Equitable access to diagnosis and treatment for individuals with rare and less common cancers, including neuroendocrine cancer

About Australian Genomics

Australian Genomics is an Australian Government initiative supporting genomic research and its translation into clinical practice. Through broad engagement and a national collaborative approach, it achieves two key objectives: to improve efficiency, reach and timeliness of genomic research projects, and to support Commonwealth State and Territory health departments in the implementation of genomics research outcomes by refining and communicating evidence to inform policy development.

Australian Genomics engages with current and emerging government policy and priorities to identify gaps and opportunities, to support policy and action for integrating genomic technologies into the health system. By interfacing with consumers, governments, industry and global genomics initiatives, Australian Genomics drives change and growth in the sector.

Further, Australian Genomics is a key supporter of the emerging Indigenous Genomics agenda, most visible through its direct support for the Australian Alliance for Indigenous Genomics (ALIGN), funded through the Medical Research Futures Fund (MRFF).

Australian Genomics thanks the Senate for the opportunity to provide input to this Inquiry.

Rare and less common cancers

The Australian Institute of Health and Welfare (AIHW) reported that 17% of cancer diagnoses were rare cancers, 13% less common cancers, and 70% were common cancers. However, rare and less common cancers accounted for nearly 42% deaths[1]. Concerningly, Indigenous Australians experience higher incidence, lower rates of access to care, and disparate mortality rates when compared to non-Indigenous Australians. Indigenous Australians are more likely to be diagnosed with and die from aggressive cancers, including those classified as rare or less common. In data from South Australia, Cancer of Unknown Primary (or CUP) was the fourth most common cause of cancer death among Aboriginal people between 1990-2010. These data indicate inequity in outcomes and that there is much work to be done to improve the prognosis for people experiencing rare and less common cancers.

[1] Australian Institute of Health and Welfare 2021. Cancer in Australia 2021. Cancer series no. 133. Cat. no. CAN 144. Canberra: AIHW.

a. barriers to screening and diagnosis, including the impact of factors such as:

i. geographic location,

In a study of rare cancer epidemiology using cancer registry data, it was found that areas in northern, western and central Australia, and Tasmania, tended to have lower survival rates[2]. AIHW reported that mortality rates for all cancers combined were highest in very remote areas and the 5-year survival rate was lowest in very remote areas[1]. This is particularly salient for Aboriginal and Torres Strait Islander people. These figures may reflect later diagnosis in people who are geographically further from the services they need to access to receive a diagnosis. Virtual care is not always an option as most cancer care is provided within metro or large regional centres, so people must travel from their homes to undergo tests. This means time away from their home, employment and families, as well as incurring travel and potentially accommodation costs. Additionally, specialised rare cancer services are mainly in the major cities of South-eastern Australia[3]. It is also common for people with rare and less common cancers to have to undergo several tests before a diagnosis is made.

Early detection is currently possible through the established breast, colon, and cervical screening programs, which identify common and rare cancers. However, there are no active screening programs that are based on genetic tests, and predictive tests are only available to those who meet stringent inclusion criteria. The DNA Screen study is trialling a model of genetic screening for hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia (genetic high cholesterol) for 18–40-year-olds. The program is determining feasibility, scalability, and public acceptance of the program to ultimately work towards a population screening program for Australia. There are existing evidence-based best practice models that have been developed and implemented for increasing cancer screening rates of Aboriginal people, particularly in those never or under screened cohorts. Some of these programs have demonstrated an increased rate of screening when developed in partnership with Aboriginal and Torres Strait Islander peoples and communities. Indigenous-led, developed or co-developed cancer screening and service pathway models will not only address access and equity barriers to health services, but provide culturally appropriate ways and means to navigate them in partnership with mainstream healthcare service providers[4,5].

[2] Dasgupta P, Cameron JK, Cramb SM, et al. Geographical and spatial disparities in the incidence and survival of rare cancers in Australia. Int J Cancer. 2023 Apr 15;152(8):1601-1612. doi: 10.1002/ijc.34395. Epub 2022 Dec 21.

[3] https://knowledge.rarecancers.org.au/knowledgebase/health-professionals

[4] https://www.breastscreen.org.au/news/cultural-shawl-project-increasing-breast-screening-in-aboriginal-women-wins-vichealth-award/

[5] https://www.breastscreen.org.au/news/cultural-screening-shawls-make-their-way-to-act/

The responsibility of translating the rapidly increasing knowledge about cancer causing genetic variants into health practice cannot be left to the research sector and research funding: the investment, infrastructure and knowledge must be built up in the genetics services and research rapidly translated into sustainable health system screening and diagnostic services.

