rare cancers AUSTRALIA

RARE SOLUTIONS

A TIME TO ACT

FOREWORD

"I'm not going to do this anymore, Richard" was how the last conversation I ever had with a patient started last year. We'll call him 'John'. John had just made the decision to stop treatment, not because it wasn't working (it was too early to say) but because of the $9,000 per month cost. John explained that he wasn't prepared to risk leaving his wife both widowed AND impoverished. He had decided to stop treatment to make sure he left his wife in a safe place.

Then there was 'Peter' who decided he would try his treatment but only after asking his children if they were OK with him spending some of their inheritance to try and treat his cancer.

The stories are endless and they keep coming every day. As I write this foreword, we have just spoken to the son of a patient who has responded exceptionally to a drug. But after spending $110,000 the funds are running out – what does he do now?

So, I ask myself, how has it come to this? We are a wealthy, compassionate community and yet every day Australians are struggling to access available treatments that will save or extend their lives.

It's not because we don't care – I've spoken to our politicians, our public servants, our clinicians and our local pharmaceutical industry leaders. All, without exception, demonstrate enormous compassion and sympathy for our rare cancer community and they all work extremely hard trying to make things happen, but clearly, something more is needed.

We need to recognise that our current system and frameworks make life very hard for a lot of rare cancer patients and that we can only fix that if we change the way we do things. Change is always hard, but nowhere near as hard as dying prematurely because of lack of access to treatment.

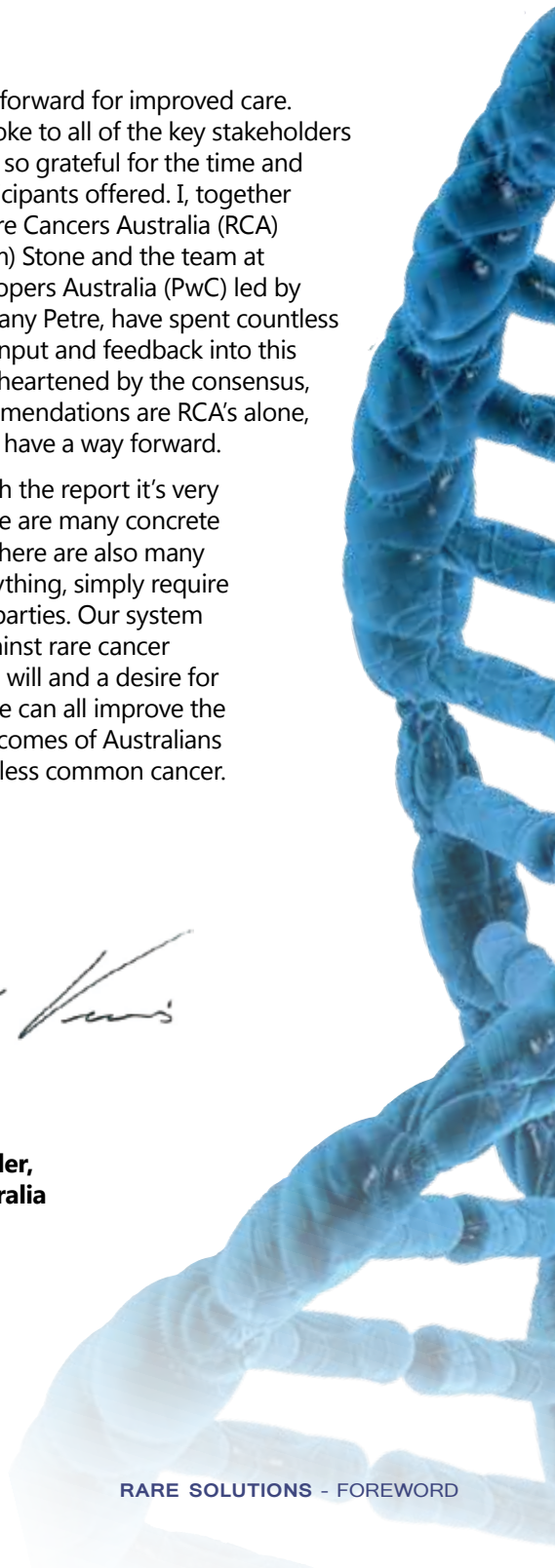
This report is a way forward for improved care. To compile it we spoke to all of the key stakeholders and I am personally so grateful for the time and thought all the participants offered. I, together with the team at Rare Cancers Australia (RCA) led by Victoria (Plum) Stone and the team at PricewaterhouseCoopers Australia (PwC) led by Marty Jovic and Tiffany Petre, have spent countless hours distilling the input and feedback into this report. I have been heartened by the consensus, although the recommendations are RCA's alone, and I am certain we have a way forward.

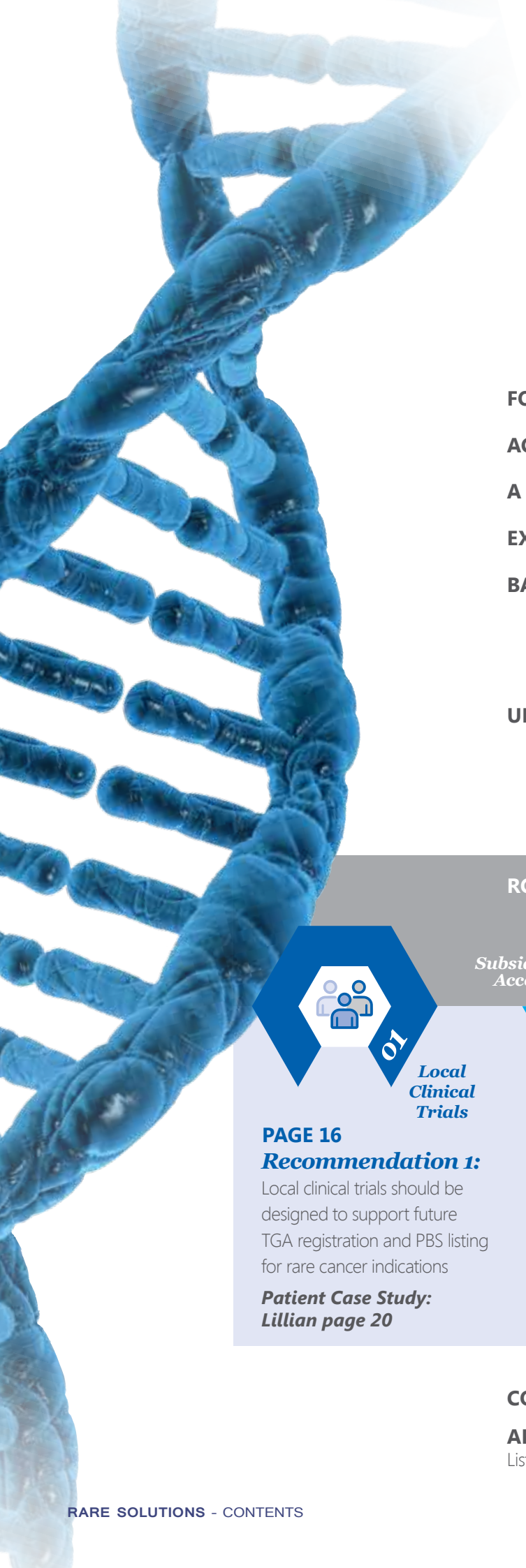
When I read through the report it's very clear that while there are many concrete recommendations there are also many that, as much as anything, simply require the good will of all parties. Our system stacks the cards against rare cancer patients. With good will and a desire for affirmative action we can all improve the lives and health outcomes of Australians living with a rare or less common cancer.

It's time to act!

Richard Vines

CEO and Co-Founder,
Rare Cancers Australia





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ACKNOWLEDGEMENTS

This report has been prepared by Rare Cancers Australia (RCA) to address the challenges faced by Australian rare cancer patients on a day-to-day basis and to provide some workable solutions to improve their lives.

In developing this report, RCA has worked closely with PwC Australia who have assisted in engaging all stakeholders and drafting the report. We would particularly like to thank Marty Jovic, Tiffany Petre and Christina Cho, who've worked incredibly hard with RCA to engage with all stakeholders and develop the recommendations herein.

We would also like to thank the other members of the core team Professor David Thomas (Kinghorn Cancer Centre), Associate Professor Clare Scott (Walter and Eliza Hall Institute), and Professor Andrew Wilson (Pharmaceutical Benefits Advisory Committee) and John Cannings OAM, for his patient perspective.

We are also extremely grateful to the many other stakeholders who gave their time so willingly to help us in drafting this report, particularly Professor John Simes (NHMRC Clinical Trials Centre, University of Sydney), Professor John Zalcberg OAM (Australian Clinical Trials Network), Dominic Tilden and Suzi Cottrell (Thema), representatives from the Department of Health, Therapeutic Goods Administration and pharmaceutical industry, Ogilvy PR and of course all of our patients who have provided feedback.

We would also like to acknowledge and thank those who have provided financial and in kind support to RCA in the creation of this report. All support is gratefully received and has been given without pre-condition or editorial input.

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Finally we would like to thank Belynda Simpson for her brilliant work in designing and laying out this report.

About Rare Cancers Australia

Rare Cancers Australia Ltd (RCA) is a charity whose purpose is to improve awareness, support and treatment of Australians with rare and less common (RLC) cancers. Every year there are over 52,000 diagnoses of RLC cancers and around 25,000 deaths.

As distinct from common cancers (breast, prostate, bowel, lung and melanoma) there is very little patient support offered to RLC cancer patients. RCA works tirelessly to ensure that this cancer group will never be forgotten or ignored again.

A message from our ambassador

In February 2017 I was delighted to become an ambassador for Rare Cancers Australia (RCA), a charity which focuses on issues very close to my heart. Growing up in Port Arlington, before moving to Belmont, Geelong, I was like any other sporty teenage girl, I had lots of friends and looked forward to joining them every weekend for netball. But, from a very young age, a niggling pain in my knee forced me to give up the sport I loved, far too early. The doctors kept telling me it was growing pains and it would go away.

It wasn't until two years later, aged 15, that a scan revealed a lump in my right knee and I was diagnosed with synovial sarcoma, a rare and aggressive cancer that forms in soft tissue. My parents and I were asking the doctor questions he just did not have answers to, presumably as he had never seen anything like it (a common issue for those diagnosed with rare cancers). There was little the doctors could do: amputation was my only chance of survival.

After a pain-staking and lengthy three months of rehabilitation, I was eventually fitted with a prosthetic leg and had to learn to walk again. Faced with the thought of not being able to play netball, I looked for a new direction, and found it in running.

Despite the challenges of learning to run with a prosthetic leg, in August 2005 I tried out for, and was accepted as a member of, the Emerging Talent squad for the London Paralympics.

Spurred on by some early wins, and with the support of my family and friends, who have always been my greatest supporters, I was able to raise enough money to purchase a new purpose-built running leg. As a sprinter and long-jumper, I have since represented Australia at the Beijing and London Paralympics, winning two medals at the latter, and now have my sights set on Tokyo in 2020.

A lot has changed in my life since my initial diagnosis. I'm now a mum to a beautiful one-and-a-half-year-old, and have a great relationship with my partner, Ryan. What has not changed as much, however, are outcomes for rare cancer patients.

Since becoming an ambassador for RCA I have witnessed first-hand how my profile has helped to further raise awareness of rare cancers. It has also made me realise that despite the improvements we've seen in terms of awareness-raising, research and funding, much more needs to be done when it comes to ensuring equitable access to treatment and better supporting Australians living with rare cancers.

