of cell therapies in Australia

Gene modified cell therapies have been assessed by MSAC and funded through the NHRA.

Kymriah

Kymriah was the first CAR-T therapy to be considered for funding in Australia. There was no precedent for the funding and assessment of an identical technology type in Australia. CAR T requires in-patient treatment, administration, and specialised care that is generally only available in some tertiary public hospitals. Therapy also had very high costs. The sponsor requested creation of a new national funding mechanism.²⁵

At its April 2019 meeting MSAC supported the public funding of Kymriah for acute lymphoblastic leukaemia in children and young adults up to 25 years old.²¹ At its August 2019 meeting, MSAC supported the public funding of Kymriah for certain patients with relapsed or refractory diffuse large B-cell lymphoma.²⁶

MSAC recommended several measures would need to be implemented to contain the risks associated with public funding and patient safety including:

- treatment delivered by a haematologist working in a multi-disciplinary team specialising in the provision of CAR-T cell therapy,
- treatment in a tertiary public hospital with appropriate credentials,
- a limit to one successful CAR-T infusion per lifetime,
- recording of data on the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR).
- Full review of clinical effectiveness, cost effectiveness and budget impact no later than 2 years post the commencement of public subsidy.²²

Separate funding arrangements for highly specialised therapies (including Kymriah) were negotiated as part of the 2020-25 National Health Reform Agreement. Kymriah is funded under those arrangements.

²⁰ European Medicines Agency, Conditional marketing authorisation - <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation>

Yescarta

Yescarta was considered by MSAC at its November 2019 meeting and out of session in January 2020 for the treatment of relapsed or refractory diffuse large B cell lymphoma, primary mediastinal b cell lymphoma and transformed follicular lymphoma. MSAC supported joint Commonwealth and State/Territory funding through the Highly Specialised Therapies Funding arrangements under the National Health Reform Agreement. MSAC considered several measures would need to be implemented to contain the risks associated with public funding including those mentioned above for Kymriah.

2.4 Challenges identified for assessment, funding, and implementation of advanced therapies

The advanced therapies considered for funding to date present complexities of high cost, greater uncertainty about the health outcomes they deliver and complex and resource intensive implementation.²³

2.4.1 Assessment and funding pathways

Through the Inquiry, industry stakeholders expressed concern that cell and gene therapies are assessed by different HTA committees (MSAC or PBAC) based on treatment setting. Industry stakeholders commented that it can be challenging for the sponsors to determine the appropriate pathways in cases where there may be potential for provision in either setting.²⁴

Applications for funding of gene therapies have been made for NHRA HST arrangements, the PBS, and under the National Blood Arrangements.

The assessment and funding pathway depend primarily on the treatment setting. Whether the treatments are eligible for funding under the PBS, require in-patient administration in a public hospital or potentially meet the definition of 'blood related product' or 'blood related service' under the National Blood Arrangement are all considered when determining the appropriate funding source and therefore assessment pathway.

Stakeholders have also raised that current arrangements do not provide for circumstances where a treatment ceases to meet the definition of HST under the NHRA, such as change from the inpatient to the outpatient setting or decrease in cost. The National Health Reform Agreement does not state how or if funding arrangements would change in these circumstances, or whether a new health

²¹ MSAC Public Summary, April 2019, Tisagenlecleucel (CTL019) for treatment of refractory CD19-positive leukaemia and lymphoma.

²² MSAC Public Summary, November 2019, Tisagenlecleucel (CTL019) for treatment of refractory CD19-positive leukaemia and lymphoma - www.msac.gov.au/internet/msac/publishing.nsf/Content/1519.1-public.

²³ Newcastle University (UK) National Institute of Health Research Innovation Observatory – Horizon Scan for ATMPs October 2021 - www.io.nihr.ac.uk/wp-content/uploads/2022/01/Horizon-Scan-for-ATMPs_October2021-v2.0.pdf.

²⁴ Standing Committee on Health, Aged Care and Sport, Inquiry into approval processes for new drugs and novel medical technologies in Australia, Chapter 6, Health Technology Assessment and the Pharmaceutical Benefits Advisory Committee - www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/Newdrugs/Report/section?id=committees%2freportrep%2f024755%2f77593.

technology assessment would be required to deliver funding through alternative arrangements. Inconsistency could also arise if a class of treatments or treatments for the same indication are assessed and funded through different pathways.

An example of a HST that has potential to move from the inpatient setting to the outpatient setting is CAR T cell therapies. Although currently administered in the inpatient setting, delivering CAR T cell therapy in the outpatient setting is being contemplated. To date this has not been adopted as standard clinical practice for multiple reasons, including logistic and reimbursement issues and patient safety concerns.²⁵

2.4.2 Evaluation

Evidence

A study involving 22 European HTA organisations found that advanced therapies were considered the most challenging to evaluate.²⁶ The main challenge identified for evaluating these therapies is the lack of high-quality data and high uncertainty associated with the design of clinical trials used to determine the safety and effectiveness of these therapies.²⁷ The lack of high-quality data and clinical uncertainty leads to challenges in:

- determining whether new therapies offer an improvement over available alternatives,
- determining cost effectiveness and
- decision making.

The genetic conditions that are treated by advanced therapies are often rare to ultra-rare, resulting in small numbers of participants in trials. The trials relied on by the PBAC for nusinersen for example contained 121 participants (for infantile-onset SMA) and 126 participants (for childhood onset SMA).

The duration of the clinical trials is also much shorter than the claimed duration of effect. The clinical trials relied on for nusinersen ran for 13 months and 15 months respectively, whereas the duration of treatment could be for a patient's lifetime.

Notwithstanding small numbers in trials, gene therapies and gene silencing oligonucleotides have been created to treat the most common genetic alterations in patients with genetic diseases. Methods for producing individualised therapies are being developed to enable treatment of patients with rarer gene alterations that cause the same disease. It is unlikely that for each rare gene alteration there will be enough participants to generate sufficiently robust evidence to estimate long term safety and effectiveness.

²⁵ Myers, G. D., Verneris, M. R., Goy, A., & Maziarz, R. T. (2021). Perspectives on outpatient administration of CAR-T cell therapy in aggressive B-cell lymphoma and acute lymphoblastic leukemia. *Journal for Immunotherapy of Cancer*, 9(4), e002056 – doi.org/10.1136/jitc-2020-002056.

²⁶ Hogervorst MA, Vreman RA, Mantel-Teeuwisse AK, Goettsch WG. Reported Challenges in Health Technology Assessment of Complex Health Technologies. *Value Health*. 2022 Jun;25(6):992-1001 - pubmed.ncbi.nlm.nih.gov/35667787/.

²⁷ Trapani D, Tay-Teo K, Tesch ME, Roitberg F, Sengar M, Altuna SC, Hassett MJ, Genazzani AA, Kesselheim AS, Curigliano G. 2022. Implications of Oncology Trial Design and Uncertainties in Efficacy-Safety Data on Health Technology Assessments. *Current Oncology*. 29(8):5774-5791 - www.ncbi.nlm.nih.gov/pmc/articles/PMC9406873/.

Cost

Advanced therapies are the most expensive for a course of treatment. The PBS dispensed price for nusinersen is \$110,000 for each dose to be delivered to patients every 4 months. The PBS dispensed price for Zolgensma is over \$2.5 million for the single dose.²⁸

2.4.3 Implementation

Recommendations for funding of gene and gene modified cell therapies have included complex implementation requirements due to high cost, patient safety concerns, and uncertainty about long term safety and effectiveness.

Implementation requirements in recommendations for subsidy of cell and gene therapies have included:

- treatment delivered in specialist settings and appropriately credentialed facilities
- data on use and outcomes to be recorded and reported back to Commonwealth and state and territory governments
- outcomes based risk sharing arrangements
- full review of clinical effectiveness, cost-effectiveness, and budget impact at a certain time after commencement.
- registries for collecting long-term safety and effectiveness data (whether disease-based or therapy-based registries are optimal is to be determined)
- need to consider the retention of patient genetic data to inform the long-term analysis of safety and/or effectiveness (noting the period of mandated genetic data storage may be shorter than that for monitoring therapy outcomes).

For highly specialised therapies funded under the NHRA, states and territories decide when and where the therapy will be provided.

The anticipated increase in number and diversity of advanced therapies to be marketed in the future will present significant resourcing challenges, particularly if new data collections are required for these products. The formation of registries and who is best placed to manage them will require policy consideration. Registry considerations for health technologies will be discussed further in future HTA Review papers.

2.5 Tumour-agnostic cancer therapies

Historically, cancers have been classified and treated based on features observed in cancer tissue and/or the organ the cancer cells have come from.²⁹ These features of a cancer are often referred to as the cancer's histology. New gene sequencing technologies have progressively led to grouping of different cancers according to the presence of particular 'biomarkers' such as specific gene alterations, expression of particular genes, or other proteins or molecules in the cancer or in other tissues.²⁹

Tumour-agnostic therapies are cancer treatments that are authorised for use based on particular

²⁸ PBS – www.pbs.gov.au.

²⁹ C Corti, G Antonarelli, C Valenza, et al. Histology-agnostic approvals for antibody-drug conjugates in solid tumours: is the time ripe? *Eur J Cancer*, 171 (2022), pp. 25-42 - www.sciencedirect.com/science/article/abs/pii/S0959804922002799?via%3Dihub.

biomarkers in the cancer or other tissues, rather than the cancer’s histology.³⁰ A tumour agnostic therapy may be used to treat cancers from multiple different organs of origin if they carry the same biomarker.³¹

2.5.1 Development, market approval and Australian funding status

This analysis identified six therapies that have proposed tumour-agnostic indications that have market authorisation across Europe, the US and Australia. While four are approved for subsidy in Australia, only Vitrakvi (larotrectinib) is subsidised based on the presence of a biomarker as opposed to cancer histology.

Table 5 Tumour-agnostic therapies

Drug name (Brand name)	Potential tumour agnostic indication	EMA*	FDA*	TGA*	Australian Subsidy
Pembrolizumab (Keytruda®)	Tumours that have high level of microsatellite instability (MSI-H); a defect in a mismatch repair gene (dMMR); or high tumour mutational burden (TMB-H)	Y	Y	Y	No submission for tumour agnostic indication
Larotrectinib (Vitrakvi®)	Solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion	Y	Y	Y	2022 (PBS) for paediatric NTRK tumours
Entrectinib (Rozlytrek®)	Solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion	Y	Y	Y	No submission to PBAC for tumour agnostic indication
Dostarlimab (Jemperli®)	Tumours that have a defect in a mismatch repair gene (dMMR);	Y	Y	Y (P)	No submission to PBAC for tumour agnostic indication
Dabrafenib (Tafinlar®) and Trametinib (Mekinist®)	Stage 4 cancers that have a BRAF V600E mutation	Y	Y	Y	2019 (PBS) No submission to PBAC for tumour agnostic indication
Selpercatinib (Retevmo®)	Cancers with RET gene fusions	Y	Y	Y (P)	N

Y = registered or funded. N = not registered or funded. * Registered indication may or may not be tumour agnostic. P = Provisional registration (TGA) = Involves early access to vital and life-saving medicines through time-limited registration³²

In June 2021, the NIHR Innovation Observatory undertook a rapid horizon scan for ‘potential’ tumour agnostic therapies that were within an approximate 5-year timeframe to obtaining a product licence in the EU/UK.³³ The horizon scanning results identified:

³⁰ NIHR Innovation Observatory: Horizon Scan for Histology Independent Therapies targeted at Cancer - www.io.nihr.ac.uk/wp-content/uploads/2021/12/Horizon-Scan-for-Histology-Independent-Technologies_June-2021_AAC_V1.0.pdf.

³¹ FDA, Tissue Agnostic Drug Development in Oncology – Guidance for Industry - www.fda.gov/media/162346/download.

³² Therapeutic Goods Administration, Provisional approval pathway: prescription medicines - <https://www.tga.gov.au/provisional-approval-pathway-prescription-medicines>

³³ Newcastle University (UK) NIHR Innovation Observatory, Horizon Scan for Histology Independent Therapies targeted at Cancer: www.io.nihr.ac.uk/wp-content/uploads/2021/12/Horizon-Scan-for-Histology-Independent-Technologies_June-2021_AAC_V1.0.pdf.

- 194 potential tumour-agnostic therapies identified in the scan, ~6% (n=12) were estimated to be launched in the UK in less than 3 years.
- Tumour-agnostic therapies in the pipeline predominantly target solid tumours.
- A growing number of target haematological cancers.
- Majority of tumour-agnostic therapies are in phase I/II and II trials and utilise ‘basket’ trial designs; identification of the basket trial design is not always readily apparent from the clinical trial records.

