GARVAN INSTITUTE OF MEDICAL RESEARCH

PROPOSAL:
A NATIONAL GENOMIC CANCER MEDICINE PROGRAM FOR RARE AND LESS COMMON CANCERS

There are around 180 rare and less common cancers, from ovarian cancer to chordomas, a cancer of the bones of the spine.

Rare and less common cancers account for one-third of all cancers, but are responsible for half of all cancer deaths in Australia.

The ground-breaking field of genomics will have a huge impact for people with rare, high-mortality cancers. To save these lives we need to support the expansion of the next generation of genomic cancer treatment infrastructure.

Professor David Thomas
Head, Genomic Cancer Medicine Program
Director Cancer Division
Garvan Institute of Medical Research

Mr Andrew Giles
Chief Executive Officer
Garvan Research Foundation

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1. EXECUTIVE SUMMARY

In Australia this year, an estimated 52,000 people will be diagnosed with a rare or less common cancer and 25,000 of those people will die from their disease.

Patients who participate in clinical trials benefit by comparison with those receiving standard of care. A national rollout of Garvan's Genomic Cancer Medicine Program (GGCMP) would provide ALL Australians with rare and neglected cancers access to a clinical trial, in their home states.

The GGCMP also uses genomic technologies to identify cancers at an earlier, curable stage in families with a genetic predisposition to rare cancers.

The national Genomic Cancer Medicine Program would cost $88 million over five years.

A Federal Government investment of an estimated $50 million over five years, matched by leveraged funding from industry and philanthropy, will enable the establishment of six centres of excellence Australia wide to deliver clinical trials to almost 3,000 Australians affected by rare cancers.

2. THE POTENTIAL OF GENOMICS

The unlucky Australians…
Despite being individually uncommon, when combined, 'rare' or less common cancers account for 30% of cancers diagnosed – and up to 50% of cancer deaths. While mortality rates for common cancers have dropped over recent decades, incidence and mortality rates for 'rare', high-mortality cancers are actually rising. In fact, the 'unlucky' Australian with a 'rare' cancer is almost twice as likely to die as a patient with a common cancer.

Cancer is usually considered a disease of older people, with mortality rates increasing with age for most cancers. Many rarer cancers, however, affect children and young families. For Gen X, Gen Y, and children, 'rare' high-mortality cancers are the leading cause of disease-related death in Australia.

There are a number of reasons for the high mortality rates for rare and less common cancers. These include lack of focused multidisciplinary care, incorrect or delayed diagnosis and lack of access to new and emerging treatments.

Clinical trials are essential to develop new therapies, and there is ample evidence that clinical trials represent the best, cost-effective standard of care for cancer patients. However, such trials are rarely available to patients with these cancers.

As governments use information gained from trials when deciding if they will fund a new drug, this compounds the lack of access to effective therapy. It is critical that government, academics, clinicians and the pharmaceutical industry work together to develop trials of new treatments for patients with rare cancers.

The solution – Garvan's Genomic Cancer Medicine Program
Several recent advances have now set the scene for new hope to address the tragedy of Australians living with rare or less common cancers who face few treatment options, and lack of affordable access to drugs and a bleak prognosis.

These include:

- Advances in medical research mean that cancer patients can now be treated on the basis of the genomics of their disease, rather than where in the body the cancer has occurred. The genome is the complete set of genetic information we inherit from our parents, present in all the cells of our bodies, and which determines our health and susceptibility to disease. This genomic medicine approach to treatment promises better and more effective treatments with fewer side effects – the right drug to the right patient at the right time.

- Recent world-first US Food and Drugs Administration (FDA) approval for a cancer drug based on a genetic biomarker, not the location of the site of the tumour. FDA drug approval is based on evidence that a drug is safe and effective for its intended use and

that its health benefits outweigh its known and potential risks for the intended population. The genomic cancer medicine approach has been validated with the accelerated FDA approval on 23 May for Merck & Co's (MSD in Australia) Keytruda in adults or children with the MSI-H or dMMR genetic variant. Keytruda works by targeting the cellular pathway known as PD-1/PD-L1 (proteins found on the body's immune cells and some cancer cells).

- In Australia, while the drug registration and reimbursement approval bodies, such as the Therapeutic Good Administration (TGA) and the Pharmaceutical Benefits Advisory Committee (PBAC) have different standards of evidence to the US FDA, principally around financial cost effectiveness, the Federal Government has recently approved Opdivo for use beyond melanoma, to lung and renal cancer, and Rare Cancers Australia succeeded in getting Vorinostat listed for a rare form of lymphoma.

- The promising early results from the novel design of Garvan's Genomic Cancer Medicine Program clinical trials that seek to find if a certain drug works on the basis of certain genetic biomarkers. The drugs can be ones that are used in other cancers or diseases and repurposed. There are no placebos or control groups in these trials. Everyone who is eligible for the trial (has a biomarker, is fit enough to go on a trial) is given access to a test drug.

In 2014 Garvan's Genomic Cancer Medicine Program was established as part of a $24 million, four-year investment by the NSW State Government to facilitate research programs into genomic medicine and to use genomic technologies improve patient outcomes. The funding provided by the NSW State Government will see Garvan's Genomic Cancer Medicine Program continuing through part of 2018, matched by philanthropy. The issue, however, is not the continuation of a research program, but that this program has only just begun to reveal the extent of the unmet need.

Garvan's Genomic Cancer Medicine Program applies an innovative 'basket' clinical trial design based on the principles of precision medicine, in which patients are treated on the basis of their individual genomic profile, irrespective of where the tumour started.

The role of precision oncology in the future of cancer therapeutics is the subject of active research. At this stage, there is unequivocal evidence of benefit of the concept of biomarker-linked therapy, although formal proof of clinical benefit for rare cancers in general is pending. However, there is little doubt that research leads to improved outcomes for cancer patients, and that patients who participate in clinical trials benefit by comparison with those receiving standard of care.

In fact, Garvan's Genomic Cancer Medicine Program has already uncovered huge unmet need. From a planned base in October 2016 of 150 patients over the first 12 months, more than 230 people have already applied, solely by word of mouth. There are currently 44 patients (20%) trialling two drugs, with another 45 (20%) on immunotherapy trials, 12 (5%)

people have died waiting to get on a trial and the remainder are waiting for results of their genomic screening. These people have come from all around the country (and even New Zealand). More than 400 people are expected to join the Garvan's Genomic Cancer Medicine Program by the end of 2017, with many traveling thousands of kilometres to access the program, as this is the only clinical trials program of its kind in Australia.

