



Walter+Eliza Hall

Institute of Medical Research

DISCOVERIES FOR HUMANITY

Walter and Eliza Hall Institute of Medical Research submission to the Senate Select Committee into Funding for Research into Cancers with Low Survival Rates

March 2017

Committee Secretary
Select Committee into Funding for Research into Cancers with Low Survival Rates
Department of the Senate
PO Box 6100
Canberra ACT 2600

Dear Secretary,

We warmly welcome the opportunity to provide our perspective to the Senate regarding the urgent need for revised funding for research into cancers with low survival rates.

The Walter and Eliza Hall Institute of Medical Research, established in 1915, holds a pre-eminent position in Australian medical research, with around 1000 staff and students and an annual budget of approximately \$100 million. The Institute's research focuses on cancer as well as infectious disease and chronic inflammatory and immune diseases.

In addition to world-class research programs in common cancer types including breast cancer, colon cancer, prostate cancer and lung cancer, the Institute's researchers focus on rare blood disorders, leukaemia, lymphoma and multiple myeloma, and have developed programs for ovarian and pancreatic cancer, and streamlined research into rare cancer types. The Institute has a strong national and international reputation for performing highly influential research and for translation that leads to long-term improvements in disease diagnosis and treatment. The Institute is the first medical research institute in Australia to have an active Consumer Advisory Panel, which is chaired by Dr Judith Slocombe, and a full-time Consumer Coordinator. These provide real-world advice on aspects of medical research important to our community, including gaps in access to medical research.

The Institute's cancer research teams aim to make discoveries that shape contemporary scientific thinking, increase understanding and improve prevention, diagnosis and treatment of cancer. This includes engaging with our stakeholders to improve outcomes, building support, appropriate governance and secure resourcing, particularly for new areas of medical research. For cancers with low survival rates, including cancers of the lung, pancreas, ovary and brain, some haematologic malignancies and many rare cancers, we are particularly engaged in developing research expertise and supporting the development of national infrastructure and research networks that are required to fuel research that improves outcomes for patients.

Twenty-seven clinician scientists with joint appointments at the Institute and at relevant teaching hospitals, in most cases, are responsible for driving the pre-clinical research that is so important for developing clinical trials, in particular, investigator-led trials. The Institute is also currently providing research training to more than 25 clinicians, many of whom maintain clinical appointments. Contributors to this submission are responsible for clinical translation of the low survival cancer types outlined above.

Within the terms of reference of this enquiry into the impact of health research funding models on the availability of funding for research into cancers with low survival rates, **we wish to address:**

- 1. NHMRC funding models that disadvantage many low survival cancers**
- 2. New funding models to support appropriate clinical trials**
- 3. Strategies to improve survival rates across low survival cancers**
- 4. National coordination of medical and research data essential to enable change**

Background

Implicit in the enquiry reference document is an assertion that there is inappropriate funding of research into cancers with better survival rates. It is important that such notions be addressed with data. In fact, the data (see below) reveals that these research investments have delivered considerable benefits in cancer survivals. A natural consequence of major breakthroughs in understanding the cause of a cancer, or its biology, is new ways to prevent it or treat it. Such breakthroughs 'seed the ground', so that additional investment 'fertilises the field', and increases attraction for further investment in research, clinical trials and adoption of new treatment or preventions strategies.

Common cancers

For many of the 50 per cent of cancer patients diagnosed with a common cancer type where considerable NHMRC and philanthropic funding has been invested, five-year relative survival rates improved impressively between 1982-1987 and 2006-2010¹, for example:

- breast cancer (72% to 89%),
- colorectal cancer (48% to 66%)
- prostate cancer (58% to 92%).

For the other common cancer types, lung cancer (8% to 14%) and melanoma (86% to 91%), we saw modest increases in five-year survival rates. It is noteworthy that approvals for new targeted therapies have greatly improved the outlook for patients with metastatic melanoma since this time period².

For lung cancer, the common cancer type with the lowest survival, encouragingly the discovery of important molecular subtypes of lung cancer, enabling the matching of new targeted therapies for some people with particular subsets of lung cancer, is heralding meaningful improvements in outcomes for others³.

These improvements in survival for common cancer types coincide with higher levels of research funding for, and novel discoveries in, these cancer types, across the areas of prevention, screening, early diagnosis and treatment, both with conventional (chemotherapy) and new targeted therapies matched to the cancer. Lung cancer remains the major challenge here.