A basket trial is a type of clinical trial that tests how well a new drug or other substance works in patients who have different types of cancer that all have the same mutation or biomarker.³⁴ In basket trials, patients all receive the same treatment that targets the specific mutation or biomarker found in their cancer.³⁴

2.5.2 Assessment for funding of tumour-agnostic therapies in Australia

Tumour-agnostic therapies are assessed through the ‘co-dependent’ pathway where medicines are assessed by the PBAC and the associated test for molecular alterations or biomarkers is assessed by the MSAC. Tumour-agnostic therapies to date have been subsidised through the PBS. The necessary tests for detecting molecular alterations or biomarkers are subsidised through the MBS.

Vitrakvi

Vitrakvi (larotrectinib) is registered in Australia for the treatment of metastatic solid tumours that have a neurotrophic tyrosine receptor kinase gene fusion. The PBAC considered larotrectinib at its November 2020, December 2020, November 2021, and March 2022 meetings for the targeted treatment of *NTRK* fusion solid tumours that are unresectable locally advanced, metastatic, or locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection.

The main PBAC concerns raised in the November 2020 public summary document were in relation to uncertainty about the effectiveness in the proposed subpopulations with low frequency *NTRK* fusions.¹ The PBAC also noted that collectively, the single-arm design of the larotrectinib studies, small patient numbers (due to rarity of *NTRK* fusion cancers), potential heterogeneity in disease characteristics and treatment outcomes by tumour type, the impact of confounding of overall survival from subsequent treatments received post-progression in the larotrectinib studies amongst other factors contributed to a high degree of uncertainty about the magnitude of incremental benefit of larotrectinib.

At its March 2022 meeting, the PBAC recommended larotrectinib for the treatment of paediatric patients with *NTRK* fusion tumours and adult patients with high frequency *NTRK* fusion tumours (specifically mammary analogue secretory carcinoma (MASC) and secretory breast carcinoma) noting that MSAC supported funding the co-dependent *NTRK* testing to determine eligibility for treatment with larotrectinib in all paediatric patients, and adult patients with high frequency *NTRK* fusion cancer types.³⁴

The treatment is expected to address a high and urgent unmet clinical need in patients with *NTRK* fusion tumours, noting most tumour types in paediatric patients and the tumour types specified for the adult high frequency subgroup are rare cancers with limited treatment options.

³⁴ US National Cancer Institute, Dictionary of Cancer Terms – Basket Trial - www.cancer.gov/publications/dictionaries/cancer-terms/def/basket-trial.

The Pre-Sub-Committee Response (PSCR) indicated that tumour types were not specified for paediatric high and low frequency subgroups due to ethical considerations, as all paediatric patients have access to NTRK fusion testing through the Zero Childhood Cancer Initiative. The Economics and Evaluation Subcommittees (ESCs) considered specifying tumour types for the adult population only was reasonable. Larotrectinib was the first medicine to be subsidised through the PBS for a tumour agnostic indication.

2.5.3 Challenges identified for assessment, funding, and implementation of tumour agnostic therapies

Several the main issues for the assessment, funding and implementation of tumour agnostic therapies are identified in the FDA guidelines for Tissue Agnostic Drug Development in Oncology.³¹

Table 6 key challenges for assessment of tumour agnostic therapies

Issue	Description
Generalisation across cancer types	Development of histology tissue agnostic drugs involves generalisation of treatment effects based on data observed in some cancer types to other cancer types with the same molecular alteration where no subjects (or a limited number of subjects) were included in the clinical trial. This creates greater uncertainty about a drug's effectiveness across all individual cancer types.
Rarity of mutation types	If the mutation targeted by the drug is rare across different cancers (such as NTRK fusions), there will be a high degree of heterogeneity in populations, disease characteristics, pharmacokinetics, and pharmacodynamics, that will impact overall survival. This increases uncertainty when determining comparative safety and efficacy.
Availability of satisfactory therapies	If satisfactory therapies are already available, uncertainty about effectiveness increases risk that patients will be provided a treatment that is less effective than what is available.
Diagnostics	The efficacy of tumour-agnostic therapies is dependent on the availability of accurate and reliable diagnostic tests that can identify patients irrespective of cancer type. Variability in specimen collection and handling across tumour types can reduce the accuracy and reliability of diagnostic tests.

Some of these issues were also explored by the PBAC in its August 2018 advice to the then Minister for Health on options for listing PD-(L)1 checkpoint inhibitors for multiple cancer indications on the PBS.³⁵ In its advice, the PBAC noted several challenges in the assessment, funding, and implementation of pan-tumour listings for PD-(L)1 inhibitors which noted variability in results of trials of tests for biomarkers.³⁵

The available evidence often does not show a consistent relationship between biomarker status and treatment outcomes across tumour types. Therefore, it becomes difficult to generalise to tumour types not in the studies when the available evidence already suggests there are inconsistent treatment benefits.

³⁵ PBAC advice, August 2018, PD-1 and PD-L1 checkpoint inhibitor immunotherapies: options for subsidy consideration for multiple cancer types - www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/agenda/august-2018-pbac-special-meeting.

3 Emerging antibody-based therapies

3.1 Antibody-drug conjugates

Antibody-drug conjugates are composed of monoclonal antibodies linked to cytotoxic drugs used to treat cancer. They are designed, in principle, to widen the therapeutic window of those drugs by limiting their delivery specifically to cells that express the target antigen of the selected monoclonal antibody.³⁶ The claimed advantage of these therapies is that they deliver otherwise toxic cancer therapies directly to cancer cells and enable higher doses to be delivered to the cancer while reducing the toxicity for the rest of the body.³⁷

3.1.1 Development, market approval and Australian funding status

Mylotarg (gemtuzumab ozogamicin) was the first antibody-drug conjugate to be approved by the FDA in 2000.³⁷ This analysis identified 12 antibody drug conjugates that have market authorisation across the US, Europe, and Australia. Five are approved for subsidy in Australia.

Table 7 Antibody drug conjugates

Drug name (Brand name)	Indication	EMA	FDA	TGA	Australian subsidy
Gemtuzumab ozogamicin (Mylotarg®)	Combination therapy with standard anthracycline and cytarabine for the treatment of patients aged 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia, except acute promyelocytic leukaemia	Y (O)	Y	Y	Y
Brentuximab vedotin (Adcetris®)	To treat adult patients with previously untreated stage III or IV classical Hodgkin lymphoma in combination with chemotherapy.	Y (O)	Y	Y	Y
Inotuzumab ozogamicin (Besponsa®)	Treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia	Y (O)	Y	Y	Y
Ado- trastuzumab emtansine (Kadcyla®)	Adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Treatment of patients with HER2-positive metastatic (Stage IV) breast cancer who previously received trastuzumab and a taxane, separately or in combination.	Y	Y	Y	Y
Sacituzumab govitecan (Trodelvy®)	Treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received at least two prior systemic therapies, including at least one prior therapy for locally advanced or metastatic disease	Y	Y	Y	Y

³⁶ Drago, J.Z., Modi, S. & Chandarlapaty, S. Unlocking the potential of antibody–drug conjugates for cancer therapy. *Nat Rev Clin Oncol* **18**, 327–344 (2021). pubmed.ncbi.nlm.nih.gov/33558752/.

³⁷ Fu, Z., Li, S., Han, S. *et al.* Antibody drug conjugate: the “biological missile” for targeted cancer therapy. *Sig Transduct Target Ther* **7**, 93 (2022). www.nature.com/articles/s41392-022-00947-7.

Drug name (Brand name)	Indication	EMA	FDA	TGA	Australian subsidy
Polatuzumab vedotin (Polivy®)	In combination with rituximab, cyclophosphamide, doxorubicin, and prednisone is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma. In combination with bendamustine and rituximab is indicated for the treatment of previously treated adult patients with diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplant.	Y (O)	Y	Y	Not recommended by PBAC Nov 2019 and 2022
Enfortumab vedotin (Padcev®)	Treatment of urothelial carcinoma	Y	Y	Y	Recommended by PBAC March 2023
Fam- trastuzumab deruxtecan (Enhertu®)	Breast cancer	Y	Y	Y	Recommended by PBAC March 2023
Moxetumomab pasudotox (Lumoxiti®)	Treatment of adults with hairy cell leukaemia (HCL)	N	Y	N	N (Not registered)
Belantamab mafodotin (Blenrep®)	Treatment of multiple myeloma	Y (O)	Y	N	N (Not registered)
Loncastuximab tesirine (Zynlonta®)	Treatment of adult patients with relapsed or refractory large B-cell lymphoma	Y	Y	N	N (Not registered)
Tisotumab vedotin (Tivdak®)	Treatment of adult patients with recurrent or metastatic cervical cancer	N	Y	N	N (Not registered)

Y = registered or funded. N = not registered or funded. O = Orphan medicine (EMA): A medicine for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs.

While antibody drug conjugates have existed for over 20 years, some are expecting a significant increase in the number brought to market in the near future. Over 100 further antibody-drug conjugates are currently under clinical development.³⁷

3.2 Bi-specific antibodies

Antibodies with specificity for one target — called monoclonal antibodies — were the first cancer immunotherapy to achieve widespread clinical use.³⁸ Bi-specific antibodies recognize two distinct molecular targets such as cancer cells and the T cells that eliminate cancer cells.³⁸ Bi-specific antibodies are a new strategy of cancer immunotherapy.³⁹

Bi-specific antibodies are designed to achieve different functions through single or multiple mode of actions: bridging tumour cells and immune cells for redirected cytotoxicity, blocking two targets to inhibit tumour growth, promoting immune cell functions, or facilitating the formation of protein

³⁸ Garfall, A. L., & June, C. H. (2019). Trispecific antibodies offer a third way forward for anticancer immunotherapy. *Nature (London)*, 575(7783), 450–451. www.nature.com/articles/d41586-019-03495-3.

³⁹ Wu, Y., Yi, M., Zhu, S. et al. Recent advances and challenges of bispecific antibodies in solid tumors. *Exp Hematol Oncol* 10, 56 (2021). ehonline.biomedcentral.com/articles/10.1186/s40164-021-00250-1.

complexes.⁴⁰ Most bi-specific antibodies developed to date are bispecific T-cell-engagers, designed to redirect and/or activate CD3-expressing cytotoxic T cells against a specific tumour target on malignant cells. Other bi-specific antibodies classes include therapies that target immune checkpoints, oncogenic signalling pathways and cytokines.⁴¹

Bi-specific antibodies have also been trialled in regenerative medicine infectious diseases treatment (such as HIV), haematological disorders, and cancer depending on their design and multiple mode of actions.⁴⁰ More than 85% of bi-specific antibodies in clinical trials are cancer therapeutics.⁴⁰

The first bi-specific antibody to be used clinically, catumaxomab, was approved by the European Union (EU) for use in malignant ascites in 2009.⁴² It was assessed as safe for use in the outpatient setting in patients with malignant ascites secondary to gynaecological tumours including epithelial ovarian cancer and metastatic breast cancer, however was it was taken off the market in 2014 due to financial reasons.⁴² Its EMA market authorisation was subsequently withdrawn in 2017.⁴²

3.2.1 Development, market approval and Australian funding status

Currently, there are 13 bi-specific antibodies with market authorisation across Europe, the US and Australia. Seven are TGA registered, of which two are subsidised through the PBS and one is subsidised under the National Blood Agreements.

Table 8 Bi-specific antibodies

Drug name (Brand name)	Indication	EMA	FDA	TGA	Australian Subsidy
Blinatumomab (Blincyto®)	Treatment of adult and paediatric patients with B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%	Y (C, O)	Y	Y (O)	Y PBS
Faricimab-svoa (Vabysmo®)	Neovascular wet age-related macular degeneration and diabetic macular oedema	Y	Y	Y	Y PBS
Emicizumab (Hemlibra®)	Haemophilia A	Y	Y	Y	Y (National Blood Agreement)
Amivantamab-vmjw (Rybrevant®)	Non-small cell lung cancer	Y (C)	Y	Y (P)	N (No submission)
Tebentafusp-tebn (Kimmtrak®)	Unresectable or metastatic uveal melanoma	Y (O)	Y	Y	Not recommended by PBAC March 2023
Cadonilimab® or AK104	Treatment of patients with cervical cancer	N	N	N	N (Not registered)

⁴⁰ Wang, S., Chen, K., Lei, Q., Ma, P., Yuan, A. Q., Zhao, Y., ... Li, N. (2021). The state of the art of bispecific antibodies for treating human malignancies. *EMBO Molecular Medicine*, 13(9), e14291–n/a. doi.org/10.15252/emmm.202114291.

⁴¹ Esfandiari, A., Cassidy, S., & Webster, R. M. (2022). Bispecific antibodies in oncology. *Nature Reviews. Drug Discovery*, 21(6), 411–412. doi.org/10.1038/d41573-022-00040-2.