Based on evidence to date, we expect that 25% of patients will have a biomarker that matches them to one of the trial drugs, 65% will be offered an immunotherapy trial and 10% will die before a trial is available to them. Initially only people with late stage disease in any rare or less common cancer, who had exhausted all treatment options were selected for the Garvan's Genomic Cancer Medicine Program, but we are now trying to enrol earlier in the disease course, to avoid deaths while waiting for results and allowing external tests to replace our own internal testing.

The drugs used in the Garvan's Genomic Cancer Medicine Program include one repurposed drug, and two novel immunotherapies. In the next six months we intend to expand the trial to include another three repurposed approved drugs.

Pharmaceutical Benefits Advisory Committee, fit-for-purpose trials and conditional drug access

In their recent report, *Rare Solutions: A Time to Act*, launched by the Hon Greg Hunt MP, Minister for Health, Rare Cancers Australia called for trial designs to aim to provide evidence that would allow drug registration submissions to the TGA and PBAC. Discussions have begun with PBAC as to how to ensure that our trials, particularly in the national context, are fit-for-purpose in terms of assisting them with data for drug listing for rare and less common cancers.

We also have indications that positive data from such clinical trials will encourage pharmaceutical companies to initiate their own phase 2 trials to confirm our results, hastening the drug approval process.

Additionally, there are potentially effective drugs that fail recommendation for unconditional listing due to a lack of data in the Australian context. A national Genomic Cancer Medicine trials program may also provide the PBAC with a mechanism for providing immediate but conditional access to novel drugs in rare cancers, while capturing the additional real-world data required for unconditional approval.

These post-market trials would be designed in collaboration with the PBAC, Garvan Institute for Medical Research, NHMRC-Clinical Trials Centre, Rare Cancers Australia and the pharmaceutical industry and study real-world treatments under clinical trial conditions to produce real-world data where it is lacking. This 'fusion' trial mechanism would allow a determined number of patients to access drugs, while data on agreed endpoints (evidence of

benefit, health resource utilisation, etc), is collected over an agreed timeframe. With this real-world data in hand, PBAC would then be able to make a firm decision as to whether to list unconditionally, or not to list. These fusion trials would be a shared risk-benefit partnership between pharma, government, researchers and patients, to address unresolved issues and enhance access to novel therapies for patients with rare cancers.

This model could also be used beyond rare cancers to include other cancers and other diseases, such as autoimmune and other chronic conditions.

3. INTERNATIONAL EXAMPLES OF SIMILAR TRIAL PROGRAMS

We need local clinical trials because they provide access to experimental treatment for Australians with rare or less common cancers. The nature of rare cancers means that combining international efforts will be essential to gathering sufficient numbers to make progress with these diseases and Australia is well-positioned to contribute to the global effort. Finally, as international pharmaceutical trials are rarely designed to meet the criteria for listing a drug on the Australian PBS, real-world data in the Australian context adds important evidence to the drug approval process.

There are several overseas trials available where we can combine data to increase the knowledge base about rare cancers.

- USA - NCI Match (Molecular Analysis for Therapy Choice) for patients with advanced solid tumours, once they have progressed on standard treatment for their cancer, or if they have a rare cancer for which there is no standard treatment. Beginning in July 2015, NCI-MATCH is a precision medicine cancer treatment clinical trial with 19 treatment arms for patients whose tumours have a specific genetic change. Most treatment arms will enrol 35 patients. The drugs included in the trial have either been approved by the FDA for another cancer or are still being tested in other clinical trials but have shown some effectiveness against tumours with a particular genetic change.

  Initially Match aimed to reserve around 25% of their places for patients with rare or uncommon cancers. So far, the trial has exceeded this goal, with about 60% of the enrolled patients having cancers other than colon, rectal, breast, non-small cell lung, or prostate. Treatments are considered promising if at least 16% of the patients in an arm have tumour shrinkage. The trial is also evaluating the percentage of patients whose disease does not worsen for at least six months, progression-free survival, time to progression of the cancer, and side effects of the treatments.

- USA - TAPUR Launched in March 2016, the Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a study by the American Society of Clinical Oncology (ASCO) that aims to describe the performance (both safety and efficacy) of 17 commercially available, targeted anti-cancer drugs prescribed for treatment of patients with advanced cancer who have exhausted options or who have no standard treatments, and have a potentially actionable genomic variant. The study provides approved targeted therapies, catalogues the choice of genomic profiling test by clinical oncologists and aims to learn about the utility of registry data to develop hypotheses for additional clinical trials.

  More than 300 participants are now enrolled on study drugs, over more than 100 sites. The age of eligibility has been recently been lowered to expand access but there is no special focus on rare cancers. Researchers are looking for objective

tumour response or stable disease at 16 weeks after treatment initiation. The study also collects information on progression-free survival, overall survival, duration of treatment on study and treatment-related adverse events.

- Netherlands - DRUP is a Dutch national study on behalf of the Center for Personalised Cancer Treatment (CPCT) to facilitate patient access to commercially available, targeted anti-cancer drugs to determine the potential efficacy in treatment of advanced cancers with a known molecular profile. Beginning in September 2016, the study is available in several Dutch hospitals for patients with an advanced tumour, multiple myeloma or B cell non-Hodgkin lymphoma for which standard treatment options are no longer available. The trial drugs have been approved and are commercially available within the Netherlands, but are normally used for treatment of other tumour types. Researchers plan to enrol up to 1000 patients in the study, which will run for at least the next three years and test from 12 to 20 drugs. DRUP is similar to the American TAPUR trial (above) and the groups are working to ensure that the two studies complement each other, rather than duplicate efforts.

- Canada – Princess Margaret Cancer Centre IMPACT (Integrated Molecular Profiling in Advanced Cancer Trial) and COMPACT (Community Oncology Molecular Profiling in Advanced Cancer Trial) are two clinical trials being run by the Princess Margaret Cancer Centre that base treatment on the molecular profile of each patient's tumour. COMPACT is the second stage taking the model to community partners beyond The Princess Margaret. Like IMPACT, COMPACT focuses on advanced solid tumours in breast, colorectal, ovarian and non-small cell lung cancer, and will involve 500 patients per year being treated at other centres.