There are significant barriers to address for genetic screening tests to become more widely available, evidenced by the inadequate uptake of genomic interventions to-date. Many reasons underly this, but include that genetic test are often matched to a specific drug in co-dependent applications to Medical Services Advisory Committee (MSAC) and Pharmaceutical Benefits Advisory Committee (PBAC) sponsored by pharmaceutical companies - and they work through Health Technology Assessment (HTA) very slowly.

Genetic and genomic-based screening and diagnostic services can be effectively rolled out remotely. Two examples include the DNA Screen and Mackenzie's Mission (Australian Reproductive Carrier Screening) studies – where education and consent materials are delivered online and swabs for buccal samples for genetic tests are mailed to the participant. Self-collected samples are returned to the diagnostic laboratory by post. The failure rate of such samples is very low and the cost and barriers to participation are decreased. It is noted that an increase in genomic screening programs at scale would result in additional pressures on relevant health services including education of primary health providers, and increased demand on genetic counselling services.

To lessen the impact of geographic factors on screening and diagnosis, models of virtual care and remote clinics must be scaled up, and at-risk individuals, families and communities identified for closer engagement and health screening. Models for delivery of health literacy and prevention programs also need to be designed so they can have Australia-wide reach, utilising the best available technological solutions. The University of Melbourne and Peter MacCallum Cancer Centre have recently announced the establishment of a new precision cancer care centre, one of its key aims being to close the gap in regional access to expert services[6]. Genomic testing may be an important element of preventative and long term cancer care into the future.

ii. cost,

There are few MBS funded tests relevant to screening and diagnosis (genetic or imaging) for rare and less common cancers, and there is no reimbursement for comprehensive cancer genomic profiling. If

[6] https://www.unimelb.edu.au/newsroom/news/2023/july/the-university-of-melbourne-and-peter-mac-to-establish-precision-cancer-care-centre

individuals diagnosed with rare and less common cancers are put into a position where they have to pay the full cost for genomic profiling of their tumour to inform suitability for clinical trial participation or even to select standard therapies, this puts in place a foundation of inequity from the beginning of the cancer journey. When patients are matched to the right drug, in a timely manner, the outcomes can be significantly improved[7] and this drives people and their families to pay, if they are able. The inequity experienced by those who cannot afford tests or treatment is a situation that should not exist in Australia.

One thousand clinically indicated proactive screening tests (covering cancer, cardiovascular disease (CVD), metabolic disease and other conditions) have been ordered through one provider in Australia, with 98% of those tests ordered including screening for medically actionable cancer gene variants. Although the test is wholly funded by the patient, proactive screening may be a positive step for families who would otherwise experience ineligibility for MBS reimbursed tests (due to complicated and restrictive inclusion criteria or clinical guidelines), delayed testing through other clinical pathways, or that MBS ordered tests cover too narrow panels of genes to have utility. The level of public interest in DNA Screen, and relatively low uptake of this proactive screening test, indicate that cost remains a contributor to access. Making screening tests more available is warranted given that proactive panel tests have high utility – with up to 1 in 6 people screened having a medically actionable variant identified[8].

Another financially relevant issue is that individuals who have genetic or genomic testing in Australia currently have no permanent protection against insurers using their genetic information to discriminate against them. This may mean that insurers could refuse or increase premiums for life insurance and some other insurance products. For some, this serves as a strong deterrent from having screening or predictive testing and the legislation needs to change, since the industry self-regulated moratorium currently in place does not provide confidence in appropriate protection[9].

[7] Fountzilas E, Tsimberidou AM, Vo HH, Kurzrock R. Clinical trial design in the era of precision medicine. Genome Med. 2022 Aug 31;14(1):101. doi: 10.1186/s13073-022-01102-1.
[8] Haverfield, E.V., Esplin, E.D., Aguilar, S.J. et al. Physician-directed genetic screening to evaluate personal risk for medically actionable disorders: a large multi-center cohort study. *BMC Med* **19**, 199 (2021). https://doi.org/10.1186/s12916-021-01999-2
[9] Tiller, J., Bakshi, A., Dowling, G. et al. Community concerns about genetic discrimination in life insurance persist in Australia: A survey of consumers offered genetic testing. *Eur J Hum Genet* (2023). https://doi.org/10.1038/s41431-023-01373-1

iii. cultural and language barriers,

Cultural and language barriers are significant issues affecting access of our Australian population to health care, hindering certain communities from receiving the standard of care they should expect. Migrant and other underserved communities may have issues navigating, and be wary of, both the health system and research/clinical trial opportunities. The fears of these communities may be broad ranging, and include fear of unaffordable out-of-pocket costs, questioning of residency status, stigmatisation, and discrimination. It is important to understand the concerns of such communities so that barriers can be addressed.