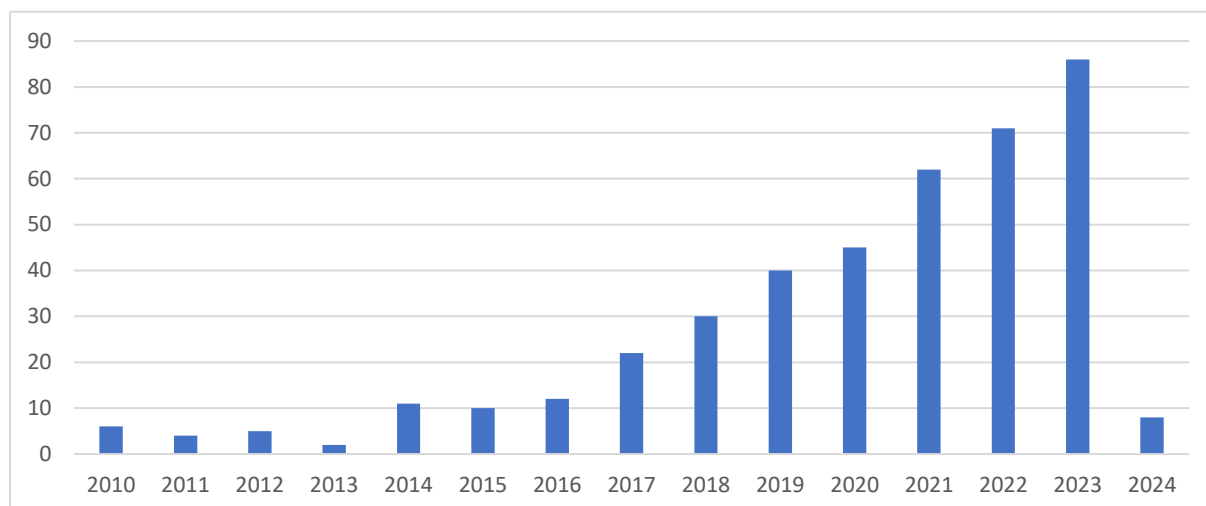
⁴² Runcie, K., Budman, D.R., John, V. et al. Bi-specific and tri-specific antibodies- the next big thing in solid tumor therapeutics. *Mol Med* 24, 50 (2018). doi.org/10.1186/s10020-018-0051-4.

Drug name (Brand name)	Indication	EMA	FDA	TGA	Australian Subsidy
Mosunetuzumab (Lunsumio®)	Treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy	Y (C, O)	Y	N	N (Not registered)
Teclistamab (Tecvayli®)	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.	Y (C)	Y	Y (P)	N (No submission)
Catumaxomab (Removab®)	Intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible	W	N	R	N (Not registered)
Glofitamab (Columvi®)	Diffuse large b-cell lymphoma	Y (C, O)	Y	Y (P, O)	N
Epcoritamab- bysp (Epkincy)	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy	Y (C, O)	Y	N*	N (Not registered)
Talquetamab- tgvs (Talvey)	Relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody	Y (C, O)	Y	N*	N (Not registered)
Elranatamab- bcmm (Elrexfio)	Relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody	Y (C)	Y	N*	N (Not registered)

Y= registered or funded. N = not registered or funded. W = withdrawn. R = rejected. P = Provisional registration (TGA) = Involves early access to vital and life-saving medicines through time-limited registration. C = Conditional marketing authorisation (EMA): A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. The marketing authorisation holder is expected to provide comprehensive clinical data at a later stage. O = Orphan medicine (EMA): A medicine for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs. O = Orphan medicine (TGA): Sponsors receive a fee waiver to help bring medicines for a small population to market. * = submission currently under evaluation with regulator.

The number of new clinical trials evaluating novel bi-specific antibodies has been increasing at an annual rate of 20.44%.⁴⁰ A similar number of trials targeting solid tumours were observed compared with those targeting haematological malignancies.⁴⁰

Figure 2 Clinical trials using bispecific antibodies reported to ClinicalTrials.gov since 2010



The intervention/treatment search term 'bispecific antibody' was queried on the registry on February 7, 2024. Clinical trials are plotted by the date they were first posted in the database.

3.2.2 Challenges identified for assessment, funding, and implementation of new antibody-based therapies

While there appears to be a rapid increase in the development of antibody-based therapies, this analysis did not identify any unique challenges posed by these technologies when compared to other drugs. It has been several years since the first antibody-drug conjugates and bispecific antibodies were marketed. Several have now been assessed and funded in Australia.

3.3 Monoclonal antibodies as passive immunisation strategy

Monoclonal antibodies have been developed which offer passive immunisation against an increasing number of viral and bacterial infectious diseases⁴³. Unlike vaccines, they offer immediate protection, and some have an extended duration of action⁴⁴. For infectious diseases with defined seasonality, there is potential to use long-acting monoclonal antibodies similarly to vaccines such as influenza vaccines to achieve seasonal protection.

3.3.1 Development, market approval in Australia

Monoclonal antibodies are in development for HIV, RSV, influenza, hepatitis C virus, malaria, rabies, Human Cytomegalovirus and Ebola. There are long-acting monoclonal antibodies that are approved in Australia for viral prophylaxis by the TGA.

3.3.2 Assessment and funding of long-acting anti-infective monoclonal antibodies in Australia

Current funding pathway for monoclonal antibodies is through the PBS. However, with the increasing number of monoclonal antibodies being developed as passive immunisation strategy consideration needs to be given about whether the PBS or NIP is the appropriate funding mechanism.

⁴³ Pantaleo, G., et al., *Antibodies to combat viral infections: development strategies and progress*. Nature Reviews Drug Discovery, 2022. **21**(9): p. 676-696.

⁴⁴ WHO, *Product Delivery and Research*, in [https://www.who.int/teams/immunization-vaccines-and-biologicals/product-and-delivery-research/monoclonal-antibodies-\(mabs\)-for-infectious-diseases](https://www.who.int/teams/immunization-vaccines-and-biologicals/product-and-delivery-research/monoclonal-antibodies-(mabs)-for-infectious-diseases). 2023.

4 Other emerging therapies

In its recent publication, the World Health Organization (WHO) presented its findings of a global horizon scan on emerging technologies and trends relevant to global public health conducted in 2020 and 2021.⁴⁷ They identified 15 priority topics that may have a significant impact on global health over the next two decades. Genetically engineered phages and microbiome therapies were two of the topics identified.⁴⁷

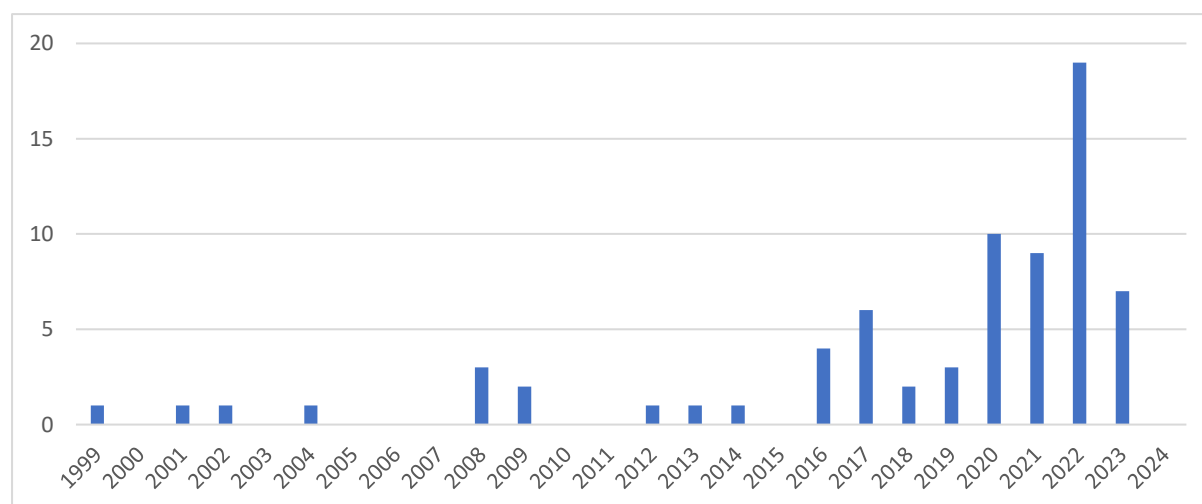
4.1 Phage therapy

Phages are viruses that infect bacterial cells⁴⁵. They have been studied and used for just over 100 years⁴⁶. During most of that time, in at least some parts of the world, phages have been used as antibacterial agents.⁴⁶ This application is commonly called phage therapy.⁴⁶ Interest in phage therapy has been increasing – due to potential for it to be a new strategy against antimicrobial resistance and improvements in genetic modification methods.^{46,47}

4.1.1 Development, market approval, and Australian funding status

There are currently no phage therapies with FDA and TGA market authorisation. Over the past 7 years, the number of clinical trials registered in ClinicalTrials.gov that use phages has increased (Figure 3).⁴⁸ Most of the registered trials are exploring the use of phages as antimicrobials.⁴⁸

Figure 3 Clinical trials of phage therapy reported to ClinicalTrials.gov since 1999.



The registry was queried using the method set out in Strathdee, SA et al. The key word “phage” was queried on the registry on February 7, 2024.⁴³

⁴⁵Patient-centred outcomes research institute, May 2022, Horizon Scanning High Potential Disruption Report - www.pcori.org/sites/default/files/PCORI-Health-Care-Horizon-Scanning-System-High-Potential-Disruption-Report-May-2022.pdf.

⁴⁶ Gibb B, Hyman P, Schneider CL. The Many Applications of Engineered Bacteriophages-An Overview. Pharmaceuticals (Basel). 2021 Jun 30;14(7):634. www.mdpi.com/1424-8247/14/7/634.

⁴⁷ WHO, Emerging trends and technologies: a horizon scan for global public health apps.who.int/iris/rest/bitstreams/1413551/retrieve.

⁴⁸ Strathdee SA, Hatfull GF, Mutalik VK, Schooley RT. Phage therapy: From biological mechanisms to future directions. Cell. 2023 Jan 5;186(1):17-31.

www.sciencedirect.com/science/article/pii/S0092867422014611?via%3Dihub.

Expanded access and compassionate use

- Internationally

In the United States, phages intended for clinical therapeutic use are regulated as biological products by the Centre for Biologics Evaluation and Research (CBER) at the FDA.⁴⁹ The primary route for a patient to access phage therapy is to enrol in a clinical trial.⁴⁹ For patients who cannot access or do not qualify for clinical trials, they can access phage therapy through the expanded-access pathway (also referred to as compassionate use).⁴⁹ Expanded access and compassionate use cases have risen exponentially but have varied widely in approach, methodology, and clinical situations in which phage therapy might be considered.⁴⁹

- Australia

Phage Australia is a national network of phage researchers and clinician scientists who aim to professionalise phage therapy as the third major intervention for infectious diseases.⁵⁰

Currently, Phage Australia can only provide phage therapy in compassionate cases.⁵⁰ Phage Australia aims to make the therapy widely available across the Australian health system by establishing it in the Australian (and international) pharmacopeia through a national industry ecosystem of genomics and informatics, diagnostics, clinical trials, manufacturing and international biobanks.⁵⁰ Over the next five years, they aim to deliver precision phage therapy to Australians and define its role for prescribers and patients across the Asia Pacific region.⁵⁰ They also plan to work with regulators to find a place for phage therapy in the national pharmacopoeia – established standards for pharmaceutical substances and medicinal products which assist in the quality control of medicines in Australia.

4.1.2 Challenges identified for assessment, funding, and implementation of phage therapy

There are several challenges to widespread use of phages were identified by the WHO in its Emerging trends and technologies: a horizon scan for global public health report.⁴⁷ Several of these challenges are not unique to phages and would apply equally to any other new treatment. These include:

- Bacteriophages might add significant short-term health care costs to infection treatment, including costs of treatment and costs related to infrastructure or staffing changes needed to administer the treatment.
- There might be a significant learning curve for clinicians to use these treatments. This might result in additional health care costs related to clinician education or increased burden on the health care system while clinicians take time away from treating patients to undergo such training.
- Health disparities might increase if the treatment is available only in certain areas, if the treatment is cost-prohibitive for some patients, or if some clinicians cannot undertake the necessary training because of either financial or time restrictions.
- Fast-turnaround and precision diagnostics to guide their rational use may be required.

⁴⁹ Suh GA, Lodise TP, Tamma PD, Knisely JM, et al; Antibacterial Resistance Leadership Group. Considerations for the Use of Phage Therapy in Clinical Practice. *Antimicrob Agents Chemother.* 2022 Mar 15;66(3): [Considerations for the Use of Phage Therapy in Clinical Practice | Antimicrobial Agents and Chemotherapy \(asm.org\)](https://doi.org/10.1128/AAC.11877-21).