  From March 2012 to July 2014, 1893 patients were enrolled, 1640 tested and 15% of those were subsequently treated on 277 therapeutic clinical trials. Only 84 patients (5%) were treated on 89 genotype-matched trials, even though the study has found that patients in genotype-matched trials were more likely to achieve response than patients in genotype-unmatched trials.

4. AUSTRALIAN RARE CANCER TRIALS AND RESEARCH

Local studies have also been developed to improve access for rare cancer patients to genomic testing and/or targeted therapy including:

- iPREDICT at the Peter MacCallum Cancer Centre (Peter Mac), the Melbourne Genomics Health Alliance (MGHA) Solid Cancers flagship program aimed at evaluating the benefits of genomics in clinical practice, including identifying which patients are likely to benefit from genomic sequencing, when the test should be conducted, and the impact of testing on healthcare and outcomes for different clinical indications.

- NOMINATOR at Peter Mac, Royal Adelaide Hospital, St John of God Subiaco Hospital and the Royal Brisbane and Women's Hospital aimed at assessing the feasibility of performing genomic testing of rare cancers to match the cancer to treatment.

- THINC-Rare a trial of a combination therapy with ipilimumab and nivolumab in rare cancers at the Austin Hospital, soon to open at Monash and Peter Mac.

Australian Rare Cancer Data Portal

Key to streamlining care and research for rare cancer patients is the collection, aggregation, analysis and transferability of data from patients and clinical trials. The Australian Rare Cancer Portal concept is being led by Associate Professor Clare Scott, from the Walter and Eliza Hall Institute and includes the Victorian Comprehensive Cancer Centre (VCCC), the Clinical Oncological Society of Australia (COSA) Rare Cancer group, NHMRC-CTC, Garvan Institute of Medical Research, the Universities of New South Wales and South Australia, and Rare Cancers Australia. This consists of lead clinicians in each state and territory uploading their pathology reports into a centralised rare cancer portal where advice from the most relevant expert specialist can help to confirm diagnosis, provide management guidelines and recommendations and assist with access to treatment, including advice about clinical trials.

The consolidation of consistent information about patient outcomes and other clinical information is also invaluable in terms of clinical trials design and potential TGA and PBS approvals. Data from the Australian Rare Cancer Portal can be integrated with *My Health Record* (MHR) or the new REDCap BioGrid rare cancer database, which also has the ability to integrate data with international collaborators. The input of good data into a national registry will ensure the best, most efficient selection of the right patients for a national Genomic Cancer Medicine Program.

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Aligning these Australian rare cancer programs with an Australian Genomic Cancer Medicine Program will ensure a unified approach nationally and ready access to expert knowledge and support.

5. PROPOSAL: THE AUSTRALIAN GENOMIC CANCER MEDICINE PROGRAM (AGCMP)

We propose a national expansion of Garvan's Genomic Cancer Medicine Program, to become the Australian Genomic Cancer Medicine Program (AGCMP) underpinned by Garvan's research model and coordinated by the NHMRC Clinical Trials Centre (NHMRC-CTC), to begin in 2018. The AGCMP will provide genomic testing and access to collaborative clinical trials for 6,000 Australians with rare and less common cancers across six Australian centres of excellence in cancer research and treatment.

- **New South Wales – The Kinghorn Cancer Centre/Garvan Institute of Medical Research**
  The Kinghorn Cancer Centre is a joint venture between the Garvan Institute of Medical Research and St Vincent's Hospital, Sydney. It was built in 2012 to realise the promise of innovative personalised medicine for people affected by cancer by bringing together researchers and clinicians onto a single site to enable research findings to be rapidly translated into clinical application for the diagnosis, treatment and prevention of cancer, with the prospect of improving cancer outcomes for all Australians.

- **Queensland – Princess Alexandra Hospital**
  Princess Alexandra Hospital is a tertiary health care centre, providing care in most major adult specialties. The Hospital is nationally recognised for our expertise in trauma management and organ transplants and is one of Australia's leading academic and research health centres. The Princess Alexandra Hospital is a major medical research precinct, hosting the Translational Research Institute (TRI), as well as a new Clinical Research Facility for the discoveries made at TRI to be trialled in a safe clinical environment.

- **South Australia – Central Adelaide Local Health Network (CALHN) incorporating the Royal Adelaide Hospital (RAH) and the Centre for Cancer Biology (CCB)**
  Royal Adelaide Hospital is Adelaide's (and South Australia's) largest hospital. The Centre for Cancer Biology contains the Australian Cancer Research Foundation (ACRF) Cancer Genomics Facility and the Cancer and Blood Clinical Trials Unit. RAH is a state-of-the-art facility embedded in a new biomedical precinct comprising University of Adelaide Health and Medical Sciences Building, the University of South Australia Health Innovation Building (including the CCB), and the South Australian Health and Medical Research Institute (SAHMRI). SAHMRI2, with the Southern Hemisphere's first proton therapy unit, is also planned. The ACRF Cancer Genomics Facility has NATA accreditation for genomic sequencing and the RAH Cancer Clinical Trials Unit carries the largest portfolio of trials in SA.

- **Tasmania – Royal Hobart Hospital**
  Royal Hobart Hospital (RHH) is Australia's second oldest hospital and first began serving the Hobart community in 1804. The Royal provides a comprehensive range of general and specialty medical and surgical services, including many statewide services such as cardiac surgery, neurosurgery, extensive burns treatment, hyperbaric medicine, neonatal

and paediatric intensive care, and high-risk obstetrics. Research areas include various forms of cancer, Cystic fibrosis, asthma, diabetes, Jack Jumper research, Vitamin D, oxygenation of pre-term infants and predicting recovery following brain trauma.

- **Victoria – The Victorian Comprehensive Cancer Centre (VCCC)**
  The VCCC was established in 2009 and consists of the Peter MacCallum Cancer Centre, Melbourne Health (including The Royal Melbourne Hospital), the University of Melbourne, Walter and Eliza Hall Institute of Medical Research, Royal Women's Hospital, Royal Children's Hospital, Western Health, St Vincent's Hospital Melbourne (including St Vincent's Institute), Austin Health (including the Olivia Newton-John Cancer Research Institute and Austin Lifesciences) and Murdoch Children's Research Institute.