This new report, *Rare Solutions – A Time to Act*, is a timely way to further highlight the many issues facing Australians living with rare cancers, but to also table actionable recommendations that, if implemented, can make a real difference now, and in the years to come.

I very much hope that the many industry, governmental and advocacy stakeholders that were instrumental to the report's development, can now come together, and move quickly to ensure all Australians impacted by rare cancers can benefit without delay from the recommendations herein.

Kelly Cartwright OAM

Australian Paralympic Gold Medallist and Rare Cancer Survivor

EXECUTIVE SUMMARY

A patient diagnosed today with a rare or less common (RLC) cancer is almost twice as likely to die as a patient with a common cancer.[1] These 'rare' Australians, who collectively account for approximately one third of all cancers and half of all cancer deaths[2], simply don't receive the same level of support, or have access to the same treatment options, as those with more common cancers, and they pay for that inequity with their lives.

There are, for example, a number of innovative, targeted[3] treatments that are already available in this country for patients with common cancers that could, at the very least, be life-extending for RLC cancer patients. Unfortunately for most RLC cancer patients, however, they cannot access these medicines without being admitted to a clinical trial or finding the money to pay for it themselves.

The current models for drug discovery, development and access approvals are not designed in a way that delivers outcomes for patients with RLC cancers. The small patient population sizes for each RLC cancer indication mean fewer global clinical trials, less information about support for the disease, and insufficient data to support registration and reimbursement in Australia.

It should also be noted that industry designed global trials often aim primarily to produce evidence for U.S Food and Drug Administration (FDA) Registration and this does not necessarily result in outcomes sufficient to satisfy the evidentiary requirements of the Pharmaceutical Benefits Scheme (PBAC) for high cost medicines.

The challenges around RLC cancers are complex, and Australia is not the only country looking for solutions. However, the challenges and complexity cannot be a barrier to action. In addition, the number of RLC cancers will grow with advances in technology and our understanding of cancer. It is therefore of the utmost importance that we begin to think differently about how we diagnose and treat cancer patients, as they all effectively become rare, based on their molecular biomarkers.

This report has been developed to further raise awareness around the challenges that Australians with RLC cancers face and to recommend feasible actions to improve health outcomes for them. The recommendations are based on Rare Cancer Australia's experience in supporting patients, our advocacy over the last five years and consultations with various key stakeholders.

RLC patients are at the heart of everything that RCA does and they need to be included in the further development and implementation of solutions for the future.

RCA Recommendations

There are many potential ways to improve access to cancer treatment options for RLC cancer patients, some more radical and feasible than others. In writing this report RCA focussed on recommendations that would lead to improvements for people with RLC cancers today and in the near future. The following criteria were used to guide consultations with key stakeholders and the development of our recommendations in this report:

- The primary focus is to improve access to safe and effective treatment options for people with RLC cancers;
- Recommendations should first lead to immediate improvements but also provide guidance for the longer term perspective where relevant;
- Potential improvements should be relevant for most, if not all RLC cancer types, with priority to be given to super rare and rare indications at all times where such prioritisation is necessary and accelerates outcomes;
- Recommendations to address a broad range of challenges across the four major areas discussed in section 2 (R&D and clinical trials, linking information, market entry and affordable access);
- Recommendations should work within existing Australian legislative structures and priorities (such as the Australian Health Technology Assessment fundamentals) and so should be fiscally responsible and not require major legislative change; and
- Recommendations and actions should not focus on one stakeholder group taking all of the responsibility but should lead to a fair contribution and collaboration from all relevant stakeholders, including RLC cancer patients.

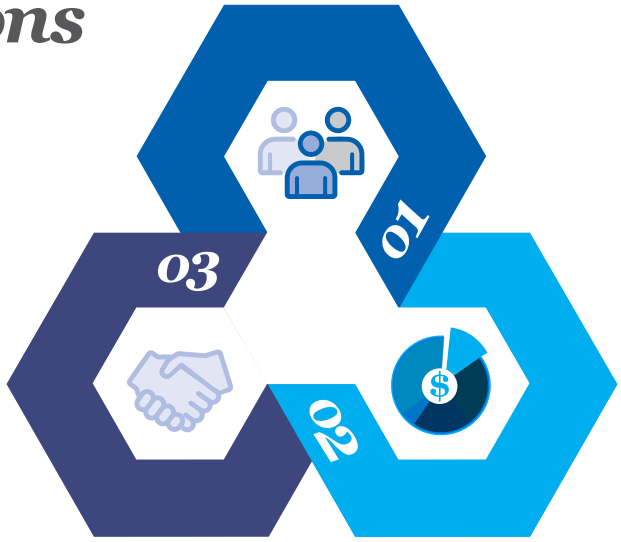
1. Rare Cancers Australia. (2016). *Just a Little More Time: Rare Cancers Update Report*. Retrieved from: http://bit.ly/JaLMT-2
2. Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW. Retrieved from: http://bit.ly/2uqk0TJ
3. For the purposes of this report 'targeted therapies' are considered to be both therapies for genetic mutations and immunotherapies.

Recommendations

01 ***Local Clinical Trials***
Test and confirm local clinical trial designs for future TGA registrations and PBS listings

02 ***Subsidised Access***
Use flexible approaches to gain subsidised access

03 ***Collaboration***
Improve structured collaboration that provides consistency and standards for all stakeholders



Based on the criteria opposite, RCA's experience over the last five years and consultations with key stakeholders, RCA now makes the following high level recommendations:

1. Local clinical trials should be designed to support future TGA registration and PBS listing for rare cancer indications

1.1 Evidence for future PBS listing to be considered as one of the key outcomes for investigator led clinical trial design

1.2 Local investigator led clinical trials to have more flexible inclusion criteria, without compromising patient safety

1.3 Additional funding to support local clinical trials for RLC cancers

1.4 Global clinical trials should be expanded to include more RLC cancer patients

2. Use flexible approaches within existing frameworks to gain access to subsidised medications for super rare cancers

2.1 Pharmaceutical companies to explore and capitalise on flexibility within existing frameworks (e.g. managed access or risk sharing) to proactively seek registration and reimbursement for rare indications

2.2 PBAC to consider provisional (conditional)[4] listing of medicines for rare cancer indications where appropriate

2.3 New targeted therapy submissions to the Therapeutic Goods Administration (TGA) and PBAC should include rare indications using a multi-indication submission

3. Improve structured collaboration to provide consistency and standards for all stakeholders

3.1 Australia to have an appropriate national framework that provides leadership, oversight and support to Australians living with a RLC cancer

3.2 Patients to have a consistent and equitable experience that also supports the development of further evidence for future patients

3.3 Australia to have a nationally consistent approach to collect outcomes data for all patients with RLC cancers

These recommendations require contributions from all stakeholders including clinicians, patients, researchers, government and the pharmaceutical industry to be successful and can make a difference immediately (in the next year) and over the next five years, if we work together.

To meet the above recommendations RCA has developed the following set of actions to help deliver immediate impact. Some of the recommended actions are focussed on immediate tasks and financial support to drive tangible changes in the next two years. Other actions are focussed on increasing collaboration and convening important stakeholders to further develop solutions with the aim of system wide changes to be in place in the next five years.

4. Medicines could be listed for a limited amount of time while additional data (e.g. patient outcomes) is collected to develop further evidence for a potential standard PBS listing

EXECUTIVE SUMMARY

The immediate recommended actions include:

- The Australian Government to invest more in local investigator led clinical trials for RLC cancers. This can be achieved through an equitable amount of national cancer research funding to be allocated to RLC cancers research, based on estimates of total burden of disease (e.g. approximately 1/3 of cancer diagnoses[5]). Currently $350 million is spent on total cancer research per annum[6], therefore it is recommended that at least $100 million be directed to RLC cancer research per annum to be more equitable. At least half of this, $50 million, could be allocated to RLC cancer research through the Medical Research Future Fund (MRFF), Cancer Australia, and the National Health and Medical Research Council (NHMRC) funding next year as a starting point.
- In the next year RCA will invite leading cancer researchers, the TGA, the PBAC and Medical Services Advisory Committee (MSAC), where appropriate, to convene, discuss and agree a way forward for innovative trials and the potential to have more flexible study inclusion criteria, using current studies to guide the conversation. After this, all investigator led trials that include RLC cancers should be designed in this way.
- Through Medicines Australia, pharmaceutical companies to explore and develop a point of view over the next year on expanding global clinical trials (with local sites) to include more RLC cancer patients, and the parameters and incentives to make it possible. If appropriate, a working group should be organised to support implementation.
- Pharmaceutical companies to use the TGA provisional registration process to list all relevant rare indications, that meet TGA criteria, starting with medicines that are not yet TGA registered as shown in the examples listed in Appendix A, within the next two years.
- PBAC and local pharmaceutical companies to use a provisional/conditional process for all future rare cancer submissions where additional effectiveness evidence is required to support potential PBS listing, starting with the medicines that are not yet listed in Appendix A.
- RCA to invite industry, the Department of Health, TGA, and the PBAC to help develop the principles and guidelines to prepare successful multi-indication submissions to enable successful use within a year (by August 2018).
- The Department of Health to engage internal (e.g. PBAC and the Australian Digital Health Agency) and external stakeholders (e.g. leading oncologists and patient organisations) to discuss and agree the approach and next steps to using My Health Record (MHR) as a tool to capture patient outcomes for provisional TGA and PBS approvals.
- The pharmaceutical industry and the Australian Government to provide funding to establish the national leadership and collaboration network in 2017-18 and support RCA to lead the actions for recommendations 1 and 2.
- RCA to convene key stakeholders, in late 2017, to discuss and agree the national leadership approach and priorities including the potential way forward with My Health Record (MHR). Discussions to ensure that all RLC cancer patients and their clinicians can utilise MHR (or an appropriate alternative)[7] in the future to build evidence, support research and provide information for a national registry.

In summary, these recommendations have the potential to make a real difference for people with RLC cancers in Australia, but action needs to be taken now. We are all accountable to the 52,000 RLC cancer patients who will be diagnosed this year,[8] and those already living with an RLC cancer, and their families, so it is on all of us to take the steps necessary to improve the research, treatment and support available to them.

5. Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW. Retrieved from: http://bit.ly/2uqk0TJ
6. Cancer Australia, 2015. Cancer Research in Australia: an overview of funding initiatives to support cancer research capacity in Australia 2006 to 2011. Retrieved from: http://bit.ly/2ti6nGB
7. The most logical and recommended approach is to use the My Health Record however in the event that access to MHR data cannot be guaranteed to appropriate rare cancer researchers, it is essential that an alternative, such as the REDCap rare cancer database be utilised.
8. Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no. 101. Cat. no. CAN 100. Canberra: AIHW. Retrieved from: http://bit.ly/2uqk0TJ

BACKGROUND

Purpose

In 2012 Rare Cancers Australia (RCA) was formed to improve awareness, support and treatment of Australians with rare and less common (RLC) cancers. Since then RCA has written a number of reports, including two *Just a Little More Time* reports, focusing on the state of research, diagnosis and treatments for RLC cancers in Australia.

This report has now been developed to further raise awareness around the challenges that Australians with RLC cancers face and to recommend feasible actions to improve health outcomes. These recommendations will ultimately lead to more 'rare' research being conducted with the evidence generated used to better inform decision making and generate increased access to affordable treatment options for people with RLC cancers in Australia.

