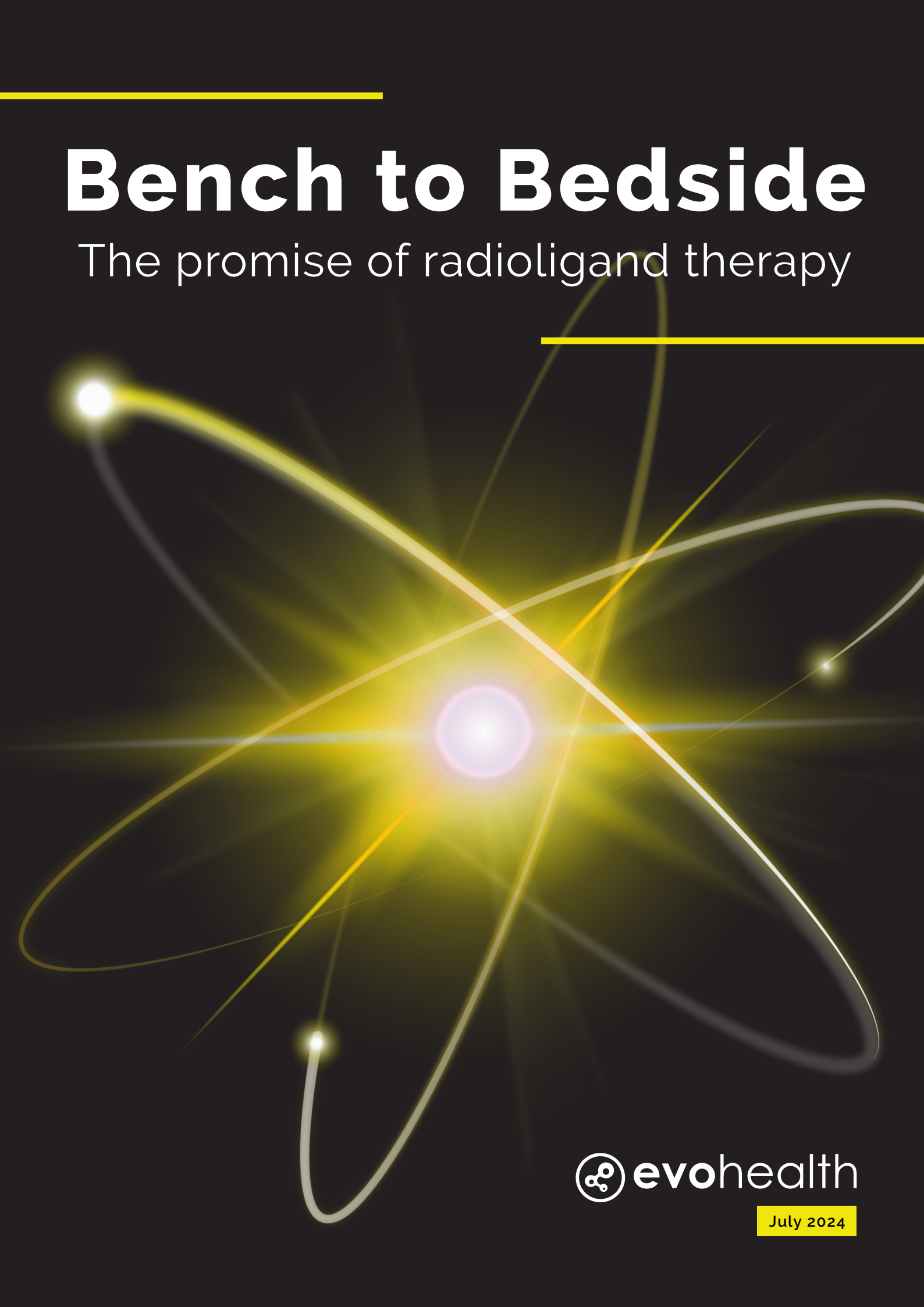
Bench to Bedside

The promise of radioligand therapy



evohealth

July 2024

Evohealth acknowledges that we work on the traditional lands of many Aboriginal clans, tribes, and nations.

We commit to working in collaboration with Aboriginal and Torres Strait Islander communities and peoples to improve health, emotional and social well-being outcomes in the spirit of partnership.

About **Evohealth**

The delivery of healthcare is complex.
Our focus is not.

Better health for all Australians.

BENCH TO BEDSIDE

THE PROMISE OF RLT

CONTENT.

ABOUT **THIS REPORT**

Background

Bench to Bedside: The promise of Radioligand Therapy is an evidence based independent report analysing the potential advantages of Radioligand Therapy (RLT) as a precision medicine for Australians with cancer. This report makes recommendations to ensure Australian patients have equitable access to safe, efficacious and regulated RLT in Australia and was independently authored by Evohealth.

Approach

The report has been informed by:

- a comprehensive review of published academic and grey literature; and
- interviews with Australian clinicians, researchers and patient advocacy groups.

The report received funding from Novartis Australia. Novartis representatives did not participate in the development of the report to ensure the independence of Evohealth.

ACKNOWLEDGEMENTS

Evohealth wishes to acknowledge the ongoing support from the individuals and organisations who contributed to this project.

We would like to acknowledge the contributions of **Prostate Cancer Foundation of Australia** and **NeuroEndocrine Cancer Australia** for sharing stories of patients who have been affected by cancer. Their contributions have highlighted the real-world benefits of RLT and the positive impact on patient quality of life.

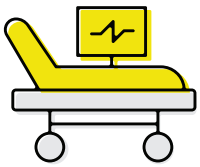
We also extend our sincere appreciation to the clinical, research, government and industry stakeholders from various organisations who participated in interviews and provided their invaluable contributions and insights to the report.

The expertise provided by individuals and organisations has played a pivotal role in shaping our approach and ensuring that the content of this report is relevant and contributes to creating a positive impact for all Australians.

EXECUTIVE **SUMMARY**

Australia's growing cancer challenge

Cancer is one of Australia's biggest killers, touching almost every Australian directly, or indirectly through their loved ones. [1] The impact goes beyond the health and lives of our citizens though, putting significant financial strain on the broader health system. [2]



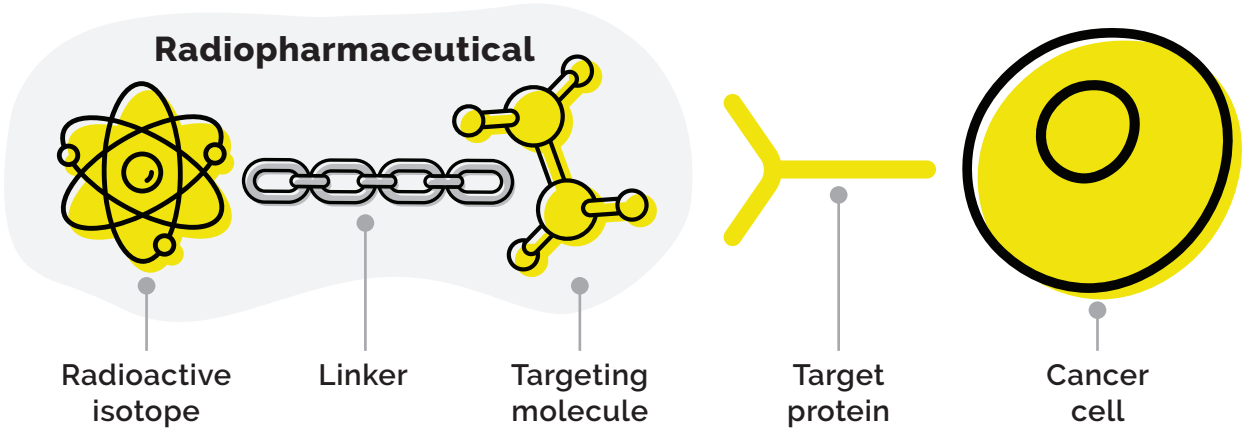
An estimated
~ 165,000 Australians
received a cancer diagnosis
in 2023 [1]

An estimated
~ 49,996 Australians
died from cancer in 2022 [3]

In Australia, cancer cost
$10.1 billion in 2015-16 [2]

Traditional cancer treatment options encompass surgery, radiation, chemotherapy, and immunotherapy. Chemotherapy, a non-targeted treatment, can cause hair loss, vomiting, diarrhoea, infections, numbness and ulcers. In contrast, Radioligand therapies (RLT) are set to advance in cancer care with a precision medicine approach. RLT are a type of radiopharmaceutical that uses radioactive molecules to kill cancer cells, largely sparing healthy tissue and limiting patient side effects. (Figure 1). [4, 5]

Figure 1 - Components of a radiopharmaceutical



Source: Adapted from What are Radiopharmaceuticals? | IAEA [6]

Radioligand revolution

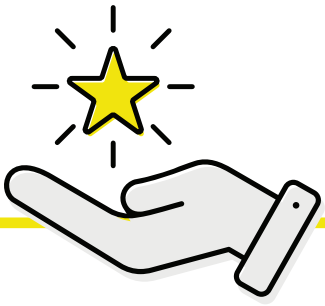
Although the use of radiopharmaceuticals in cancer treatment is not new, recent advancements have enhanced their specificity, bringing a new era of precision medicine.

Treating patients precisely with RLT is made possible by using targeted ligands that specifically bind to receptors or targets on cancerous cells, largely sparing normal cells from harm. [7-10] Often RLT is used in conjunction with a diagnostic agent (e.g. a theranostic pair). [8, 10-12]

Precision medicine is possible as the treatment can be:

- **personalised** by selecting and interchanging radioisotopes or targeting compounds based on the patient's disease characteristics. [8, 10-12]
- **customised** for dosage and therapy duration based on the patient's actual and predicted response.[10, 13, 14]
- **monitored** for treatment response through visualisation with Positron Emission Tomography (PET) scanners and Single Photon Emission Computed Tomography (SPECT) scans. [8, 10-12]

With thousands of Australians touched by cancer each year, there is an urgent need to provide equitable access to effective treatments such as RLT at scale. [1, 3]



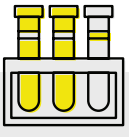
Radioligand therapies, as a precision medicine, **offer hope to cancer patients in Australia.**

Recognition of the potential of RLT is evident in the global development pipeline, with numerous clinical trials in various stages of development including for prostate, lung, breast, brain and thyroid cancers, as well as some solid tumours. [15-17] As RLT edges from the bench to bedside, Australia must consider how it can prepare to deliver on the promise of these therapies safely, equitably and at scale.

46 active or complete clinical global RLT trials

23

phase zero,I and
phase I/II clinical trials



18

phase II clinical trials

5

phase III clinical trials
advanced prostate cancer

Source: Evohealth developed from multiple sources [15-17]

Is Australia ready to deliver on the promise of RLT?

Our research reveals **three reasons** why Australia is well placed to embrace and deliver on the promise of precision medicine and propel RLT from bench to bedside.

Australia has:

1. **world leading nuclear medicine physicians** who have a proven track record in delivering impactful RLT clinical trials;
2. **enticing clinical trial conditions,** including regulatory approval exemptions, tax offset incentives, streamlined coordination, recruitment and ethical approval pathways; and
3. **the necessary resources, capability and existing infrastructure** that can be leveraged to deliver these innovative therapies to patients locally and, with strategic investment in commercial opportunities, globally.

We know that by investing in more research, as well as leveraging our national expertise and experience, we can attract more clinical trials, as well as continuing our privileged position as a first wave country for the launch of new therapies.

Through our robust regulatory and reimbursement systems, we can provide universal access to safe, effective, and quality-manufactured RLT, ensuring a smooth transition from bench to bedside. Registered and reimbursed therapies must meet high standards, enabling widespread, standardised patient care and supporting the goals of Australia's National Medicines Policy (NMP). Without registration, access is limited to clinical trials and compassionate use programs, which are insufficient for safe, broad, universal access.

Australia can propel RLT from bench to bedside.

To date, Australians have only benefited from access to RLT agents through clinical trials, and in some circumstances, compassionate access programs. Clinical trials, whilst necessary to develop the data needed to inform our regulatory and reimbursement processes, are only offered to a small number of patients, and are not a solution for broad universal access as envisioned under our NMP.

Australians expect and deserve to have access to safe, effective and high-quality care. Achieving this requires new innovations, such as RLT, to transition from bench (aka. experimental therapies) to bedside (aka. registered and reimbursed standard of care therapies).

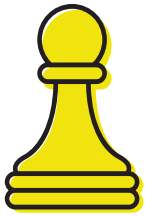
Australia's registration and reimbursement systems are essential for providing equitable access to therapies that are proven to be safe, effective and of high quality.

Experimental RLT is also only feasible on an individual patient use basis. As the population eligible for RLT grows, scaling will require access to registered therapies. Importantly, for broad population use, registered RLT products, manufactured in accordance with Good Manufacturing Practice (GMP) must be the gold standard of patient care.

To embrace the potential of RLT and take it from bench to bedside, we have developed **three recommendations** that leverage Australia's expertise and reputation, as well as our robust regulatory and reimbursement system. These are

RECOMMENDATION 1

Develop and promote an expert endorsed statement that clearly articulates Australia's unique capability and capacity to deliver global RLT clinical trials.