- **Western Australia – Sir Charles Gairdner Hospital**
  Sir Charles Gairdner Hospital (SCGH) is one of Australia's leading teaching tertiary hospitals, providing a comprehensive range of clinical services including trauma, emergency and critical care, orthopaedics, general medicine, general surgery and cardiac care. It is home to WA's only comprehensive cancer centre – the largest cancer treatment centre in the State – and is the state's principal hospital for neurosurgery and liver transplants. SCGH has an international reputation for ground-breaking medical research, and is home to Nobel Laureate Professor Barry Marshall, who was awarded the Nobel Prize for Medicine in 2005 for his groundbreaking work on the bacterial causes of stomach ulcers. SCHG is also a partner in the Linear centre for early phase clinical trial research. The Linear centre was formed in 2010 as a collaborative venture between The Harry Perkins Institute and the Departments of Health and Commerce to form a focal point for Australian clinical and medical research, bringing world-first clinical trials to Western Australia and making innovative therapies available to the WA community

The Australian Genomic Cancer Medicine Program will provide a framework for standardised consent, including telehealth to consent people remotely, biobanking of tumour material and genomic profiling. This data and biobanked material would be available for further research. The trials program is co-ordinated by the NHMRC-CTC, with the genomic analysis led by Garvan. Data remains with the NHMRC-CTC in Sydney, accessible to all and easily integrated into a national rare cancer registry with data from other rare cancer projects.

The NHMRC-CTC is an internationally recognised clinical trials data centre, led by Professor John Simes, and has a proven track record in multi-centre investigator-initiated clinical trials. Collaboration with the NHMRC-CTC has been pivotal to the development of the GGCMP. The Australian Genomic Cancer Medicine Program will also offer screening to 1800 Australians through the Cancer Risk in the Young (RisC) study and follow-up monitoring to those seen to be at high risk of developing cancers.

We currently estimate the inkind and funding from Garvan and collaborators to be **more than $18M** over the five-year period.

The proposal in numbers

We estimate the program could treat the following number of Australians over the next five years. The timing of activation of sites nationally follows a six-monthly schedule. We have not included New Zealand in this proposal, but would expect the opportunity to co-invest with the New Zealand government in this program.

	2018	2019	2020	2021	2022	TOTAL
Garvan Institute's Kinghorn Cancer Centre	150 *	250	250	250	250	1150
Victorian Comprehensive Cancer Centre	75	150	150	150	150	675
Central Adelaide Local Health Network		50	75	75	75	275
Royal Hobart Hospital		25	50	50	50	175
Princess Alexandra Hospital			120	120	120	360
Sir Charles Gairdner Hospital				50	100	150
TOTAL	225	475	645	695	745	2785
RisC Cancer Screening**		300	400	500	600	1800
TOTAL WITH RisC SCREENING	225	775	1045	1195	1345	4585

* Note that funds from the NSW Office of Health and Medical Research to NSW will cover some fraction of accrual in NSW in the 2018 period, but expire in 2019.

** The Cancer Risk in the Young study will enrol 1800 patients (18-40 years of age) onto a whole-genome sequencing program. We estimate 200 individuals will be identified as at increased cancer risk, and these will be enrolled onto a monitoring program based on annual whole-body MRI.

How we intend to roll out the program

The Australian Genomic Cancer Medicine Program will utilise the governance structure of a Cooperative Research Centre (CRC). An eminent Australian will chair the board, whose members will include representatives of the participating centres, community organisations, the NHMRC Clinical Trials Centre and Garvan Institute of Medical Research.

The Australian Genomic Cancer Medicine Program will be an incorporated independent entity and any profits will be re-invested in its own infrastructure, and will build on existing collaborations with the pharmaceutical, biotech and imaging industrial entities, mentioned below.

We will work in partnership with relevant government agencies and develop a full and detailed risk and mitigation strategy in line with the approach required by the CRC model. This will cover policy implementation and reputational risks, as well as those related to dependence on key personnel.

Program evaluation

The success of the Program will be measured by:

- the number of patients with rare cancers who participate in the program
- the extent to which trials yield a novel indication for drug use. Treatments will be considered promising if around 20% of the patients in a trial respond.
- the extent to which the Program becomes self-sustaining through industry partnerships and commercialisation.

The national program will also work closely with the Health Economics team at University of Sydney, led by Professor Deborah Schofield, to measure the costs and benefits of the program. Professor Schofield has extensive experience in government including as Director of the Health Portfolio at The Treasury and Director Acute Care Finance, and then Director PBS Budget Policy in the Australian Government Department of Health.

Australian Genomic Cancer Medicine Program rollout costs

We estimate the AGCMP would cost a total of $88M over five years, this includes:

- $50 million from the Federal Government
- $18 million inkind and actual contributions from collaborating centres of excellence
- $15 million inkind and actual support from industry
- $5 million from philanthropy

Government support is asked for:

	2018	**2019**	**2020**	**2021**	**2022**	**TOTAL**
Screening (a)	1660000	2760000	3508000	3728000	3948000	15604000
NHMRC Clinical Trials Centre (b)	600000(c)	1300000	1339000	1379170	1420545	6038715
Garvan Central Office (d)	500000	515000	530450	546364	562754	2654568
Site Trials Costs (e)	360000	76000	1032000	1112000	1192000	3772000
Molecular Pathology (f)	370000	381100	392533	404309	416438	1964380
RisC Cancer Screening program (g)		1068800	1425000	1780000	2137600	6411400
Rare Cancers Data Portal (h)	1000000	1000000	1000000	1000000	1000000	5000000
Patient support and advocacy (i)	1000000	1000000	1000000	1000000	1000000	5000000
Program evaluation (j)	600000	600000	600000	600000	600000	3000000
TOTAL	6090000	8700900	10826983	11549843	12277337	49445063

(a) Consent, data collection, specimen processing, sequencing, validation, and report from a molecular tumour board. Includes 1 FTE data managers, 2 FTE bioinformatics and 0.1 FTE/site pathology. Molecular pathology can be site-specific or provided by central nodes (eg Garvan and VCCC). Molecular and clinical data on screened cohort stored at Garvan. An additional FTE is provided to each site for recruitment.

