

# CANCER FORUM



**March 2015**

**Volume 39 Number 1**

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FORUM: Rare cancers

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Tom Reeve Award for Outstanding Contribution  
to Cancer Care

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Remembering Dr Nigel Gray AO and  
Professor Donald Metcalf

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# CANCER FORUM



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# CANCER FORUM

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## RARE CANCERS: HOW FAR HAVE WE COME AND WHERE SHOULD WE BE HEADING? EXTENDING EVIDENCE-BASED CARE TO PEOPLE WITH RARE CANCERS



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### Abstract

Approximately one third of Australians who die of cancer do so from one classified as being 'rare'. While there have been significant recent improvements seen for many patients with common cancer types, this has not been observed for the majority of patients with a rare cancer diagnosis. At the same time, the proportion of patients who are being diagnosed with a cancer that is classified as being rare is increasing, in part due to the realisation that even common cancers may in fact fall into the rare category once they are classified according to specific molecular changes. Strategies undertaken previously for some rare cancer types, for example pediatric and haematologic malignancies or sarcoma, serve as a guide for ways to improve the care of all rare cancer types. In this forum, Australian leaders in managing rare cancers provide an overview of what rare cancers are and some of the strategies for improving management of patients.

Around one fifth of Australians who are diagnosed with cancer and one third of Australians who die of cancer might reasonably have their disease classified as a rare cancer. A practical definition of 'rare' comes from the RARECARE group, being 'an incidence rate of <6 cases per 100,000 population per year'.<sup>1</sup> However, the average outcome for patients with a rare cancer is inferior to those with more common cancers when analysed separately within these data. For the 50% of cancer patients diagnosed with a common cancer type (breast, bowel, lung, melanoma and prostate), five-year relative survival rates improved between 1982-1987 and 2006-2010.<sup>2</sup> In contrast, there has been little change (5% or less) in five-year survival for people with other less common cancer types over the same period, for example, for cervical, laryngeal and pancreatic cancer.<sup>3,4</sup> Despite increases in five-year survival rates for liver, gall bladder and unknown primary cancers and stable rates for brain cancer and mesothelioma, five-year survival rates remained very low for these rare cancer types (~20% or less) between 2006-2010. Better outcomes were seen for testicular (91% to 98%) and thyroid (84% to 96%) cancer. Most other patients diagnosed with one of many types of rare cancers endure a long road to diagnosis, with little specific information or evidence-based care available, even after a diagnosis is finally made.

Nevertheless, three categories of rare malignancy - childhood cancers, haematologic malignancies and sarcoma - have been associated with notable improvements over the last three decades, and these serve as useful guides as to how we may improve the outcome for rare cancers in general.

### Childhood cancers

The care of children with cancer is based on decades of highly organised and centralised clinical research that has focused on optimising dose, scheduling and combinations of conventional chemotherapeutics and supportive care.<sup>5</sup> Through academic-led, non-commercial clinical trials, overall five-year survival rates of over 80% from the time of diagnosis have been achieved. This is despite the fact that drug development programs for childhood cancers are scarce due to both the rare nature of all childhood cancers and limited pharmaceutical industry investment in new drugs for them.

### Haematologic malignancies

Easy and safe access to malignant cells for analysis by flow cytometry has facilitated basic science research in haematologic malignancies, allowing a greater

understanding of their biology and hence how they may be treated. Despite accounting for only 10% of cancer burden and deaths, they have received one third of PBS cancer expenditure,<sup>4</sup> reflecting the successful implementation of effective treatments arising from research, both basic and clinical. Paradoxically, the rarity has facilitated scientific advance, by enabling focus on distinctive morphologic, cytogenetic and molecular characteristics to develop targeted therapies, as described by Chew and Roberts in this forum.<sup>6</sup> As a result, two rare leukaemias (acute promyelocytic leukemia and chronic myeloid leukemia), which have poor prognoses when treated with cytotoxic chemotherapy, are now considered to have very favourable prognoses with targeted therapies.

## Sarcoma

Bone and soft tissue sarcomas account for only ~1% of all adult solid malignant tumors, yet represent more than 70 distinct tumor subtypes. Obtaining the correct diagnoses of specific subtypes of sarcoma is becoming increasingly important in delivering tailored and optimal medical care, as outlined by Bae and Desai.<sup>7</sup> The management of one of these, gastrointestinal stromal tumor, has served as a prototypic model for the development of other molecularly-targeted therapies. Unexpectedly, the first clinical trial in this rare disease using imatinib, the tyrosine kinase inhibitor targeting the KIT and PDGF receptors, showed dramatic improvements in disease control and led to its accelerated approval within three years. Opportunities in Australian centres to lead or participate in sarcoma-focused trials have improved due to the establishment of local and international collaborative infrastructure, and may lead to improvements more broadly for sarcoma patients.

## Where should we be heading with rare cancers in Australia?

The strategies undertaken previously for the rare cancer types described above would appear to be a rational starting point if we wish to facilitate improvement in the care of all rare cancer types. Increased national coordination is required due to the rare nature of these diseases, as by definition it will be difficult to accumulate sufficient cases for statistically meaningful studies to be done without this. The aim of any such endeavours should be focused in several ways: i) to facilitate more accurate diagnosis, including molecular analysis, allowing focus on distinct rare cancer subsets; ii) participation in small, focused clinical trials and/or streamlining of management protocols with international collaboration; and iii) national and international data capture of patient management and outcomes.

In this issue of *Cancer Forum*, we have brought together expert reviews and opinions from leaders in

the management of and research into rare disease. Chan, Goldstein and Zalcborg provide an overview of Neuroendocrine Tumours (NETs),<sup>8</sup> which illustrates how an anatomically disparate group of tumours may be considered as one group defined by their biology (arising from a single cell type of origin). Grimison illustrates how improvements in disease classification have led to more reliable prognostic criteria, multi-disciplinary management, international collaboration and implementation of evidence-based guidelines resulting in dramatic improvements in the outcomes for those diagnosed with testicular cancer.<sup>9</sup> Harrison and Friedlander describe how evidence-based care developed through national and international cooperation can be brought to the clinic for patients with gynaecologic cancers, over half of which may be defined as being rare.<sup>10</sup>

More children and adults under the age of 40 die of brain cancer than of any other cancer type. The great challenge posed by glioblastoma multiforme is slowly being addressed by molecular characterisation, as described by Field and Rosenthal.<sup>11</sup> The clinically diverse group of tumours referred to as 'head and neck cancers', are being found to have distinctive molecular features, as described by Lim, Solomon and Rischin.<sup>12</sup> Despite their rarity, approaches integrating targeting of key molecular drivers into centralised care and protocols are impacting clinical practice. The discovery of rare molecular alterations in lung adenocarcinoma, as described by Hasovits and Pavlakis,<sup>13</sup> raises challenges in their identification and the selection of the most appropriate model for clinical trial design for testing potential new treatments.

## The potential of genomics technologies

The extraordinary potential of next generation sequencing (NGS) technology makes it possible for the rare cancer types described above to be divided into molecular 'subsets' for more accurate study. This may, paradoxically, reduce the ~200 rare cancer subtypes identified by RARECARE,<sup>1</sup> to a more manageable number of 'molecular' groupings, providing some context as to prognosis and treatment direction for those patients for whom we currently have little in the way of evidence-based guidance. Many common cancers types may also become 'rare' by molecular association, as has been described above for molecular subsets of melanoma and lung cancer.

NGS technology allows analysis of DNA sequence, RNA expression, as well as regulation by the epigenome, microRNAs and other phenomena and will transform the way we think of rare cancers. NGS platforms are under local development for clinical analysis of tumour tissue and also have the potential to provide analysis of a liquid biopsy from the peripheral blood of circulating tumour DNA,<sup>14</sup> and for less expensive analysis of tumour-derivatives (methylated DNA).<sup>15</sup> One

approach of using an NGS platform to identify potential therapeutic targets in high grade epithelial ovarian cancer is reviewed by Kondrashova and Waring.<sup>16</sup> Utilising these molecular approaches, diagnosis will no longer be pigeon-holed in an organ or histologic subtype, but better 'matched' to molecularly similar tumour types, with direct therapeutic relevance. Just as studying a rare cancer, such as BRCA1/2-associated high-grade serous ovarian cancer (HGSC) can have relevance for related yet BRCA1/2 WT HGSC,<sup>17</sup> matching rare cancers to common cancers may allow their management path to be deduced by association. Context specific tailoring will likely be required, as BRAF mutations require different therapeutic approaches in colorectal cancer compared with melanoma.

However, plausible hypotheses may provide treatment options for patients who have no 'standard of care'. An innovative approach, involving molecular analysis of cancer of unknown primary or CUP, is described by Guccione and Bowtell.<sup>18</sup> Indeed, many rare cancers could be seen as 'cancers of unknown molecular primary' (CUMP) and might be matched accordingly using NGS platforms.

In the near future, it may be more efficient to perform molecular analysis on each rare cancer at the time of first diagnosis, in order for the best molecular match to guide a management plan. Likely prognosis and the most appropriate management and treatment may be better estimated than from our current anatomical and histological characterisation. While at present, molecular analysis of rare cancers is not funded, it is logical to think that within a relatively short number of years, that will become the priority, as it will become less acceptable to treat people based on histology and imaging alone. True evidence-based guidelines for each rare cancer type will take longer, however, as information from molecular profiling, leading to hypothesis-generated choice of treatment, will need to occur within research studies. Even these data will not reach the stringent requirements for regulatory approvals and funding decisions, heralding ongoing challenges for some time to come.

Designing clinical trials for small numbers of patients is challenging. Approaches for studies limited by small patient numbers have been described, using Bayesian methods, optimising external controls, robust biomarker incorporation and adaptive designs e.g. 'basket trials'.<sup>19</sup> International endeavours will be essential and have been building recently, including: the International Rare Cancer Initiative (<http://www.irci.info/>);<sup>3</sup> international clinical trial groups such as the Gynaecologic Cancer Intergroup, who have recently published consensus statements on the management of 20 rare gynaecologic cancers;<sup>20</sup> and at a more basic research level, the Cancer Genome Atlas rare cancer projects (<http://cancergenome.nih.gov/cancersselected/RareTumorCharacterizationProjects>).

## We are all in this together: consumer and community engagement

In this era of significant genomic changes ahead of us, it is of great importance to involve Australian patients and their families, as all too often they feel they have to fight to find support and management options in our current system. Together, we can be more strategic, designing and harnessing new approaches, including innovative ways of accessing new treatments. The common themes recurring throughout are of the need for centralised coordination of management and research of rare cancer patients and of the potential utility of detailed molecular analysis. One approach to this has been to develop a website that allows individual rare cancer patients, or their approved proxy, to enter clinical data into a database. Details are available at [CART-WHEEL.org](http://CART-WHEEL.org) and this program enables the community to work with researchers as a partnership.<sup>21</sup> Additionally, support for consumers, patients and their families is provided by Rare Cancers Australia, a charity whose purpose is to improve awareness, support and treatment of Australians with rare and less common cancers <http://www.rarecancers.org.au/>.

We hope that this issue of *Cancer Forum* will inform and inspire readers about rare cancers, and at the same time show that there is significant hope for improved outcomes that may yet reach the same levels we have seen for other cancer types.

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## RARE HAEMATOLOGIC MALIGNANCIES: BAD DISEASES CAN HAVE GREAT OUTCOMES WHEN THE RIGHT TREATMENTS ARE DISCOVERED

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### Abstract

Individual haematologic malignancies are uncommon when compared to solid tumours. Careful definition of distinct subtypes of leukaemias and lymphomas by marrying clinical characteristics with distinct morphological and genetic features has greatly advanced understanding of pathobiology, leading to novel treatments and improved prognoses of different leukaemias and lymphomas. We examine the success stories of acute promyelocytic leukaemia and chronic myeloid leukaemia, and explore how next generation sequencing will empower translational research and treatment advances for rare haematologic malignancies.

### Introduction

While haematologic neoplasms account for approximately one-sixth of all non-cutaneous cancer diagnoses, each individual type of blood cancer is uncommon. The incidences of acute myeloid leukaemia (AML), non-Hodgkin lymphoma and Hodgkin lymphoma were 4, 20 and 2.7 cases per 100,000 respectively in the US in 2011.<sup>1</sup> In contrast, 140 new diagnoses of prostate cancer and 130 new diagnoses of breast cancer per 100,000 were made in the same year. Haematologic neoplasms are markedly heterogeneous, with more than 35 subtypes of acute leukaemias, 35 subtypes of non-Hodgkin lymphoma and six subtypes of Hodgkin lymphoma currently recognised.<sup>2</sup> Each individual subtype of haematologic neoplasm can therefore be

considered a rare disease. However, this has not prevented significant advances from being made in understanding the pathobiology of these diseases and in their treatment. Paradoxically, the rarity has facilitated scientific advancement, by enabling focus on their distinctive morphologic, cytogenetic and molecular characteristics to develop targeted therapies. In this article, we will review how two rare leukaemias with poor prognoses when treated with cytotoxic chemotherapy, are now considered to have very favourable prognoses with targeted therapies.

### Acute promyelocytic leukaemia

Acute promyelocytic leukaemia (APL) is a subtype of AML, with an incidence of 0.27 cases per 100,000 per year



and no difference in frequency between age groups.<sup>3</sup> APL as a distinctive disease was first described in 1957 by Hillestad.<sup>4</sup> The patients presented with bleeding diathesis and died within hours to six days of hospital admission from disseminated intravascular coagulopathy. Hillestad presciently described APL as "... the most malignant form of acute leukaemia."

APL is characterised by an excess of abnormal promyelocytes with prominent Auer rods in the bone marrow. In classical APL, only occasional aberrant promyelocytes may be found in the peripheral blood. A variant form of APL with hypogranular promyelocytes, also known as 'microgranular' APL, presents with a higher promyelocyte count in the peripheral blood. In the late 1970s, the French-American-British Co-operative Group classified APL and 'microgranular' APL as M3 and M3 variant respectively.<sup>5,6</sup> The ability to identify APL by morphology is crucial for early diagnosis and treatment of this deadly disease. This is supplemented by APL's specific cytogenetic and molecular abnormalities (described below).

Daunorubicin was the first chemotherapeutic agent effective in treating APL, achieving complete remission (CR) in 58% of patients with decreased bleeding complications.<sup>7</sup> The addition of cytarabine increased CR to 68-72% but median duration of CR remained short at only 24 months.<sup>8,9</sup>

It was hypothesised that APL could be due to a defect that prevents promyelocytes from differentiating to more mature granulocytes. After Breitman et al showed that all-trans-retinoic acid (ATRA) induces differentiation in an APL cell line (HL-60) and APL cells obtained from patients, the clinical efficacy of ATRA was first shown by the Chinese in 1988, when all 24 patients given ATRA monotherapy achieved CR.<sup>10-12</sup> Within 10 years, ATRA plus chemotherapy had become the gold standard, and four year disease-free survival had increased from <40% to 71-93%.<sup>7,9,13-15</sup>

At the same time, arsenic trioxide was also introduced for the treatment of relapsed APL. Arsenic alone resulted in CR in 85-90% of patients.<sup>16-18</sup> In a subsequent study, arsenic in combination with ATRA resulted in rapid and safe induction of remission with no relapses.<sup>19</sup> Most recently, in a randomised trial, the two-year overall survival for patients treated with ATRA and arsenic was 99%, compared to 91% in patients treated with ATRA and chemotherapy.<sup>20</sup> APL may be the first cancer where cytotoxic therapy can be safely replaced with a combination of a vitamin and a mineral in order to affect a cure in nearly all patients.

The success in treating APL is related to its molecular pathogenesis. It was recognised early that APL cells had a translocation between chromosomes 15 and 17,<sup>21,22</sup>

t(15;17)(q21;q22) that fuses the PML on chromosome 15 with RAR on chromosome 17.<sup>23,24</sup> The PML-RAR is measured using reverse transcriptase polymerase chain reaction (RT-PCR) allowing early detection of relapse. The chimeric protein exerts a negative effect on the normal function of PML and RAR proteins, disrupting cellular processes, including granulocytic differentiation.<sup>25</sup> The constant incidence of APL over different age groups suggests that APL has a single rate limiting mutation, namely PML-RAR.<sup>26</sup> Arsenic and ATRA work by binding to the PML and RAR moieties respectively, thereby causing degradation of PML-RAR and allowing differentiation of the promyelocytes, and extinction of the leukaemic clone.

In five decades, APL has changed from an invariably deadly disease to a highly curable one. While the revolution in treatment occurred prior to our comprehensive understanding of the molecular pathogenesis of the disease, the use of molecular assays enabled minimal residual disease to be used as a validated surrogate for cure, accelerating the development of clinical algorithms. The current challenge is to translate the lessons learned from APL to other forms of acute leukaemia.

## Chronic myeloid leukaemia

Chronic myeloid leukaemia (CML) ideally exemplifies how understanding the biology of a rare cancer enables the development of a targeted therapy that revolutionises care and clinical outcomes. The incidence of CML is estimated to be 0.6 to 2 per 100,000 per year, with a median age at diagnosis of 60 to 65 years.<sup>27,28</sup> More than 90% of patients present in chronic phase CML with splenomegaly and leukocytosis. CML is diagnosed by identifying its pathognomonic peripheral blood features of basophilia, eosinophilia and granulocytes in various stages of maturation and by confirming the presence of the fusion oncogene, BCR-ABL.<sup>2</sup>

In 1960, Nowell and Hungerford reported the presence of a 'minute' chromosome in seven cases of CML. In 1973, Rowley demonstrated that the Philadelphia chromosome consisted of a reciprocal translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)).<sup>29</sup> In subsequent research, this translocation was shown to involve the ABL oncogene on chromosome 9 with a small breakpoint cluster region (BCR) on chromosome 22.<sup>30,31</sup> The chimeric bcr-abl mRNA encode a protein with increased tyrosine kinase activity compared to wild-type ABL.<sup>32-35</sup> BCR-ABL was shown to be pivotal in leukaemogenesis when expression of BCR-ABL in mice induced phenotypes resembling CML.<sup>36,37</sup>

Treatment prior to 2000 comprised interferon or hydroxyurea, but this rarely changed the natural history of the disease. Over several years, patients would progress from chronic phase CML to accelerated phase and then to a blast crisis that

resembled acute leukaemia. Allogeneic haematopoietic stem cell transplant is potentially curative in 70-80% of younger patients, but requires a compatible stem cell donor, a medically fit patient and an acceptance of risks of transplant-related mortality and long-term morbidity.<sup>38</sup> Therefore, better therapies were required and BCR-ABL was an attractive target given its role in the pathogenesis of CML.

In pre-clinical studies, a tyrosine kinase inhibitor (TKI), STI 571 (imatinib), inhibited the proliferation of cell lines expressing BCR-ABL and reduced tumour formation in mice.<sup>39</sup> Imatinib also decreased the formation of BCR-ABL colonies from peripheral blood and bone marrow samples of patients with CML by 92-98%. Imatinib did not inhibit the formation of normal colonies from the patient samples, demonstrating the specificity of the compound to BCR-ABL. A phase I clinical trial of imatinib commenced in 1998 on patients with chronic phase CML who were resistant to interferon therapy; 53 of 54 (98%) patients achieved complete haematologic response without significant toxicity.<sup>40</sup> These findings were confirmed in additional trials and in 2001, imatinib was approved by the Food and Drug Administration for use in CML.<sup>41-44</sup>

Long-term follow-up of the randomised trial revealed that 93% of newly diagnosed patients treated with imatinib remain alive and progression-free after six years.<sup>45</sup> Allogeneic stem cell transplantation is now rare for CML, whereas in 2001, CML was the most common indication for the procedure. Molecular monitoring of BCR-ABL transcripts in the blood is standard, and enabled intervention with second generation TKIs (dasatinib, nilotinib and ponatinib) where imatinib resistance due to well recognised mutations in ABL are observed.<sup>46,47</sup> Imatinib and other same-in-class drugs (dasatinib, nilotinib, ponatinib) have transformed CML into a truly 'chronic' disease, controlled with a daily tablet. Further, in patients with undetectable minimal residual disease (using sensitive RT-PCR measurement of BCR-ABL transcripts), it may even be appropriate to stop imatinib, with 40% of patients remaining disease-free off therapy.<sup>48,49</sup>

Research questions remain on the optimal duration of treatment, the choice between various TKIs as optimal first and second line therapy, and the care of the now rare patient with CML in blast crisis.

## Future for other rare haematologic malignancies – the era of next-generation sequencing

Recently, improvements and widespread adoption of next generation sequencing (NGS) have enabled us to sequence and analyse genetic material with ease and at a reduced cost. NGS promises to revolutionise research and management of haematologic malignancies.<sup>50</sup> The

ability to perform whole genome sequencing of an individual patient's neoplasm has already identified recurring mutations in previously unsuspected genes e.g. IDH1 and DNMT3A in AML.<sup>51,52</sup> As AML is broken down into 25-35 subtypes, grouped according to their underlying driver mutations, the field anticipates the development of new treatment approaches for each.

While for APL and CML, it took decades to understand the basic cytogenetic and molecular mechanisms of the disease and develop pathobiology-specific therapies, for AML and other haematologic neoplasms, NGS promises to accelerate these timelines to mere years. The challenges of the 21st century will be in understanding the data generated from NGS and applying it to individual patient care. In this area, haematologic neoplasms will likely to continue to blaze a path.

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# ADVANCES IN OUR UNDERSTANDING AND MANAGEMENT OF SARCOMAS – RARE BONE AND SOFT TISSUE CANCERS

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### Abstract

Bone and soft tissue sarcomas are rare, accounting for approximately 1% of all adult solid malignant tumors. Although these cancers are categorised under the same banner of 'sarcoma', they in fact represent more than 70 distinct tumor subtypes, correct diagnoses of which are becoming increasingly important in delivering tailored and optimal medical care. The dramatic impact of imatinib on the management of gastrointestinal stromal tumor has served as a prototypic model for the development of other molecularly-targeted therapies. However, patients and their families affected by sarcomas still face significant challenges in accessing appropriate cancer care, as do their counterparts affected by other rare cancers. This review paper summarises recent advances in management of sarcomas, and in particular highlights the importance of progress in molecular genetics of sarcomas and how these findings have enabled the discovery of targeted therapeutic agents.

Sarcomas are a heterogeneous and relatively rare group of malignant tumours that develop in bone and soft tissue, accounting for approximately 21% of all paediatric solid cancers and less than 1% of all adult cancers.<sup>1</sup> Patients and their families affected by sarcomas face a number of similar challenges in receiving optimal cancer care as their counterparts with other rare cancers do, from delays in making a correct diagnosis to a lack of readily available clinical expertise and access to effective therapies, given a limited opportunity to participate in clinical trials and even limited access to reimbursed agents. Sarcoma patients are markedly over-represented by adolescents and young adults, leading to an even greater impact on number of years of life lost to this disease, when compared to other cancers.

There are more than 70 distinguishable subtypes of sarcomas, which exhibit different behaviors, incidence and response to treatment.<sup>2</sup> Despite these challenges, the diversity in disease subtypes, many of which are defined by molecular phenotypes, has in fact served as a fertile ground in driving therapeutic development of agents to target these, as exemplified by the success of imatinib in transforming the prognosis of patients affected by advanced gastrointestinal stromal tumour (GIST) – a subtype of soft tissue sarcoma. We review recent advances in sarcoma management, highlighting the success story of imatinib therapy for patients with advanced GIST as a flag bearer for what can

be achieved when rationally applying an expanding knowledge of molecular biology to the development of targeted agents.

### Imatinib success story in advanced GIST

Success stories of improvements in survival in rare cancers are not complete without re-addressing the development of imatinib for treating advanced GIST. Historically, patients with metastatic or inoperable GIST had a very poor prognosis because of the highly resistant nature of these tumours to conventional chemotherapy.<sup>3</sup> In the late 1990s, a Japanese group at the University of Osaka first showed that GIST was driven by activating mutations in the c-kit oncogene.<sup>4</sup> The first clinical trial using imatinib – a tyrosine kinase inhibitor known to target the KIT and PDGF receptors – showed dramatic improvements in disease control and led to its accelerated approval by the US Food and Drug Administration in 2001, only three years after the Hirota paper was published.<sup>4,5</sup>

In a disease in which median survival was less than a year for patients with advanced/metastatic disease, survival is now at least five years.<sup>6,7</sup> Subsequently, in 2008, imatinib received further accelerated approval for adjuvant use in patients with resected GIST,<sup>8</sup> with further data demonstrating an even greater impact in patients with high risk for recurrence following potentially curative resection.<sup>9</sup> A multitude of further insights have

come through a greater depth of understanding of KIT biology, including how specific mutations in KIT or PDGF predict response to imatinib and next-generation kinase inhibitors,<sup>10,11</sup> and in mechanisms of resistance to imatinib have led GIST to be considered a model disease in how to implement a personalised approach to treating cancers.<sup>12</sup> Therapeutic applications of imatinib have also expanded to other soft tissue sarcomas such as dermatofibrosarcoma protuberans, with the discovery of a characteristic translocation leading to an autocrine dependence on PDGF signalling also targetable by imatinib.<sup>13</sup>

### **Molecular complexities and heterogeneity of sarcomas**

Bone and soft tissue sarcomas are marked by their heterogeneity and complexity in histology and molecular biology. Sarcomas are collectively rare and individual subtypes comprise many rarer entities, posing significant challenges to pathologists outside specialist sarcoma centres. There are more than 50 distinct subtypes of soft tissue sarcoma alone.<sup>2</sup> Delays in reaching a correct diagnosis is the first limiting step in accessing appropriate care for patients with sarcomas. The misclassification rate of sarcomas based on histopathology alone, was reported to be up to 20% in the early 1990s.<sup>14</sup> Unfortunately this still remains true with potentially devastating consequences. We now have consistent, albeit low level, evidence that expert review results in a change to diagnosis in a significant proportion of cases ranging from a minor discordance in tumour grade to a false positive or false negative diagnosis of malignancy.<sup>15-17</sup> Therefore, whenever a sarcoma is suspected clinically or biopsied, or even possibly resected outside a sarcoma specialist setting, a timely review of the diagnosis is strongly recommended.