RECOMMENDATION 2

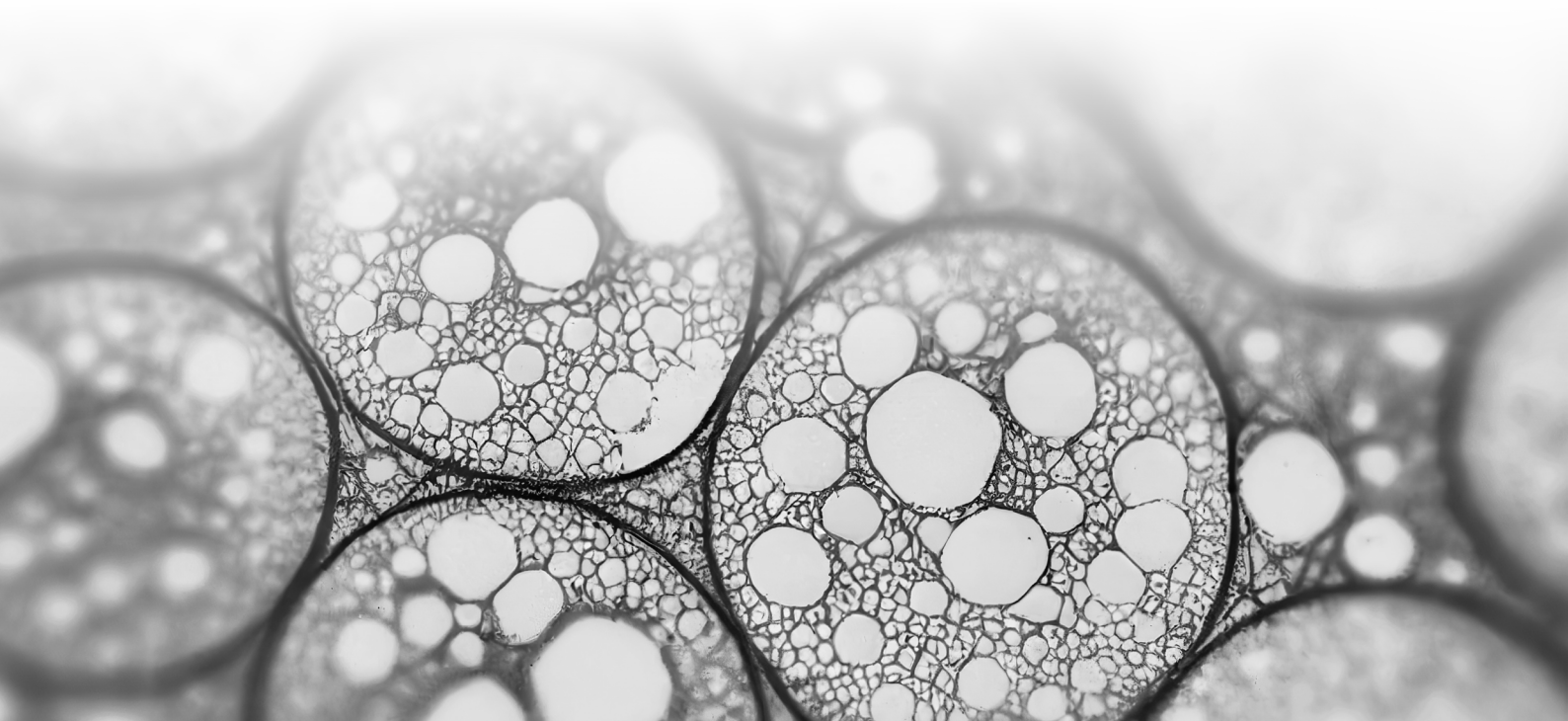
Establish a national working group to develop and implement Australia's nuclear medicines strategy, This strategy should include support for more RLT clinical trials, plans to provide equitable patient access to safe, efficacious and registered RLT, as well as enable sovereign manufacturing capability and capacity.

RECOMMENDATION 3

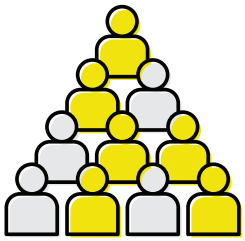
Develop a Government funded program ready to provide equitable patient access to safe, efficacious and regulated RLT.

By taking decisive action today, we can secure equitable access for all Australians and establish our nation as a global leader in RLT access, research and clinical trials.

There is significant opportunity for Australia to build upon its global leadership in RLT research and development, by stewarding the translation of research to broad and equitable patient access to registered therapies that are safe, effective and capable of scale.



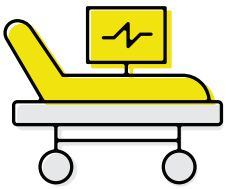
AUSTRALIA'S **CANCER LANDSCAPE**



~165,000 Australians were estimated to be **diagnosed with cancer** in 2023 [1]

~49,996 Australians lost their lives to cancer in 2022. [3]

$10.1 billion was spent on cancer diagnosis and treatment in 2015-16 (most recent estimates). [2]



>200,000 Australians are projected to be diagnosed with cancer in 2033. [1]

AUSTRALIA'S ADVANCED **NUCLEAR MEDICINE NETWORK**

Australia has

1
nuclear reactor

18
cyclotrons
[8, 23]

111
PET scanners

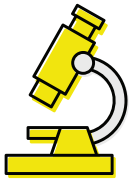
REVOLUTIONISING **TREATMENT WITH RLT**

46 active or complete clinical trials for therapeutic RLT [15-17]

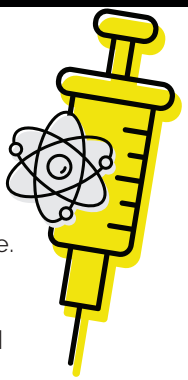
No RLT options are subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia.

RADIOPHARMACEUTICAL **REVOLUTION**

The global radiopharmaceutical market is projected to exceed AUD **$21 billion by 2031.** [18, 19]



Radioligand therapy (RLT) is a type of innovative radiopharmaceutical that realises the promise of precision medicine. **Early studies for the use of RLT for neuroendocrine tumours** were undertaken in the **1980s and 1990s.** [10]



Over 25 different radiopharmaceuticals

are used for diagnosis and treatment in Australia's nuclear medicine centres, with over **189,040 nuclear medicine imaging studies** conducted in a single year over 2023-24. [20-22]

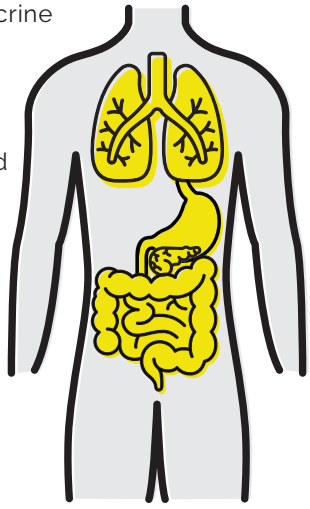
A small number of Australian prostate and neuroendocrine cancer patients **have benefited from access to RLTs through clinical trials.**

QUANTIFYING **NEUROENDOCRINE TUMOURS**

~5,437 new cases of neuroendocrine tumours were estimated to be diagnosed in 2022. [26]

51 per cent was the five-year survival rate for patients diagnosed with neuroendocrine tumours between 2014-18. [26]

72 per cent reduction in the risk of disease progression (or ~14.3 additional months) among patients with gastro-entero-pancreatic neuroendocrine tumours treated with RLT as a first-line therapy, compared to standard treatment. [27, 28]

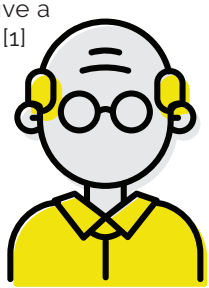


PROSTATE CANCER INSIGHTS

~25,500 men were estimated to receive a new prostate cancer diagnosis in 2023 [1]

~3,743 men were estimated to have died from prostate cancer in 2023. [1]

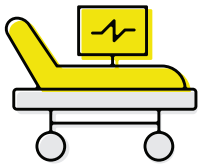
~372,000 Australian men are predicted to be living with, or navigating life post prostate-cancer, by 2040. [24]



increase in overall survival of up to **15.3 months compared to 11.3 months** for metastatic castration-resistant prostate cancer patients receiving RLT in addition to standard care, compared to standard care alone. [25]

WHAT CAN BE DONE ABOUT **AUSTRALIA'S GROWING CANCER CHALLENGE?**

Cancer is one of Australia's biggest killers, touching almost every Australian directly, or indirectly through their loved ones. [1] It not only costs our citizens their health and lives, but comes at significant expense to the broader health system. The most recent estimates from the Australian Institute of Health and Welfare (AIHW) indicate that approximately $10.1 billion was spent on diagnosing and treating cancers in Australia during the 2015-16 financial year. [2] This is set to grow as more patients are diagnosed. It is estimated that Australians diagnosed with cancer will increase from 165,000 in 2023 to over 200,000 in 2033. [1]



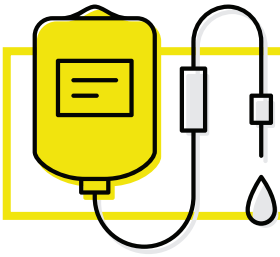
An estimated **165,000 Australians** received a cancer diagnosis in 2023. [1]

An estimated **49,996 Australians** died from cancer in 2022 [3]

In 2015-16, **$10.1 billion** was spent on diagnosing and treating cancers in Australia. [2]

Cancer, as a physiologically complex disease, requires a combination of treatment approaches. [29] These include surgery, radiation therapy, chemotherapy and immunotherapy. [30] These combinations are deployed by cancer type and stage of diagnosis, with the ultimate goal for most patients being management of cancer, not cure. [29]

It is common for treatments to have side effects that can negatively impact a patient's quality of life. [31] Thus, clinicians and researchers are continually searching for better therapeutic approaches that, in lieu of a cure, not only halt disease progression, but also have fewer toxic effects.



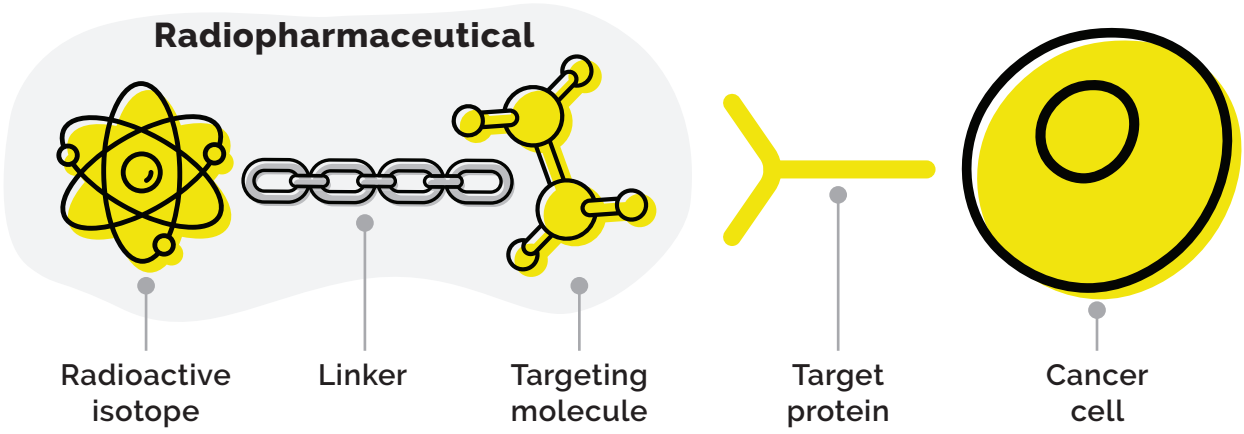
Australian clinicians and patients **want and need more options for treating cancers.**

RADIOPHARMACEUTICAL REVOLUTION – **NEXT GENERATION OF HOPE**

As clinicians search for new options to treat cancer patients effectively and safely, the next generation of precision radiopharmaceuticals sit poised to improve cancer care. Radiopharmaceuticals are not new. They have been an essential part of nuclear medicine practice for decades.

How do radiopharmaceuticals work?