Less common cancers

Increases in five-year survival were also observed for some less common cancer types between the periods 1982-1987 and 2006-2010¹, for example, uterine (75% to 82%) and kidney (47% to 72%) cancers. However, despite small increases for ovarian (32% to 43%), oesophageal (10% to 17%) and stomach (17% to 27%) cancers, survival rates remain low and clearly new therapies are urgently needed. In contrast, there has been little change (5 per cent or less) in five-year survival rates for people with other less common cancer types, in particular, pancreatic cancer (3% to 5%), which is projected to be the second leading cause of cancer death in coming years, and brain cancer (20% to 22%).

Rare cancers

A practical definition of 'rare' comes from the European RARECARE group: an incidence rate of <6 cases per 100,000 population per year^{4,5}, which covers several hundred different types of cancers. Although each type is rare, collectively these rare cancers account for 24 per cent of all cancers diagnosed each year and for an even higher proportion of cancer deaths – 30 per cent of Australian deaths due to cancer. AIHW reports that cancers with poor prognoses tend to be rare, with some exceptions noted above¹.

Despite modest increases in survival rates for some rare cancer types, namely 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 at approximately 20 per cent or less (approximately 5 per cent for mesothelioma) between 2006-2010. It is of great concern for the future that the incidence and mortality rates for rare, high-mortality cancers are rising⁶. Most other patients diagnosed with one of many types of very rare cancers endure a long road to diagnosis, with little specific information or evidence-based care available and poorer outcomes^{5,6,7}. Not surprisingly, without evidence-based care these Australians have a very low survival.

Characteristics of low survival cancers

We view many low survival cancer types as:

- 'less common' or 'rare';
- attracting insufficient research funding to generate the initial breakthroughs needed; and
- with accordingly less in the way of evidence-based care specific to that cancer type.

As improvements in survival require early detection and/or better treatment, all of which start with research, this remains a great challenge for all cancers with poor survival rates, whether they are common, less common or rare cancer types. We argue that cancers with currently low survival, such as brain, lung, pancreas and many rare cancers require additional funding for research⁸, and this should not detract from quality research in cancers with better outcomes, where major challenges still remain.

1. NHMRC funding models that disadvantage many low survival cancers

The barriers

Current NHMRC funding models favour applications associated with the highest track record and research feasibility. These have often been associated with cancer types where breakthroughs have already been made, and the impetus to build from that base has been both strong and rational. As success begets success, historically funding for research that has proved successful has facilitated the development of track record, thereby increasing the competitiveness of researchers in that area. For these common tumour types there is far greater potential for collaborations to be built with other groups working on the same tumour type, which can make for a stronger application and are favourably reviewed in an era where collaboration is increasingly encouraged. Where tumour types are inherently difficult to treat, and breakthroughs have not yet emerged, it can be very difficult to convince grant reviewers that a project's feasibility is high. Yet those treatment-resistant cancer types require more research, not less.

In the current climate of NHMRC project grant success rates being universally lower than 20 per cent, an even slightly less competitive track record, or feasibility (for example, based on the

difficulty of obtaining tissue from sufficient numbers of cases of a rare cancer type) mean that NHMRC success is not guaranteed for even the very best of research proposals.

It is extremely difficult for a laboratory to run a consistent program with an expert team focusing on one of these low survival cancer types, without a greater certainty of funding or of building collaborations with other researchers working on the same tumour type. This leads to many researchers investing their energies in studying common cancer types with a higher chance of successful funding.