### **Current management of bone and soft tissue sarcomas**

The mainstay of sarcoma management in 2014 remains a multimodality approach using surgery, chemotherapy and radiotherapy, which are dependent on high quality radiology, pathology and increasingly molecular pathology input. Not all patients diagnosed with sarcomas require all three modalities, and the subtleties in managing a complex and rare disease are therefore critically dependent on an expert multidisciplinary approach. As an example, the survivorship of children with osteosarcoma and Ewings sarcoma in the last 30 years has changed significantly, from less than 20% to a five-year disease free survival in excess of 60% for those with localised disease, mainly due to the integration of intense chemotherapy regimens with surgery and radiotherapy.<sup>20,21</sup> In addition, limb-preserving surgery has evolved to the point that amputation is rarely required, leading to significant improvements in quality of life for affected patients.<sup>22</sup>

The role of chemotherapy remains controversial for patients with soft tissue sarcoma, with a lack of evidence in survival benefit in the treatment of operable disease.<sup>23,24</sup> It is generally reserved for patients with metastatic disease in palliating symptoms. Integrating our knowledge on risk stratification of sarcoma subtypes is enabling better patient and treatment selection for specific systemic therapies, and once again requires high quality expert care delivered through specialist sarcoma services.

### **Multidisciplinary management – a tautology**

The utmost importance of involving a multidisciplinary team cannot be overstated in sarcoma management. Sarcoma treatments vary by tumour subtype, grade and stage. The duration and intensity of sarcoma therapy can often be intensive and prolonged, with combinations of chemotherapy, surgery and at times radiotherapy required to maximise the chance of cure, as is typically the case in Ewing sarcomas or osteosarcomas. Many published series consistently report inferior outcomes for patients whose sarcoma treatment is initiated in non-specialist centers, with some studies estimating that up to half of all patients with soft tissue sarcoma are managed outside specialist centres.<sup>18,19</sup>

Given the rarity and often complexity in diagnosis and treatment, a sarcoma expert centre can facilitate access to appropriate imaging, biopsy and histopathology review by expert pathologists. From there, cases are discussed in a multidisciplinary meeting, similar to the ways in which other more common tumor streams manage their patients these days. In Australia, there are several dedicated sarcoma centres, which are affiliated with Australasian Sarcoma Study Group, the national cooperative group driving sarcoma research in this region.

### **Recent development in novel therapies**

An ever increasing number of novel agents are being explored and added to our expanding armamentarium against specific subtypes of soft tissue sarcoma. The recent addition of pazopanib to the Pharmaceutical Benefits Scheme listing for the indication of non-adipocytic soft tissue sarcomas in Australia will assist patients' access to this targeted option.<sup>25</sup> Despite its activity in certain soft tissue sarcoma subtypes, access to trabectedin unfortunately remains difficult for patients in Australia. Interestingly, some of the new agents with the highest impact have been in rare and classically chemo-resistant subtypes, which not surprisingly are known to now have strong single oncogenic drivers.<sup>26-28</sup> Despite some extraordinary responses in these rare sarcomas, obtaining regulatory approval and reimbursement in Australia remains unlikely with our current mechanisms, an issue that is increasingly becoming a challenge with

even 'common' cancers when broken down into their requisite subgroups.

The next wave of new treatments in sarcomas will likely continue to come from translating the molecular findings from the first generation of in-depth genomic studies that will continue to provide insights into targetable subtypes, even if rare.<sup>29</sup> In addition to this, efforts will also need to focus on understanding the functional impact of the many translocations that are well defined in many sarcoma subtypes, and how these can be targeted.

Sarcomas are considered favourable models for the development of novel agents targeting specific molecular aberrations because these alterations are often well characterised. However, the heterogeneity of sarcomas and limited number of patients per individual sarcoma subtype pose significant challenges in developing clinical trials. Despite this, the international sarcoma community has recognised this as a challenge that must be overcome, and now places a high priority on collaborative efforts to conduct trials even in extremely rare subtypes, as critical for us to make any progress. Until recently, opportunities were scarce in Australian centres to lead or participate in sarcoma-focused trials. However, this has improved considerably in recent years due to the establishment of local and international collaborative infrastructure.<sup>30</sup> With challenges in getting timely approval to novel agents, trials remain an important potential source of access to novel agents for patients with sarcomas and other rare cancers.

## Conclusion

Over the past decade we have witnessed remarkable developments in our understanding of the molecular genetics of cancer. As we continue to unravel the molecular mechanism of sarcoma pathogenesis, more opportunities will arise in discovering potential targets and novel therapeutic approaches in treating patients with bone and soft tissue sarcomas. In parallel, developing and implementing new methodologies for well-designed clinical trials will become crucial in moving us closer to delivering truly personalised cancer care to patients affected by this rare and diverse group of cancers.

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# NEUROENDOCRINE TUMOURS - MODELS FOR RARE TUMOUR MANAGEMENT

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## Abstract

Neuroendocrine tumours have posed a challenge for the development of research and management strategies because of their rarity and heterogeneity, both from clinical and molecular perspectives. Classification and increased understanding of the molecular landscape has been made possible by the use of reproducible pathological measures and the study of familial forms of the disease. Clinical trials have shown the importance of multi-centre collaboration, appropriate patient selection and stratification by site. These strategies can be applied to other rare malignancies, hopefully resulting in better molecular understanding and improved treatments.

Neuroendocrine tumours (NET) were first described in the medical literature more than a century ago, with the term 'carcinoid tumour' being coined by Obendorfer in 1907. They are relatively rare, but are increasing in incidence, from 1.7/100,000 in 1980-89 to 3.3/100,000 in 2000-06 in Australia – which may be due to increased awareness and detection of these tumours.<sup>1</sup>

Although NETs share a common origin in enterochromaffin cells, this cell type is located in various organs throughout the gastrointestinal tract, as well as the bronchi. Classically, NETs have been grouped embryologically by their site of origin (foregut, midgut or hindgut). Considered as a group, they display striking variation in clinical presentation. Some tumours may be slow-growing and relatively asymptomatic, some may cause symptoms due the production of biologically active hormones and yet others

grow rapidly with an aggressive clinical course. This has complicated attempts to design and interpret clinical trials in this area and hampered attempts to formalise a treatment strategy for all NETs.

The great variance in clinical course has driven the need for a classification system to predict risk, culminating in the publication of the World Health Organisation (WHO) classification in 2010. The study of specific pathogenic mutations underlying familial NETs has also helped elucidate molecular pathogenesis in sporadic cases. While the exact criteria for grading NETs remains the subject of much discussion, the principles behind the classification and treatment of NETs by histological features and ultimately molecular pathways, rather than by anatomic location alone, provide valuable insights into the treatment and investigation of other rare tumours.

**Table 1:** 2010 World Health Organisation (WHO) classification of neuroendocrine tumours

Grade	Mitotic count (mitoses per 10 high power fields)	Ki-67 index	Traditional nomenclature	WHO/ENETS nomenclature
Grade 1	<2mit/10HPF	<3%	Carcinoid, islet cell tumour	Neuroendocrine tumour, Grade 1
Grade 2	2-20mit/10HPF	3-20%	(Atypical) Carcinoid, islet cell tumour	Neuroendocrine tumour, Grade 2
Grade 3	>20mit/10HPF	>20%	Small cell carcinoma, large cell neuroendocrine carcinoma	Neuroendocrine carcinoma (large cell or small cell type)
Mixed adenoneuroendocrine carcinoma (MANEC)				
Hyperplastic and pre-neoplastic lesions				

**Mit:** Mitoses **HPF:** High power fields **ENETS:** European Neuroendocrine Tumour Society

## Molecular heterogeneity and classification

NETs display molecular heterogeneity – having a wide variation in the degree of histological aggressiveness, as characterised by the number of mitoses in the pathological specimen, as well as by determination of the proliferation marker Ki67. WHO published its first classification of neuroendocrine tumours in 1980 with four categories - carcinoid tumours, mucocarcinoid tumours, mixed forms of carcinoid adenocarcinoma and pseudotumour lesions. The subsequent revisions in 2000 and 2010 reflected a shift away from purely morphological classifications towards histological grading by mitotic rate and Ki67 labelling (see table 1) – proven prognostic factors in gastrointestinal but also pulmonary NETs.<sup>2,3</sup>

The classification of gastroenteropancreatic NETs (GEPNETs) by mitotic rate and Ki67 labelling provides valuable lessons in the management of other rare tumours. The paucity of cases may make it difficult to develop pathological markers of risk. As a result, mitotic count and Ki67, being somewhat reproducible and feasible in all histological subtypes, are promising potential candidates for risk stratification. The development of objective, quantitative models of risk stratification are essential in order to develop both accurate prognoses and test new therapeutic modalities, and this would be an important starting point in the study of any rare tumour.

The study of families affected by NETs and the genetic syndromes underlying this phenotype led to research into genetic mutations underlying the pathogenesis of NETs. While some genetic mutations were largely confined to familial cases of NETs, some occurred with considerable frequency in sporadic NETs, paving the way to further understanding of pathogenesis and providing possible therapeutic targets.

### MEN1 and VHL: genetic clues from familial neoplasia syndromes

Multiple endocrine neoplasia type 1 is an autosomal dominant disorder caused by mutation in the MEN1 gene on chromosome 11q13. It is classically associated with parathyroid and pituitary neoplasms, as well as GEPNETS. Patients with MEN1 germline mutations are more likely to develop functional NETs, particularly gastrinomas and insulinomas; conversely patients with Zollinger-Ellison syndrome have a high likelihood of germline MEN1 mutations (20-60%),<sup>4</sup> and is in fact the first clinical symptom of MEN1 syndrome in 40% of affected patients.<sup>5</sup> While menin, the protein product of MEN1, has been suggested to interact with various nuclear proteins involved in regulation of gene transcription, its exact function has not been fully defined.

Von Hippel Lindau disease is another autosomal dominant disorder caused by mutation of the VHL gene, resulting

in a high lifetime incidence of various tumours, most commonly haemangioblastomas of the central nervous system, renal cell carcinomas (clear cell subtype) and pheochromocytomas. It is also associated with pancreatic neuroendocrine tumours (pNETs) with a lifetime incidence of 9-17% in case series,<sup>6,7</sup> most commonly presenting in patients in their 20s and 30s.

The VHL gene is responsible for producing pVHL, a tumour suppressor protein which acts via degradation of HIF1 and HIF2, proteins active in the angiogenesis pathway. Thus, defective production of pVHL would remove normal physiological controls on cell growth and predispose to tumorigenesis.

The above association has led to hypotheses regarding the possible tumorigenic role of MEN1 and VHL in GEPNETS. Massive exome sequencing of 48 small intestinal NETs have confirmed deletions in MEN1, but also have pointed to other potential key mutations in FGFR2, HOOK3, VHL and BRAF among others.<sup>8</sup> Other case series have detected MEN1 deletions in a majority of sporadic gastrinomas, as well as some insulinomas and pulmonary carcinoids.<sup>9,10</sup>

The above examples illustrate the importance of studying familial cases of rare malignancies, continuing a tradition that began with the study of retinoblastoma and the subsequent development of the Knudson two-hit hypothesis. This approach can lead to elucidation of the genomic structure underlying carcinogenesis and direct research towards relevant therapeutic targets.

### Lessons in clinical trial design from GEPNETs

One of the lessons learnt from GEPNET trials is the difficulty in accruing the patient numbers needed for a phase III trial. Given the rarity of this disease, timely accrual in a trial context is aided by a multicentre, collaborative approach. For example, even though the PROMID trial which evaluated the role of long acting octreotide versus placebo reported significant results with only 85 randomised patients, this was achieved by 18 German academic centres pooling their referral base over seven years.<sup>11</sup> The Raymond trial, which examined the role of sunitinib in pNETs (see below), improved on this by enlisting 42 centres in 11 countries,<sup>12</sup> resulting in accrual of 171 patients over only two years. Rare tumours, more so than other types, require close collaboration to achieve sufficient power in a randomised study to advance the evidence base.

Secondly, heterogeneous rare diseases need to be stratified to define populations that will benefit from treatment. Differential efficacy has been observed in trials of targeted agents, showing benefit in pNETs, but not other GEPNETS. Sunitinib, a multitargeted tyrosine



kinase inhibitor, was trialled in GEPNETS in a phase II trial.<sup>13</sup> This demonstrated response rates of 16.7% in pNETs, but only 2.4% in non-pancreatic NETs. A follow-up placebo-controlled phase III randomised trial confirmed clinical benefit of sunitinib in pNETs, with improvement in progression-free survival from 5.5 to 11.4 months.<sup>12</sup> Similarly, the RADIANT trials, investigating the use of single-agent everolimus in the treatment of GEPNETS, showed an improvement in progression free survival in pNETs (RADIANT-3)<sup>14</sup> but not in other GEPNETS (RADIANT-2).<sup>15</sup> This may be due to the differing biology of tumours. While the presence of mutations in the mTOR pathway targeted by everolimus is well established in pNETS (15% demonstrating mutations in TSC, PTEN or PIK3CA), evidence linking it to other GEPNETS is scarce. Despite the progress that has been made in molecular taxonomy, there remains a real need to investigate the presence/absence of molecular differences between pNETs and other GEPNETS in terms of key pathways such as mTOR and VEGF.

For rare diseases with significant heterogeneity, the selection of appropriate subgroups is extremely important. The PROMID study restricted accrual to patients with well-differentiated (Ki67<2%) midgut NETs.<sup>11</sup> This stringent criterion may have led in part to the slow accrual noted above, despite involvement of multiple centres. In addition, while the PROMID trial showed significant improvement in time to progression, its results were difficult to extrapolate to other grades and sites of tumours. The proof of anti-tumour efficacy for somatostatin analogues in other GEPNETs was only determined recently in the CLARINET trial (Lanreotide placebo in grade 1-2 GEPNETs),<sup>16</sup> showing improvement in PFS. Designing trials for rare tumours needs to strike a fine balance between selection of similar patients and clinical feasibility/applicability.

## Nuclear medicine in diagnostics and therapeutics

The diagnostic and treatment models utilised in GEPNETs can be generalised to other rare tumours. The search for a specific imaging modality can give valuable information regarding the stage of the tumour and gauge response to therapy. The use of fluorodeoxyglucose and gatate positron emission tomography (PET) in GEPNETs has revolutionised the evaluation of GEPNETs. Fluorodeoxyglucose PET is used to detect poorly-differentiated disease, whereas Gatate PET detects well-differentiated disease which overexpresses somatostatin receptors. Gatate PET allows for accurate localisation of disease, but given that the scan reflects sites of octreotide uptake, also predicts for anatomic sites which will take up the administered peptide receptor radionuclide therapy (PRRT), therefore predicting for its effectiveness prior to treatment. Given the linkage of the active radionuclide (such as <sup>177</sup>-Lutetium) to

octreotide/octreotate, PRRT has the potential to localise treatment to sites of disease showing octreotide uptake. This approach is mirrored in the treatment of other malignancies such as radioiodine scan in the workup for iodine-131 therapy for metastatic papillary and follicular thyroid cancer. If targetable receptors exist in other rare tumours, this would provide valuable investigation and potential treatment modalities.

## Conclusion

Rare tumours, such as GEPNETs, pose unique challenges in oncology. Issues such as low incidence, molecular and clinical heterogeneity, and optimal trial design, are recurring themes and need to be addressed to facilitate research and progress in the area. Research into other rare cancers would be well served by adopting the above recommendations, hopefully speeding progress towards improved understanding and outcomes from such approaches.

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## RARE UROGENITAL TUMOURS – TESTICULAR CANCER AND BEYOND

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### Abstract

Rare urogenital tumours likely to be encountered by oncologists include testicular cancer, non-urothelial tumours of the bladder and urethral and penile cancers. Testicular cancer is a rare but highly curable urogenital tumour that typically occurs in men aged between 15 and 40 years. Factors responsible for the current success of treatment for testicular cancer include identification of reliable prognostic criteria to define risk and guide choice of therapy, multi-disciplinary management in expert centres, sustained research including international collaboration on practice-changing randomised controlled trials, and implementation of evidence-based guidelines. Unmet needs in testicular cancer include: improving the effectiveness and reducing the complications of treatment; addressing short and long-term survivorship issues; reducing exposure to radiation from repeat imaging; and better understanding the epidemiology and tumour biology. There is also a need to identify sustainable, targeted support for ongoing collaborative testicular cancer research. Australia is at the forefront of research into testicular cancer and recent achievements are outlined. Other rare urogenital tumours have significantly worse outcomes than testicular cancer and lack high-level evidence to guide therapy. Strategies to improve outcomes are discussed.

Rare urogenital tumours likely to be encountered by oncologists during their career include testicular cancer, non-urothelial tumours of the bladder and urethral and penile cancers. This review will outline factors responsible for the current success of treatment for testicular cancer, as well as unmet needs worthy of ongoing collaborative research. Other rare urogenital tumours have significantly worse outcomes than testicular cancer and lack high-level evidence to guide therapy. Strategies to improve outcomes that have been successful in testicular cancer are discussed.

Germ cell tumour of the testis, commonly referred to as testicular cancer, is the most common malignancy in men aged between 15 and 40 years in Australia and many Western countries.<sup>1,2</sup> Although highly curable and only comprising about one in 100 cases of male cancer, each year there is a disproportionately high number of years of healthy life lost due to young age at diagnosis. In 2012, there were an estimated 740 cases in Australia, resulting in 20 deaths and almost 1000 years of healthy life lost.<sup>1</sup>

The incidence of testicular cancer has increased dramatically in populations of European ancestry since the 1970s for unknown reasons.<sup>2</sup> Testicular cancer incidence is highest (>5 per 100,000 individuals) in Northern and Western Europe, followed by Australasia and North America, and lowest (<1 per 100,000 individuals) in Africa and Asia. Incidence is higher by a factor of five in whites compared to blacks in the United States. In contrast to incidence rates, mortality rates have declined significantly in Western countries since the 1970s to very low levels (0.2 per 100,000 individuals), such that it is one of the most highly curable solid malignancies.<sup>2</sup>

About 80% of patients are diagnosed with early stage disease that is curable with surgery, followed in some cases by chemotherapy or radiotherapy, whereas the remaining 20% have advanced disease at diagnosis, typically requiring primary chemotherapy.<sup>3,4</sup> More than 95% of patients are cured, however over a third with advanced disease and the worst prognostic features will relapse and die despite best available chemotherapy.

## Factors in the success of treatment for testicular cancer

The dramatic improvement in survival of patients with testicular cancer over the last 50 years relates to landmark advances, such as the identification of reliable tumour markers to detect metastatic disease, refinements in radiotherapy to cure seminoma, the introduction of cisplatin-based combination chemotherapy to cure metastatic disease and refinements of post-chemotherapy retroperitoneal lymph node dissection.<sup>5</sup>

Such advances in this rare malignancy have occurred following sustained and methodological research, including: a series of practice-changing randomised controlled trials requiring international collaboration; identification of reliable prognostic criteria to define risk and guide choice of therapy; strong multi-disciplinary collaboration between the fields of medical and radiation and surgical oncology, pathology and radiology; and implementation of evidence-based guidelines by the oncology community.

Testicular cancer makes up a significant proportion of cancer survivors, due to the typically young age at diagnosis and the successes in its management. Unmet needs in testicular cancer requiring further study include improving the effectiveness and reducing the complications of treatment, long-term and short-term survivorship issues, reducing exposure to radiation from computed topography (CT) scans, and a better understanding of the epidemiology and tumour biology of subsets of testicular cancer. There is also a need to identify sustainable, targeted support for ongoing collaborative testicular cancer research.

There is a need for more effective treatment for patients who present with advanced disease and/or poor prognostic features, or who relapse after initial therapy, as well as a need to reduce the acute side-effects and long-term complications of treatment for those who are likely to be cured. Outcomes are better for patients with advanced disease who are treated in high-volume centres,<sup>6-8</sup> perhaps due to better compliance with, and quality of, chemotherapy and post-chemotherapy surgery. Outcomes could be improved for patients from remote rural areas by referral to high-volume centres, shared care models, and virtual multi-disciplinary meetings.

## Tumour biology

The biology of testicular cancer remains poorly understood. A better understanding of the genetics and molecular signatures of testicular cancer could better select patients who require more aggressive or tailored treatment, and avoid over-treatment in other patients. The most pressing clinical questions in stage I testicular cancer are to identify genetic variants within a tumour that identify a group of patients at sufficiently high risk of relapse to justify the short and long-term toxicity of adjuvant therapy, and a group

of patients at sufficiently low risk of relapse to avoid both the toxicity of adjuvant therapy, and the inconvenience and radiologic exposure of intense surveillance. The most pressing clinical questions in relapsed testicular cancer are to identify genetic variants within an individual that alter how a person's body processes chemotherapy, and genetic variants within testicular cancer that make it inherently resistant to standard chemotherapy. Results could lead to the design of tailored treatments for such individuals that could incorporate a higher dose of or an alternative form of chemotherapy. Clinical trials targeting subgroups of men with testicular cancer would pose challenges due to low patient numbers, which would be best addressed via national and international clinical trial group collaboration, as discussed below.

## Survivorship issues

Two-thirds of testicular cancer survivors had significant unmet needs between six months and five years after treatment, according to a recent cross-sectional study led by Ben Smith et al and conducted by the Psycho-oncology Cooperative Research Group (PoCoG) and Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).<sup>12</sup> The most common unmet needs related to life stress, fear of cancer recurrence, need for help for problems with relationships and sex life, and financial concerns. Many of these concerns are similar to those for survivors of breast and other more common cancers, but survivors of testicular cancer, often young men, may not accept interventions which have been designed for a much older person or for women. There is a need for the design and testing of custom-designed psychological interventions and support tailored to the needs of this young age group.

The majority of men with testicular cancer will be cured and live for over 50 years following completion of treatment. There is currently a paucity of information about the long-term physical and psychological complications of testicular cancer and its treatment, and how these complications can be prevented or best managed.

The risk of second cancers is increased in testicular cancer survivors who receive chemotherapy by 2.1-fold, and radiotherapy by 2.6-fold, compared with surgery alone. The risk of cardiovascular disease, such as heart disease or stroke, is also increased in testicular cancer survivors who receive chemotherapy by 1.7-fold, and radiotherapy by 1.2-fold.<sup>9</sup> The absolute incidence of second cancer or cardiovascular disease due to chemotherapy or radiotherapy for testicular cancer is likely to be quite significant. There is an opportunity to reduce long-term morbidity and mortality through minimising use of unnecessary adjuvant therapy for stage I disease.

A recent observational study reported by O'Carrigan et al and conducted by the ANZUP found that up to one third of testicular cancer survivors had some

degree of hypogonadism.<sup>10</sup> This is likely to relate to abnormal development of the remaining testis, sometimes compounded by chemotherapy. This is an under-recognised problem and may result in long-term health issues, including cardiovascular disease, osteoporosis, altered sexual function and poor quality of life.<sup>11</sup>

A patterns of care survey conducted by ANZUP found that the typical patient with early stage testicular cancer underwent eight or nine CT scans over a five year period in order to screen for recurrence.<sup>13</sup> The radiation exposure from these CT scans could lead to secondary cancers.<sup>14</sup> There is a need for further research that could reduce radiation exposure by determining the optimal number of CT scans required during follow-up, and investigation of other imaging such as low-dose CT scans and magnetic resonance imaging. There is also a need for Australian clinicians to adopt a standardised evidence-based surveillance schedule.

A vibrant research community supporting innovation in testicular cancer research remains vital for future improvement of care in this group. Trials in this disease are now almost exclusively possible only through cooperative trials groups. Because testicular cancer is uncommon, the pharmaceutical industry and non-commercial granting bodies assign low priority to funding such research despite its importance. Furthermore, many proposed clinical trials to refine treatment, need to be performed with international collaboration in order to recruit sufficient numbers of patients in a timely fashion. Recent Australian funding initiatives from Cancer Australia, Cancer Councils, Cancer Institute NSW, Sydney Catalyst, and the Movember GAP5 initiative are welcomed. Sustainable ongoing funding models for research will need to be identified to continue this work.

### **Current Australian research activities in testicular cancer**

Australia is at the forefront of clinical research to improve outcomes for testicular cancer and other germ cell tumours. Groups including ANZUP and PoCoG, in collaboration with the National Health and Medical Research Council Clinical

Trials Centre at the University of Sydney, have conducted eight phase II and III clinical trials and pilot and observational studies over the last 10 years in testicular cancer across multiple centres in Australia and New Zealand. Studies relate to: optimising the efficacy of chemotherapy for metastatic disease;<sup>15-17</sup> reducing the toxicity of chemotherapy;<sup>18,19</sup> identifying survivorship issues relating to chemotherapy-induced cognitive dysfunction,<sup>20</sup> hypogonadism,<sup>10</sup> and psychosocial unmet needs;<sup>12</sup> and addressing patterns of care in stage I disease.<sup>13</sup> Ongoing Australian research includes a current phase III trial of accelerated bleomycin etoposide and cisplatin BEP chemotherapy in intermediate and poor prognosis metastatic disease, led by ANZUP and funded by Cancer Australia, incorporating collection and biobanking of 150 blood and tissue samples for planned translational studies funded by Sydney Catalyst, as well as a pilot study to develop a custom-designed online psychological intervention to address unmet needs in testicular cancer survivors led by PoCoG and funded by Cancer Council NSW.