(b) Protocol development, contracts, data management and statistical support; liaison with pharmaceutical partners.
(c) Note that the funds from the NSW Office of Health and Medical Research to NSW will cover some fraction of accrual in NSW in the 2018 period, but expire in 2019.
(d) National senior program coordinator and secretarial support, travel, coordination and communications budget. It also includes telehealth functions to support remote enrolment for regional/rural participants.
(e) Assuming 20% of screened patients are enrolled onto a trial module; with a per capita cost of $7,000/patient. This includes site trials unit costs, and allowance for up to two biopsies and serial blood specimen collection. These funds would be paid to sites as an upfront payment for year 1, and then retrospectively based on per capita enrolment. Also funds for shipping of samples/biospecimens to Garvan Translational Oncology.
(f) Molecular pathology: staff roles include target validation following screening, immuno-oncology and other cell-based assays, including flow cytometry and molecular assays.
(g) RisC program includes initial costs of enrolling 1800 patients onto whole-genome sequencing program, plus costs of enrolling 200 individuals identified as at increased cancer risk, who will be offered monitoring based on annual whole-body MRI.
(h) Data collection, aggregation and transferability is essential to link programs nationally and internationally and will be facilitated by an innovative web-based data portal. This data will be contributed to global efforts under the leadership of Associate Professor Scott.
(i) Patient support including transport and accommodation for people on trials, the development of information materials for patients and carers.
j) Economic analysis of benefits of the program over current care. In addition, this includes a health economics evaluation and modelling for pharmaceutical industry partnerships.

We are asking the Government for an investment of $50 million over the forward estimates to enable us to nationally expand the Australian Genomic Cancer Medicine Program

Total Financial Implications	**Current year ($m)**	**Current year + 1 ($m)**	**Current year + 2 ($m)**	**Current year + 3 ($m)**	**Current year + 4 ($m)**	**Ongoing ($m)**
Expenses	$0	$12m	$12.8m	$12.6m	$12.6m	$0
Total Budget Result Impact	**$0**	**$12m**	**$12.8m**	**$12.6m**	**$12.6m**	**$0**
Does the proposal require ongoing funding?			Yes, in some capacity.			

The recently published landmark report by the Australian Clinical Trials Alliance and the Australian Commission on Health and Quality in Healthcare on the *Economic evaluation of investigator-initiated clinical trials conducted by networks* shows a return of $5.80 for every $1 invested in network trial research, aside from the clear benefits to patients.

Sustainability through commercialisation and industry partnerships
Industry support is at the heart of the AGCMP model, with pharmaceutical companies providing access to trial drugs, drug information and some trial support. The AGCMP model provides pharmaceutical companies with a shared-risk mechanism for compassionate access to drugs off-label, while generating data that may inform the repurposing of drugs and future drug development. Promising signals of benefit will translate into further clinical trials, shortening drug development times, and more rapidly bringing drugs to market. While pharmaceutical industry provides essential support, it is at arm's length and in no way interferes with trial design or results.

The following companies are currently in partnership with the GGCMP:

- Pharmaceutical industry
    - Astrazeneca
    - Roche
    - Pfizer
    - Eisai
    - Loxo Oncology
- Diagnostic imaging
    - Siemens
- Biotechnology
    - Illumina
    - Genome.One

We currently estimate the inkind and actual leverage from industry partnerships at **more than $15.1M** over the five-year proposal period.

Philanthropy is an important part of our funding
To date around $1 million has been raised from the philanthropic efforts of the Garvan Research Foundation to support Garvan's Genomic Cancer Medicine Program, including $650,000 from the Vodafone Foundation and $100,000 from Paul and Wendy Jeans, whose daughter Cathie died from gallbladder cancer.

It is estimated that the Garvan Research Foundation will raise approximately $5 million from philanthropy in this period that will also be applied to patient support and advocacy. This includes phone support, transport and accommodation for people to access the program.

Broad Stakeholder Support
Rare Cancers Australia, which has crowdfunded for drug access for individuals, have agreed to fundraise for 16-person trial modules on the AGCMP. Richard and Kate Vines from Rare Cancers are strong supporters of Garvan's Genomic Cancer Medicine Program as the program and its national direction reflect the primary recommendations in the recently released *Rare Solutions: A Time to Act* report. There is no way to move to an era of genomic medicine for rare cancers other than through a program like the AGCMP.

Within the Australian Genomic Health Alliance (AGHA), Richard Vines chairs the Consumer Committee, while Professor David Thomas is co-chair of the AGHA Cancer flagship, along with Professor Stephen Fox.

The following groups have provided in-principle support to the AGCMP proposal.

- Rare Cancers Australia
- Cancer Voices
- Brain Tumour Alliance Australia
- Pancare Foundation
- #PurpleOurWorld
- Tour de Cure
- Ovarian Cancer Australia
- CanToo
- Canteen
- Unicorn Foundation

6. NATIONAL ADVISORY COMMITTEE

Professor Mark Wainwright AM
Professor Wainwright served as seventh Vice-Chancellor and President of the University of New South Wales from June 2004 until June 2006 and Deputy Vice-Chancellor (Research) from 2001 to 2004. As an academic researcher at UNSW from 1974, in 1989 he was awarded a personal chair for his research in catalytic reaction engineering. In 1991, he was appointed Dean of the Faculty of Engineering, a position he held until the end of 2000. During 1998 and 1999 he concurrently held the position of Pro-Vice-Chancellor (Research). In 2004, he was awarded an AM for his service to chemical engineering as a researcher and academic, and to tertiary education. In 2006, he was appointed by the Department of Foreign Affairs and Trade of the Australian Government to the position of Chair of the Australian-China Council for a period of five years. In the same year, he was appointed Chair of the New South Wales General Sir John Monash Awards Panel. In 2007, he was appointed Chair of the National Computational Infrastructure Steering Committee by the Department of Innovation, Industry, Science and Research. In 2008, he was appointed chair of INTERSECT Ltd. For the past decade, Mark has been the Chair of the Smart Services Co-operative Research Centre Board, the Sydney School of Entrepreneurship Board, the TAFE NSW Higher Education Governing Council and the Cancer Institute NSW Grants Program.