⁵⁰ Page Australia website, www.phageaustralia.org.

4.2 Microbiome-based therapies

Microorganisms colonising humans (the microbiota) impact every organ system and influence disease resistance and susceptibility.⁵¹ The collective genomes of microorganisms that live on humans is often referred to as a microbiome. The microorganisms that inhabit the intestines of humans vary in composition and are impacted by diet and exposure to antibiotics.⁵¹ The discovery of associations between composition of microorganisms inhabiting intestines and disease susceptibility and growing understanding of the mechanisms by which symbiotic microorganisms and their metabolites impact human health have led to the development a number of therapies that seek to alter the composition of microorganisms in the gut.⁵¹ There are currently five categories of microbiome therapy:

- 1. Faecal microbiota transplantation:** Involves the transfer of faeces or complex communities of microbiota developed in vitro into the bowel of patients.
- 2. Diet and prebiotics:** Involves supplementation of microbiota-targeted substrates to promote a compositional change to microbiota
- 3. Symbiotic microbial consortia:** Involves transfer of a group of isolates selected and designed to promote microbiota functions.
- 4. Engineered symbiotic bacteria:** Transfer of bacteria that colonise a targeted site and are engineered to have a desired function or deliver a desired product or metabolite.
- 5. Microbiota-derived proteins and metabolites:** Direct supplementation with proteins and metabolites.⁵¹

4.2.1 Development, market approval and Australian funding status

This analysis identified three microbiome-based therapies that have market authorisation across Europe, the United States and Australia. Currently, there are no microbiome-based therapies subsidised in Australia. Australia was the first country in the world to provide regulatory approval for a donor-derived microbiome drug product.

Table 9 Faecal microbiota transplant products

Therapy	Indication	EMA	FDA	TGA	Australian Subsidy
Biomictra®	Restoration of gut microbiota in the treatment of recurrent CDI	N	N	Y	N (No submission)
Rebyota®	Prevention of recurrence of CDI in individuals 18 years of age and older	N	Y	N	N (Not registered)
SER-109®	Treatment of <i>Clostridioides difficile</i> infection	N	Y	N	N (Not registered)

Y= registered or funded. N = not registered or funded

Faecal microbiota transplantation (FMT) is currently being investigated for the treatment of several different medical conditions, with one of the main uses being in the treatment of patients with

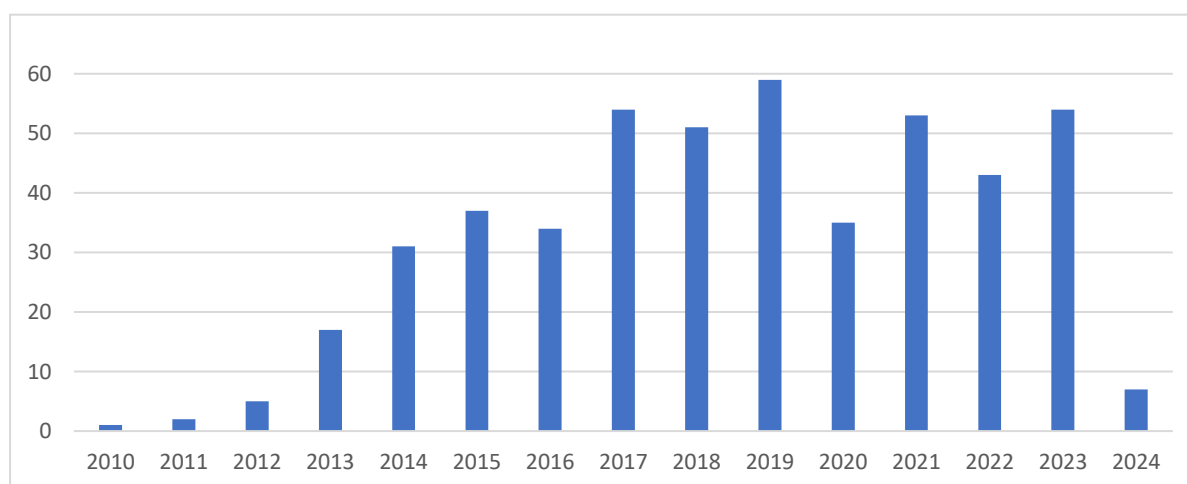
⁵¹ Sorbara, M.T., Pamer, E.G. Microbiome-based therapeutics. *Nat Rev Microbiol* **20**, 365–380 (2022). www.nature.com/articles/s41579-021-00667-9.

recurrent *Clostridioides difficile* infections (CDIs).⁵² There is also emerging evidence of efficacy for treatment of ulcerative colitis (UC), chronic relapsing-remitting mucosal inflammatory bowel disease (IBD) and increasing interest in the use of FMT products for a range of other conditions.⁵³

Table 10 Examples of microbiome-based therapies in development and clinical trials, as of 2022

Type	Delivery	Product	Current phase
Faecal microbiota transplantation or fractionated, partially undefined communities	Enema	Rebiotix RBX2660 for recurrent CDI	III
	Oral capsule	Finch Therapeutics CP101 for recurrent CDI	II
	Oral capsule (Firmicutes spores)	Seres Therapeutics SER-109 for recurrent CDI	III
	Oral capsule (lyophilized stool suspension)	Rebiotix RBX7455 for recurrent CDI	I
Prebiotics	Dietary supplement (with chickpea, peanut, soybean flours and green banana)	Microbiota-directed complementary food prototype (MDCF-2) for moderate acute malnutrition	II
Symbiotic microbial consortia	Oral capsule (40 lyophilized isolates)	NuBiyota MET-2 for CDI	I
	Oral capsule (8 lyophilized isolates)	Vedanta Biosciences VE303 for CDI	II

Figure 1 Clinical trials using faecal microbiota transplantation reported to ClinicalTrials.gov since 2010.



The registry was queried using the method set out in Sorbara and Pamer (2022). The intervention/treatment search terms 'FMT', 'faecal microbiota transplantation', 'faecal transplant', 'faecal transplantation' were queried on the registry on February 7, 2024. Clinical trials are plotted by the date they were first posted in the database.⁵¹

⁵² EMA, Faecal Microbiota Transplantation EU-IN Horizon Scanning Report - www.ema.europa.eu/en/documents/report/faecal-microbiota-transplantation-eu-horizon-scanning-report_en.pdf.

⁵³ TGA, Faecal microbiota transplant products regulation - www.tga.gov.au/products/biologicals-blood-and-tissues-and-advanced-therapies/biologicals/faecal-microbiota-transplant-products-regulation.

4.3 Therapeutic Vaccines

Therapeutic vaccines use a person's immune system to treat disease. Therapeutic vaccines stimulate a person's immune system to destroy cells that are causing disease, such as cancer cells.

4.3.1 Development, market approval and Australian funding status

This analysis identified 3 therapeutic vaccines that have market authorisation across Europe, the United States and Australia.

Table 11 Therapeutic vaccines

Therapy	Indication	EMA	FDA	TGA	Australian Subsidy
Sipuleucel-T (Provenge®)	Prostate Cancer	W	Y	N	N (No submission)
Talimogene laherparepvec (Imlygic®)	Melanoma	Y	Y	N (cancelled in 2021)	N (Not registered)
Bacillus Calmette-Guerin (OncoTICE®)	Invasive bladder cancer	Y	Y	Y	Y

To date, therapeutic vaccines have been developed for various cancers, however numerous additional therapeutic vaccines are being trialled for a range of communicable diseases (such as human papilloma virus, hepatitis b virus, human immunodeficiency virus, hepatitis C virus and COVID) and non-communicable diseases such as cancer, hypertension, Alzheimer's disease, amyotrophic lateral sclerosis, diabetes and dyslipidaemia.⁵⁴

4.3.2 Challenges identified for assessment, funding, and implementation of phage therapy

This analysis did not identify challenges unique to these therapies. However, similar to cell and gene therapies, there are some autologous therapeutic vaccines in development that will present similar challenges to therapies that can be created for very small populations.⁵⁵

4.4 Emerging vaccine manufacturing technologies

There are several emerging vaccine technologies such as m-RNA, recombinant⁵⁶ and cell-based manufacturing technologies.⁵⁷ Unlike traditional vaccine manufacturing methods, these do not use eggs. Advantages of cell culture-based technology, in addition to clinical effectiveness, have been

⁵⁴ Tian, Y., Hu, D., Li, Y. et al. Development of therapeutic vaccines for the treatment of diseases. *Mol Biomed* 3, 40 (2022) - <https://link.springer.com/article/10.1186/s43556-022-00098-9>.

⁵⁵ Sondak VK, Sabel MS, Mulé JJ. Allogeneic and autologous melanoma vaccines: where have we been and where are we going? *Clin Cancer Res*. 2006 Apr 1;12(7 Pt 2):2337s-2341 <https://pubmed.ncbi.nlm.nih.gov/16609055/>.

⁵⁶ US Centres for Disease Control and Prevention, Recombinant Influenza (Flu) Vaccine https://www.cdc.gov/flu/prevent/qa_flublok-vaccine.htm.

⁵⁷ US Centres for Disease Control and Prevention, Cell-Based Flu Vaccines <https://www.cdc.gov/flu/prevent/cell-based.htm>.

identified in academic literature.^{58,59} These range from the manufacturing quality, timely production, and ability to scale-up manufacturing, and vaccination program implementation aspects, primarily the use of alternative influenza vaccines for individuals with egg allergy or anaphylaxis^{60, 61}. Alternative needle free vaccine delivery methods have been developed such as nasal sprays⁶² and dermal patches.⁶³ These may provide advantages in addition to clinical effectiveness such as needle free administration, thermostability, and potential self-administration of vaccines in the future.

⁵⁸ Rankin W., Cell-Based Influenza Vaccines as an Alternative to Egg-Based Vaccines, *Journal of Science and Technology Law* <https://jost.syr.edu/cell-based-influenza-vaccines-as-an-alternative-to-egg-based-vaccines/>.

⁵⁹ Rajaram S, Boikos C, Gelone DK, Gandhi A. Influenza vaccines: the potential benefits of cell-culture isolation and manufacturing. *Ther Adv Vaccines Immunother*. 2020 Feb <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7036483/>.

⁶⁰ Australasian society of clinical immunology and allergy, ASCIA Guidelines – Vaccination of the egg-allergic individual, <https://www.allergy.org.au/hp/papers/vaccination-of-the-egg-allergic-individual>.

⁶¹ Australian Immunisation Handbook, Influenza (flu) <https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/influenza-flu>.

⁶² US Centres for Disease Control and Prevention, Live Attenuated Influenza Vaccine [LAIV] (The Nasal Spray Flu Vaccine), <https://www.cdc.gov/flu/prevent/nasalspray.htm>.

⁶³ Vaxxas, Product Applications, <https://www.vaxxas.com/product-applications/>.

Emerging linked health technologies

5 Precision medicine: medicine linked genetic and genomic testing

The term 'precision medicine' is used for broad range of treatments and methods for diagnosing and treating patients. Precision medicine is used to describe the concept of targeting of health interventions to the needs of an individual patient based on their predicted response or risk of disease. However, definitions vary across regulatory agencies, industry, and academia. The terms precision, personalized, individualized, and P4 are often used interchangeably when describing the concept of precision medicine.⁶⁴

A common feature of precision medicine is the use of molecular methods to predict a person's response to a health intervention or risk of disease. These molecular methods include:

- genetic testing and testing for other biomarkers
- genomics and other 'omics' (metabolomics, microbiomics, proteomics and transcriptomics)
- epigenetics (associated with gene-environment interaction)
- gene editing technologies used in gene and gene modified cell therapies (refer to section 2)
- the development of targeted therapies specific to an individual's disease profile.⁶⁵

The goal of precision medicine is to target the right treatments to the right patients at the right time.⁶⁶ This is not a new concept. However recent advances in the above molecular methods and the ability to aggregate large datasets have led to the development of new tools that promise greater precision in the targeting of health interventions to individual patient needs.

⁶⁴ Muin J Khoury. The Shift From Personalized Medicine to Precision Medicine and Precision Public Health: Words Matter!. 2016. blogs.cdc.gov/genomics/2016/04/21/shift/.

⁶⁵ Australian Council of Learned Academies, Horizon Scanning Series, The Future of Precision Medicine in Australia - acola.org/hs2-precision-medicine-australia/.

⁶⁶ FDA, Precision Medicine - www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine.

5.1 Genetic and genomic testing

There is no accepted definition of how a genetic test differs from a genomic test.⁶⁷ The following definitions have previously been used:

Genomic testing: testing of many genes or the entire genome at once. This can include gene panels, whole exome sequencing and whole genome sequencing.⁶⁸

Genetic testing: testing of single genes or a small number of genes with testing performed in series, one step at a time.⁶⁹

Examples of types of genetic and genomic tests are provided in Table 12. Genetic and genomic testing can be used for both somatic and germline testing (Table 13).