### **Other rare urogenital tumours**

Other rare urogenital tumours likely to be encountered by oncologists during their career are listed in table 1. Each tumour type is notable for its relative five-year survival being significantly lower than that of germ cell tumours and apart from testicular and penile cancer, being lower than that of all cancers combined, which in Australia is 66%.<sup>1</sup> As to be expected, outcomes are best for patients with localised disease amenable to complete surgical resection.

Management of penile cancer has evolved to reduce the morbidity of treatment for localised disease by organ-preserving resection, definitive radiotherapy and laser therapy, with weak to moderate levels of evidence for lymph node dissection and combination chemotherapy to improve outcomes for locally advanced and metastatic disease.<sup>21,22</sup> Progress in other rare urogenital tumours has been slower. The role of extended lymph node dissection and radiotherapy for locally advanced disease has not been clearly established. Conventional chemotherapy for metastatic sex cord stromal tumours of the testis,

**Table 1: Rare urogenital tumours**

Organ	Rare histologies	Incidence per 100,000 per year	Relative 5-year survival
Testes	Germ cell tumours	2.9	95%
	Sex cord (Leydig cell, Sertoli cell, etc)	0.02	84%
Penile	Squamous cell	0.6	73%
Bladder	Squamous cell	0.4	34%
	Adenocarcinoma	0.3	40%
	Urachal	0.2	60%
Urethra	Urethral cancer	1	53%

Source of data<sup>23,24</sup>

non-urothelial tumours of the bladder and urethral cancer is generally not effective, with recommended regimens based on low levels of evidence, and minimal or no evidence for adjuvant chemotherapy following complete resection of localised or locally advanced disease.

There are a number of strategies to improve outcomes for such rare urogenital tumours that can be drawn from the success in testicular cancer:

- Firstly, the development of expert centres for management of rare urogenital tumours, supported by strong multi-disciplinary teams analogous to that for sarcomas, gynaecologic and testicular cancer. Such centres would focus and enhance both clinical expertise and research efforts. Their success would rely on the referral of the majority of patients within a region for expert pathology review, clinical assessment, and where appropriate, ongoing treatment. Technology to overcome geographical and logistic barriers, such as virtual multi-disciplinary meetings, may help.
- Secondly, prospective clinical and translational research, including observational studies to identify prognostic factors that can guide therapy, and the conduct of adequately powered clinical trials of novel interventions including, where feasible, randomised controlled trials. Such research requires development of strong national and international collaborations.
- Thirdly, the ongoing development and dissemination of clinical guidelines for the management of rare urogenital tumours into the oncology community, based on the highest level of evidence, to reduce reliance among clinicians on case reports and non-systematic reviews.

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# OVER HALF OF ALL GYNAECOLOGIC CANCERS ARE RARE: BARRIERS AND CHALLENGES TO IMPROVING OUTCOMES

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## Abstract

Evidence-based medicine is the bedrock for optimal clinical practice and relies on using the best available evidence from randomised controlled trials to guide management for an individual patient. Over 50% of gynaecological cancers are classified as 'rare', which creates additional challenges in carrying out clinical trials and establishing a robust evidence-base for treatment. It is now clear that epithelial ovarian cancer, one of the most common gynaecological cancer types, is not a distinct entity, but is comprised of multiple distinct subtypes which differ in their biological behaviour and response to treatment. Simply treating all patients with epithelial ovarian cancer as a uniform entity in large clinical trials will be a legacy of the past and this is applicable to most other types of gynaecological cancers as well. As we move rapidly into the era of genomic profiling, there will be an exponential increase in the number of patients identified with 'rare' gynaecological cancers. Standard clinical trial design and traditional endpoints will have to change and international collaboration will be essential if we are to develop better treatments for our patients. Additional challenges, including funding, as well as regulatory requirements, will need to be overcome. This review will focus on national and international efforts to advance our understanding and management of patients with rare gynaecological cancers.

Over 50% of gynaecological cancers are classified as 'rare'.<sup>1</sup> There is a disparity in the outcome of patients with rare cancers, compared to patients with more common cancers, where there is often a large body of evidence from clinical trials. This is well illustrated by the inferior outcomes of patients with rare subtypes of epithelial ovarian (e.g. clear cell and mucinous) and endometrial (serous and carcinosarcoma) cancers, compared with the more common subtypes of high grade serous ovarian cancer and endometrioid cancer of the endometrium.<sup>2-6</sup> Establishing the best treatment for patients with rare gynaecologic cancers is difficult, due to a paucity of clinical trials designed to establish outcomes for patients with rare cancers.

Ideally, all patients with rare gynaecological cancers should have their pathology reviewed by a gynaecological pathologist and managed within a multi-disciplinary framework, with access to clinical trials and rare cancer registries. However many patients are not referred to a tertiary centre for management with demographics often dictating where patients receive care.

There is an international effort to meet the challenge of research in rare cancers, including rare gynaecological cancers, and this has laid the groundwork for multi-centre and international trials and registries.

## Gynaecological Cancer InterGroup Rare Cancer Tumour Working Group

The Gynaecological Cancer InterGroup (GCIG) established a Rare Cancer Tumour Working Group, which includes representatives from each of the international gynaecological trials groups, including The Australian and New Zealand Gynaecological Oncology Group (ANZGOG). This group meets on a biannual basis with the aim to develop consensus guidelines for management of women with rare gynaecological tumours, address the national and international barriers to rare cancer research, identify key priorities for research and develop and conduct clinical trials. The GCIG Rare Cancer Tumour Working Group has discussed establishing an international rare gynaecological web-based cancer registry. However, barriers such as patient confidentiality and data security, inherent in international registries, have delayed this initiative progressing.

The Rare Cancer Working Group has developed a number of novel strategies to provide clinical support for clinicians treating patients with rare cancers. The GCIG website includes a clinical question and answer forum, where members can request advice on the management of rare cancers. This allows clinicians to obtain second opinions from international experts. A range of such consensus

statements has recently been published to help in the management of patients with rare gynaecological cancers (table 1) and these will be updated on a regular basis.<sup>7</sup> Clinical trial development is underway for a number of rare cancers, which will be discussed below.

**Table 1: GCIG Consensus Review Topics**

Ovarian and uterine carcinosarcoma
Low malignant potential tumours
Low grade serous carcinoma
Sex cord tumour
Germ cell tumour
Squamous ovarian carcinoma
Small cell carcinoma cervix
Small cell ovarian carcinoma
Vulva and vaginal melanoma
Ovarian carcinoid tumour
Mucinous carcinoma
Clear cell carcinoma ovary
Clear cell carcinoma cervix and uterus
Trophoblastic disease
Low grade endometrial stromal sarcoma
High grade uterine sarcoma
Uterine serous carcinoma
Adenosarcoma
Uterine and ovarian leiomyosarcoma
Glandular carcinoma of the cervix

### International Rare Cancers Initiative

The International Rare Cancers Initiative was established in early 2011 as a joint initiative between National Institute for Health Research, Cancer Research Network, Cancer Research UK, National Cancer Institute and the European Organisation for Research and Treatment of Cancer. Recently, the Institut National du Cancer in France and other national bodies have joined/initiated joining. The primary objective of The International Rare Cancers Initiative is to facilitate international clinical trials in rare cancers with a focus on diseases where there is no or very limited clinical trial data.

Within gynaecological cancers, sarcomas have been identified by The International Rare Cancers Initiative as a priority for trial development, with several studies under

consideration. The first phase III study is underway in uterine-confined leiomyosarcomas, randomising patients to adjuvant docetaxel and gemcitabine, followed by doxorubicin versus observation (NCT01533207). This study opened in June 2012 and aims to enrol 216 patients. A second phase II trial is soon to open randomising patients with high-grade uterine sarcoma to maintenance carbozantinib or placebo after chemotherapy with doxorubicin +/- ifosfamide (NCT01979393).

### Clinical trials in rare gynaecological cancers

When designing a clinical trial, a primary statistical consideration is powering the study adequately in order to answer the clinical question. This is the central challenge in rare gynaecology cancer research. In addition to difficulty in recruitment, there can be challenges in estimating power calculations. Phase III trial data is often used to estimate treatment effect sizes, but for rare gynaecological cancers this information is usually not available. Limited information from phase II trials or historical controls may have to be used, reducing the likelihood of a successful trial outcome.

Billingham et al have proposed a novel approach for clinical trials in rare diseases. They propose that a reverse philosophy is used in rare diseases where the design starts with the number of patients that is feasible to collect within a sensible time frame and then, based on a Bayesian analysis, show that this amount of data could provide useful information on which to make clinical decisions in the future.<sup>8</sup> For example, given a predicted number of events, the design is evaluated by: (i) demonstrating the information that the trial could provide for a range of possible observed results and prior distributions; and (ii) given a pre-specified decision criteria, using simulation to determine the probability that the trial will make the correct decision under different underlying true scenarios.

Phase III clinical trials in gynaecological cancers have commonly allowed the inclusion of patients with rare subtypes. For example, in advanced ovarian cancer trials, patients with mucinous and clear cell cancers are included, but are poorly represented and typically account for only <5% of patients accrued.<sup>9-13</sup> Recently, the Japanese Gynaecological Group successfully completed the first phase III clinical trial focusing on clear cell cancer of the ovary. This trial randomised 650 patients with stage I-IV clear cell ovarian cancer to six cycles of carboplatin and paclitaxel or cisplatin and irinotecan. Recruitment was completed in less than five years. There was no difference demonstrated in two-year progression free survival or overall survival.<sup>14</sup> This was a remarkable effort and made possible by the higher incidence of clear cell cancer of the ovary in the Japanese population and the dedication of the investigators and patients. A phase II trial of sunitinib in recurrent clear cell cancer of the ovary has just been completed and based on the high frequency

of PIK3CA mutations in clear cell cancer, a first line trial of temsorolimus in combination with carboplatin and paclitaxel is now underway (NCI-2011-02653).

Less successful was the GOG-mEOC trial (NCT01081262), which closed in August 2013 due to poor recruitment, with only 10% of the target 332 patients. This was the first phase III clinical trial for mucinous ovarian cancer which was investigating the standard regimen for all epithelial ovarian cancer, or carboplatin and paclitaxel versus oxaliplatin and capecitabine with or without bevacizumab as first-line therapy for stage II-IV or recurrent stage I (chemo-naïve) mucinous ovarian or fallopian tube cancer. The number of eligible patients with advanced stage mucinous cancers was lower than anticipated and many centres did not open the trial due to the rarity of these tumours and the costs of opening a trial which may recruit only one or two patients. This is an ongoing challenge with rare tumour trials.<sup>15-16</sup> This study also encountered funding problems with the use of off-label drugs, standard for one tumour type (for example, bowel cancer) but not approved for another (for example, ovarian cancer), another common barrier for rare cancer research.

There are ongoing studies for patients with low-grade serous ovarian cancer, which is quite distinct from high-grade serous ovarian cancer. Low grade serous ovarian cancer is difficult to treat with a poor response rate to chemotherapy.<sup>17-18</sup> Documented mutations in BRAF or KRAS oncogenes have driven interest in MEK inhibitors, with two phase III trials underway. The MILO trial (NCT01849874) is testing MEK162 versus physician choice and the LOGS trial (NCT02101788) is testing the MEK inhibitor, trametinib versus physician choice.

For the treatment of low-risk gestational trophoblastic disease, GOG0275 opened in June 2012. It is a phase III randomised trial of Actinomycin-D versus multi-day Methotrexate. In addition to the primary outcome of complete response, this trial also has several secondary endpoints, including quality of life assessments (NCT01535053). This trial will be important in defining standard care for this highly curable malignancy.

For very rare cancers, conducting phase III randomised clinical trials may not be feasible and clinicians must rely on phase II trials instead. Interpreting results of such trials can be challenging. Appropriate endpoints need to be considered in the design. Response rate may not be the best indicator of activity for some agents. Progression free survival or time without symptoms may be more appropriate endpoints, particularly with targeted therapies. Trials that incorporate early stopping rules can prevent patients receiving ineffective treatment and allow investigators to redirect research efforts. Interpreting the outcome of phase II trials can be difficult in the absence of prior clinical trials or good historical controls, although if the treatment effect size is large, this is less problematic.

Randomised phase II trials provide an internal control, however larger patient numbers would be required. Sequential testing of new treatments is another potential way of overcoming this problem.

There is considerable time and cost associated with any clinical trial. Opening rare cancer trials which may only accrue a few or no patients is time-consuming, expensive and often unrewarding. The PARAGON trial, which is being conducted by the ANZGOG, provides one way to overcome this problem.<sup>19</sup> The PARAGON trial is a series of seven individual phase II studies embedded in a single 'umbrella' or 'basket protocol'. It includes a subset of patients with epithelial ovarian cancer, endometrial cancers, uterine sarcomas and sex cord stromal tumours, who all share the common study entry requirement of having an ER/PR positive cancer, which are more likely to respond to hormonal therapies. Patients are treated with the aromatase inhibitor, anastrozole. The novel design of this study has been attractive to a large number of participating centres in Australia and the UK. It is recruiting well and will be successfully completed.

For extremely rare cancers, small case series and case reports may be the only data available. There have been efforts to establish case series for rare gynaecological cancers across institutions both nationally and internationally.<sup>20-21</sup> Case studies provide little more than anecdotal evidence, with a natural tendency for selection bias in cases submitted for publication.

## How can we pick molecular targets?

There is much interest in identifying potential treatment targets in gynaecological cancers. PARP inhibitors are the most successful example of the effort to identify a subset of patients with epithelial ovarian cancer most likely to benefit from treatment. Women with high grade serous cancer, who have been shown to have inherited a germline mutation in the breast and ovarian cancer predisposition genes, BRCA1 or BRCA2, have the best outcomes following maintenance therapy in platinum sensitive relapsed disease.<sup>22-23</sup> Several phase III trials are underway for BRCA1/2 mutation carriers and patients with high-grade serous ovarian cancers with Olaparib (SOLO1 NCT01844986, SOLO2 NCT01874353) and Niraparib (NCT01847274). Translational research will be essential to identify potentially actionable mutations and other aberrant signalling pathways in rare gynaecologic cancers. This is an area of intense international effort and the GCIG and International Rare Cancers Initiative have an important role in underpinning these approaches.

## Can we use data from similar cancers at other anatomic sites?

Extrapolating from the experience in other more common tumour types has been of value in patients with rare



gynaecological cancers. For example, the management of malignant ovarian germ cell tumours has been based on advances in the management of men with testicular germ cell tumours. Bleomycin, etoposide and cisplatin is the standard chemotherapy regime in males and is equally effective in female patients.<sup>24-25</sup> There are some trials of novel therapies for patients who have failed platinum-based therapies, open to both male and female germ cell patients.

Across the UK and several European countries, centralisation of management of women with gestational trophoblastic disease has improved survival compared with countries that have not adopted this model.<sup>26</sup> Gestational trophoblastic disease and germ cell tumours are good examples of rare cancer subtypes where this should be considered. There is currently no centralisation in Australia for the management of rare gynaecological cancers.

### Rare cancer registries and gynaecological cancers

CART-WHEEL.org is a web-based rare tumour database which facilitates identification and annotation of rare gynaecologic cancers.<sup>27-28</sup> At present this resource is under-utilised by patients with gynaecological cancers. ANZGOG is committed to developing strategies to promote patient awareness and increase recruitment. This could facilitate pre-clinical research identifying potential actionable aberrations to underpin novel clinical trial design. Ethically approved research projects can apply to access information held by the CART-WHEEL.org, including the entity holding stored tissue for the cases in question. Currently, CART-WHEEL.org research projects are in place for small cell ovarian cancer and high-grade mucinous ovarian cancer.

### Conclusion

Over the last decade, there has been significant progress in establishing national and international rare cancer networks, with the specific aim of facilitating research and improving outcomes in women with rare gynaecological cancers. There are many challenges in carrying out clinical trials in these patients, which require national and international collaboration. Registries for patients with rare cancers, such as CART-WHEEL, could facilitate urgently needed research.<sup>27</sup> Translational studies will increase our understanding of rare tumour biology and identify potential drug targets. The number of patients with rare tumours is expected to increase exponentially as genomic profiling divides and subcategorises patients with more common tumours into smaller distinct molecular subsets. Achieving better outcomes for our patients will only be achieved through increased collaboration and improved funding of rare cancer research.

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## BRAIN TUMOURS: SUCCESSES AND CHALLENGES ON THE OTHER SIDE OF THE BLOOD-BRAIN BARRIER

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### Abstract

Tumours of the central nervous system encompass a large variety of cancers, ranging from slow-growing to rapidly progressive. Although comparatively rare in adults, central nervous system malignancies are relatively common in children, adolescents and young adults, resulting in substantial and ongoing morbidity, significant loss of effective life-years and a heavy burden on family and carers. In fact, more children and adults under the age of 40 die from a brain tumour than from any other cancer. As such, their effect on the community is greater than the apparent low incidence would otherwise indicate. This article focuses on adult brain tumours and in particular glioblastoma. Glioblastoma is rare, but is an example of a disease where treatment has been improved through better understanding of its molecular characteristics, as well as through international clinical trials. We will also discuss some challenges in rare tumours where level one evidence for optimal management is unlikely to ever exist.

Brain tumours are a heterogeneous group of diseases, with over 100 types and subtypes, benign and malignant. Figure 1 shows the types of malignant brain tumours operated on most commonly at Royal Melbourne and Melbourne Private Hospitals, both busy tertiary referral centres.

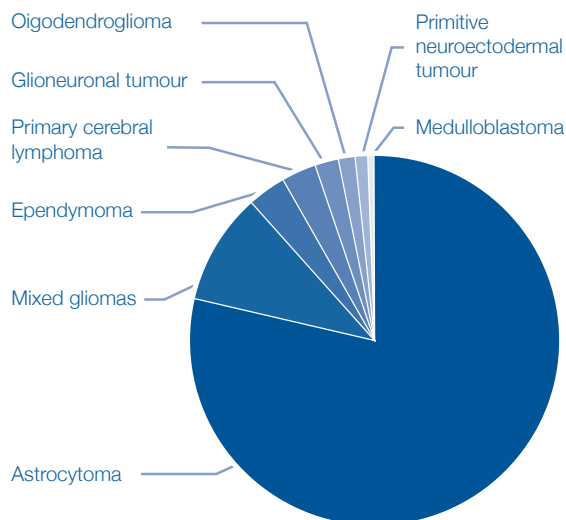
In this paper, we focus on adult malignant brain tumours, accounting for 1.5% of all new cancers diagnosed annually in Australia.<sup>1</sup> The most recent Australian Institute of Health and Welfare cancer incidence and mortality data indicate that in 2010, 1680 Australians were diagnosed with a malignant brain tumour and in 2011, over 1200 died from the disease, a sobering observation that incidence is closely matched by mortality.<sup>2</sup>

### Aetiology and molecular biology

For the most part, the aetiology and risk factors for brain cancers remain unknown. Only 5% of brain tumours are attributable to rare familial cancer syndromes such as Turcot or Li-Fraumeni Syndromes.<sup>3</sup> Ionizing radiation exposure may increase brain tumour risk, more commonly at least 10-15 years after radiation.<sup>4</sup> There is no clear association between mobile phone use and brain tumours, despite some contention in the literature.<sup>5-7</sup> As is the case for many other cancer types, histological description of brain

tumours is now transitioning to molecular characterisation and, importantly, treatment strategies are being modified accordingly. Table 1 describes some of these molecular markers and their significance and utility.

**Figure 1:** Pie chart of malignant tumour types at Royal Melbourne and Melbourne Private Hospitals on Australasian Comprehensive Cancer Outcomes Research Database (ACCORD) – from 1999-2014. Excludes metastases. Total n= 1252



## Rare tumours but effective management

The management of brain tumours has evolved over the last decade with the advent of improved neuro-surgical and radiation techniques, new systemic therapies, increasing numbers of clinical trials and the introduction of multi-disciplinary care. Among the most important has been the addition of temozolomide chemotherapy to radiotherapy following surgery for glioblastoma (GBM).<sup>8</sup> However, beyond chemotherapy and promising developments in targeted therapies, there are several other aspects of neuro-oncology that have developed and strengthened in recent years. This exemplifies optimal management of rare tumours.

In the Australian context, collaboration among the relatively small group of clinicians treating brain tumours has been facilitated by the development of several groups. Examples include: the Cooperative Trials Group for Neuro-Oncology (COGNO), established in 2007 to co-ordinate management of neuro-oncology trials and

facilitate discussion of potential investigation into more rare central nervous system (CNS) malignancies; the Clinical Oncology Society of Australia Neuro-oncology Group, established in 2000 which among other activities, has developed comprehensive Australian clinical practice guidelines for brain tumour management; and Cancer Council Victoria's Clinical Network Neuro-Oncology committee, established in 1999, which has produced several patterns of care studies for Victorian patients in collaboration with the Victorian Cancer Registry.<sup>9-11</sup> Co-operative groups in Australia are mirrored overseas with North American, European and Asian groups providing education, scientific and clinical development in the field.

At many hospitals, brain tumours are managed in a multidisciplinary context, with regular multidisciplinary team meetings discussing complex cases, as well as multi-disciplinary neuro-oncology clinics.<sup>12</sup> Like other tumour streams, a care co-ordinator is an essential focal point for clinicians and patients.

**Table 1:** Select molecular markers in adult malignant brain tumours\*

Glioma			
Molecular marker	Description	Impact	References
MGMT (O6-methylguanine-DNA methyltransferase) methylation	Methylation inactivates repair enzyme and renders cells more sensitive to damage from chemotherapy.	Predictive and prognostic biomarker in GBM.	32,33
IDH-1 and IDH-2 (isocitrate dehydrogenase) mutations	Krebs cycle enzyme Mutation is early molecular event. More common in grade II/III glioma (50-80%) and secondary GBM Associated with improved prognosis (PFS and OS).	May be associated with improved outcomes with chemotherapy in WHO III oligodendroglioma and oligoastrocytoma.	21,34-36
1p/19q codeletion or loss of heterozygosity	Very common in oligodendroglial tumours (up to 70%). Often but not always associated with IDH-1 mutation.	Associated with improved sensitivity to chemotherapy in WHO II and III tumours. Rare in GBM.	19,20
Molecular variants/subtypes of GBM • proneural, • classical/proliferative • mesenchymal	Distinct subclasses with difference genomic alterations.	Could potentially be used as predictive biomarkers or drug targets in future.	37-39
Medulloblastoma			
Potential therapeutic target 3 molecular variants: • sonic hedgehog (SHH) • subtype C • subtype D	Distinct differences in demographics and prognosis for each subtype.  SHH pathway activated in over 50% of adult medulloblastomas.	Potential therapeutic target.	30

\*This table is not exhaustive; many more molecular markers exist and are under investigation for their prognostic, predictive and/or targetable value.

## Standards of care and gaps in current knowledge

The traditional standards of care for many brain tumours have been largely dictated by the histopathology of the tumour, coupled with the clinical context (age and performance status). This is beginning to change, albeit slowly although in some contexts, without robust prospective evidence to guide us. Management of several brain tumours is discussed below.

### **Glioblastoma**

Although rare, glioblastoma (GBM) is the most common CNS malignancy and data from a number of randomised clinical trials is available. The EORTC-NCIC trial reported by Stupp et al,

published in 2005, remains the ‘gold standard’ management of patients with GBM under 70 years.<sup>8</sup> Several trials have attempted without success to add additional medications in the de novo setting – bevacizumab, cediranib and cilengitide.<sup>13-16</sup> In Australia, there is no standard of care for patients with recurrent GBM. Patients often receive single agent carboplatin or lomustine. Enrolment on a clinical trial is appropriate. Bevacizumab is approved by the US Food and Drug Administration, but is not Pharmaceutical Benefits Advisory Committee approved in Australia and is only available on an access program.

The most pressing clinical issues in the management of GBM include: the treatment of de novo disease in patients aged over 70 years or those with poorer performance status; the management of recurrent GBM; and the management of patients who have a non-methylated O6-Methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme. This group of patients has a poorer prognosis and is less likely to respond to current therapies including temozolomide.<sup>17</sup>

### **Grade 3 glioma**

This term encompasses pure astrocytomas, oligodendrogliomas and mixed oligoastrocytomas. Until recently, these tumours were grouped as one and standard management was surgery, radiotherapy, then temozolomide chemotherapy at disease progression. However, the prognostic and predictive value of 1p/19q co-deletion – seen in up to 70% of patients with an oligodendroglial component,<sup>18</sup> – is now recognised and two randomised trials reported striking overall survival improvements for those 1p/19q co-deleted patients who received PCV chemotherapy in addition to radiotherapy. In one study, the benefit was 14.7 years versus 7.3 years in and in the other study: 123 versus 23 months.<sup>19,20</sup> Early post-radiotherapy chemotherapy is now considered routine for patients with 1p/19q codeletions. Isocitrate

dehydrogenase (IDH) mutations may also confer benefit from chemotherapy compared with non-mutated tumours.<sup>21</sup> Of interest, these two studies evaluated PCV (procarbazine, lomustine and vincristine) chemotherapy, an old fashioned and complex regimen. Many believe that temozolomide is likely to provide equivalent results to PCV with less toxicity.<sup>22</sup>

### **Low grade glioma**

Low grade glioma (LGG) is much less common than GBM in adults, and tends to affect young adults. After surgery, management options include watching and waiting or up-front radiotherapy, with chemotherapy traditionally reserved until progression. However, updated data from RTOG 9802, comparing radiotherapy + PCV chemotherapy, versus radiotherapy alone, reported a striking overall survival benefit (13.3 versus 7.8 years, HR 0.59, p=0.03) with the combination arm.<sup>23</sup> The data are not yet available for 1p/19q co-deletion status, but given that 42% of participants had oligodendroglioma and 32% were mixed gliomas, it is assumed that much of the benefit is driven by the co-deleted tumours responding to chemotherapy. The trial also does not tell us whether co-deleted patients would do just as well with up-front chemotherapy, reserving radiotherapy for later progression. The obvious advantage of such a strategy is that the potential neurocognitive sequelae of radiotherapy, especially in a young patient population, would be delayed. As such, we favour early chemotherapy in those with 1p/19q co-deletions. In Australia, temozolomide is restricted to recurrent grade 3 or grade 4 tumours and is not routinely available for LGG.

