NeuroEndocrine
Cancer Australia

Preventing Australians from slipping through the **NET**

The first National Action Plan for Neuroendocrine Tumours (NETs) 2022 - 2027

Presented by NeuroEndocrine Cancer Australia

neuroendocrine.org.au

Statement of Acknowledgement

We acknowledge the Traditional Owners of Country throughout Australia and their continuing connection to the land, sea and community. We pay our respects to them and their cultures and to Elders past, present and emerging.

NeuroEndocrine Cancer Australia National Action Plan 2022-2027

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Foreword

Simone Leyden CEO & Co-founder

My family's first introduction to Neuroendocrine Tumours (NETS) or Neuroendocrine Cancer was not unique. We were told my sister suffered from the 'rare' condition. It was stage 4, inoperable and incurable. Like so many patients, we met this news with confusion, fear and isolation. NETs affects both men and women equally and is a disease that, despite steady increase in incidence, remains largely misunderstood, underepresented and under researched.

According to latest Australian Institute of Health and Welfare (AIHW) figures (2017), the average Australian has a 1 in 55 chance of developing a neuroendocrine tumour. Compare this to a 1 in 136 chance of developing a brain tumour, 1 in 135 chance of oesophageal cancer, and 1 in 89 chance of developing stomach cancer. Most cancers, whilst uniformly devastating, are well-known, supported and have incentives for research. Despite the surprisingly high incidence and high morbidity rates, NETs remain under-represented in local cancer research.

Neuroendocrine Cancer took the lives of two of the most recognisable people of our generation, Steve Jobs (2011) and Aretha Franklin (2018). Lack of awareness and understanding of the disease led to expansive misreporting of the condition in the media leading to a missed opportunity to raise public awareness. Ethically, we should not have to rely on the death of a celebrity to elevate the conversation about a cancer. It should be based on the burden for the individual and the community - not what is popular. All Australian cancer patients should have the right to be seen, heard, supported, with access to the best international level of care, irrespective in which body part their disease appears.

NETs can develop in many organs of the body, beginning in the specialised cells of the body's neuroendocrine system. These cells have traits of both hormone-producing endocrine cells and nerve cells, and help control many of the body's funtions. So, in some way they don't "own an organ" like breast or bowel cancer, they "own a whole system". As this report will seek to highlight, diagnosis and subsequent treatment is long and often adhoc. This cancer is complex and diverse with no two NET patients being the same, which makes this cancer ideal for the next generation of precision medicine and therapy.

Over the last 11 years since the inception of NeuroEndocrine Cancer Australia (formerly Unicorn Foundation) we, as patients and advocates, have worked passionately side-by-side with our dedicated clinicians, nurses, researchers and specialists to face the many challenges of elevating the recognition of NETs as a cancer. On a national and international level, we have developed clinical guidelines, published studies on unmet needs and quality of life, developed and designed patient and healthcare information and education, funded clinical trials and research including a national tumour registry, and funded and facilitated much needed support through connecting to peer groups and a specialist telehealth NET nurse service. All of these initiatives have been a first of their kind globally, and have been adopted by numerous clinicians and centers of excellence across the nation and the world.

NeuroEndocrine Cancer Australia's achievements are wide and wonderful. They have been made possible by the strong partnership with our passionate community whose generosity in time and money make our lofty vision of success achievable. With the rise in Australian's facing this diagnosis and more families having to navigate the complex NET journey, we are now calling on the support of our Australian State and Federal governments to show global leadership, to not shy away, but focus on and challenge the inequities NET patients face in access to support, information, treatments, education and research relative to other types of cancers.

Over 22,000 Australians currently live with Neuroendocrine Tumours. The time to support them in their daily battle from their debilitating symptoms is now. We wish to challenge the reader to understand the scope of the problem. Indeed, there are more patients living with NETs than pancreatic, oesophageal and stomach cancers combined. No longer can Neuroendocrine cancer be the 'forgotten' cancer, and no longer should Australian patients slip through the NET.

Partners for Change

PeterMac
Peter MacCallum Cancer Centre
Victoria Australia

ENETS
EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

INCA
International Neuroendocrine Cancer Alliance

MOGA
Medical Oncology Group of Australia

Cancer Nurses Society of Australia

APNETS
Asia Pacific NeuroEndocrine Tumour Society

esa
endocrine society of australia

Cancer Council

Tour de Cure
CURING CANCER
CHANGING LIVES

AGITG
AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP

AUSTRALIAN AND NEW ZEALAND SOCIETY OF NUCLEAR MEDICINE

Clinical Oncology Society of Australia

About the Plan

There is growing recognition within Australia of the need for improved awareness, education, diagnosis, treatment and research into Neuroendocrine Tumours (NETs). This National Action Plan for Neuroendocrine Tumours emerges from the combined efforts of patients, advocacy groups, clinicians, researchers and supporters to have NETs acknowledged as a distinct heterogenous cancer, that has a substantial health burden in Australia.

The Federal Health Department and Cancer Australia's acknowledgement of Neuroendocrine Tumours through the funding and current development of the first Optimal Care Pathway is a significant step forward, however, it is widely agreed that additional support to the actions and priorities in this document are needed to ensure the success of the Optimal Care Pathway.

This pioneering National Action Plan provides a platform for improving the awareness, understanding, treatment of, and research into, Neuroendocrine Tumours in Australia. Investment into Neuroendocrine Tumour awareness, support, education, diagnosis, treatment, and research will benefit both men and women of all ages affected by NETs, as well as their families, partners, carers, and employers with earlier diagnosis and intervention, broader multi-disciplinary treatment options and clear care management pathways made possible.

The National Action Plan is aligned to the goals of the National Cancer Plan currently under development. It shares the aim that all Australians live healthier lives by being person centred, equity focused, encompass the whole patient journey, future focused, collaborative, data focused and strengths based. The National Action Plan builds on existing work and is designed as a tool to enhance activities already underway and to guide the development of new and innovative policies and approaches. The National Action Plan is solution focused, capatilising on existing infrastructure and investment, especially with the centres of excellence model put forward as a pilot to be further developed under the provision of Innovative Models of Care within the National Health Reform Agreement (NHRA 2020-2025).

There is potential for the identified priorities of education and awareness, clinical management, care, data and research, as outlined in the National Action Plan, to consider for other rare and less common cancers where appropriate.

Executive Summary

Every 2 hours an Australian is diagnosed with Neuroendocrine Tumours (NETs), and in 2021 NETs is estimated to be the 7th most diagnosed cancer. Source: AIHW 2021

Being diagnosed and then living with Neuroendocrine cancer is crippling to an increasing number of Australians.

Patient stories are similar, they have to persist for 5-7 years for a correct diagnosis, often not believed or misdiagnosed with conditions such as irritable bowel syndrome, anxiety, depression or stomach ulcers which is stressful and takes a huge toll. By the time a correct diagnosis is made, after years of unnecessary interventions and tests, 60% have stage 4 advanced disease.

This burden is manifested by years of professional testing and consultation yielding erroneous diagnoses from poor awareness.

The goal of this pioneering National Action Plan for Neuroendocrine Tumours (NETs) 2022 – 2027, is to highlight the need for greater awareness of neuroendocrine cancers as a distinct group of cancers and the significant impact on individuals, their families and the healthcare system.

The common themes throughout the Action Plan are the high emotional, financial and morbidity burden of a NET diagnosis. This effects not only the individual, their families and communities, with depleted quality of life, financial toxicity and high economic costs, but also the healthcare system.

Unlike more common cancers, NET patients can live for many years with advanced metastatic disease. With this comes the reliance and usage of every facet of the healthcare system from emergency departments, to specialists, to imaging, to allied health and much more.

This National Action Plan distills over a decade of research and experience NeuroEndocrine Cancer Australia has acquired from NET patients and families, the NET medical community, industry partners and national and international medical societies.

The goal of the document is to put forward achievable actions to assist in minimising this reliance on the system, and improving patient outcomes through:

- Increased support for patients through the provision of specialist NET telehealth nurses, specific and targeted awareness campaigns and healthcare professional education
- Nation-wide implementation of an optimal care pathway and referral frameworks
- Greater support for the health sector in delivering treatment and care to patients with neuroendocrine cancers through centres of excellence and use of a NET data registry
- Increased access to research funding

Australia is well-positioned to deliver these outcomes and already has in place many of the critical building blocks essential for success. An approach that is central to the implementation of this Plan's recommendations, is to leverage existing capabilities, expertise and infrastructure.

The COVID-19 pandemic has highlighted just how vitally important investment in the healthcare system is to maintaining thriving and productive communities. Patient organisations such as NeuroEndocrine Cancer Australia are an integral part of the system empowering Australians through disease specific support (telehealth nurse triage), accurate and appropriate health literacy information and education, and minimising unecessary interventions through referrals to specialists and centres. All these activities, with modest investment, ease the burden on an already overwhelmed hospital system through greater patient self management.

Terminology

Throughout this paper, Neuroendocrine Tumours (NETs) is used as the overarching term. However, it is recognized that this represents a diverse range of malignancies arising in different organ systems and can have varying presentations and clinical course. These can include indolent tumours despite distant spread, severe hormone- related symptoms, or rapidly progressive disease with premature death.

What we want to achieve with the first Australian Neuroendocrine Tumour Action Plan 2022-2027.

Eight Key Actions

This National Action Plan under the guidance of NeuroEndocrine Cancer Australia, plans to establish, consolidate and expand within the following areas over the next five-year period.

1. NET specialist telehealth nurses
2. Information & resources
3. Education of healthcare professionals (HCPs)
4. National awareness campaign
5. Optimal Care Pathway
6. Data Registry (PLANET)
7. Centres of Excellence
8. Targeted research

> The purpose of this Action Plan is to inform stakeholders, particularly those in policy making, health and government, about the incidence of Neuroendocrine Cancers in Australia and their impact and cost to individuals, families, carers and the economy.

Who we are? – NeuroEndocrine Cancer Australia

NeuroEndocrine Cancer Australia (NECA) is the only Australian not-for-profit foundation focused on raising awareness, providing support, and education of neuroendocrine tumours (NETs).

Founded in 2009, following one family's experience with this once thought to be rare cancer– and the challenges they experienced as a result – NECA's purpose is to achieve earlier correct diagnosis for patients, delivery of appropriate management and to ultimately to find a cure.

> Our vision is to be the champions of earlier diagnosis and a cure for Neuroendocrine Cancer.

Our Mission

We aim to:

- Assist and support patients and carers, through support groups and access to networks of expertise
- Advocate for access to new and appropriate investigations and treatments
- Raise awareness and knowledge of neuroendocrine cancers with the medical community and general public
- Encourage and support Australian based research in the area of neuroendocrine cancers.

NECA provides significant support to patients living with neuroendocrine cancers and their families around Australia. NECA supports patients whilst at the same time aiming to raise awareness and knowledge of NETs within the medical community and the general public.

Actively collaborating with and membership of, numerous medical societies and institutions ensures that out work is clinically relevant and appropriate. NECA's Research Advisory Panel is comprised of global leaders in this field.

NECA has also worked to raise awareness of NETs through supporting the founding of the Unicorn Foundation New Zealand and as a founding member of the International Neuroendocrine Cancer Alliance (INCA) which represents 26 countries globally.

Despite NECA's work both in Australia and overseas and the growing awareness of some less common cancers, huge disparities remain in the awareness of NETs, in the knowledge and education of healthcare professionals about these tumours, and in access to specialised care, diagnostics, treatments and research.

What we’ve achieved in 10 years

Over the last 10 years, NECA has relied on funding from their small but generous community. This funding, including support from industry, allowed for neuroendocrine cancer research including clinical trials, development of information and education resources for patients and healthcare professionals, as well as establishing and sponsoring the National Neuroendocrine Tumour registry and Patient Reported Outcome Measurements app (PLANET). In addition, NECA funds the only national specialist telehealth NET nurse helpline with a focus on providing support to rural and remote areas.

Whilst NECA recognises the Federal Health Government grant they received to build resources and assist with education of healthcare professionals (not including specialist nurse support) this grant of $70,000 a year over 4 years (2017-2021) has completed. It is acknowledged that this grant was gratefully received and thoroughly utilised with activities delivered over and above expectation.

NECA is a founding member of the International Neuroendocrine Cancer Alliance (INCA) that currently represents over 26 NET patient organisations across the globe and works in collaboration with NET specific medical societies across 6 continents.

Support	Awareness	Education	Research	Advocacy
Funded National specialist NET telehealth & referral service	312,000+ NET Community interactions on social media	Developed first RACGP Category 1 NET modules	Raised $700k+ for clinical trials CONTROL NETs & NABNEC	Collaboration with cancer societies & patient organisations around the world
↓	↓	↓	↓	↓
740 + support group meetings	2,000,000+ social media impressions	200+ nurses educated	Presented 108 conference posters around the world	National Optimal Care Pathway
↓	↓	↓	↓	↓
Distributed 35,000 booklets	1,000,000+ website views	1000+ HCPS	Authored 22 peer reviewed journal publications	3 inquiry submissions & public hearings
↓	↓	↓	↓	↓
Developed first ever multi-media information	7,000,000+ media reach through editorial	Developed first Australian College of Nurses NET modules	Sponsored the only national NET Tumour registry	25,000+ signatures to state & federal Parliaments

What are Neuroendocrine Tumours?

Neuroendocrine cancer, often known as neuroendocrine tumours or NETs, is a disease of the neuroendocrine system. Neuroendocrine cells create, store and release hormones and peptides or small proteins that support bodily functions. As with other cancers, NETs develop when these neuroendocrine cells change and begin to divide uncontrollably. They then form solid masses or tumours.

NETs tend to be different from other solid tumours as they arise from the cells of the diffuse endocrine system rather than from cells of a specific organ or tissue. They can also secrete hormones and other substances, such as insulin, gastrin and glucagon. NETs that secrete these hormones are called functioning NETs and can result in patients, in addition to their cancer, developing other clinical conditions, such as debilitating diabetes, carcinoid syndrome and gastric ulcer disease.

NETs can arise in various parts of the body and often grow slowly. As a result, patients may live with the burden of disease and its associated cost for many years. However, some are aggressive and can lead rapidly to death without successful treatment.

The majority of NETs are located in the digestive system or in the respiratory tract and these are commonly known as gastroenteropancreatic NETs or GEP-NETs (65% of all NETs) and Lung-NETs (25%). GEP-NETs can be found in many organs including the pancreas, stomach, duodenum, small bowel, appendix, colon, and rectum.

Tumours with neuroendocrine features that are found outside the gastrointestinal or respiratory systems include[1]:

- Pheochromocytoma and adrenocortical carcinoma (which originate in the adrenal glands)
- Merkel Cell Carcinoma (in the skin)
- Paragangliomas (which occur in the nervous system)
- Thymic NETs (found in the thymus)
- Medullary thyroid cancer (in the thyroid)
- In the ovaries and testes
- In the prostate and breast
- Neuroblastomas (which are the most common cancer in children under five years of age).

NETs tend to be poorly understood because the heterogeneity of the tumours, the non-specific nature of patients' symptoms when presenting to healthcare professionals, their unique biology and a general lack of awareness of them[2].

NETs can be sporadic in nature or associated with familial, or inherited, conditions. These include Von Hippel-Lindau (VHL), Multiple Endocrine Neoplasia syndrome (MEN) types 1, 2 (2A and 2B), Tuberous Sclerosis and Neurofibromatosis Type 1.

> In 2021 it is estimated that Neuroendocrine Tumours will be the 7th most common cancer diagnosis in Australia (after breast, prostate, melanoma, colorectal, lung & non-hodgkin lymphoma). AIHW 2021

Where Neuroendocrine Cancer can develop & spread

Incidence and Prevalence

The incidence of NETs has historically been thought to be very low and consequently they were categorised as a 'rare cancer'.