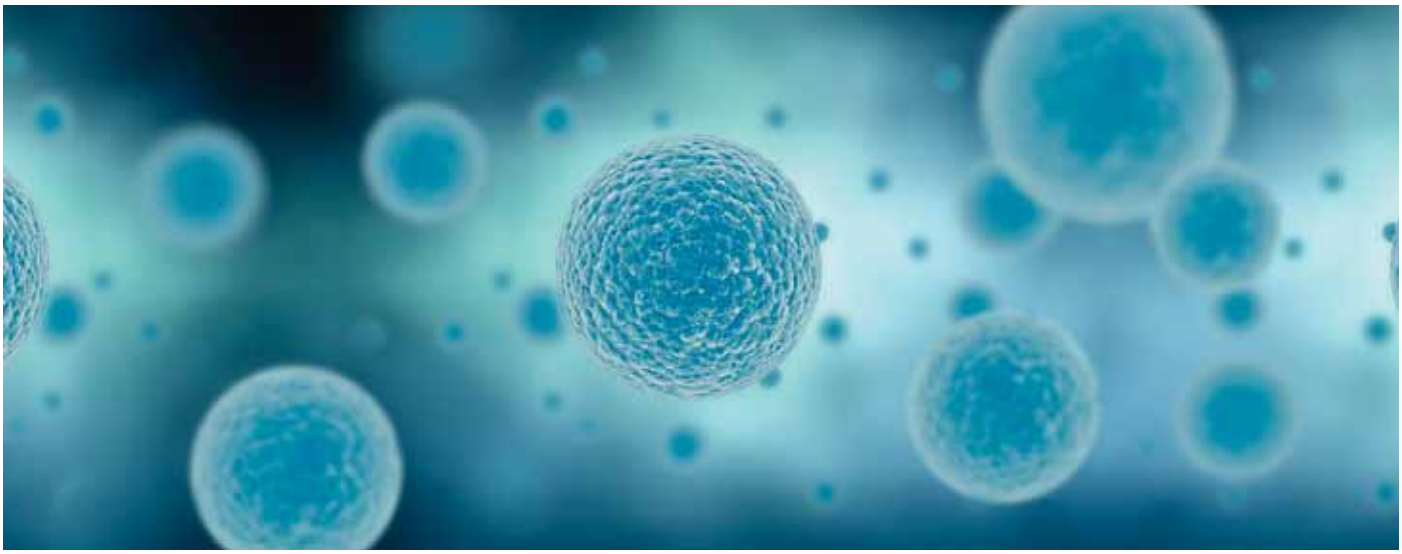
Patients with RLC cancers are disadvantaged compared to other cancer patients because they have limited access to new, effective treatments and clinical trials. The challenges around RLC cancers are complex and Australia is not the only country looking for solutions. However, the challenges and complexity cannot be a barrier to action. There are targeted therapies available in Australia right now that could help people with RLC cancers and there needs to be responsible approaches to improve affordable access to these. The recommendations in this report are meant to enhance collaboration and be a catalyst for action.

The recommendations are based on Rare Cancer Australia's experience in supporting patients, our advocacy over the last five years and consultations with various key stakeholders including:

- RLC cancer patients;
- Clinicians and researchers;
- Patient representatives;
- Independent health economists;
- The Australian Government Department of Health;
- The Pharmaceutical Benefits Advisory Committee (PBAC);
- The Therapeutic Goods Administration (TGA); and
- Pharmaceutical industry representatives.

It was encouraging that all of the above stakeholders were willing to discuss the challenges and potential solutions for RLC cancer patients in Australia. This is important as the recommendations in this report and future progress will require contributions from all stakeholders, including patients.

It should be noted that the recommendations in this report were developed by RCA and don't necessarily represent the views of all the various stakeholders consulted.



BACKGROUND

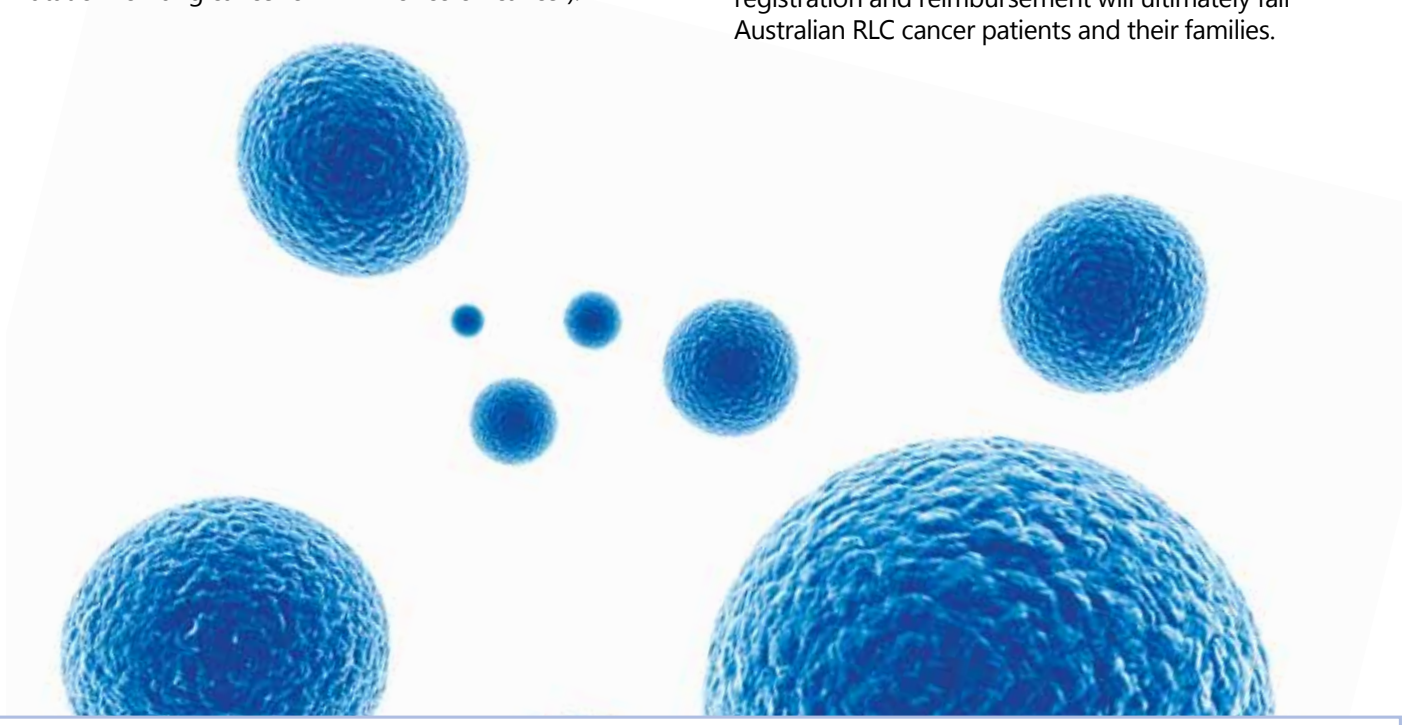
All cancers could become 'rare' at a genomic level

Advances in medical research have improved our understanding of the individuality of cancer, so that where once a cancer was defined by its anatomical location, or cellular behaviour, there is the potential for them to be categorised according to their molecular pathology.[9]

This means that while there remain many 'discrete' rare cancers, such as cancer of the mouth, oesophagus, larynx, and mesothelioma, we are now increasingly able to define more subsets of common cancers according to their genetic abnormalities through molecular diagnosis, and discover new biomarkers (e.g. EGFR mutation for lung cancer or HER2 for colon cancer).

With every advance in our understanding of the individuality of cancer we also see a growing number of cancers that we know to be rare or to have rare definable subgroups. There is the potential for researchers, and pharmaceutical companies, to target specific medicines to these genetic abnormalities and thereby increase the benefit of treatment to selected, individual patients.

It is therefore of the utmost importance that we begin to think differently about how we diagnose and treat cancer patients as they all become rarer; sticking with the status quo for conducting research, registration and reimbursement will ultimately fail Australian RLC cancer patients and their families.



Definition of rare cancers and the Australian context

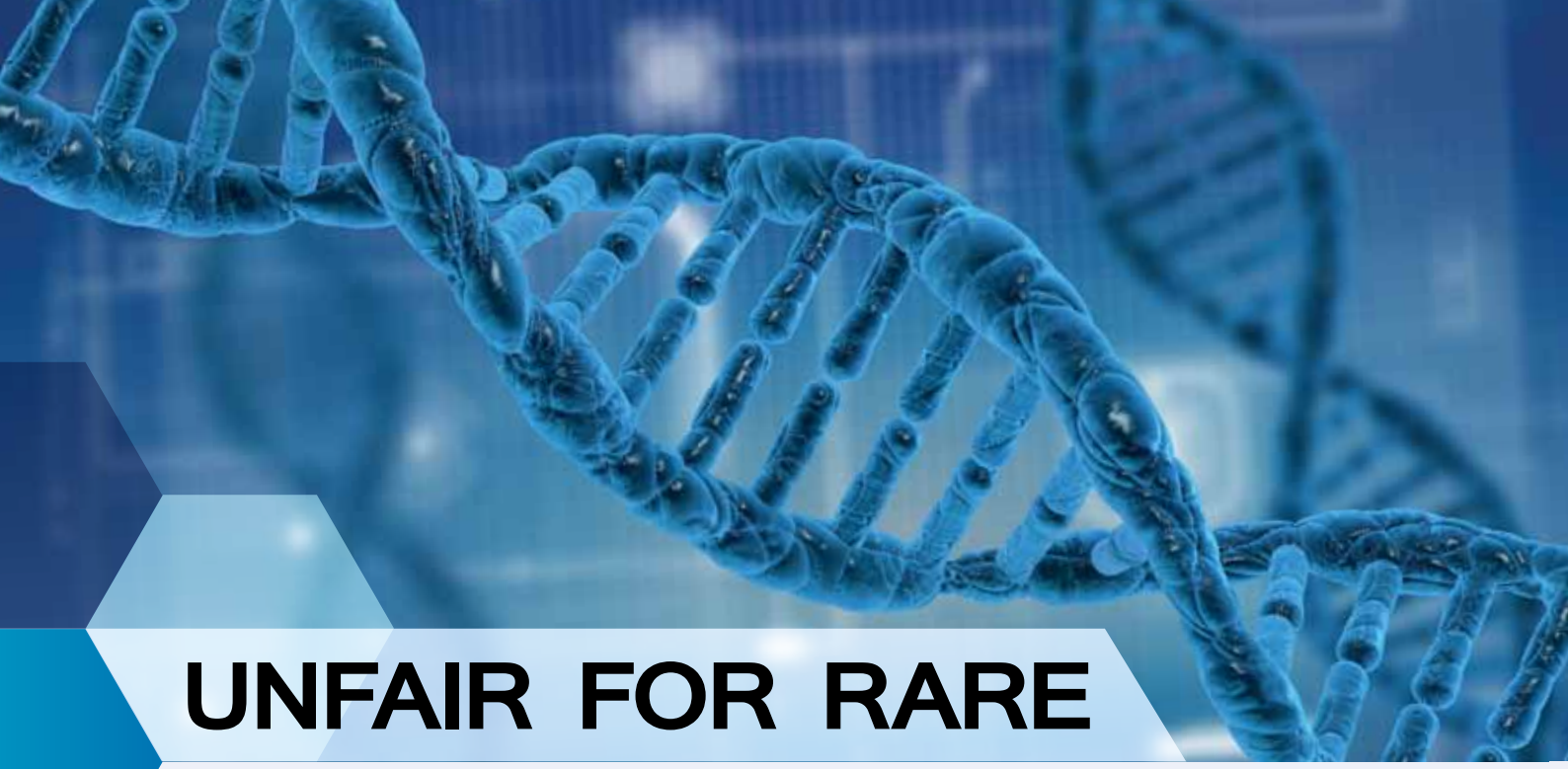
Since 2012, RCA have used the following definitions for rare and less common cancers, based on the RARECARE definition[10]:

- 'Less common' are defined as those cancers with an incidence of between 6 and 12 (inclusive) per 100,000 Australians per annum;
- 'Rare cancers' are defined as those with an incidence of less than 6 per 100,000 Australians per annum;

'Super rare cancers' are defined as those with an incidence of equal to, or less than, 2 per 100,000 Australians per annum, this equates to approximately less than 480 Australians per year. The recommendations in this report are meant to support all of the patients in each of the above categories. We envisage an immediate priority to be given to super rare and rare indications at all times where such prioritisation is necessary to accelerate outcomes.