### **Rare brain tumours**

Medulloblastoma is a rare cancer representing only 5% of all adult CNS malignancies.<sup>24,25</sup> Much of the literature on adult medulloblastoma is in the form of case reports and small cohort studies. Management has largely been extrapolated and modified from the paediatric population, with no accepted standard of care world-wide. A recently published international patterns of care survey, mainly from Australia, reported that cranio-spinal irradiation was common, as was post-radiotherapy chemotherapy, but the regimens varied considerably – up to 10 different regimens were described – reflecting the uncertainty as to optimal management of this disease in adults.<sup>26</sup>

Ependymoma, a rare tumour involving the spinal cord more frequently than brain, represents only around 3% of CNS malignancies.<sup>27</sup> While surgery with or without radiotherapy is the predominant management strategy for ependymoma, chemotherapy is considered for recurrent disease. However, to date, chemotherapy has not been shown to improve outcome in this disease, and clearly improvements are needed.

## Clinical trials: feasible, possible, and do-able for rare tumours in Australia

Despite their rarity, there are many successful clinical trials for CNS malignancies. Further, Australian centres have contributed significantly. These range from large international phase III studies to local phase I studies. A number of Australian sites are participating in early phase studies in which experimental drugs are attempting to inhibit molecular targets such as EGFR, EGFRv3, FGFR, PI3 Kinase and others. COGNO has conducted a number of Australian studies, including the recently completed CABARET study that recruited over 120 patients in 12 months across Australia.<sup>28</sup>

For rarer tumours such as ependymoma and medulloblastoma, the difficulty lies in the fact that it is unlikely that large scale randomised studies will ever be conducted, and trials, where available, would ideally need to be multi-centre and multi-national studies. To this end, the US-based Collaborative Ependymoma Research Network foundation has established two clinical trials for chemotherapy and targeted therapy in adults with ependymoma.<sup>29</sup> It may be possible in the future for Australian centres to collaborate with overseas foundations in order to involve Australian patients in these research efforts.

## Ongoing challenges

A major challenge for neuro-oncology is applying limited objective evidence to routine clinical practice. Clinical information and direction often comes from retrospective post hoc subgroup analyses from clinical trials while at the same time, novel biomarkers come to light. Do we accept the limitations of retrospective review and change our practice, or should we await prospective confirmation? In some cases for example, there appears to be compelling benefit of chemotherapy for 1p/19q co-deleted oligodendrogliomas. In other diseases, such as management of medulloblastoma or ependymoma, we need to accept that there will never be robust randomised phase III trial data to support our management decisions.

Another challenge is the potential danger of 'leaping ahead' for patients with incurable aggressive tumours such as GBM, and attempting to incorporate drugs into clinical practice where evidence does not yet exist. It is understandable that even clinicians may clutch at straws if there is a small chance of benefit when faced with a patient in front of us. This is exemplified by the use of bevacizumab in GBM. After favourable single arm studies and non-comparative randomised phase 2 trials in the recurrent disease setting indicated benefit, at least anecdotally, many clinicians in the US began using the drug in de novo GBM. However, the subsequent AvaGlio and RTOG 0825 studies did not show an overall survival benefit when using bevacizumab in this context.<sup>13,14</sup>

Prognostic and predictive biomarkers should play a stronger role in the future to tailor and guide clinical practice, but in some ways they are still in their infancy. 1p/19q status is now routinely used to guide treatment decisions in grade 2 and 3 gliomas, whereas IDH mutations and MGMT methylation status have yet to reach a tipping point of guiding decisions.

The field of neuro-oncology has many of the same issues and hindrances as that of other rare tumours. First, rare tumours such as medulloblastoma are more common in the paediatric patient population, but the management of these patients cannot be extrapolated to the adult population due to fundamental differences in tumour biology and tolerability of therapies.<sup>30</sup> Secondly, tumours must undergo expert neuropathology review. Indeed a review of ependymoma patients demonstrated that 14.6% were reclassified on expert neuropathology review.<sup>31</sup> Third, there has been a reluctance to allow neuro-oncology patients access to generic phase 1 studies.

Finally, within Australia, access to drugs is not the same as in the US. Thus, evidence and recommendations from US studies and organisations such as the National Comprehensive Cancer Network Clinical Practice Guidelines may not always be relevant in the Australian context. This may be frustrating, but is occasionally overcome by compassionate drug access (e.g. via a hospital or a pharmaceutical company) if available evidence is deemed to warrant it for individual circumstances.

## Summary and conclusion

Brain tumours are rare in adults, but significant progress has occurred in recent years, changing the face of neuro-oncology in Australia and worldwide. The ongoing challenges are not simply because these tumours are rare, but also resistant to many therapies and in most cases incurable. However, continuing discoveries and clinical trials, as well as substantial work in collaboration and networking, will continue to facilitate progress in all aspects of CNS oncology, from diagnosis through to management and supportive care.

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# MOLECULAR INSIGHTS INFLUENCING THE MANAGEMENT OF HEAD AND NECK CANCERS

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## Abstract

Head and neck cancers represent a clinically diverse group of tumours with distinctive molecular features. Understanding the importance of characteristic molecular changes has permitted the definition of a new clinicopathological entity - the Human Papillomavirus (HPV) related subset of oropharyngeal squamous cell carcinomas that are generally associated with a good prognosis. We briefly discuss the key clinical and pathological differences between HPV-related and HPV-unrelated oropharyngeal disease and the underlying molecular differences, and we also consider how these features can inform clinical management. For rarer head and neck tumours or those that lack effective systemic treatment options, such as salivary gland tumours, sinonasal carcinomas and NUT midline tumours, we discuss how an understanding of underlying molecular features can facilitate the exploration of novel treatment options. Thus we demonstrate in this brief review, that despite the rarity of most head and neck cancers, evolving insights into the key molecular drivers are impacting on clinical practice.

Though commonly grouped together on the basis of anatomical proximity, the generic terminology of 'head and neck cancer' (HNC) refers to a miscellany of clinically and molecularly diverse tumours that arise from more than 15 anatomical subsites and comprise several different histotypes. From a clinical perspective the term HNC is often used to refer to mucosal squamous cell carcinomas, but evidence of differences in patient outcomes according to anatomical subsite and aetiology, have highlighted the need for research in more uniform cohorts.

Despite the rarity, HNCs are generally successfully managed with combinations of surgery, radiotherapy and chemotherapy delivered by a multidisciplinary team. The complexities of the sensitive anatomical location, the toxicity of treatment, and the functional consequences of both the tumour and treatment mandates management of these tumours by an expert team, and there is evidence of better outcomes in larger more experienced centres.<sup>1</sup>

The identification of the molecular changes that characterise subsets in HNC has been useful to improve disease stratification and has impacted upon patient management.<sup>2-8</sup> We will highlight selected key molecular insights in HNC.

## Head and neck squamous cell carcinomas and the role of the Human Papillomavirus

The discovery of the causal role of the Human Papillomavirus (HPV) in the majority of oropharyngeal

squamous cell carcinomas (OPSCCs) in many countries, including Australia, exemplifies how translational research has improved the clinical management of HNC.

The role of HPV has been clearly defined only in the oropharyngeal subsite, where overexpression of p16 is an established robust surrogate marker of the HPV-induced subset of OPSCC.<sup>3,9</sup> Importantly, HPV-related OPSCC represents a distinct clinicopathological and molecular entity associated with a favourable prognosis regardless of treatment modality.<sup>3,10-14</sup> A summary of clinicopathological differences between HPV-related and HPV-unrelated disease is provided in table 1.

From an epigenetic level to protein level, the clinical variances between HPV-related and HPV-unrelated disease are also reflected from a molecular perspective.<sup>15-21</sup> Characteristic molecular differences include the lack of association with TP53 mutations or major chromosomal abnormalities in HPV-related disease,<sup>17,18,22</sup> while the majority of non-HPV related head and neck squamous cell carcinomas (HNSCC) harbour TP53 mutations,<sup>19,20,23</sup> and are known to demonstrate field cancerisation effect.<sup>19-21,23</sup> A recent publication using the data from the Cancer Genome Atlas HNSCC Working Group identified the poor prognostic effect of 3p deletions in both HPV-related and HPV-unrelated disease.<sup>22</sup> However, for HPV-unrelated disease with simultaneous TP53 mutation and 3p deletion, the additional presence of mir-548k miRNA and MUC5B gene mutations identified further subgroups with even worse survival.

**Table 1:** Summary of the key clinicopathological differences between HPV-related oropharyngeal squamous cell carcinomas (OPSCCs) and HPV-unrelated head and neck squamous cell carcinomas (HNSCCs).

Variable	HPV related HNSCC	HPV-unrelated HNSCC
Anatomical subsite	Oropharynx (base of tongue, tonsil)	Any
Age	Younger	Older
Risk factors	Increased number of sexual partners, HIV positive status, cannabis use	Tobacco smoking, excess ethanol intake
Male : Female incidence	More common in males	More common in males
Overall incidence	Increasing	Generally decreasing
T-category	Generally lower	Any
N-category	Generally higher	Any
Characteristic histological feature	Basaloid	Any
Characteristic radiological feature	Often demonstrates cystic change in nodes	Any
Response to therapy	Favourable	Variable
Prognosis	Favourable	Variable
Key common molecular features	Overexpression of p16 by IHC, TP53 wild-type	Variable p16 overexpression, TP53 mutated

Molecular dissimilarities between diseases may also serve as differential neo-antigenic stimuli for the host immune system,<sup>24-28</sup> although HPV also employs mechanisms to directly facilitate immune evasion.<sup>28,29</sup> Early clinical trials of antibodies targeting the programmed cell death-1 (PD-1) pathway have demonstrated efficacy in tumours characterised by genomic heterogeneity,<sup>30</sup> of which HNSCC is one of the top most mutated tumours defined by whole exome sequencing.<sup>31</sup> It is yet to be established whether the differences in immune responses observed for HPV-related and HPV-unrelated HNSCC impact on patient prognosis, or the effectiveness of immunotherapies.<sup>24,25,32</sup>

In the oropharynx, predominantly HPV subtype 16 contributes to carcinogenesis through the characteristic production of the E6 and E7 viral oncoproteins.<sup>33-35</sup> E6 mediates the ubiquitination of p53, and E7 disrupts retinoblastoma protein (pRb) function. With the combined loss of both tumour suppressors, unrestricted cell cycling occurs and apoptosis is evaded. p16 overexpression detected by immunohistochemistry is an established surrogate marker for HPV-related OPSCC, and results secondary to loss of a negative feedback loop mediated through pRb9. Thus, p16 overexpression is a surrogate marker of good prognosis that occurs only as a bystander effect of the HPV.

The definition of p16 'positivity' or overexpression, is a key consideration to ensure its use as a robust surrogate

marker for the presence of HPV. For OPSCC, p16 'positivity' is commonly defined as strong intensity staining in more than 70% of cells, although less stringent criteria are still considered sufficient.<sup>3,9</sup> For all other HNSCC, whether p16 immunohistochemistry is an adequate surrogate marker of HPV, and whether p16 overexpression by itself is prognostic, remains to be established.

In general, outside of the oropharyngeal subsite, HPV mediated disease is known to occur much less frequently than for OPSCC, although the exact incidence is hindered by diagnostic limitations of methodology chosen, the use of heterogeneous cohorts limiting insight into subsite specific differences, and the use of small cohorts with a small number of observed events.<sup>36-39</sup> Caution should be used in interpreting the literature in light of the methodology used, as ultimately only methodology such as reverse-transcriptase PCR or in-situ hybridisation are able to detect transcriptionally active or integrated HPV to infer causality.<sup>40</sup> Other techniques, including viral genotyping and serology may overestimate the prevalence of the virus through detection of viral DNA not contributing to carcinogenesis. p16 immunohistochemistry lacks specificity for HPV given that other somatic aberrations, such as gene amplification or mutation of Rb, can also alter p16 expression. Similarly, absence of p16 staining does not indicate the loss of the protein, but rather demonstrates a lack of overexpression, exemplified by the absence of staining of normal tissues.<sup>41</sup>



An additional noteworthy point is that p16 and HPV status should not be interpreted in isolation. The significance of p16 or HPV as a prognostic marker needs to be interpreted in the light of clinical information, given the abrogation of a favourable outcome for patients with a strong smoking history, T4 disease, or greater than N2a disease.<sup>3,42</sup> Reports in cohorts of HPV-related OPSCC of late disseminating metastatic disease to locations unusual for HPV-unrelated disease, and of longer survival in patients with metastatic disease, further emphasises the different tumour biology observed between the two disease entities.<sup>43,44</sup>

While further research is required to understand the role of HPV in other HNSCC subsites, the ability to identify patients with OPSCC who have a favourable prognosis has led to interest in whether de-escalation of treatment can minimise toxicity without compromising efficacy. This is of particular relevance given the younger age of patients with HPV-related disease. Numerous trials are currently enrolling patients with HPV-related disease, including the Trans-Tasman Radiation Oncology Group (TROG) 12.01 study which investigates the benefit of weekly cetuximab and radiotherapy versus weekly cisplatin and radiotherapy, in patients with low risk HPV-related OPSCC.

### Salivary gland tumours

Salivary gland tumours include a spectrum of rare but distinct cancers, including the more indolent adenoid cystic carcinomas and the highly aggressive salivary ductal carcinomas. Tumours can arise from the three major components of the organ – the ducts, the acini and the myoepithelial cells, with disease occurring most commonly in the parotid gland.<sup>5</sup> The World Health Organisation classification of salivary gland tumours includes 24 malignant epithelial tumours, in addition to benign tumours associated with malignant counterparts.<sup>45</sup> Treatment is generally limited to surgery and radiotherapy, with these tumours demonstrating a high propensity for metastasis and recurrence without proven effective chemotherapy options.

While adenoid cystic carcinomas can arise from any location, it most frequently occurs in the major salivary glands of the head and neck. A recurrent translocation, t(6:9)(q22-23;p23-24), has been commonly identified in adenoid cystic carcinomas regardless of the site of origin of disease, in both primary and recurrent disease.<sup>6,46-50</sup> The most common fusion product occurs between MYB, an oncogene encoded for on chromosome 6 and NFIB, a nuclear factor encoded on chromosome 9. Disruption to the MYB locus been identified as a putative poor prognostic biomarker.<sup>50,51</sup> MYB activation resulting from the fusion mediates carcinogenesis mainly through its role controlling transcriptional elongation, but is additionally involved in the maintenance of cellular proliferation, inhibition of cellular differentiation, apoptosis and cell adhesion.<sup>46,51</sup> Due to

variable breakpoints in MYB and NFIB, a large number of fusion transcript variants are expressed.<sup>46,50</sup> Disruption of the MYB pathway has also been identified to occur through gene amplification, mutation and overexpression in up to 80% of all adenoid cystic carcinomas, indicating that it is likely to be a seminal event in carcinogenesis.<sup>6,48-50</sup> A DNA fusion vaccination based immunotherapy targeting MYB has been developed and shows anti-tumour efficacy in mouse models.<sup>52</sup> Other potentially targetable aberrations observed in adenoid cystic carcinomas include canonical activating PIK3CA mutations, FGFR activating mutations and alterations of the FGF-IGF-PI3K pathway in up to 30% tumours.<sup>6,48</sup>

Salivary ductal carcinomas are aggressive tumours that can arise from malignant transformation of pleomorphic adenomas or can occur de novo, and demonstrate both in-situ and invasive patterns.<sup>5</sup> Of particular interest, salivary ductal carcinomas demonstrate features in common with other glandular carcinomas, like breast and prostate carcinomas, with these similarities lending insight into promising treatment options.<sup>53,54</sup> A therapeutically exploitable feature of salivary ductal carcinomas, is its expression of hormone receptors (e.g. oestrogen, progesterone, androgen) and expression of transmembrane receptors (e.g. HER2, EGFR, c-kit).<sup>5,45,55,56</sup> Compared to other salivary gland tumours, salivary ductal carcinomas may be defined by the presence of androgen receptor expression, which occurs in up to 40% of cases,<sup>55,57</sup> with these tumours also known to overexpress HER2. Given the successful use of targeted therapies in prostate and breast carcinomas, similar treatment algorithms have been employed for salivary ductal carcinomas, with reports of the success of androgen deprivation therapy and of HER2 inhibition.<sup>56,58-60</sup> A recent study also reports the identification of canonical PIK3CA mutations in salivary ductal carcinomas, which holds additional therapeutic promise.<sup>61</sup> The rarity of salivary ductal carcinomas hinders the investigation of the efficacy of these therapies, although progressive molecular characterisation of the disease has assisted in the provision of promising therapeutic options, as demonstrated in the literature and in our experience (figure 1).

### Sinonasal carcinomas

Although a relatively small anatomical region, the sinonasal cavities give rise to some of the most complex and histological diverse groups of tumours.<sup>7,45,62</sup> Tumour types include intestinal-type adenocarcinomas, esthesioneuroblastomas (olfactory neuroblastoma) which only occur in the sinonasal subsite, sinonasal undifferentiated carcinomas, large and small cell neuroendocrine carcinomas and germ cell tumours. The clinical management of these diverse tumours is complex due to the proximity to the orbit and brain, with frequent neural involvement and resultant significant functional and aesthetic challenges for management with surgery and radiotherapy.

As the name implies, intestinal-type adenocarcinoma has a histological resemblance to the intestines, and has a predilection for the ethmoid sinus.<sup>7,45</sup> Wood dust and leather dust exposure are recognised risk factors for the development of disease.<sup>63</sup> Several sub-classifications of intestinal-type adenocarcinoma exist, but most commonly refer to the colonic, papillary, solid and mixed subtypes, all of which demonstrate patterns of CK7, CK20, CDX2 and MUC staining.<sup>64</sup> Given the morphological similarities to intestinal tumours, it has been of interest to determine whether the molecular changes in intestinal-type adenocarcinoma are similar. Alterations of DCC are observed similar to intestinal malignancies, but in contrast, intestinal-type adenocarcinomas express an intact Wnt signalling pathway (APC and -catenin),<sup>65</sup> demonstrate lower frequency mutations in KRAS and BRAF and have intact mismatch repair gene function.<sup>66</sup> Similar to other HNCs, TP53 and CDKN2A are frequently disrupted in intestinal-type adenocarcinomas, but EGFR overexpression is less common.<sup>20,65,67</sup> In the advanced/metastatic setting, although not proven, these tumours are reported to demonstrate response to 5-fluorouracil and platinum-based chemotherapy regimens which are effective for both colonic and head and neck carcinomas.<sup>7</sup>

NUT midline carcinoma is a recently described tumour characterised most commonly by a t(15:19) translocation. A fusion oncogene between NUT (nuclear protein in testis) and BRD4 (bromodomain-containing protein 4) results, although other fusion products between NUT and other bromodomain and extra-terminal domain

associated genes have been detected.<sup>68-71</sup> The fusion product is observed to inhibit squamous differentiation while maintaining cellular proliferation, and is also known to activate histone acetyl-transferase which indirectly, but paradoxically decreases overall acetylation levels.<sup>70</sup> This genetically defined, very rare, poorly-differentiated variant of squamous cell carcinomas arises in midline anatomical regions, and occurs in the head and neck region second most frequently to the thorax, with a possible preference for the sinonasal subsite.<sup>72</sup> These tumours occur in younger aged patients and confer a dismal median overall survival of 6.7 months.<sup>73</sup> Though rare, NUT midline carcinomas are of clinical interest due to the therapeutic promise of bromodomain inhibitors and histone deacetylase inhibitors, partnered with the development of a robust immunohistochemical antibody to detect the NUT protein.<sup>70,72</sup>

Beyond HPV status, no validated biomarkers are known to direct therapeutic decisions even for the more common HNSCC. However, the emerging understanding of the molecular features of rare head and neck cancers, many of which do not respond well to current systemic therapies, is likely to lead to the development of more effective therapies.

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**Figure 1:** FDG-PET maximum intensity projection images of a patient with salivary ductal carcinoma treated with sequential targeted therapy. The tumour strongly overexpressed androgen receptors detected by IHC, and HER2 receptors detected by IHC and confirmed by FISH. Following referral for symptomatic metastatic disease, the patient was initially commenced on a GnRH agonist (goserelin acetate).



- A.** Disease progression was observed following treatment with single agent therapy and thus, cyproterone acetate 100mg TDS was additionally commenced. This maintained stable disease for two months.
- B.** Disease progression was observed again following dual androgen blockade, and weekly paclitaxel with trastuzumab therapy was commenced.
- C.** Within approximately 10 weeks, a complete metabolic response was obtained, with radiological and clinical regression of palpable disease observed. The response has been maintained for over 14 months and is ongoing.

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# RARE MOLECULAR SUBSETS AMONG LUNG TUMOURS - WHAT MAKES THEM STAND APART FROM THE COMMON?

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## Abstract

While there is no universally agreed upon definition, rare malignancies are often defined as those with an incidence of <6 per 100,000 population. However, increasingly, commonly occurring cancers are being subdivided into smaller molecular cohorts defined by the presence of driver molecular aberrations. Non-small cell lung cancer of the adenocarcinoma histological subtype is one such example, with approximately three-quarters of cases now able to be defined according to key molecular changes that drive cancer cell growth and with the potential to be targeted therapeutically. Activating mutations in the epidermal growth factor receptor and the use of specific tyrosine kinase inhibitors reflect the realisation of a personalised approach to a molecular subset in lung cancer that improves patient outcomes. However, the frequency of rare oncogenic drivers in lung adenocarcinomas is in the order of 1-2%, which raises challenges in their identification and selection of the most appropriate model for clinical trial design of potential treatments. This review will highlight the potential and pitfalls of rare molecular alterations in lung adenocarcinoma.

Rare cancers, when considered together, constitute a major public health issue and pose particular challenges in diagnosis and treatment. However, their true burden on society is difficult to estimate, in part due to the lack of an international standardised definition. There is no universally agreed upon numerical cut-off and definitions vary based on either incidence or prevalence, or take into account disease severity or availability of therapy. In Europe, rare diseases are often defined as those with a prevalence of <50/100,000, while the US Orphan Drug Act defines it as diseases affecting <200,000 of the total US population.<sup>1</sup> However, there are inherent limitations in using prevalence as a measure of disease rarity, particularly in the context of cancer, due to the impact of disease-related survival. The project Surveillance of Rare Cancers in Europe (RARECARE) has proposed an alternate definition based on incidence, using a threshold of <6/100,000. Using this definition, rare cancers constitute 22% of all cancers diagnosed in Europe and have been shown to have inferior outcomes as compared to their more common counterparts. The discrepancy in survival between rare and common cancers becomes apparent more than one year after diagnosis, suggesting a lack of effective treatments accounts for the poorer survival observed for rare cancers.<sup>2</sup>

Regardless of its precise definition, the landscape of what constitutes a rare cancer is changing due to

the increasing identification of molecular subsets within commonly occurring cancers. These subsets are defined by the presence of specific oncogenic aberrations that drive cancer cell growth and have the potential to be targeted therapeutically. A prime example is that of non-small cell lung cancer (NSCLC), a common malignancy that is the leading cause of cancer-related deaths worldwide, whose classification has evolved into distinct molecular subsets defined by the presence of actionable driver oncogenes. These molecular subsets and the development of small molecule tyrosine kinase inhibitors (TKIs) have advanced the personalised approach to lung cancer care and improved patient outcomes. However, this approach has associated challenges, in part due to the rarity of some molecularly defined subsets, resulting in issues surrounding accurate patient identification and development and validation of targeted therapeutic approaches. This review will discuss the evolution of lung cancer management and how it has been shaped by the emerging genomic classification, with a particular focus on rare molecular subtypes of lung adenocarcinoma.