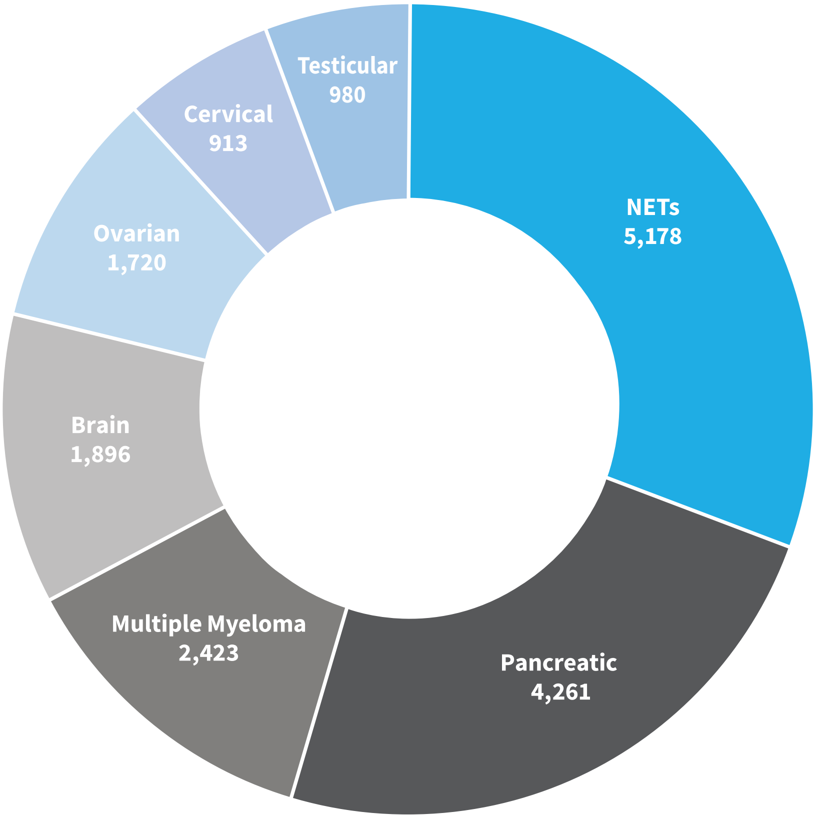
This is no longer the case. In 2021, it is estimated that 5,178 people will be diagnosed with NETs in Australia (age-standardised incidence rate of 16.9 per 100,000 people) and when considered as a group of cancer types, NETs will be the 7th most commonly diagnosed cancer in Australia (after breast, prostate, melanoma of the skin, colorectal, lung and non-Hodgkin lymphoma).[3]

The increase in the incidence of NETs is partly attributed to greater awareness of the disease and improved diagnostics.[4] In 2016, there were 4,108 new cases of NETs diagnosed in Australia compared to the nearly 5,178 estimated in 2021, a 21% increase.

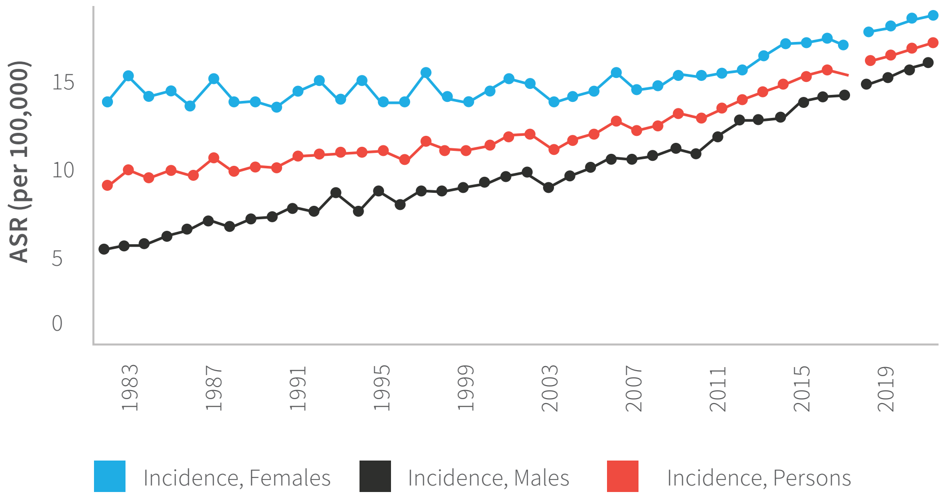
NETs impact men and women equally and are indiscriminate in affecting people from adolescence into old age.

Over 10,000 Australians diagnosed between 2011 and 2015 currently live with NETs and 20,508 people living had been diagnosed with NETs in the 33 years from 1983 to 2015. Neuroendocrine cancers are the second most prevalent gastrointestinal malignancy after colorectal (bowel) cancer with over 20,000+ Australians living with the disease.

> The increase in the number of people living with NETs and the increasing incidence of them, reinforces the need to improve awareness, diagnosis and management of NETs.

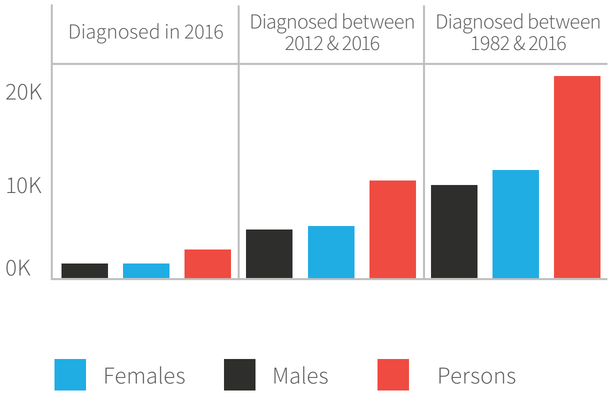


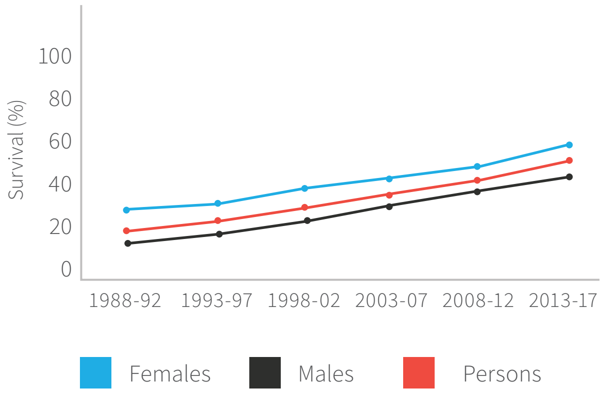
Incidence across Australian Men and Women



There has been a steady rise in both men and women being diagnosed and we expect this upward curve up to continue.

Survival and Prevalence

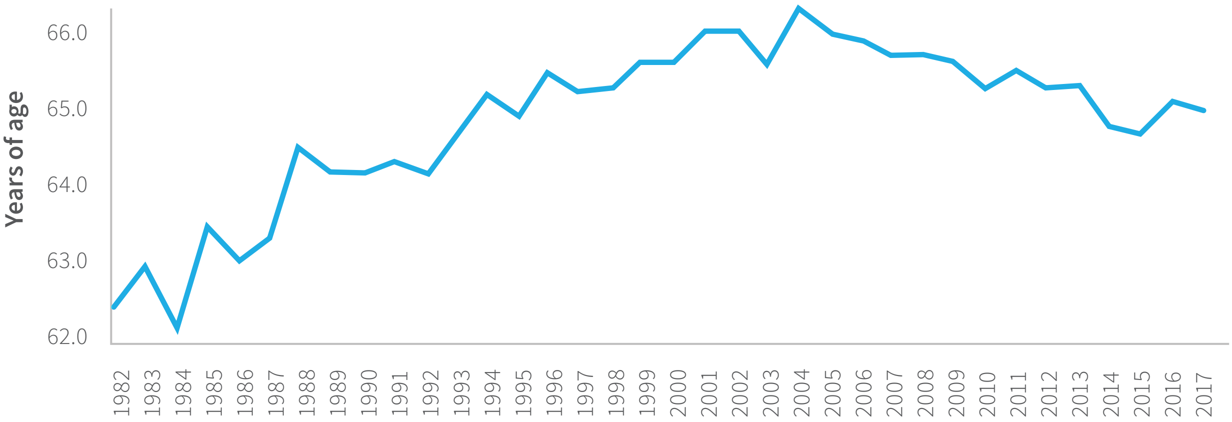




22,161 Australian's live with NETs, which are more than pancreatic, oesophageal and stomach cancer combined.

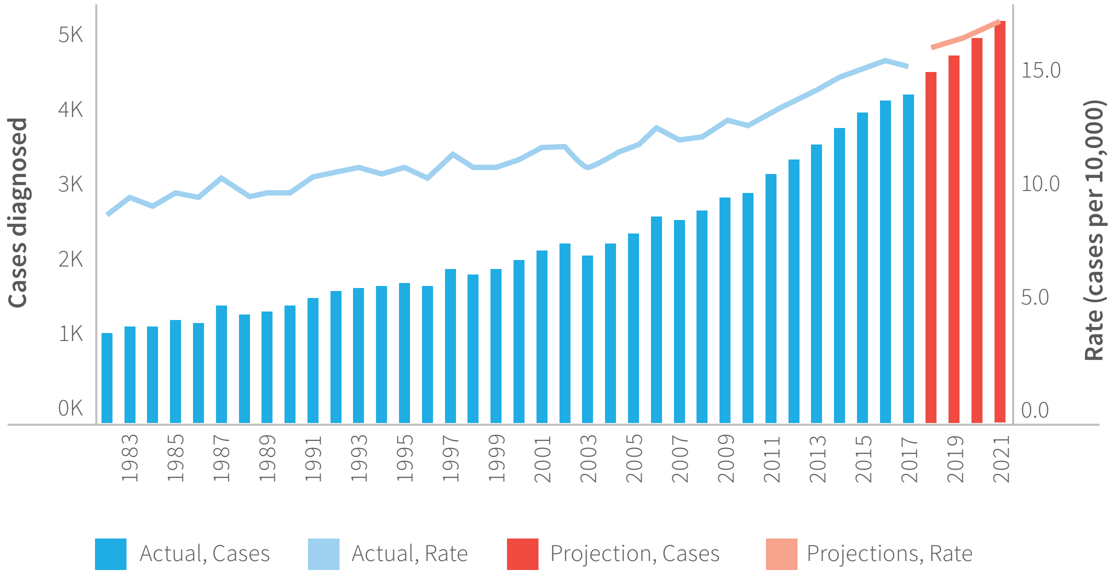
Whilst there is an increase in survival, 5- year survival for all NETs remains under 50%.

Mean age at diagnosis



Mean age at diagnosis in 2017 was 65. Trend indicates younger patients being diagnosed.

Projected incidence



In 1983 there were 1,292 diagnosis of NETs, in 2021 there is a projected 5,178 new NET diagnosis an increase of 75%.

Symptoms

The type of symptoms a person may have as a result of having a NET depends on many factors. These include the type of NET, the location of the NET, whether the NET has spread, whether it is secreting hormones, the type of hormones it secretes and how those hormones might affect the body.

A key challenge for patients with NETs however, is that the symptoms can be very vague and overlap with many more common symptoms.[5] A patient may not experience any symptoms or may have symptoms that are misdiagnosed as other conditions or disorders other than cancer for many years.

Symptoms may include diarrhoea, abdominal cramps, vomiting, reflux, skin flushing, anxiety, and tiredness as well as weight loss and changes in blood pressure or heart rate. Pancreatic NETs can also influence the level of sugar in a person's blood, causing symptoms of diabetes or as a result of very low glucose levels (hypoglycaemia).

Patients who do experience symptoms may have carcinoid syndrome which is most often associated with NETs which arise in the lungs or small intestine. Carcinoid syndrome occurs when a NET releases significant quantities of serotonin.

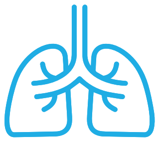
Symptoms include flushing of the skin, particularly of the face and neck, rash, wheezing, anxiety, diarrhoea, bowel urgency, fast or irregular heartbeat, abdominal pain, fatigue, low blood pressure and heart damage. Carcinoid syndrome has a very significant impact on patients' physical and social functioning and can prove highly distressing, isolating and debilitating. Many patients cannot go out or maintain their normal activities due to the symptoms. [6]

With this wide range of symptoms patients are often misdiagnosed for many years. Common misdiagnoses include conditions such as irritable bowel syndrome, abdominal pain, menopause, asthma, fatigue, nausea and even anxiety. These misdiagnoses mean that patients usually experience significant delays before being correctly diagnosed and, as a result, are likely to have a more severe form of disease due to their cancer spreading to other parts of their bodies.

Just some of the symptoms NET patients present with

Flushing

Diarrhoea Gastric pain



Wheezing

Irregular Heartbeat

Diagnosis

Lack of awareness by both healthcare professionals and the general community mean that NETs are frequently misdiagnosed. This misdiagnosis is not helped by the fact that many symptoms that patients have because of their NET might be thought to be caused by another condition.

These delays in diagnosis not only impact patient survival and quality of life but also involve significant unnecessary use of health care resources.[7]

Time to diagnosis

A global survey of patients with NETs found that patients have NET-related symptoms for a median of 9.2 years before they are accurately diagnosed.[8] The most vicious consequence of this avoidable delay is that, by the time they receive a correct diagnosis, many patients have progressed to a higher stage of their cancer as a result of their cancer spreading to other parts of their bodies.

During this period, patients are usually seen by numerous different specialists and are repeatedly subjected to an extensive variety of tests, some of which may be inappropriate. Patients are often given a variety of treatment recommendations and these often both conflict with each other and contribute to ongoing delays in receiving an accurate diagnosis and appropriate treatment. [9]

This global evidence is reinforced by other studies that indicate that a mean duration of the first symptom prior to diagnosis was 53.8 months.[9] However, this timeframe was longer, at 67.7 months, for patients with Lung-NETs.

80% of patients saw their GP regarding their symptom prior to receiving a diagnosis of a NET and there was a mean of eleven visits prior to patients being diagnosed. This is despite the fact that 63% of patients reported that their first symptom was either severe or very severe.[10]

Almost one-third of patients experienced their first encounter with secondary care as a result of an unplanned admission via a hospital emergency department.[11]

Patient experience in this regard points strongly to the fact that it is not avoidance of health care that delays patient diagnosis but rather lack of onward referral to secondary care or for appropriate investigations in primary or secondary care that cause this delay.[12]

In Australia the three most likely healthcare professionals to have ordered the diagnostic test that led to a patient's initial diagnosis are general practitioners, surgeons and gastroenterologists who referred 30.1%, 21.1% and 12.7% of patients respectively. **Patients are joint fourth most likely to suggest the diagnostic test that led to their initial diagnosis.[13]** This was the experience of 10.2% and presumably related to independent investigation of internet sites, emphasizing the importance of information platforms that cater for not only for primary care physicians but also for patients.

30%
diagnosed in Emergency Departments

60%
stage 4 at diagnosis

9.2
years median time to diagnosis

Diagnosing a NET

NETs can be diagnosed using a variety of different tests and tools. In the event that a patient is suspected of having a NET, tests that will be performed are likely to include:

Blood tests, including a test for chromogranin A, which is a hormone marker for NETs.

Urine tests to measure for breakdown products of serotonin, which can be produced by NETs.

Computerised tomography (CT) or **Magnetic Resonance Imaging** (MRI) to scan and image the body's internal organs.

Bronchoscopy to view the lungs.

Endoscopy/Colonscopy to look at the stomach and/or digestive tract.

Positron Emission Tomography (PET) to scan for cancer cells. Two key PET scans are used to identify NETs – Gallium-68 DOTATATE and F-18 fluordeoxyglucose (FDG) which one is used depends on the type and grade of tumour suspected.

Biopsy sample of tumour tissue is taken from a patient for the purposes of examination and diagnosis.

Echocardiogram (ECG) to investigate the condition of the heart valves as these can be affected by some functional NETs.

Stage and Grade

Grading

As with all cancers, NETs are graded according to how active cancer cells are dividing, which influences the speed at which both primary and secondary tumours are likely to grow. This process of division is called mitosis and the rate of this division is the primary measure by which cancers are graded. For NETs, a specific pathology review of cancer cells is called the Ki-67 labelling index. It is used to report the percentage of cells that are preparing to divide. Patients with NETs who have a low Ki-67 index have a more favourable prognosis and longer survival than those with a high Ki-67 index, but the slow growth of tumours may delay diagnosis until distant spread has occurred limiting the ability to cure disease by surgery.

There are three grades in the grading system with Grade 1 being the lowest and Grade 3 the highest. Grade 1, or low grade, cancers usually grow slowly and the cancer cells look only a little different from other surrounding cells.

Grade 2, or intermediate, cancer cells sometimes look slightly different from normal cells and are growing faster than Grade 1 cells whilst Grade 3, or high grade, cancers have cells that may look very different from normal cells and are growing substantially faster.[14] What was formerly a single Grade 3 group is now divided into well-differentiated Grade 3 NET and poorly differentiated Neuroendocrine Carcinoma (NEC), which is when the cells cease to resemble normal neuroendocrine cells.

Whilst grading a NET helps identify the best treatment pathway for a patient, unlike the majority of cancers, low grade NETs can still be associated with metastases and debilitating hormone secretion.