Table 12 Categories of genetic and genomic tests

Test/technology type	What it looks for	Example target/s/test	Function
Single variant test	Single variant in a specific gene	A specific variant in the haemoglobin subunit beta gene ⁷⁰	For individuals with clinical signs and symptoms, suspicion of, or family history of Sickle Cell Disease. ⁷¹
Single gene test	Multiple variants in a specific gene	vitamin K epoxide reductase gene	Identify patients who have increased sensitivity to warfarin to guide drug dose. ⁷²
Gene panel test	Variants in more than one gene ⁷⁰	Genes associated with epilepsy or neuromuscular disorders	Provide diagnostic information regarding a person's risk of having a genetic epilepsy disorder. ⁷³ This can help guide treatment to manage and prevent additional seizures or other related health problems. ⁷⁴
Whole genome/exome/transcriptome sequencing	Assembles the sequence for the bulk of an individual's DNA or RNA, then usually restricts analysis to a virtual panel of relevant genes ⁷⁰	Variations associated with a range of diseases that can cause the signs/symptoms seen in the patient	Used when the suspected condition or genetic cause is uncertain. ⁷⁰ Can be used when single gene testing has not provided a diagnosis. Supports re-analysis of previously unreported genes/variants because the sequence assembled is greater than that analysed.

⁶⁷ Payne, K., Gavan, S., Wright, S. *et al.* Cost-effectiveness analyses of genetic and genomic diagnostic tests. *Nat Rev Genet* **19**, 235–246 (2018). www.nature.com/articles/nrg.2017.108.

⁶⁸ Australian Genomics, About Genomics - www.australiangenomics.org.au/about-genomics/.

⁶⁹ Garvan Institute of Medical Research, Genomics and Genomic Testing - www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics/learn-about-genomics/for-gp/genetics-refresher-1/genomics-and-genomic-testing.

⁷⁰ National Library of Medicine (US) – MedlinePlus, What are the different types of genetic tests - medlineplus.gov/genetics/understanding/testing/types.

⁷¹ Fulgent Genetics, Sickle Cell Disease (HBB Single Gene Test) - www.fulgentgenetics.com/Sickle-Cell-Disease.

⁷² Franceschini N, Frick A, Kopp JB. Genetic Testing in Clinical Settings. *Am J Kidney Dis*. 2018 Oct;72(4):569-581 - www.ncbi.nlm.nih.gov/pmc/articles/PMC6153053/.

⁷³ Epilepsy Foundation, Genetic Testing for Epilepsy - www.epilepsy.com/causes/genetic/testing.

⁷⁴ Fulgent Genetics, Epilepsy Comprehensive NGS Panel - www.fulgentgenetics.com/epilepsy-comp.

Test/technology type	What it looks for	Example target/s/test	Function
Algorithmic genomic test	Algorithmic interpretation of information about genes and/or their expression (sometimes in conjunction with clinical information)	Gene expression profiling tests in breast cancer; homologous recombination deficiency (HRD) testing; polygenic risk scores	The algorithm result can have prognostic and/or predictive value.

Table 13 Somatic and germline testing

Test type	What it looks at	Purposes
Germline	Inherited variants that are present throughout the body (including tumour cells) and have been present since birth. ⁷⁵	<ul style="list-style-type: none"> • Diagnosing or estimating susceptibility to genetic/hereditary diseases, including cancer predisposition • Allowing cascade testing of biological relatives • Allowing reproductive carrier testing and foetal testing to support informed reproductive decision-making • Providing prognostic information • Predicting response to specific therapies to facilitate selection of optimal treatment choice, and/or tailor dosages
Somatic	Acquired mutations in a confined set of cells or tissue. This is also known as tumour testing or tumour sequencing. ⁷⁵ Somatic genetic testing will examine a piece of tissue or tumour taken through a biopsy or surgery and look for mutations that have occurred spontaneously. ⁷⁵ These mutations are typically isolated to the tumour or area where cancer exists in the body. ⁷⁵	<ul style="list-style-type: none"> • Facilitating diagnosis of cancer type, and/or refining or refuting the diagnosis • Providing prognostic information • Determining suitability of therapy by finding predictors that may impact treatment response

5.1.1 Applications of genetic and genomic testing in disease management

In hereditary disease, the utility of genetic testing may be used to:

- i. Make, refine or refute the diagnosis of a heritable disease
- ii. Inform the effect of the genetic variant on disease outcome in the absence of treatment change (i.e., prognosis)
- iii. Predict the patient’s response to a change in management given the genetic variants detected, and so inform therapy selection
- iv. Inform risk to other family members
- v. Determine risk of the patient’s genotype (and that of their reproductive partner, and potentially foetus) to support informed reproductive decision-making

In many cancer types, there are clinical guideline-based recommendations for genetic testing that:

- i. Informs making, refining, or refuting a diagnosis
- ii. Informs the effect of the genetic variant on disease outcome in the absence of a change in management (i.e., prognosis)

⁷⁵ Ovarian cancer research alliance, Germline vs Somatic Testing – ocrahope.org/news/germline-vs-somatic-testing-genomic-vs-genetic-testing.

- iii. Predicts the patient’s response to a change in management given the genetic variant(s) detected, and so informs therapy selection
- iv. Where the cancer is identified as being caused by a germline variant, or identifies a cancer predisposition syndrome through cascade testing, informs the risk to other family members

5.1.2 Regulation of genetic testing

In vitro diagnostic (IVD) products are regulated by the Therapeutic Goods Administration. Unless exempt, all IVDs that were introduced to the Australian market after 1 July 2010 must be included in the ARTG before they can be legally supplied.⁷⁶ All commercially supplied IVD medical devices must be included in the ARTG prior to supply in Australia and must have available evidence to support the device safety, performance and manufacture relevant to the risk of the device. Laboratories can develop their own tests or modify commercially supplied tests, known as in-house IVD medical devices, which are subject to different regulatory requirements and do not require inclusion in the ARTG (except class 4 in-house IVDs which are the highest risk devices).

Standards for genetic testing by providers such as in-house laboratories and pathology services are formulated by the National Pathology Accreditation Advisory Council. These standards provide guidance to laboratory about the expected level of safe and good quality laboratory practice. These standards underpin the accreditation requirements specified in the *Health Insurance (Accredited Pathology Laboratories—Approval) Principles 2017*.

5.2 Genetic tests for detection of pathologic gene variants

Genetic tests for detection of pathologic gene variants are used to diagnose inherited diseases and cancers, predict response to treatment, or estimate the likelihood of a person developing a particular disease. They include single gene tests, gene panel tests and whole genome sequencing with use of a digital panel to detect variants in specific genes.

Recently, several genetic tests have been developed for the specific purpose of determining the safe and effective use of particular therapies, and genomic testing is also emerging for this purpose. These are defined by regulatory bodies as ‘companion diagnostics’, and as ‘co-dependent tests’ when assessed for public funding. Companion diagnostics include the tests that are used for tumour-agnostic therapies (see section 7.3) but also tissue specific therapies where the presence of a particular variant or biomarker is necessary to determine access to treatment (for example: patients must carry a *BRCA1* or *BRCA2* variant to be eligible to receive niraparib for high grade stage III/IV epithelial, fallopian tube or primary peritoneal cancer).

5.2.1 Development, market approval and Australian funding status

Genetic tests have been used in diagnosis for many years. In Australia, they are available in a wide range of care settings and are subsidised through the MBS, funded in public hospitals through activity-based funding under the National Health Reform Agreement (NHRA), funded through other state and territory arrangements, or are available privately.

The number of companion diagnostics with market approval have increased significantly from 9 approved by the FDA in 2010 to 44 by the end of 2020.⁷⁷ Currently there are FDA approved tests for 38 biomarkers. Of these, tests for 10 FDA approved biomarkers are currently subsidised through

⁷⁶ TGA, Regulation of IVDs - www.tga.gov.au/regulation-ivds-laboratory-specific-information.

⁷⁷ Jørgensen JT. The current landscape of the FDA approved companion diagnostics. *Transl Oncol*. 2021 Jun;14(6) - pubmed.ncbi.nlm.nih.gov/33714919/.

the MBS.

Note that genetic tests used to determine access to a therapy will not necessarily always be regulated by the TGA as “companion diagnostics”, because that regulatory term only describes where the applicant to the regulator makes a companion diagnostic claim (requiring the TGA’s simultaneous consideration of either an application for, or approval of, the corresponding medicine or biological) and the TGA accepts the claim. It does not include, for example, detection of a gene variant leading to a change related to a surgical intervention (such as avoiding a biopsy or indicating an implantable cardiac device).

Table 14. Biomarkers targeted by FDA approved companion diagnostics and MBS funding status

Biomarker	Drug	Indication	PBS listed drug has a corresponding MBS item for biomarker detection
ALK/ALK	alectinib brigatinib ceritinib crizotinib lorlatinib	Non-Small Cell Lung Cancer	Yes
BRAF	atezolizumab with cobimetinib and vemurafenib cobimetinib with vemurafenib dabrafenib dabrafenib with trametinib encorafenib with binimetinib encorafenib with cetuximab trametinib vemurafenib	Melanoma Non-Small Cell Lung Cancer Colorectal Cancer	Yes
BRCA1/ BRCA2	olaparib rucaparib talazoparib	Breast Cancer Metastatic Castration Resistant Prostate Cancer Ovarian Cancer Pancreatic cancer	Yes (for olaparib and niraparib and for some indications)
ATM	olaparib	Metastatic Castration Resistant Prostate Cancer	No (Not required for access)
C-Kit	imatinib mesylate	Gastrointestinal Stromal Tumours - Tissue	No (Not required for access)
deficient mismatch repair (dMMR) proteins	dostarlimab-gxly pembrolizumab	Endometrial Carcinoma (EC) - Tissue Solid Tumours	No (Not required for access)

Biomarker	Drug	Indication	PBS listed drug has a corresponding MBS item for biomarker detection
<i>EGFR (HER1)</i>	afatinib amivantamb cetuximab dacomitinib erlotinib gefitinib mobocertinib osimertinib panitumumab	Non-Small Cell Lung Cancer Colorectal Cancer	Yes
<i>ERBB2</i>	fam-trastuzumab deruxtecan-	Non-Small Cell Lung Cancer	No (Not PBS listed)
<i>ERBB2 (HER2)</i>	ado-trastuzumab emtansine fam-trastuzumab deruxtecan-nxki pertuzumab trastuzumab	Breast Cancer Gastric and Gastroesophageal Cancer	Yes
<i>ESR1</i>	elacestrant	Breast Cancer	No (Not PBS listed)
<i>EZH2</i>	tazemetostat	Follicular Lymphoma Tumour	No (Not PBS listed)
<i>FGFR2</i>	infigratinib pemigatinib	Cholangiocarcinoma	No (Not PBS listed)
<i>FGFR3</i>	erdafitinib	Urothelial cancer	No (Not PBS listed)
<i>FLT3 (ITD/TDK)</i>	gilteritinib midostaurin	Acute myeloid Leukemia	Yes
<i>FOLR1</i>	mirvetuximab soravtansine-gynx	Epithelial Ovarian Cancer	No (Not PBS listed)
<i>HLA</i>	tebentafusp-tebn	Uveal melanoma	No (Not PBS listed)
<i>IDH1</i>	ivosidenib olutasidenib	Acute myeloid leukemia Cholangiocarcinoma	No (Not PBS listed)
<i>IDH2</i>	enasidenib	Acute myeloid leukemia	No (Not PBS listed)
<i>Ki-67</i>	abemaciclib	Breast Cancer	No (Not required for access)
<i>KIT</i>	imatinib	Aggressive Systemic Mastocytosis	Yes
<i>KRAS/KRAS</i>	adagrasib cetuximab panitumumab sotorasib	Non-Small Cell Lung Cancer Colorectal Cancer	Yes
<i>KRAS and NRAS</i>	panitumumab	Colorectal Cancer	Yes
Liver iron concentration imaging	deferasirox	Non-Transfusion-Dependent Thalassemia	No (Not required for access)

Biomarker	Drug	Indication	PBS listed drug has a corresponding MBS item for biomarker detection
<i>MET</i>	capmatinib	Non-Small Cell Lung Cancer	No (Not PBS listed)
MSI-High	pembrolizumab	Solid Tumours	No (Not required for access)
HRD	niraparib olaparib	Ovarian Cancer	No (Not required for access)
NTRK1, NTRK2 and NTRK3 <i>NTRK1, NTRK2 and NTRK3</i>	larotrectinib entrectinib	Solid Tumours	Yes
<i>NTRK1, NTRK2, and NTRK3</i> fusions	entrectinib	Solid Tumours	Yes
<i>PDGFRB</i>	imatinib	Myelodysplastic Syndrome / Myeloproliferative Disease	Yes
PD-L1	atezolizumab cemiplimab-rwlc nivolumab with ipilimumab pembrolizumab	Non-Small Cell Lung Cancer Urothelial carcinoma Cervical Cancer Oesophageal Squamous Cell Carcinoma Head and Neck Squamous Cell Carcinoma Triple-Negative Breast Cancer	Yes (for some indications)
<i>PIK3CA</i>	alpelisib	Breast Cancer	No (Not PBS listed)
<i>POMC, PCSK1 and LEPR</i>	setmelanotide acetate	Obesity	No (Not PBS listed)
proficient mismatch repair (pMMR) proteins	pembrolizumab with lenvatinib	Endometrial Carcinoma	No (Not PBS listed)
<i>RET</i>	pralsetinib selpercatinib	Non-Small Cell Lung Cancer Medullary Thyroid Cancer	No (Not PBS listed)
<i>ROS1</i>	crizotinib entrectinib	Non-Small Cell Lung Cancer	Yes
t(9;21) Philadelphia chromosome	nilotinib	Chronic Myeloid Leukemia	Yes
Tumour mutational burden High (TMB-H)	pembrolizumab	Solid Tumours	No (Not PBS listed)
<i>TP53</i>	venetoclax	B-cell Chronic Lymphocytic Leukemia	Yes

5.2.2 Assessment for funding of genetic tests

Genetic tests are subsidised through the MBS are assessed by the MSAC. Definable benefit(s) of a genetic test is related to both the test setting (for example at disease presentation, at screening of asymptomatic individuals, cascade or carrier testing of family members), and to the test utility(ies).