## Evolution of lung cancer classification and management

Historically, the most important classification of lung cancer rested upon the distinction between small cell and NSCLC, as their different biological behaviour conferred

different prognostic implications and necessitated different treatment regimens. NSCLC can be further classified histologically into adenocarcinoma, squamous cell carcinoma and large cell carcinoma subtypes. However, in the past, distinguishing between subtypes was not essential as therapy was empirical. Despite advances with the use of platinum-based chemotherapy, introduction of second-line and maintenance therapies, it was clear a therapeutic plateau had been reached with empirical chemotherapy.<sup>3-6</sup>

The start of personalisation of lung cancer management came in the mid-2000s, with the recognition of different efficacy and toxicity profiles of certain agents according to histological subtype. Pemetrexed demonstrated superior progression-free survival and overall survival in patients with non-squamous cell carcinoma histology, while bevacizumab, an anti-angiogenic agent, was noted to increase the risk of severe pulmonary haemorrhage in patients with squamous cell carcinoma.<sup>7,8</sup>

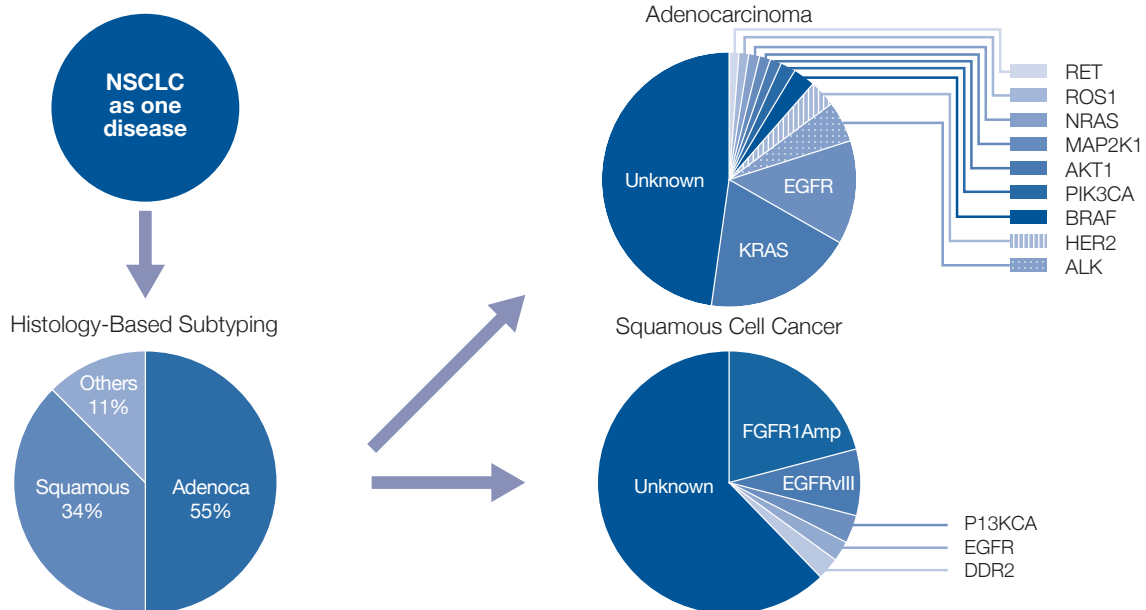
Around this time, small molecule TKIs directed against epidermal growth factor receptor (EGFR), with its signalling pathway long recognised to play an important role in cancer cell proliferation, angiogenesis and metastases.<sup>9</sup> The early trials of the first generation EGFR TKIs showed modest benefits in unselected populations, however it was noted that a subset of patients demonstrated dramatic and durable responses. It was subsequently recognised that mutations within the EGFR gene conferred exquisite sensitivity to these agents.<sup>10</sup> Subsequent studies have selected patients for the presence of an activating EGFR mutation and have shown the use of a targeted agent in this population to result in progression-free survival of

approximately one year. Overall survival for patients with EGFR mutations receiving relevant TKI therapy at some point along their treatment course now approaches two years.<sup>11</sup>

The targeting of EGFR in lung cancer demonstrated that a personalised approach can result in significantly improved patient outcomes. It also highlights that personalisation of lung cancer management requires the ability to identify and define molecular subsets of patients according to the presence of a 'driver mutation' that is responsible for the initiation and maintenance of cancer growth that can be targeted therapeutically. Through evolving molecular profiling, driven by projects such as the Cancer Genome Atlas Research Network, a deeper understanding of the molecular abnormalities in NSCLC has been acquired and a genomic classification has emerged.<sup>12</sup> This progress over time is outlined in figure 1.

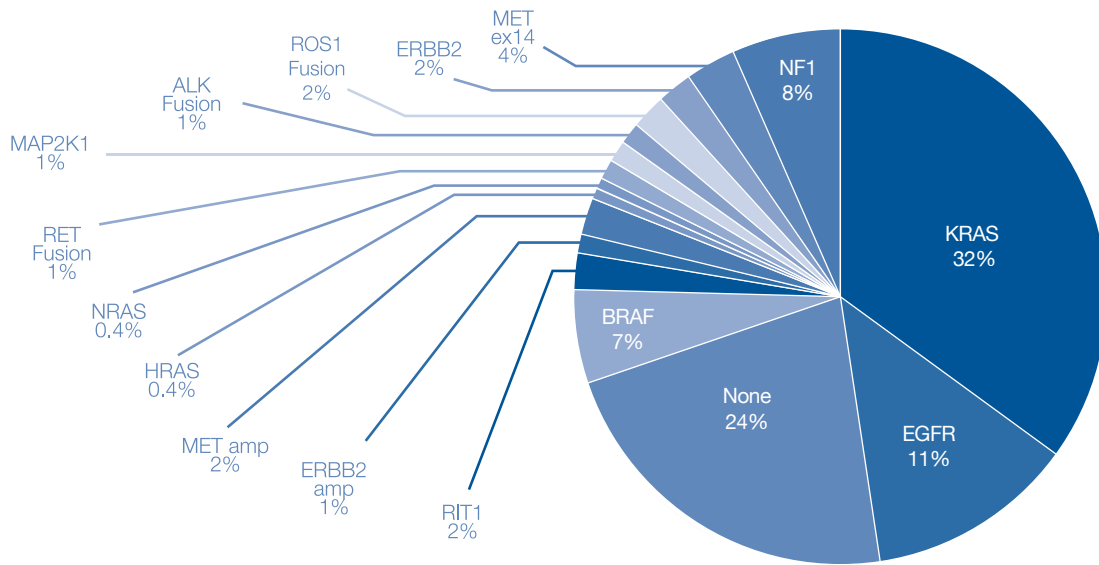
While it holds great potential, comprehensive molecular analysis is not without its challenges. NSCLC shows a high rate of somatic mutations and genomic rearrangements, which can make distinguishing passenger events from driver gene alterations difficult.<sup>13</sup> While the proportion of tumours that lack an identifiable driver lesion continues to decline, what has emerged is that many of the more recently recognised molecular subsets occur at a frequency of approximately 1% (figure 2).<sup>12</sup> The following discussion highlights new emerging rare molecular subsets within lung adenocarcinoma (see table 1), whose molecular profiling is more advanced than that of SCC, and addresses future challenges in the management of these rare molecular subsets.

**Figure 1: Evolution of NSCLC classification.**



Reproduced with permission from Li et al.<sup>49</sup>

**Figure 2:** Driver oncogenes in lung adenocarcinoma.



Adapted with permission.<sup>12</sup>

**Table 1:** Selected rare molecular subgroups of lung adenocarcinoma

Molecular target	Prevalence	Clinico-pathological characteristics	Targeted therapeutic agents	
			Approved	In development
ALK rearrangements	2-7%	Younger age Non-smokers	Crizotinib Ceritinib	Alectinib AP26113 PF-0463922 TSR-011 ASP3026 X-396 Hsp90 inhibitors
ROS1 rearrangements	1-2%	Younger age Non-smokers	-	Crizotinib Ceritinib AP26113 ASP3026
RET rearrangements	1-2%	Non-smokers	-	Cabozantinib Sunitinib Sorafenib Vandetanib
HER2 mutations	2-4%	Non-smokers	-	Irreversible pan- ERBB inhibitors Hsp90 inhibitors mTOR inhibitors
BRAF mutations	3-5%	Former or current smokers	-	Vemurafenib Dabrafenib MEK inhibitors

## Rare molecular subsets of lung adenocarcinoma

### ALK

ALK is a transmembrane receptor tyrosine kinase not normally expressed in the lung. In 2007, ALK rearrangements were reported for the first time in NSCLC and were recognised to result in constitutive ALK activity that mediates oncogenesis.<sup>14</sup> The most common rearrangement occurs between EML4 and ALK, although other fusion partners do exist.<sup>15</sup> ALK rearrangements are detected in approximately 2-7% of unselected NSCLC cases.<sup>16</sup>

With its identification, there was an immediate effort to screen and enrol patients onto a phase 1 trial of crizotinib, a MET, ROS1 and ALK inhibitor. In this trial, ALK positive patients were determined by a break-apart fluorescence in-situ hybridisation assay and were found to have an overall response rate of 61% and median progression-free survival of 9.7 months.<sup>17</sup> Similar results were observed in the subsequent phase II trial.<sup>18</sup> Crizotinib was granted accelerated US Food and Drug Administration approval in ALK-positive NSCLC based on the results of these single-arm studies.<sup>19</sup> In subsequent phase III trials, crizotinib has been shown to be superior to second-line chemotherapy and recently presented first-line data show superior median progression-free survival and overall response rate.<sup>20,21</sup> No overall survival benefit has been observed, which most likely reflects patient cross-over to crizotinib after progression on chemotherapy.

The duration of clinical benefit observed with crizotinib is limited by the development of acquired resistance. A number of resistance mechanisms have been observed, including the acquisition of secondary ALK mutations and alternate tyrosine kinase activation, including ERBB family pathway activation, KIT amplification and KRAS mutations.<sup>22,23</sup> A number of more potent second-generation ALK inhibitors are under evaluation and have shown promising preliminary activity in patients who are both crizotinib-naïve or have developed acquired crizotinib resistance.<sup>24-27</sup> One such agent, ceritinib, received accelerated Food and Drug Administration approval in April 2014, with confirmatory trials still in progress.<sup>28</sup>

### ROS1

ROS1 is a tyrosine kinase receptor that shares a high degree of sequence homology with ALK.<sup>29</sup> It can form oncogenic fusion proteins with several different partners and these gene fusions are observed in approximately 1-2% of all NSCLC patients.<sup>30,31</sup> Crizotinib has demonstrated activity in patients harbouring ROS1 rearrangements detected by fluorescence in-situ hybridisation, with preliminary results from the expansion cohort of an ongoing phase 1 study (NCT00585195) showing an overall response rate of 56%.<sup>32</sup> A number of clinical trials are ongoing, evaluating

second and third generation ALK inhibitors in this molecular cohort (NCT01964157, NCT01449461, NCT01284192).

### RET

RET is a receptor tyrosine kinase involved in cell proliferation, migration and differentiation. Two specific gene fusions have been described in NSCLC (CCDC6-RET, KIF5B-RET), which result in the constitutive activation of the RET kinase and are estimated to occur in approximately 1% of NSCLC.<sup>33</sup> A number of multi-targeted kinase inhibitors have clinical activity against RET, including sunitinib, sorafenib, vandetanib and cabozantinib, however their place in the management of RET-rearranged NSCLC is yet to be elucidated.<sup>34</sup> A phase II study evaluating cabozantinib in RET fusion-positive advanced NSCLC is ongoing (NCT01639508). An early report of the first three patients enrolled on this study describes two confirmed partial responses, with prolonged disease stabilisation in the third.<sup>35</sup>

### HER2

HER2 is a membrane-bound tyrosine kinase of the ERBB family. The identification of EGFR mutations in lung cancer led to renewed interest in investigating activating mutations of HER2. Mutations have been identified in approximately 2-4% of patients. Most are in-frame insertions in exon 20, which result in constitutive activation of the HER2 kinase in a ligand-independent manner.<sup>36</sup> Transgenic mouse models have confirmed the oncogenicity of HER2 mutations.<sup>37</sup>

It is hypothesised that HER2 mutations may be more relevant in lung carcinogenesis than overexpression or amplification, and can act as a predictive biomarker for the use of targeted therapies. The role of irreversible pan-ERBB TKIs has gathered the most interest in this setting.<sup>38</sup> There have been case reports and preliminary data of objective responses to afatinib and dacomitinib in a small number of patients harbouring HER2 mutations.<sup>39,40</sup> However, the results do not appear as robust as observed with the use of TKIs in other oncogene-addicted tumours.

### BRAF

BRAF is downstream of KRAS in the MAP kinase pathway. BRAF mutations were first identified in 2002, with a particularly high prevalence in melanoma.<sup>41</sup> This led to a search for BRAF mutations in NSCLC, where they have been identified in approximately 3-5% of cases. Approximately half the mutations identified are V600E.<sup>42</sup> The BRAF inhibitor dabrafenib received 'breakthrough therapy' designation from the Food and Drug Administration following preliminary efficacy data from a phase II study demonstrating an ORR of 54% in patients with BRAF V600E mutation-positive NSCLC.<sup>43</sup>



As tumours harbouring non-V600E BRAF mutations are unlikely to respond to V600E-specific inhibitors such as dabrafenib, inhibitors of downstream targets such as MEK are under evaluation.<sup>44</sup>

### Impact and challenges of the molecular characterisation of NSCLC

The evolving characterisation of molecular subsets of NSCLC has resulted in a paradigm shift in lung cancer management. Many clinical practice guidelines now recommend biomarker testing for EGFR mutations and ALK rearrangements for all tumours with an adenocarcinoma component.<sup>45,46</sup> The increasing awareness of treatment-by-histology interactions and different observed frequencies of driver mutations according to histological subtype has resulted in a change to the histological classification of NSCLC. There is new emphasis on the importance of distinguishing between histological subtypes and strategic use of samples to preserve sufficient tissue for subsequent molecular studies.<sup>47</sup>

Despite its merits, the genomic classification of lung cancer still poses many challenges, including issues of access at a public health level, tissue availability, data interpretation and clinical trial design. These are discussed below.

### Access to molecular testing

It is critical for molecular profiling to be available to all NSCLC patients in order to personalise treatment decisions by molecular subgroups. For example, France has introduced a program that offers free molecular diagnostic testing for all patients with solid tumours.<sup>48</sup> However, the results of molecular testing are highly dependent upon the quality and quantity of tumour tissue available and the technology platform utilised.<sup>34</sup> As an increasing number of genomic subgroups are identified, gene-based molecular tests that focus on a single biomarker are no longer adequate. The advent of multiplex testing has enabled the evaluation of mutation status or expression of several genes simultaneously, thus maximising diagnostic information from limited tumour tissue and avoiding unnecessary time delays from sequential biomarker testing. However, such approaches require a significant investment in bioinformatics in order to aid a clinician's decision-making as to which genomic data is relevant to an individual patient's treatment.<sup>49</sup>

With the increasing awareness of inter and intra-tumoural heterogeneity, and as mechanisms of acquired resistance continue to be elucidated, it is apparent that a single genomic profile from a single tumour site at one time-point is insufficient.<sup>50</sup> Serial biopsies over the course of a disease, particularly at times and sites of disease progression, may provide a more accurate genomic analysis and insights into appropriate strategies to overcome the emergence of acquired resistance. The need for serial biopsies has

led to interest in the potential role of minimally invasive techniques, such as molecular analysis of circulating tumour cells and free DNA.

### Clinical trial design

It is increasingly unlikely that large randomised trials in unselected lung cancer patients will yield clinically significant results. In this evolving molecular era, smaller trials selecting patients defined by molecular aberrations are necessary for therapeutic development. However, there is also the risk that molecularly stratified trials may miss other targets for drug development. Furthermore, the small size of newly identified molecular subsets decreases the relative cost-effectiveness of developing novel agents and thus reduces the appeal to the pharmaceutical industry.<sup>1</sup>

The appropriateness of the traditional phases of drug development is less certain for targeted therapies. This is in part reflected by the Food and Drug Administration's accelerated approval program, which is designed to facilitate patient access to new therapies while post-marketing studies are conducted to confirm efficacy and safety. However, foregoing randomised phase III trials altogether has its disadvantages, including less definitive efficacy and toxicity data. There is an urgent need for novel clinical trial designs to improve the efficiency of the drug-development process, enable testing of multiple molecular targets and increase patient access to investigational agents.<sup>51</sup> For instance, the BATTLE (biomarker-integrated approaches of targeted therapy for lung cancer elimination) trial demonstrated the feasibility of identifying subsets of NSCLC patients more likely to benefit from a specific agent and the incorporation of an adaptive design to guide treatment selection for subsequently enrolled patients.<sup>52</sup>

### Conclusion

It is becoming increasingly clear that common tumours such as NSCLC are composed of multiple rarer subgroups defined by the presence of an oncogenic alteration. The identification and targeting of driver mutations has enabled a paradigm shift from empirical to personalised care and resulted in improved patient outcomes. However, important challenges still need to be overcome, including the issues of acquired treatment resistance, rational clinical trial design and treatment selection and support for ongoing research and development. Identifying relevant molecular subtypes and matching patients with appropriate targeted therapies is crucial for the progress of cancer management.

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# IS GENOMICS MAKING RARE CANCERS COMMON AND COMMON CANCERS RARE?

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## Abstract

While rare cancers account for a large percentage of total cancer cases, there has been little improvement in the overall survival rates for patients with rare cancers. This can partially be attributed to the difficulties in conducting clinical trials for rare cancers, since it can be challenging to accrue sufficient patient numbers of a rare subtype to demonstrate drug efficacy. A number of rare cancer types however, share genetic drivers with common cancers, which can be therapeutically targeted. Therefore, if patients are stratified by the molecular and genetic characteristics of their tumour, instead of stratifying them by their tumour type, targeted medicine could be a more achievable aim. In order to classify cancers by their genetic composition, we need to perform complex genomic testing, utilising next-generation sequencing technology. In this review, we discuss the screening approaches available for implementing such tests and the challenges that come with them, with an example of a small gene panel used in the Australian Ovarian Cancer Assortment study.

While cancer types prevalent below six cases per 100,000 people per year are classified as rare, the combined frequency of all rare cancers accounts a significant proportion of total cancer cases, around 22%.<sup>1</sup> Due to their individual rarity, rare cancers have been less well studied than common cancers. As a result, there are fewer proven effective therapies and, consequently, poorer overall survival rates. Recent studies have shown that many rare cancers are more likely to have less complex genomes, with several possessing highly specific dominant driver mutations that offer new therapeutic targets and treatment opportunities. This common characteristic helps unite the individually rare cancers into a collective of different tumour types that may benefit from a shared molecularly - directed approach to diagnosis and treatment.

One of the greater obstacles we face in improving outcomes for patients with rare cancers is the traditional model for conducting clinical trials, where typically, large numbers of patients are required in order to prove drug safety and efficacy, and to demonstrate improvement over standard treatments in a given patient population. Due to their rarity, it is difficult, and not infrequently impossible, to accrue sufficient numbers of patients with rare cancers in order to demonstrate a statistically significant improvement.<sup>2</sup> Consequently, most rare cancer types lack proven treatments that have been developed specifically for the particular tumour. Instead, many rare cancers are treated in the same manner as their more common counterparts, which completely ignores their unique genetic makeup, biology and response to treatments. This problem becomes even more apparent when the cancer type is further stratified by the molecular mechanisms into even smaller subgroups. Indeed, the majority of

cancer types are highly heterogeneous, meaning that most common cancers are in fact a collection of rare molecular subtypes.<sup>3</sup> So, with the emergence of routine molecular screening and molecular subclassification, most common cancers are also going to become rare. Learning how to deal with rare cancers can, therefore, teach us how to better manage all cancer types.

An example of a rare tumour type, helping to identify new treatment options for a more common tumour type, is high-grade serous ovarian cancer. This is the most common lethal subtype of ovarian cancer, which for decades set the standard of care for most other types of ovarian cancer, despite their obvious differences.<sup>4</sup> The term 'serous' denotes that the cell type resembles the cells that normally line the fallopian tube and their finger-like projections, the fimbria, that help capture the ova as they are released from the ovary.<sup>5</sup> This distinguishes this type from other types that arise from the endometrium, germ cells and ovarian stroma. The term 'high grade' refers to the aggressive behaviour and degree of nuclear atypia exhibited by this subtype which is a manifestation of underlying genetic changes, mostly TP53 mutations, that characterise this subtype. Acquired TP53 mutations largely distinguish high grade serous tumours from the more indolent 'low grade' subtype that has a different set of molecular changes, notably in the MAP Kinase pathway. Approximately 50% of all high-grade serous ovarian cancers have defects in a DNA repair mechanism known as homologous recombination (HR).<sup>6</sup> Until recently, it was thought that most HR-deficient tumours were caused by germline mutations in the breast cancer susceptibility genes, BRCA1 and BRCA2. However, extensive studies of the genomes of different tumour types have shown

that germline, somatic and epigenetic changes in many of the genes that encode proteins that form the HR DNA repair complex can also lead to HR deficiency.<sup>7</sup> Indeed, mutations in these other HR genes increase the proportion of HR-deficient ovarian cancer from 18%, caused by inherited BRCA1 or BRCA2 mutations, to 50%. Furthermore, these additional HR genes are also inactivated in some breast, peritoneal, pancreatic, prostate and probably several other cancers.<sup>8-11</sup> The unrelated observation that HR-deficient tumours, which are unable to repair double strand DNA breaks, are more sensitive to platinum based chemotherapy (which causes double strand DNA breaks) and are uniquely sensitive to PARP inhibitors, which prevent HR-deficient but not HR-proficient cells from repairing the DNA damage,<sup>12</sup> has opened up promising new therapeutic options for not only patients with high-grade serous ovarian cancer, but also potentially other more common HR-defective tumours.

The next challenge to improving outcomes for patients with rare cancers is developing new diagnostic tools to screen tumours for clinically relevant genetic abnormalities. Sanger sequencing has been the method of choice for mutation detection by diagnostic laboratories, where it is ideally suited to screening single genes for inherited or acquired mutations. However, Sanger sequencing is not scalable and becomes a very expensive and time-consuming process when screening multiple genes. In the last decade, the development of next-generation sequencing (NGS) has improved sequencing efficiency many thousand-fold and now provides a low-cost and high throughput approach for performing large-scale genomic analysis in a clinical setting.

While NGS has opened up a lot of opportunities to perform more complex genomic testing, there are still a number of difficulties in utilising it as a comprehensive genomics analysis tool in a diagnostic setting. Firstly, it is still expensive to perform deep whole-genome sequencing in order to ensure that all regions of the genome are properly covered, especially in a cancer genome, where polyploidy, intra-tumour heterogeneity and purity of the sample can cause additional difficulties.<sup>13</sup> Secondly, the amount of data generated by sequencing whole genomes is overwhelming and requires expensive storage.<sup>14</sup> Thirdly, the analysis of large-scale sequencing data is complex and requires highly-skilled bioinformaticians to make sense of the data and experienced medical geneticists to interpret its clinical significance.<sup>15</sup> Finally, even when the data is of high quality and is analysed appropriately, the interpretation of the results in a clinical context can be very difficult, as we are still learning about the function of large regions of the human genome. However, NGS technology is also able to interrogate specific genomic regions of interest with great depth and accuracy. This approach is being rapidly adopted in a diagnostic setting and has the potential to transform the way in which rare cancers are diagnosed, classified and treated.

## Small gene panels

Moving forward from single gene tests performed by Sanger sequencing to whole-genome sequencing can be done in stages. By developing small gene panels (5-100 genes), which are affordable in a clinical setting and relatively easy to analyse, we can start covering cancer types that share common mutations, genes or pathways.<sup>16</sup> The early panels tended to capture oncogenes with dominant activating mutations that either conferred drug sensitivity such as EGFR mutation and EGFR tyrosine kinase inhibitors in lung cancer or, resistance exemplified by KRAS mutations and EGFR monoclonal antibodies in colorectal cancer. More recently, panels designed to capture multiple genes that can inactivate common drugable pathways are emerging. As mentioned earlier, the HR pathway is an ideal candidate because a panel can be used to screen tumour samples for mutations that confer sensitivity to PARP inhibitors. The ability to quickly, accurately and rapidly screen tumour samples from a large number of patients with a rare tumour type will greatly increase the pool of patients potentially eligible for enrolment in a clinical trial.

The Australian Ovarian Cancer Assortment Trial is an example of how small gene panels may benefit rare cancers. The project is designed to develop a NGS diagnostic tool that would help to stratify patients with ovarian cancer into treatment categories based on the molecular composition of their tumours. This project not only aims to look at the most common subtype of ovarian cancer (high-grade serous), which accounts for 70% of all ovarian cancer cases, but also to capture molecular events that occur in the rarer subtypes of ovarian cancer, including low-grade serous, mucinous, endometrioid, clear cell, granulosa and dysgerminoma subtypes. A panel of 29 genes, which are known to be mutated in these subtypes of ovarian cancer and can be potentially therapeutically targeted, was developed for screening by NGS technology.

The initial aim of the project is to determine the feasibility and acceptability of this new molecular screening approach before introducing the test into routine care. It is important to introduce this new approach under ethical research guidelines to ensure that the assay is properly validated and accredited, and that only appropriate patients are tested in order to minimise any harm to patients caused by unforeseen risks, such as the generation of false results or false hope, and inadvertent delay in obtaining standard of care therapy. The initial phase aims to screen 60 patients with advanced ovarian cancer irrespective of the subtype, with a goal of stratifying them into various treatment groups. It will provide insight into the utility of small gene panels as a diagnostic tool for ovarian cancers. So far, 13 cases have been screened, with most containing at least one clinically significant mutation. Several cases have shown an unexpected degree of complexity, resulting in difficulties and delay in test interpretation. However, we are hopeful that with more exposure to tests like this, it

will become easier to understand tumour progression and resistance mechanisms, and to determine the most suitable treatment approaches.

### Genome, exome and sub-exome sequencing

At the other extreme from single gene tests is whole genome sequencing. Since this covers all three billion bases of the human genome, it has the potential to reveal all genetic changes within a tumour. However, this is enormously complex and, currently, way beyond the means and scope of routine diagnostic laboratories, and would not be a judicious use of scarce healthcare resources.

Whole-exome sequencing provides sequencing data for all coding regions of the genome, which is approximately 1/1000 of the scale of whole genome sequencing. Sub-exome sequencing uses similar technologies, but focuses on specific areas of the exome. Several commercial panels are now available that target the coding regions of only those genes known to be associated with human disease. Such 'clinical exomes' are likely to become the mainstay of diagnostic genetics laboratories for the analysis of rare diseases, as they are likely to provide the most cost-effective way to interrogate the relevant parts of the genome that will allow the consolidation of potentially hundreds or thousands of individual genes or disease-specific tests into a single platform. Being a universal test that can be used to screen any type of common or rare cancer, it should provide simplicity to diagnostic laboratories, where a single test can be used to detect the majority of molecular abnormalities irrespective of the prevalence of the tumour in the community.