Stage

In addition to the grading system for cancers, there is also a staging system. Staging is used to describe the extent of local and distant spread. Diagnostic tests are used to determine a cancer's stage and this knowledge is used to help to decide what kind of treatment is best. Staging can also help predict a patient's chance of recurrence or survival.[15]

There are different stage descriptions for different types of NETs . For some NETs, this is the same staging system as used for other cancers with, for example, the staging of a lung NET being the same as the one used for the staging of non-small cell lung cancer. In contrast, NETs found in the gastrointestinal tract and pancreas have their own staging system based on the location and characteristics of the tumour.[16]

As a general rule, however, most cancers are grouped in four key stages. Stage I is generally a small primary lesion without spread to adjacent nodes, Stage II typically involves a more advanced primary lesion or involvement of nodes close to the tumour, making surgery still a feasible option, and Stage III is when cancer has spread to more distant nodes, making the likelihood of surgical cure low. In Stage IV, the cancer has spread (metastasised) to distant parts of the body.[17]

As with the grading system, a lower number stage is generally associated with better patient outcomes. However, it is important to note that doctors cannot predict the outcomes for a patient with NET purely on which stage of the disease they have.

Significance of grade and stage at diagnosis

Whilst for many cancers, the stage of the cancer at diagnosis is a key indicator to likelihood of survival, this is less clear in relation to NETs. A number of studies indicate that, in fact, the grade of a NET at the time of diagnosis is the more accurate indicator of prognosis than is stage.[18]

Risk factors

Some inherited conditions including Von Hippel-Lindau (VHL), Multiple Endocrine Neoplasia syndrome (MEN) types 1, 2 (2A and 2B), Tuberous Sclerosis and Neurofibromatosis Type 1, can mean that people have a greater risk of developing a NET. Although these are individually rare, collectively heritable mutations account for a larger proportion of cases than for almost all other cancers. Accordingly, screening for genetic drivers is increasingly relevant.[19]

Survival

Patients diagnosed with NETs have a 48% chance of surviving for 5 years compared with the general Australian population.[20] Survival rates vary significantly however, with patients who have Grade 2 or 3 tumours at the time of their diagnosis having a higher risk of dying of their cancer than those with a Grade 1 tumour.[21]

Western Australian data indicates that the 5-year survival rate for people diagnosed with grade 1 and 2 NETs has increased substantially from 78% in 1995-1999 to 93% in 2010-2014. In addition to this, the 5-year survival rates of people diagnosed with Grade 3 NETs more than doubled during that time from 21% to 45%. Both incidence of NETs and survival rates are increasing.[22] Earlier diagnosis and prompt treatment are the keys to improved survival rates and ongoing symptom management and improved quality of life.

Treatment

Treatment options

Treatment of patients with NETs varies significantly across Australia. This differs from many other cancers where clear and optimal care pathways have been established. Progress on maintaining consistency of treatment has been constrained due to a limited understanding of how NETs originate and develop, a lack of research models, evolving changes in how NETs are classified and treatment is sequenced, limited investment in research and lack of acknowledgement of this cancer by government and regulatory bodies.[23]

Optimal treatment will require consensus within the medical profession, which may also require further research to acheive. NECA is grateful to the Clinical Oncology Society of Australia (COSA) for their recognition of the need for up to date clinical guidelines, with the new addition to be released in 2021 under the guidance of the NET special interest group.

Whilst the following treatment options are recommended as part of the overall care, eligibility, effectiveness and sequencing of treatments is determined on an individual patient by patient basis, and best outcomes are acheived through a multi-disciplinary approach.

> A key takeout from this Action Plan is that there should be optimal pathways for NETs based on the best available evidence, the practice of current Centres of Excellence and greater awareness of referral pathways.

Surgery

Surgery is the most common treatment for people with NETs and who have early-stage disease. Ideally, surgery should be performed in facilities with specialist NET units and where the surgeon is part of a multidisciplinary team.

The type of surgery needed will depend on the type of cancer the patient has and whether the cancer is early-stage or advanced. There are two key types of surgery including:

- Curative surgery where the cancer has not spread outside the area where it originated. The aim is to remove the tumour as well as some of the surrounding tissue to ensure all cancer is removed
- Palliative or 'debulking' surgery which occurs when the tumour has spread or become too large to remove completely. In this instance, the aim is to reduce the size and bulk of the tumour in order to provide relief of symptoms or to increase the likelihood of response to other forms of therapy that might subsequently be applied.

Chemotherapy

Chemotherapy may be an option for higher grade (Grade 2/Grade 3) NETs, especially in patients with pancreatic or lung NETs. Unfortunately most NETs, especially of Grade 1 type, do not respond well to chemotherapy. Some chemotherapy treatments are given intravenously in hospital or in a day procedure facility, but increasingly the dominant chemotherapy used in NETs is by a tablet that is swallowed. There are side effects from chemotherapy which need to be well managed by trained staff.

Treatment cycles vary and can be daily, weekly fortnightly or monthly and the duration of a cycle as well as the number of cycles a patient may require depends on the medications used and the type of NET being treated. Most are given until patients either progress or develop intolerable or life-threatening side-effects of treatment. Very few patients cease treatment as a result of cure.

Targeted therapy

Targeted drugs work differently from standard chemotherapy drugs. These drugs target specific parts of cancer cells. They are sometimes helpful when chemotherapy is not, and often have different side effects than chemotherapy.

Targeted therapies do not work for all patients. In best practice to determine whether their cancer will respond to a targeted therapy, patients have tissue samples taken from their cancer and tested. If their cancer involves genes or proteins that will respond to the therapy, patients may then start targeted therapy. As these therapies act to slow the growth of cancer, many of them need to be taken for long periods of time and patients may require regular testing to monitor their progress and for the relatively frequent onset of side-effects. Currently there is little evidence that NET tissue biomarkers are predicative of response to these targeted agents and therefore they are usually given without specific diagnostic evaluation.

Medication

Somatostatin analogues (SSAs), are versions of naturally occurring somatostatin, which is a hormone that regulates the release of several other hormones and chemicals from internal organs. It is primarily used to control some symptoms caused by NETs but can also slow down the growth rate of a patient's cancer. SSAs can help reduce the rate at which NETs secrete hormones and thereby help to control symptoms associated with carcinoid syndrome, such as diarrhoea and facial flushing, but can also be effective in controlling other functional NET syndromes.

Imaging

Imaging plays a vital role in NETs. It is important to note that, while imaging is traditionally considered solely as a diagnostic tool, it can also be used as treatment.

Certain nuclear medicine imaging tests especially Gallium 68 DOTATATE and FDG PET/CT can provide crucial information to guide where tumours are, guide which lesion to biopsy, and help to determine the best treatment modality for patients, selecting patients for Peptide Receptor Radionuclide Therapy (PRRT) and avoiding futile surgery. Imaging can also determine disease biology and prognosis. It is therefore a recommendation to government to extend the Medicare Benefits Schedule (MBS) application and reimbursement to include all NETs regardless of origin, and that listing restrictions are minimal to ensure its best use as a diagnostic and treatment tool.

New tracers targeting the somatostatin and other cell- surface receptors may open the way for new forms of Peptide Receptor Radionuclide Therapy (PRRT). For example, trials are now underway with Copper 64 (Cu-64) imaging agents that can select patients for the use of treatment using the therapeutic radionuclide, Cu-67. Cu-64 can provide more accurate prediction of radiation dose that would be delivered to both tumour and normal tissues and may help to improve both the effectiveness and safety of PRRT. This will be particularly important in younger patients.

Radiation therapy

Radiation therapy destroys cancer cells by utilising high energy rays generated by a machine and directed into the body.

Radiation therapy is not usually used to treat NETs. However, if the cancer has spread to the bones, and there are symptoms such as pain from advanced neuroendocrine cancer, radiation therapy will be considered.

Liver Directed Therapies

In the event that a tumour has spread to the liver, it may be possible to have hepatic artery embolisation (HAE) which blocks the blood supply to those tumours. This is done by a radiologist accessing an artery in the groin and inserting a catheter into the main blood supply to the liver, the hepatic artery. Tiny particles called microspheres are then injected into the catheter and these particles act to block the blood supply which causes the tumour to shrink or even die. This procedure may be combined with an injection of chemotherapy or microspheres containing chemotherapy which is called transcatheter arterial chemoembolization (TACE) and usually requires overnight admission to hospital.

There is also Selective Internal Radiation Therapy (SIRT) which is used to treat liver metastases which cannot be removed by surgery. It is a similar procedure as HAE, however, the tiny beads contain radioactive substance which interferes with the tumour cell DNA and slow the growth.

Another liver directed therapy is Radiofrequency Ablation (RFA). This procedure is performed using ultrasound or CT guidance. A needle is inserted into the abdominal wall and into the liver tumour. Once in place, a generator is used to deliver a rapid alternating current or radiofrequency energy producing high level of heat that destroy the cancer cells. Relatively few NET patients have metastatic disease exclusively to the liver, and therefore most of these treatments are to control only a portion of patient’s disease.

Peptide receptor radionuclide therapy (PRRT)

PRRT is a form of radiation therapy which is appropriate for a significant proportion of patients with lower grade and some higher grade NETs. A necessary requirement is demonstration of high expression of somatostatin receptors found on a Gallium 68 DOTATATE PET scan.

PRRT use small cell-targeting proteins, called peptides, that are similar to the body's natural circulating hormone somatostatin and combines these with radionuclides to create a radiopharmaceutical called a radiopeptide. This is then injected into the patient's bloodstream where the radiopeptide identifies the neuroendocrine tumour cells and attaches itself to them. The radiopeptide then acts to deliver a high and targeted dose of radiation directly to the cancer cells. [24]

One such therapy is Lutetium-177 Octeotate (Lutate) which is a very specific therapy that can only be used when tumours express a large number of somatostatin receptors. Most NETs show an increase in somatostatin receptors. If this therapy is being considered, a diagnostic scan is performed via a Gallium 68 DOTATATE PET scan to distinguish if the tumours are positive for somatostatin receptors. The fact that radiopeptides are highly selective in specifically reaching and impacting the NET cells while minimising the amount of healthy tissue exposed to radiation means this is an extremely targeted therapy. As a result, it is usually well-tolerated.

As well as generally relieving hormone-related symptoms, PRRT is also highly effective in controlling advanced, metastatic or inoperable and progressive NETs. Beneficial effects can be observed even without necessarily shrinking tumours and survival can be increased by slowing the progression of NETs. Progression free survival and overall survival advantages have been demonstrated in clinical trials. [27]

PRRT is generally well tolerated by patients. The treatment is scheduled along with relevant imaging over a couple of days with approximately 8 weeks break between each of the four sessions. Each session lasts around four hours and patients may be given oral chemotherapy or other agents before their PRRT in what is called combination therapy.[25] Some examples of this are provided in case studies below and Australia is a global leader in research in this area.

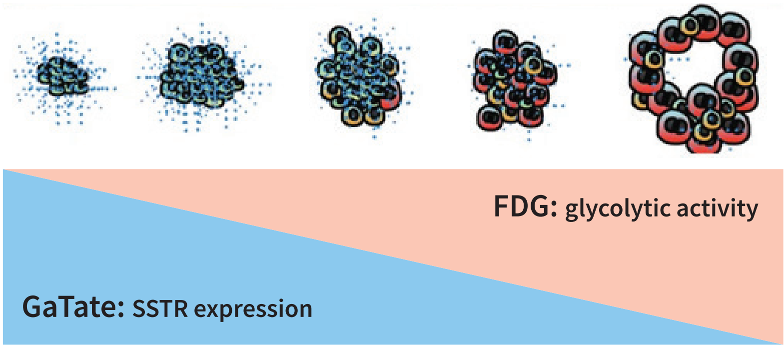
It should be noted that, in Australia, most PRRT is provided as outpatient therapy which is not the case elsewhere in the world. As a result, Australian patients are relieved of the burden of hospital admission and the healthcare system benefits from significant cost savings. An exception to this is requirement of brief hospitalization in patients with severe hormone-related symptoms that can flare early after treatment and may need management.

Immunotherapy

Whilst traditionally NETs have been considered to be unresponsive to PD-1 / Immunotherapy treatment due to the very low infiltration of immune cells in these tumors, and low number of genetic mutation events, recent studies have shown some promise. In a recent Australian study CA209-538 it was concluded that combination immunotherapy with two drugs, demonstrated significant clinical activity in subgroups of patients with advanced NETs including patients with atypical bronchial carcinoid and high-grade pancreatic NETs. Further studies and investment is needed.

Summary of grade, imaging and treatment

Use of imaging is integral in diagnosis, treatment decisions and monitoring for all NETs



	Well Differentiated NET			Poorly Differentiated NEC
ENETs Grade (European, Neuroendocrine Tumor Society)	G1	G2	G3	G3
Ki67 index, %	<2	3-20	>20	>20

NEC: neuroendocrine carcinoma (limited role for PRRT)

Slowly Growing → *Rapidly Growing*

Imaging can direct optimal choice of therapy

GRADE 1

- Observation
- SSA
- PRRT
- SSA
- Chemotherapy

GRADE 2

- Everolimus
- Sunitinib
- PRRT
- Surgery
- Liver directed therapies

GRADE 3

- Chemotherapy
- PRRT
- Immunotherapy (yet to be determined)

Graphic source: Image adpated from Hofman MS, Hicks RJ et al. Discover Med 2012 –New classifications for pancreatic NENs

Role of multidisciplinary teams

The care of patients with NETs is complex since patients may have multiple treatment options both at the time of diagnosis and throughout their patient journey. Ideally, a patient with NETs will be reviewed and cared for by a multidisciplinary team (MDT) of specialised NET-focused healthcare professionals so their care is coordinated and represents best practice.

Regardless of whether this team is formally established, a number of different healthcare professionals will likely be involved in providing care to a patient with NETs. There is no doubt that coordinating this and ensuring a high degree of collaboration delivers optimal outcomes for patients.

The team looking after a patient with NETs may include a surgeon, a medical oncologist, a radiation oncologist, a nuclear medicine specialist and technician, a gastroenterologist, an endocrinologist, a lung physician, a cardiologist, a palliative care specialist, a GP, pathologist, interventional radiologist and a specialist nurse.

In addition, a range of allied health professionals are also likely to be needed and these may include dietitians, psychologists or other counsellors, physiotherapists, social workers and an occupational therapist. When a child has neuroblastoma, the team will also include a paediatric oncologist and other specialists in childhood cancer.

While ideal, numerous patients with NETs do not have access to an MDT. In general NET MDTs exist in metropolitan hospitals with the result that patients living in regional areas frequently miss out. Unfortunately, when patients from regional areas are discussed by an MDT, it is not unusual for there to be a lack of communication back to the treating doctor with the result that less-than-optimal care is delivered. The challenges would be overcome by a structured, shared care model as described in this document.

Australia's current position

Australia plays a leading role in a number of new therapeutic treatments for NETS as well as research to inform better diagnosis, treatment and management. The first treatment of a patient with NET using PRRT occurred at the Peter MacCallum Cancer Centre in 1996, 25 years ago. Since then, the number of Australian centres specialising in NETs and delivery of PRRT has grown. They are pioneering the use of PET for characterization of disease and use of PRRT in combination with chemotherapy influencing global practice.

Under the auspices of NECA and their vision for early diagnosis and cure, patients and healthcare professionals are being provided with reliable information about NETs whilst registries and big data informatics hold the key to the future. In addition, the delivery of care via a novel management system that involves numerous specialties within the hospital system has emerged which offers the opportunity for patients to access evidence based best practice care and management both now and in the future. This has been achieved despite significant barriers including little to no funding and lack of knowledge by policy makers of the disease.

Treating patients

Australia is leading the way in development of radiopharmaceuticals, radiolabeled receptor-binding peptides, imaging and PRRT – the precision therapies needed to treat patients with NETs.

Theranostics is the term used to describe the combination of using one radioactive drug to identify (diagnose) and a second radioactive drug to deliver therapy to (treat) the main tumour and any metastatic tumours. Significant advocacy and other work has been undertaken to ensure access to NET patients and there is no doubt that this has made a difference to Australian patients.

More Australian NETs patients rate their care as excellent than in any other country surveyed, with 38% of patients considering this to be true. A further 34% of patients considered their care to be very good, a figure only exceeded by France at 40% and Germany at 39%.[26]

This should not be taken to mean that Australian patients are receiving optimal treatment as this is clearly not the case. 27% of patients still identify the need for a wider range of treatments for NETs as the most significant thing that would help with the ongoing management of their NET, while the fact that 24% of them have utilised emergency care in the past twelve months also points to the need for improvement.

Education of Healthcare Professionals

Recognising the importance of GP awareness and education to achieve earlier diagnoses of NETs, NECA has worked with education company Arterial to develop a series of online education modules accredited by Royal Australian College of General Practitioners. The course meets the Category One requirements, meaning that it represents one-third of a GP's Continuing Professional Development (CPD) for a three-year period. This enhances its attractiveness as does the subject and comprehensive nature of the resource.