Richard Vines Rare Cancers Australia
Founder and CEO, Rare Cancers Australia, Richard attended the University of Melbourne where he studied maths and statistics. He then trained as an Actuary but was seduced by the fledgling IT industry before qualifying. After several years working in software development, Richard formed his own software company which he then sold in 1990 before embarking on a second software venture in Europe. In 1996, Richard returned to Australia where he was retained by an American company to establish a sales channel in Australia. In 2001 Richard left the IT industry and worked in a number of not-for-profits associated with retail, politics and health. In 2012, Richard and his wife Kate established Rare Cancers Australia, a patient advocacy group whose mission is to improve the lives and outcomes for rare cancer patients.

Professor David Thomas The Kinghorn Cancer Centre, Sydney
Head of Cancer Research at Garvan and Director of the Kinghorn Cancer Centre, a collaboration between Garvan and St Vincent's Hospital, Sydney. NHMRC Principal Research Fellow, David is an oncologist with a particular focus on the impact of genomics on cancer medicine and public health. David is the originator of Garvan's Genomic Cancer Medicine Program that brings together researchers and clinicians to translate research findings into the clinic. His work has had significant translational impact leading to a new therapeutic option for patients with advanced bone disease. He established a national infrastructure for clinical research into sarcomas, the Australasian Sarcoma Study Group. As Director of the statewide adolescent and young adult cancer service, onTrac@PeterMac, he played a significant role in the development of adolescent and young adult oncology.

Paul Jeans Chancellor University of Newcastle, New South Wales
Paul Jeans has been Chancellor of the University of Newcastle since 2013. Until his retirement in 2000, in a career spanning 42 years, he held senior roles in BHP where he was Executive General Manager/CEO of BHP's Ferrous Minerals Business and earlier three of its Steel Businesses, which included responsibility for both Newcastle and Port Kembla Steelworks. His earlier career focused on engineering and he rose to become General Manager of BHP Engineering. Paul has led manufacturing, mining, logistics and technical services businesses through periods of growth, significant change and efficiency improvement, major capital expansion and international operation. He has been chair of the Newcastle Port Corporation, Orinoco Iron CA, Associated Airlines, World Marine and General Insurances and six BHP subsidiary companies. Paul has also been a Director of Foster's Brewing Group, Energy Australia, Ausgrid and five BHP subsidiary companies.

Professor John Simes NHMRC-CTC, Sydney
Professor Simes, Director, NHMRC Clinical Trials Centre and Sydney Catalyst Translational Research Centre, is a leading international researcher in clinical trials, particularly in cancer, cardiovascular disease, diabetes and neonatal medicine. As Senior Principal Research Fellow and Director of the NHMRC Clinical Trials Centre, University of Sydney, he leads a team of 200 who collaborate nationally and internationally to improve health practice and health outcomes through better use of clinical trials research. His work has had a significant impact on current knowledge and clinical practice. He practices as a medical oncologist in neuro-oncology.

Associate Professor Clare Scott Victorian Comprehensive Cancer Centre.
Associate Professor Clare Scott, Victorian Cancer Agency Clinical Fellow, Walter and Eliza Hall Institute of Medical Research, Peter MacCallum Cancer Centre, VCCC
Associate Professor Scott, Sir Edward Dunlop Research Fellow, Walter and Eliza Hall Institute of Medical Research (WEHI), is a medical oncologist at the Royal Melbourne Hospital and Peter Mac and a Laboratory Head at WEHI. In the lab, she studies ovarian cancers and other rare cancers in novel cancer models, particularly from the perspective of 'matching' the wiring of a patient's cancer to treatment.

Andrew Giles Garvan Research Foundation
CEO of the Garvan Research Foundation since 2011, Andrew Giles was previously CEO of the Prostate Cancer Foundation of Australia (PCFA)(2004 to 2011). In that time he oversaw its transformation from a small NSW-based organisation, mainly driven by passionate cancer survivors, into the peak body for prostate cancer research, awareness and support in Australia. Due to the development of Movember from a small, targeted campaign in 2004 just for PCFA, into the world-wide event it was by 2010, Andrew was able to help transform the way prostate cancer research was funded in Australia and internationally. Prior to PCFA, Andrew worked with some leading not-for-profits including UNSW Sydney, The Shepherd Centre for Deaf Children, The Scots College, Bellevue Hill, The University of Sydney and Sydney Children's Hospital, Randwick. Andrew Giles is a director of Research Australia and a director of The Fundraisings Institute of Australia.

7. PROJECT LEADERSHIP TEAM

Professor David Thomas The Kinghorn Cancer Centre, Sydney. Head of Cancer Research at Garvan and Director of the Kinghorn Cancer Centre, a collaboration between Garvan and St Vincent's Hospital, Sydney. NHMRC Principal Research Fellow, Professor David Thomas is an oncologist with a particular focus on the impact of genomics on cancer medicine and public health. His work has had significant translational impact leading to a new therapeutic option for patients with advanced bone disease. He established a national infrastructure for clinical research into sarcomas, the Australasian Sarcoma Study Group. As Director of the statewide adolescent and young adult cancer service, onTrac@PeterMac, he played a significant role in the development of adolescent and young adult oncology.

Associate Professor Clare Scott VCCC, Victoria, Victorian Cancer Agency Clinical Fellow, Walter and Eliza Hall Institute of Medical Research, Peter MacCallum Cancer Centre. Associate Professor Clare Scott is a medical oncologist at the Royal Melbourne Hospital and Peter Mac and a Laboratory Head at WEHI. In the lab, she studies ovarian cancers and other rare cancers in novel cancer models, particularly from the perspective of 'matching' the wiring of a patient's cancer to treatment.

Professor Stephen Fox VCCC, Victoria, Head Molecular Pathology Laboratory. Professor Fox is also Director of Pathology at Peter Mac and Professorial Fellow in the Department of Pathology at the University of Melbourne. From doctoral work in pathology at Oxford, UK, he moved to Christchurch, New Zealand in 1996 as a Specialist Anatomical Pathologist and Senior Lecturer at the University of Otago and established the de novo and angiogenesis research laboratory. He returned to Oxford in 2001 as Clinical Reader in Pathology as part of the Cancer Research UK Chemopathology Group, while still coordinating the Christchurch laboratory. In 2006 he moved to Melbourne where he holds numerous positions of responsibility both within Peter Mac, state-based organisations and international organisations. He established a laboratory at Peter Mac focusing on prognostic and predictive markers, together with the molecular pathology of cancer. As a clinical pathologist, he focused on translating many of the new genomic tests including KRAS, BRAF, ALK and HER2 in colorectal, breast, lung and melanoma. He is recognised as an expert in breast and molecular pathology.