9. Rare Cancers Australia. (2016). *Just a Little More Time: Rare Cancers Update Report*. Retrieved from: http://bit.ly/JaLMT-2

10. Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, et al. Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer. 2011;47:2493–511.



UNFAIR FOR RARE

In 2017, an estimated 52,000 people will be diagnosed with a rare or less common (RLC) cancer 25,000 will die from the cancer in Australia.[11] This accounts for half of all cancer deaths, and seven per cent of total disease burden in Australia.[12] Many of these people did not have access to treatment options simply because their cancers are rare.

While there have been considerable improvements in mortality rates for all cancers combined over the last twenty years, these improvements have not been seen in rare and super rare cancers.[13] In fact, a patient diagnosed today with a rare or less common cancer is almost twice as likely to die as a patient with a common cancer.

RLC cancers affect all ages and claim the lives of:

- One Australian child every four days;
- One Gen Y every day;
- 10 Gen Xs every day; and
- more Australians, aged 60-69, than any other cause of death.[14]

The current model for the discovery, development and reimbursement of treatments is not suitable for patients with RLC cancers. There are, for example, a number of innovative, targeted treatments that are already available for patients with common cancers that could, at the very least, be life-extending for RLC cancer patients. However, the small patient numbers often results in insufficient data to support registration and reimbursement for RLC cancer indications. Between 2010 and 2016, five medications were listed on the PBS for rare cancer indications, compared to 49 for all cancers.[15]

R&D and Clinical Trials	Difficulties associated with conducting research for rare cancers, including funding, small patient numbers, clinical trial design and more
Linking Information	Connecting patients, clinicians and researchers to improve treatment options
Market Entry (TGA)	TGA registration is necessary for eventual PBS listing
Affordable Access (PBS)	Improving affordability of treatments for people with rare cancers, mainly through PBS listings

11. Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no. 101. Cat. no. CAN 100. Canberra: AIHW. Retrieved from: http://bit.ly/2uqk0TJ
12. Rare Cancers Australia. (2017). Submission to Senate Inquiry for Funding Research into Cancers with Low Survival Rates. Retrieved from: http://bit.ly/RCASurvivalRates
13. Panageas, K. S. (2015). Clinical trial design for rare cancers - why a less conventional route may be required. Expert Review of Clinical Pharmacology, 8(6), 661–663. Retrieved from http://bit.ly/2tvN9YY
14. Rare Cancers Australia. (2016). Just a Little More Time: Rare Cancers Update Report. Retrieved from: http://bit.ly/JaLMT-2
15. Wonder Drug Consulting (2016). Analysis of PBAC submissions and outcomes for medicines for patients with cancer (2010-2016). Report prepared for Medicines Australia Oncology Industry Taskforce. Retrieved from: http://bit.ly/2us3YIh

The following section outlines in more detail some of the major reasons why there are limited treatment options for people with RLC cancers in Australia.

R&D and clinical trials

There is relatively limited investment in clinical trials for RLC cancers compared to the total burden of disease.[16] For example, results from the 2015 Audit of Cancer Research in Australia showed that only 2% of national government funding for all cancer research went to solid rare tumours between 2006 and 2011.[17]

The small populations of people with RLC cancers generally make it difficult to develop a profitable product considering the development costs and relatively small market size. In addition, the small patient population sizes make it difficult to conduct gold standard randomised clinical trials. There are not enough people to develop larger sized trials,[18] patients are often mis-diagnosed[19] and many of those that are diagnosed can be geographically isolated and unable to reach the more sophisticated infrastructure which is available in Australia to support these patients.

There are also ethical issues with having a 'control' treatment in clinical studies, as often there are no standard treatments identified for RLC cancer participants, meaning that the alternative treatment on the trial in question is not proven to be relevant for that RLC cancer patient.[20] Many trials have strict selection criteria excluding those who have had previous experimental treatment, meaning that rare cancer patients might only get one chance to have a treatment as, for many, no standard treatment recommendations exist.

It should also be noted that industry designed global trials often aim primarily to produce evidence for FDA registration and this does not necessarily result in outcomes sufficient to satisfy the evidentiary requirements of the PBAC for high cost medicines.

Linking information

Due to small patient populations and fewer studies and experts in RLC cancers, there is less information and support available for RLC cancer patients and their clinicians. It can be difficult to find the most knowledgeable local expert to help a patient with a rare cancer to best manage their illness and find appropriate treatment options (if available).

Time poor doctors, who may never have seen a specific rare cancer, may rely soley on old treatments which they are already familiar with and which are PBS listed. As such, the most appropriate treatments, often only available through clinical trials, compassionate access schemes or personal funding, may not be accessed by doctors for their patients. Additionally, the national clinical trial databases are not easily navigated and many patients must therefore rely on outside expertise, if available, to help them find potential trials.

As a result patients can feel isolated, experience delays in treatment or miss critical opportunities to save or extend their lives.

16. Rare Cancers Australia. Funding for Treatment of Rare Cancers in Australia. Retrieved from: http://bit.ly/RCATreatmentFunding
17. Cancer Australia. (2015). Cancer Research in Australia: an overview of funding initiatives to support cancer research capacity in Australia 2006 to 2011. Retrieved from: http://bit.ly/2ti6nGB
18. Rare Cancers Australia. (2015). Submission Access to Cancer medicines Senate Inquiry. Retrieved from: http://bit.ly/MedicineAccess
19. The McKell Institute. (2014). Funding Rare Disease Therapies in Australia. Retrieved from: http://bit.ly/2utTcBt
20. Rare Cancers Australia. Funding for Treatment of Rare Cancers in Australia. Retrieved from: http://bit.ly/RCATreatmentFunding

UNFAIR FOR RARE

Market entry (TGA)

The inherent lack of clinical trial data creates a barrier to registration for companies and, where data does exist, delays in registration from the TGA often occur. There are no TGA application fees for orphan designated drugs, however companies have to invest a significant amount of resource to prepare large applications for RLC cancers. They may be unwilling to do this if a subsequent PBS listing is unlikely due to paucity or quality of data, or if the patient population sizes are very small.

The TGA is in the process of finalising the expedited pathways for perscription medicines, including Provisional Approval (limited time provisional registration of promising new medicines that do not meet full clinical requirements) and Priority Review (reduced review timeframe to a target of 150 working days under certain circumstances).[21] The TGA developments are promising, however registrations for rare cancers are still reliant on pharmaceutical companies' willingness to invest in registration.

Without TGA registration, a medicine cannot be listed on the PBS. Medicines are TGA registered and PBS listed based on specific cancer indications (specific medical condition). This means that a new registration and PBS listing is needed for each indication where a cancer medication could be relevant. By law, medicines can be prescribed for a second indication by a doctor, once a drug has been approved for a first indication (off-label use), but this results in extreme inequity of care, as only a small number of wealthy patients could afford the huge monthly costs of new medicines (many thousands of dollars).

Affordable access (PBS)

PBS listing of medicines for RLC cancers provides subsidised and affordable access to otherwise very costly medicines for Australians. By law[22], new medications need to be assessed for effectiveness and costs compared to existing therapies to ensure medicines listed on the PBS represent value for money. With the limited clinical trial information available it is difficult to prove cost effectiveness under the standard assessment guidelines.

Pharmaceutical companies may be deterred from seeking PBS listing due to the limited evidence, high potential for rejection and the resources needed to prepare a submission for a relatively small economic return. In addition, sometimes the studies for patients with RLC cancers have been conducted by other groups such that the company doesn't have access to the data, or data of sufficient quality, to make a formal application to the TGA/PBAC.

21. Skerritt, J. (2017). What's trending in medicines regulation? TGA. Retrieved from: http://bit.ly/2uqlhtU

22. Australian Government. The National Health Act 1953. Retrieved from: http://bit.ly/2uu6LRs

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Faculty of Medicine, Nursing and Health Sciences, Monash University

Consultant Medical Oncologist, Peter MacCallum Cancer Centre

Clinical Trial Resourcing

The mission of the Australian Clinical Trials Alliance (ACTA) is to promote effective and cost-effective healthcare in Australia through investigator-initiated clinical trials and clinical quality registries that generate evidence to support decisions made by health practitioners, policy-makers, and consumers.

Rare cancer patients generally have lower survival rates because of the limited research conducted and resulting fewer treatment options. The low patient population sizes in rare and less common cancers presents a considerable challenge to cancer research and clinical studies to support these patients will by nature be more complex. The cancer research community (nationally and internationally), regulators and funders need to invest and collaborate to overcome the challenges and complexity.

The gold standard for clinical research on the effectiveness of a new drug is the randomised clinical trial. However, the only way to conduct such clinical trials for most rare and less common cancer types is through national and international collaborations. The infrastructure and support for these collaborative trials is lacking. And, it is extremely difficult to achieve sufficient funding in the current NHMRC funding environment.

Another major limiting factor in Australia is the lack of a central database (cancer registry) to document the number of rare cancers in Australia and the related molecular phenotype, to help build evidence for researchers to improve diagnosis and treatment.

Additional funding is needed to support novel clinical trial designs and a national, consistent approach to collect cancer diagnoses, treatment and outcomes information for patients with rare and less common cancers (indeed all cancers). In addition, Australian participation in international randomised clinical trials will be of great benefit and these studies have proved difficult to fund using existing mechanisms. Most importantly, understanding that patients with rare and less common cancers have poor survival because of inadequate research funding makes it all the more important to modify the system in order to accommodate the fruits of this research when advances are identified.

RCA RECOMMENDATIONS

There are many potential ways to improve access to cancer treatment options for RLC cancer patients, some more radical and feasible than others. In writing this report RCA focused on recommendations that would lead to improvements for people with RLC cancers today and in the near future.

The following criteria were used to guide consultations with key stakeholders and the development of our recommendations in this report.

- The primary focus is to improve access to safe and effective treatment options for people with RLC cancers;
- Recommendations should first lead to immediate improvements but also provide guidance for the longer term perspective where relevant;
- Potential improvements should be relevant for most, if not all RLC cancer types, with priority to be given to super rare and rare indications at all times where such prioritisation is necessary and accelerates outcomes;
- Recommendations to address a broad range of challenges across the four major areas discussed on page 11 (R&D and clinical trials, linking information, market entry and affordable access);
- Recommendations should work within existing Australian legislative structures and priorities (such as the Australian Health Technology Assessment fundamentals) and so should be fiscally responsible and not require major legislative change; and
- Recommendations and actions should not focus on one stakeholder group taking all of the responsibility but should lead to a fair contribution and collaboration from all relevant stakeholders, including RLC cancer patients.

Based on the above criteria, RCA's experience over the last five years and after consultation with key stakeholders, RCA now makes the following recommendations:

1. Local clinical trials should be designed to support future TGA registration and PBS listing for RLC cancer indications;
2. Use flexible approaches within existing frameworks (e.g. managed access or risk sharing) to gain access to subsidised medications for super rare cancers in particular; and
3. Improve structured collaboration to provide consistency and standards for all stakeholders.