Launched in 2020, supported by unrestricted educational grants from Novartis and IPSEN, these online modules are the first of their kind globally. They were designed by a multi-discipline steering committee, following extensive assessment of the gaps in experience and knowledge of Australian General Practitioners, specifically in relation to their care and treatment of patients with NETs.[27]

This assessment found that 74% of GPs had seen a patient prior to their diagnosis but only 5% had suspected a NET. The most common referral given to the patient by the GP was to a gastroenterologist followed by a colorectal surgeon. An oncologist was the third most likely referral given.

As a result of this assessment, the education modules are designed to build awareness of neuroendocrine tumours amongst healthcare professionals and have the specific goal of helping **reduce the period of time to diagnosis from an average of 5-7 years to less than 1-2 years.**

NECA has also been involved in delivering education to hospital departments and nurses through the delivery of in-services and they recently launched an online course accredited by the Australian College of Nursing. In addition, NECA has developed numerous webinars, factsheets, and other resources for use by healthcare professionals as well as presenting at numerous national and international conferences. In 2016, NECA convened the 4th World Theranostics Congress and, in 2018, the Asia Pacific Neuroendocrine Tumour Society (APNETs) conference. In 2019 NECA conducted a pre-congress Symposium providing comprehensive NET education for 100 nurses at the Cancer Nurses Society of Australia.


NA 1.25

Research

Australia is home to some of the global leaders in the treatment and research of NETs as well as to leading researchers in key areas such as molecular and genomic research. As such, Australian specialists lead the way in areas such as the development and use of theranostics to diagnose and treat NETs and the use of combined PPRT and chemotherapy. It should be noted that many of these advancements have been due to philanthropic funding. The following represent some examples of the work currently being undertaken.

PRRT and the study of cellular-repair mechanisms

Professor Rod Hicks and his team at the Peter MacCallum Comprehensive Cancer Centre recently attracted funding from the US-based Neuroendocrine Tumor Research Foundation (NETRF) for a four-year Accelerator Project to explore an integrated pre-clinical and clinical evaluation of DNA-repair mechanisms in identifying patient response to PRRT. This will help identify which patients will respond best to PRRT and why others are resistant to this form of therapy. By understanding this resistance better, it is hoped that improvements in response can be achieved thereby enabling more patients to attain a durable positive response.

In addition, the research team will test new combinations of PRRT with medicines designed to prevent cancer cells from repairing themselves. Laboratory tests will initially identify which therapies act to “turn off” the repair mechanisms within cells and then a clinical trial will be performed to test these targeted therapies in combination with PRRT in patients.

These studies will be supported by experts from around Australia and New Zealand with specialties ranging from medical physics, genomics, clinical expertise, cancer imaging, medical oncology. This project highlights a holistic approach to research, combining fundamental science with translational research and clinical expertise.[28]

PPRT in combination with immunotherapy

Merkel Cell Carcinoma (MCC) is a highly aggressive neuroendocrine tumour of the skin with an estimated associated mortality of 15% to 33%. Australia has the highest incidence of MCC in the world and our specialists are leading the way in its study and treatment.

Using medicines that have already been studied in patients with advanced Merkel Cell Carcinoma and shown to generate lasting responses, in a Medical Research Future Fund sponsored trial led out of the Peter MacCallum Cancer Centre, Australian specialists are now exploring how these medicines might be combined with PRRT for patients who have advanced stage MCC but who do not respond to immunotherapy.

A trial is currently underway looking at how one of these medicinal agents, Avelumab, combined with either PRRT or conventional fractionated radiotherapy may help patients with advanced metastatic MCC. [29]

CONTROL NETs & NABNEC Clinical Trials

In addition to these examples, NECA has provided funding to two clinical trials – CONTROL NETs and NABNEC.

The aim of CONTROL NETS, led by Prof Nick Pavlakis of Royal North Shore Hospital, and which is currently in its follow-up stage, is to identify the optimal treatment to improve disease control in patients with advanced Grade 1 and Grade 2 NETs. The study aims to determine how a combination of chemotherapy plus PRRT can work to help control pancreatic neuroendocrine and mid-gut, or small bowel, neuroendocrine tumours. [30]

NABNEC, in contrast, is comparing how two different chemotherapy treatments improve patients’ disease response rates in high grade Neuroendocrine Carcinoma (NEC). The study aims to identify which of the treatments is the most promising for further investigation.

The trial will also look at patients’ survival outcomes and any side effects they experience as a result of their treatment. Blood, tissue and other biomarkers will be collected for translational research that will help increase understanding of neuroendocrine cancers. [31]

The role of circulating tumoral DNA (ctDNA) – NET SANGUIS Trial

Pancreatic neuroendocrine tumors (PNETs) have variable biology, with no validated biomarkers to predict behaviour or treatment response. Circulating tumoral DNA (ctDNA) has been utilised in other cancers as a biomarker for mutation detection, drug target identification and direct change of therapy. ctDNA has been detected in patients with PNETs: its utility as a biomarker in the disease course of PNET patients has not been assessed. The aim of the observational/longitudinal SANGUIS trial led by Prof Michael Michael of Peter MacCallum Cancer Centre and recruiting at 6 Australian sites, is to evaluate the associations of ctDNA with tumoral mutation profile, histological grade and PET imaging phenotype at baseline and to determine the associations of ctDNA with therapy response and survival. The study hopes to Identify correlations between ctDNA with tumoral mutational profile, histological grade and imaging phenotype. Identify associations with therapy response and survival. Develop prospective trials to evaluate ctDNA as a biomarker for the treatment individualisation of patients with PNETs.

Research and collaboration in Australia lead to access in New Zealand

For many years New Zealand NET patients needing access to PRRT and nuclear imaging were forced to travel to Peter MacCallum for diagnostics and treatment. In 2013 with the assistance of Unicorn Foundation Australia (now NECA), Unicorn Foundation NZ was formed with their first key advocacy success, the delivery and funding of the first PET scanner with Gallium 68 for NET patients. In 2020/2021 after years of advocating and the consequence of boarder closures, the first national NZ PRRT service was funded by the Ministry of Health. The expertise and specialists used to run this service benefit from the collaborative sharing of knowledge and research from the Nuclear Medicine department at Peter MacCallum and other Australian sites, of which without, this milestone may not have been possible.

Data Registry (PLANET)

NECA has sponsored the only national Neuroendocrine Tumour registry which aims to fill the data gap which exists due to a lack of randomised clinical trials in neuroendocrine cancers, and the inefficiencies in the state cancer registries. This registry – called PLANET **(PLAnning for optimal treatment of NETs)**– is designed to act as a real-world observational study that collects information about patients with NETs and their treatment so that the resulting data can be used for scientific research and to improve the understanding and treatment of NETs.

Developed in collaboration with the eResearch Department at the University of Melbourne and the Peter MacCallum Cancer Centre with the aid of an initial grant from IPSEN Australia, the PLANET registry also has an associated mobile app that allows the secure recording of "real time" NET Patient Reported Outcomes (PROs) data in one location. This includes patient reported outcome measurements (PROMs), such as validated quality of life (QoL) surveys.

In addition, while facilitating the capture and storage of information, PLANET also allows (with patient approval) the transfer and sharing of patient information between relevant clinicians and specialists. This is the first time that real time collection of patient-reported outcomes has been connected to hospital data and it has already shown promise in guiding optimal patient care, through assisting in improved communication in consults, resulting in improved time utilisation and patient satisfaction.

Whilst being able to track and analyse patient data and allow patients to enter their own information in real time, PLANET also includes diagnostic tools, demographics, treatment options, treatment outcomes, and information about management of side effects.

It provides one registry for the many types of NETs. The Peter MacCallum Cancer Centre, Royal North Shore Hospital, Fiona Stanley Hospital, Royal Brisbane and Women's Hospital, and Queen Elizabeth Hospital are all participants.[32]

Centres of Excellence in NETs

The convergence of traditional medical specialties, such as surgical procedures with therapeutics, plus developments in immunotherapies, genetics, nuclear medicine and big data informatics are enabling a significant shift toward more patient specific treatments or precision medicine.

Due to specialised treatments, like PRRT, neuroendocrine cancer is at the forefront as one of the most advanced areas in precision medicine and this treatment is available at a number of Australian public hospitals.

Two of these hospitals – the Peter MacCallum Cancer Centre in Melbourne and Royal North Shore Hospital in Sydney – have recently been recognised as Centres of Excellence by the European Neuroendocrine Tumor Society (ENETs), joining an elite group of centres globally.

These Centres of Excellence (COEs) have leveraged the expertise from their hospital campuses, together with that of both local and international pharmaceutical and medical companies, to undertake world leading research and optimal targeted patient care. These centres, together with NET Centres at the Royal Brisbane & Women's Hospital, Queen Elizabeth Hospital and Fiona Stanley Hospital, have access for patients to genomic expertise; pre-clinical trials through to translational clinical trials; MDTs specifically for NETs; coordinated care; and access to radiopharmaceuticals. In addition, they utilise the PLANET registry and NECA's resources and support services as part of their coordinated patient care.

The framework underpinning the Centres of Excellence management of NET patients provides care in such a way that it removes or ameliorates many of the challenges currently facing patients with this cancers. Greater awareness of these centres is needed to ensure patients are referred there at an early stage of their patient journey where possible.

These Centres of Excellence are independently certified and audited and benefits reported by certified Centres include:

- Treating more NETs patients provides economies of scale and deeper clinical experience
- More structured cooperation across the Centre
- Improved MDT Meetings involving more in-depth discussions and consistent specialist participation
- Shared care models
- Better patient documentation
- Improved patient follow up, quality control, statistical data collection and review
- Improved research and enrolment of more patients in clinical trials
- Meaningful discussions with external peers during audits
- Improved recognition and awareness both within the Centre and externally of its capabilities
- Possibility of recognising affiliated referral partners. [33]

A proposal of this Action Plan is to establish satellite and referral hospital sites in each state (metro and regional) with shared care and referral frameworks in place, which will ensure all NET patients can access optimal continuum care regardless of where they live.

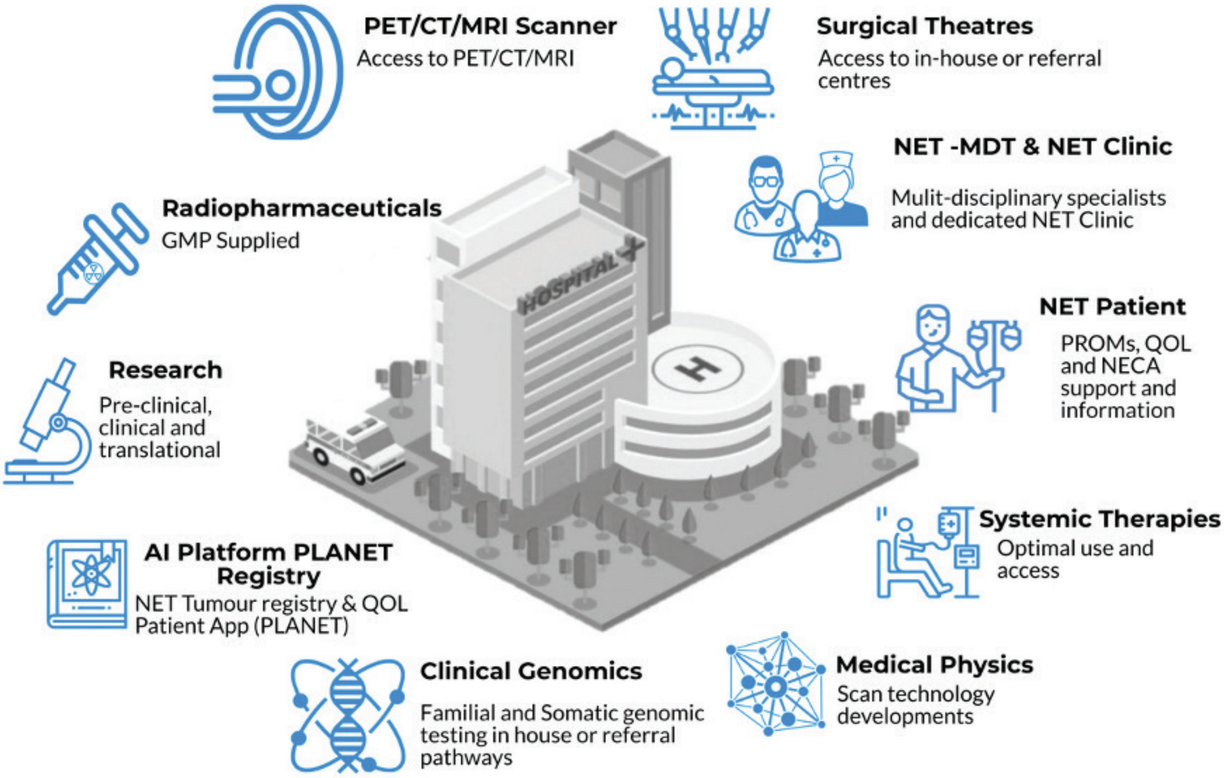
Formalising and evaluating this referral process is a project currently being undertaken by Gippsland Regional Integrated Cancer Service (GRICS) and Peter MacCallum Cancer Centre, funded by a Victorian Cancer Agency grant. The NET Pathway project will be launched and evaluated in 2021/2022 with the premise of being a replicable model for other metro and regional hospitals treating NET patients.

In addition to these benefits which support improved patient outcomes, Centres of Excellence offer governments and policy makers an opportunity to deliver equity and access to NETs patients closer to that experienced by Australians with more common cancers, particularly those living in our capital cities.

Doing this will not only leverage the investment Australia has already made into public health, technology infrastructure and R&D, maximising the return on taxpayers' investment but, at the same time, offer Australia the opportunity to export these services throughout the Asia Pacific.

> This Action Plan recommends that these five state-based Centres of Excellence are used to pilot the Innovative Model of Care in line with the National Health Reform Addendum 2020 – 2025.

The ideal model of a NET Centre of Excellence



Significant challenges remain

Although Australia is achieving much in relation to the diagnosis, management and treatment of patients with NETs and in research and health infrastructure, significant challenges remain for patients, their families and the healthcare system more generally.

Patients still experience:

- Significant delays before receiving a diagnosis
- A lack of clarity about the treatment and management options and any support services available to them
- Regional and rural Australia have difficulty in accessing appropriate treatment and referrals to specialist care
- All patients experience high out-of-pocket costs
- Patients face challenges in relation to their work lives and employment because of debilitating symptoms.
- There is also no doubt that more research is needed into NETs to bring these cancers and the progress made in relation to them in line with the experience of other cancer patients in Australia.

Misdiagnosis – exacerbates patient problems

Living with NETs has significant impact on patients' personal lives with 37% of global patients reporting no better than fair to very poor health. This is unsurprising given that, due to delayed diagnoses, over 60% of patients have metastases (Stage 4 cancer) at the time of their diagnosis.[34,35]

56% of patients experience general fatigue, muscle fatigue and weakness, 48% have diarrhoea, and 41% suffer abdominal cramping or pain, many on a daily basis. 71% of patients report a moderate to substantial impact of NETs on their daily life with 70% noting concerns about their energy levels and 39% reporting an impact on their ability to care for their family.

Patients' emotional wellbeing and that of those around them is also impacted by the experience of living with a NET. 60% of patients found that living with a NET affected their emotional health substantially. This can be due to social isolation and to the impact of side effects of their NETs. Patients experiencing symptoms such as faecal urgency report being scared to go out in case they have an embarrassing accident.

The impact on the emotional health of family and friends is also substantial for 48% of NET patients while relationships with friends and family were reported as substantially impacted by 34% of patients.[35] 20% of patients saw a therapist to help them manage the emotional impacts of having a NET.

A study which involved mainly Australian patients reinforces this data. 76% of patients felt their emotional health was impacted by NETs and 75% said that they were less able to participate in leisure activities. Access to a supportive network to help manage and treat their NETs was extremely important to patients participating in the study and 85% reported the patient support program that was the focus of the study had a positive impact on their Quality of Life (QoL).[36]

The impact of NET on mental health can also be seen in the diagnoses many patients received prior to their NET diagnosis. 22.3% of patients had previously been diagnosed with an anxiety or psychosomatic type condition whilst a further 8.5% had received a diagnosis of a psychiatric disorder.

Misdiagnosis of Neuroendocrine Cancer

The symptoms of Neuroendocrine Tumours are often mistaken for those of more common conditions.