The solutions

- i) **Establish a priority process for project grant funding for research into cancers with low survival, particularly less common and rare cancers, where funding is not currently directed⁸.** This could be achieved within NHMRC as sequestered funding, or within Cancer Australia as a priority-driven cancer research stream. The latter could be templated upon the Priority-driven Collaborative Cancer Research Scheme, managed by Cancer Australia in collaboration with the NHMRC, which has been successful in ensuring quality research is funded if it meets certain criteria. Thus, feasibility and track record would continue to be judged on their merits, but compared within this priority stream at the grant review panel level, rather than against the track record and accomplishments of better researched cancer types. We envisage that applicants would check a box, nominating that their grant be judged within the Priority Low Survival Scheme, and then make an argument as to why their research fulfils the aims of that scheme. The disadvantage is that researchers may have to change the direction of some of their research, but the advantage is that they would have a better chance of being funded based on novel ideas, and solid, feasible research within the context of low survival cancer applications. This would be distinct from the existing Priority-driven Collaborative Cancer Research Scheme, which aims to coordinate funding of priority-driven cancer research at the national level and to foster collaboration between cancer researchers and consumer participation in cancer research. These aims, whilst worthy, do not go as far as to ensure that a significant portion of the NHMRC Project Grant system would be directed towards low survival cancers.
- ii) **Do not restrict this priority stream to certain tumour types:** allow the researcher to make their argument to the grant review panel that the cancer type they are studying is a low survival type, as we cannot predict which of the many low survival cancer types might have compelling biology. There are also rare subtypes of common cancers that remain under-researched, which could also be considered under the banner of 'rare cancers'. It must be acknowledged that the increased funding of single tumour stream grants, from 38 per cent in 2003-2005 to 59 per cent in 2009-2011 (p46, *Cancer Research in Australia*, Cancer Australia 2014⁸), does not leave much funding opportunity for the hundreds of tumour types that need new approaches to treatment. If necessary, the few cancer types with higher survival and better funding exposure (colorectal, prostate, breast, melanoma, leukaemia) could be excluded.
- iii) **Encourage applications for five year grants** to allow expert team building.
- iv) **Encourage both translational and basic science grants**, as these are both important aspects of developing new and innovative approaches to diagnosis and treatment.

The availability of a priority stream for low survival cancers is highly unlikely to reduce the quality of research funded, as still only the top proportion of grants would be funded. It would ensure that many investigators, who would otherwise not choose to study a cancer that is either rare or has low survival, would feel emboldened to do so.

2. New funding models to support appropriate clinical trials

The barriers

The challenges to establishing clinical trials are manifold and vary between cancer types, and also according to whether the cancer is rare or common. Space precludes a detailed discussion of them all, but recurring themes are that:

- i) access is limited for patients with rare cancers, as trials will not be available in all major treatment centres;
- ii) access for patients in rural Australia is difficult when the trial requires frequent attendance at a capital city centre;
- iii) the time taken to establish a trial is disproportionately long compared to the survival time of patients with low survival cancer; and
- iv) pharmaceutical companies are risk adverse when it comes to initiating adequately sized trials in cancers with low incidence.

The solutions

A new approach to clinical trial design will be needed involving streamlining at all levels of clinical trial development:

- i) **Encourage basket trial designs**, approved for the addition of “modules” based on molecular marker or drug class (eg immunotherapy). An example of this is the Molecular Screening and Therapeutics Study (MoST) study (PI D Thomas, Garvan Institute).
- ii) **Support of the Australasian Teletrial Model** to encourage accrual of patients to a suitable clinical trial regardless of geography within a state. For example, patients in Victoria would have access to a trial open in Victoria at the closest comparable hospital. ‘Teleoncology’ models of care offer the opportunity for patients living outside major metropolitan centres to access clinical trials closer to home, reducing the need for travel. The Australasian Teletrial Model was developed by the Clinical Oncology Society of Australia (COSA) Regional and Rural Group and is endorsed by the COSA Council. While the principles of operation for primary and satellite centres are the same, site-specific governance and processes need to be developed for effective implementation. The Walter and Eliza Hall Institute is a founding partner of the Australasian Teletrial model ⁹.
- iii) **Streamlining of ethical approval through a coordinated national system is of the utmost importance.** The time spent obtaining multiple ethical approvals in order to put Australian patients with the same disease on the same trial in different states causes critical delays, with impact on patients’ opportunities to receive treatment. Harmonisation of human research ethics committees at a national level should be facilitated. Similarly, governance needs to be streamlined. The Walter and Eliza Hall Institute is attempting to do this via the REx system and the Australasian Teletrial Model will assist.
- iv) **Encourage the addition of ‘bolt-on’ rare cancer cohorts** (10-20 per cent of the patient numbers for that trial), to be absorbed into current clinical trials, as a way to ensure access for rare cancer patients to all therapeutics, once they have been proven to be safe (phase 2/3 trials). Data from the rare cancer cohort should be collected and shared across trials, rather than being analysed within the specific trial, and the involvement of drug approval agencies in encouraging this approach would be imperative. Providing an advantage for companies participating in this endeavour would be reasonable.