Further detail on each recommendation is provided in the following sections.

Recommendation 01

Local clinical trials should be designed to support future TGA registration and PBS listing for rare cancer indications

Local clinical trials are valuable and benefit people with RLC cancers in two ways. First, the trials provide access to treatment, although experimental, to people who may have no, or very limited, options for access. Second, the trials also add to the evidence base on effective treatments for people with RLC cancers in an Australian context. When there is considerable evidence that a treatment is effective for certain RLC cancers, then the next step after clinical trials would be TGA registration and PBS listing to allow equitable access for people in Australia.

The PBAC guidelines provide detailed instructions on what evidence is required to recommend PBS listing of a new medication, however it is more difficult to meet these criteria with the data limitations for RLC cancers (see page 12). An additional challenge is that global pharmaceutical trials aren't necessarily designed to meet the criteria for the PBAC health technology assessment in Australia (which is different from other countries). For example, many global trials would be designed to meet the United States Food and Drug Administration (FDA) standards that don't require the cost effectiveness analysis that the PBAC does.

There are examples of where the PBAC has taken the limitations for rare cancers into consideration and allowed for more flexible assessments, for example with the 2017 listing of Vorinostat for cutaneous T-cell lymphoma (see box page 22).

Despite the challenges with RLC cancers it is important to develop the best evidence reasonably possible (which will vary on a case by case basis) and it should therefore be the aim for all new research, relevant to RLC cancers, to support eventual quality and fit for purpose TGA applications and PBAC submissions.

1. Evidence for future PBS listing to be considered as one of the key outcomes for investigator led clinical trial design

Local investigator led clinical trials should be designed to ensure that data collected is also suitable for use in TGA and PBAC applications should there be positive effectiveness outcomes for the rare indication.

To support this, researchers, potentially led by the Australian Cancer Clinical Trials Groups (funded by Cancer Australia), should consult with the TGA, PBAC and MSAC (where appropriate) and patients to discuss future clinical trial designs, limitations, resulting evidence and considerations for potential future registration or listing. After multiple consultations there may be consistent themes or advice that emerge and could be used to develop principles or a framework for future trial designs. After agreed guidance is in place, it should be mandatory for all future RLC cancer related trials to show consideration of these to obtain public funding.

Testing innovative clinical trial designs with the relevant approval bodies would be valuable considering the rapid pace of innovation around cancer treatments. For example, the trend towards precision medicine, with the diagnosis and treatment of people based on their genetic feature (biomarker), could lead to new ways of categorising and approving treatments in Australia. Indeed, while this report was being written, the US FDA for the first time ever approved a cancer treatment for patients with a common biomarker, rather than the anatomical location of the cancer.[23]

In Australia there are already a variety of innovative approaches being developed such at the Cancer Molecular Screening and Therapeutics (MoST) Program which uses molecular screening to help identify targeted treatment options for patients with advanced cancer and unmet clinical need (focus on rare and neglected cancers). Results from these local trials will be valuable for future PBS listings.

2. Local investigator led clinical trials to have more flexible inclusion criteria, without compromising patient safety

Most clinical trials have strict inclusion criteria in order to create homogeneous population groups to better statistically assess the potential effectiveness of a treatment. However, this clinical research standard further limits the already low patient population sizes for RLC cancer trials. It also creates results that may not be generalisable in the real world and means that many patients are excluded from trials and access to innovative medicines (e.g. if a patient has had a previous cancer or tried other cancer treatments).

The inclusion criteria for local RLC cancer clinical trials should be more flexible to allow broader patient participation and PBAC should consider, and allow for,

23. U.S. Food & Drug Administration. (2017). *FDA approves first cancer treatment for any solid tumor with a specific genetic feature. Retrieved from: http://bit.ly/2qpQ9oh*

additional flexibility in assessing PBAC submissions to support this. For example, basket studies include patients with different RLC cancer types (who are potentially suitable for a specific drug), in one trial with the intention of tracking the outcome of each patient individually. A bundle of baskets, or an 'umbrella study', includes different drugs on various arms, enabling the design of the trial to adapt to the needs of the patient population, without having to stop and initiate many new, small trials. This requires sophisticated ethics and governance support, which is available today.

3. Additional funding to support local clinical trials for RLC cancers

Funding in local investigator led clinical trials is one way for Australia to invest in more equitable access to treatment options for patients with RLC cancers through immediate access to experimental medications and the development of clinical evidence for the future. The Medical Research Future Fund (MRFF) is a promising development and sufficient funds should be allocated from the MRFF to support RLC cancer clinical trials.

In addition, if local investigator led clinical trials are better designed to meet future PBAC requirements (see recommendation 1.1), then there should be an increased likelihood for future PBS listing which would benefit the pharmaceutical companies supplying relevant treatments to Australia. With a higher potential for PBS funding, there should be increased investment from pharmaceutical companies (funding and providing experimental treatments) for local investigator led clinical trials.

4. Global clinical trials should be expanded to include more rare cancer patients

Global pharmaceutical companies could include rare indications in all relevant standard local phase 2 and 3 targeted therapy trials. Associate Professor Clare Scott, from the Walter and Eliza Hall Institute of Medical Research (see page 19), has been working with international colleagues to gain support for the Treat Rare Collect data and Share (TRICEPS) approach where a cohort of rare cancer patients are added to local trials (about 10% of the trial patients). Data for these patients would be assessed separately from the common cancer indications and shared centrally across trials to better build evidence on scale.

In Australia, the Government could support these efforts through standard approaches such as tax deductions for the clinical trial costs for rare patients or extended intellectual property rights for rare indications.

Immediate Actions:

1 **The Australian Government to invest more in local investigator led clinical trials for RLC cancers. This can be achieved through an equitable amount of national cancer research funding to be allocated to RLC cancers research, based on estimates of total burden of disease (e.g. approximately 1/3 of cancer diagnoses[24]). Currently $350 million is spent on total cancer research per annum[25], therefore it is recommended that at least $100 million be directed to RLC cancer research per annum to be more equitable. At least half of this, $50 million, could be allocated to RLC cancer research through MRFF, Cancer Australia and NHMRC funding next year as a starting point.**

2 **In the next year Rare Cancers Australia will invite leading cancer researchers, the TGA, the PBAC and MSAC (where appropriate) to convene, discuss and agree a way forward for innovative trials and the potential to have more flexible study inclusion criteria, using current studies to guide the conversation. After this, all investigator led trials that include RLC cancers should be designed in this way.**

3 **Through Medicines Australia, pharmaceutical companies to explore and develop a methodology over the next year to allow expansion of global clinical trials (with local sites) to include more rare cancer patients, and the parameters and incentives to make it possible. If appropriate, a working group should be organised to support implementation.**

24. Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW. Retrieved from: http://bit.ly/2uqk0TJ

25. Cancer Australia, 2015. Cancer Research in Australia: an overview of funding initiatives to support cancer research capacity in Australia 2006 to 2011. Retrieved from: http://bit.ly/2ti6nGB

Professor John Simes

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Medical Oncologist, Royal Prince Alfred Hospital & Chris O'Brien Lifehouse

The Molecular Screening and Therapeutics (MoST) study as an innovative approach at the Garvan Institute and NHMRC Clinical Trials Centre

Professor David Thomas

NHMRC Principal Research Fellow

Director of The Kinghorn Cancer Centre and Head of the Cancer Division of the Garvan Institute in NSW

The Molecular Screening and Therapeutics (MoST) Study:

An innovative clinical trial for patients with rare cancers from the Garvan Institute and NHMRC Clinical Trials Centre

The MoST study is an innovative clinical trial that uses a flexible genomics-based screening platform to find clinically actionable variants as the basis for treatments for rare cancer patients. MoST personalises treatment based on an individual's unique genomic 'fingerprint'.

There is value in testing whether effective therapies for more common cancers may work in rare cancers based on:

- Universal access to genomic profiling regardless of cancer type
- Development of broadly applicable measures of clinical benefit, and
- A more efficient clinical trials design that provides access to a range of treatments.

The MoST clinical trial offers multiple treatment options, so that all participating patients in a MoST trial can benefit and is designed to increase treatment options now for patients with rare cancers, to accelerate and increase clinical research capacity, and ultimately to inform future models of precision medicine.

Within 12 months of opening for recruitment, MoST has already shown that genomic cancer profiling can identify treatable options for a significant portion of patients who previously had none.

The MoST has already undertaken genomic profiling on over 200 rare cancer patients from Perth to Auckland, and from Hobart to Darwin to try and identify new treatment options.

Associate Professor Clare Scott

Victorian Cancer Agency Clinical Research Fellow and Laboratory Head, Stem Cells and Cancer division Walter and Eliza Hall Institute of Medical Research

Medical Oncologist, Peter MacCallum Cancer Centre, Royal Melbourne and Royal Women's Hospitals

Treat Rare, Collect Data and Share (TRICEPS) Study

Our current global system restricts access for many rare cancer patients to clinical trials of targeted therapies, leading to a paucity of data, lack of drug approvals, and inequity of access for rare cancer patients unless they can pay for their treatment

The TRICEPS approach provides threefold access to data from rare cancer patients, further leveraged by uploading of data into a central location internationally, to enable data analysis of each drug across rare cancer types; data would be available to academia or pharma in a transparent manner, for analysis, publication and submission to drug approval authorities.

1. **To bolt-on additional 10% cohorts of rare cancer patients to phase 2/3 pharma-led clinical trials** of targeted therapies which have already been approved for one indication, for rare cancer patients who have a tumour abnormality relevant for the experimental drug/combination pathway being tested; prior agreement by drug approval authorities that the bolt-on cohort would not impact analysis of the core trial will be essential (including toxicity, which may differ from the toxicity observed in the core trial patient population, e.g. melanoma patients)
2. **To collect data via the academic community of rare cancer patients receiving treatments,** including new targeted therapies, including via the BioGrid Australia REDCap Rare Cancer Database, which will be shared with international colleagues in order to generate identical datasets or other databases
3. **To encourage data collection by pharma** across their many trials of a particular drug for all rare cancer patients included in phase 1 trials (at an active dose); phase 2/3 trials and basket trials including investigator-initiated: currently these data are not being pooled; addition of data from academia may increase data for patients with a particular rare cancer type receiving a particular drug

Data would be shared via a central repository (e.g. the National Cancer Institute US Genomics Data Commons (NCI GDC) repository); if a good response is observed for particular rare cancer types, then phase 2 trials could be planned. "Bolt-on" and other data would be analysed in aggregate for a specific drug. Some of these data exist today, but are lost to analysis. Central deposition of data, with transparent access processes would transform the availability of data and underpin new drug approvals.

TRICEPS is designed to increase access for rare cancer patients to novel targeted therapies, underpin new drug indications for pharma and reduce emphasis on public and philanthropic funding of targeted therapeutic trials for rare cancers.

Next steps: engagement of the Australian government and drug approval bodies in the development of TRICEPS, alongside the US NCI GDC and the International Rare Cancer Initiative (IRCI – the peak international body for rare cancer trial design, with whom TRICEPS is being developed by Assoc Prof Scott, COSA member on IRCI board) will enable Australia to take a leading role in developing the proof of principle trials and data collection required, benefiting Australians with rare cancers as soon as possible.

LILLIAN

LUNG CANCER (ROS1 GENE MUTATION) AGE 36

Lillian Leigh, 36, from Sydney has lived with the rare, ROS1-mutated form of non-small cell lung cancer since her initial diagnosis in October 2014, two days after her 34th birthday. Lung cancer caused by mutation of the ROS1 gene affects just 1-2% of non-small cell lung cancer patients and often those diagnosed are young, non-smokers, just like Lillian.