Symptoms

Abdominal Pain
Nausea
Diarrhoea
Indigestion
Weight Loss
Flushing
Persistent Cough
Vomiting
Wheezing
Gastrointestinal bleeding

1 IN 2*
NET patients report
being originally diagnosed
with something else

5+ YEARS
From first symptoms to
correct time of diagnosis

Incorrect Diagnosis

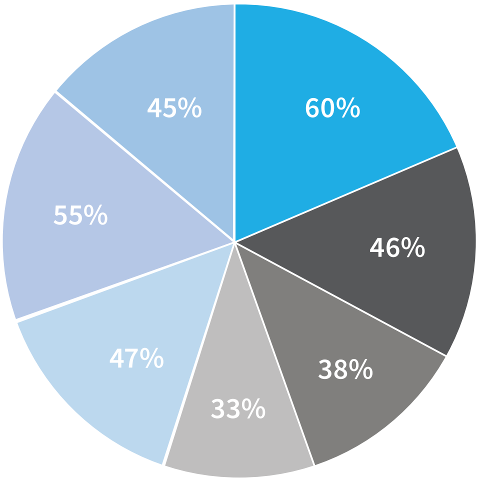
Stomach Ulcers
Irritable Bowel Syndrome
Pneumonia
Gastritis
Asthma
Anxiety
Depression
Neurosis
Menopause

Correct Diagnosis
Neuroendocrine Cancer

% of NET patients misdiagnosed per country

From a recent global study conducted by the International Neuroendocrine Cancer Alliance (INCA), 60% of Australian respondents reported being misdiagnosed at least once, but most commonly multiple times with another condition. The most frequent misdiagnosis was Irritable Bowel Syndrome and gastritis. The number of patients misdiagnosed in Australia is more than in other countries including Canada, China, United Kingdom, France, Germany and the United States.

Source: Survey of Challenges in Access to Diagnostics and Treatment for Neuroendocrine Tumor Patients (SCAN) 2019



> If I had wishes, it would be for medical professionals to be far more informed about Neuroendocrine Cancer so that patients in search of a diagnosis are not floundering around in what can seem an unresponsive system; so that patients can be correctly diagnosed in a more timely manner and receive earlier, appropriate treatment.
>
> **Jasmine is now being treated with medication.**

Misdiagnosis and delays: Jasmine's story [37]

In 2009, Jasmine underwent an operation to remove both her ovaries before, in early 2012, having a routine ultrasound for an unrelated and pre-existing medical condition.

Whilst these ultrasounds were routine for Jasmine, this one was different. The radiographer identified either a desmoid or potentially a neuroendocrine tumour.

A series of appointments then followed witha variety of specialists who showed, according to Jasmine, "varying degrees of interest". At one, she was the subject of a mistaken identity and, at another, the specialist lost interest in the discussion when it became apparent that she was a patient, not someone who was coming to take his blood sample.

The referral she bore received scant attention and a desmoid tumour was diagnosed. Jasmine questioned whether this was in fact the case given the original suggestion that it might be a neuroendocrine tumour. She was assured that it was a desmoid tumour.

Subsequently Jasmine located a specialist in soft tissue tumours and, after discussion with her GP, was referred to him. When asking if it were possible to identify whether her tumour was in fact a desmoid or neuroendocrine tumour, she was told yes – this could be done via a blood test to check her Chromogranin A levels, a protein commonly secreted by neuroendocrine tumours.

Further testing occurred, including a CT scan and consideration of her case by an MDT. A small bowel resection was then performed and a neuroendocrine tumour diagnosed.

On returning to her original gynaecologist post-diagnosis, the gynaecologist reviewed Jasmine's updated medical history and then excused herself for some time.
On her return, she apologised to Jasmine for the original surgery to remove her ovaries which, in retrospect, she deemed "possibly unnecessary" as the ultrasound used to diagnosis the problem may instead have indicated a presence of a neuroendocrine tumour. Jasmine also later received acknowledgement from the first specialist she visited of his misdiagnosis of a desmoid tumour.

Only one specialist NET telehealth nurse for all of Australia

Significant benefits could be generated for patients from the availability of more specialist NET telehealth support nurses in Australia. At present, NECA is able to fund one telehealth specialist NET nurse to provide support and information to patients and, while an excellent and much appreciated patient resource, this is simply insufficient.

Patients with NETs who interact with the NECA-funded nurse report the benefits they receive from her support – "all information regarding the disease itself, any treatment side-effects and information regarding drugs or potential issues when we are actually having treatment" and "she is our lifeline and we need to clone her". [38]

Patients report deep concerns however, about the fact that there is just one nurse and are clearly worried about the impact of her workload on her personally as well as on her capacity to continue to perform her role long term "her work load is massive which makes me wonder how long she can continue in the role before bowing out frustrated…or exhausted", "not sure how only one person can do this" and "in all honesty if she gets sicks or heaven forbid change[s] jobs, there are thousands of us that will literally have nowhere to go for information or…help". [39]

This concern for the NET nurse is well founded. The NET telehealth nurse operates an Australia-wide telephone support service – 1300 287 363 – Monday, Wednesday and Fridays from 9am to 5pm together with internet communications during that period. In 2020, they received over 1,500 patient contacts. The nurse also moderates two private Facebook groups for patients and their families affected by NETs. These groups have 1,500 members and grew by 20% last year.

In addition, the nurse assists in coordinating patient and healthcare professional forums during the year; helps organise nearly 100 face to face support group meetings across all states and territories; assists with referral pathways for patients and their doctors; advises on access to MDTs and clinical trials; participates in delivering educational symposiums for cancer care nurses both nationally and internationally; provision of research information and weekly live video broadcasts.

The support service, as might be expected, provides a disproportionate number of services to patients living in regional and rural Australia. This again highlights the difficult situation these patients are in and the inequity of their access to treatment as well as information and support.

From 2019-2021 the Federal Health department has funded nurses / cancer care coordinators for:

Organisation	Australians diagnosed in 2020*	Funding
McGrath Foundation	19,807	$41 million
Prostate Cancer Foundation	16,741	$40.4 million
Lung Foundation	13,258	$6.9 million
Neuroendocrine Tumours	**4,970**	**$0**
Ovarian Cancer	1,532	$2.6 million

It should be noted that this funding only covers the last 3 years and not the millions allocated before 2019.
NECA has received $0 for nurse support in 11 years.

NET Telehealth Nurse Annual Workload

1800+
requests for information & support online & over the phone

50
healthcare professional training sessions facilitated

45
informative video updates on social media

550+
social media interactions

350
referral phone calls with healthcare professionals & hospitals

60+
industry clinical studies read

1800+
patient/carer file updates

1500+
patient/carers managed in private Facebook group

Birgitte sought her own information and finally identified the NECA website, which she describes as ‘fantastic’.

Healthcare practitioners require better education about NETs

To support patients in the most appropriate manner and to deliver quicker, more accurate diagnoses, healthcare practitioners require better education and information about NETs. While traditionally thought of as rare, the incidence of NETs diagnosis has increased to the less common category, which places an onus on healthcare practitioners to be more informed and equipped to help their patients with more information and a faster diagnosis.

Whilst, as outlined above, NECA has developed various modules for GP education, Birgitte’s story indicates the need for better education to be made available for all healthcare practitioners.

Capacity to provide better information and support to patients: Birgitte’s story

Birgitte considers herself to be “one of the fortunate NET patients” whose tumour was found early and treated successfully with surgery.

She was diagnosed with a NET in her caecum following a regular bowel screening test and subsequent colonoscopy in mid 2020. She had had no symptoms before this, was very fit and healthy and felt both physically and mentally well.

Although pleased that her tumour was in a place that was easy to see and to remove, Birgitte remains deeply concerned that, before her surgery and during her time in hospital, neither her surgeon nor any of the other staff involved in her care provided her with further information about NETs. Nor did they direct her to anywhere where she could find reliable information. In fact, none of the nursing staff mentioned the terms ‘cancer’ or ‘neuroendocrine tumour’ for the entire four days Birgitte was in hospital.

As a professional with a science degree, on her discharge, Birgitte sought her own information and finally identified the NECA website, which she describes as ‘fantastic’. It had a lot of good, relevant and reliable information and Birgitte wrote an email to the NECA telehealth NET nurse who responded within a couple of hours. After talking for twenty-five minutes, Birgitte had “received more information about NET[s] as well as comfort…than [she] had had from my surgeon or staff at the hospital”.

Further, when raising this with her surgeon, Birgitte was cautioned that the website had information that was more relevant to patients with different NETs to hers or with more serious complications. Accepting this, Birgitte remains concerned that targeted information was not provided to her and isn’t routinely provided to all patients.

Patients lack access to information and resources

Patients with NETs experience a lack of access to information regarding disease management and treatment pathways, and report that they are unclear and hard to navigate.[40]

Sadly, globally, only 30% of patients and 18% of patient advocates believe that they are provided with all or most of the information they require, whilst 97% of advocates and 91% of patients believe that patients are forced to search for information themselves.[41]

This experience is mirrored in Australia. 28% of Australian patients cite a lack of access to reliable information about their NET and 30% have issues with access to information about their own health condition.[47] Patients also report feeling 'lost' or 'forgotten' within the health system.

This is hardly surprising in light of Jasmine's experience above although it is also worth noting the support provided to patients by patient groups, such as NECA, reporting that 70% of patients rely on them for their information.[42]

Patients need better access to medical specialists

Global survey data reports that around half of all patients believed that more knowledgeable NET medical providers and a better coordinated NET medical team would improve their care.[43]

In Australia, better access to NET specialists is needed with 25% of patients saying that they either do not know of one or have never heard of one.[44]

Access to multi-disciplinary teams is also limited. While 72% of Australian and New Zealand patients have an MDT involved in their care, patients, patient advocates and healthcare professional are unanimous that there is insufficient contact with these groups.[45]

Concerns about access to multi-disciplinary teams are reinforced with more recent Australian data reporting that 15% of patients have no access to an MDT at all while a further 18% say that their MDT does not meet sufficiently often. Only 40% of patients had accessed an MDT in the twelve months prior with the lack of MDT being the second most pressing issue facing patients.[46]

Delays exist in receiving medical professionals' opinions in 22% of cases and in receiving ongoing monitoring tests in 11%. A further 20% of patients are concerned about the lack of experts to provide a first or second opinion of their case.[47]

Australian patients with NETs are clear that better access to experts or an expert medical centre specialising in NETs and more healthcare professionals knowledgeable about NETs are required to assist with the management of their NET.[48] Dedicated NET nurse coordinators would be invaluable in this regard.

Patients need better access to treatment, imaging and care

Despite often having frequent medical visits and tests, access to treatment continues to be a challenge for patients with NETs.

Global survey data further reports that 60% of patients wished they had access to a wider range of treatment options specific to NETs.[49] Sadly, this is reinforced by data that indicates that around a quarter of patients and healthcare professionals – 23% and 25% respectively – believe that patients' requirements for care are often not fully met.[50]

Australian data reinforces this with Australian patients with NETs being clear that better access to a wider range of treatment options is required to help manage their NET.[51]

In Australia, PRRT is only available in certain specialised public treatment centres and, where patients do not live near one of these, they are either forced to visit privately owned facilities and pay significant out-of-pocket costs or travel to a metropolitan area for treatment. This has both significant impacts on access and costs for patients living in regional areas and can lead to patients not getting the treatment they need. Some of the inequities involved in this particular area of cancer care are demonstrated in Lynda's story in this Plan.

High out-of-pocket costs

In 31% of cases, patients indicated that cost was something they considered when determining their cancer treatment. There is, for example, no MBS rebate for important blood tests including BNP for heart screening (carcinoid heart disease) or Chromogranin A, and the cost of scans varies significantly across the country. While some State-based funding of PRRT has been achieved through advocacy of NECA, there is no Federal funding of this therapy through either the PBS or MBS and where access to funded treatment is lacking, significant out-of-pocket expenses are incurred in the private sector, which offers limited expertise but is an increasing source of such treatment.

Australian patients spend a significant portion of their household income on NET-related expenses. 15% of patients report spending between 11 and 20 percent of their annual household income on these expenses. This is higher than in any other country or region reviewed with the exception of the United States where 15.9% of patients spend this amount. This needs to be considered in light of the much higher prices prevailing in US healthcare. [52]

46% of Australians spend up to 10 percent of their annual household income on these expenses also with the global average for this level of expenditure being only 38.1%.

Other studies show that expenses for Australian patients with NETs include both direct and indirect cost with the most common being for transport, medication, doctors' visits and hospital admissions. Total mean costs over a three-month period are reported as A$1698 with the highest costs being for medical tests, travel-related expenses and specialist visits. 30% of patients report that the most common highest expense they face is for PET and MRI scans. [53]

Interestingly, global studies show that Australian patients have the highest percentage of patients who face out-of-pocket expenses in the Asia Pacific Region and lowest percentage whose NET-related expenses are entirely met by either state healthcare or their insurance. This is the case for only 14% of Australian patients compared to over 50% of patients living in France and even 17.5% of those living in North America.

Impact of NETs on employment and work lives

NETs affect a relatively younger age group than most advanced cancers, and thus have the potential to impact work with follow on effects on family and the community.

Patients who are in work report the need to take significant time off work due to their cancer (attending medical appointment and treatments) and one-third of them had reduced their working hours as a result of their condition and ongoing care. Nearly one-third of patients also indicated that their cancer had prevented them from gaining employment.

Amongst patients who are retired, 44% reported that they had retired early due to their condition and one-third of those in work intended to retire early because of it. [54]

40% of Australian NET patients spend more on treatment than they expected.

43% of patients identifying this as significant stress for them and their families.

Economic Impact on Australian Patients with Neuroendocrine Tumours

Study of Australian NET patients showed

40%
of respondents reported spending more on the cost of treatment then expected.

$1,698
Total mean out-of-pocket costs over 3 months

31%
reported the cost was a consideration in choosing cancer treatment

2/3
of respondents had at least one co-morbid condition or disease risk factor

Rural
patients reported travel & accommodation expenses as their largest expense

30%
of respondents reported the highest expense was for PET & MRI scans

44%
of respondents retired earlier due to their cancer

33%
of those working said they would retire early due to their cancer

Conclusion

Study highlights include

- The dual problem of cumulative out-of-pocket costs and early unanticipated retirement
- The highest costs reported by NET patients were for medical tests incl. PET and MRI
- Financial hardship exists and many had to reduce capacity to work contributing to financial stress

Fatigue and early retirement: Mark's story

In September 2016, Mark was returning from a footy trip in Thailand when he started to feel a bit off. A few weeks later he was still suffering diarrhoea as well as stomach and side cramps. In November, it came to a head and his wife took him to the nearby emergency department.

Mark was subjected to a few tests before being told he had typhoid. He was isolated, given the typhoid vaccine, and told he would be fine in a few days.

Just before Christmas Day that year and the day before his 49th birthday, Mark was back in emergency with cramps. More tests were performed and then an ultrasound was done. All of a sudden, he discovered he had a 'medical team' and it was obvious that something wasn't great.

He was told he had lesions in his bowel and that it looked like bowel cancer. He had a gastroscopy and a colonoscopy that week and, at his doctor's appointment the following week, he was told there were no cancerous growths and that all the relevant cells had been removed. Mark and his family were so relieved and "couldn't have been happier".

Two weeks later, the cramps were back and an appointment was made to see a surgeon. The surgeon knew a bit about NETs and wanted to do a simple blood test, really to discount NETS but "you do have the symptoms".

A week later, Mark had a diagnosis of a NET and thought it would be a "simple chemo treatment and remission like friends that had leukaemia or breast cancer…[it was] nothing like it".

Describing his treatment as a "rollercoaster", Mark considers himself lucky to be diagnosed within a couple of months "but subsequently treatments have been varied".

Like many other NET patients, Mark has had a variety of treatments – oral chemotherapy a couple of times, intravenous chemotherapy a few times and, from the beginning, monthly injections of an SSA – he's now had 50 or so of what he terms "these butt harpoons".

For the first couple of years, he managed to maintain a reasonable lifestyle. He kept working at his job in civil construction which he loved but slowly he started work later and finished earlier. His company was "amazing' but eventually he had to retire three years ago and, especially with intravenous chemotherapy, is fatigued all the time. He sleeps a lot and does what he can but acknowledges that "just house maintenance … take[s] it out of me now. When I think where I was three years ago till now [it] actually saddens me…now I sleep a lot and can't work".

> **Mark can't understand why some groups get so much funding, especially for research, while others don't.**
>
> We are just that forgotten small group that doesn't count, Mark says, as we don't have a 'trendy' cancer, yet ironically we are the ones more likely to die from what we have.

Inequity of NETs on people living in regional and rural Australia

In addition to the impact on patient outcomes of living in regional and rural Australia, unsurprisingly, research shows that the financial impact of NETs on patients living in rural areas is more significant. Travel and accommodation expenses are 30% of this group's highest out-of-pocket expense compared to only 13% of those Australians living in urban areas. This financial impact on patients is also indicative of the greater impact that a NET has on those people living in regional and rural Australia because of the need to travel significant distances to access medical care and spend time away from home to get treatment. [55]

The NECA telehealth NET Nurse support service receives a high proportion of rural patient calls for support when compared to the population, 48% regional v 52% metro. This is due to the lack of cancer specialists in rural areas, especially in neuroendocrine cancer. On average patients must travel over 300km to a specialist centre in the metro area creating a huge burden on patients and carers. In the local community there are huge unmet needs in the knowledge and experience of GPs to manage these patients' long term, leading to suboptimal care for patients, and an enormous reliance on the current NECA telehealth NET Nurse to educate both the patient and the medical staff providing treatment.