Professor Michael Brown Central Adelaide Local Health Network**,** South Australia. As Head, Translational Oncology Laboratory, Professor Michael Brown operates the Royal Adelaide Hospital Cancer Clinical Trials Unit and is a senior consultant medical oncologist in the Royal Adelaide Hospital Cancer Centre. Professor Brown subspecialises in the care of patients with advanced melanoma or lung cancer. His clinical research is focused mainly on facilitating rapid access to new targeted therapies and on early phase clinical trials for testing new immunotherapies for the treatment of melanoma and lung cancer. His laboratory research is focused mainly on understanding better how to direct T cells, the 'generals' of the immune system, toward cancer targets.

Professor Hamish Scott Centre for Cancer Biology, South Australia
Professor Hamish Scott is Head of the Molecular Pathology Research Laboratory at the Centre for Cancer Biology, Head of Molecular Pathology at SA Pathology and Affiliate Professor in both the Schools of Medicine and Molecular and Biomedical Science at the University of Adelaide and an Adjunct Professor at the University of South Australia. Professor Hamish Scott did his PhD and first postdoc at the Women's and Children's Hospital and the University of Adelaide, where he led the discovery of genes for three rare human diseases. Eleven years later this resulted in either FDA approved therapy (2003) or clinical trials of novel therapies for these diseases. In 1995, Professor Scott moved to the University of Geneva Medical School in Switzerland where his focus was, and remains, the application of genetic and genomic technologies to understand diseases processes to improve diagnoses and treatment. He led international collaborations in identification of human genes causing Down syndrome and rare forms of genetic deafness and autoimmunity (eg arthritis and multiple sclerosis). This continues to have profound effects on our understanding of basic biology of Down syndrome, hearing and the immune system and led to new therapeutic strategies in these and related diseases. This was also the start of his interest in cancer and leukemia as children with Down syndrome have a low incidence of solid tumours and a high incidence of leukaemia.

Professor Ken O'Byrne Princess Alexandra Hospital, Queensland
Professor in Medical Oncology in the School of Biomedical Sciences at the Queensland University of Technology (QUT) and consultant oncologist, in 2013 Professor O'Byrne moved to the Princess Alexandra Hospital (PAH) and the Queensland University of Technology (QUT) section of the Translational Research Institute (TRI) from St James's Hospital and Trinity College, Dublin. He has conducted translational 'bench-to-bedside-and back-again' research over the past 25 years with a focus on solid epithelial tumours, in particular in thoracic malignancies. Professor O'Byrne is an expert in translational and clinical research, specialising in cancer incorporating basic science, biomarkers, therapeutic target evaluation and phase 1, 2 and 3 clinical trials collaborating with both academic and industrial partners. His major contribution has been the development of multidisciplinary research teams and organisations and he plays a lead role in the clinical trials unit on the PAH campus.

Professor Sunil Lakhani Pathology Queensland, Queensland
Head, Discipline of Pathology at the University of Queensland (UQ) Centre for Clinical Research, Professor Sunil Lakhani is also Head of Molecular and Cellular Pathology at the UQ School of Medicine; State Director, Anatomical Pathology, Pathology Queensland, and Head of the Breast Group at the University of Queensland Centre for Clinical Research at the Royal Brisbane and Women's Hospital. Prior to his move to Australia in 2004, he was Professor of Breast Pathology at The Institute of Cancer Research and The Royal Marsden Hospital, London, UK. His research interests include lobular carcinoma and its variants, normal and stem cells, tumours with a basal phenotype, mechanisms of brain and distant metastases and familial breast cancer.

Professor Michael Millward Sir Charles Gairdner Hospital, Western Australia Professor Millward is the foundation Chair of Clinical Cancer Research, University of Western Australia and Head of Medical Oncology at Sir Charles Gairdner Hospital, Perth, Australia. He has a strong track record in delivering clinical trial outcomes, particularly with novel therapeutics and phase 1 and 2 studies. He is an international expert on thoracic malignancies and melanoma. Since November 2008 he has been the President of the Australasian Lung Cancer Trials Group.

Dr Rosemary Young Royal Hobart Hospital, Tasmania
Dr Rosemary Young is a senior staff specialist in the Department of Clinical Haematology and Medical Oncology at Royal Hobart Hospital, and the Hobart School of Medicine, University of Tasmania. Dr Young is also a collaborator in research on Leukaemia with the Lowenthal Group at the Menzies Institute for Medical Research.

Functional Committees

- Clinical Trials Working Group (led by Simes/Thomas)
- Molecular Pathology Working Group (led by Fox/Scott/Lakhani)
- Business Development Group (led by Thomas/Vines)
- Advocacy and patient support (led by Vines)
- Health Economic and Program Evaluation (led by Schofield)
- Early detection and risk management (led by Thomas)
- Data curation and integration (led by Scott)
- International program linkage (led by Scott)

8. ABOUT THE GARVAN INSTITUTE OF MEDICAL RESEARCH & GARVAN RESEARCH FOUNDATION

The Garvan Institute of Medical Research has pioneered insights into some of the most widespread diseases affecting our community today. It was established by the Sisters of Charity with the mission to make significant contributions to medical research that will change the directions of science and medicine and have major impacts on human health.

Research at Garvan has focused upon understanding the role of genes and molecular and cellular processes in health and disease as the basis for developing future preventions, treatments and cures. Since 1963, significant breakthroughs have been achieved by Garvan scientists in the understanding and treatment of diseases such as cancer, diabetes and obesity, neurological diseases such as Alzheimer's, Parkinson's, hearing loss, mental illnesses and eating disorders, osteoporosis, Immunological diseases such as asthma, rheumatoid arthritis, multiple sclerosis and Sjogren's syndrome. Garvan's ultimate goal is prevention, treatment or cure of these major diseases.