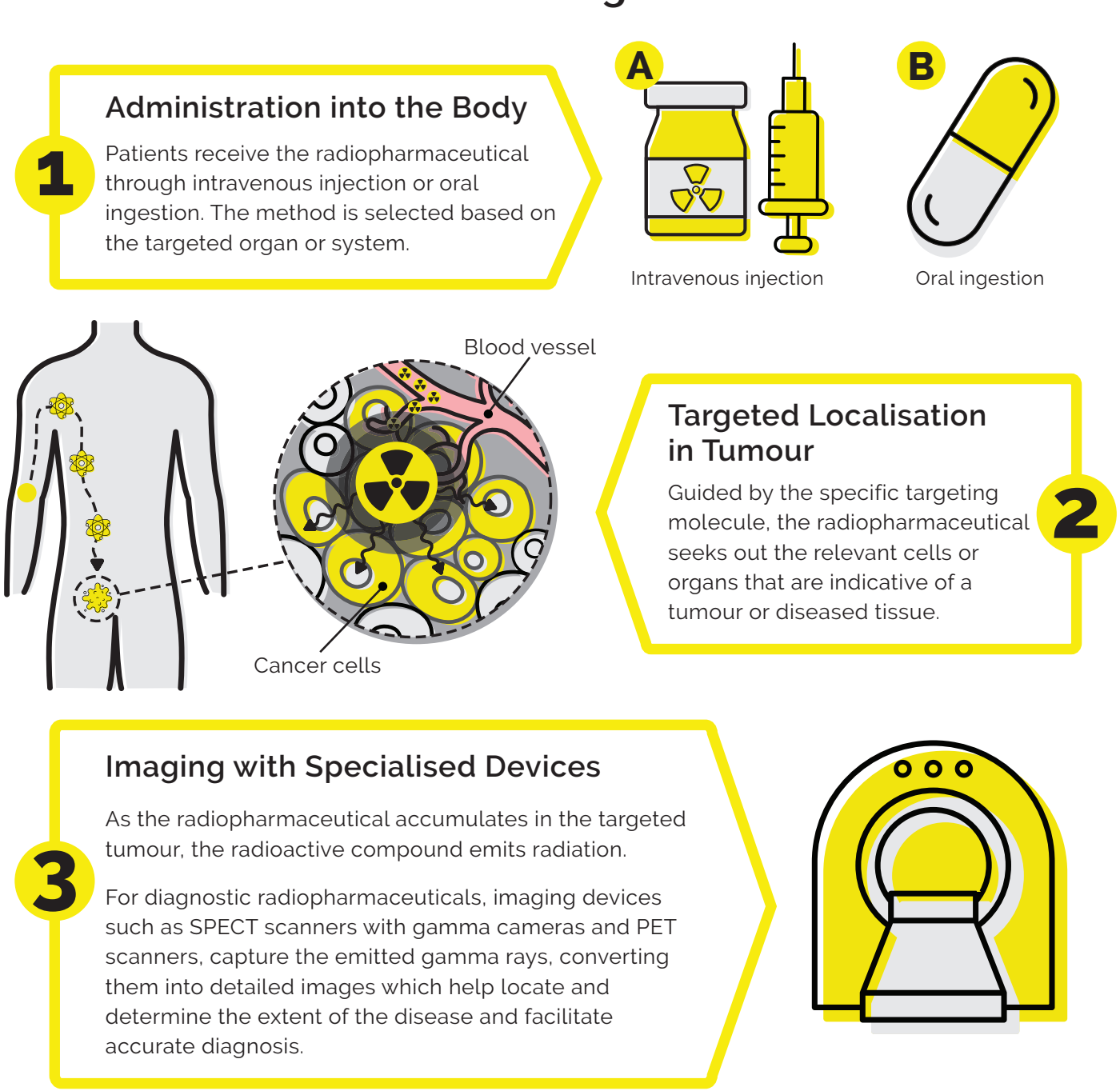
Figure 1 - Components of a radiopharmaceutical



Source: Adapted from What are Radiopharmaceuticals? | IAEA [6]

Radiopharmaceuticals contain a small amount of radioactive material, known as a radionuclide or radioisotope, typically attached to a targeting molecule (Figure 1). [4, 5] When introduced into the body, the targeting molecule seeks out the relevant cells or organ. [4, 5] The radionuclide then emits radiation that can either then be seen with special machines, such as Positron Emission Tomography (PET) scanners and Single Photon Emission Computed Tomography (SPECT) scanners, to detect disease (i.e. diagnostic radiopharmaceutical) and/or kill cells to treat disease (i.e. therapeutic radiopharmaceutical). This process is depicted in Figure 2. [4, 5]

Figure 2 – How radiopharmaceuticals are used to diagnose disease



Source: Adapted from What are Radiopharmaceuticals? | IAEA [6]

The radionuclide component of a radiopharmaceutical varies depending on whether it is used for diagnosis or treatment. [4, 5] This is due to their differing radiation profiles. [10, 12, 13, 22] Table 1 describes the three main types of radiation, their properties, uses, and some common examples. The properties of radionuclides, including their ability to damage cells (strength) and distance the radiation can travel (penetration), is also detailed, relevant to their use in diagnosis versus therapeutic applications. Currently, over 25 different radiopharmaceuticals are routinely used in Australia's nuclear medicine centres for diagnostic and treatment purposes. [22]

Table 1 – Different radiation produced by various radionuclides and their clinical uses

Radiation Type	Properties	Medical Use	Examples of radionuclides
α Alpha Particles	Very high energy (~3 particles needed to kill cells) and short range (width of 1-3 cells). Used for targeted cancer therapy due to their high energy and short travel distance in tissues. Can potentially kill circulating metastatic disease as well as other tumours without damaging healthy tissue.	Therapeutic	Radium-223 (Ra-223) used in prostate cancer treatment; Actinium-225 (Ac-225) trialled for use in prostate cancer.
β Beta Particles	Have lower energy (multiple particles needed to kill cancer cells compared to alphas) and longer range (10-100 cell widths). Can penetrate deeper into tumour clusters than alpha particles, but may be difficult to target circulating cells in metastatic disease.	Therapeutic	Iodine-131 (I-131) used to treat thyroid cancer; Yttrium-90 (Y-90) used to treat liver cancers; Lutetium-177 (Lu-177) used to treat prostate cancers.
γ Gamma Rays	Have the lowest energy (least damaging to cells) and longest range (hundreds to thousands of cell widths). Can penetrate deeply into the body and, due to long range, are detected by imaging devices, providing high-resolution images.	Diagnostic imaging	Technetium-99m (Tc-99m) is used extensively in SPECT scans for various diagnostic purposes, including cardiac, bone, and renal imaging.

Source: Evohealth developed from multiple sources [10, 12, 13, 22]

While the term 'radiopharmaceutical' may be unfamiliar to many Australians, it's likely that they or someone they know has had a diagnostic imaging test. Procedures used to identify blood cancers, bone diseases, brain tumours, heart disease and Alzheimer's disease often use radiopharmaceutical agents. [32] In the twelve months to July 2023, Medicare Benefits Schedule (MBS) data reveal that over 189,040 nuclear medicine studies[1,2] that employ various radiopharmaceuticals were undertaken in Australia. [20, 21, 33] Radiopharmaceuticals are and will continue to be a critical part of many Australian patients' treatment journeys in cancer and other care.

For cancer patients, however, hope lies in the use of the next generation of precision radiopharmaceuticals for treating cancer. With several radiopharmaceutical therapies being investigated in clinical trials, and some already available internationally, Australian patients and clinicians look forward to harnessing the power of these innovative therapies soon. [15-17, 34-36]

> *"…radiopharmaceuticals with antitumour effects, have seen rapid development over the past decade. Although some formulations are already approved for human use, more radiopharmaceuticals will enter clinical practice in the next 5 years, potentially introducing new therapeutic choices for patients."*
>
> **– Radiotheranostics: a roadmap for future development. [14]**

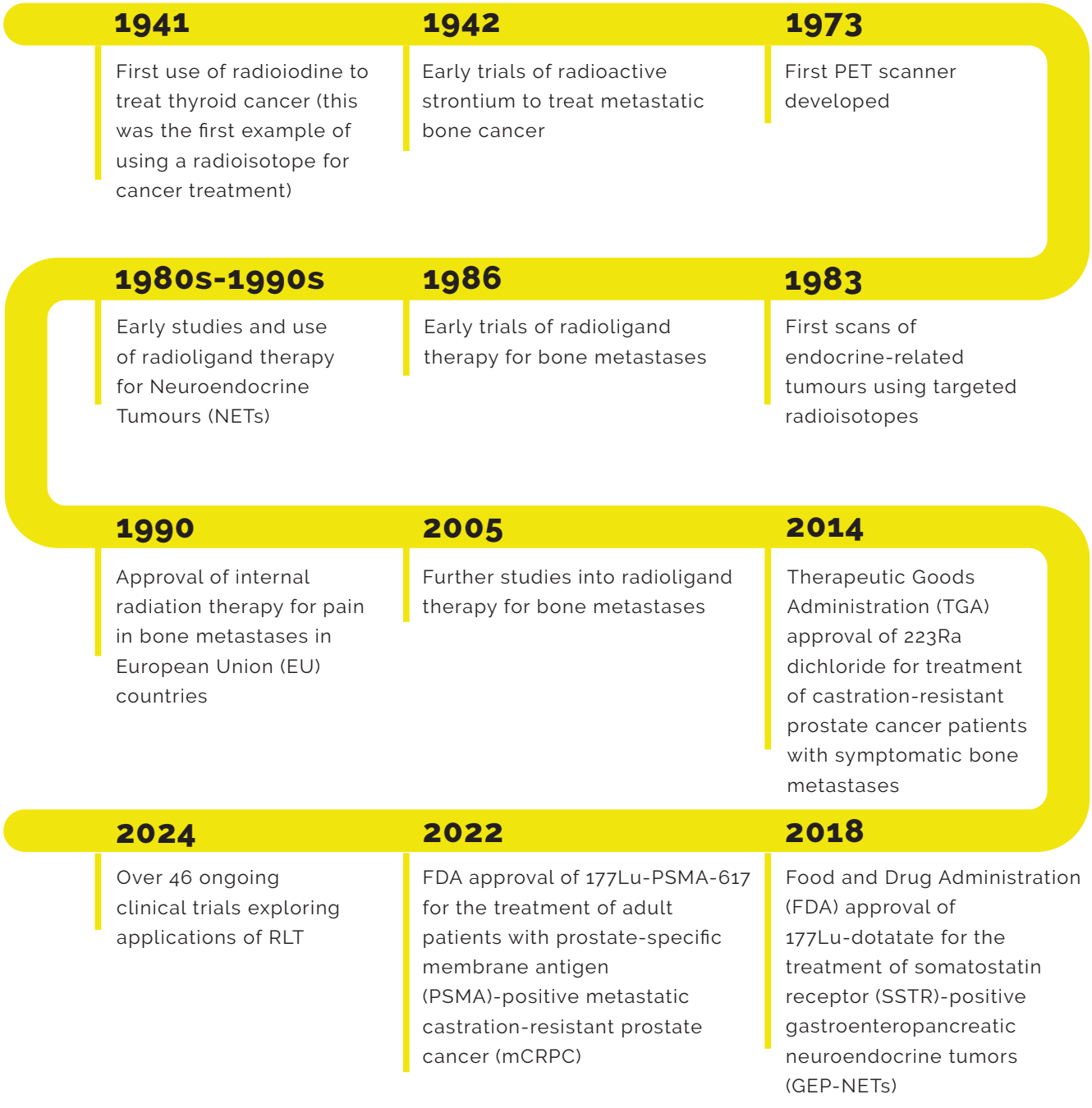
[1]MBS item numbers used: 61333, 61336, 61341, 61523, 61524, 61525, 61527, 61529, 61538, 61541, 61553, 61559, 61560, 61563, 61564, 61565, 61571, 61575, 61577, 61598, 61604, 61610, 61612, 61620, 61622, 61628, 61632, 61640, 61644, 61646, 61647.

[2]Nuclear medicine studies produce images by detection of radiation from different parts of the body after a radioactive tracer is given to the patient. Examples include: PET scans, MRI, CT. [3]

Radiopharmaceuticals have come a long way

Historically, to target a cancerous cell, radiopharmaceutical agents mimicked a physiological process. For example, cancer cells typically consume more glucose than other cells as they rapidly divide, so radiopharmaceuticals that appear 'glucose-like' to the body are taken up in areas where cancer cells are proliferating and thus can be imaged. [7] This physiological approach is decades old and began with the discovery and use of radioactive iodide in 1941, which is now a mainstay of treatment for thyroid cancer. [7] The journey from then, to the promise of the new targeted precision therapies today, is depicted at Figure 3.

Figure 3 – Timeline of development of nuclear medicine and therapeutic radiopharmaceuticals



Source: Adapted from multiple sources [10, 15-17, 34, 35]

Radiopharmaceuticals harness the power of precision

Radiopharmaceuticals have evolved and now with the introduction of new agents and innovative approaches, precision medicine is possible. This type of care offers benefits to patients by providing therapy that is specifically targeted to a patient's disease, thereby improving efficacy and reducing adverse effects.

Radioligand therapies (RLTs)[3] are one type of innovative radiopharmaceutical that can realise the promise of precision medicine. RLT utilises a targeting compound, designed to identify specific molecules that are only found, or more likely to be found, on cancerous cells in the body. [37] Figure 4 describes the relationship between nuclear medicine, radiopharmaceuticals, including specific targeting mechanisms and agents.

One prominent example is for prostate cancer. prostate specific membrane antigen (PSMA), a protein that is found in high volumes on prostate cancer cells. [38] PSMA levels are used to diagnose disease, monitor progression and as a target for treatment of prostate cancer. [38] The more precise the targeting ligand is for markers expressed on cancer cells, the more likely it is to only be taken up by, and kill, those cells, leaving healthy tissue undamaged. [37] This precision approach to medicine reduces adverse effects for the patient that are commonly encountered with systemic therapies. [37, 39] RLT can also be combined with other treatments (chemotherapy, immunotherapy etc.) which may minimise tumour resistance and have the potential to delay cancer progression.