Aboriginal and Torres Strait Islander people still experience unacceptable levels of racism and discrimination in many of our public health services and hospitals. The AIHW recently published data from the Australian Reconciliation Barometer which showed the proportion of Indigenous Australians reporting racial discrimination by doctors, nurses and/or medical staff has increased since 2014 (11% in 2014 to 20% in 2022)[10]. These and other barriers such as: insufficient regional and remote cancer screening and treatment services, insufficient Indigenous clinicians and specialist health staff, existing health co-morbidities, and insufficient culturally appropriate resources, further widen existing health equity gaps. Creating culturally safe service pathways are needed to ensure Aboriginal and Torres Strait Islander people engage in and with, emerging best-practice models of diagnoses and care so that they have the opportunities, health benefits and improved outcomes currently afforded to most other Australians. We suggest there is a need for development of an Indigenous Governance Framework and continued evolution of guidelines for implementing the optimal care of Aboriginal and Torres Strait Islander people with cancer, to include rare and less common cancers[11].

There are many ways to address cultural and language barriers, including awareness raising and education delivered in culturally appropriate ways; the translation of education and consent materials into different languages; engaging community, cultural and religious groups and their leaders in communication, and the use of translators and community liaisons in health care settings.

[10] Cultural safety in health care for Indigenous Australians: monitoring framework, Summary - Australian Institute of Health and Welfare. https://www.aihw.gov.au/reports/indigenous-australians/cultural-safety-health-care-framework/contents/summary

[11] Australian Government Cancer Australia. A guide to implementing the optimal care pathway for Aboriginal and Torres Strait Islander People with cancer. https://www.canceraustralia.gov.au/sites/default/files/publications/optimal-care-pathway-aboriginal-and-torres-strait-islander-people-cancer-guide/pdf/optimal_care_pathway_for_aboriginal_and_torres_strait_islander_people_with_cancer_the_guide.pdf

These factors need to be made a priority for funding, and must include specific consideration for the needs of Indigenous Australians.

Genomic research projects are making progress in these areas. A flagship project of the Centre for Population Genomics (collaboration between the Garvan Institute of Medical Research (NSW) and Murdoch Children's Research Institute (VIC), OurDNA, aims to increase inclusion of diverse Australian communities in DNA databases to increase the ability to accurately diagnose genetic conditions. This work has been built on strong foundations of engagement with community stakeholders to develop culturally aligned approaches. The National Centre for Indigenous Genomics is developing critically important genetics and genomics resources for Aboriginal and Torres Strait Islander communities in collaboration with community controlled health organisations, to support choices about genomic health and genomic research participation. The Mackenzie's Mission study also used inclusive information and consent pathways, such as providing translator services at in person appointments, as well as language translations of written information and consent materials. These are all examples of the significant efforts the genomic research community have made to improve inclusion and reduce barriers to participation. Community participation and equity need to remain priorities for major research funders, including government, the National Health and Medical Research Council (NHMRC) and Medical Research Future Fund (MRFF).

iv. type of cancer, and

Rare and less common cancers can be difficult to diagnose because the symptoms can be shared with other less serious conditions, may seem unusual, or appear in people that aren't expected to get cancer (including children). They may go through several rounds of tests before being diagnosed. For these reasons, diagnosis may occur later than for other cancers, with significant impact on a patient's chances of survival.

When it comes to any cancer diagnosis, faster diagnosis needs to be a priority to guide treatment. Across Australian Genomics' 6 cancer flagship cohorts, 48% of 2768 participants had clinically actionable findings from their cancer genomic test (range 6%-100% depending on cancer type and approach)[12]. This figure was 100% for Acute Lymphoblastic Leukaemia (a rare cancer), which used

[12] Stark Z, Boughtwood T, Haas M, et al. Australian Genomics: Outcomes of a 5-year national program to accelerate the integration of genomics in healthcare. Am J Hum Genet. 2023 Mar 2;110(3):419-426. doi: 10.1016/j.ajhg.2023.01.018. PMID: 36868206; PMCID: PMC10027474.

mRNA sequencing to identify genetic abnormalities along with a broad range of other diagnostic tests to inform clinical decision making.