Lillian is the proud mother of her beautiful daughter and the wife of a wonderful husband. She has a strong and extensive support group of kind and loving family and friends, and is a qualified social justice lawyer.

The signs and symptoms of Lillian's cancer diagnosis were easy to miss. She had a persistent cough for two months prior to her diagnosis, but had dismissed it as a post-viral cough. She also woke up one morning with a sore left shoulder and arm, but didn't think too much of it because the pain went away quickly. The left side of her neck was sore the same day and she felt a small unusual lump sitting just above her collarbone. Upon further investigation, initially through ultrasound, and then through biopsy, Lillian received the most shocking news: she was diagnosed with primary lung cancer.

Lillian's treatment experience is one that many Australians living with rare cancers face. The only available treatment for her was not available on the Pharmaceutical Benefits Scheme (PBS) for ROS1, and continues to be the case three years since Lillian's diagnosis. As is often seen, the same treatment has already been available for the more common cancer type (ALK-mutated lung cancer) for over two years.

This meant that Lillian was forced to pay around $7,500 for her monthly treatment course. She acknowledges that she is one of the lucky few who has been able to finance her treatment course with the generous support of family and friends, but knows that the majority of Australians living with rare cancers are not so unfortunate, and ultimately miss out on potentially life-saving treatments.

Lillian feels the inequity that exists by way of the fiscal restraints to access. She is also keen to highlight the knowledge shortfall that prevents those with rare cancers being informed of, and ultimately being able to access, treatments that could benefit them.

Lillian knows of others living with rare cancers that have since passed. Their inability to access treatments, through the PBS, that are available for more common cancers but have also shown to be of benefit for rare cancer types has cost them their lives. Through her own experience of living with a rare cancer, as well as the experiences of those she has met, Lillian wants to see change at a policy level, to ensure the rare cancer community is not left behind.

Whilst Lillian's condition is currently stable, at the back of her mind remains the concern about what to do as and when she requires a new treatment course, and the question of whether treatments available for more common cancers will also be available for people like her, with rare forms of the disease. At the forefront of her mind, though, is everything for which she is grateful. Lillian is determined not to sit by and let the disease define her whole life. As she puts it, she endeavours "to live everyday with love and thankfulness in [her] heart, whether with or without cancer."

Recommendation 02

Use flexible approaches within existing frameworks to gain access to subsidised medications for super rare cancers

Where there is reasonable evidence that a medicine would be effective for a certain rare cancer then it should be listed on the PBS to maximise access for people in Australia.

For a medication to be listed on the PBS, it needs to be TGA registered and approved by the PBAC. By law the PBAC must assess a medicine's clinical effectiveness, safety and cost-effectiveness ('value for money') compared with other treatments. The data limitations from even well-designed rare cancer clinical trials makes it difficult to conduct the same level of robust cost effectiveness analyses that would be needed for standard submissions.

Pharmaceutical companies and other sponsors should use the flexible approaches in place (or being developed) to increase PBS listings for super rare cancers and relevant government bodies should apply flexibility in assessing submissions for rare cancers considering the data limitations that exist for these small populations.

1. Pharmaceutical companies to explore and capitalise on flexibility within existing frameworks (e.g. managed access or risk sharing) to proactively seek registration and reimbursement for rare indications

There are medicines currently registered and listed in Australia for common cancers that could be relevant for rare cancer indications as well (See Appendix A). For example Anti-PD1 Immunotherapies listed for the common cancer indication of melanoma have numerous indications (current & near-future) that face potential access issues as a result of being a rare cancer – e.g. squamous cell carcinoma of the head and neck, hepatocellular carcinoma, glioblastoma, non-small cell lung cancer, small cell lung cancer, renal cell carcinoma, lymphoma and gastric, bladder, and oesophargeal cancers.

Without TGA registration, a medicine cannot be PBS listed and Australia relies on pharmaceutical companies to register these medicines with the TGA, a critical first step to PBS listing. Certain incentives are already in place to support TGA registrations of rare diseases. There are no registration fees for medicines with 'Orphan Status' and the assessment process is meant to be simpler for a second indication. However, sponsor companies still need to invest significant resources to prepare a high quality submission and, historically, some have not been willing to do so given the uncertainty around subsequent reimbursement with limited evidence for RLC cancers.

The TGA is currently developing the Provisional Approval registration process which has the potential to allow approval of RLC cancer indications where the limited data could be subsequently enhanced by further real-world evidence. For the Provisional Approval process to be possible, there will need to be an agreed approach on the collection of patient outcomes data for the post-market safety and efficacy assessments. These assessments could potentially be enabled by a patient's My Health Record, providing a secure online summary of patient's health records. In order to improve data collection, patients and their clinicians could be required to agree to, and support, the terms of measurement and sharing of data to gain access to the provisional treatment. The post market analysis for the TGA and PBAC will be complex (particularly for rare cancers) and so additional resources and capability may be needed to support this in government.

If MHR is to be used to collect this data it will be critical that de-identified and aggregated data is available for research and evaluation. If this is not possible, a separate data collection vehicle will be needed.

With the TGA process improvements underway, the registration processes should be made simpler and faster for medicines where the rare indication is already approved in other markets (e.g. FDA or EMA).

RCA's successful listing of Vorinostat is an example of the PBAC and the pharmaceutical company being flexible to support the listing. It is an example of a rare, successful submission from a non-profit organisation, however this should be an exception, and not the standard for rare cancer submissions. After TGA registration, pharmaceutical companies should use provisional approaches and multi-indication submissions to attain PBS listing for rare indications. In short, the success of Vorinostat shows what is possible when flexibility and determination are shown by clinicians, suppliers and Government.

Recommendation 02

RCA successfully lists Vorinostat on the PBS in 2017

Vorinostat was TGA approved in 2009 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease subsequent to prior systemic therapies. In the 2011 PBAC submission by MSD, Vorinostat was rejected for this rare indication due to 'unacceptably high and uncertain cost-effectiveness ratios.' The quality of data in the submission was noted by PBAC to be extremely limited with small study sizes with heterogeneous, non-comparative data.

In 2016, RCA worked with MSD to invest in additional analysis conducted by THEMA (a health economics consultancy firm) to support a high quality resubmission to PBAC for CTCL. Through PBAC flexibility in the assessment of the submission (e.g. allowing comparison to palliative care for the cost effectiveness analysis) and successful price negotiations, Vorinostat was PBS listed on 1 July 2017. This is an example of an unusual, and yet successful submission from a non-profit organisation and further proves that PBS listing is possible with flexibility from the PBAC and the pharmaceutical company, despite limitations in the clinical effectiveness data.

My Health Record

The My Health Record (MHR) is an online health record that stores a digital summary of patient's health information including treatments, diagnoses and details of interactions with the healthcare system. The MHR is an important part of the national health reform agenda and is meant to support an agile and sustainable system including more empowered patients.

For the MHR to be successful, currently patients' need to opt in to participate and health professionals need to take the time to upload important patient data. Complete digital patient health records can help patients to better understand their health condition and be more empowered as people can access a summary of their personal health information whenever they want. The

2. PBAC to consider provisional (conditional) listing of medicines for rare cancer indications where appropriate

A provisional PBS listing could be a solution in situations where there is a high level of uncertainty in a PBAC submission for a rare cancer indication and additional real world evidence will help to build the case for eventual PBS listing. This approach could build on current risk share arrangements or managed access schemes currently in use and being developed (with Medicines Australia).

As with the TGA provisional listing, patient outcomes and data would need to be measured in an agreed and consistent approach to support high quality data. This could potentially be enabled by patients' My Health Record as well. After an agreed timeframe (e.g. two years), the combined outcomes from the provisional listing would be assessed and there would be a decision to either list the medicine for the rare indication or remove the provisional listing if the medicine does not appear to be effective. Removing a provisional listing could be politically difficult, however it is not responsible or helpful for patients to have medicines listed that are not effective. Existing patients continuing to benefit on a delisted medicine would of course need to be protected.

Pricing of items listed on the PBS will be challenging. Our system relies on evidence based calculations and in many

MHR data could also be used as a tool to collect and analyse patient outcomes on a national scale. For rare cancer patients, the MHR could be the tool to provide a nationally consistent approach to collecting needed outcomes data (e.g. cancer progression) for provisional access to costly cancer treatments.

For this to be possible patients and their clinicians would need to participate and patients would need to approve access to their data for the government to assess. The recent decision by the Commonwealth Government to move the MHR system to opt-out for patients will ensure that all rare cancer patients will have a record by the end of 2018. It will therefore be important for clinicians to register and upload data to the MHR system to utilise the benefits of this piece of national infrastructure for rare cancer patients.

circumstances the available data will be quite small. Success will require both sponsors and Government acting in good faith and being reasonable about what is possible around evidence and prices, for the betterment of Australians living with a RLC cancer.

3. New targeted therapy submissions to the TGA and PBAC should include rare indications using a multi-indication submission

Where a new medicine is coming to Australia and there is evidence of potential impact in rare indications, there should be the potential to include the rare indications in submissions to the TGA and PBAC more consistently, to create multi-indication submissions.

This has the potential to reduce resource investments for the sponsors and government bodies through fewer submissions in total and speed up access for people with RLC cancers.

Guiding principles need to be established to support successful development of multi-indication submissions. For example, one principle could be that the rare indications should be included in original submissions and not introduced during the negotiation process.

Immediate Actions:

1 **Pharmaceutical companies to use the TGA provisional registration process to list all relevant rare indications, that meet TGA criteria, starting with medicines that are not yet TGA registered as shown in the examples listed in Appendix A, within the next two years.**

2 **PBAC and local pharmaceutical companies to use a provisional/ conditional process for all future rare cancer submissions where additional effectiveness evidence is required to support potential PBS listing, starting with the medicines that are not yet listed in Appendix A.**

3 **RCA to invite industry, the Department of Health, TGA, and PBAC to help develop the principles and guidelines to prepare successful multi-indication submissions to enable successful use within a year (by August 2018).**

4 **The Department of Health to engage internal (e.g. PBAC and the Australian Digital Health Agency) and external stakeholders (e.g. leading oncologists and patient organisations) to discuss and agree the approach and next steps to using My Health Record as a tool to capture patient outcomes for provisional TGA and PBS approvals.**

JONATHAN

METASTATIC MERKEL CELL CARCINOMA (ROS1)
STAGE IV
AGE 77

Professor Jonathan Pincus, 77, from Glenelg, South Australia has lived with a rare form of skin cancer, known as metastatic Merkel cell carcinoma, since finding a small lump under his chin, buried deep beneath his trademark beard, in January 2014.

When people think about skin cancer, Professor Pincus notes, their minds typically jump to the big three: basal cell carcinoma, squamous cell carcinoma, and melanoma. His very rare and aggressive form of skin cancer falls outside of these categories. In 2017, close to 14,000 Australians will be diagnosed with melanoma compared to just 300 who will be diagnosed with Merkel cell carcinoma.

Jonathan has three children, and is a grandfather to ten. He and his wife Priscilla have lived in Adelaide since the mid 1980s, apart from a year working overseas.

The signs and symptoms of Merkel cell carcinoma – as with many types of rare cancer – are easily missed; the condition often appears as a single, painless lump. After Jonathan discovered the lump under his chin, it "set off a wave" of doctors' visits, surgeries and what seemed to be endless sessions of radiation. Given the stage of Jonathan's cancer at his primary diagnosis, it was then "a waiting game," as it was highly likely that another lump would be discovered.

Suffice to say, another lump was found under his right armpit, almost a year to the day after he found his first, and others soon followed. With surgery offering limited options for him, and having refused chemotherapy, Jonathan took his fate into his 'own hands.'