Working in pairs

RLT can be used for both imaging and treatment by 'swapping out' the radioisotope used for each procedure. [11] This combined precision medicine approach to diagnostics and therapy is termed 'theranostics' (Figure 4). Theranostics offers both the clinician and patient some certainty when it comes to care, particularly for monitoring treatment effect versus disease progression, as well as making informed clinical decisions about when it is time to cease treatment altogether. [11]

Real-time insights (through imaging studies) show how well the therapeutic agent is targeting cancer cells, allowing for adjustments in treatment protocols as needed. The diagnostic capabilities of theranostics enable clinicians to assess changes in tumour size, metabolism, and response to therapy with greater accuracy, facilitating timely decisions on the continuation or modification of treatment plans to optimise patient outcomes. [11] This means that the number of treatments can be personalised to patient response, potentially limiting the time needed in treatment and broader risks of the therapy.

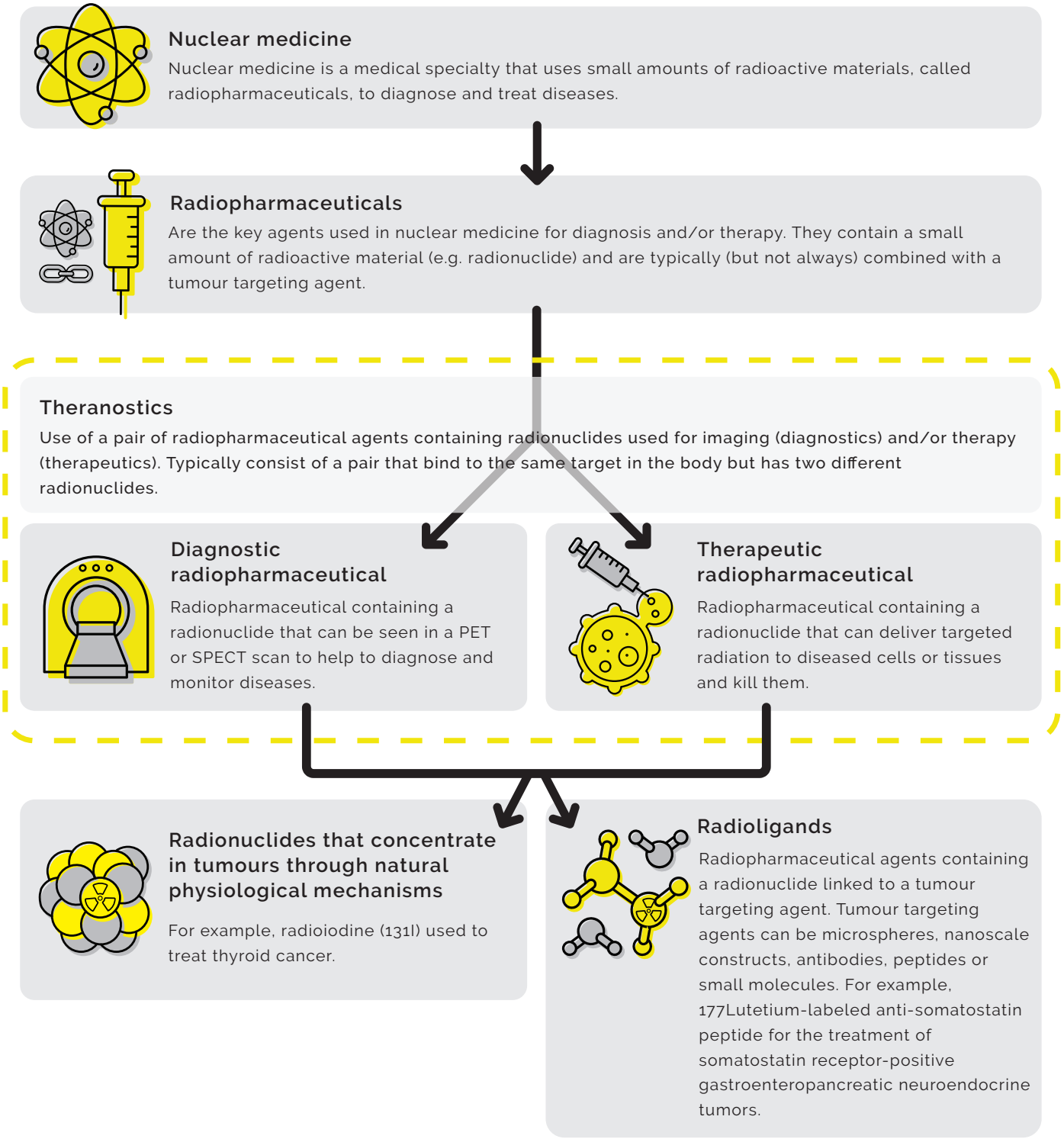
> *"Theranostics is the concept of small molecule proteins that are labelled to different radionuclides and can be used for either diagnosis or therapy, dependent on whether they are labelled with an imaging or therapy radionuclide. By directly targeting the cancer cells with imaging and then for therapy, this approach embodies the philosophy of precision medicine – right drug, right time, right dose"*
>
> **- Professor Louise Emmett,**
> *Director of Theranostics & Nuclear Medicine, St Vincent's Hospital Sydney [40]*

[3]Various terms are used for radioligand therapy, including peptide-receptor radionuclide therapy (PRRT), systemic radiation therapy, targeted radionuclide therapy, targeted radiotherapy and molecular radiotherapy. [10]

"I really fully expect over the next decade we're going to see a lot of mixing and matching. Different emitters, different targets to try to optimize the balance of toxicity and efficacy…"

- Dr Alan Bryce,
Chief Clinical Officer, City of Hope Cancer Centre Phoenix [12]

Figure 4 – Relationship between nuclear medicine, radiopharmaceuticals and radioligands

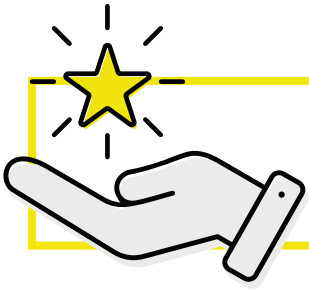


Source: Evohealth from multiple sources. [7, 41]

By specifically targeting cancerous cells through the identification of uniquely expressed markers, without damaging healthy tissue, and enabling theranostic practices, new generation radiopharmaceutical agents, such as RLT, epitomise the promise of precision medicine.

Precision medicine is possible because RLT:

- Utilises targeted ligands that **specifically bind to receptors or targets** on cancerous cells, largely sparing normal cells from harm. [7-10]
- Enables the **identification of patients most likely to respond** positively when used in conjunction with a diagnostic agent (e.g. a theranostic pair). [8, 10-12]
- Can be **personalised to meet the patient's needs** by selecting and interchanging radioisotopes or targeting compounds based on the patient's disease characteristics, enhancing efficacy and minimising adverse effects. [8, 10-12]
- Allows for **personalised dosage and therapy duration** based on the patient's actual and predicted response.[10, 13, 14]
- **Enables monitoring of response** through visualisation with PET and SPECT scans.



Radioligand therapies, as a precision medicine, **offer hope to cancer patients in Australia.**

THE HOPE OF **PRECISION CANCER CARE**

RLT is a pioneering advancement in oncology, offering new hope and improved outcomes for certain cancer types. Today, this approach is beneficial for Australians with prostate cancer and NETs, providing a promising alternative where traditional treatments may fall short. Already, a small number of Australian patients have benefited from innovative RLT through clinical trials.

> *"Since being diagnosed with prostate cancer, Rob Barker has had ten operations and a host of other treatments, including hormone implants and injections, radiation and chemotherapy. This has come at a cost of hundreds of thousands of dollars to him and his wife and a lot of side effects. But receiving RLT has given Rob renewed hope." [42]*

Precision prostate cancer care

In 2023, an estimated **25,500 men** received a new prostate cancer diagnosis. [1]

Approximately **3,743 deaths** were estimated to be related to prostate cancer in 2023. [1]

By 2040, an estimated **372,000 Australian men** will be living with or beyond prostate cancer. [24]

Prostate cancer treatment is typically tailored to each patient based on factors such as cancer stage, age, comorbidities, and symptom severity. [43] Due to its slow-growing nature, aggressive treatment is not always recommended. [43] Younger men with low-risk localised prostate cancer may opt for 'active surveillance'[4], while older individuals who have been diagnosed with prostate cancer undergo 'watchful waiting'[5] for symptom development. [43] For those patients treated with conventional methods, such as chemotherapy and radiation, severe ongoing side effects such as fatigue, nausea, vomiting, and diarrhoea can follow therapy. Over 16 per cent of patients who have undergone surgery for prostate cancer regret their decision due to negative impacts on their quality of life, including urinary incontinence, erectile or bowel dysfunction. [44, 45]

[4]Active surveillance for low-risk, localised prostate cancer involves closely monitoring the cancer,s progression through regular prostate-specific antigen tests, digital rectal examinations, MRI scans, and occasional biopsies. Treatment is deferred unless there are signs of cancer growth or worsening, allowing patients to avoid potential treatment side effects, while ensuring timely intervention if necessary. [43]

[5]Watchful waiting involves monitoring for symptoms or changes following diagnosis with prostate cancer. Regular prostate-specific antigen tests are undertaken, and if symptoms like bone pain arise, patients are offered treatment to manage these symptoms. [43]

RLT offers patients with advanced disease a targeted, effective treatment option that not only improves survival rates, but also enhances quality of life by minimising damage to healthy tissues and reducing side effects. [10, 46, 47]

RLT and prostate cancer

Metastatic castration-resistant prostate cancer (mCRPC) is a type of advanced prostate cancer that has metastasised outside of the prostate gland and does not respond to conventional hormone therapy to lower testosterone levels. [48] Despite the availability of several therapies that delay progression of disease, mCPRC is incurable. [25, 49]

These metastatic lesions often express high levels of PSMA, which is identified as a target for RLT. RLT offers a viable option, providing not only a potential extension of survival but also significant improvements in quality of life, including reduced risk of side effects such as erectile dysfunction, loss of libido, weight gain, muscle weakness and shrinkage, anaemia, and the depression and fatigue typically faced with hormone therapy. [10, 46, 47]

> *"With RLT there are fewer side effects so [patients] have the opportunity to get out and mow the lawn, spend time with their grandkids, play a round of golf. They get that quality of life back"*
>
> **- Dr Jane Fish,**
> *Global Director of Cancer Research and Clinical Trials, Movember [42]*

RLT clinical trials, specifically Lu-177-PSMA agents, have shown that men with mCRPC not only live longer but also experience significantly reduced pain, improved mobility, and overall better quality of life compared to chemotherapy and hormone therapy. [25, 50] This quality time with loved ones cannot be underestimated, and is the true benefit of these innovative treatments. When a cure is not possible, the next best outcome is providing patients with more time and improved quality of life.

RLT in addition to standard care has been shown to increase overall survival up to **15.3 months** for metastatic castration-resistant prostate cancer **patients receiving therapy** compared to 11.3 months for patients receiving standard care alone. [25]

Patient story – Peter[6]

Peter was diagnosed with prostate cancer seven years ago and has twice undergone surgery plus radiation and hormone therapy, as well as two rounds of RLT. Peter reports that his results since receiving RLT have been remarkably good, much better than expected. "In the early years of diagnosis, I became very depressed every time I had treatment and the cancer reappeared, years of hoping followed by intense disappointment." Since receiving RLT, Peter recalls that "for the first time I now feel quite confident that the worst is over and having a potential rest from androgen deprivation therapy is a huge boost to my morale and is having a positive effect on my partner. Life is returning to what it was more than seven years ago. RLT has given us hope." Peter reflects that "the cruel part about [the lack of universal affordable access to RLT] is people who can afford it can usually have better quality of life with reduced pain than those who can't afford it."

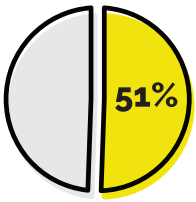
There is hope that these benefits will soon reach those in earlier stages of their prostate cancer journey too. Ongoing clinical trials are exploring the potential of RLT in early-stage treatment, aiming to compare its effectiveness directly with other therapies. These randomised head-to-head trials will provide crucial insights into whether RLT can effectively delay or mitigate disease progression at an earlier stage, potentially reducing the necessity for more aggressive treatments with significant side effects. [10]

Hope for NETs

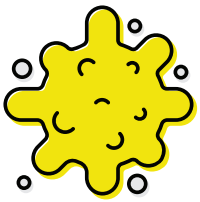
The neuroendocrine system is a group of glands and nerve cells that make and release hormones into the bloodstream. These hormones are responsible for controlling normal functions of the body such as digesting food. Neuroendocrine cells are found throughout the body but are mainly in the gastrointestinal tract, pancreas and lungs. NETs arise from these neuroendocrine cells. [51]

In Australia, the burden of NETs is significant, with more than 5,000 people estimated to be diagnosed in 2022. [26] The five-year relative survival rate for individuals diagnosed with NETs in Australia was 51 per cent between 2014-2018. [26]

In 2022, an estimated **5,437 new cases** of NETs were diagnosed. [26]



The five-year (2014 – 2018) survival rate for patients diagnosed with NETs was **51 per cent**. [26]



In 2021, NETs were estimated to be the **7th most diagnosed** cancer. [52]

[6]To maintain confidentiality, patient's name has been changed.