The MSAC Guidelines identify the hierarchy of evidence and value for each utility of investigative technologies encompassed and quantified in the HTA.⁷⁸ The 2021 update to the MSAC Guidelines describes the relative weight given by MSAC to differing clinical utilities (or types of values) of investigative technologies, which may include an assessment of the 'value of knowing' a test result.

5.3 Gene expression testing

Gene expression tests gather and analyse information about the genes that are being expressed in certain tissues (such as cancer cells) to determine risk of disease. They include tests that measure the expression of many genes (gene expression profile tests), tests for the expression levels of specific genes (such as PD-L1), and tests for gene fusions and exon skipping.

5.3.1 Development, market approval and Australian funding status

There are several tests that are in use overseas and Australia. They can include commercial products (such as EndoPredict) or in house analyses (such as immunohistochemical examination demonstrating loss of expression of mismatch repair proteins).

5.3.2 Assessment for funding of gene expression testing

There have been several applications for gene expression tests to MSAC. Several tests that determine the presence or absence of the expression of a particular gene (such as the test for *NTRK* gene fusions which determines eligibility for subsidised access to larotrectinib) are subsidised. There have been several applications to list tests that measure levels of gene expression on the MBS.

⁷⁸ MSAC, Guidelines (version 1.0, May 2021).

[www.msac.gov.au/internet/msac/publishing.nsf/Content/E0D4E4EDDE91EAC8CA2586E0007AFC75/\\$File/MSAC%20Guidelines-complete-16-FINAL\(18May21\).pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/E0D4E4EDDE91EAC8CA2586E0007AFC75/$File/MSAC%20Guidelines-complete-16-FINAL(18May21).pdf).

⁷⁹ MSAC advice, A prognostic RT-qPCR test for prediction of risk of distant recurrence of breast cancer under endocrine treatment - www.msac.gov.au/internet/msac/publishing.nsf/Content/1408.1-public.

Gene expression profiling tests in early breast cancer

Over the past decade MSAC has considered multiple applications to fund various brands of gene expression profiling tests for patients with early breast cancer. These tests quantify the expression of multiple genes in breast cancer cells in conjunction with clinical information to generate a risk score that may determine the prognosis of breast cancer patients.

At its November 2022 meeting, MSAC supported the creation of a new MBS item for the gene expression profiling test EndoPredict®.⁸⁶ MSAC advised the test had modest incremental prognostic value in establishing the risk of distant recurrence of breast cancer in patients at intermediate risk of recurrence. MSAC did not accept predictive value had been demonstrated, so advised the test results should not be used to change management.

Prior to its support for EndoPredict®, MSAC had not supported public funding for any gene expression profiling test in early breast cancer. In its consideration of focussed applications for three brands of gene expression profiling test in July 2021, MSAC accepted that the tests provided some modest prognostic information however no application provided sufficient evidence for additional prognostic value beyond current standard of care.

5.4 Polygenic risk scores

A polygenic score (PGS, also called polygenic risk score or PRS) is a calculation of the risk that a person may develop particular diseases using information about the gene variants they carry across multiple genes. An increasing number of gene variants that are associated with a higher risk of disease are being identified through studies known as genome wide association studies.⁸⁰

The Australian Genomics PGS Incubator Project reports that PGS has potential to be used to:⁸⁰

- inform population screening and provide personalised risk estimation for screening or preventive treatments/interventions (also in combination with environmental and biomarker risk factors)
- aid in disease diagnosis (e.g., to distinguish between type 2 diabetes and late-onset type 1 diabetes)
- provide information that can modify risk for a person carrying a pathogenic genetic variant associated with a high risk of disease (Mendelian disorders).
- assess a patient's prognosis after developing disease
- help with treatment decisions/pathways (e.g., to inform use of statin therapy for individuals at high risk of coronary artery disease (CAD) or hormone treatment in those at high risk of breast cancer) and guide therapeutic interventions (the use of PGS in pharmacogenomics is not yet well developed but is under investigation and, in general, much larger genome wide association studies are needed to generate PGS in this context).

5.4.1 Development, market approval and Australian funding status

Currently PGS is primarily used for research. There are few commercial products being marketed. A horizon scan undertaken by the Newcastle University Innovation Observatory in 2021 identified

⁸⁰ Australian Genomics, Polygenic Score Incubator Project - www.australiangenomics.org.au/wp-content/uploads/2022/11/Polygenic-Score-Incubator-Project-Report_30Aug2022.pdf.

seven companies and products where PGS is used.⁸¹ The horizon scan found that companies with commercial offerings are limited to relatively few disease areas. The horizon scan found that there was significant interest in the application of PGS – due to a high number of academic and commercial publications on the subject. The horizon scan also concluded that most activity revolves around early-stage research and technologies that are not yet commercialised.

5.4.2 Assessment for funding of PGS in Australia

MSAC is yet to consider any applications for PGS.⁸⁰ It has considered risk scores incorporating genetic information for predicting response to treatment, for example in breast cancer, and there are many similarities with the more general issues that arise for PGS.⁸⁰

In Australia, PGS is not part of routine clinical practice, but it is available through commercial companies.⁸⁰ To access testing from these companies, tests must be ordered by a medical practitioner rather than by the consumer directly (<https://genotype.com/>).⁸⁰ Alternatively, consumers can access testing through overseas private direct-to-consumer (DTC) laboratories.⁸⁰

5.4.3 Challenges identified for assessment, funding, and implementation of PGS

Several challenges for moving PGS from research to widespread clinical translation were identified by Australian Genomics in its 2022 PGS Incubator Project Report.⁸⁰ These included:

- Test methodology: Developing test evaluation frameworks for PGS to provide evaluators with a consistent methodology for evaluation of PGS, from the laboratory test to clinical use
- Regulation: Determining the appropriate regulatory oversight to ensure the PGS is safe and effective in the clinical contexts in which it will be used and to prevent non-ethical use
- Demonstrating the clinical utility of PGS,
- Developing best practice guidelines
- Developing appropriate evidence-based education for health professionals and the public
- Ensuring that health disparities are not exacerbated by inequitable access to PGS tests
- Need for large-scale testing of subpopulations to establish the ‘control’ group for risk scoring development
- Ongoing refinement of risk scoring over time as more data and knowledge is accrued, and subpopulations encompassed

Through its national consultation Australian Genomics also identified the following research gaps relating to:⁸⁰

- Demonstrating the value of PGS
- The utility for PGS in specific clinical contexts needs to be demonstrated
- Infrastructure requirements
- Ethical and legal implications
- Understanding and education.

A further challenge with PGS (and other algorithmic genomic tests) is to ensure they are not inequitably effective across different ethnicities. Because Aboriginal and Torres Strait Islanders and other ethnicities are underrepresented in genomic databases, if those databases were used to develop the PGS/algorithm, then they may be less effective for determining risk in individuals from ethnicities where different genetic variants are more common.

⁸¹ Newcastle University (UK) NIHR Innovation Observatory, Horizon Scan for Polygenic Risk Scores - www.io.nihr.ac.uk/wp-content/uploads/2022/01/NIHR-IO-Polygenic-Risk-Scores-Rapid-Scan-March-2021.pdf.

5.5 Challenges identified for Assessment for funding of medicine linked genetic and genomic tests

5.5.1 Variation in testing platforms and across care settings

A variety of platforms can be used for genetic and genomic testing, and several are used in different settings across Australia. They include commercial products or in house tests and include all the types set out in Table 12. They can determine the presence or absence of a pathogenic variant in a genome and their expression in different tissues. New tests, particularly panel tests and gene sequencing have the potential to supersede existing single gene tests. There is currently no register of genetic or genomic testing in Australia.

Algorithms for analysing genetic information collected in tests are likely to evolve with continued research findings on association between particular genetic variants and disease or response to treatment. Because of this, genetic and genomic tests have the potential to change the treatment algorithm at different points, and this can have flow on implications for treatment and the criteria used to determine whether access should be subsidised.

5.5.2 Lack of evidence of clinical effectiveness

Evidence of clinical effectiveness for diagnostic technologies is often under-developed and undermines the credibility of evaluation. This is exacerbated by an increasing number of sub-categories of diseases identified as more genetic determinants of disease have been discovered.⁸⁶ This issue is sometimes referred to as increasing stratification.

Identification of disease-causing variants is good for patients as it allows causes of illness and plausibly effective treatments to be identified.⁸³ However this presents a challenge for HTA and subsequent decision making which relies upon statistically robust evidence of safety and efficacy of health technologies in a population. Where there are variants unique to one or a few patients, there is unlikely ever to be an adequate evidence base to prove a health technology would be effective for that variant – even where the effectiveness of a health technology is plausible. One method for addressing this that has been utilised by the MSAC is to support funding of a treatment for patients with a broader range of variants to a particular gene than was explored in trials where it is plausible that the treatment would be effective in those patients.⁸²

⁸² PBAC, Public Summary May 2021, Encorafenib, www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-05/files/encorafenib-psd-may-2021.pdf.

⁸³ MSAC, Public Summary April 2021, *BRAF* V600 testing to help determine eligibility for PBS access to Braftovi (encorafenib), in patients with metastatic colorectal cancer (Stage IV), www.msac.gov.au/internet/msac/publishing.nsf/Content/1617-public.

***BRAF V600* testing**

At its April 2021 meeting, the MSAC considered testing to help determine PBS access to encorafenib in patients with metastatic colorectal cancer (Stage IV). The MSAC noted that the clinical trial only enrolled patients with the V600E variant and so could not assess the effect for patients who are V600 negative or had another V600 variant. The MSAC also noted that the literature states that *BRAF V600E* accounts for >90% of the *BRAF* variants found in colorectal cancer and suggest that other rarer variations might behave similarly. MSAC considered it was biologically plausible for other *BRAF V600* variants respond similarly to encorafenib. The MSAC considered that patients with rarer variants would not be eligible for treatment if the proposed MBS and PBS listings were restricted to *BRAF V600E*. The MSAC therefore supported testing for all V600 variants and considered that testing should not be limited to V600E.⁹²

At its May 2021 intracycle meeting, the PBAC agreed that the PBS restriction for encorafenib for the treatment of adults with metastatic colorectal cancer should refer broadly to V600 status (without reference to V600E specifically).⁹²

5.5.3 Potential value in multiple areas

Genetic and genomic testing can have value in multiple areas, particularly where a large amount of genetic information is collected. These areas include:

- determining whether a particular treatment will be effective
- broader clinical utility (likelihood the test will improve health outcomes by prompting an intervention)
- prognostic value (determination of risk of disease or expected course of disease)
- personal utility (value for the patient in knowing diagnosis).⁸³

Applications to list a new single gene on the MBS test to determine access to a PBS medicine may seek narrower use than the potential purposes for which the test could be used.