The small gene panels that cover common actionable mutations in common cancer types are likely to become the most cost-effective front line diagnostic test for patients with cancer. The clinical exome is likely to become the second-line test for rare cancers (in which the rare disease-specific mutation may not be captured in a small panel) and in patients whose tumours contain complex pathway alterations, such as patients whose tumours have progressed following multiple rounds of chemotherapy. A number of studies have already employed this sub-exome sequencing approach for classification of rare cancer types.<sup>17,18</sup>

There are however, still a number of hurdles that need to be overcome in order for sub-exome and whole-exome sequencing to become a routine diagnostic test for screening cancers. These technologies do not capture many other genetic alterations (e.g. rearrangements, promoter mutations) or changes in gene expression, and methylation. They also reveal many genetic alterations that are of unknown clinical significance. It is not uncommon to identify thousands of such alterations in a single tumour, many of which have not been previously described. It

is therefore going to be a huge challenge to pinpoint an unexpected but key targetable alteration in each case. Improving our ability to accurately predict the significance of novel or rare events is going to require the establishment of global databases in which this information can be shared and interrogated. It is likely that many of these alterations will be shared across multiple tumour types as they invariably affect universal pathways that regulate cell growth rather than lineage determination. Accordingly, rare tumours and rare molecular subtypes of common tumours are going to be increasingly classified according to their therapeutically relevant pathways rather than their organ or presumed cell of origin.

Paradoxically, genomic technologies are making common cancers rare (by subclassifying them into smaller subtypes) and rare cancers common (by grouping them together into common treatment categories). Hopefully, by improving diagnosis and identifying targeted treatment options we can make both common and rare cancers rare in our communities.

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# CARCINOMA OF UNKNOWN PRIMARY – RARE BUT RIPE FOR HELP FROM GENOMICS?

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## Abstract

The treatment of most cancer patients is based on first determining where the cancer arose anatomically – lung, breast, prostate and so on. For a group of patients with disseminated disease, this crucial starting point is missing. Carcinoma or adenocarcinoma of unknown primary is a diagnosis made where the likely site of origin cannot be detected. Here we describe the use of molecular genetic tests to improve both the identification of site of origin for carcinoma of unknown primary patients and possible novel treatment options based on the presence of specific mutations. We outline the Solving Unknown Primary Cancer study, which is aimed at determining the utility of molecular testing in carcinoma of unknown primary.

Carcinoma of unknown primary (CUP) accounts for approximately 3-5% of all cancer diagnoses,<sup>1</sup> is the sixth most common cause of cancer death in Australia,<sup>2</sup> and the fourth most common worldwide.<sup>3</sup> CUP encompasses a heterogeneous group of metastasised tumours for which, following extensive investigation, a primary anatomical site of origin cannot be identified. CUP has among the lowest 12-month survival rate of all cancers, with only 23% expected to survive beyond one year.<sup>2</sup> Because cancer treatment is predominantly based on site of origin, CUP poses significant challenges when applying conventional treatment paradigms. Identifying the primary tumour is also important to allow patients affordable access to drugs and to enter clinical trials. The lack of a definitive primary anatomical site often restricts treatment options to palliative chemotherapy, which lacks the effectiveness and precision of modern day cancer medicine,<sup>4</sup> and results in significant patient uncertainty and distress.

## Can modern technologies improve CUP outcomes?

Cancer medicine is being transformed by the use of molecular analyses, including rapid and comprehensive DNA sequencing, to diagnose cancer with increased precision and predict the best therapeutic approaches for specific cancer types.<sup>5-7</sup> Targeted treatment approaches can be instituted when specific mutations are detected in a tumour sample for which specific small molecule inhibitors have been developed. The presence of so called actionable mutations in a sample may have implications for diagnosis, prognosis and prediction of therapeutic response.<sup>8</sup>

The recent development of advanced genomic tools presents a unique opportunity to improve the current management of CUP by implementing an approach that integrates molecular tests to both define the tissue of origin and also identify therapeutically actionable mutations. The use of molecular tumour profiling to identify tissue of origin and profiling for actionable mutations could form the basis of a new standard evaluation paradigm for CUP patient assessment.

### *Tissue of origin molecular profiling*

Pattern of expression of the ~20,000 genes in the human genome is highly cell and tissue lineage-dependent, and individual cellular gene signatures are generally retained during cancer development, even in those cancers that metastasise from the primary tissue site.<sup>9-13</sup> The retention of tissue-specific expression by cancer forms the basis of a simple concept whereby a database of gene expression is developed from a range of solid cancers against which an unknown tumour, such as a CUP, can be bioinformatically referenced to predict the primary site of origin.<sup>13,14</sup> Current commercially available tests that implement molecular tumour profiling include CUPGuide™ and bioTheranostics Cancer Type ID. These assays use probability scores to predict the tissue of origin or at least reduce the options to a narrower list of differential diagnoses.<sup>13,14</sup> Evaluation of the tests is hampered by the fact that there is no definitive and widely-used standard for the diagnosis of CUP and therefore understanding the accuracy of a CUP prediction is problematic. Assay development typically relies on the ability to predict site of origin for a series of known cancers in a blinded fashion. For example, the CUPGuide assay can predict site of origin of known metastatic deposits with 89% accuracy.<sup>8</sup> Another approach is to test a cohort

of samples where site of origin was initially uncertain, but became apparent at some later stage through additional clinical or diagnostic information. In such cases, the use of a site of origin test could have reduced the time to definitive diagnosis and implementation of directed therapy.

Both CUPGuide and Cancer Type ID report findings as high, moderate, low or no significant match, based on the similarity levels of a test tumour to a known metastatic tumour. CUPGuide emphasises the additional use of detailed clinical, histological and radiological findings, together with analysis of gene expression signatures to accurately identify the site of origin of a tumour.<sup>13,15</sup> The use of similarity scores is not without its challenges and complexities, and results can be inaccurate or inconclusive.<sup>16</sup> Results may predict several likely sites of origin with only 'moderate' similarity, and may therefore fail to provide definitive information for clinicians and patients. As described below, we have recently used large-scale DNA sequencing to identify potentially actionable mutations.<sup>17</sup> This assay also yields information about carcinogen exposure, such as tobacco smoke or sunlight exposure, and this may also narrow the search of potential site of origin of a CUP sample.

### **Profiling for actionable mutations – next generation sequencing**

DNA sequencing technologies have been important in identifying patients with inherited predisposition to cancer.<sup>18</sup> More recently, sequencing of the human genome has led to a personalised approach to oncology that is now being used clinically to predict the efficacy of drugs and to identify variants that guide therapeutic selection.<sup>19-21</sup> Examples include EGFR mutation or amplification in non-small cell lung cancer and colorectal cancer to determine patient suitability for EGFR tyrosine kinase inhibitors, or BRAF mutation detection to predict likely response of thyroid cancer or melanoma to BRAF inhibitors such as vemurafenib.<sup>22-27</sup> Compared with traditional Sanger sequencing, which has been limited to single gene 'hot spots', the recent development of massively parallel or next generation sequencing (NGS) has reduced cost and increased sequencing output enormously, allowing real-time assessment of hundreds to thousands of genes in individual patients, including those with CUP.

Using targeted exome capture of more than 700 genes followed by NGS, we have identified potentially clinically actionable mutations in 75% (12 out of 16 cases) of CUP patients, where a likely site of origin could not be identified.<sup>17</sup> The strength of the prediction of a clinical approach in this small retrospective series varied and more cases need to be evaluated to determine the clinical applicability of mutation profiling in CUP, including identification of the most common mutations that are likely to be encountered in these patients.

## **Integrating genomics into the treatment of CUP**

In 2013-14, Cancer Australia and the Victorian Cancer the Agency funded the 'Solving Unknown Primary Cancer' (SUPER) study. It is collecting clinical data and psychosocial experiential information as a foundation resource for future studies. It will also identify the unique psychosocial aspects of CUP, comparing quality of life, communication and supportive care needs of patients with CUP to matched control cases with advanced cancer of a known primary. Additionally, the study is integrating the two approaches of gene expression profiling and NGS DNA sequencing to investigate their utility in the optimal clinical assessment of CUP. When reporting real-time molecular evaluation of CUP tumours, using both the diagnostic genetic expression profiling and mutation profiling, four possible outcomes of the two tests are possible (table 1).

**Table 1:** Possible outcomes of molecular tests for tissue of origin (CUPGuide) and a search for actionable mutations can yield results where neither are informative (outcome 1), tissue of origin is predicted but no actionable mutations are identified (outcome 2), actionable mutations are identified but tissue of origin yield no result (outcome 3); or both tests yield a positive result identifying both tissue of origin and actionable mutations (outcome 4).

Outcomes	Tissue of origin test	Mutation profiling for actionable mutations
1	Tissue of origin predicted	No actionable mutation/s identified
2	No tissue of origin predicted	Actionable mutation/s identified
3	Tissue of origin predicted	Actionable mutation/s identified
4	No tissue of origin predicted	No actionable mutation/s identified

Determining the frequency of outcomes of the tests across a large patient cohort is critical in designing a future randomised clinical intervention trial based on test findings. SUPER will identify common mutations across a large series of CUP patients to inform trial design, particularly which drugs and industry relationships are likely to be most needed. In the meantime, SUPER will obtain information from clinicians following the provision of molecular information to measure the clinical impact of both assays in altering treatment plans and patient outcomes. SUPER will also provide practical information, including how often biopsies are able to provide sufficient material for successful application of the tests and approaches to assay development with the limited material often available for CUP patients. Where actionable mutations are found, we will record the circumstances where a suitable drug could be accessed, whether through an existing clinical

trial, compassionate access or through patient payment. We also expect to find germline mutations that are associated with increased genetic risk of cancer that may both explain the development of CUP in some patients and provide useful information to family members for cancer risk-reduction.

## Future for CUP

Past studies have indicated that in a majority of CUP cases, a primary tumour is found in post-mortem autopsy,<sup>28</sup> suggesting that current diagnostic methods are not advanced enough to effectively manage or provide CUP patients with a targeted therapeutic approach. There is a clear need for the integration of genomics in the diagnosis and management of CUP, and more specifically molecular profiling for both site of origin and actionable mutations has much to contribute in delineating the many complexities of this diagnosis.

Governing ways to integrate this approach into current management will be essential in successfully advancing the diagnosis and treatment of patients with CUP. Within this setting, there are likely to be complexities that will need to be overcome. While actionable mutations are likely to be identified, accessibility to targeted drugs available may be problematic. Currently, it is not uncommon for oncologists to label a CUP patient as having a specific tumour type, even when diagnostic uncertainty remains, to facilitate provision of treatment with a drug where rebated access is limited to specific cancer types.<sup>29</sup>

The translation of potential targeted drugs from one setting to another is not always easily applied. For example, vemurafenib can successfully inhibit BRAF (V600E) oncoprotein in melanoma, but has little effect on colon cancer patients who have the same BRAFV600E mutation.<sup>30</sup> Molecular tumour boards, which involve scientists, bioinformaticians, molecular pathologists, and clinicians, are needed to interpret the findings of molecular tests and to establish a standardised approach in incorporating molecular profiling results into the management of CUP. Despite these challenges, it appears likely that incorporating molecular profiling will improve the quality of life and outcomes of CUP patients in the near future.

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# OBITUARIES

## DR NIGEL GRAY AO

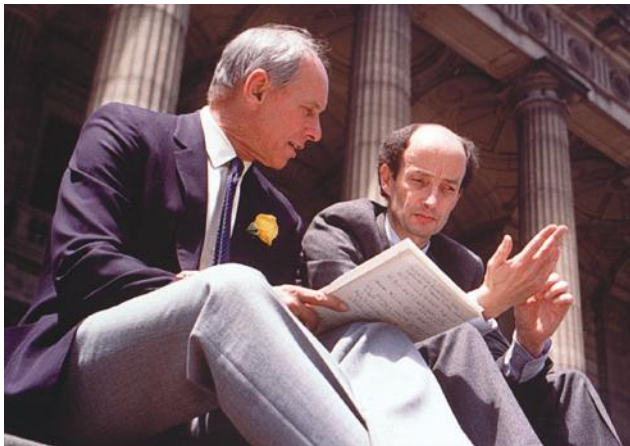
12 SEPTEMBER 1928 – 20 DECEMBER 2014

### Todd Harper,<sup>1</sup> David Hill,<sup>2</sup> Mike Daube<sup>3</sup>

1. Chief Executive Officer, Cancer Council Victoria, Australia.

2. Honorary Associate and former Director, Cancer Council Victoria, Australia.

3. Curtin University, Western Australia and President of the Australian Council on Smoking and Health.



Dr Nigel Gray will be remembered as a remarkable agent of change and a pioneer of public health both here in Australia, and overseas.

Director of Cancer Council Victoria from 1968 until 1995, Nigel transformed it from a respected medical charity into one of Australia's most prominent health organisations with a global influence.

Tobacco control was in its infancy when Nigel became Director, and a major part of the change since then can be attributed to his efforts. His work on tobacco alone may have resulted in his preventing more disease than any other Australian.

Characteristically, he made tobacco control simple by establishing clear, evidence-based policy objectives, which from the 1970s became the basis for a global consensus among health authorities.

Nigel pressed for health warnings, led public education and advocacy, helped establish robust behavioural research in both cancer and smoking, and played a crucial role in the campaign to ban tobacco advertising.

Combining rigorous science, clear thinking and more than a dash of his legendary debonair approach, Nigel responded to an interest expressed by the then Health Minister, David White, to introduce legislation for a ban. They ran a meticulous campaign to get the Victorian Tobacco Bill through Parliament with bipartisan support, along with a special tax on tobacco products that

established VicHealth, with funds to replace tobacco sponsorship. This model was subsequently adopted around Australia and in other countries.

Nigel also instigated the use of forceful anti-smoking ads. These included a series with distinguished scientist, Sir Macfarlane Burnet, and television stars Warren Mitchell (*Till Death Do Us Part*) and Miriam Karlin (*The Rag Trade*). The ads weren't allowed on air on the basis that they attacked a commercially promoted product (tobacco), but Nigel created a furore about Australia's Nobel Prize winner being banned from TV. The ban was rescinded and anti-smoking campaigns on television became a common sight.

President of the Union for International Cancer Control from 1990 to 1994, Nigel led the development of the first comprehensive policy approaches to tobacco control, including for the World Health Organisation and other international health groups. Not content with developing the policy, he led the first programs to promote international action on tobacco, including in developing countries.

He served as chair or member of many state, national and international committees on a wide range of health issues, and was a member of the Monash University Council for 14 years. The approaches he helped to develop for tobacco control have been adapted for other issues, such as obesity and alcohol. Nigel was also instrumental in developing many other cancer control initiatives that Australians now take for granted, such as the 'Slip, Slop, Slap' campaign.

After retiring in 1995, Nigel worked in Europe, first at a cancer research institute in Milan and then at the International Agency for Cancer Research. From this base, he spoke at many major conferences and published powerful, evidence-based papers and book chapters on tobacco control policy, in particular on the constituents of tobacco smoke and how to modify the risks.

To honour his extraordinary contributions to cancer control, the Cancer Council Victoria Nigel Gray Award for Achievement in Tobacco Control was established in 2005. The biennial award, announced at the Oceania Tobacco Control Conference, recognises an individual's contribution in tobacco control.



# OBITUARIES

He was recognised for his own work with an array of awards, including Officer of the Order of Australia, honorary doctorates from Melbourne and Monash Universities, and the American Cancer Society's Luther Terry Award for achievement in tobacco control.

Nigel fitted in well wherever he was, whether speaking to students or at the House of Commons in London. When he spoke at an international cancer congress in Cairo, the patron of the Egyptian Cancer Society, Mrs Sadat, went home and persuaded her husband, the President, to issue a decree banning television advertising of cigarettes.

Many of those who worked with Nigel benefited from his generosity and mentorship. Generous to a fault, he had the highest degree of personal integrity in all matters. He was strong and daring, but absolutely incapable of taking advantage of anyone weaker than himself. While quietly-spoken, he was nevertheless outspoken about unethical, dubious and wrong-headed practices in his

field, regardless of who was deserving of the criticism.

The tobacco industry often identified him as a significant threat to their business, with a once-confidential Philip Morris report from the 1980s noting that:

*"It is the Australian, Dr Gray, who appears to have done more than any other individual to bring the anti-tobacco movement together in the international sense, to exert pressure on governments and other influential bodies."*

Nigel continued his dedicated work on tobacco control into his ninth decade. Always alongside him have been his family who meant so much to him, with his wife Ann accompanying Nigel on many of his travels.

His commitment to applying research knowledge and to well-grounded advocacy, and his ability to bring out the best in those working with him have created a legacy that will be remembered and admired for many decades to come.

## PROFESSOR DONALD METCALF

26 FEBRUARY 1929 – 15 DECEMBER 2014

**Douglas Hilton, Warren Alexander, Nicos Nicola, Ashley Ng**

The Walter and Eliza Hall Institute of Medical Research



Donald Metcalf was born in Mittagong, a small country town in the southern highlands of New South Wales, Australia. The son of schoolteachers, he grew up across country New South Wales during the time of the Great Depression and World War II.

Always inquisitive, Metcalf, 'Don' to those who knew him, became a conscientious student and obtained a

scholarship to study medicine at the University of Sydney. During his degree, Metcalf undertook his first scientific studies into the ectromelia virus, an experience he would regard as incredibly formative. He graduated in 1953 with a Bachelor of Medicine and Surgery and began his medical residency where he met his future wife, Josephine, a partnership that would last a lifetime.

Metcalf's interest in blood cell and leukemia development took precedence over his medical career when he was awarded the Carden Fellowship from the then Anti-Cancer Council of Victoria, to work at the Walter and Eliza Hall Institute of Medical Research in Melbourne. Under the directorship of the eminent virologist Sir Macfarlane Burnet, who it must be said, was not particularly enamoured of cancer research, Metcalf spent two years working on the vaccinia virus. Ever the renegade and true to the terms of his fellowship, Metcalf's experiments branched out to investigating thymus biology and the role of this organ in leukemia development. To further his skills in cancer research, Metcalf undertook a post doctoral fellowship at Harvard University with the Hungarian-born Jacob Furth, whose ideas on forms of cancer development as an imbalance of cell regulators would significantly influence his thinking.

Metcalf returned to the Walter and Eliza Hall Institute keen to find regulators controlling blood cell formation. The key to this research would be the discovery of the technique that would allow the growth of individual blood cells in vitro. That moment would arrive in 1965. Ray Bradley, a scientific collaborator of Metcalf's at the University of Melbourne, showed Metcalf small cellular colonies, which had serendipitously been grown from mouse bone marrow in semi-solid agar. They realised that the growth of these colonies, each derived from a single cell, required the addition of something to the medium in culture. These were proposed as soluble 'factors' that supported the survival and growth of clonogenic myeloid bone marrow and spleen blood cell colonies in tissue culture. Metcalf and Bradley termed these 'colony stimulating factors' (CSFs).

This semi-solid agar culture system would allow not only the growth of blood cells in vitro, but also provided a method of detecting and quantifying the concentrations of the proposed but yet undiscovered CSFs. As science goes, much would hinge on this astute observation, which was also made contemporaneously by a group in Israel. Optimising this clonogenic culture system laid the groundwork for the purification and genetic cloning of the CSFs, a Herculean task that would take several decades and hundreds of collaborators. In addition, this culture system provided Metcalf with the method with which he would explore the hierarchy of blood cell development in great detail throughout his career, beginning at what he regarded as the apex of progenitor cell development, the multipotential blast colony-forming cell. Together with James Till and Ernest McCullough, Metcalf was a pioneer in the understanding of the hematopoietic hierarchy.

Metcalf led the effort to purify and clone CSFs from the front. Now Deputy Director of the Walter and Eliza Hall Institute under the new Director, Sir Gustav Nossal, Metcalf formed a team across the institute and the Melbourne branch of the Ludwig Institute for Cancer Research. This included the central players of Nick Nicola, Antony Burgess and Richard Stanley, who possessed the necessary expertise and commitment to the task. Purification of CSFs required the development of the then emergent technologies of protein purification by High Performance Liquid Chromatography, to demonstrate the existence of four principal CSFs that supported myeloid colony growth and differentiation.

Ultimately, it was amino acid sequencing and the development of molecular biology that allowed the cloning of the murine and human genes for CSFs. It speaks to Metcalf's fastidiousness, that he was only convinced that a pure CSF had been discovered when in possession of the gene for the CSF. Metcalf's leadership had ushered in the era of molecular haematology, which ultimately made possible the efficiencies of scale required for CSF production for research and clinical applications. The

Parkville group obtained extensive amino acid sequence for murine G-CSF and GM-CSF in collaboration with Lindsay Sparrow from the CSIRO. A further collaboration between Metcalf, Burgess, Nicola, Anne Kelso, Nick Gough and Ashley Dunn led to the cloning of the murine GM-CSF gene; the G-CSF gene being cloned by Nagata in Japan.

Ever at the forefront, Metcalf single-mindedly sought to translate his discoveries into benefits for patients with blood cancers. Clinical trials and translational research were now well underway and defined clinical uses for CSFs, in particular G-CSF for supporting neutrophil (white cell) recovery following chemotherapy. It was the unexpected finding that stem and progenitor cells moved into peripheral blood following injection of G-CSF, first recognised by Metcalf and Uli Dührsen in collaboration with clinicians Richard Fox, Glenn Begley and William Sheridan, that led to the paradigm shift in mobilising stem cells into the blood for collection, largely replacing bone marrow as a stem cell source for transplantation.

Although CSFs can be used therapeutically to boost blood cell production, more recently John Hamilton, Burgess, Ian Wicks and others, along with Metcalf, recognised a 'dark side' to their action in inflammatory disease. This led to interest in using CSF antagonists in treating diseases such as rheumatoid arthritis. Following identification of the cell surface receptors for CSFs, led by Metcalf, David Gearing, Gough and Nicola, programs that target both ligand and receptors have reached phase III clinical trials.

At the centre of this maelstrom of activity stood Metcalf. A brutally honest but giving collaborator with a penchant for deep thinking, that provided him with rare insight and great foresight. He possessed natural qualities of leadership, engendering great respect and, indeed, affection from his colleagues who effectively became an extended family to him. Known for his formidable work ethic and exacting scientific observations to the point of obsession, he remained at the laboratory bench and beside his beloved microscope for his entire career.

We will miss him dearly.

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# AWARD

## TOM REEVE AWARD FOR OUTSTANDING CONTRIBUTIONS TO CANCER CARE



The Tom Reeve Award for Outstanding Contributions to Cancer Care, offered annually by the Clinical Oncology Society of Australia, formally recognises a national leader who has made a significant contribution to cancer care.

Since its inception in 2005, where the inaugural award was presented to Professor Tom Reeve himself, there have been eight recipients of this prestigious award. In 2014, the winner of the Tom Reeve Award was Professor John Zalcberg OAM.

Professor Zalcberg has been a national and international leader in oncology for many years. His contributions have spanned clinical and laboratory research, health policy and fostering consumer participation as well as the nurturing of future leaders.

Professor Zalcberg accepted the award and delivered his oration at the COSA Annual Scientific Meeting in Melbourne on 3 December 2014. He reflected on his journey through ‘the mysterious universe of clinical trials’ and highlighted that patients more than ever before, are now, to use the words of Tom Reeve himself, “front and centre”.



*John Zalcberg pictured with Sandro Porceddu (2014 COSA President)*

It's a great honour to have been nominated for and to receive the Tom Reeve Award.

Firstly, I'd like to acknowledge previous recipients of this award, all of whom I've had the great privilege of working with in some way. Ian Frazer, David Ball, Phyllis Butow, John Forbes, Patsy Yates, Lester Peters, Martin Tattersall, Alan Coates and of course, Tom himself.

An award like this means so much, being acknowledged by your peers, people I respect and admire – thank you COSA, thank you everyone – I'm extremely grateful.

One of the first people I thought to contact after hearing of the award, was Tom himself.

I'd known Tom over the years, but the Great Dividing Range had separated us in my early career. So my memory of working with Tom was of being approached by an affable, wise, slightly older statesman to join yet another committee. But Tom did so in a way that ‘no’ just simply wasn't an answer. “Join the Steering Committee for the colorectal guidelines.” – sure Tom. “Write an article for *Cancer Forum*.” – sure Tom!

He was a man who could reflect on a lifetime of working with governments, with clinicians and patients for the common good. Tom seemed delighted at my receiving the award, and on reflecting on the changes he'd observed over the years, he made the point that patients more than ever before, are now, to use his words “front and centre”.

It's a point I couldn't agree with more strongly. As I've recently met with politicians or officials within the Department of Health to discuss health-related issues, I've become more and more aware of the role of the consumer, the call of the patient ... perhaps expressed more succinctly, the poet in me might muse, “of the deafening echoes from silent voices” – but I'll return to this theme a little later.

Of course, I know how important the voice of the consumer is from personal experience. My wife's been a patient three times – a cancer survivor and I dare not disregard what she has to say ... she tells me that often ... although I must say, I've always welcomed her wise and sensible point of view and am very pleased that Lynette is here to share this event with me this evening.

But to return to my theme, I hope that our consumer community will achieve their real strength in unity and

# AWARD

in doing so, facilitate their potential role in engaging and leading a much more detailed and sophisticated discussion about the future of cancer care in the modern era, particularly with respect to the research and quality agenda.

While clinical research is critically important, it is fundamentally a process which allows all of us, whether consumers, scientists or clinicians, to ask: "How can we do it better?" I know it sounds easy, but it's actually quite difficult. I still recall arriving in Toronto to complete my clinical training. It was the mid 80s – the decade that brought us the first mobile phone, the first PC, global warming, the sinking of the Rainbow Warrior, the shooting of John Lennon, Halley's comet ... and a time I could grow more hair on my head, than my face...

I'd just finished my PhD, moved to Toronto with Lynette and our two kids (aged four and two years) – and thought that laboratory research was the future of medicine – the ants pants of cancer research. Shortly after my arrival, I was talking to the head of research at the Princess Margaret Hospital. He was a very eminent, and highly respected stem cell scientist, and when I proudly proclaimed this epiphany - a future of test tubes, genetically inbred mice, of DNA and RNA solving the problems of health care; he looked at me deliberately and said v-e-r-y slowly "...that's because you don't understand what clinical research is all about ..."