NETs typically form in the gastrointestinal tract, pancreas, and lungs. [53] These tumour types are often slow growing but can metastasise and lead to debilitating symptoms such as bone pain, spinal cord compression and an abnormally high concentration of calcium in the blood. [52, 54] Excess calcium can have widespread effects through the body and can impact the:

- kidneys: causing increased thirst and urination;
- digestive system: leading to symptoms like vomiting and constipation;
- bones and muscle: leading to weakening of the bones and muscles;
- brain: leading to confusion, drowsiness and fatigue and even depression; and
- heart: causing palpitations, irregular heartbeat. [55]

Gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) are a type of NET that develop in the gastrointestinal tract, including the pancreas, stomach, small intestine, colon, rectum and appendix. [56] GEP-NETs can give rise to hormonal symptoms, known as carcinoid syndrome, which include diarrhoea, flushing, skin lesions, wheezing and valvular heart disease. [56-58]

Patients diagnosed with NETs have described the unpredictable nature of the disease, including experiencing a piercing pain in the stomach region, which would subside and then come back intermittently, often after a year or even longer, escalating to excruciating amounts of pain. [59]

> *"This is unbearable I can't live with this."*
>
> **- Patient diagnosed with NET [59]**

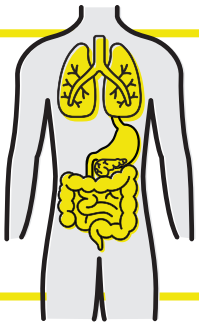
Surgery remains the primary approach for managing early-stage NETs, either aiming for complete tumour removal (curative surgery) or reducing tumour size and symptoms (palliative or 'debulking' surgery). [52] Chemotherapy is typically used for higher-graded NETs and may not be effective for those classified, Grade 1. [52] Additionally, medications such as somatostatin analogues help manage symptoms and reduce cancer growth, especially for functional NET syndromes. [52] Whilst surgery plays a key role in the treatment and management of NETs, studies show that following surgery, patients can experience an increase in side effects, such as fatigue and pain, even three years after the surgery. [60] Moreover, patients who have undergone surgery for NETs have high rates of depression following treatment. [60] Like prostate cancer, treatment with chemotherapy for patients with NETs results in a number of side effects that impact their quality of life, including loss of appetite, weight loss, tiredness, increased risk of infection, bleeding and bruising, diarrhoea or constipation and hair loss. [61]

While surgery, chemotherapy and medications like somatostatin analogues play a significant role in the management of NETs, they often cause significant side effects. RLT offers a promising alternative to these patients.

RLT for treatment of GEP-NETs

RLT can be administered to patients with GEP-NETs in cases where conventional treatment options such as surgery, chemotherapy, or somatostatin analogues, have not been effective in controlling the disease or managing symptoms. [62] Additionally, RLT may also be a consideration for patients with advanced or metastatic GEP-NETs, who are not candidates for surgery or for whom the disease has progressed despite other treatments. [62]

RLT targets somatostatin receptors, which are molecules overexpressed on the surface of NET cells. [63] Clinical trials have shown that RLT targeting somatostatin receptors reduced gastrointestinal symptoms associated with carcinoid syndrome, whilst minimising damage to surrounding tissues which improves the quality of life of patients. [57, 64, 65] Patients on RLT can then return to work, as well as participate in family and social activities. [57]



Research has demonstrated a **72 per cent reduction in the risk of disease progression (or ~14 additional months)** among patients with GEP-NETs treated with RLT as a first-line therapy, compared to standard treatment. [27, 28]

Patient story – John[7]

John underwent RLT in April, the day before his birthday. Initially, he and his wife felt nervous, not knowing what to expect. However, following the treatment, John experienced minimal side effects, mainly tiredness and some hair thinning. His wife has noticed that his hair has somewhat recovered since then.

It has been eight months since John's final RLT cycle, and he reports feeling good within himself. Although his energy levels are still a bit low, his wife is pleased to see that he has put on weight. She believes that overall, John's experience with RLT has been positive for both of them. She "imagines that if he needs to do it again in a couple of years, he will say yes".

A small number of Australians are benefiting from these therapies through clinical trials and compassionate access pathways, however we need to prepare to receive these therapies and enable future broad universal access at scale for all those who need them. This can be achieved by facilitating these therapies through our robust regulatory and reimbursement systems, designed to ensure safe and equitable access for all Australians.

Australian cancer patients are experiencing better quality of life and receiving more time when treated with RLT. These patients expect universal access to safe and effective RLT for all who need it.

[7]To maintain confidentiality, patient's name has been changed.

A 'PLATFORM-LIKE' TECHNOLOGY **WITH MULTIPLE APPLICATIONS**

Similar to the much-lauded mRNA vaccine technology used to rapidly produce COVID-19 vaccines, RLT is a 'platform-like' technology with versatile and multiple applications across various types of cancer. Both the radioisotope and targeting component can be interchanged depending on the targeted disease, generating multiple applications for use. With the potential to be adapted and optimised for different cancer types, by offering a customisable treatment option, RLT could revolutionise how we combat cancer.

> *"Well, these are fantastic drugs. It's a fantastic platform as well. RLT is really, I think, highly amenable to rapid development of new approaches, to new molecules. I think there's every reason to be very optimistic about what the future of this looks like."*
>
> **- Dr Alan Bryce,**
> *Chief Clinical Officer, City of Hope Cancer Centre Phoenix [12]*

For each disease specific molecule identified, numerous radioisotopes can be paired to deliver targeted radiation at differing potencies within the body. In this way both solid tumours and metastatic cancers can be treated (Table 2). [15-17]

Table 2 – Cancers being treated or investigated for treatment with RLT

Cancer type	Example RLT platforms (isotope and cancer targeting agent)
Lung cancer	Pb-212 – Penitaxther
Renal cell carcinoma	Lu-177 – PSMA
Breast cancer	Lu-177 - NeoB
Advanced salivary gland cancer	Lu-177 – PSMA
Thyroid cancer	Lu-177 – Dotatate
Prostate cancer	Lu-177 – PSMA Ac-225 – PSMA Tb-161 – PSMA
Neuroendocrine cancer	Lu-177 – Dotatate

Source: Evohealth [15-17, 66-69]

As research and development (R&D) in the field of RLT continues to expand, the observed benefits for prostate cancer and NET patients are likely just the beginning. Globally, there are 46 active or completed RLT clinical trials investigating earlier lines of treatment and alternate therapeutic radioligands other cancers. [15-17, 66-69]

As a 'platform-like' technology, drug discovery and development timeframes can also potentially be expedited. Once a suitably selective targeting agent is identified, it then only needs to be paired with a suitable radionuclide, of which prior research has identified many (Table 1 & 2). Fortunately, RLT is amenable to different types of targeting agents, including small molecules, monoclonal antibodies, microspheres, nanoscale constructs and/or peptides. [7]

RLT's versatility and precision not only promise to improve outcomes in challenging cancers but also hold potential for addressing a broader spectrum of cancers in the future. This makes RLT a compelling innovation that brings new hope to patients and clinicians alike. Australia must be prepared to help develop these RLT innovations and to provide universal access to registered therapies that are proven safe and effective in the future.

RLT serves as a pivotal platform-like technology in oncology, offering versatile and precise targeting capabilities that promise to revolutionise cancer treatment by improving outcomes across diverse cancer types while minimising side effects.

AUSTRALIA'S **REPUTATION, EXPERTISE AND EXPERIENCE**

With the discovery and development of lutetium ligands for treating neuroendocrine and prostate cancers, radiopharmaceuticals, particularly theranostic pairs, are taking their place as the next pillar of cancer care, with Australian clinicians and researchers at the forefront of research and development. Punching well above our weight, Australia now has a significant opportunity to harness our collective experience and become a global RLT development powerhouse.

> *"…[Australia's] relatively well-funded health system and its long-established rigorous training of physicians and supporting staff, has stimulated more rapid growth and earlier adoption of theranostics and therapeutic nuclear oncology when compared to many other countries around the world."*
>
> **- Dr Nat Lenzo,**
> *in 'Theranostics in Australia: The Importance of Vision and Training, and the Power of Collaboration' [70]*

Australia's nuclear medicine clinicians are the key to our global reputation. Their unique training pathways have fostered an interest in treating disease, rather than just diagnosing it. This, coupled with collaborative university - hospital partnerships and regulatory exemptions, has provided the ideal setting for RLT R&D that subsequently has led to a stellar global reputation.

Australia has a substantial share of global nuclear medicine expertise, with impressive track records in R&D of RLT. This has been credited to **several unique factors including**:

- **Historical training pathways** for nuclear physicians have included internal medicine training pathways that fostered an interest in clinical practice, research and collaboration with academic institutions, to create a subspecialty of therapeutic nuclear oncology. This is in comparison to only offering nuclear medicine training pathways grounded in radiology that tend to focus more on diagnosis rather than clinical treatment. [70]
- **Close relationships** established between public hospitals and universities that fostered joint endeavours in developing RLT. [70]
- **Regulatory exemptions** that facilitated access to unapproved radiopharmaceuticals for research and compassionate access purposes, that promote early adoption of RLT and the initiation of investigator-led clinical trials for newly discovered agents. [70]

To date, Australian clinicians and researchers have conducted multiple investigator-led trials for lutetium based radioligand treatments. [25, 71] Despite our small population compared to global competitors, we successfully recruited and ran both the TheraP and VISION pivotal trials that developed the data to inform registration of Lu-177-PSMA therapies in the United States. [25, 66, 71] These successful Australian investigator-led studies produced promising therapeutic entities, which became primary targets when the company was acquired by a global pharmaceutical company. [25, 71]

Novartis' acquisition of Endocyte

In December 2018, Novartis completed its acquisition of Endocyte, a biopharmaceutical company based in the US. The acquisition included Endocyte's potential first-in-class radioligand Lu-177-PSMA-617 for USD $2.1 billion. [72] Since then, the Phase III clinical trial VISION for Lu-177-PSMA-617 for prostate cancer has been completed. The results of the trial show that the radioligand prolonged the overall survival and delayed progression of cancer when added to standard care in patients with PSMA-expression metastatic castration-resistant prostate cancer. [25]

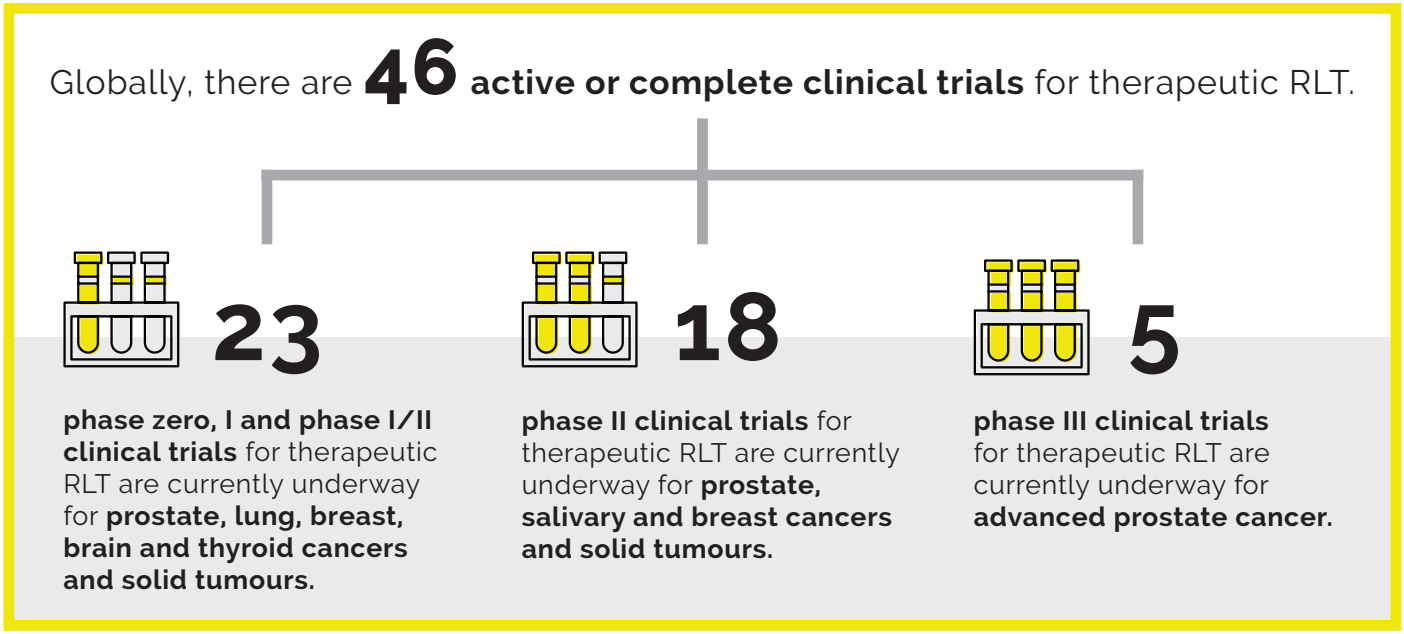
Australian clinicians extraordinary contribution to RLT R&D is set to continue with nine further clinical trials currently underway on our shores. [15-17] With a robust foundation in medical research and clinical excellence, Australia is well-positioned to attract continued investment and expand leadership in this field. By leveraging our homegrown expertise, and collaborative ethos, we are primed to drive RLT innovations that not only enhance treatment outcomes but also elevate Australia's profile as a global hub for cutting-edge oncological therapies.