5.5.4 Uncertainty of cost-effectiveness estimates

The economic benefits of genetic and genomic testing are difficult to assess because they depend on a multitude of factors that can be challenging to clearly determine, including the:

- full range of upstream and downstream costs
- rate at which the cost of tests is reducing
- extent to which the new precision testing can be implemented in practice to achieve the proposed benefits (for example: reducing the amount of preventable illness and increasing successful treatment outcomes and reducing associated harm).⁸³

5.5.5 Timing of MSAC and PBAC consideration for co-dependent technologies

Through the Inquiry, industry stakeholders raised concern about separate consideration of drugs and tests by the MSAC and PBAC and associated timing. Industry stakeholders stated that they found it challenging to navigate making submissions for the two committees.

6 Theranostics

Theranostics refers to the pairing of diagnostic biomarkers with therapeutic agents that share a specific target in diseased cells or tissues.⁸⁴ The pairing of biomarkers with therapeutic agents is said to facilitate more accurate patient selection, prediction of treatment response and tissue toxicity, and response evaluation, with the goal of better health outcomes. Theranostics can be defined as any combination of diagnostic and therapeutic modalities, where:

- Diagnostic procedures
 - can identify patients who are candidates for a specific treatment, and/or monitor progress.
 - usually involves the use of imaging methods (e.g. nuclear medicine) for the visualization and quantification of the expression of a target.
- A therapeutic component
 - treats the condition in a targeted manner, based on the diagnostic information.
 - involves the use of therapeutic compounds, including nonradioactive⁸⁴ or radioactive molecules binding to this target (the same target as for imaging).

Theranostics can be categorized as: radiotheranostic, nanotheranostic, magnetotheranostic and optotheranostic, by using radionuclides, nanoparticles, magnetic particles and optical probes, respectively.⁸⁵ Radiotheranostics (also known as nuclear theranostics) are the main type of theranostic that have been marketed to date.

6.1 Radiotheranostics

Radiotheranostics combines molecular imaging (primarily PET and single-photon emission computed tomography (SPECT)) with targeted radionuclide therapy⁸⁶ (also called radioligand or radiopharmaceutical therapy). This involves using radioactive compounds to image biologic phenomena by means of expression of specific molecular targets such as cell surface receptors or membrane transporters, which is then followed by the use of the radioligand therapy⁸⁴ that delivers ionizing radiation to the tissues that express these targets, activating programmed cell death.⁸⁵

In radioligand therapy, small molecules, peptides and/or antibodies are used as carriers for therapeutic radionuclides, typically those emitting α -, β - or auger-radiation.⁸⁶

6.1.1 Development, market approval and Australian funding status of radiotheranostics

The radiopharmaceutical precursor, Lutetium (177Lu) chloride was listed on the ARTG on 11 January 2022 and included in the Black Triangle Scheme* for the for the treatment of non-resectable or metastatic neuroendocrine tumours (NETS) expressing somatostatin subtype 2 receptors when coupled with a suitable carrier molecule.⁸⁷ In clinical practice it is combined with ligands DOTATATE (also known as DOTA-octreotate; forming 177Lu-DOTATATE) or PSMA-617 (forming (177Lu)–PSMA-617) (Table 15). Currently there are no radioligand therapies approved for subsidy in Australia.

⁸⁴ Gomes Marin, J. F., Nunes, R. F., Coutinho, A. M., Zaniboni, E. C., Costa, L. B., Barbosa, F. G., ... Buchpiguel, C. A. (2020). Theranostics in Nuclear Medicine: Emerging and Re-emerging Integrated Imaging and Therapies in the Era of Precision Oncology. *Radiographics*, 40(6), 1715–1740.

⁸⁵ Duan H, Iagaru A, Aparici CM. Radiotheranostics - Precision Medicine in Nuclear Medicine and Molecular Imaging. *Nanotheranostics*. 2022 Jan 1;6(1):103-117. www.ntno.org/v06p0103.htm.

⁸⁶ Bodei, L., Herrmann, K., Schöder, H. et al. Radiotheranostics in oncology: current challenges and emerging opportunities. *Nat Rev Clin Oncol* 19, 534–550 (2022). www.nature.com/articles/s41571-022-00652-y

⁸⁷ TGA Australian prescription medicine decision summary, Lutetium chloride - www.tga.gov.au/resources/auspmd/lutetium-177lu-chloride.

LuTate, Lutetium-177 PSMA and ¹⁷⁷Lutetium PSMA i&t (177Lutetium PSMA imaging and therapy) are currently clinically used in Australia under the TGA’s Special Access Scheme.

Table 15 Examples of Radioligand therapies and companion diagnostic agents with regulatory approval

Drug name (Brand name)	Indication	EMA	FDA	TGA	Australian Subsidy
Lutetium Lu 177 vipivotide tetraxetan (Pluvicto®), formerly Lutetium-177 (177Lu)–PSMA-617	Adult patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)	Y	Y	N	N
Gallium (68Ga) gozetotide (Locametz®) (companion diagnostic agent for Pluvicto)	Detection of PSMA-positive lesions, including selection of patients with metastatic prostate cancer for whom Pluvicto is indicated	Y	Y	N	N
Lutetium Lu 177 dotatate or LuTate or 177Lu-DOTATATE (Lutathera®)	Somatostatin receptor-positive gastroenteropancreatic (GEP)-NETs	Y	Y	N, SAS	N
Gallium G68 DOTATATE preparation kit (NETSPOT) (companion diagnostic agent for Lutathera/LuTate)	Radioactive probe will help locate tumours in adult and pediatric patients with somatostatin receptor positive NETs.	N	Y	N	N
¹⁷⁷ Lutetium (177Lu)- PSMA i&t	Metastatic castration-resistant prostate cancer	N	N	N, SAS	Not recommended in Jul 2022 (MSAC)
Flotufolostat F 18 (Posulma)	Radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions	N	Y	N	N

Y = registered or funded. N = not registered or funded. SAS = TGA special access scheme.

There are a large number of radiotheranostics in late-stage clinical development (phase 3).⁸⁸ Radiotheranostics in development are anticipated to target a larger range of cancers, as well as other diseases.⁸⁸ Accordingly, the radioligand market is expected to experience significant growth in 2021-2027 driven by increase in cancer prevalence and expansion of the scope of radioligand therapy.⁸⁸

6.1.2 Assessment for funding of radiotheranostics and radiopharmaceuticals generally

Radiopharmaceuticals are assessed by MSAC for funding through the MBS. Recent examples of MSAC applications for radiopharmaceuticals include:

- 1686 - ¹⁷⁷Lutetium PSMA i&t (not supported in July 2022)

⁸⁸ Newcastle University (UK) NIHR Innovation Observatory, May 2021, Horizon scan report for Radioligand Technologies www.io.nihr.ac.uk/wp-content/uploads/2022/01/NIHR-IO-Radioligand-Rapid-Scan-May-2021.pdf.

1268 - Radium 223 – castration-resistant prostate cancer patients with symptomatic bone metastases (recommended in April 2014).^{89 90}

Radium 223

MSAC supported public funding of Radium 223 at its April 2014 meeting. However, MBS fees for these services are listed in the legislative instrument, as is the requirement for all MBS items. Radium 223 was not listed on the MBS because it was not able to accommodate the special pricing arrangement requested by the sponsor.¹⁰²

¹⁷⁷Lutetium PSMA i&t

At its July 2022 meeting the Medical Services Advisory Committee considered ¹⁷⁷Lutetium PSMA i&t for the treatment of metastatic castrate resistant prostate cancer. The application requested MBS listing of:

- prostate specific membrane antigen positron emission tomography/computerised tomography (PSMA PET/CT) to determine eligibility for
- ¹⁷⁷Lutetium PSMA imaging and therapy (177Lu PSMA i&t) and 24-hour post-therapy single-photon emission/computed tomography/computerised tomography (SPECT/CT).

MSAC did not support public funding. MSAC acknowledged the clinical need for this therapy, and that patients prefer it over other last-line options. MSAC also considered it to be a safe and effective therapy option for men with metastatic-resistant prostate cancer who have failed most other standard available therapies. However, MSAC was not convinced that, as proposed and on the basis of the available evidence, ¹⁷⁷Lutetium PSMA was good value for money.

6.1.3 Challenges identified for assessment, funding, and implementation of theranostics

Barriers to the implementation of radioligand therapies include issues with supply of radioactive isotopes, lack of specialist professionals, hospital capacity and infrastructure needed to deliver this therapy, such as PET scanners, and infrastructure for disposal of radioactive material.⁸⁸

6.2 Other theranostics

Feraheme® (ferumoxytol), belonging to the other theranostic categories, is a type of superparamagnetic iron oxide nanoparticle (SPION) with FDA approval. It is used for the treatment of iron-deficiency anaemia in patients with chronic kidney disease.⁹¹ However, ferumoxytol is also being used off-label as an MRI angiography agent in patients with renal failure who cannot be given gadolinium and in clinical trials for the characterization and mapping of metastatic lymph nodes and hepatic masses.⁹¹ FerroTrace® is a new type of SPION tracer, currently in clinical trials.⁹²

⁸⁹ MSAC public summary, April 2014, Radium 223 -

[www.msac.gov.au/internet/msac/publishing.nsf/Content/9FDFA4B8321267F0CA25801000123BA1/\\$File/1268%20-%20MSACPSD%20-%20Radium%20223%20\(D14-1275528\).PDF](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/9FDFA4B8321267F0CA25801000123BA1/$File/1268%20-%20MSACPSD%20-%20Radium%20223%20(D14-1275528).PDF).

⁹⁰ PBAC public summary, November 2017, Radium 223 - www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2017-11/radium-psd-november-2017.

⁹¹ Thakor AS, Jokerst JV, Ghanouni P, Campbell JL, Mittra E, Gambhir SS. Clinically Approved Nanoparticle Imaging Agents. J Nucl Med. 2016 Dec;57(12):1833-1837 - www.ncbi.nlm.nih.gov/pmc/articles/PMC5126695/.

⁹² Ferronova, Our Technology, www.ferronova.com.au/our-technology/.

7 Medicine linked digital health technologies

Digital health is an umbrella term referring to a range of technologies that can be used to treat patients and collect and share a person's health information. Digital health has a broad scope, and includes:

- mobile health and applications (such as SMS reminders via mobile messaging, wellness apps, Medicare Online and COVID check-in apps)
- electronic prescribing
- electronic health records (including My Health Record)
- telehealth and telemedicine
- wearable devices (such as fitness trackers and monitors)
- robotics and artificial intelligence.⁹³

There are a growing number of digital health technologies that can impact the assessed safety and effectiveness of the therapies and medicines that are in scope for the HTA Review. They can do this in a number of ways, including through improving diagnosis, improving selection of therapies to treat conditions, improving delivery of therapies and improving adherence and providing alternative measures of health outcomes.

The Therapeutic Goods Administration regulates some digital health technologies where they meet the definition of a medical device under section 41BD of the *Therapeutic Goods Act 1989*.⁹¹

7.1.1 Types of digital health technologies that can impact the safety and effectiveness of other therapies

The types and varieties of digital health technologies that can impact the safety and effectiveness of other therapies are broad. Some of the main categories are described below.

Medication adherence applications

The main function of medication adherence applications is to remind patients to take their medicines. However, they can also include other supports that have potential to increase adherence, such as educational resources and dosage instructions. This supports quality use of medicines and can improve health outcomes associated with particular medications.

Electronic health records

When maintained, electronic health records provide prescribers information about patients' history of diagnoses, medications and allergies. This can improve the safety of medicines by identifying contraindications and preventing drug interactions.

Computerised clinical decision support systems

Clinical decision support systems comprise software that is designed to support clinical decision-making. Their functions are broad and can include diagnosis, prognosis, prescription, and determination treatment suitability. These systems are increasingly using artificial intelligence and

⁹³ AIHW, Digital Health, <https://www.aihw.gov.au/reports/australias-health/digital-health>

large datasets (particularly in imaging fields) to improve diagnoses and determine the most appropriate treatments.⁹⁴

Health monitoring devices

A number of devices have been developed that monitor patients' treatment response. These devices can monitor patients' vital signs or particular biomarkers and can alert patients and health care professionals about changes to a patient's health status. Health monitoring devices can aid decision making about appropriate treatments and dosages, and can be linked to drug delivery devices (such as insulin pumps). These include devices that:

- predict cardiovascular events and health outcomes - which could be used in association with a therapy to assess treatment response and identify any safety issues.
- assist evaluation of therapeutic effect of anti-parkinsonian drugs
- monitor inhaler utilisation in asthma.
- continuous glucose monitoring.

Algorithms for assessing cancer recurrence risk and treatment response based on genomic profiling (e.g. EndoPredict®, Oncotype DX® and MammaPrint).

The software algorithms that support gene expression profiling and polygenic risk scores described in part 7 also fit under the umbrella term of digital health technologies.