The development of the Australian Genomic Cancer Medicine Program has been enabled by the Garvan Research Foundation thanks to the generous support of its philanthropic benefactors. The Garvan Research Foundation supports the work of the Garvan, through the realisation of its vision to create an innovative and collaborative environment in which world-class researchers, utilising the most advanced technology, are able to work in partnership with clinicians, patients and the community to develop research programs that combine fundamental science with strong clinical interactions that have major impacts on human health.

CONTACT:

Andrew Giles | Chief Executive Officer
Garvan Research Foundation
[redacted]

9. APPENDIX

A. LETTER FROM PAUL AND WENDY JEANS

23 July 2017

Mr Andrew Giles
Chief Executive Officer
[redacted]

Dear Andrew,

My wife and I lost our eldest child, our daughter Cathie to a rare and terrible cancer in August 2015.

Cathie's first indication of her illness only became evident some eight months earlier, when, despite the fact that she was suffering from metastasised cancer, she had negligible symptoms but sought a diagnosis. Cathie was a vibrant, busy, fit mother of three teenage sons. At 49, she and her husband Joe had everything to look forward to.

Cathie's initial diagnosis was inconclusive and she was initially given chemotherapy for colon cancer. This treatment had no positive impact and, only after her liver started to fail necessitating the insertion of bile duct stents, was her condition diagnosed as gall bladder / bile duct cancer [cholangio carcinoma].

She was then subjected to a campaign of the "standard" chemotherapy drugs prescribed for bile duct cancer. These also had no positive impact.

At the same time, I received advice from very senior medical colleagues that we should have Cathie's genome mapped and analysed. We had her tissue taken to the USA and the suggested mapping and analysis carried out. This work not only suggested that the "standard" bile duct cancer chemotherapy drugs were unlikely to work, but that two other drugs [normally used for other cancers] might.

Despite the fact that she was by then in terrible condition, wearing five external bags [colostomy, bile drains x 2, fistulas x 2], she commenced a third chemotherapy campaign using the drugs recommended by the genome specialists in the USA. Two rounds of this chemotherapy saw Cathie's

cancer markers lowered by 80% but by then it was too late to save Cathie and we lost our precious daughter.

There are a number of important learnings we can take from Cathie's tragedy

1. Rare cancers are a terrible, and growing significant cause of suffering and cost to society
2. We must find ways of diagnosing rare cancers accurately and earlier
3. We must explore the potential for identifying high-risk individuals through genetic screening
4. In addition to searching for new therapies, we must think more laterally about the potential use of existing therapies in novel circumstances [treating cancers on their genetic makeup rather than their body location]

As a consequence of our experience, we became aware of the Garvan Genomic Cancer Medicine Program and the wonderful work being undertaken by Professor David Thomas and his team.

We are proud to remember Cathie through our support for Professor Thomas' MoST Program and its Immunotherapy Sub Study as well as the important work being done into Cancer Risk.

We are prepared to unequivocally advocate support of the unique and critically important work being done at the Garvan Institute and await your call as to how best we can rally the rare cancer community to support your approach to the Federal and State Governments, as well as the broader community.

Yours Sincerely

Paul and Wendy Jeans

[redacted]

B. PERSONAL STORY - DARIN MALLAWARACHCHI

In 2012, Darin Mallawarachchi, age 59, slipped on the staircase and hit his tailbone. The ensuing scan revealed a 3cm chordoma tumour, a rare type of bone cancer, on the sacrum, the triangular bone just above the bottom tip of the spine. Darin had been in good health, going to the gym and very active.

'Although I was lucky that the tumour was detected very early, it was still such a shock,' said Darin. 'I have three grown-up daughters and three grandchildren. My whole family is very worried and stressed.'

Following successful surgery to remove the tumour in September 2012, it took Darin six long months to recover from postoperative complications. On MRI scan in December 2013, a new 2cm tumour was detected, although it was treated with stereotactic radiation it continued to grow.

As a result, in March 2015, Darin underwent radio frequency ablation treatment, instead of surgery, to remove the tumour as far as possible, but follow-up scans in October 2016 showed the residual tumour had increased in size, and in November 2016, he was treated with radio and microwave ablation therapy. However, he was left with pain at the base of his spine and right leg, which is also now weaker, along with bladder and bowel problems.

'In early 2017, I was enrolled into the MoST immunotherapy clinical trial at Garvan, following introduction by Rare Cancers Australia. Hopefully the immunotherapy treatment can destroy the residual cancer cells at the base of the nerve.

'It is true that life is different now and I am not quite the same person as before, however, life continues to hold much happiness, and hope. I am able to keep positive. I have grown stronger and more determined to take each day as it comes and beat this cancer.

'Garvan is providing pioneering research and clinical trials treatment to cancer patients in Australia, but the availability of the clinical trials isn't widely known. It's vital that more patients have access to rare cancer drug trial programs.'

By August 2017, after six months on the trial, Darin's cancer is responding to therapy and there is evidence that the tumour is shrinking.

C. PERSONAL STORY - ZARA D'COTTA

Zara D'Cotta was diagnosed with a localised breast cancer nine days before her 30th birthday – and then two years later, she was diagnosed with a melanoma on the morning of her breast cancer anniversary. 'I spent my second birthday in three years recovering from surgery, waiting to find out if my cancer had spread,' said Zara.

Zara had had a lumpectomy for her breast cancer, followed by six weeks of exhausting daily radiotherapy. Zara then started the anti-hormone medication, tamoxifen.

'My side effects were so severe I had to stop working. Just putting one foot in front of the other felt like a huge task. At its worst I felt hazy and couldn't do basic things like drive my car. I'd burst into tears for no real reason. After 15 months, I stopped taking tamoxifen because of the degree to which it was affecting my quality of life.

'Thankfully, my melanoma hadn't spread to any nerve or blood cells. I had surgery to remove all the surrounding tissue and didn't require any further treatment.

'It was an extremely difficult time for us all. It was when I received the call from my surgeon to say that my breast cancer hadn't spread and my mum burst into tears with relief that I realised how worried she had been.

'My mum was diagnosed with breast cancer one month after my breast cancer diagnosis. It was a different type of cancer to mine, and I tested negative for the BRCA gene mutation, so we are not sure whether they are genetically linked.

'I am really excited to be part of the Genetic Cancer Risk in the Young study. When I was first diagnosed with cancer four years ago, I was prepared to accept that I may never know why I got cancer. To think that I may soon know the reasons is absolutely mindboggling.'