Australia punches well above its weight with a large portion of the world's therapeutic nuclear medicine experts calling our shores home.

AUSTRALIA AS A **RLT CLINICAL TRIAL DESTINATION**

Clinical trials benefit patients with early access to innovative RLT. Additional economic benefits also flow to Australia as the host nation. Economic benefits that accrue from the expanding RLT pipeline (Figure 5) include attracting foreign investment, generation of intellectual property, infrastructure development, research funding and skilled job creation. [73]

Figure 5 – RLT clinical trials by phase



Source: Evohealth adapted from multiple data sources [15-17]

The benefits of RLT clinical trials extend beyond the patient

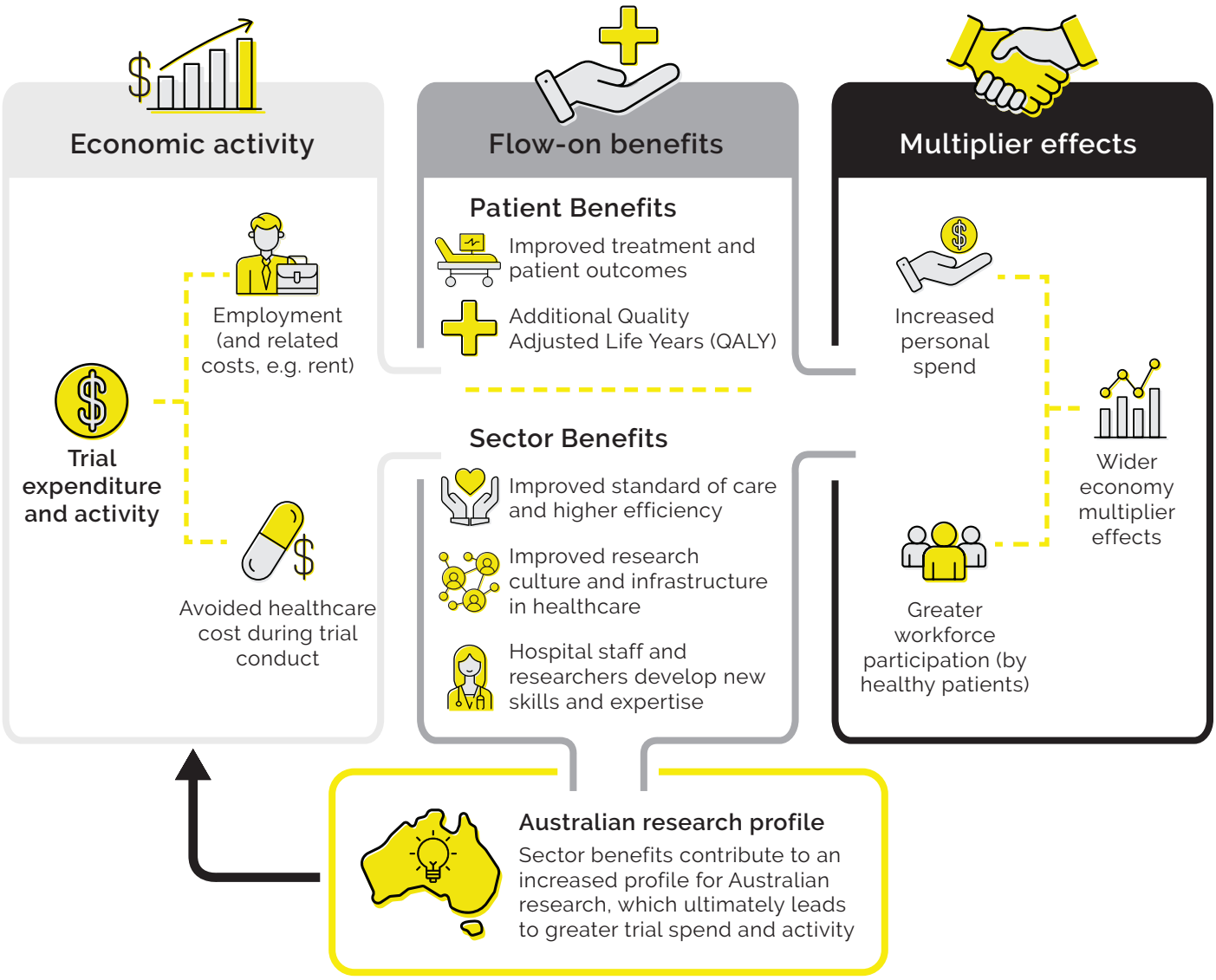
These 46 RLT clinical trials are good news not only for patients and clinicians awaiting further treatment options, but also for those who are fast enough to capitalise on the economic opportunities they may provide. Figure 6, from MTPConnect's 2021 report on Australia's Clinical Trials Sector describes the relationships between clinical trials and the economic activity generated by them, including the flow on benefits and multiplier effects observed from hosting research and improving patient care and lives. [73]

Figure 6 highlights how clinical trials

- contribute to Australia's economy:
- improve patient and sector outcomes;
- generate wider economic benefits; and
- enhance Australia's standing in global research. [73]

Ultimately, clinical trials are a good thing for our patients, our healthcare system and our broader economy.

Figure 6 – Benefits of clinical trials in Australia



Source: Adapted from MTPConnect Australian Clinical Trials Sector Report 2021 [73]

In 2022, over 90,000 Australians benefitted from early access to medicines through clinical trials, generating an estimated $1.6 billion in expenditure in Australia. [74] The stable development pipeline of RLT not only includes numerous clinical trials but attracts substantial investment from multiple multinational pharmaceutical companies (See box 'The global appetite and market for RLT is growing'). RLT presents a significant investment opportunity for Australia and a fundamental component of any national strategy to attract more clinical trials.

The global appetite and market for RLT is growing

In recent years, the market for RLT has witnessed remarkable expansion, with projections indicating that the global market will exceed **AUD $21 billion by 2031**. [18, 19]

Moreover, merger and acquisition activity totalling **USD $17.1 billion over the past eight** years has played a key role in driving the market's growth. Notable examples include: [75, 76]

- Novartis' acquisition of Mariana Oncology for USD $1.75 billion planned for early 2024;
- Eli Lilly and Company's acquisition of POINT Biopharma Global for USD $1.4 billion in late 2023;
- Bristol Myers Squibb paid USD $4.1 billion for RayzeBio's phase III clinical trial actinium product. This also included acquisition of their pipeline and manufacturing capabilities over 2023-24. [77]
- In 2018, Novartis acquired Endocyte for USD$2.1 billion, gaining access to Pluvicto and its pipeline. Endocyte had obtained the license for Pluvicto from ABX for $12 million a year earlier. [78]
- In 2018, Novartis acquired Advanced Accelerator Applications for $3.9 billion, obtaining rights to Lutathera and its companion diagnostic, along with certain Phase I/III trial candidates and established experience and infrastructure. [79-81]

This surge in growth is fuelled by various factors, including increased investment in health infrastructure such as nuclear medicine facilities worldwide, and the recognition of the potential of these therapies to revolutionise cancer care. [18]

Australia's attractiveness for RLT clinical trials

As a priority RLT clinical trial destination, Australia has world leading experts, enticing clinical trial conditions and enviable frameworks and systems for coordinating and managing trials. These conditions include our regulatory conditions for unapproved therapeutics and clinical trials approval, tax incentives and extensive clinical trial coordination networks.

- **Regulation of unapproved therapies and clinical trials** - Unlike other countries Australia's therapeutic regulations allow production of unapproved radiopharmaceuticals in certain settings under exemption, which has enabled use in clinical trials and preparation for individual patient use without much issue. [9] This coupled with the country's streamlined regulatory approval processes for clinical trials (aka. Clinical Trials Notification (CTN)[8] and Clinical Trials Approval (CTA)[9] schemes) is very appealing and relatively straight forward for those wishing to conduct trials. [82, 83]
- **R&D tax incentive** - Our R&D tax incentive encourages companies to invest in R&D activities by offering tax offsets for eligible activities, companies and trials. [84] In the past, these offsets have made Australia approximately 60 per cent cheaper, after tax incentives, to run clinical trials compared to the United States. [85]

[8]The CTN scheme is used by the TGA to authorise the supply of unapproved therapeutic goods to participants of clinical trials in Australia. The CTN scheme may be used for earlier phases studies where there is adequate preclinical data available, particularly regarding safety. [82]

[9]The CTA scheme is the process of evaluation which involves reviewing of scientific data by the TGA prior to the commencement of a trial. This is particularly useful for therapeutic goods that are in the early stages of development. The CTA scheme is generally for high risk or novel therapies where not much is known about its safety. [82]

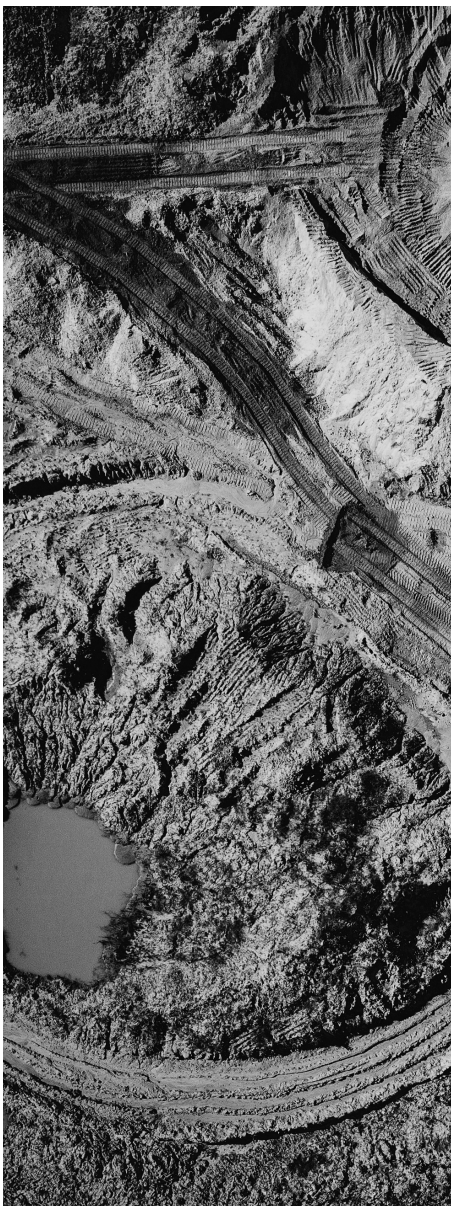
- **Coordinated trials network** - Australian clinicians and researchers have also established a unique clinical trial network, known as the Australasian Radiopharmaceutical Trials Network (ARTnet), that supports the coordination and recruitment necessary for multicentre clinical trials involving radiopharmaceuticals. As a result of these collaborations through ARTnet, Australia continues to expand its access to improved therapeutic agents. [86]
- **Coordinated system for human research, including clinical trials** – Australia is also in the process of implementing a national platform for approval and reporting processes necessary to grant ethical approval for human research and clinical trials. The aim of this platform is to make it easier for patients, researchers, industry representatives, and sponsors to conduct, participate and invest in high-quality and ethically conducted research in Australia. [87] In the 2024-25 Budget, the Government invested $18.8 million over two years to continue the development of this 'National One Stop Shop for Clinical Trials and Human Research' and continue support for the systems currently in place. [88]

Australia needs to promote these strategic advantages to ensure that it not only maintains but increases the number of clinical trials conducted here and all the benefits that will accrue.

The RLT development pipeline presents the opportunity for Australia to expand the number of RLT clinical trials to provide early access to therapies for patients and realise economic returns.

LEVERAGING AUSTRALIA'S **RESOURCES, CAPABILITY AND INFRASTRUCTURE**

Australia's strategic advantage in RLT research, development and clinical delivery is supported by its abundant natural resources, local capability, and advanced infrastructure. Access to critical materials, such as medical isotopes, coupled with a skilled workforce and state-of-the-art facilities, creates an ideal environment for pioneering cancer treatments and translating them into standard clinical practice. All these elements can come together to position Australia as a leader in the global landscape of RLT innovation.