The experience of patients from regional and rural Australia further exacerbates the existing inequities.

> The inequality of cost for services between city and regional Australia is something that both Federal and State Governments need to address. **– Lynda**

Living in regional Australia – no MDT and high out-of-pocket costs –Lynda's story

Lynda first presented to her GP with pain in July 2010 thinking that she had gastro because it was going around at work. She had blood tests and then, due to elevated results on some of those, an ultrasound which found a mass in her pancreas and a metastasis in her liver.

She was admitted to hospital several times while surgeons unsuccessfully tried to get a biopsy of her liver and, eventually, without a conclusive result, it was assumed she had pancreatic adenocarcinoma.

After additional tests, including a CT scan, an MRI, a colonoscopy and blood tests to measure her chromogranin A levels, she started chemotherapy with three weeks on, one week off plus a daily growth inhibitor tablet.

Despite this, in February 2011, an additional CT scan showed disease progression.

In August 2011, Lynda sought a second opinion where her original diagnosis was questioned as was her disease progression. Later that month, following further consultation with her GP and radiologist, it was confirmed that her disease had in fact not progressed and she and her family requested further investigation, questioning whether she may in fact have a pancreatic-NET.

Eventually, in August 2011, one year after being diagnosed incorrectly with pancreatic adenocarcinoma, Lynda was diagnosed with a NET and had a scan to test for octreotide which tested negative but cost her $2,500 out-of-pocket.

Even though a NET had been confirmed, Lynda was not referred to a specialist NET centre.

Finally after numerous requests from Lynda she was referred in October 2012 for a GA 68PET scan in Sydney. This scan showed positive Somatostatin receptor avid Neuroendocrine Tumours, with significant disease progression since previous PET in 2010.

Lynda ceased her chemotherapy and in November 2012 she was referred by her GP to the Peter MacCallum Cancer Centre in Melbourne and has had various treatments including PRRT in Sydney and Melbourne from 2012 to now.

Lynda's experience meant that, for the first two years, her family lived with the expectation that every scan would show that she'd die soon. Living in an area without access to some of the treatments she needs means that the financial cost to her and her family have been, and continue to be considerable.

Lynda requires dual PET/CT scans every six months to monitor her tumours as they remain active. Where she lives, the scans she needs are only available through a private centre at a cost of $800 each with no Medicare rebate. In a capital city, she would be able to access through the NET specialist hospital.

Insufficient NET research occurs

Almost half of all healthcare professionals believe that research into NETs needs to be put on equal footing with that of other major cancers with 49% identifying this as an issue. 74% of patients and patient advocates agree with this assessment, adding to the concern that NETs are neglected compared to other significant cancers.

In terms of the research that these groups believe is needed, patients and patient advocates rank research into improving diagnosis as their highest priority whilst healthcare professionals would prioritise the need for clinical trials to test new treatments and improve existing ones. Research into improving quality of life (QoL) for patients with NETs and controlling their symptoms is considered highly important by all groups.

60% of patients and 77% of patient advocates believe that participation in a clinical trial positively contributes to a patient's treatment regime however, overall, only 16% of patients indicated that they had been in a clinical trial with 76% of those having only participated in one. [57]

Unfortunately, even when research is proposed, it is not always funded. CONTROL NETs, as mentioned above, supported 75 patients with NETs into a trial and was recognised globally as a 'practice changing' trial. Despite this, the NHMRC rejected funding this trial five times and patients' treatment was eventually fully funded by NECA and a grant from Tour de Cure.

Controlling NETs through research: Sandra's story

"There is nothing here for you. Go home. Palliative care."

These are words Sandra was told when she was diagnosed with functional neuroendocrine tumours.

She had had surgery to resect her primary NET which was in her small intestine and it had gone well. Surely, she thought, she simply now needed to get well and strong and everything else would fall into place.

Scans showed otherwise and Sandra's cancer had spread to her liver and lymphatic system. SSAs helped hold the cancer at bay but made her feel sick and then scans revealed significant progression of the cancer in her liver. Nine months after her diagnosis, Sandra was sure she was going to die.

She joined a trial – CONTROL NETS – at the Royal North Shore Hospital which had the goal that patients could gain fifteen months of life without progression or growth of their cancers. She was randomly allocated to the group who would receive PRRT.

She took oral chemotherapy at home in preparation for the PRRT. This helped her avoid long spells in hospital and allowed her to enjoy sitting in her garden even when she was feeling nauseated, tired and weak.

Sandra received four cycles of PRRT with CapTem Lutate between April and September 2017. They challenged her but partial remission at the half-way point was amazing. Her tumours continued to shrink over the following months with this previously untried combination of therapies.

Now Sandra continues her injections with SSAs but she has been stable for four years – three times longer than the trial had anticipated – with more of her life to still look forward to. Without the trial and the care she received, Sandra says that "in all probability I may not still be living with NETs but another of its victims, surrendering my life to insidious tumours resistant to most known, allowable treatments".

> This trial would not have been possible, and Sandra and 75 other Australians, would not have had access to it without the funding it received as a result of NECA's fundraising.

Neuroendocrine Tumour Action Plan 2022 – 2027

1 **NET specialist telehealth nurses**

2 **Information & resources**

3 **Education of healthcare professionals (HCPs)**

4 **National awareness campaign**

5 **Optimal Care Pathway**

6 **Data Registry (PLANET)**

7 **Centres of Excellence**

8 **Targeted research**

> Governments' acknowledgement, understanding and funding of all aspects of the National Action Plan is essential, as the incidence of NETs continue to rise and the burden of disease impacts negatively on both the individual and the entire health system.

Call for Action

Commonwealth and State Governments agree on four strategic priorities to guide Australia's health system between 2020 and 2025. These included:

- Improving efficiency and ensuring financial sustainability
- Delivering safe, high-quality care in the right place at the right time, including in nationally cohesive health technology assessment
- Prioritising prevention and helping people manage their health across their lifetime including through empowering people through health literacy
- Driving best practice and performance using data and research, including in enhanced health data. [59]

The National Action Plan recommendations align strongly with these strategic priorities – including in relation to improving efficiency and helping deliver financial sustainability of the health system. In addition, they will help both patients and healthcare professionals to ensure that appropriate care is delivered to patients with NETs at the right time and in the right place, informed by enhanced health data and research.

A plan to deliver on the recommendations

Given the infrastructure and health system already existing in Australia, delivering on the recommendations of this Action Plan can be achieved in the period 2022- 2027. The following section outlines how this can be done with eight actions split between the Federal and State Governments. All these actions are designed to help bring the time of diagnosis for patients with NETs down from the current mean of over five years to less than two years by 2027. This is an ambitious goal but can be delivered with strong commitment, investment in resources and information, and a coordinated plan.

It should be highlighted once more that whilst the Federal Government and Cancer Australia recognise the need for the development and implementation of an Optimal Care Pathway (OCP) for Neuroendocrine Tumours, without supporting the actions recommended in this document, the OCP may be ineffective. The OCP relies on some degree of Healthcare Professional and general public knowledge and awareness of the disease and the ability to access specific information, resources and referral pathways. Therefore, it is imperative that funding for the recommendations be considered with this holistic view.

In consideration of funding, Actions 1-6 and Action 8 fall within the remit of the Federal Government with Action 5 and Action 7 being a joint Federal and State opportunity.

1 NET specialist telehealth nurses

ACTION ONE: Support for specialist NET telehealth nurses and oncology social workers

There is an urgent need for service expansion given that one nurse currently supports the over 22,000+ patients living with NETs in Australia. With this one nurse currently in the process of leaving NECA, patients will shortly be at risk of increasingly sub-optimal care.

NECA has reviewed current and future patient need and found that an additional 5 NET telehealth nurses are required over the next 5 years, ideally with one located in each of the eastern states as well as South Australia and Western Australia. This staggered yearly approach, is a very modest investment over the next 5 years, and will not cause additional burden to the hospital system. It will instead alleviate demands, and provide an opportunity to an alternative nursing career path, whilst retaining these important skills in serving the Australian community.

At the same time as delivering the services desperately needed, these nurses would also work to develop a supportive care model involving specialised oncology social workers to facilitate in person peer support. This would help patients facing care and other challenges while at the same time ensuringwell-rounded and comprehensive services that would act as a conduit between patients, their families and their specialist care teams.

To ensure consistent and effective delivery of services and information as well as to support effective data collection, these nurses should be funded through the patient group, NECA, as occurs with the provision of other specialist nurse services (Prostate cancer, Ovarian Cancer).

These telehealth NET nurses would provide disease specific advice, as well as provide referral to allied health, specialists, services, and centres and be integral to shared care models. This model, and the infrastructure that supports it, is already proven by NECA to provide intangible benefit to the public and private healthcare systems.

This a small investment when compared to other cancer streams and will provide significant benefits. Working in conjunction with the NET specialist nurses in the hospital will provide continuity of care, referral pathways and provide equity of care for regional and remote patients.

ACTION TWO: Continual development of multi-media resources and information

In addition to building greater clinical awareness of NETs, patients require greater information and support. Whilst some of this will be generated as a result of greater clinical awareness, there is a need to provide the general public with more information about NETs to help with symptom identification. A public awareness campaign, like those undertaken in regards to other cancers and disease conditions, is needed to build public understanding and knowledge.

Capacity also exists to improve the utilisation of existing resources to provide better information to patients. Many patients with NETs are not provided with written reports following consultation with their specialists and these, together with clearly reported outcomes of MDT meetings, would be valuable without representing a significant impost. Being referred to NECA for support would provide additional resources and information.

In the last 5 years NECA has printed over 35,000+ patient booklets and distributed NET information to hospitals and GPs around the country from Esperance (WA) to Townsville (QLD) and everywhere in between.

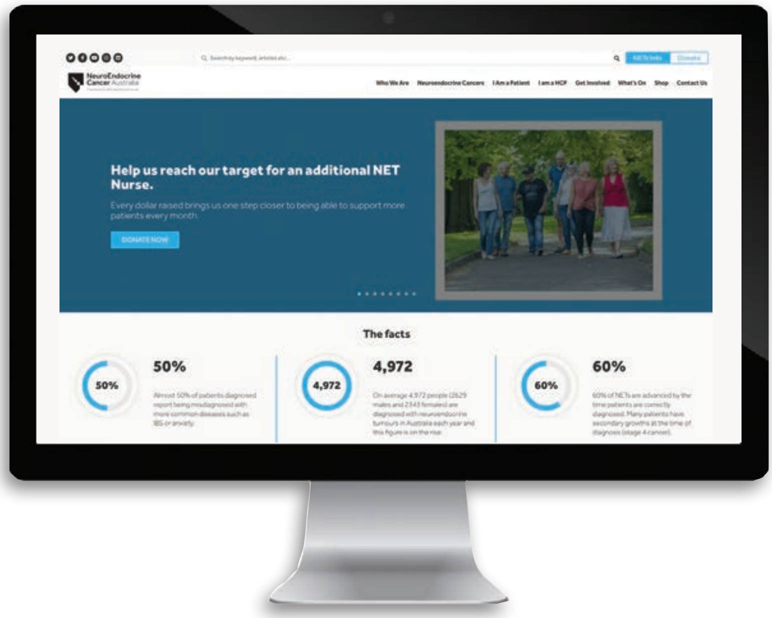
These resources are at a great cost both in production and distribution (postage), and as consumer driven and medically vetted information are trusted and greatly relied upon. These booklets as well as the website having 250,000 unique sessions in the last year and 66% being new users, show the importance of these evolving resources to NET patients across the country.

With nearly 70% of patients who receive support from NECA rating it as helpful or extremely helpful, continual investment is imperative.

NECA's role in providing trusted information to patients should be supported through a grant to develop additional information and resources to patients. Already recognised as a significant source of support and information NECA is aware that with limited resources they have not been able to reach even further disadvantaged CALD communities.

It would be their goal to expand their suite of resources to various languages to be more inclusive.

These resources would include web-based information, podcasts, videos, as well as information provided through other channels.



Help us reach our target for an additional NET Nurse.

Every dollar raised brings us one step closer to being able to support more patients every month.

The facts

50%

Almost 50% of patients diagnosed report being misdiagnosed with more common diseases such as IBS or anxiety.

4,972

On average 4,972 people (2629 males and 2343 females) are diagnosed with neuroendocrine tumours in Australia each year and this figure is on the rise.

60%

60% of NETs are advanced by the time patients are correctly diagnosed. Many patients have secondary growths at the time of diagnosis (stage 4 cancer).

3 Education of healthcare professionals (HCPs)

ACTION THREE: Enhanced education for healthcare professionals

Increasing clinical awareness of NETs and their treatment is critical to ensuring that patients with NETs receive an earlier diagnosis.

Given the increasing annual number of patients diagnosed with NETs and the delays in their diagnoses, early diagnosis before disease has spread/metastasized will improve survival.

No Australian should experience the extensive delays in diagnosis that occur with NETs, especially when 63% of patients report that their initial symptoms were either severe or very severe.

Increasing clinical awareness could be achieved by a number of initiatives that should be implemented immediately. These include:

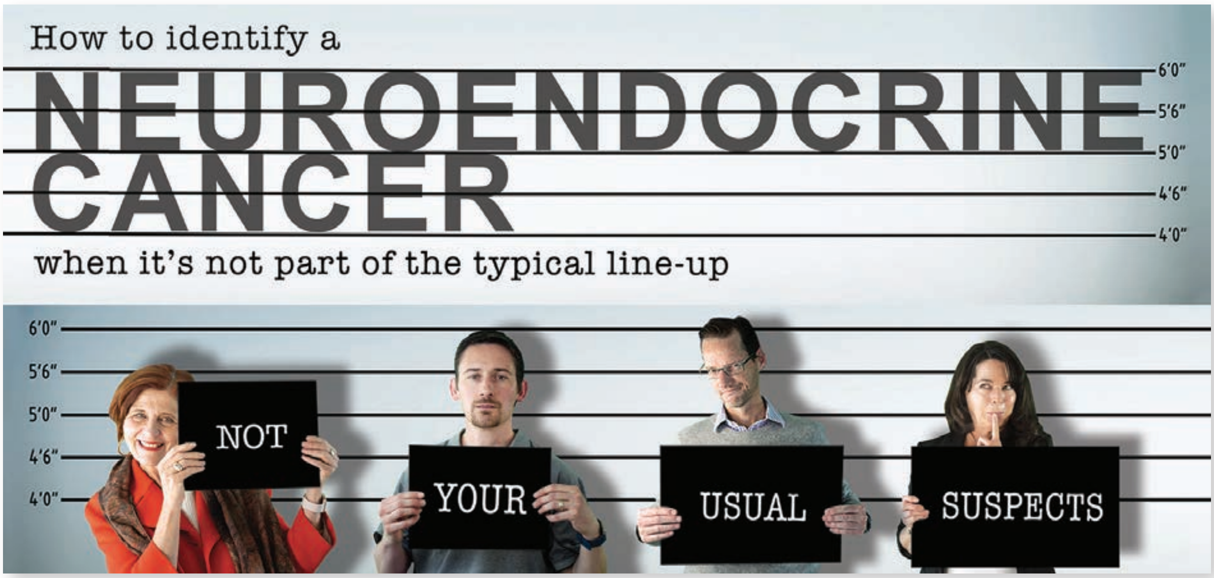
- Promotion of the existing NET education modules to more healthcare professionals
- Education of healthcare professionals through their medical colleges and societies, to provide them greater confidence in referring patients according to clinical guidelines
- Engagement with tertiary institutions to assist with reviews of current curriculums
- Encourage nurses and other healthcare professionals to specialise in NETs. The success of breast cancer nurses is a clear template for this initiative.

Education modules for General Practitioners and nurses have already been created by NECA and are accredited by their relevant Colleges (Royal Australian College of General Practitioners and Australian College of Nurses). More needs to be done to promote these modules to ensure uptake amongst the targeted healthcare practitioners.

In addition, more national in-services are needed in our national hospitals. These NECA led in-services are critical in directly engaging medical specialists and nurses, and helping them understand the clinical and other challenges faced by patients so they can provide appropriate and meaningfully support. **Delivered online they have the ability to reach rural and remote hospitals and are not impacted by COVID-19 restrictions.**

A nurse would be employed to oversee all elements of the extended education program which would, amongst other matters:

- Deliver a minimum of two in-services each month
- Develop additional materials for healthcare practitioners, mail-outs and e-news
- Media and podcast development
- Masterclass program would be developed and rolled out twice a year with education regarding MDTs and shared care models.
- GP registry is also proposed to be developed allowing better capture of data regarding patients, referral patterns and other treatment information.