3. Strategies to improve survival rates across low survival cancers

The barriers

Improvement in survival rates of low survival cancer types requires improved knowledge about that cancer type. Many low survival cancer types are under-researched and in many cases we know very little about the cell of origin, about how to prevent that cancer type, about its critical Achilles' heels that could be targeted by therapy, and how the cancer evolves under treatment pressure. Basic research is needed and this is the time to spread the benefits of the genomic revolution across tumour types that have been under-investigated to date. This research is difficult to enable because:

- i) correct histologic diagnosis of less common or rare cancer types can be difficult;
- ii) molecular testing of these cancer types is usually not funded and therefore needs to be performed within the research setting – which again, is usually not focused on rare cancer types;
- iii) accurate medical advice regarding diagnosis, molecular testing and choice of therapeutic is often siloed across Australia, with expertise often being available but not always coordinated;
- iv) access for patients with less common or rare cancer types to new targeted therapies is usually extremely limited or not available unless privately funded – which is out of the reach of most patients; and
- v) prevention or early diagnosis of rare or less common cancers, such as pancreatic cancer, are under-researched and extremely challenging.

The solutions

The solution starts with research – essential for all aspects of diagnosis, molecular characteristics, optimal treatments and better still, prevention. Improving the NHMRC funding model for low survival cancers (above) is critical.

The funding of current proposals to the Medical Services Advisory Committee for molecular panel testing of cancers including rare cancers is also vital to improving diagnosis and treatment.

For patients with rare cancers, for whom there is poor availability of diagnostic and treatment options, a national network to facilitate patient management would enable these patients to be brought into line with patients diagnosed with a more common cancer. The components required are being developed at major centres, but this does not provide streamlined access for all patients.

We propose that a national coordinated network, in the form of a NHMRC Centre of Research Excellence, would provide the critical impetus to speed up patients' access to expert opinion and underpin improvements in access to research and critical drug therapies. A secure information portal is required, linked to this national network, and staffed by dedicated administrative staff and clinical medical oncology fellows, who are supervised by rare cancer experts familiar with the rare cancer national network. This proposal has been designed in detail and has the support of ten senior cancer clinicians and researchers throughout Australia.

The additional missing link, essential to the streamlined activity described above, is a robust national data collection process as outlined below.

4. National coordination of medical and research data essential to enable change

The barriers

For low survival cancers, many of which are rare, we have very poor data to guide treatment for our patients. This makes data collection even more important for low survival cancers.

We need to ensure the right treatment for the right patient, which will save healthcare dollars, by unlocking the value of existing health data. For low survival cancers, improving data connections would be transformative for urgently needed research and care delivery.

Personalised health care, delivering the optimal treatment to each individual based on their specific situation, dictates that healthcare delivery and medical research should be more closely linked. Delivering the promise of personalised medicine is dependent on reliable and rapid access to all of an individual's data. We need a greater focus on prevention and early diagnosis, where there are proven strategies that are cost effective and reduce disease impact.

Linking data on many patients allows the efficiency and effectiveness of health care delivery to be examined, with a focus on quality and cost-effectiveness. The UK National Institute for Health Research has proven that cost savings in health can occur as a result of health services research, which would be facilitated by an integrated data model.

Challenges to achieving this include:

- i) most tumour tissue stored in Australia is not linked to high-quality clinical data;
- ii) the storage of patient tumour / blood samples with linkage to patient data is not currently approached or funded in a coordinated, national way;
- iii) improved research and healthcare delivery requires coordinated access to high quality data linkage of both health and medical research information and this is not available;
- iv) currently, electronic data remain in silos, with each dataset existing in relative isolation. Electronic Medical Records (EMRs) have limited interaction with the hospital and research communities. Much molecular data remains inaccessible to clinician and researcher alike, and wealth of government data, such as the Medical Benefits Scheme (MBS / Pharmaceutical Benefits Scheme (PBS) / National Death Index (NDI) data are difficult to access; and
- v) state- and territory-based data linkage units such as those within the Population Health Research Network (PHRN) specialise in linking population data from government managed health, education and community services for project-specific linkage such as births, deaths, perinatal, emergency department, admitted patient, mental health and cancer registry population datasets – and that is where the linkage stops.

To summarise the issue, there is no comprehensive real-time ongoing clinical data linkage across Australia.

The solutions

- i) **Access to a patient's tumour sample in order to determine suitability for treatment** Accessing patient samples, most importantly diagnostic archival tissue and any tumour biopsies or surgeries performed since diagnosis, is critical and should be 'standard of care', reimbursed by a MBS code (currently researchers are charged \$200-300 per case just to retrieve tissue). A new MBS code for accessing stored tumour samples, to ensure access to patients' biospecimens for improved health care delivery and research potential, would invigorate the medical research

sector. These tissues are essential for a growing list of routine clinical tests and to support translational research, on which many patients will depend for their access to treatment and health care delivery. Precision medicine is simply not possible without tumour sample access.