There is a lack of publicly available genetic tests for rare and less common cancers. However, where genetic tests are available, they should be considered a first line test – it has been shown in other rare disease contexts that this saves valuable time[13], reduces health care costs and improves outcomes. Such genetic tests should also be offered as comprehensive panel tests involving multiple genes which are tested concurrently rather than as separate tests on single genes, which again saves valuable time.

The National Health Service (NHS) England is significantly scaling up its precision oncology and cancer screening by making all people with a diagnosis of an advanced cancer eligible for genetic profiling of their cancer. This is a significant advancement as about 40% of cancers diagnosed will be eligible, amounting to genomic profiling of cancer samples from around 400 newly diagnosed patients per day. This has been made possible through automated end to end solutions which address bottlenecks in the DNA sequencing and analysis steps[14]. The program is launching now, and Australia should actively seek learnings from this NHS service.

At the same time, we need less invasive tests for cancers to improve patient experience, and sampling procedures that better meet the requirements of genome sequencing (in addition to histopathology) and re-sampling over time. For example, advancements in the use and reliability of circulating tumour DNA (pieces of DNA from cancer and diseased cells that are found in the bloodstream) to diagnose and monitor cancer are increasing. This may aid in the efficiency of obtaining a tumour sample where the tumour is difficult to access, diagnosis of a cancer and also offer a mechanism for monitoring treatment. The Australian Genomics EBUS-TBNA lung cancer flagship evaluated a lung aspirate procedure for obtaining samples for whole exome and whole genome sequencing to identify targets that have treatments available. This was shown to be an effective method for determining the molecular signature compared with standard biopsy. This and more recent follow-on studies have been welcomed for lung cancer – a typically stigmatised and understudied form of cancer.

[13] Stark Z, Schofield D, Martyn M et al., Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. Genetics in Medicine. 2019 Volume 21, Issue 1, Pages 173-180. https://doi.org/10.1038/s41436-018-0006-8.
[14] https://blog.congenica.com/congenica-announces-ea-program-for-its-novel-precision-oncology-solution

v. availability of treating practitioners;

The availability of treating practitioners with familiarity and comfort with offering genetic research and clinical trial opportunities to their patients is essential. Currently, some research projects give patients access to molecular testing and comprehensive genomic profiling, with subsequent access to novel treatments. All organisations involved in the delivery of health services need to create a culture of research - making awareness of and access to genetic research and clinical trial delivery a priority for their sites. To do this, they must afford health care professionals the time to upskill in the delivery of research and clinical trials and to lead these activities at their sites. They must remove unnecessary governance barriers. A thriving research culture brings many benefits to organisations, the most important being increased treatment options, and culture of excellence, and ultimately, better outcomes for patients. The Australian Commission on Safety and Quality in Health Care Clinical Trials Governance Framework should be implemented by all eligible organisations.

Another factor may be that healthcare professionals managing patients are not aware of the availability of some testing options (particularly non-MBS reimbursed tests), and so achieving better workforce education may be a factor in making the range of proactive screening and diagnostic options more available to Australians.

b. barriers to accessing appropriate treatment;

The barrier preceding selection of appropriate precision treatment is getting a molecular test, because if a person with cancer can get a test, they have the chance to be matched to an existing or novel therapy. Often clinical trials are more effective than the therapies currently approved as standard care.

Research ethics and governance processes need to be more agile and receive timely approval so that Australia is an attractive clinical trial destination. The number of trials, Australian site participant allocations for international trials, and clinical trials efficiency all need to be improved – only 8% of people with cancer participate in trials in Australia[15]. In a recently published PROSPERO umbrella review of the benefits of participation in clinical trials the authors found that 18.7% of people favoured participation; 71.7% had no statistical difference; and 9.5% favoured non-participation. Further, in 27 of 48 cancer trials reviewed, they found that 55.1% reported statistically significant better outcomes for participants. Overall, statistically relevant benefits and no harmful effects with

[15] Unger J, Vaidya R, Hershman D et al. Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation, *JNCI: Journal of the National Cancer Institute*, Volume 111, Issue 3, March 2019, Pages 245–255, https://doi.org/10.1093/jnci/djy221

participating in randomised controlled trials was reported[16]. We also know that participants in clinical trials do better overall due to increased health and clinical monitoring, testing and access to ancillary services.