4 National awareness campaign

ACTION FOUR: A national NET awareness campaign

With growing numbers of patients with NETs and the experience of those to date, there is no question that a national NETs awareness campaign is needed, targeted at both the public and healthcare practitioners.

Raising the awareness of symptoms patients experience when they present to doctors is essential to diminish delayed diagnoses . Shortening this timeframe will also help patients have investigations to expedite diagnosis and access to treatment, improving their prognosis and helping with issues relating to mental and physical wellbeing, financial stress and quality of life.
Similar campaigns have been proven successful in symptom awareness campaigns in Ovarian, Breast and Bowel cancers.


WORLD NET CANCER DAY, NOVEMBER 10

2018 CAMPAIGN TOOLKIT

JOIN US IN 2018
#LETSTALKABOUTNETS
www.incalliance.org
INCA

5 Optimal Care Pathway

ACTION FIVE: Development and implementation of National NET Optimal Care Pathway

The Australian Government and Cancer Australia, is to be commended on their commitment to develop an Optimal Care Pathway for Neuroendocrine Tumours as announced in April 2021. The investment into this has the potential to significantly impact outcomes for patients with NETs and, importantly, clarify the path of patients' treatment journeys. It is the hope that through this work additional funding for scans, diagnostics and treatments will be provided.

Ensuring that this Optimal Care Pathway is developed in a timely manner and rolled out to clinicians and other healthcare professionals as soon as practical is critical in both highlighting the existence of NETs and ensuring that patients with NETs receive best practice treatment.


Cancer Council

Optimal Care Pathways

> It is the recommendation of this Action Plan, that investment in Actions 1-4 are imperative in ensuring that the National Optimal Care Pathway is implemented successfully.

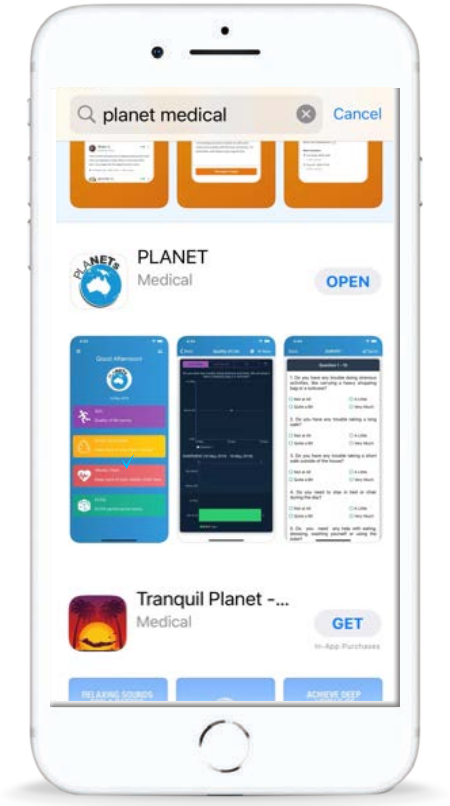
6 Data registry (PLANET)

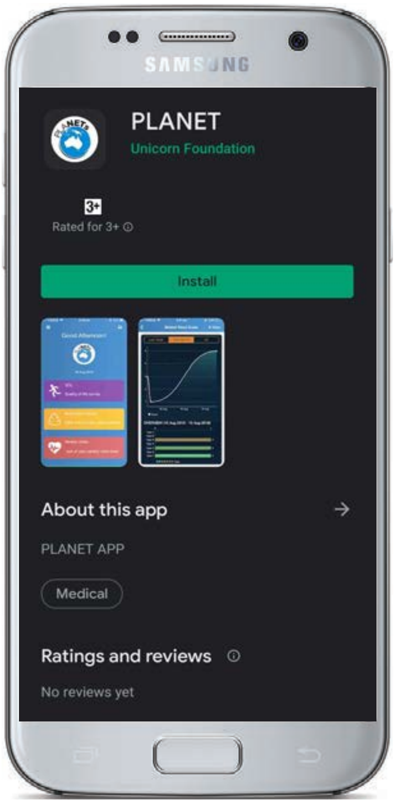
ACTION SIX: Data Registry (PLANET)

The PLANET Registry represents a world class model of the collation of information about patients with NETs and their treatment. The resulting data will support advances in scientific research and treatment of patients. Patient reported outcomes as reported by the associated mobile app is critical to this, given the small patient numbers and lack of clinical trials in this disease area and, over time, will help inform and refine the optimal patient pathway.

The web based PLANET Registry has been future proofed to enable future AI capabilities, integrating data such as tissue biomarkers, genomics, populations, next gen sequencing. It will also enable consultation across sites further benefiting regional and rural patient access.

Funding is needed to support a data manager and part-time nurse to coordinate with the various sites utilising PLANET, work with the design team at the University of Melbourne and design and disseminate information about PLANET and recruitment to the PROMs app.





> In the absence of randomised clinical trials, this registry is a large scale observational study collecting data in the 'real world', that will guide optimal treatment decisions, improve care and most importantly patient outcomes.

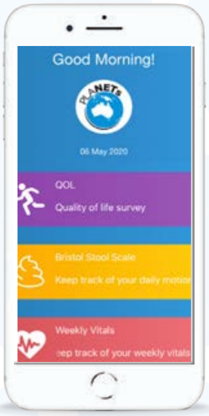
NeuroEndocrine Cancer Australia, in collaboration with the eResearch department at Melbourne University, have developed a world class Neuroendocrine Tumour (NET) registry and mobile app.

The app allows patients to safely and securely record vital data directly into the registry, such as:

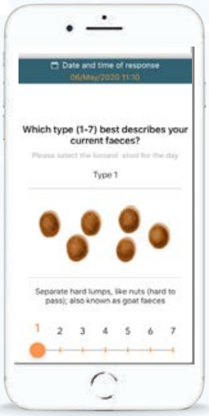
- Quality of Life survey
- Bristol Stool Scale
- Monthly Vitals
- ECOG Performance

PLANET Registry & App benefits:

- Safe and secure (patient information de-identified)
- Endorsed by Melbourne University eResearch department
- Streamlining the collection of accurate patient data
- Assisting in the collection of vital data for the future care and treatment of NET patients



Quality of Life Survey



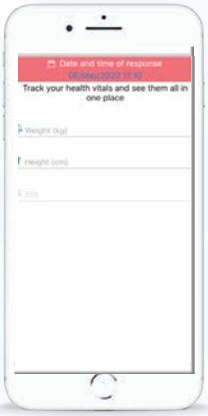
Which type (1-7) best describes your current faeces?

Please select the loosest stool for the day

Type 1

Separate hard lumps, like nuts (hard to pass); also known as goat faeces

Bristol Stool Scale



Track your health vitals and see them all in one place

Weekly Vitals

Press on the number to see the level that best describes your ECOG performance scale.

○ 0 ○ 1 ○ 2 ○ 3 ○ 4

ECOG Performance

7 Centres of Excellence

ACTION SEVEN: Pilot an Innovative Model of Care (National Health Reform Agreement) utilising the current NET Centre of Excellence Model

The Centres of Excellence in NETs are based on over twenty years of experience and build on infrastructure already existing in each state. The European Neuroendocrine Tumour Society (ENETS) COE-NETs already globally accrediated at Peter MacCallum Cancer Centre and Royal North Shore should be augmented with other centres in each other state as soon as possible through proportional investment in each state.

The NET centres at the Royal Brisbane and Women's, Queen Elizabeth and Fiona Stanley Hospitals are already delivering outstanding care to patients with NETs.

Providing funding and resources to the ENETs COEs and extending the framework to the other hospitals ensures that all Australians have improved patient care by delivery of comprehensive patient management and data collection, access to best practice in diagnostics, novel therapies, precision medicine, disease management and research of patients, reducing the number of inappropriate interventions that currently occur.

This will improve the sustainability of the health system whilst simultaneously acting to mitigate the significant inequities that exist both for patients with NETs and specifically those patients with NETs who live in regional and rural Australia.

Further this would build upon the globally recognised Centre of Excellence (European Neuroendocrine Tumour Society) framework and enable it to adapt and evolve in the highly innovative and promising area of theranostics in which Australia is also a leader.

The National Health Reform Agreement (NHRA) shows the intent by the Federal and State Governments to explore and trial new and innovative approaches to public hospital funding in order to improve efficiency and health outcomes as outlined in areas such as transplant and burns units. The trialing of an 'innovative model of care' for a period of time is suggested as a means of undertaking this activity as outline in section A99 of the Health Reform Addendum.

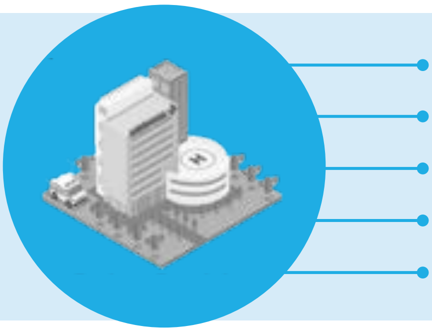
NECA recommends that the framework underpinning the Centres of Excellence in NETs be utilised as the first trial undertaken by the Federal and State Governments. With much of the infrastructure in place and two of the centres already recognised globally for their excellence, this offers an ideal and readily available model for trialing the proposed Innovative Model of Care and in an area of unmet patient need where improvement could be demonstrated whilst at the time a new funding model explored.

To deliver on this, state funding would be needed to support the employment of hospital NET nurses, data management and any additional infrastructure requirements. Federal funding would be required for access to theranostics, highly specialised drugs, research and clinical trials.

This funding would, at the same time, be offset by savings from inappropriate or unnecessary treatments and support the exploration and development of treatment models that could be expanded into other treatment areas, capturing additional efficiencies and benefits both to healthcare funding and, critically, patients.

Centre of Excellence:

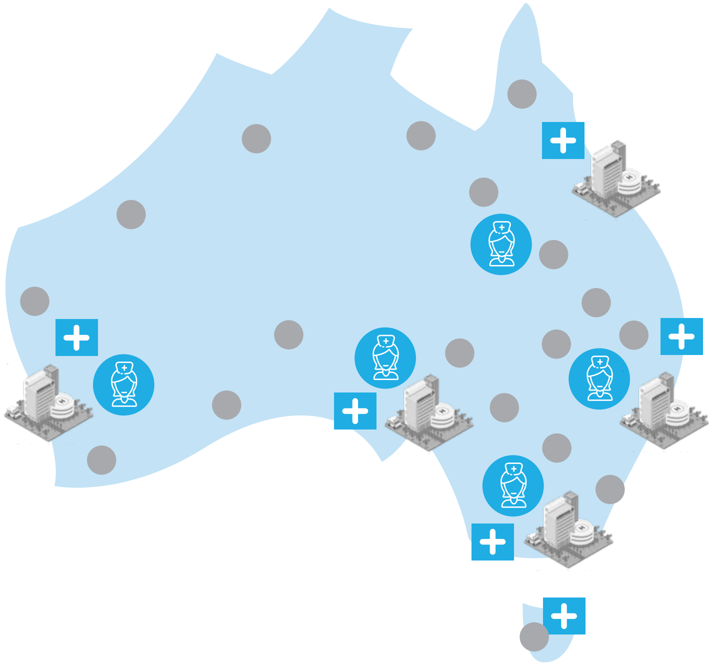
Similar in make-up to other centralised centres of excellence, such as hyperbaric chambers, heart/lung units and burns facilities.



- Diagnostics and Data Capture
- Ongoing Research and Development
- Precision Targeted Therapy
- Made to Measure Treatment
- MDTs – Integrated State and National

Proposed structure by 2027

- NET COEs
- ● Regional and Metro referral centres and shared care pathways
- + Satellite sites with NET MDTs but limited access to Theranostics
- NeuroEndocrine Cancer Australia NET Telehealth nurses



Funding Model

Individual states are responsible for infrastructure, services and workforce. →

State
- Big Data & Genomics
- Advance Diagnostics
- Surgery
- Multidisciplinary Team

Federal Government is responsible for radiopharmaceuticals and regulatory governance →

Federal
- Research and Clinical Trials Oversight
- Block Funding of Radiopharmaceuticals
- Regulatory Oversight (ADEC, PBAC, MSAC equivalent)
- Mgt. governance through the Health Chief Executives Forum (HCEF formerly AHMAC)

→

Centre of Excellence – NET

Benefits of unified research, development and care

Patient Benefits
- Better health outcomes
- Precision targeted therapy
- Reduction in unnecessary and costly interventions
- Equitable access
- Dedicated MDT
- Integrated care pathway
- Centralised patient data
- Patient support and information

Policy Benefits
- Continual loop for ongoing Research and Development
- Accurate treatment targeting
- Reduction in costs of unnecessary interventions
- Centralised price negotiation
- Access and equity in uncommon disease
- Infrastructure fully utilised
- Collaborative Research and Development investment opportunities
- Maintain Australian leadership
- Export potential of products and educational expertise
- Integrated R&D, care funding

8 Targeted NET research

ACTION EIGHT: Targeted Call for Research (NHMRC/MRFF) for Neuroendocrine Tumours

Leveraging Australia's existing leadership role in relation to research and treatment would enable Australia to consolidate this position.

Targeting funding to NET research as it is toward other health conditions, such as mental health, paediatric cancers, ovarian cancers and dementia. This can be done within existing budgetary allocation such as the Medical Research Future Fund (MRFF) so it can be cost neutral while efficient. Although there are some funding rounds within the MRFF and the National Health and Medical Research Council that are relevant, either directly or indirectly to NETs, there is no dedicated allocation of funds to research these cancers, nor is there a focus through Emerging Priorities and Consumer Driven Research. Introducing a dedicated funding allocation is critical to supporting the researchers and institutions working in this area and in addressing the health needs of this growing yet neglected patient cohort.

In a clinical area where investigators are already over- committed to clinical practice and often have little administrative or other support, dedicated funding would provide access to resources to meet the current grant deadlines and criteria and encourage additional investigators and researchers to the field. Enticing young investigators to specialise in NETs is a challenge due to lack of awareness and stable funding, both with the potential to be combated through a dedicated scheme. There are exciting opportunities that Australian NET researchers could contribute to with regards to:

- Earlier diagnosis
- Combination therapies
- Innovative Theranostics

Utilising collaborative networks through the National Centres of Excellence model (Action seven), would strengthen national and international collaboration and would facilitate collaboration between laboratory research and clinical research, driving forward improved outcomes for NET patients.

Benefits to patients by addressing these challenges

There is no doubt that more needs to be done, particularly given the significant burden that NETs place on patients, their families and the healthcare system. The experience of patients illustrated in the case studies in this paper also show that significant improvements could be achieved for these patients and those who care for them.

Implementing the above Actions, would ideally focus on achieving quicker diagnoses for patients; enabling them to get more appropriate treatment earlier; and deliver access to healthcare professionals with the right expertise at the right time.

In addition, addressing these issues would help ameliorate the significant inequities that currently exist between patients with NETs and those with more common or familiar cancers.

Economic benefits of addressing these challenges

Current Costs and Benefits

There are a variety of economic benefits that will be generated by addressing the challenges above. In relation to the introduction of an optimal care pathway for both the diagnosis and treatment of NETs, there are four key sets of economic benefits. These are:

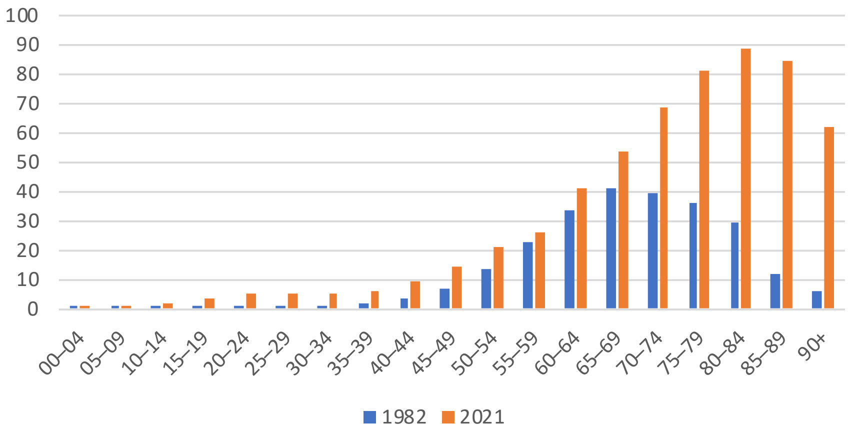
1. Reduction in waste within the health system, including:
    a. Misallocated expenditure on inappropriate investigations and treatments, such as surgery, chemotherapy, radiotherapy and hospital and emergency admissions, because of incorrect patient diagnoses
    b. Additional diagnostic activity that is undertaken when it becomes clear the illness persists despite the initial, or several, course(s) of treatment
    c. Ongoing use of other health system resources to help patients manage their quality of life which would be unnecessary if their initial diagnosis were correct.
2. Accompanying this reduction in allocative efficiency – and thus productivity – in healthcare expenditure, there is a loss of individual productivity where:
    a. NET patients spend more time out of the workforce or other productive activity, which is a cost both to them in terms of income and to the wider economy in regard to participation
    b. The problem of misdiagnosis means that there is a risk that otherwise treatable conditions may become chronic and intersect with the physical and mental health comorbidities associated with a long period of non-arrested illness
    c. The onflow from this is often an associated reduction in productivity for family and others who stop work or other economically valuable activity so they can undertake personal care.
3. Where patients are treated in the public health system, delays in time to proper diagnosis and treatment of patients with NETs have the effect of increasing waiting lists. This means that the costs of illness are also increased for other patients whose time to treatment is delayed.
4. There is the economic value of reduced health-related quality of life (HRQoL) which is experienced by the patient and also commonly by carers.