A lifelong academic, Jonathan took it upon himself to research new and emerging treatment options for metastatic Merkel cell carcinoma, knowing there were few, if any, options left for him to consider. He was greatly helped by his niece, a medical scientist, who introduced him to one of Australia's leading immunotherapy researchers in Melbourne; and he is grateful to his local oncologist for arranging and supervising his treatment.

Thus far, Jonathan has had 21 treatments, which have cost him over $85,000. His only financial assistance came from the manufacturer, who provided Jonathan three of his first infusions for free, and will supply his future infusions at a heavily discounted price. Jonathan appreciates that he is fortunate to be in a position to be able to afford the therapy – knowing many in similar positions are less fortunate, and ultimately miss out on potentially life-saving treatments.

If he had been diagnosed with the more common skin cancer - melanoma - his treatment outlook would be different, and would be funded through the Pharmaceutical Benefits Scheme (PBS).

Since starting on immunotherapy in October 2015, Jonathan has enjoyed eighteen months in remission, which has allowed him to continue travelling, work part time, and enjoy time with his family.

An economist by trade, Jonathan is keen to see policy change from the Government and greater leadership from the pharmaceutical industry, so that Australians living with rare cancers get more affordable access to emerging treatments. While he acknowledges that this is no easy feat, he is optimistic about what can be achieved from the recommendations included in this report.

03

Collaboration

Recommendation 03

Improve structured collaboration to provide consistency and standards for all stakeholders

Australian RLC cancer patients have very different experiences depending on where they live, what cancer they may have, how their clinician refers them to further specialists and how empowered they are. Confusion and delays in the process can be extremely costly for people who may only have a few months to live; some patients are not able to find the right specialists or experimental treatment in time. The patient experience from symptoms, to diagnosis and treatment needs to be more consistent and equitable for patients with RLC cancers in Australia.

In addition, leaders and key stakeholders (particularly patients and patient organisations) in Australia need to better work together to define how we can improve the situation for people with RLC cancers. There needs to be an agreed national approach to collection, storage, care and analysis of patient outcomes information to add to the limited knowledge base around the effectiveness of RLC cancer treatments and to collaborate internationally.

1. Australia to have an appropriate national framework that provides leadership, oversight and support to Australians living with a RLC cancer

A national leadership network that includes representation from various stakeholders such as leading oncologists and researchers, patient organisations, the Government and representatives from the pharmaceutical industry, is needed to:

- Define national standards and practice for the management, and coordination, of care for people with RLC cancers (e.g. best approach to refer to specialists or clinical trials) to help them better navigate the system;
- Nominate and agree national clinical experts to manage RLC cancer cases;
- Centrally review RLC cancer cases as needed and rapidly ensure feedback of expert advice to the patient and their treating doctors;
- Train the workforce by building appropriate clinical teams in each state, with central coordination, essential for such rare cases;
- Agree principles for collecting and sharing information nationally and internationally;[26]
- Identify gaps and solutions in the patient experience for advocacy; and
- Support implementation of recommendations in this report.

Enhanced collaboration, leadership and consistency will support recommendations 1 and 2 in this report. Rare Cancers Australia and collaborators have started to develop some of the needed leadership for RLC cancer patients in Australia, however additional collaborative relationships, funding and support will be needed to meet the scale and impact required.

26. The most logical and recommended approach is to use the My Health Record however in the event that access to MHR data cannot be guaranteed it is essential that an alternative, such as the REDCap Rare Cancer Database be utilised

03

Collaboration

Recommendation 03

2. Patients to have a consistent and equitable experience that also supports the development of further evidence for future patients

When patients are diagnosed with a RLC cancer they should have either direct access or access through their treating physician to national clinical experts that can help patients and their treating clinicians navigate the system. These clinical experts should be experts in supporting RLC cancer patients in the system, including referrals to other leading local and international specialists for RLC cancers. They should access, understand and refer to relevant clinical trials and, where none are available, the experts should help patients identify and navigate other options.[27]

3. Australia to have a nationally consistent approach to collect outcomes data for all patients with RLC cancers

Currently, outcomes are not tracked for RLC cancer patients accessing experimental treatments in Australia (e.g. compassionate access schemes or self-funded patients). Collecting diagnostic and health outcomes data for all RLC cancer patients in Australia in a consistent way would add to national and international evidence and improve the potential for treatment opportunities for RLC cancer patients in the future.

The My Health Record could be used as a tool for relevant government bodies to track patient outcomes for provisional access to treatments once a Secondary Use Framework is in place. It will also be critical for the resulting My Health Record data to be used for research purposes and the eventual development of a national registry. This will require further consideration such as, patient approvals for third parties to access the data; discussions to support this should be initiated immediately. If it is not possible to use the My Health Record data, then patient outcomes should be recorded in purpose build solutions such as the BioGrid Australia REDCap Rare Cancer Database being developed by the Walter and Eliza Hall Institute of Medical Research.

In addition, anonymised data could be shared with international collaborators, in a secure way, to start to develop the scale needed for more complex analyses. There is the potential for Australia to become an international leader in developing real world outcomes data and solutions for RLC cancer patients. For this to be possible, patients and their clinicians need to participate in the My Health Record and agree to share data for the broader benefit of the community. The decision by the Commonwealth Government to move the My Health Record to an opt-out system will ensure that nearly all patients have a record, so clinicians will need to decide to register and send data to the My Health Record system if they are not already doing so.

Immediate Actions:

1 **The pharmaceutical industry and Australian Government to provide funding to establish the national leadership and collaboration network in 2017-18 and support RCA to lead the actions for recommendations 1 and 2.**

2 **RCA to convene key stakeholders, in late 2017, to discuss and agree the national leadership approach and priorities including the potential way forward with the My Health Record. Discussions to ensure that all RLC cancer patients and their clinicians can utilise the My Health Record (or an appropriate alternative) [28] in the future to build evidence, support research and provide information for a national registry.**

27. Such as compassionate access schemes, the Life Saving Drugs Program, the TGA Special Access Scheme and the Rule of Rescue

28. The most logical and recommended approach is to use the My Health Record however in the event that access to MHR data cannot be guaranteed to appropriate rare cancer researchers, it is essential that an alternative, such as the REDCap Rare Cancer Database be utilised.

WAYNE

HIGH-GRADE MAXILLARY ADENOCARCINOMA

AGE 58

What started as a lingering toothache with no clear cause in mid-2014 set Wayne Higgs, now 58, from Perth, on a journey that he could never have envisaged. A father to two daughters, and a grandfather to two grandsons, Wayne had recently returned from walking the Kokoda Track in Papua New Guinea when it was discovered, after many misdiagnoses and an unnecessary root canal, that a growth in his right sinus was high-grade maxillary adenocarcinoma.

Only around 150 Australians are diagnosed with adenocarcinoma of the maxillary, aka the sinus, per year. Tellingly, none of the oncologists, surgeons or ear, nose and throat specialists that have dealt with Wayne have ever encountered another case of the condition.

Adenocarcinoma of the nasal cavity and sinuses is associated with specific risk factors, including exposure to wood dust, workplace chemicals, and other organic compounds. A furniture upholster by trade and former motor trimmer, Wayne's maxillary adenocarcinoma is likely to be related to his decades of exposure to chemicals at work.

Maxillary adenocarcinoma is often diagnosed in late-stages, as its symptoms – like nasal congestion and recurrent sinusitis – can be easily missed and mistaken for less serious conditions.

When Wayne finally received his diagnosis, he started on a gruelling round of invasive surgeries, radiation and chemotherapy. The first of five surgeries involved a 17-hour operation to remove the malignant tumour and reconstruction of the bone structure on the right-hand side of his face.

Given the stage of Wayne's cancer at diagnosis, it came as no surprise when he was diagnosed with another adenocarcinoma, this time above his right eye, six months after his first surgery. He then underwent a further four operations, which, drastically, involved the removal of his eye, followed by radiotherapy. His third tumor, found in late 2015, was deemed inoperable and it was then that Wayne was unfortunately given a terminal prognosis.

Unlike many other types of more common cancers, there are no emerging therapy options for maxillary adenocarcinoma, nor any clinical trials currently underway in Australia. Wayne feels grateful for the great lengths his medical team has gone to, to try to find options for him, but he now accepts that sadly for him, his options have run out.

What he is now focused on, and where he feels he can make a difference, is to raise awareness of the need for suitable protection against workplace hazards, and of the need for more to be done to better-support Australians living with rare cancers.

CONCLUSION

There has been significant progress in the last five years in raising awareness and supporting RLC cancer patients to navigate the system. However, RLC cancers continue to present a variety of complex issues to our research and regulatory systems, while at the same time killing Australians, young and old, every day. It is time for us all to act and do more about ensuring that RLC cancer patients have the same access to the best available treatments, as those with common cancers.

This report proposes a set of recommendations that can make a difference immediately (in the next year) and over next five years if we work together to get it right. These recommendations require contributions from different stakeholders including clinicians, patients, researchers, government and the pharmaceutical industry to be successful. The challenge is too complex for any one group to solve on their own.

Most importantly, the recommendations and actions here aim to:

- **Increase the number and scope of RLC cancer clinical trials;**
- **Improve data collection and consequent availability of evidence for use in registration and reimbursement decision-making;**
- **Facilitate national healthcare networks; and**
- **Ultimately reduce the inequity for RLC cancer patients in Australia.**

Some of the recommended actions are focussed on immediate tasks and financial support to drive tangible changes in the next two years. Other actions are focussed on increasing collaboration and convening important stakeholders to further develop solutions with the aim of system wide changes to be in place in the next five years. Also, we envisage an immediate priority to be given to super rare and rare indications at all times where such prioritisation is necessary to accelerate outcomes.

In summary, **over the next two years** there need to be more TGA registrations and PBS listings of medications for rare cancer indications, making use of provisional approaches and multi-indication submissions. The successful listing of Vorinostat this year, for patients with CTCL, is just one example of how a flexible approach can have a hugely positive impact for small patient populations. Appendix A shows a list of medications that are approved in other countries and could impact thousands of Australians. RCA calls for these treatments to be immediately considered for provisional TGA registration and PBS listing for the relevant rare indications.

RCA is also seeking for the My Health Record to be utilised to better empower and inform patients and support the evidence base around rare cancer treatments, using real world patient outcomes. Further, RLC cancer patients should be able to better navigate the system through an organised national network.

In the next five years there should be nationwide investigator led and pharmaceutical clinical trials for RLC cancers that will be designed in a way that develops evidence for further PBS listings. There should also be a robust rare care registry (leveraging the My Health Record) that is used for local and international research that leads to further solutions for RLC cancer patients.

The immediate recommended actions include:

- The Australian Government to invest more in local investigator led clinical trials for RLC cancers. This can be achieved through an equitable amount of national cancer research funding to be allocated to RLC cancers research, based on estimates of total burden of disease (e.g. approximately 1/3 of cancer diagnoses).[29] Currently $350 million is spent on total cancer research per annum[30], therefore it is recommended that at least $100 million be directed to RLC cancer research per annum to be more equitable. At least half of this, $50 million, could be allocated to RLC cancer research through MRFF, Cancers Australia and NHMRC funding next year as a starting point.
- In the next year RCA will invite leading cancer researchers, the TGA, the PBAC and MSAC (where appropriate) to convene, discuss and agree a way forward for innovative trials and the potential to have more flexible study inclusion criteria, using current studies to guide the conversation. After this, all investigator led trials that include RLC cancers should be designed in this way.
- Through Medicines Australia, pharmaceutical companies to explore and develop a point of view over the next year on expanding global clinical trials (with local sites) to include more RLC cancer patients, and the parameters and incentives to make it possible. If appropriate, a working group should be organised to support implementation.