In Australia, there is no mandatory requirement to collect or report on the number of Aboriginal and Torres Strait Islander people who are screened, enrolled, complete or withdraw from a clinical trial. ANZCTR data for the period 2006-2020 showed that of the nearly 18,500 clinical trials registered in Australia, only 145 (<0.8%) were and focussed on Aboriginal and Torres Strait Islander people. This small number of clinical trials was more likely to cover the health areas of ear conditions, public health and infections. While important, they fail to address the many health conditions that contribute to the highest levels of health burden experienced by Indigenous Australians including CVD, mental health and cancer.

One reason promising treatments are not available as standard care is due to the difficulties associated with HTA processes for PBS listing. HTA processes for advanced health interventions such as genomics and advanced therapeutics are no longer suitable and HTA reforms will be essential to enable high-cost novel therapies to be trialled, implemented and evaluated. While there has been the perception among stakeholders that the current HTA Policy and Methods Review is focussed on PBAC and medicines availability, interrogation of both MSAC and PBAC is needed to fully understand and respond to the issues for genomic informed cancer care. This is because many somatic testing applications to MSAC are linked to a therapeutic application through PBAC in co-dependent submissions. Co-dependent applications are notoriously difficult to navigate, slowing access to potentially lifesaving, or life-prolonging treatment options.

MSAC and PBAC have rigid assessment frameworks that fail to consider secondary order effects of genomics (to family, carers), real world evidence (lived experience) and limit 'value' of an intervention to the well-worn but incomplete quality adjusted life years rubric. A report published by Rare Cancers Australia and Canteen Australia last year showed that for every $1.04B invested by government in cancer technologies, services and treatments over 5 years, the return in social value could be $3.17B[17]. The report called for the inclusion of assessment of social value in all HTA. This is something that we also support.

[16] Bouzalmate-Hajjaj A, Massó Guijarro P, Khan KS, Bueno-Cavanillas A, Cano-Ibáñez N. Benefits of Participation in Clinical Trials: An Umbrella Review. Int J Environ Res Public Health. 2022 Nov 21;19(22):15368. doi: 10.3390/ijerph192215368.

[17] https://rcararecancers.blob.core.windows.net/assets/contentpage_htmlcontent/RCA4279%20Counting%20the%20Cost%20Report-final.pdf

c. the adequacy of support services after diagnosis;

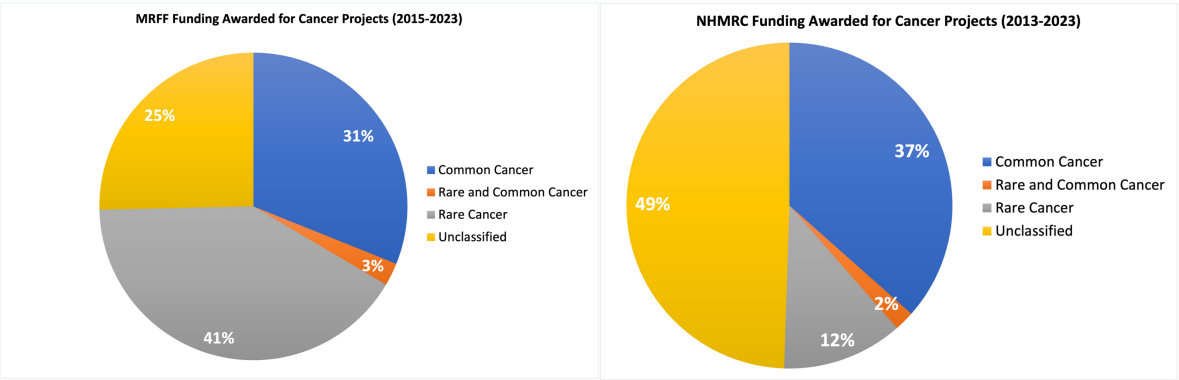
There are organisations in Australia that play an immeasurable role in supporting people and their families who are experiencing rare and less common cancers. Organisations include (but are not limited to):

- Rare Cancers Australia
- Pancare Foundation
- NeuroEndocrine Cancer Australia
- Peter MacCallum Cancer Centre
- Leukaemia Foundation
- Cancer Council

Ongoing support and funding to these organisations is critical.