7.1.2 Assessment for funding of digital health technologies in Australia

Digital health technologies have received market authorisation internationally and have been funded under Australia's subsidy schemes. These include continuous glucose monitoring, and gene expression profiling tests that use algorithms to calculate risk of disease. Digital health technologies that assist with service delivery such which is already funded are not subsidised separately to the service that is subsidised.

⁹⁴ <https://www.nature.com/articles/s41746-020-0221-y>

8 Appendix 1: Glossary of Terms

Term {related terms}	Definition
Advanced therapies {Advanced therapy medicinal products (ATMPs)}	<p>A term used to describe innovative therapies. The TGA uses the following definition for advanced therapies:⁹⁵</p> <ul style="list-style-type: none"> a. Gene therapies <ul style="list-style-type: none"> i. the substance is used in or administered to human beings to regulate, repair, replace, add, or delete a genetic sequence AND ii. the substance is involved in the therapeutic, prophylactic, or diagnostic effect of the product b. Gene modified cell therapies c. Cell and tissue therapies that: <ul style="list-style-type: none"> i. are not devices ii. have been classified as class 3 or 4 biologicals. d. Either a or b in combination with a device
Australian Register of Therapeutic Goods (ARTG)	<p>The register of therapeutic goods for human use that may be imported to, supplied in, or exported from Australia.⁹⁶</p>
Basket Trial {Bucket trial}	<p>A type of clinical trial that tests how well a new drug or other substance works in patients who have different types of cancer that all have the same mutation or biomarker.³⁴ In basket trials, patients all receive the same treatment that targets the specific mutation or biomarker found in their cancer. Basket trials may allow new drugs to be tested and approved more quickly than traditional clinical trials. Basket trials may also be useful for studying rare cancers and cancers with rare genetic changes.</p>
Biomarker	<p>A characteristic (usually measured by a test) by which a pathological or physiological process (e.g. disease, response to treatment) can be identified. A biomarker may be defined by the presence or absence of a characteristic, or it may be defined by a quantity of a parameter above or below a specified threshold.¹⁰⁰</p>
Co-dependent⁹⁷ {Co-dep}	<p><u>Health technologies</u> that are dependent on each other, such that their use needs to be combined (either sequentially or simultaneously) to achieve or improve the intended effect on <u>health outcomes</u> of <i>either</i> health technology. <i>For example: When a specific diagnostic test is needed prior to administration of a pharmaceutical.</i></p>

⁹⁵ <https://www.tga.gov.au/advanced-therapies>.

⁹⁶ https://www.pbs.gov.au/industry/useful-resources/glossary/Glossary-of-Terms_Final-15Apr-13.pdf.

Conditional marketing authorisation, EMA³³	The approval of a medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine’s benefits outweigh its risks, and the applicant should be in a position to provide the comprehensive clinical data in the future.
Evaluation Sub-Committee (ESC), MSAC⁹⁷	ESC is one of two sub-committees of MSAC (the other sub-committee being PASC). ESC primarily advises MSAC on issues and uncertainties arising from the evidence presented in an assessment report. ESC meets three times per year (usually in February, June, and October), and MSAC’s ESC should not be confused with PBAC’s Economics Sub-Committee.
Economics Sub-Committee (ESC), PBAC⁹⁷	ESC is a sub-committee of the PBAC that advises it on the quality, validity and relevance of economic analyses and evaluations submitted in support of listing of medicines on the PBS. ESC also advises PBAC on methodological developments in collecting, analysis and interpreting clinical and economic data, and on the content of PBAC guidelines.
Device	Used to imply ‘medical device’ Any instrument, apparatus, appliance, material, or other article that: ¹⁰⁰ <ul style="list-style-type: none"> • is used for humans • is intended to diagnose, prevent, monitor, treat or alleviate a disease or injury, or modify or monitor anatomy or physiological functions of the body • generally achieves its purpose by a physical, mechanical, or chemical action.
Diagnosis	The identification of a medical condition by investigation. ⁹⁶
Economic evaluation	A comparative analysis of the costs and outcomes of health technologies. An umbrella term covering cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, cost minimisation analysis and cost-utility analysis. The analysis involves identification, measurement, and valuation of the differences in costs and outcomes caused by substituting health technologies. ⁹⁶
European Medicines Agency (EMA)	The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU
Fast track	A process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. ⁹⁸ The purpose is to get important new drugs to the patient earlier and addresses a broad range of serious conditions. ⁹⁸
Food and Drug Administration (FDA)	The FDA is the United States regulatory body that is responsible for ensuring that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective.

⁹⁷ [Conversations for Change \(joyn-us.app\)](#).

⁹⁸ [Fast Track | FDA](#).

Genetics	The study of how genes work and transmit information from parents to offspring. ⁹⁹ It can help us understand the risk of inheriting a genetic disease. ⁹⁹
Genetic testing	Testing of single genes or a small number of genes with testing performed in series, one step at a time. ⁶⁹
Genetic variant – germline {Germline variant}	A gene change in a body’s reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline variants are passed on from parents to offspring at the time of conception. ¹⁰⁰
Genetic variant – somatic {Somatic variant}	A gene change that occurs after conception in non-germline cells, which is neither inherited nor passed on to offspring. ¹⁰⁰
Genomics	The study and mapping of genomes – the full set of genetic instructions for an organism. ⁹⁹ It includes both human and other genomes and how these interact with the environment. ⁹⁹
Genomic testing	Testing of many genes or the entire genome at once. This can include gene panels, whole exome sequencing and whole genome sequencing. ⁶⁸
Health technology	A technology used in a health care system, for example, therapeutic services (such as medicines, procedures, blood products), medical devices, investigative medical services (such as diagnostic tests, imaging services, population screening tests), equipment and supplies, organisational and managerial systems, and programs of health delivery. For the purposes of some definitions in these guidelines, particularly in relation to existing health technologies, this usual definition is extended to include any medical service, placebo, or watchful waiting instead of an active health technology. For ease of reading, the word ‘technology’ is used throughout the document but applies to all types of technology or services. ¹⁰⁰
Health Technology Assessment (HTA)	A range of processes and mechanisms based on scientific evidence to assess the comparative quality, safety, efficacy, effectiveness, and cost-effectiveness of health technologies. ⁹⁶ OR Health Technology Assessment (HTA) involves a range of processes and mechanisms that use scientific evidence to assess the quality, safety, efficacy, effectiveness and cost effectiveness of health services. ⁹⁷ The purpose of HTA is to provide policy-makers, funders, health professionals and health consumers with the necessary information to understand the benefits and comparative value of health technologies and procedures. This information is then used to inform policy, funding, and clinical decisions, and assist with consumer decision-making.

⁹⁹ [Genetics and genomics | Australian Government Department of Health and Aged Care.](#)

¹⁰⁰ [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/E0D4E4EDDE91EAC8CA2586E0007AFC75/\\$File/MSAC%20Guidelines-complete-16-FINAL\(18May21\).pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/E0D4E4EDDE91EAC8CA2586E0007AFC75/$File/MSAC%20Guidelines-complete-16-FINAL(18May21).pdf).

	<p>The key questions that a HTA aims to answer for each new health technology, in comparison to alternative interventions, are:</p> <ul style="list-style-type: none"> • Is it safe? • Does it improve health outcomes? • Is it cost effective?
High cost, Highly Specialised Therapies	<p>TGA approved medicines and biologicals delivered in public hospitals where the therapy and its conditions of use are recommended by MSAC or PBAC; and the average annual treatment cost at the commencement of funding exceeds \$200,000 per patient (including ancillary services) as determined by the MSAC or PBAC with input from the Independent Hospital Pricing Authority; and where the therapy is not otherwise funded through a Commonwealth program or the costs of the therapy would be appropriately funded through a component of an existing pricing classification.¹⁰¹</p>
Indication	<p>The medical condition, disease or disorder that is the reason for starting clinical management.⁹⁶</p>
Medical Services Advisory Committee (MSAC)	<p>An independent HTA advisory committee of the Australian Government that primarily advises the health minister on whether it supports the public funding of proposed health technologies and other medical services.⁹⁶</p> <p>OR</p> <p>An independent, non-statutory committee, and meets three times per year (usually in March, July, and November).⁹⁷ MSAC appraises new medical services/technologies proposed for public funding and provides advice to Government on whether a new medical service/technology should be publicly funded. Amendments and reviews of existing services funded on the Medicare Benefits Schedule (MBS) or through other programs (<i>for example, blood products or screening programs</i>) are also considered by MSAC.</p>
Medicare Benefits Schedule (MBS)	<p>Under the authority of the <i>Health Insurance Act 1973</i>, a listing and description of the professional services for which a Medicare benefit is payable by the Australian Government, the amount of a patient's cost that is met through a government rebate, and any conditions applying to the use of that service.⁹⁶</p> <p>OR</p> <p>Under the authority of the <i>Health Insurance Act 1973</i>, the MBS is a listing and description of private (not publicly provided) professional medical and allied health services, for which a Medicare benefit/rebate is payable by the Australian Government (and any conditions applying to provision of that service).⁹⁷ The benefit/rebate is the amount of a private patient's cost that is met by the Government, and varies depending on whether the private patient is treated as an admitted/in-hospital patient (75% rebate) or out-of-hospital patient/non-admitted outpatient (85% rebate). The MBS includes information</p>

¹⁰¹ https://federalfinancialrelations.gov.au/sites/federalfinancialrelations.gov.au/files/2021-07/NHRA_2020-25_Addendum_consolidated.pdf.

	<p>on additional out-of-hospital rebates provided under the Extended Medicare Safety Net and Greatest Permissible Gap. The MBS is available online, as a searchable document.</p>
Orphan drug, TGA	<p>An orphan drug is a medicine, vaccine or in vivo diagnostic agent that meets the requirements of regulation 16J of the Therapeutic Goods Regulations 1990. Orphan drug designations allow for a waiver of application and evaluation fee for registration in the Australian Register of Therapeutic Goods (ARTG)¹⁵.</p>
Orphan medicine, EMA	<p>A medicine for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs.⁹</p>
Pharmaceutical Benefits Advisory Committee (PBAC)	<p>An independent HTA advisory committee of the Australian Government that primarily makes recommendations to the health minister on the listing of medicines in the PBS.⁹⁶</p> <p>OR</p> <p>PBAC is an independent expert body, appointed by the Australian Government.⁹⁷ Members include doctors, health professionals, health economists and consumer representatives. Its primary role is to recommend new medicines for listing on the PBS and vaccines for the National Immunisation Program. No new medicine can be listed unless the committee makes a positive recommendation. PBAC meets three times a year, usually in March, July, and November. When recommending a medicine for listing, PBAC takes into account the medical conditions for which the medicine was registered for use in Australia, its clinical effectiveness, safety, and cost-effectiveness ('value for money'), compared with other treatments. PBAC has two sub-committees to assist with analysis and advice in these areas: the Drug Utilisation Sub-Committee (DUSC); and Economics Sub-Committee (ESC) – <i>not to be confused with MSAC's ESC</i>.</p>
Pharmaceutical Benefits Scheme (PBS)	<p>Under the authority of the National Health Act 1953, a listing and description of the medicines that are subsidised by the Australian Government, the amount of that subsidy and any conditions applying to the use of that medicine.⁹⁶</p> <p>OR</p> <p>The PBS has been in existence since 1948 and is governed by the <i>National Health Act 1953</i> (Commonwealth).⁹⁷ The PBS provides a list (Schedule) of all medicines that can be dispensed to patients at a government-subsidised price. This list (Schedule) is part of the wider Pharmaceutical Benefits Scheme, managed by the Department of Health, and administered by Services Australia.</p> <p>This Schedule is available online and updated monthly. The online (searchable) version contains:</p> <ul style="list-style-type: none"> • All drugs/medicines listed on the PBS.

	<ul style="list-style-type: none"> • Information on conditions of use for the prescribing of PBS medicines. • Detailed consumer information on medicines that have been prescribed by your doctor or dentist; and • What you can expect to pay for medicines.
Predictive	Typically use to refer to change in management, rather than cascade testing.
Precision medicine	Precision medicine, sometimes known as "personalized medicine" is an approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles. ⁶⁶ The goal of precision medicine is to target the right treatments to the right patients at the right time. ⁶⁶
Priority review, FDA⁵⁰	A designation that will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications
Provisional registration, TGA	Provisional registration allows certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where the benefit of early availability of the medicine outweighs the risk inherent in the fact that additional data are still required. ³⁵
Technology	A simplified term for all types of health technology or services. ¹⁰⁰
Therapeutic Goods Administration (TGA)	A division of the Australian Government Department of Health and Ageing that regulates the quality, safety, and efficacy of therapeutic goods available within Australia. ⁹⁶
Vaccine	A suspension of attenuated or killed microorganisms administered for the prevention, amelioration, or treatment of infectious diseases. ⁹⁶