So I began my journey into this mysterious universe of clinical trials – slowly understanding the underlying principle of what we were trying to achieve – simply stated: "How do we do it better?" In working to this objective, I started to ask: "Why aren't consumers helping to drive this agenda?" Not so much the scientific nitty gritty, but the fundamental principles...

- How much of taxpayers' funds should be spent on research?
- How much support should be allocated to clinical and translational research, compared to basic research?
- What are the key research priorities?
- How much focus should there be on improving quality of care?

These are but some of the many questions that we all struggle with, and yet a debate in which too many of our consumers and consumer organisations are strangely silent. I believe it's critical that patients and consumers not only get involved in this conversation, but actually lead it. Through greater engagement of the consumer voice, COSA is the ideally placed organisation to facilitate these discussions - enhancing interactions with policy makers

as the peak professional body to a role in auspicing the consumer groups which collectively and separately help lead the agenda.

I recall one of my earliest experiences with the power of the consumer movement was during the time I was Chair of the Australasian Gastrointestinal Trials Group (AGITG). The AGITG is a co-operative trials group that has had a long and proud history of listening to and involving consumers.

We'd just completed the trial of imatinib in patients with metastatic gastrointestinal stromal tumours. The drug was approved by the Therapeutic Goods Administration and submitted to the Pharmaceutical Benefits Advisory Committee (PBAC) for reimbursement. It was rejected twice and on the third occasion it was deferred, so that without PBAC approval, only the wealthy would be able to afford the \$45,000 annual cost to receive this drug. As a clinical community we were outraged! We'd seen how valuable this drug had been for patients who would otherwise have died within months.

One of the first patients that we treated was so sick that he actually started imatinib while in ICU, only to walk out of hospital some weeks later. Given such an impact, oncologists were understandably quite emotional about getting access to this drug. But now that it had essentially been rejected by the PBAC, we didn't know where to turn, or how to express our frustration.

At that time, we employed someone at the AGITG who had been active in the AIDS community and with his input, we organised a bus to take a group of patients from Sydney to Canberra. We planned to have a picnic on the Parliament House grounds to protest the PBAC decision. As the date got closer, anticipation and anxiety – mainly mine, grew - many patients had volunteered to join us on this protest, and the bus was full.

But I was starting to get very uncomfortable about this fateful rendezvous with A Current Affair or Sixty Minutes. This was not something we'd ever done before. I spoke to our organiser and said: "I'm worried about this. What if someone gets sick along the way?"

So he organised for a nurse to join the bus - in case anyone became ill en-route. But even so I was getting more and more nervous.

Two days beforehand, we cancelled the trip.

We just didn't feel we had enough experience to take this on. But we didn't give in and instead, through our consumer voice, organised a national petition campaign. Within two weeks, we had 30,000 signed petitions – that was back in 2001! And remember, these were the days before Facebook, or Twitter or Snapchat! I handed these

30,000 submissions to the consumer representative on the PBAC a few days later. Several weeks later, Department of Health representatives phoned the drug company and invited them back to the table to talk about their PBAC submission. The people had spoken and the rest is history.

More recently, I have been working with an organisation called the Cancer Drugs Alliance to improve the access of Australian cancer patients to novel drug therapies. As many of you will be aware, access to such medicines in Australia is often years behind other developed countries. Through this alliance, we've seen what's been possible in the UK through the influence of consumers. British consumers demanded better access to new cancer treatments, recognising that while some drugs will only result in marginal benefits, others will result in dramatic impacts on the lives of patients. These same consumers fought for and helped create the UK Cancer Drug Fund.

In Australia, we're nowhere near as far along in our implementation of a solution to this terrible problem of inequity to treatment, but if we want to fix the current problems, then neither clinicians nor industry can do this on their own. Fortunately, the Cancer Drugs Alliance does involve consumers – we're a tripartite organisation, bringing strength from each sector, and hopefully we'll eventually see a government that understands and addresses the need for faster and more equitable access to new treatments for our patients – patients who don't have time to wait while committees deliberate about the dollars.

Both the consumer and the clinical members on our Board are working closely with the pharmaceutical industry, with the understanding that if we want new drugs, if we want better drugs, if we want drugs that fit most appropriately into existing treatment algorithms, then we must work together, and ultimately with government, to achieve these objectives. As some of you will know, we were very pleased to hear of the just-announced Senate Inquiry into Access to Cancer Drugs – a very important opportunity for all of us.

My time at Peter Mac provided a fantastic opportunity to pursue a research agenda, although admittedly, my first attempt at applying for a job there many years earlier, had been unsuccessful. During that memorable interview, I was very seriously scolded for not having any experience in clinical research – not that I'm bitter of course! It was a fair criticism, a viewpoint illustrating the modus operandi of an institution devoted to improving cancer care for patients, throughout a proud 50 year history of clinical research.

For me, I finally got it. Together, clinicians, scientists, and consumers – we must do better. We will do better. Our patients deserve nothing less – 'only the best' as they say.

After leaving Peter Mac earlier this year after a 17 year stint, I've since joined the School of Public Health and Preventive Medicine at Monash University. There my work relates to supporting clinical quality registries that measure variations in cancer outcomes across our community.

It's been an exciting and rewarding experience to be involved with the many committees and organisations devoted to these causes. Ironically, I can still remember returning from overseas in the late 80s and speaking to the medical superintendent as they were called at the time. "Are there any committees I can join?" I asked. "I don't seem to be a member of any." Famous last words! Since then, my big problem has always been learning to say no – but when I can see the potential to make things better... well, it's an addiction.

Although it often involves the occasional evening email, or weekend paper work, it's an experience I highly recommend. So when the likes of Tom Reeve – or organisations whose causes you support, come calling, invite you to join a committee – please give it some thought. There's always room at the table for a fresh pair of eyes and new ideas.

As for the clinical quality registries, as the costs of health care continue to escalate, we desperately need evidence that the services and treatments we recommend as clinicians actually work, work beyond the experience of the highly selected group of patients enrolled on to pivotal registration studies. As these costs inexorably grow, the day is fast approaching when governments and insurance companies will want to pay for outcomes, not consumables or services.

Clinical quality registries not only measure outcomes, but are one of the most powerful tools we have for improving the quality of patient care – and hence my interest. They interface with clinical trials and help form the self-improving health system.

Funding such new programs in the current fiscal environment is always going to be a challenge and as always in health, and perhaps not surprisingly, if not appropriately, there are competing agendas. Whether the creation of a \$20 billion Medical Research Future Fund – the MRFF, will assist in resolving this tension remains to be seen. But as you might expect, everyone's angling for a piece of the MRFF pie. Some want more for fundamental research, others more for clinical research.

But I would argue, we need consumers to help lead the way through this dilemma.

What do the patients of today and tomorrow want? What is their perspective on how this pie is to be divided? We need leading organisations like COSA to continue to engage with consumers and help them drive the agenda –

# AWARD

the 'silent voice' no more, the 'echoes ever more piercing'.

So in closing Tom, we hear the message - patients are front and centre, caring for our patients is what drives us to achieve more, but it's our patients and their communities who we need help from. We need them to take the lead now, not tomorrow, because together we can create the future we want for our children - a future they deserve and expect.

I'm deeply honoured to be the recipient of the Tom Reeve Award for 2014, but couldn't have achieved anything without many friends and mentors, such as Michael

Friedlander and David Goldstein, in addition to many members of the team within the AGITG, colleagues such as Danny Rischin and Guy Toner, and many other friends at Peter Mac, and of course my secretary for over 20 years, known to everyone as 'Emilia'.

Lastly and most importantly, to my family, I wish to thank Lynette and our two children Nicole and David. They have stood beside me, at times in front of me, but always behind me to make all of this possible.

Thank you.

*Searching for evidence-based information on cancer?*

## Cancer Guidelines Wiki

Web-based clinical practice guidelines - accessible  
**ANYWHERE, ANYTIME**

### Online, evidence-based recommendations for:

- Lung cancer treatment
- Advanced prostate cancer
- Early stage endometrial cancer
- Nutritional management for head and neck cancer
- Approach to gastroenteropancreatic neuroendocrine tumours
- Psychosocial management of AYAs diagnosed with cancer
- Psychosocial management of AYA diagnosed with cancer
- Surveillance colonoscopy
- Sarcoma
- Cancer pain management
- Early detection of cancer in AYAs
- Fertility preservation for AYAs diagnosed with cancer
- Barrett's Oesophagus and Early Oesophageal Adenocarcinoma

**with more guidelines regularly being added**





## MEETING THE CANCER CHALLENGE: THE ROLES AND GOALS OF CANCER AUSTRALIA

The next five years will see a new focus in the work of Cancer Australia.

In collaboration with key stakeholders, including health professionals, researchers and consumers, Cancer Australia has identified a set of targeted and achievable goals for 2014 to 2019.

The goals are laid out in the new Cancer Australia strategic plan, which was released in November 2014.<sup>1</sup>

### The cancer challenge

Everyone knows someone affected by cancer. In 2015, about 132,000 Australians are expected to be diagnosed with cancer — an average of 360 people each day. This number is projected to continue to rise and in 2020, about 150,000 people are expected to be diagnosed with cancer in Australia.<sup>2</sup>

Although Australians experience among the highest cancer survival rates in the world, and survival rates are improving, cancer still remains a leading cause of death — three in every 10 deaths in Australia are from cancer.<sup>3</sup>

Cancer diagnosis and treatment are therefore key components in Australian health care. Decisions around cancer care will affect thousands of Australians and have a major impact on our health budget.

In addition, a number of trends being seen now will affect the needs and expectations around cancer care in the future:

- **More people are being diagnosed with cancer:** Largely driven by an ageing population, it is estimated that the number of new cancer cases diagnosed in Australia will increase by 3.3% per year between 2010 and 2024.<sup>4</sup>
- **More people are living with cancer:** Cancer survival has increased from 47% in 1982–87, to 66% in 2006–10.<sup>5</sup> An increasing proportion of the population is living longer after a cancer diagnosis, often requiring ongoing treatments, support and long-term follow-up care.
- **Cancer expenditure is increasing:** Cancer expenditure by government, private health insurers and individuals increased from \$2.9 billion to \$4.5 billion between 2000–01 and 2008–09.<sup>6</sup>

- **Cancer treatments and technologies are advancing:** Developments in our understanding of the molecular basis of cancer are changing approaches to cancer prevention, detection, diagnosis, treatment and monitoring. However, many new treatments are complex and costly.
- **Outcomes still vary between different groups:** Cancer mortality varies according to where you live, your socioeconomic status, whether you are of Aboriginal or Torres Strait Islander descent, and by cancer type.

Meeting the cancer challenge is therefore about making sure that all Australians are provided with the best possible cancer care, and that treatment and resources are used most effectively. This approach will deliver optimal outcomes for people with cancer, as well as value for the health system.

### Cancer Australia's roles

Cancer Australia was established in 2006 by the Australian Government as a specialist agency to provide leadership in cancer control. Cancer control focuses on addressing the impact of cancer by reducing cancer incidence and mortality and improving the quality of life for people affected by cancer, through the systematic implementation of evidence-based strategies for prevention, screening, early detection, diagnosis and treatment, and supportive, follow-up, palliative and end-of-life care.<sup>1</sup>

The Cancer Australia Act 2006 specifies a number of roles for Cancer Australia, including:

- Providing national leadership in cancer control.
- Guiding scientific improvements to cancer prevention, treatment and care, and overseeing a dedicated budget for research into cancer.
- Making recommendations to the Australian Government about cancer policy and priorities and assisting with their implementation.
- Coordinating and liaising between the wide range of groups and health care providers with an interest in cancer.



## Development of the strategic plan

Cancer Australia's Strategic Plan 2014–2019 was developed by Cancer Australia in collaboration with key stakeholder groups, including consumers and the community, researchers and data custodians, health professionals, service planners and deliverers, as well as the staff and the Advisory Council of Cancer Australia. A number of consultations were held in 2013, including one-on-one interviews with key stakeholders and four planning forums attended by around 150 external participants.

Feedback gathered through the stakeholder consultations indicates that the case for cancer control remains as strong and relevant as ever, as does the need for a specialised agency to shape the cancer control agenda and guide investments in the health system. As a national body with an evidence-based and credible reputation, Cancer Australia can use its position to shape and guide best practice and reduce duplication across the system.

## Cancer Australia's goals

The strategic plan includes a set of four goals to guide Cancer Australia's work over the next five years:

- **Shape national cancer control in Australia** by leading the development of an agreed national agenda for cancer control, assisting decision makers at all levels to make informed responses to current and emerging issues and risks in national cancer control, and partnering across the national health system for improved cancer control.
- **Improve cancer outcomes** by building the knowledge base to drive improvements that reduce unwarranted variations in cancer outcomes, including for groups at risk due to sociodemographic status, cancer stage or tumour type, and developing national indicators across the continuum of cancer control to drive and monitor improvements in cancer outcomes.
- **Inform effective and sustainable cancer care** by developing a national framework that defines best practice and sustainable models of care across the cancer care continuum, and identifying areas to optimise safe and effective care, including through new models of care.
- **Strengthen capability for national cancer control** by aligning cancer research with evidence-based priorities for national cancer control, and undertaking analysis,

synthesis and interpretation of evidence to develop informed responses to issues in cancer control.

## Cancer Australia's levers are evidence and collaboration

In taking on the cancer challenge, Cancer Australia has two main levers: evidence and collaboration.

Evidence-based practice is essential to improving cancer outcomes and care. Cancer Australia identifies gaps in our knowledge across the continuum of cancer care and supports development of the evidence base, including through research grants. It also assesses the evidence that is continually being developed. As the science of cancer and genomics is one of the most rapidly changing areas in health, the analysis and interpretation of an increasing volume of scientific research and national data is critical to identifying the factors affecting cancer control.

Most importantly, Cancer Australia works to ensure that evidence is translated into policy and practice by developing position statements, clinical guidance, models of care and community information around the practical application of evidence. It is critical that Australian decision makers (at the policy, service planning, clinical and personal levels) have an authoritative, national 'source of truth' for information and evidence about cancer. Cancer Australia aims to be that source.

National cancer control also requires partnership. Collaboration is essential, as cancer treatment involves so many groups — health professionals, health service managers, researchers and consumers. It is important that there is communication and collaboration between them all. Cancer Australia is the key link between all the various organisations involved in cancer care in Australia, and uses an effective engagement model to drive collaboration.

## Seeing the impact

Cancer Australia's new goals represent a shift in the focus of the organisation. In developing the new strategic plan, Cancer Australia looked at the key needs and questions currently facing cancer care in Australia and the unique contribution it could make. In this way, Cancer Australia has clearly identified where it can have an impact and will focus its work in these areas over the next five years.

Cancer Australia stakeholders will see a number of impacts resulting from this:

**For health professionals and services,** Cancer Australia's development of national best-practice models of care will directly guide their practice. The establishment of national indicators for cancer control will also support service delivery and practice improvements.

**For researchers,** Cancer Australia will continue to align cancer research funding with evidence-based priorities and establish international cancer research collaborations focused on priority areas.

**For the community,** Cancer Australia will promote safe and effective treatment based on the best available evidence and aim to reduce differences in cancer outcomes between groups. Cancer Australia will also provide access to the best available evidence to support decision making.

**For all stakeholders,** their involvement and support will be vital to the implementation of the new strategic plan. Cancer Australia looks forward to working with the Australian Government and the cancer control community around a shared agenda, to deliver informed and effective cancer control and ultimately better outcomes for all people affected by cancer in Australia.

**Professor Helen Zorbas AO**  
Chief Executive Officer, Cancer Australia

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## BEHAVIOURAL RESEARCH AND EVALUATION UNIT (BREU), CANCER COUNCIL SA

### Use of the distress thermometer in the context of a telephone-based cancer information and support service. An exploratory study.

While the validity of the distress thermometer (DT) for the measurement of psychological distress has been examined in several cancer settings, little is known about user experience of the DT and its utility and acceptability in telephone-based cancer support services. Using a mixed-methods design, eligible callers (individuals diagnosed with cancer and family/friends, N=100) responded to a questionnaire that included DT ratings and the Depression Anxiety and Stress Scale-21 (DASS-21). Comfort in asking about and responding to the DT was assessed for both nurse operators and callers.

A purposively selected subgroup was then interviewed (n=20) and content analysis was used to thematically categorise responses. Analysis of variance indicated distress reduced significantly over the course of the call, regardless of caller type or gender. Caller DT scores correlated with DASS-21 depression ( $r=.45$ ,  $p=.000$ ), anxiety ( $r=.56$ ,  $p=.000$ ) and stress ( $r=.64$ ,  $p=.000$ ) subscales. Both callers and nurses reported comfort in using the DT. Qualitatively, some callers reported the DT as easy to answer and conversational, while others expressed difficulty responding to the scale.

Future research could explore the impact of methods of DT delivery (e.g. point in call, methods of introduction) on caller distress, psychosocial outcomes and uptake of referral to other support services.

### Exploring patterns in sun-related behaviour in adolescents and triathletes

Australia has one of the highest rates of skin cancer, which is largely preventable by adopting sun protection practices. Research indicates that regular adoption of multiple sun protection behaviours (i.e. protective clothing, sunscreen, hat, shade, sunglasses) is uncommon and people adopt different behaviours in different contexts. This suggests that these behaviours may not have the same underlying motivations and may require tailored strategies to improve uptake. This report describes the findings of two studies that explored patterns in sun-related behaviours. The first study investigated sun protection practices in adolescents and the second study investigated sun protection among triathletes.

Data for the investigation of adolescent sun protection behaviour were collected via the Australian Secondary Schools Alcohol and Drug Survey (ASSAD), which is tri-annual survey of students' health behaviours. Analyses were based on data collected from students in South Australia in 2011. In total, data were available for 2875 students aged 12 to 17 years. Participants were asked to indicate how often they participated in seven sun-related behaviours between 11am and 3pm in summer on a five point scale - 1 (never), 2 (rarely), 3 (sometimes), 4 (usually) or 5 (always). Participants also reported skin tone dissatisfaction, tanning intentions, and agreement with several statements addressing beliefs about the desirability and risks of tanning.

# REPORTS

A principal components analysis was run to identify underlying factors. Sun-related behaviours could be reduced to three components. Items that loaded on component 1 were wearing a hat, wearing sunscreen and wearing protective clothing. This was labelled 'sun protection'. Items that loaded on component 2 were wearing sunglasses and deliberately wearing briefer clothing. This was labelled 'appearance-enhancement'. Items that loaded on component 3 were seeking shade and time indoors. This was labelled 'shade behaviour'.

Appearance-enhancement was associated with higher skin tone dissatisfaction, stronger intentions to tan, stronger beliefs about the attractiveness of a tan, and perceived peer norms in support of tanning. These measures were associated with sun protection and shade behaviour but in the opposite direction. In general, misperceptions about the risks of tanning were more likely to be associated with shade behaviour (lower misperceptions) than with sun protection and appearance-enhancement, however the patterns of associations with sun protection behaviours varied depending on the specific question and gender.

This work has been reported in Hutchinson A, Prichard I, Ettridge K & Wilson C. *Int J Behav Med.* 2014 and Corsini N, Hutchinson A, Prichard I, Sharplin G, & Wilson C. E-poster presentation. World Cancer Congress, Melbourne. Dec 2014.

The second study investigated motivations underlying sun protection practices in a sample of triathletes in clubs from around Australia. In total, 101 triathletes were recruited (47 female, average age was  $37.51 \pm 10.99$  years). Participants completed an online survey which included questions about sun protection, including how often they participated in sun protection behaviours at triathlon competitions in the past season on a five point scale - 1 (never), 2 (a few), 3 (half), 4 (most) or 5 (every competition). Sun protection behaviours included: wearing sunscreen; wearing a hat/visor (run and bike leg); wearing a top that covered the shoulders; wearing sunglasses (run and bike leg); and seeking shade after the event. Participants also completed a range of other

questions, including whether or not their club had a sun protection policy and their susceptibility to sunburn.

A principle components analysis revealed a similar pattern of results to those described in the adolescent sample. Items that loaded on component 1 were wearing a shoulder-covering top and wearing sunglasses (Appearance-enhancement). Wearing sunglasses loaded negatively on the appearance-enhancement component, meaning that triathletes who wore sunglasses were less likely to wear a shoulder-covering top and vice versa. Items that loaded on component 2 were wearing sunscreen and wearing a hat (sun protection). Seeking shade loaded on component 3 (shade behaviour).

Appearance-enhancement was lower among triathletes who reported belonging to a club with a sun protection policy, compared with triathletes who did not have or did not know whether their club had a policy. There were no differences in sun protection or shade behaviour by policy status. Sun protection and shade behaviour were significantly associated with greater reported susceptibility to sunburn. Appearance-enhancement was not associated with reported susceptibility to sunburn.

These findings indicate that sun-related behaviours can be understood in terms of a smaller number of themes. The traditional 'slip, slop, slap' sun protection behaviours group together and are likely to be motivated by sun protection concerns. Wearing sunglasses however, appears to be motivated more by appearance-based concerns and is associated with sun exposure behaviours. Seeking shade does not group with traditional sun protection behaviours. This may reflect the fact that shade behaviour is affected by environmental factors such as the availability of shade structures. The similarity in patterns of behavioural groupings seen in both an adolescents and an adult population suggest that these groupings may be robust. Strategies to engage people in sun protection should consider the possible motivations underlying different sun protection behaviours. Interventions to address appearance-based concerns should be considered a priority.

## CENTRE FOR BEHAVIOURAL RESEARCH IN CANCER (CBRC), VICTORIA

### **Non-smokers, smokers and former smokers respond to various electronic cigarette advertisements**

Internationally, electronic cigarette (e-cigarette) advertising and promotion is increasing rapidly, with widespread promotion on television, YouTube and retail websites.

These ads commonly portray the hand-to-mouth action of 'vaping' in a very glamorous manner, and include claims of advantages over regular cigarettes and increased social status. CBRC is conducting a study to assess responses to e-cigarette ads among non-smokers, former smokers and smokers using an adaption of a standard ad pre-testing protocol.

Six groups were conducted (n=6-8 per group), two of which included 18-24 year-old non-smokers, two 25-55 year-old former smokers, and two 25-55 year old smokers. Each group viewed and rated one of two sets of eight ads and participated in a group discussion about each ad. All groups included two to three participants who had previously tried e-cigarettes but excluded regular e-cigarette users. Preliminary analyses from the qualitative discussions indicate glamorous ads with few references to product advantages were most appealing to non-smokers, whereas those detailing product advantages were most appealing to smokers. Few ads appealed to former smokers, who were especially concerned that a smoking-like behaviour could be promoted as glamorous. Quantitative analyses will examine the extent to which different e-cigarette ads may potentially promote 'vaping' and tobacco smoking.

With Australian authorities yet to decide on regulatory measures for e-cigarette production and promotion, this study will provide some indication of the potential effects of different e-cigarette advertising in Australia.

## **Patterns of care in adolescents and young adults with cancer**

Each year, about 900 Australian adolescents and young adults (AYAs, aged 15-24 years) are diagnosed with

cancer. Research shows that AYA patients have had the smallest improvement in survival over the last 20 years of any age group. Also, for cancers that occur in both children and AYAs, survival is worse among AYA patients. The reasons for this are not well understood. A National Health and Medical Research Council project grant (\$645,000) will fund a study to examine these issues in Victoria, Queensland and New South Wales. Additional funding (\$100,000) was obtained from CanTeen and The Kid's Cancer Fund to extend the study to the remaining Australian states and territories. The project is a retrospective review of hospital medical records. It aims to collect treatment and outcome data for all AYAs diagnosed with leukaemia, soft tissue sarcoma, bone cancer and central nervous system tumours between 2007 and 2012. These diagnoses account for about 20 per cent of AYA cancers and were selected for their relatively poor outcomes.

Data collection is now complete for all Eastern states, with 870 patients' files reviewed. It will be completed nationally by mid-2015. The results will be used to identify the modifiable health-system factors and practices that influence patterns of care for AYAs with cancer so that clinical outcomes can be improved. The study is complemented by a patient survey that examines how to improve AYA experiences of cancer care.

## **NEWCASTLE CANCER CONTROL COLLABORATIVE (NEW-3C), NSW**

### **Life expectancy discussions in a multi-site sample of Australian medical oncology outpatients**

Patient-centred cancer care requires that patients receive the information they want about their life expectancy. A multi-site study of 1431 medical oncology outpatients across 11 Australian cancer treatment centres identified the proportion of patients who received their preferred level of information about life expectancy, and the socio-demographic, clinical and psychological factors associated with patients' perceptions.

Patients completed a cross-sectional survey indicating the extent to which the information they received about their life expectancy aligned with their preferences for this information. Almost one quarter (24%) of patients perceived they received too little information, 4% received too much information, 22% neither wanted nor received any information, and 50% received all the information that they wanted about their life expectancy. Patients had greater odds of receiving too

little information (rather than all the information they wanted) if they were not in remission, did not know their cancer stage at diagnosis, or were anxious or depressed. Patients had greater odds of receiving too much information if they were younger, had a more advanced cancer and did not know their cancer stage at diagnosis. Patients had greater odds of not wanting or receiving information if they were older and did not know their cancer stage at diagnosis. A majority of outpatients perceive that they receive the amount of life expectancy information that they prefer. However, there is room for improvement.

Health care providers should routinely assess whether patients have received preferred information regarding their life expectancy.

### **Prevalence and correlates of current smoking among medical oncology outpatients**

Smoking after being diagnosed with cancer can have detrimental impacts on treatments and increases the risk

of additional cancers. Smoking cessation interventions for patients with cancer show mixed results, thus data on prevalence and correlates of smoking are needed to better target at risk patients. This study explored: (a) the prevalence of self-reported current smoking; and (b) the demographic and psychosocial factors associated with self-reported smoking among outpatients attending a medical oncology clinic.