d. the adequacy of Commonwealth funding for research into rare, less common and neuroendocrine cancer; and

Due to lower incidence rates, rare and less common cancers have traditionally attracted less funding than research into more common diseases, including cancers. In the preparation of this submission, we reviewed MRFF and NHMRC investments in cancer research. The analysis found that for the MRFF approximately $159M (41%) has been invested in rare and less common cancer research, compared with $120M (31%) on common cancer ($98M in cancer funding was unable to be categorised based on available information). The NHMRC investment in rare cancer was $201M (12%), while investment in common cancer was $614M (37%) ($831M unclassified based on available information). Whether these investments are justified given that rare and less common cancers account for 42% deaths from cancer is a question that should be considered in the design of priorities for the next five years of MRFF. With reviews of all MRFF Missions underway, it will be important to maintain investment in rare and less common cancers while inequity in outcomes for people with these cancers remains.



MRFF and NHMRC investments in cancer research*

*(*categorisation of projects was based on publicly available summary information and best efforts to label cancers as 'rare' or 'common')*

Recently, Lu and colleagues[18] outlined a model of population-based genomic profiling to find the right participants for clinical trials, which ultimately makes it more feasible to include participants with rare cancers in clinical trials. There have historically been fewer trials for rare cancers since it is hard to conduct trails on low numbers of patients, but new models like that described could be transformational. This is the model adopted by Precision Oncology Screening Platform Enabling Clinical Trials (PrOSPeCT) which has attracted $185M in investment through a public-private partnership. PrOSPeCT will involve recruitment of 23,000 Australians including from rural, regional and remote areas.

There has also been $50M to fund the Australian Genomic Cancer Medicine Program and a $67M funding boost to the Zero Childhood Cancer program to expand its program nationally, with the aim of providing genetic testing to all children diagnosed with cancer in Australia. These investments will need to be appropriately leveraged and the processes and learnings from them made transferrable and sustainable beyond the current funding period. Where these activities are occurring in the research domain the importance of rapidly shepherding evidence and outcomes into mainstream practice - as evidenced in the United Kingdom – is important. Private-public partnership models will be important for scalability and funding that support pan-cancer genomic profiling approaches should be explored for further expansion by existing and new funding schemes.

In an upcoming report Rare Cancers Australia will propose that to improve equity across cancer care including the way we look at research funding, cancer categories like "common", "rare" and "less

[18] Lu, C.Y., Terry, V. & Thomas, D.M. Precision medicine: affording the successes of science. *npj Precis. Onc.* **7**, 3 (2023). https://doi.org/10.1038/s41698-022-00343-y

common" should be deemphasised. This is because we now know more about molecular signatures of cancers and that those that were traditionally considered common have rare subtypes. If we continue the way we have been, as more people are diagnosed with rare cancer subtypes they will experience the inequity that those with rare and less common cancers traditionally have. If we instead consider each cancer as defined by its molecular signature there will be more rare and less common cancers. The expected value of this frameshift will be in the opening up of funding and clinical trial opportunities for cancer patients who have traditionally fallen into these under resourced categories and as a result have had less treatment options.

e. any other related matters.

Recommendations:

- Ensure cancer screening, diagnostic and treatment services are resourced to identify rare and uncommon cancers early and manage them effectively; reaching the whole Australian population no matter where they live, their background or socioeconomic position;
- Further support and resource comprehensive cancer centres and consortia to extend their services to regional, rural and remote areas nationally;
- In partnership with Aboriginal and Torres Strait Islander people, create holistic cancer awareness programs that identify barriers to early detection of rare and uncommon cancers;
- Resource and develop culturally safe screening, diagnosis and treatment pathways that increase support and access for Aboriginal and Torres Strait Islander peoples;
- Increase clinical trials' access to Aboriginal and Torres Strait Islander peoples, and mandate reporting of all Indigenous participants screened, enrolled, completed or withdraw from research/clinical trials registered in Australia;
- Develop an Indigenous Governance Framework and continued evolution of guidelines for implementing the optimal care of Aboriginal and Torres Strait Islander people with cancer, to include rare and less common cancers;
- Ensure all people diagnosed with cancer have access to comprehensive and cost-effective genomic profiling as standard of care;
- Implement the recommendations of the 'New Frontier: better health for all Australians' report that relate to standardise research ethics and governance for increased access to clinical trials; and
- Ensure all people can access clinical trials and precision oncology therapies.