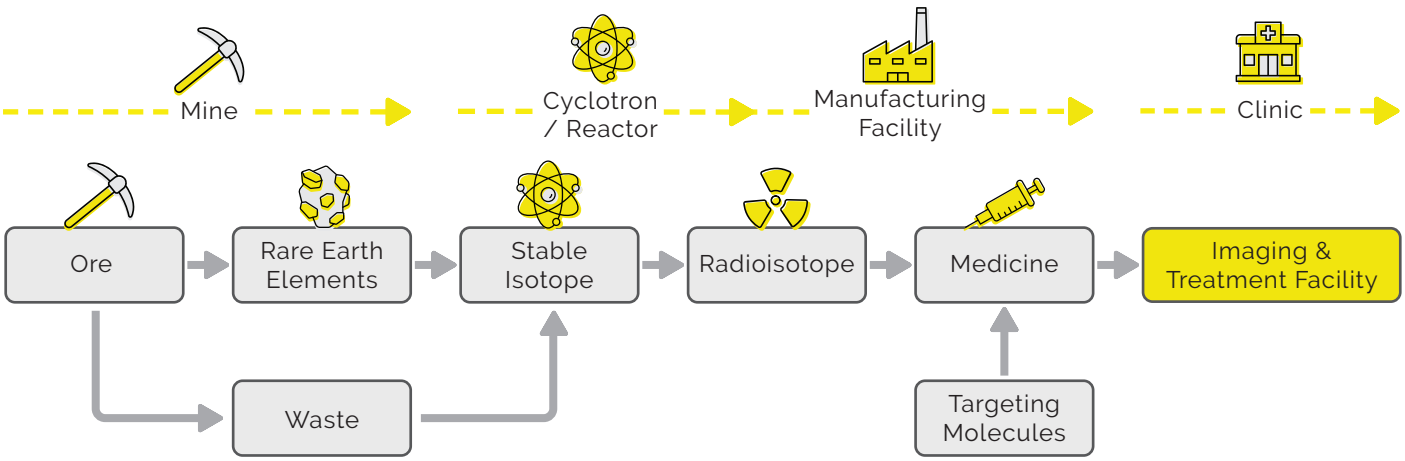
Access to raw materials

Australia is well known for natural resources, such as lithium and uranium, which have been mined and commercialised for many years. [89] As a result, two seemingly unrelated industries, mining and nuclear medicine, may have the potential to produce a circular economy in Australia. [18] Mining typically poses many environmental challenges, with one being what to do with toxic waste (i.e. tailings) produced from the mine. [90] Tailings consist of crushed rock, water, trace quantities of metals such as copper, mercury, cadmium, and zinc, as well as additives used in processing, including by-products of petroleum, sulfuric acid, and cyanide. [91]

If not disposed of properly, tailings can have significant adverse impacts on the environment and the safety of humans. Fortunately, recent work has found that some of the waste produced may be able to be repurposed for the production of radioisotopes needed for radioligand therapies (Figure 7). [18]

This has been extensively highlighted by MTPConnect in 'From Mines to Medicine.' This presents a unique opportunity to establish a circular economy that may benefit the Australian economy, environment and patients accessing RLT in the future. [18]

Figure 7 – Radiopharmaceutical supply chain



Source: MTPConnect From Mines to Medicines [18]

Local capability

Australia's capability to develop and deliver RLT is supported by numerous universities, hospitals, and locally-owned companies. These entities play vital and sometimes overlapping roles in the nuclear medicine ecosystem, including discovery and production of radioisotopes and radiopharmaceuticals for clinical use or research, safe transport of radioactive materials, and administration of therapies to patients. Table 3 summarises some of the key elements of Australia's nuclear medicine ecosystem, their role, and examples of companies/institutions involved.

Table 3 - Key Elements of Australia's Nuclear Medicine Ecosystem

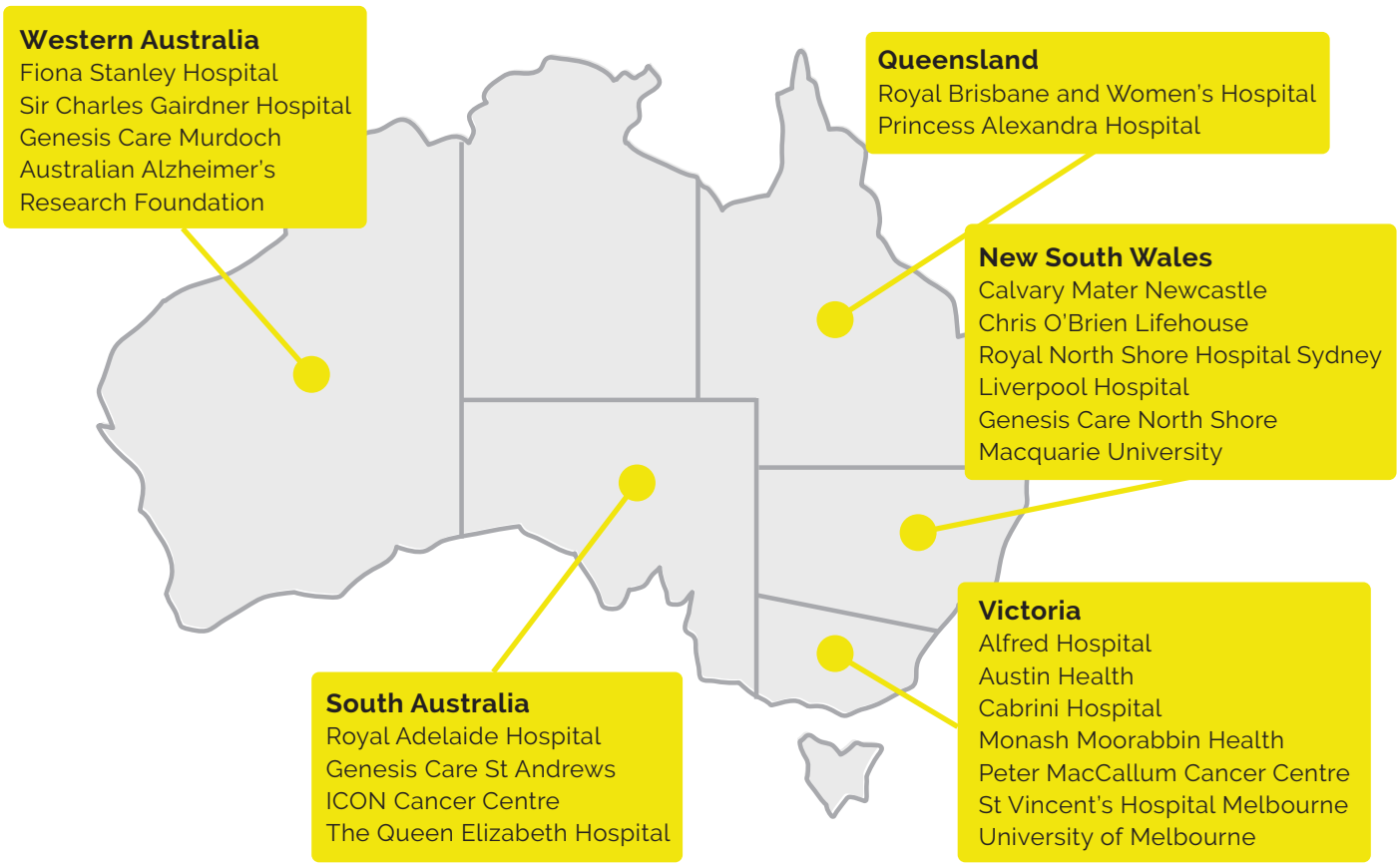
Key element	Role	Sample of Companies/Institutions*
Hospitals	Clinical application of RLT, including clinical trials operation	• Royal Adelaide Hospital • Queen Elizabeth Hospital • Peter MacCallum Cancer Centre • Austin Health • Royal Brisbane and Women's Hospital • St Vincent's Hospital Sydney
Local Companies	Production and supply chain management of radioisotopes and radiopharmaceuticals	• Australian Nuclear Science and Technology Organisation (ANSTO) • ENTX • AdvanCell Isotopes • Molecular Imaging and Therapy Research Unit, South Australian Health and Medical Research Institute (MITRU SAHMRI) • Telix Pharmaceuticals • Cyclopharm
Research Institutions	Fundamental research in nuclear medicine and R&D of RLT	• CSIRO • Prostate Theranostics Imaging Centre of Excellence (ProsTIC) at Peter MacCallum Cancer Centre • MITRU SAHMRI • University of Queensland
Transportation Services	Safe transport of radioactive materials	• Smartways
Regulatory Bodies	Oversight and regulation of nuclear medicine activities	• Australian Radiation Protection and Nuclear Safety Agency (ARPANSA)
Clinical Trials Organisations	Conducting or coordinating trials to evaluate new radiopharmaceuticals and therapies	• ARTnet • CMAX • Royal Adelaide Hospital • Queen Elizabeth Hospital • Royal Brisbane and Women's Hospital • Austin Health • Monash Moorabbin Health • Peter MacCallum Cancer Centre • ICON Cancer Centres
Training and Education Providers	Training for nuclear medicine professionals	• University of Sydney • University of Queensland • University of South Australia • University of Adelaide • Australian National University • Australasian Association of Nuclear Medicine Specialists (AANMS)
Infrastructure maintenance	Production or maintenance of specialised equipment (e.g. cyclotrons, nuclear reactor)	• ANSTO • Cyclowest • SAHMRI • Cyclotek

*Not an exhaustive list

Source: Evohealth from multiple sources. [18, 92-95]

Previous experience coordinating and conducting RLT clinical trials has resulted in many of Australia's major hospitals understanding best practice RLT treatment and patient care. Figure 9 reveals the multiple centres currently involved in delivering RLT through clinical trials. While these institutions have typically treated small patient cohorts, with further support their operations could be scaled up and their expertise shared throughout the nuclear medicine ecosystem to upskill and prepare other institutions to deliver RLT to patients.

Figure 9 - Locations of RLT research and clinical trials in Australia



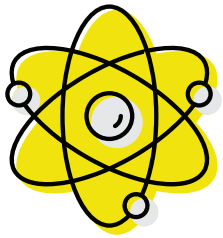
Source: Evohealth [16]

The success of the Australian nuclear medicine ecosystem speaks for itself with numerous high-quality trials continuing to be coordinated and conducted here. [15-17] There is no doubt that Australia has a solid foundation to build upon to capitalise on the opportunities of RLT for Australian patients and the economy.

Existing infrastructure

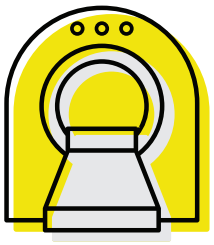
Australia boasts a robust and advanced infrastructure capable of supporting the delivery of RLT. Our well-established healthcare system includes state-of-the-art medical facilities, research institutions, and specialised cancer treatment centres that are equipped with the latest technology and staffed by highly trained professionals. The existing infrastructure includes:

- **Access to specialised medical facilities** such as nuclear medicine departments in most major hospitals and specialised cancer treatment centres in most states and territories. For example, the Peter MacCallum Cancer Centre in Melbourne is renowned for its comprehensive cancer care and advanced research capabilities, offering cutting-edge RLT treatments and clinical trials through its ProsTIC program. [96]
- **Supply of radiopharmaceuticals** from ANSTO's Lucus Heights Open Pool Australian Lightwater (OPAL) nuclear reactor and several medical cyclotrons across the country to produce radioisotopes for diagnostic and therapeutic and research purposes. [8]
- **Access to PET scanners** in most nuclear medicine departments around the country. [23]



Australia has **one nuclear reactor.** [8]

Australia has **18 cyclotrons.** [8]



Australia has **111 PET scanners.** [23]

Australia has also demonstrated commitment to continue to upgrade and replace critical components of this infrastructure, future proofing RLT delivery. Some of these investments include:

- In 2023, Monash University received $5.2 million in investment from the Victorian Higher Education State Investment Fund. [97] With the funding, Monash University will build a cyclotron as part of a precision radiopharmaceutical research and innovation facility, which will be developed close to the Victorian Heart Hospital within the Monash Technology Precinct. [97] The high energy cyclotron will have the energy and capability to produce a wide range of PET radio halogens and radio materials such as carbon-11, nitrogen-13, fluorine-18, copper-64, gallium-68 and zirconium-89. [98]
- In 2021, the Australian Government provided $30 million in funding to ANSTO to enhance Australia's nuclear medicine production. This initiative involved replacing the current Nuclear Medicine Processing and Distribution Facility with a new Nuclear Medicine Facility at ANSTO's Lucas Heights campus. Currently, ANSTO supplies 70-85 per cent of Australia's nuclear medicine requirements, enabling 10,000 – 12,000 procedures weekly. [99]

The new facility aims to bolster Australia's sovereign capability in nuclear medicine manufacturing. This funding will also support the ongoing maintenance of the existing facility until the new Nuclear Medicine Facility is commissioned and operating in the mid-2030's. The Government's investment ensures Australia's long-term access to critical nuclear medicines. [99-101]

These direct investments in our nuclear medicine ecosystem infrastructure demonstrate an appetite for expanding and growing this innovative industry. It also likely minimises the additional investment needed to establish sovereign capability in manufacturing Good Manufacturing Practice (GMP) approved RLT.

Australia has a well-established nuclear medicine ecosystem that can be leveraged to deliver these innovative therapies to patients locally and, with strategic investment in commercial opportunities, globally.