- Pharmaceutical companies to use the TGA provisional registration process to list all relevant rare indications, that meet TGA criteria, starting with medicines that are not yet TGA registered as shown in the examples listed in Appendix A, within the next two years.
- PBAC and local pharmaceutical companies to use a provisional/conditional process for all future rare cancer submissions where additional effectiveness evidence is required to support potential PBS listing, starting with the medicines that are not yet listed in Appendix A.
- RCA to invite industry, the Department of Health, TGA, and the PBAC to help develop the principles and guidelines to prepare successful multi-indication submissions to enable successful use within a year (by August 2018).
- The Department of Health to engage internal (e.g. PBAC and the Australian Digital Health Agency) and external stakeholders (e.g. leading oncologists and patient organisations) to discuss and agree the approach and next steps to using My Health Record as a tool to capture patient outcomes for provisional TGA and PBS approvals.
- The pharmaceutical industry and the Australian Government to provide funding to establish the national leadership and collaboration network in 2017-18 and support RCA to lead the actions for recommendations 1 and 2.
- RCA to convene key stakeholders, in late 2017, to discuss and agree the national leadership approach and priorities including the potential way forward with the My Health Record. Discussions to ensure that all RLC cancer patients and their clinicians can utilise the My Health Record (or an appropriate alternative)[31] in the future to build evidence, support research and provide information for a national registry.

In summary, these recommendations and actions have the potential to make a real difference for people with RLC cancers in Australia over the next few years but we need to act now to make is possible. We are all accountable to the RLC cancer patients in this country and to support accountability, RCA will provide a public update on all of the recommendations in this report and progress in one year's time (August 2018).

29. Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101. Cat. no. CAN 100. Canberra: AIHW. Retrieved from: http://bit.ly/2uqk0TJ

30. Cancer Australia, 2015. Cancer Research in Australia: an overview of funding initiatives to support cancer research capacity in Australia 2006 to 2011. Retrieved from: http://bit.ly/2ti6nGB

31. The most logical and recommended approach is to use the My Health Record however in the event that access to MHR data cannot be guaranteed to appropriate rare cancer researchers, it is essential that an alternative, such as the REDCap rare cancer database be utilised.

APPENDIX A

The table below contains examples of medicines that have been given FDA or EMA approval, orphan status – for rare populations, which may or may not have TGA approval, but are not currently PBS listed. This list is by no means complete, or absolute, but is intended as a guide for discussions around what medicines could be made available to Australian patients in the near future.[32]

N.B. Not included in this table, because it does not have orphan designation, but of particular note is the May 2017 decision by the FDA to grant accelerated approval to pembrolizumab for patients whose cancers have a specific genetic feature (biomarker). This was the first time the FDA, or any such agency, has approved a cancer treatment based on a common biomarker rather than the anatomical location of the tumour, and marks a huge leap forwards in how medicines are approved globally. Pembrolizumab is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumours that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

Medicine	Disease	Patient population	Date of orphan drug designation	Date of FDA approval	Date of EC approval	TGA approval status	*Comment*
Avelumab	Merkel cell carcinoma	Advanced/metastatic	21/09/2015	23/03/2017		Not approved	*No alternatives available for patient population*
Belinostat	Non-Hodgkin's lymphoma	T-cell, peripheral, relapsed/ refractory	3/09/2009	3/07/2014		Not approved	*Possible alternatives available*
Bevacizumab	Ovarian cancer	Advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, relapsed/ refractory, platinum-sensitive, later-line, combination	9/02/2006	6/12/2016		Approved	*PBS listed for earlier use, but not this specific patient population*
		Advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, relapsed/ refractory, treatment resistant (platinum)	9/02/2006	14/11/2014		Approved	*PBS listed for earlier use, but not this specific patient population*
Blinatumomab	Acute lymphoblastic leukaemia	Children/adolescents, B-cell, relapsed/refractory	16/05/2008	30/08/2016		Not approved	*PBS listed for adults*
Bortezomib	Non-Hodgkin's lymphoma	Mantle cell	18/04/2011	8/10/2014		Approved	
Bosutinib monohydrate	Chronic myeloid leukaemia	Multiple patient populations based on phase of the disease and treatment history	24/02/2009	4/09/2012	27/03/2013	Approved	
Brentuximab vedotin	Hodgkin's lymphoma	CD30 positive, post-ASCT consolidation, high risk	15/01/2009		24/06/2016	Not approved	*PBS listed for several indications, but not this patient population*
Cabozantinib maleate	Thyroid cancer	Medullary carcinoma, advanced/metastatic, first-line	6/02/2009		21/03/2014	Not approved	
Carfilzomib	Multiple myeloma	Multiple treatment stages and usages	2008	2015	2015	Approved	*Understood to be seeking PBS listing*
Crizotinib	Non-small-cell lung cancer	ROS-1 positive	13/09/2010	11/03/2016		Not approved	
Daratumumab	Multiple myeloma	Multiple treatment stages and usages	2013	2015		Approved	*Very recent TGA approval for some patient populations*
Decitabine	Acute myeloid leukaemia	Adults (>65 years), newly diagnosed and secondary	8/06/2006		20/09/2012	Not approved	
Dinutuximab	Brain cancer	Children, neuroblastoma, combination	20/12/2010	10/03/2015	14/08/2015	Not approved	
Elotuzumab	Multiple myeloma	Later-line, combination	1/09/2011	30/11/2015	11/05/2016	Approved	
Everolimus	Neuroendocrine tumour	Advanced/metastatic, gastro-intestinal/lung origin, non-functional	14/02/2008	26/02/2016		Approved	*PBS listed for other NET, and other indications*
	Tuberous sclerosis complex	Renal angiomyolipoma	8/06/2009	26/04/2012		Approved	*PBS listed for other TSC*
Ibrutinib	Chronic lymphocytic leukaemia	Multiple gene mutations and treatment stages	2012	2014	2014	Approved	
	Non-Hodgkin's lymphoma	Mantle cell, relapsed/ refractory	3/12/2012	13/11/2013	21/10/2014	Approved	
		Small lymphocytic lymphoma, 17p deletion	30/05/2013	6/05/2016		Not approved	
		Small lymphocytic lymphoma, first-line	30/05/2013	6/05/2016		Approved	
	Waldenstrom's macroglobulinaemia	Multiple treatment stages and usages	2014		2015	Approved	

32. Data in this table is compiled from the MAESTrO database with the help of Wonder Drug Consulting, July 2017

Medicine	Disease	Patient population	Date of orphan drug designation	Date of FDA approval	Date of EC approval	TGA approval status	*Comment*
Idelalisib	Chronic lymphocytic leukaemia	Later-line, combination (rituximab)	15/10/2013	23/07/2014		Approved	*Safety concerns that may delay listing*
	Non-Hodgkin's lymphoma	Follicular, later-line	26/09/2013	23/07/2014		Approved	
		Small lymphocytic lymphoma, later-line	15/10/2013	23/07/2014		Approved	
Imatinib mesylate	Acute lymphoblastic leukaemia	Children, Philadelphia chromosome positive, first-line, combination	31/01/2001	25/01/2013		Approved	
Inotuzumab ozogamicin	Acute lymphoblastic leukaemia	CD22 positive, relapsed/ refractory, later-line, monotherapy	7/06/2013		29/06/2017	Not approved	*Very recent EMA approval for some patient populations*
Irinotecan hydrochloride trihydrate (liposomal)	Pancreatic cancer	Advanced/metastatic, later-line, combination	21/07/2011	22/10/2015	14/10/2016	Approved	
Ixazomib citrate	Multiple myeloma	Later-line, combination	18/02/2011	20/11/2015		Approved	
Lanreotide acetate	Pancreatic neuroendocrine tumour	Advanced/metastatic	25/08/2011	16/12/2014		Approved	
Lenalidomide	Multiple myeloma	Maintenance	20/09/2001	22/02/2017		Not approved	*Approved for patients ineligible for stem cell transplant*
		Newly diagnosed, combination	20/09/2001	17/02/2015		Not approved	*Approved for patients ineligible for stem cell transplant*
	Non-Hodgkin's lymphoma	Mantle cell, relapsed/ refractory	27/04/2009	5/06/2013		Approved	
Mechlorethamine hydrochloride	Non-Hodgkin's lymphoma	T-cell, cutaneous, mycosis fungoides-type	22/05/2012		3/03/2017	Not approved	
Midostaurin	Acute myeloid leukaemia	Newly diagnosed, FLT3 mutation positive, combination	7/07/2009	28/04/2017		Not approved	
Nivolumab	Hodgkin's lymphoma	Later-line	23/01/2013	17/05/2016		Approved	*PBS listed for several indications, but not this indication*
Obinutuzumab	Non-Hodgkin's lymphoma	Follicular, relapsed/ refractory, later-line, combination (bendamustine hydrochloride)	19/06/2015		13/06/2016	Approved	*PBS listed but not this patient population*
Ofatumumab acetate	Chronic lymphocytic leukaemia	CD20 positive, relapsed/ refractory, combination (fludarabine phosphate and cyclophosphamide)	10/03/2009	30/08/2016		Not approved	*PBS listed but not this patient population*
		CD20 positive, relapsed/ refractory, maintenance	10/03/2009	15/01/2016		Not approved	*PBS listed but not this patient population*
Olaratumab	Sarcoma	Advanced/metastatic, combination	9/10/2014	19/10/2016	9/11/2016	Not approved	*Accelerated FDA approval*
Omacetaxine mepesuccinate	Chronic myeloid leukaemia	Accelerated phase, treatment reisistant/intolerant, later-line	10/03/2006	26/10/2012		Not approved	*Accelerated FDA approval*
		Chronic phase, treatment reisistant/intolerant, later-line	10/03/2006	26/10/2012		Not approved	*Accelerated FDA approval*
Panobinostat lactate	Multiple myeloma	Third-line, combination	20/08/2012	23/02/2015	28/08/2015	Approved	
Pembrolizumab	Hodgkin's lymphoma	Relapsed/refractory, later-line	30/12/2015	14/03/2017		Not approved	*PBS listed for melanoma, TGA registered for several indications, but not this indication*
Ponatinib hydrochloride	Acute lymphoblastic leukaemia	Philadelphia chromosome positive, treatment resistant/ intolerant (tyrosine kinase inhibitors)	20/11/2009	14/12/2012	1/07/2013	Approved	*PBS listed but not this patient population*
Ramucirumab	Gastric cancer	Advanced/metastatic, later-line, combination	16/02/2012	5/11/2014	19/12/2014	Approved	
		Advanced/metastatic, later-line, monotherapy	16/02/2012	21/04/2014	19/12/2014	Approved	
Regorafenib monohydrate	Gastro-intestinal stromal tumour	Advanced/metastatic, later-line	12/01/2011	25/02/2013		Approved	
Ruxolitinib phosphate	Polycythemia vera	Later-line	26/03/2010	4/12/2014		Not approved	*PBS listed but not this indication*
Siltuximab	Castleman's disease	Multicentric disease	26/05/2006	22/04/2014	22/05/2014	Approved	
Sorafenib tosylate	Thyroid cancer	Papillary or follicular thyroid carcinoma, advanced/ metastatic	13/11/2013		23/05/2014	Approved	
Trabectedin	Sarcoma	Advanced/metastatic	30/09/2004	23/10/2015		Not approved	
Venetoclax	Chronic lymphocytic leukaemia	Multiple gene mutations and treatment stages	2012	2016	2016	Approved/Not Approved	

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