What is immediately apparent in the economics of NETs is that the solution must rely upon better diagnostics which, in turn, requires greater awareness. This is not a marginal issue. As noted above, as recently as 2014 the mean time to diagnosis has been 52 months with 29% of patients requiring more than 5 years and nearly 60% of sufferers having metastases at the time of diagnosis. [57] This means patients have extra tests and require additional primary and allied-health care while at the same time they incur extra out-of-pocket costs so as to achieve relief from their symptoms.

If patients receive their principal diagnosis earlier, then the costs of each NET should revert to the normal burden of disease without the opportunity cost of misdiagnosis.

The impact of improved diagnosis is illustrated in Chart One which shows the different observed frequencies of NETs across the Australia population by age group in the years 1982 and 2021. Frequency is per 100,000 population. [58]

Chart One: Frequency of NETs over time



A number of observations may be made from these data. First, there has been an increase in diagnosis of NETs across all age groups. Second, there is a particular increase in the rate of diagnosis amongst older Australians. And third, there is also a notable multiple of diagnosed cases in the age groups from adolescence through to late 40s. One question which emerges here is whether the limited change in frequency for the 50-69 age group compared to that in the latter age ranges suggests a gap in diagnostic improvement for this age group.

It may be assumed that many of the avoidable costs of misdiagnosis in earlier years are now savings in 2021. The extent of these is however unclear.

Looking to efficacy of investment in treatment of NETs and using the standard model of incremental cost-effectiveness (ICER), treatments evaluated for properly diagnosed NETs have been almost universally found to sit below the threshold price of a QALY and are therefore cost-effective for the health systems in which they were considered.

These include:

- US analysis of immunosuppressants for treatment of NETs, which found a cost of US$41,702 per QALY gained [59] While this would nominally exceed the Australian threshold of AU$50,000, the relatively high cost of US healthcare should be taken into account. At the same time, even if this were equivalent to the Australian price, it would not nearly approximate the type of price increment commonly associated with rare and less common cancers
- A similar cost per QALY gained of US$42,157 in Mexico [60]
- Using the drug comparator measured above, a Swedish assessment that treatment with Lutetium 177 products offers a cost per QALY of SEK167 [61] or AU$2,682). [62] [63] This is a particularly strong endorsement of the value of ANSTO's activity in producing Lutetium for NET clinical trials in Australia [64]
- Compared to palliative care only for gastroenteropancreatic NETs, Lutetium treatment offers a mean incremental benefit of 1.33 QALY73 [65] at a cost of GBP26,830 or AU$49,635 [66]
- Relative cost-effectiveness of hepatic resection over intraarterial therapy for neuroendocrine liver metastasis with the preferred liver surgery costing an estimated US$8,427 per QALY. [67]

The conclusion here is that – once there is better diagnosis and the costs of misdiagnosis are removed – the treatment of NETs, even with emerging technologies, sits within the normal range of efficient health expenditure.

Despite these positive observations, it is acknowledged that the costs of treating patients with NETs are high and that there remains a need for more comprehensive economic analysis of treatment protocols and access to treatments. [68]

The total cost of NETs to the health system, when they are properly diagnosed, is unclear. The most recent systematic review of eight cost of illness, economic evaluation and budget impact studies, including some of those referred to above, notes a paucity of data related to resource utilisation and recommends collection and analysis of data to examine cost-effectiveness of various treatments.[69]

This is an area worthy of further research. Efficient models of care that leverage economies of scale are likely to have a positive impact on cost-effectiveness as well as providing data on "whole-of-care" management costs in comparison to real-time patient-related outcome reporting.

Beyond the public burden of care, the private costs of NETs are substantial as noted above. A recent survey of Australian patients with NETs and their families found that the mean out-of-pocket costs for NETs patients was $1,698 over a three-month period and substantial variance was experienced. This cost was associated for many patients with profound financial stress, particularly given the impact of NETs on people's ability to work and the fact that early retirement is common for patients with NETs.[70]

It should be noted here that these expenses and effects occur after a NET has been properly identified – they do not take into account the earlier costs and, importantly, the psychological burden of any period of misdiagnosis.

Prospective Costs

At this stage, data limitations mean it is not feasible to identify the potential savings associated with better and earlier diagnosis of NETs. Data collection should be undertaken to enable measurement of prospective savings.

Proper consideration will also need to be given to prospective costs. The issue of cost-effectiveness is addressed above and, while there needs to be more analysis, this means that in principle better diagnosis of NETs will be an economically efficient activity.

The other costs which will occur if this Action Plan are followed will include:

- Education and awareness costs. These should be incrementally close to zero as they can be addressed via:
  - Updated curriculum for medical students
  - Normal journal education and continuing professional education for GPs and other healthcare professionals
- Any costs associated with increased use of diagnostics including pathology, radiology and other prospective tests.

The issue which emerges from the latter point is what proportion of patients will be required to undertake further scans and pathology tests in order to rule NETs in or out. Technically, this is a question of minimising false positives for potential NET indication without excluding any of the cohort who ultimately are found to have NETs.

This will require a careful and clinically led design to ensure better diagnostic outcomes while minimising additional cost.

Other benefits of addressing these challenges

Numerous other benefits would be generated by addressing the challenges faced by patients with NETs. Many of these fall into the categories of capacity building and maximising the return on investments in public health and other scientific infrastructure and expertise that Australia has already made. Not taking advantage of the opportunities available to improve the diagnosis and treatment of NETs would result in many of these benefits being foregone when really these should be maximised to benefit both patients and the broader health and scientific ecosystem.

Better use of infrastructure and resources

As highlighted in the economics section, diagnosing and treating patients with NETs more effectively, efficiently and earlier would avoid the experience where patients are regularly subjected to repeated performance of the same medical tests. Further, it would also mean that patients would obtain optimal treatment much earlier as they would ideally receive timely referral to a NET specialist.

Both of these scenarios would result in better and more efficient use of Australia's health infrastructure and resources and avoid the waste that currently often occurs in the treatment of patients with NETs. Given these are scarce and expensive resources, the more efficient use of them is of benefit across the health system.

Enhanced medical education and awareness

Enhanced medical education and awareness would be a key benefit attained by addressing the challenges faced by patients with NETs. Providing more education about NETs to healthcare professionals across the range of medical and allied health professionals would result in them feeling more capable and confident in diagnosing NETs and more able to provide patients with appropriate and timely referral and support.

The education modules developed by NECA for GPs and already rolled out have proven valuable but expanding their use and introducing targeted education within the medical curriculum would boost the capability of a broader group of practitioners to the greater benefit of the entire health system.

Safeguard access to optimal care and support – COVID- 19

COVID-19 has bought about many challenges and none more so then to cancer patient support services. Vital peer support has moved online, or cancelled, boarder closures have restricted patients accessing their diagnostics and specialists and extended lockdowns have caused even further anxiety to isolated NET patients. Action 1 of having state based specialist NET telehealth nurses will alleviate the confusion for patients within each jurisdiction and ensure continuity of care and support. Whilst the increasing incidence and prevalence of NETs in Australia justifies the need for this workforce, COVID 19 has amplified the urgency.

Increased export opportunities and Sovereign Capability

Australia has long played an important part in the development of nuclear technology and the Australian Government's significant and long-term investment in the Australian Nuclear Science and Technology Organisation (ANSTO) is a critical part of this. Recent financial and other investments in cyclotrons and other related technology represent further testament to this work and its value.

Leveraging the clinical knowledge and capability that exists in the Centres of Excellence in NETs framework, in relation to PRRT and theranostics together with the opportunities offered by ANSTO, Australia has the opportunity to develop new export opportunities.

These could encompass teaching and training opportunities together with the sale of radioisotopes throughout the Asia Pacific region and the current Centres of Excellence could help facilitate and prove this concept. Australian Biotechnology Companies also play an important role in partnering with the Australian medical community in early phase human trials, an existing area of expertise and opportunity.

Maintaining and expanding Australia's leadership position

Supporting additional research into NETs would help maintain and build upon Australia's existing leadership position in science and boost our contribution to the global knowledge and understanding of NETs. This would both build on our existing local capacity but also act to attract others to the field as has been evidenced in various areas of scientific and research endeavour.

Further, this would strengthen Australia's clinical capacity and attractiveness as a site for clinical and other trials and research, a goal aligned with many Australian Government policies and objectives.

An enhanced regulatory and funding framework

A national approach is required to ensure that 'highly specialised therapies' can be utilised with 'highly specialised services' to enhance access and advancement of diagnostic tools and treatments, such as theranostics.

Treatments, like Gallium-68 Dotatate PET/CT and PRRT, are recognised as 'high cost, highly specialised therapies' involving the use of 'highly specialised services' and are defined by the National Health Reform Agreement – Addendum 2020-25. There is not, however a clear and efficient process for approving, registering and reimbursing these therapies and, given that many of these emerging technologies are rapidly becoming the norm, this needs to be addressed.

The Federal Government should therefore consider how best to develop a combined framework that takes elements from the Australian Drug Evaluation Committee, the Pharmaceutical Benefits Advisory Committee and the Medical Services Advisory Committee and enables the combined assessment of the safety, efficacy and cost-effectiveness of new therapies and medical technologies that treat less common cancers.

In addition, given that many of these less common diseases cannot hope to attract or to undertake traditional large randomised clinical trials due to lack of patient numbers and/or interest from industry, recognition needs to be given to real world patient outcomes, such as those reported by the NET registry, PLANET and the associate PROMS app.

At present, all these elements are separated and/or given insufficient recognition despite the fact that clinicians and policy makers are aware that they are interrelated and often interdependent in delivering real patient outcomes. As a result, safety, quality, effectiveness and cost-effectiveness of patient care in Australia is being compromised.

This is recognised, again, by the National Health Reform Agreement which states that "separate processes exists across all levels of the health system, which has the potential to duplicate effort, create inefficiencies and inconsistent advice, and delay access to innovative and emerging technologies". Further, the Addendum notes that "the development and implementation of a nationally cohesive approach to HTA is an opportunity for governments to make informed decisions to deliver safe, effective and efficient care that is financially viable and improves population health".

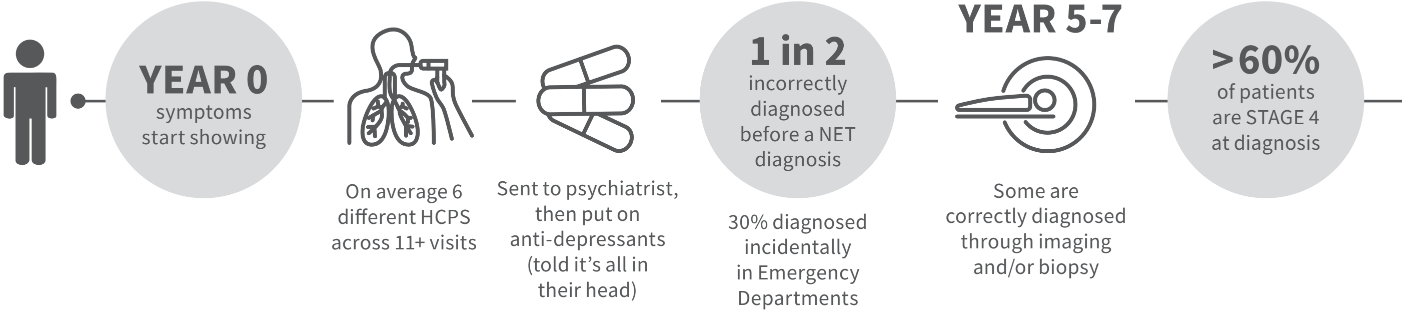
Rapid identification and implementation of an enhanced regulatory and funding framework is essential to ensure Australian patients can access the care they require at the time they need it as well as to ensure the sustainability of the Australian health care system.

A promising future

NeuroEndocrine Cancer Australia and our associated stakeholders and partners, truly believe that if the Actions outlined in this plan are funded and implemented accordingly, the increasing number of Australian's diagnosed with Neureondocrine Cancers in the future will benefit through greater awareness of the disease leading to earlier diagnosis and better outcomes and survival. Those Australians that cannot be cured as a result of earlier diagnosis, will have much improved care through comprehensive and equitable access to information, support services, referral pathways, centres of excellence and access to more clinical trials and research. All of the proposed actions in this pioneering National Action Plan for Neuroendocrine Tumours benefit from established infrastructure, experience and investment, and align seamlessly with the proposed priorities of the National Cancer Plan including person centred; equitable access across all population groups; encompass whole continuum; future focused; collaborative; data focused and strengths based.

> We welcome our Federal and State governments to tackle this National Action Plan together with NeuroEndocrine Cancer Australia, so no Australian is disadvantaged by the type of cancer diagnosis they receive, and no patient is forgotten and slips through the NET.

Patient Journey: 2021



YEAR 0
symptoms start showing

On average 6 different HCPS across 11+ visits

Sent to psychiatrist, then put on anti-depressants (told it's all in their head)

1 in 2
incorrectly diagnosed before a NET diagnosis

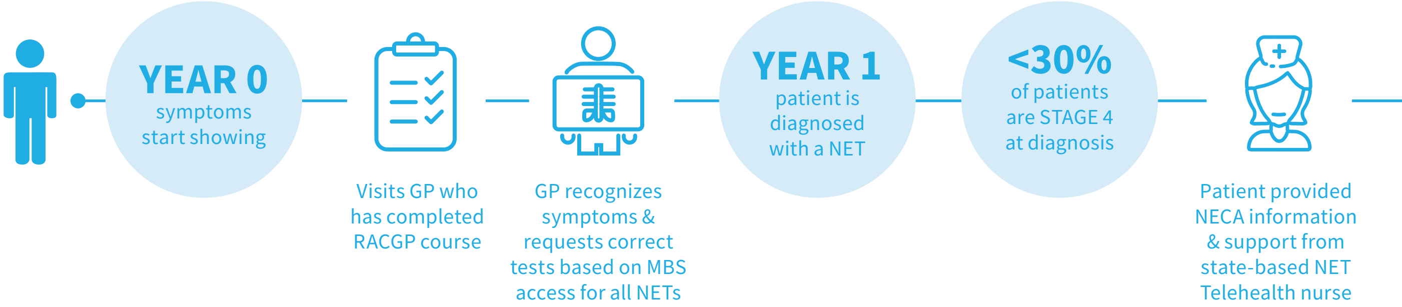
30% diagnosed incidentally in Emergency Departments

YEAR 5-7

Some are correctly diagnosed through imaging and/or biopsy

>60%
of patients are STAGE 4 at diagnosis

Patient Journey: 2027 (after implementing NECA Action Plan)



YEAR 0
symptoms start showing

Visits GP who has completed RACGP course

GP recognizes symptoms & requests correct tests based on MBS access for all NETs

YEAR 1
patient is diagnosed with a NET

<30%
of patients are STAGE 4 at diagnosis

Patient provided NECA information & support from state-based NET Telehealth nurse

Surgery often not an option due to spread of disease

Travel **300KM** on average for specialist treatment

only **10%** of patients included in clinical trials

75% report negative impact on their mental health

82% who retire early attribute it to their NETs

10 months median survival for high grade 3 NEC patients

No shared **CARE** models, patients slip through the net

NET patients are reviewed by an MDT & the best treatment plan is developed

Latest imaging **reimbursed** for all NET patients

clinical trials offered based on patients tumours

Offered genetic testing to study history of disease & find targeted therapies

<40% have to retire early due to their cancer

20 years median survival for Grade 1 & 2 patients

>70% patients survive for 5 years

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Graph Source: AIHW – Projected 2021 incidence *This chart does not include all cancers

Graph Source: Cancer data in Australia, Cancer summary data visualisation - Australian Institute of Health and Welfare (aihw.gov.au)

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Graphic Source: Recreated diagram of Prof Michael Hofman, Prof Rod Hicks et al

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