A heterogeneous sample of cancer patients aged 18 years or over was recruited from 11 medical oncology treatment centres across Australia. Patients completed a survey assessing: smoking status; socio-demographic, disease/treatment characteristics; time since diagnosis; anxiety; and depression. Univariate and multivariate mixed-effects logistic regression was used to explore patient characteristics associated with self-reported continued smoking.

A total of 1379 patients returned surveys (1338 included in analysis). Current smoking prevalence was 10.9% (n=146). After adjusting for treatment centre, patients aged 65 years and older and those without health concession cards were significantly less likely to smoke. Patients diagnosed with lung cancer and those without private health insurance were more likely to smoke. A minority of cancer patients reported continued smoking at an average time of 13 months post-diagnosis. Younger patients, patients with lung cancer, and patients with lower socioeconomic status appear to be the groups most at-risk of continued smoking following diagnosis, and represent key targets for smoking cessation intervention.

Cost-benefit analyses should be undertaken to examine the impact of such smoking cessation interventions in this sub-group.

## CANCER COUNCIL AUSTRALIA

### Gene patent laws

Cancer Council Australia has highlighted the need for patent law to change, after the Federal Court's dismissal in September of an appeal against the patenting of genetic mutations associated with breast and ovarian cancer.

Director of Advocacy, Paul Grogan, said that given the unanimous Federal Court ruling was an interpretation of Australian law, the law itself needed to change to protect healthcare consumers from gene monopolies.

"The ruling puts Australia out of step with the US, where the Supreme Court invalidated the Myriad patents," he said.

### Guidelines on Barrett's Oesophagus and Oesophageal Adenocarcinoma

Cancer Council Australia has published new clinical guidelines to help provide greater consistency in the management one of Australia's fastest growing cancers and its known precursor, Barrett's oesophagus.

Industry leaders are hopeful the guidelines for the Management and diagnosis of Barrett's Oesophagus and oesophageal adenocarcinoma will deliver improved health outcomes for patients and help reduce treatment costs.

### New cancer research report

Cancer Council welcomed an audit of cancer research funding in September, which showed the nation's overall investment had doubled over eight years, with a modest relative increase in funds for cancers causing high death rates.

*Cancer Research in Australia*, released by Cancer Australia, found a total of \$1.3 billion in cancer research was funded between 2003 and 2011, including a three-fold increase in tumour-specific projects.

### Teens tone down tanning 10 years on

Findings from Cancer Council's National Sun Protection Survey have shown adolescents are developing healthier attitudes towards tanning.

Research released in November, showed 38 per cent of young Australians (12-17 years) liked to get a sun tan, compared to 60 per cent 10 years ago

### Obesity problem highlighted at World Cancer Congress

Soaring rates of obesity in Australia and other developed countries will be a major contributor to the expected 50 per cent increase in cancer cases to 21.7 million by 2030, the World Cancer Congress was told in December.

Worldwide, the number of overweight and obese individuals increased from 857 million in the 1980s to 2.1 billion in 2013.

At the launch of the American Cancer Society's Cancer Atlas, Second Edition, at the Congress in Melbourne, Cancer Council Australia CEO, Professor Ian Olver, said it was imperative governments of developed nations come together in a sustained and coordinated effort to reign in overweight and obesity.

## CEO's of leading cancer organisations stand together in fight to reduce tobacco-related death

Cancer Research UK, the Union for International Cancer Control, the US National Cancer Institute and Cancer Council Australia have united to further research into evidence-based tobacco control, to reduce the millions of tobacco-related deaths occurring worldwide each year.

Cancer Research UK has pledged £5 million to establish, with its cancer fighting partners, the International Consortium for Action and Research on Tobacco, and fund tobacco control research programs in low-and-middle income countries, where the impact of tobacco-related cancer is greatest.

## CLINICAL GUIDELINES NETWORK

Cancer Council Australia produces concise, clinically relevant and up-to-date electronic clinical practice guidelines for health professionals. All guidelines are available on Cancer Council Australia's Cancer Guidelines Wiki platform ([wiki.cancer.org.au](http://wiki.cancer.org.au)).

### Guidelines in development

#### **Clinical practice guidelines for PSA testing and management of test-detected prostate cancer**

Cancer Council Australia, together with the Prostate Cancer Foundation of Australia, conducted a public consultation on the draft guidelines from 4 December to 16 January. The feedback is being revised and incorporated in preparation for National Health and Medical Research Council submission.

#### **Clinical practice guidelines for the prevention, diagnosis and management of lung cancer**

Cancer Council is currently developing prevention and diagnosis guidelines for lung cancer to complement our treatment guidelines. Systematic reviews are underway.

#### **Clinical practice guidelines for the management of melanoma**

Cancer Council Australia and Melanoma Institute Australia are revising the 2008 melanoma guidelines as online wiki-based guidelines. The first iteration will focus on diagnosis and management. Systematic reviews are about to commence.

#### **Clinical practice guidelines for the prevention, early detection and management of colorectal cancer**

Cancer Council has received funding from the Department of Health to revise the 2005 *Clinical practice guidelines for the prevention, early detection and management of colorectal cancer*. Work commenced in December, with the guidelines being developed through the National Health and Medical Research Council process.

#### **Clinical practice guidelines for the management of sarcoma in AYA**

In 2013, *clinical practice guidelines for the management of adult onset sarcoma* were launched. Additional questions relevant to the adolescent and young adult population are being added and will be launched in 2014.

### Guidelines on the wiki

Cancer Council's Cancer Guidelines Wiki features the following cancer-based guidelines:

- *Clinical practice guidelines for the diagnosis and management of Barrett's Oesophagus and early oesophageal adenocarcinoma*
- *Clinical practice guidelines for the treatment of lung cancer*
- *Management of apparent early stage endometrial cancer*
- *Clinical practice guidelines for surveillance colonoscopy*
- *Clinical practice guidelines for the management of adult onset sarcoma*
- *Clinical practice guidelines for the management of locally advanced and metastatic prostate cancer*
- *Cancer pain management*

### Clinical Oncology Society of Australia guidelines on the wiki

- *NETs guidelines*
- *Head and neck cancer nutrition guidelines*
- *Early detection of cancer in AYAs*
- *AYA cancer fertility preservation*
- *Psychosocial management of AYA cancer patients*

For more information regarding the clinical practice guidelines program at Cancer Council Australia contact the Head, Clinical Guidelines on 02 8063 4100.

## CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA, COSA

### 2014 Annual Scientific Meeting (ASM)

COSA held another successful Annual Scientific Meeting in Melbourne 2-4 December 2014.

More than 1200 delegates attended and over 400 abstracts were submitted. The program featured 16 concurrent sessions, 12 best of the best sessions, nine breakfast sessions, five submitted symposia, five plenary sessions and concluded with the one and only 'hot topic'.

The 41st COSA ASM highlighted cancer survivorship, supportive care and palliative care, as well as lung cancer and metastases. The Local Organising Committee, convened by Mei Krishnasamy, worked hard to develop a broad range of multidisciplinary sessions that the COSA membership has come to appreciate.

COSA is proud to have hosted the meeting in conjunction with the Union for International Cancer Control's World Cancer Congress (WCC), with delegates able to attend any COSA ASM or WCC session on our joint day, Thursday 4 December.

The opening plenary highlighted the critical importance of a multidisciplinary approach to key issues in cancer management. Speakers included Bruce Mann, Michael Hofman and Ben Solomon – all well respected Australian clinicians and researchers, and from our international faculty Normand Laperriere and Nathan Cherny. The speakers questioned the traditional polarisation of 'curable' early cancer and 'terminal' advanced cancer, as advanced imaging allows early identification of metastasis at a time where local therapy may influence the disease outcome.

Many high quality plenaries and concurrent sessions were held, with the joint COSA/WCC hot topic panel discussion rounding out the ASM. Adam Spencer chaired the session and provided provocative and challenging questions with his usual charismatic and humorous style. Discussing the topic 'Is the cost of cancer treatment worth the benefits?', panel members included David Grainger, Georgina Long, Donna Milne, Nicola Roxon, Melissa Sheldon and Robyn Ward.

The panellists recognised the high costs of research and targeted therapy expenditure, balanced by the impact these drugs could have on prolonging life. They also discussed the need for research to have freedom to grow and develop, unhindered by government interference. In closing, the panellists rated the Australian health care system – the Hon Nicola Roxon rated the system 10/10. "... not because it is perfect but because if you were diagnosed with cancer you wouldn't want to be treated anywhere else in the world."

### 2015 Annual Scientific Meeting

Save the date – 17-19 November 2015 at the Hotel Grand Chancellor, Hobart. The Local Organising Committee, co-convened by Drs Louise Nott and Allison Black, medical oncologists at Royal Hobart Hospital, is already working on the program and has secured a number of invited international experts to present on the rare cancers theme.

To ensure they develop a program of interest to the diverse COSA membership, the committee's interpretation of rare cancers encompasses: truly rare cancers; rare cancer sub types; rare forms of common cancers; rare context of cancer, for example cancer during pregnancy; and rare cancers and the challenges in treatment. We are sure there will be something of interest for everyone.

### Changing of the guard

The end of 2014 saw Associate Professor Sandro Porceddu conclude his two-year term as COSA President, and Professor Mei Krishnasamy assume the role.

In handing over the reins, Professor Porceddu thanked COSA members for their support and said he was proud of what had been achieved in the last two years.

Prof Krishnasamy said she was honoured to step into the role of COSA President and thanked Prof Porceddu for his leadership, adding that he left COSA with a strong, embedded governance structure that provided a robust platform for action.

We are also pleased to announce that Professor Phyllis Butow AM takes on the role of President Elect. Prof Butow has been a valued member of COSA for many years, representing the Psycho Oncology Cooperative Research Group on COSA Council. Prof Butow holds a number of senior positions at the University of Sydney and is a world leader in psycho-oncology research. We are honoured to have her accept the role of COSA President Elect.

For more information about COSA activities please visit [www.cosa.org.au](http://www.cosa.org.au)

**Marie Malica,**  
*Executive Officer, COSA*



## FACULTY OF RADIATION ONCOLOGY, RANZCR

### Radiation Oncology Targeting Cancer campaign – Oncology Education Evening for General Practitioners

The 'Radiation Oncology: Targeting Cancer campaign' has been very active this year, seeking to improve the profile of radiation as a sophisticated cancer treatment.

Targeting Cancer's first Oncology Education Evening for general practitioners (GPs) was held in October at Westmead Hospital. The evening was a great success with a fabulous turnout and GPs engaged and interested in the material.

We hope this will develop into a national program of GP education evenings, providing information about cancer treatments, and where radiation therapy could benefit a patient either for cure or alleviation of symptoms such as pain. The program will also familiarise GPs with radiation oncology departments and machines through a tour of facilities.

The program will roll out in at least 15 centres, thanks to some of our tireless volunteering radiation oncologists.

### Quality assurance guidelines for radiation therapy services

Delivery of safe and high quality radiation therapy services is of paramount importance to patients. The Faculty of Radiation Oncology, through its Quality Improvement Committee, has been working on a number of guidelines/position papers, and recently:

- completed a white paper on the 'Use of Imaging in Radiation Oncology'
- updated the position paper on 'Breast Cancer and Late Effects Following Radiation Therapy and Chemotherapy for Hodgkin Lymphoma'.

These documents are available at <http://www.ranzcr.edu.au/about/faculty-of-radiation-oncology/899-faculty-publication>

The following policy positions are in development and should be available in the next six months:

- Quality guidelines on delivery of stereotactic body radiation therapy.
- Quality standards for volumetric delineation in radiation oncology.

- An update of the Faculty's position paper on image guided radiation therapy.

### Australian Clinical Dosimetry Service

The Australian Clinical Dosimetry Service (ACDS) was established in 2011 (as a three-year pilot) to provide dosimetry audits for radiation therapy facilities, helping to ensure patients received the correct dose during their radiation therapy treatment. The current funding cycle for the ACDS terminated at the end of August.

The Faculty initiated an advocacy campaign for continuation of the ACDS by writing to the Health Minister, Peter Dutton, and encouraging Faculty members to write to their local MPs, to emphasise support for the ACDS as a permanent body. As a result, the Government agreed to a further two years of funding, tied to a Memorandum of Understanding with agreed performance indicators – including development of a sustainable funding model.

We are grateful to everyone who helped our advocacy efforts.

### Radiation Oncology Industry Roundtable

The Faculty of Radiation Oncology convenes an annual Industry Roundtable, providing an opportunity for stakeholders to meet and discuss current issues in radiation oncology with members of the professions, consumer advocates and College staff.

The 2014 roundtable took place at the College office in November, and was well received by around 20 industry participants.

The Faculty also continues to engage with governments and stakeholders in the broader cancer arena to advocate for radiation oncology as an essential pillar of cancer control.

### Dr Dion Forstner

*Dean, Faculty of Radiation Oncology, RANZCR*

## MEDICAL ONCOLOGY GROUP OF AUSTRALIA INCORPORATED, MOGA

### **Celebrating excellence in cancer care: Cancer Achievement Award 2014**

Professor Geoffrey J. Lindeman was presented with the MOGA-Novartis Oncology Cancer Achievement Award 2014 at the Annual Scientific Meeting in Sydney in August. This Award recognises the unique role Australian oncologists play in providing outstanding leadership in clinical practice, research and academic achievement.

Professor Lindeman is Joint Head of the Stem Cells and Cancer Division at the Walter and Eliza Hall of Medical Research Institute and Director of the Familial Cancer Centre at The Royal Melbourne Hospital. He also leads the Centre for Translational Breast Cancer Research.

### **Oncology drugs, treatments and advocacy**

MOGA's advocacy to ensure access to oncology drugs and treatments in Australia that matches developments overseas has continued apace. The 2014 Annual Horizon Scanning Report on New Developments in Medical Oncology, released in November, demonstrates the explosion of activity in oncology drug discovery and development over the last 12 months and the profession's active participation in ensuring access to new therapies.

Through the Oncology Drugs Working Group, chaired by Associate Professor Gary Richardson, MOGA systematically pursues a diversity of oncology drugs and treatment matters, including: review and streamlining of authorities; updating and derestricting indications in keeping with current clinical practice and research advances; shortage, funding and supply issues; liaising with pharma; approval and access issues; and proactively addressing oncology drugs and treatment issues with regulatory bodies and government as they arise.

### **Education and training**

The Young Oncologists Group of Australia, launched at our ASM in August, aims to support young medical oncologists who have attained their fellowship within the last five years, with a networking framework and assistance to facilitate their transition from advanced trainee to consultant.

The inaugural program featured presentations from ACORD Alumnus, Dr Katrin Sjoquist on clinical trial development and research opportunities, a masterclass

on 'What drugs when in prostate cancer' with Professor James Gulley from the US National Cancer Institute, and a session on career opportunities and options with Professor Bogda Koczwara.

The 2015 Annual Scientific Meeting 'Pathways in Medical Oncology - The Path Less Travelled' (Hobart, 5-7 August and Best of ASCO® Australia, 8 August), is being convened by Dr David Boadle, Staff Specialist in Medical Oncology at Royal Hobart Hospital.

An innovative scientific and academic program will explore contemporary challenges and advances in medical oncology research, discovery and clinical practice, including immuno-oncology. The program will also focus on less covered areas of medical oncology practice and research, such as rare tumours and haematological malignancies.

### **ACORD and international activities**

Professor Martin Stockler and the 2014 ACORD Faculty organised the largest and most successful ACORD Workshop to date. Seventy-two participants and 25 Faculty members attended the workshop on the NSW Central Coast in September. Attendees found the experience professionally and personally rewarding on all levels.

As it was the workshop's 10th anniversary, founder of the program, Professor Bogda Koczwara, returned to share her enduring enthusiasm for the program, medical oncology and clinical research.

**Associate Professor Rosemary Harrup**  
*Chair, Medical Oncology Group of Australia*

# CALENDAR OF MEETINGS

## AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
<b>March</b>			
15-18	Australian Pain Society 35th Annual Scientific Meeting 2015	Brisbane, Queensland	IDC Conferences Pty Ltd Website: <a href="http://www.dcconferences.com.au/aps2015/">www.dcconferences.com.au/aps2015/</a> Email: <a href="mailto:aps2015@dcconferences.com.au">aps2015@dcconferences.com.au</a> Phone: + 612 9954 4400
16-18	Asia-Pacific Gastroesophageal Cancer Congress (APGCC)	Brisbane, Queensland	APGCC Secretariat Website: <a href="http://www.apgcc.org/contact/">http://www.apgcc.org/contact/</a> Email: <a href="mailto:conferences@cancerqld.org.au">conferences@cancerqld.org.au</a> Phone: +61 7 3369 3731
24-26	TROG 2015 Annual Scientific Meeting	Newcastle, New South Wales	To be announced
25-28	Australia New Zealand Gynaecological Oncology Group (ANZGOG) Annual Scientific Meeting 2015	Gold Coast, Queensland	ANZGOG Website: <a href="http://www.anzgog.org.au">www.anzgog.org.au</a> Email: <a href="mailto:enquiries@anzgog.org.au">enquiries@anzgog.org.au</a> Phone: +61 2 8071 4880
<b>April</b>			
11-14	Urological Society of Australia and New Zealand (USANZ) 68th Annual Scientific Meeting	Adelaide, South Australia	To be announced
<b>May</b>			
4-8	Royal Australasian College of Surgeons Annual Scientific Meeting 2015	Perth, Western Australia	Royal Australasian College of Surgeons Website: <a href="http://asc.surgeons.org/">http://asc.surgeons.org/</a> Email: <a href="mailto:asc.registration@surgeons.org">asc.registration@surgeons.org</a> Phone: +61 3 9276 7431
24-27	13th National Rural Health Conference	Darwin, Northern Territory	National Rural Health Alliance Website: <a href="http://www.ruralhealth.org.au/">http://www.ruralhealth.org.au/</a> Email: <a href="mailto:conference@ruralhealth.org.au">conference@ruralhealth.org.au</a> Phone: 02 6285 4660
<b>September</b>			
2-4	17th AGITG (Australasian Gastro-Intestinal Trials Group) Annual Scientific Meeting	Sydney, New South Wales	ASN Events Pty Ltd Website: <a href="http://www.asnevents.net.au">www.asnevents.net.au</a> Email: <a href="mailto:eg@asnevents.net.au">eg@asnevents.net.au</a> Phone: +61 3 5983 2400
<b>October</b>			
29-31	2nd Global Advances and Controversies in Skin Cancer Conference		
<b>November</b>			
17-19	Clinical Oncology Society of Australia's (COSA) Annual Scientific Meeting 2015	Hobart, Tasmania	ASN Events Pty Ltd Website: <a href="http://www.asnevents.net.au">www.asnevents.net.au</a> Email: <a href="mailto:eg@asnevents.net.au">eg@asnevents.net.au</a> Phone: +61 3 5983 2400
<b>2016</b>			
<b>April</b>			
12-15	8th General Assembly and International Conference of the Asian Pacific Organisation for Cancer Prevention	Brisbane, Australia	Carillon Conference Management Pty Ltd Website: <a href="http://www.apocp8.org">http://www.apocp8.org</a> Email: <a href="mailto:admin@ccm.com.au">admin@ccm.com.au</a> Phone: + 61 7 3368 2644



# CALENDAR OF MEETINGS

## AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
<b>May</b>			
2-6	Royal Australasian College of Surgeons Annual Scientific Meeting 2016	Brisbane, Queensland	Royal Australasian College of Surgeons Website: <a href="http://asc.surgeons.org/">http://asc.surgeons.org/</a> Email: <a href="mailto:asc.registration@surgeons.org">asc.registration@surgeons.org</a> Phone: +61 3 9276 7431

## INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
<b>March</b>			
18-21	14th St Gallen Breast Cancer Conference on Primary Therapy of Early Breast Cancer	Vienna, Austria	St Gallen Oncology Conferences Website: Email: <a href="mailto:info@oncoconferences.ch">info@oncoconferences.ch</a> Phone: +41 (0)71 243 00 32
<b>April</b>			
23-24	Pain and Palliative care for Patients with cancer training	Monastir, Tunisia	To be announced
<b>May</b>			
24-2 June	2015 American Society of Clinical Oncology (ASCO) Annual Scientific Meeting	Chicago, Illinois	ASCO Website: <a href="http://www.asco.org">http://www.asco.org</a> Email: <a href="mailto:meetings@asco.org">meetings@asco.org</a> Phone: 571 483 1599
<b>September</b>			
16-19	18th Reach to Recovery International Breast Cancer Conference	Beijing, China	Reach to Recovery International Website: <a href="http://www.reachtorecoveryinternational.org/">www.reachtorecoveryinternational.org/</a> Email: <a href="mailto:info@rechtorecoveryinternational.org">info@rechtorecoveryinternational.org</a> Phone: +61 7 3634 5100
<b>December</b>			
8-12	38th Annual San Antonio Breast Cancer Symposium	San Antonio, Texas	Richard Markow Website: <a href="http://www.sabcs.org">http://www.sabcs.org</a> Email: <a href="mailto:sabcs@uthscsa.edu">sabcs@uthscsa.edu</a> Phone: 210-450-1550

## CANCER COUNCIL AUSTRALIA

Cancer Council Australia is the nation's peak independent cancer control organisation.

Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.



### MEMBERS

Cancer Council ACT  
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Cancer Council Northern Territory  
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Cancer Council South Australia  
Cancer Council Tasmania  
Cancer Council Victoria  
Cancer Council Western Australia

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## CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA

The Clinical Oncology Society of Australia (COSA) is a multidisciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.

It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with Cancer Council Australia.



**Clinical  
Oncology  
Society of  
Australia**

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### MEMBERSHIP

Further information about COSA and membership applications are available from:

[www.cosa.org.au](http://www.cosa.org.au) or [cosa@cancer.org.au](mailto:cosa@cancer.org.au)

Membership fees for 2015  
Medical Members: \$170  
Non Medical Members: \$110 (includes GST)

### COSA Groups

Adolescent & Young Adult  
Biobanking  
Breast Cancer  
Cancer Biology  
Cancer Care Coordination  
Cancer Pharmacists  
Clinical Trials & Research Professionals  
Complementary & Integrative Therapies  
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## Information for contributors

*Cancer Forum* provides an avenue for communication between all those involved in cancer control and seeks to promote contact across disciplinary barriers. To this end, articles need to be comprehensible to as wide a section of the readership as possible. Authors should provide sufficient introductory material to place their articles in context for those outside their field of specialisation. *Cancer Forum* is primarily a review journal, with each issue addressing a particular topic in its 'Forum'. The Forum topic and appointment of Guest Editor(s) are determined by the Editorial Board, which welcomes suggestions. Proffered papers containing primary research findings will be considered for publication in *Cancer Forum* in limited circumstances. Articles will be considered by the Editorial Board and then published subject to two peer-reviews. Generally speaking, authors are encouraged to submit their primary research findings to established cancer research or clinical oncology journals. The following information is provided for contributors invited to prepare manuscripts for *Cancer Forum*.

### Format

Prospective authors are encouraged to examine recent editions of *Cancer Forum* for an indication of the style and layout of Forum papers ([www.cancerforum.org.au](http://www.cancerforum.org.au)). All manuscripts should be submitted by email to the Forum's Guest Editor(s) and Executive Editor ([rosannah.snelson@cancer.org.au](mailto:rosannah.snelson@cancer.org.au)) as MS Word documents.

Length: 2000-2500 words.

Font: Arial - 20pt and bold for title, 12pt and bold for headings, 12pt and italics for subheadings and 10pt for text.

Following the title, include your full name, organisation and email address.

Include introductory headings and sub-headings that describe the content.

Number pages in the footer.

### Abstract

All manuscripts must include an abstract of approximately 200 words, providing a summary of the key findings or statements. No references or abbreviations should be included in the abstract.

### Abbreviations and acronyms

Abbreviations and acronyms should only be used where the term appears more than five times within the paper.

They must be explained in full in the first instance, with the abbreviation in brackets.

The Editorial Board reserves the right to remove the heavy use of abbreviations and acronyms that may be confusing to the diversity of our readership.

### Photographs, tables and graphs

Photographs and line drawings can be submitted via email, preferably in tiff or jpeg format. If images are not owned by the author, written permission to reproduce the images should be provided with the submission. A maximum of five illustrations and figures and three tables can be submitted with the manuscript. Inclusion of additional items is subject to approval by the Editorial Board. Unless otherwise specified by the authors or requested by the Editorial Board, all images, graphs and tables will be printed in black and white. All figures – including tables and graphs – will be reproduced to *Cancer Forum's* style. Figures containing data (eg. a line graph) must be submitted with corresponding data so our designers can accurately represent the information. Figures and images should be labelled sequentially, numbered and cited in the text in the correct order e.g. (table 3, figure 1). Tables should only be used to present essential data. Each must be on a separate page with a title or caption and be clearly labelled.

### Referencing

Reference numbers within the text should be placed after punctuation and superscripted. The maximum number of references is 75. Only papers closely related to the subject under review should be quoted and exhaustive lists should be avoided. Only one publication can be listed for each number. Citation of more than one reference to make a point is not recommended. The Editorial Board prefers a focus on more recent references (in the last 10 years). The list of references at the end of the paper should be numbered consecutively in the order in which they are first mentioned and be consistent with the National Library of Medicine's International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals. i.e. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med*. 2002 Jul 25;347(4):284-7.

A full guide is available at [www.nlm.nih.gov/bsd/uniform\\_requirements.html](http://www.nlm.nih.gov/bsd/uniform_requirements.html) A guide to abbreviation of journal names can be found at [https://www.library.uq.edu.au/faqs/endnote/medical\\_2010.txt](https://www.library.uq.edu.au/faqs/endnote/medical_2010.txt)

**The Editorial Board will make the final decision on inclusion of manuscripts and may request clarifications or additional information.**

For further information or confirmation of the above, please contact:

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