FROM **BENCH** TO **BEDSIDE**

To date, Australians have only benefited from access to RLT agents through clinical trials, and in some circumstances, compassionate access programs. Clinical trials, whilst necessary to develop the data needed to inform our regulatory and reimbursement processes, are only offered to a small number of patients, and are not a solution for broad universal access as envisioned under our National Medicines Policy (NMP) – See Box 'Australia's National Medicine Policy'. [102]

Australians expect and deserve to have access to safe, effective and high-quality care. Achieving this requires new innovations, such as RLT, to transition from bench (aka. experimental therapies) to bedside (aka. registered and reimbursed standard of care therapies). Australia has a robust and world leading process for enabling this access, which is detailed in Table 4 along with key opportunities for RLT that will support rapid access to this innovative, precision therapy.

Australia's National Medicine Policy

The aim of the NMP is to ensure:

- Equitable, timely, safe and affordable access to a high-quality and reliable supply of medicines and medicines-related services for all Australians.
- Medicines are used safely, optimally and judiciously, with a focus on informed choice and well-coordinated person-centred care.
- Support for a positive and sustainable policy environment to drive world-class innovation and research, including translational research, and the successful development of medicines and medicines-related services in Australia. [102]

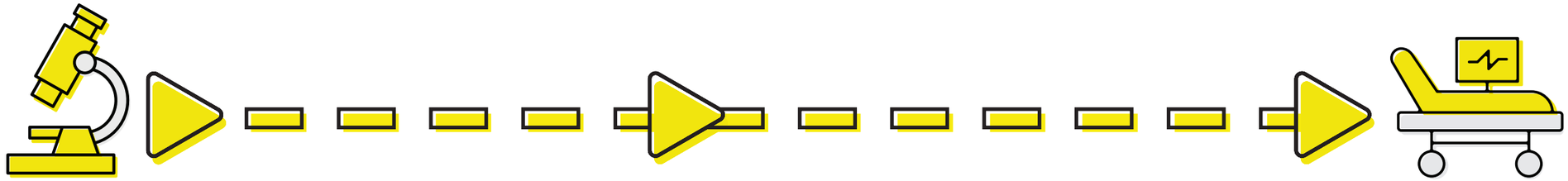
The lifecycle summarised in Table 4 is standard for all therapeutic goods. However, some regulatory exemptions exist where no registered treatment options are available, or a patient is not responding to standard care. [103, 104] When patient consent is granted, clinicians may offer experimental treatment. [103, 104] It should be noted that these exempt products come with increased risk for not only the patient, but the clinician prescribing and the overall health system, because they sit outside of normal regulatory controls. [103, 104] Experimental RLT is also only feasible on an individual patient use basis. As the population eligible for RLT grows, scaling will require access to registered therapies. Importantly, for broad population use, registered RLT products, manufactured in accordance with GMP must be the gold standard of patient care.

Australia's registration and reimbursement systems are essential for providing equitable access to therapies that are proven to be safe, effective and of high quality. As new RLTs make it through these pathways and the health system receives them into standard clinical practice, they may just revolutionise cancer care. The first therapies have set the blueprint for the tidal wave of RLTs that are in development and ready to follow.

To ensure we can capitalise on the opportunities these therapies will offer patients, and potentially the Australian economy, we must take action to prepare the broader health system to receive them at scale.

Table 4 – Transition of a therapeutic agent from bench to bedside and opportunities for RLT relating to each phase

Source: Evohealth



	Research + Development	Clinical trial	Registration	Reimbursement	Patient access
Description	Discovery of new health interventions and innovation. Australia's R+D sector is supported by a range of Government incentives, including the Medical Research Future Fund (MRFF), Modern Manufacturing Initiative and the R+D tax incentive, amongst others.[107]	Clinical trials study, across four phases, a range of interventions, including pharmaceutical treatments, disease detection and treatment and therapeutic strategies. [108]	Risk-based medicine regulation that considers the safety, efficacy and quality of the therapy, as well as regulating manufacturing of therapeutic goods. Those registered for use in Australia must be made in a Good Manufacturing Practice (GMP) facility.	Provide universal access to therapies via Government subsidised access, often via MBS or PBS. PBS Section 85 – general schedule PBS Section 100 – special supply arrangements such as administration in a hospital setting. amongst others.[107]	Models of care or service delivery for new technology, medicines or vaccines.
Purpose	To develop technology that harness cellular and biomolecular processes that have the potential to improve health outcomes.	To generate data that is necessary to inform the next steps of the life cycle, and support transition from experimental therapy to patient access, by demonstrating that a therapy is safe and efficacious.	1. Quality assessment and evaluation of the therapeutic good to assess if it has met stringent regulatory standards for safety, efficacy and quality, prior to marketing.[109] 2. TGA issues licenses and certification to facilities in Australia and globally once they have demonstrated compliance with relevant GMP code.	Health Technology Assessment (HTA) via PBAC or MSAC. Conduct evaluation to determine value against a comparator, including: • Clinical effectiveness • Safety • Cost and cost-effectiveness • Relevant clinical needs, or social, or ethical issues.[110]	Development of models of care and enabling elements such as documenting clinical governance and protocols, as well as upskilling workforce to support better patient access.
Process	Varies	Governed by National ethics guidelines, laws, and codes to protect research integrity and trial participants.	Application for registration involves expert review of all safety and efficacy data generated in clinical trials so that an informed risk assessment can be made.[109]		Often ad hoc, with fragmented responsibility across Federal and State/Territory governments.
Responsible	Researcher/Sponsor company	Sponsor company or Investigator-led trial	TGA	PBAC/MSAC	Across system
Outcome	Often partnership and collaboration to support translation to clinical trials.	Dependent upon results of clinical trial, translation to commercialisation, or not.	Listing on the Australian Register of Therapeutic Goods (ARTG)		Listing on MBS, PBS (Section 85 or Section 100).
Time	3-6 years	6-7 years	~10 months[111, 112]	1-1.5 years	Ongoing
Opportunities for RLT	Invest in finding more pairs that work because of platform technology.	Leverage national expertise and experience in RLT to attract investment in further clinical trials and place Australia as first wave country for launch of registered therapies.	Utilise Australia's robust registration framework to provide access to safe, effective and GMP manufactured RLT.	Provide universal, affordable access to safe and effective registered RLTs to all Australians who need them. Section 100 PBS program for hospital outpatients is the obvious universal access pathway for RLT.	Enhance existing healthcare system infrastructure capacity for RLTs to meet anticipated growth in clinical trials and demand for routine patient access when registered therapies become available.

[10]GMP is a collection of principles and procedures that, when adhered to, contribute to ensure the high quality of therapeutic goods. [111]

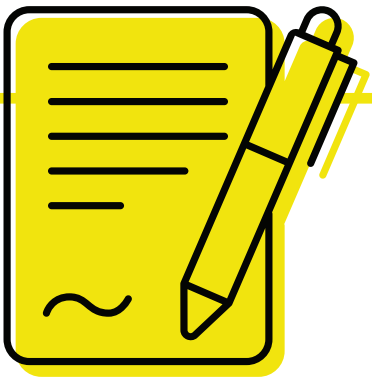
RECOMMENDATIONS

With numerous opportunities identified for RLT in nuclear medicine, we have developed three recommendations to ensure that Australia is able to capitalise on our current strong reputation, experience and stand ready to embrace the influx of RLT and provide fast access to patients.

These recommendations focus on enhancing the healthcare system infrastructure, expanding the nuclear medicine workforce, developing collaborative care pathways, establishing sovereign manufacturing capabilities, and articulating Australia's strategic advantages to attract investment.

By addressing these areas, Governments, both Federal and State/Territory, can establish sovereign capability and potentially export opportunities and ensure smooth integration of RLTs into the healthcare system, ultimately improving patient outcomes and positioning Australia as a global leader in nuclear medicine innovation.

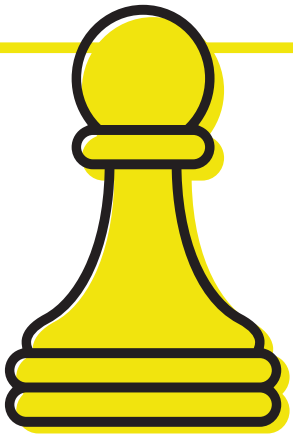
RECOMMENDATION 1



Develop and promote an expert endorsed statement that clearly articulates Australia's unique capability and capacity to deliver global RLT clinical trials.

Australia is uniquely positioned to attract and deliver a larger portion of global RLT clinical trials, thanks to our home-grown nuclear medicine expertise, proven track record, and favourable clinical trial conditions. By leveraging the knowledge and experience of our nuclear medicine physicians in conducting trials, we can clearly articulate our capabilities and attract further trials and investment. This will bring significant benefits, including early investment, early patient access to cutting-edge treatments, and economic boosts. To achieve this, an expert-endorsed statement should be developed to showcase Australia's strengths in this space. This statement can then be promoted by Austrade and key opinion leaders to foster partnerships and entice international investment that drives more RLT clinical trials to our shores.

RECOMMENDATION 2



Establish a national working group to develop and implement Australia's nuclear medicines strategy. This strategy should include support for more RLT clinical trials, plans to provide equitable patient access to safe, efficacious and registered RLT, as well as enable sovereign manufacturing capability and capacity.

To effectively receive the incoming wave of RLT and support delivering of RLT at scale in Australia, we need clear leadership, coordination, and meticulous planning. While we already boast world-renowned experts, significant clinical experience, and much of the necessary infrastructure, a unified strategic direction and targeted investment. A nuclear medicines strategy for Australia will establish a clear roadmap for advancing RLT access, by coordinating efforts across key stakeholders, optimising resource allocation, and driving targeted investment. This strategy will position Australia as a global leader in nuclear medicine innovation by:

- ensuring the efficient scale-up of clinical trials;
- enhancing patient access to registered, regulated and subsidised therapy; and
- building robust sovereign manufacturing capabilities.

Specific actions of this strategy could include:

- End to end investment planning for R&D of RLT, including identification of suitable radionuclide and cancer targeting agent pairs.
- Allocating funding to expand workforce capacity of existing therapeutic nuclear medicine infrastructure to meet future demand for RLT access across a broad range of indications.
- Partnering with stakeholder organisations and universities to develop and launch Federal programs to train and expand the nuclear medicine workforce, by upskilling existing health professionals and training new practitioners.
- Leveraging national expertise to design and implement standard coordinated collaborative RLT cancer care models, that consider the necessary expertise and patient experience as a priority.
- Supporting, through strategic partnerships and investment, the establishment of domestic manufacturing facilities to produce and export RLT.

Establishing a national working group that comprises our nuclear medicine experts and key sector stakeholders will be crucial in developing and implementing a comprehensive nuclear medicine strategy. This approach will provide the clarity of vision required to harness these opportunities and ensure Australia remains at the forefront of RLT innovation and delivery.

RECOMMENDATION 3

Develop a Government funded program ready to provide equitable patient access to safe, efficacious and regulated RLT.

RLT must be prepared and administered to a patient in a supervised clinical setting, typically a hospital department. This ensures that radiation safety protocols are adhered to, and the patient is not released into the public until their radiation levels are determined to be safe.

We already have existing funding pathways that support Australia-wide or universal access to treatment in a hospital – the PBS Section 100 program. To ensure all eligible Australians benefit from RLT, it is crucial to establish a RLT PBS Section 100 program. This program would provide equitable access to ARTG registered, GMP manufactured RLT, ensuring that all patients, regardless of their financial situation and/or location, can receive precision treatment. By subsidising these therapies, we can enhance patient outcomes, reduce healthcare disparities, and support the widespread adoption of this innovative cancer treatment across the country.

ABBREVIATIONS

Abbreviation	Description
AANMS	Australasian Association of Nuclear Medicine Specialists
AIHW	Australian Institute of Health and Welfare
ANSTO	Australian Nuclear Science and Technology Organisation
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
ARTG	Australian Register of Therapeutic Goods
ARTnet	Australasian Radiopharmaceutical Trials Network
CTA	Clinical Trials Approval
CTN	Clinical Trials Notification
EU	European Union
FDA	(US) Food and Drug Administration
GEP-NET	Gastro-entero-pancreatic neuroendocrine tumour
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
MBS	Medicare Benefits Schedule
mCRPC	Metastatic castration-resistant prostate cancer
MITRU SAHMRI	Molecular Imaging and Therapy Research Unit, South Australian Health and Medical Research Institute
MRFF	Medical Research Future Fund
MSAC	Medical Services Advisory Committee
NET	Neuroendocrine Tumour
NMP	National Medicines Policy
OPAL	Open Pool Australian Lightwater
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PET	Positron Emission Tomography
ProsTIC	Prostate Theranostics Imaging Centre of Excellence
PRRT	Peptide-Receptor Radionuclide Therapy
PSMA	Prostate Specific Membrane Antigen
R&D	Research and Development
RLT	Radioligand Therapy
SPECT	Single Photon Emission Computed Tomography
SSTR	Somatostatin Receptor
TGA	Therapeutic Goods Administration

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