- ii) **Access to a patient's clinical data in order to determine all aspects of management:** Information from the pathology and molecular analysis of a person's tumour sample is pivotal to making precision medicine decisions for that patient. This would be feasible if pathology data is integrated via linkages to the clinical data for that person. Clinical data is best captured at point-of-care data entry within the health system and must be linked with the wealth of health care data that is held centrally, such as Medical Benefits Scheme (MBS), Pharmaceutical Benefits Scheme (PBS) and National Death Index (NDI) data. At present, the data collected depend on the hospital and research with which the patient is involved – this creates inequities, against core Australian values.
- iii) **Innovative approaches to real-time data linkage are urgently required** and would be transformative, saving health care dollars and lives, creating opportunities for research and innovation and engagement by the academic medical research sector with industry, pharma and consumers. Our current inability to access accurate data for patients of a particular type or for a specific patient is no longer acceptable to the public in this day of 'instant' technology. The Medical Research Future Fund council could prioritise funding of projects that aid data integration capacity. In-kind access to government data (MBS/PBS/NDI), already collected but not practically accessible to the research/health community, could be leveraged.

A 'transformative' national solution

Data integration would allow the whole to be far greater than the sum of the parts, leveraging individual lines of investment. Preventing short-term investment in isolated efforts at data access and utilisation is critical to transforming medical research and health care delivery in this country.

One cost-effective solution to support a national framework for tissue access and data integration is to leverage the well-established and proven operational federated national data linkage platform, BioGrid Australia. BioGrid is a collaboration owned by member hospitals, universities and research institutes with a proven track record in supporting high quality national data collections and linkages across public and private hospitals for both investigator-led and industry-led research. Commencing in 2003 and still unique globally, this data linkage platform has unique legal and ethical framework and should be leveraged to support a national approach for data integration.

BioGrid's platform not only links data in real-time across diseases and jurisdictions, but it also provides integrated data to authorised researchers to interrogate, analyse and report, utilising a suite of SAS high-performance data analytics products available through BioGrid.

Key features of BioGrid are:

- i) BioGrid specialises in real-time linkage of hospital-based and managed clinical and research data such as treatment outcome, genomic, biospecimen, imaging and patient administration system data;
- ii) BioGrid is the only collaboration network that provides the federated infrastructure and processes to enable hospital-based clinical data to be linked and accessed in real-time, thus providing enduring linkages that ultimately saves time and money; and

- iii) BioGrid complies with privacy and health records legislation, both at a national and state/territory level, ensuring legal compliance for data linkage for ethically approved research.

Key benefits from a national framework for data integration include:

- increasing opportunities for prevention and early detection;
- improving patient outcomes from provision of most effective treatments;
- increasing efficiency in health service delivery providing cost savings over time;
- expanding capacity for medical research at individual and population level;
- empowering consumers to be involved in research and health care delivery;
- leveraging existing data and research to generate substantial IP opportunities; and
- enhancing industry engagement and investment to expand innovation and productivity.

The consumer, the patient is paramount

As described by Mr Les Leckie, a healthcare consumer and member of the Walter and Eliza Hall Institute Consumer Advisory Panel:

“As a patient advocate and community health person, the organisations I represent believe in patient-centred care and effective use of technology to break down silos, resulting in greater cooperation and collaboration among health professionals across all disciplines, resulting in measurable patient benefits.”

Involvement of the public, represented by the consumer voice, has the potential of ensuring acceptability to stakeholders, including government.

Conclusions

The major distinction currently between a cancer with low survival and one that has better survival now, is that the true breakthroughs haven't been realised yet – either because they haven't occurred, or haven't been built upon. More quality research is essential, and the system must find a way to prioritise excellent investigation of low survival rate cancers, while ensuring no dollars are wasted on low quality efforts.

Technological advancement has transformed many aspects of our daily lives. However, key aspects of the medical and research sector lag behind, imperiling the health of many. For example, the technology in our phones is in stark contrast to the quality and processes of the information systems on which we depend for potentially life-saving advancements and treatments.

The genomic revolution will allow us to make discoveries that were heretofore impossible. But in order to benefit from this revolution, we need to connect patients with research, cancer tissue with molecular analysis, patients with appropriate drugs and outcome data with bench to the bedside analysis of cancer evolution.

Making a difference for patients with low survival cancers is in the sights of researchers here at the Walter and Eliza Hall Institute. Coordination and appropriate funding is essential.

We are grateful for the opportunity to provide our opinions and would be happy to be contacted to provide additional information on any of these aspects.

Yours sincerely,

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