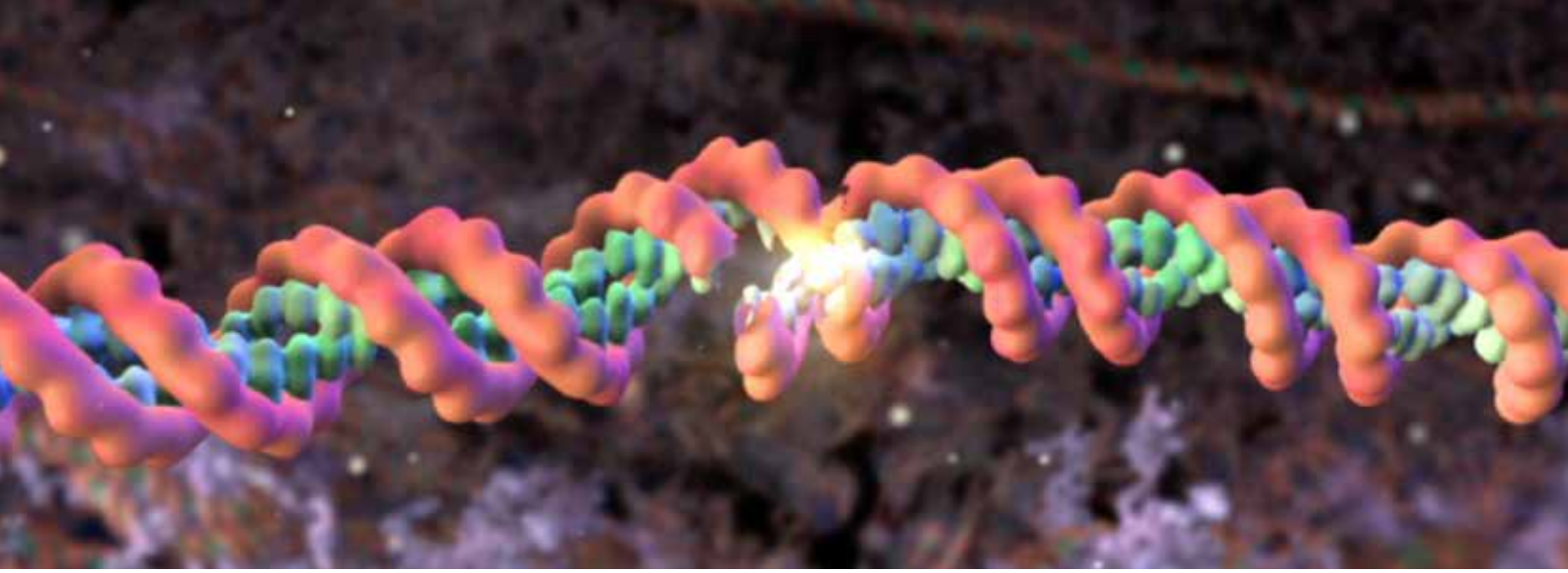

UPDATES IN RARE CANCERS

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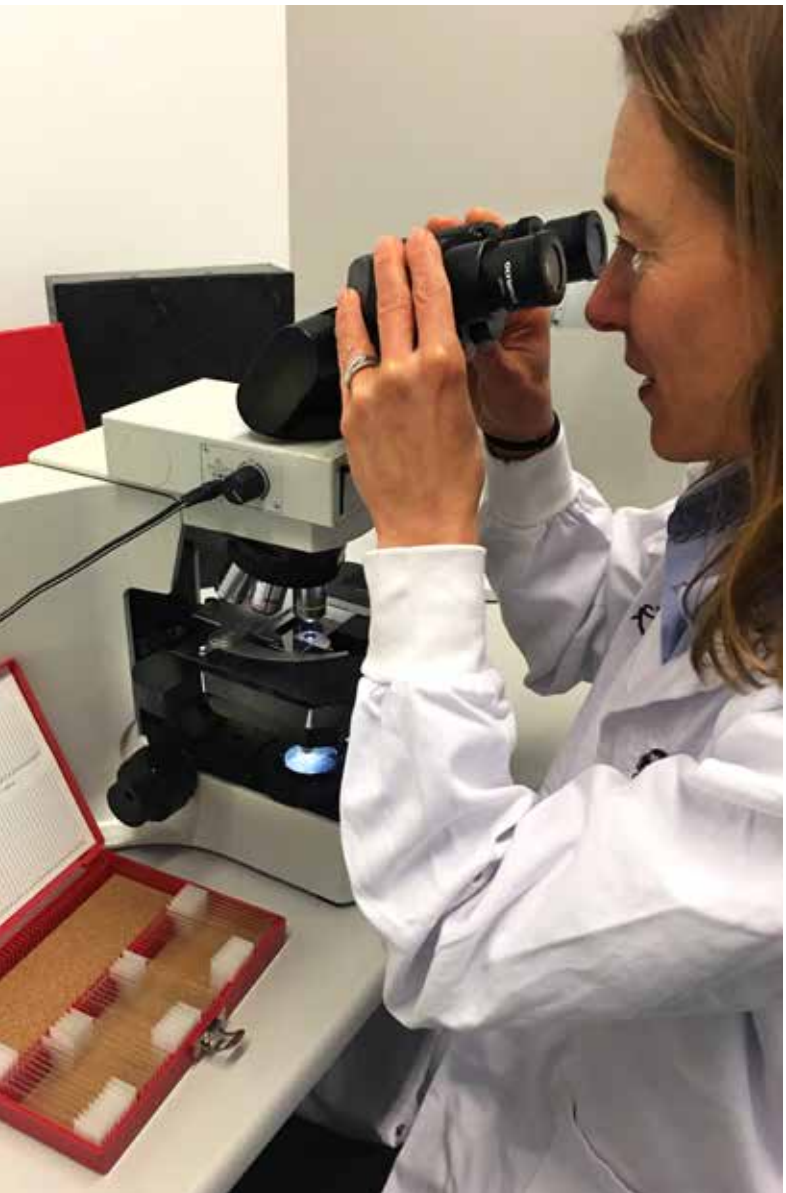


WHAT ARE RARE CANCERS?

The main four cancers – breast, prostate, bowel and lung – only account for 54% of cancers diagnosed. Most of the remaining cancers fall under the heading of 'rare and less common cancers'. Despite accounting for 20-25% of all cancer patients and one in three cancer deaths in Australia, rare cancers collectively represent a major health burden.

'Rare cancers' are as those with an incidence of less than 6 per 100,000 Australians per annum. These include:

- Brain cancers and cancers of the central nervous system
- Thyroid cancer, adrenal cancer, neuroendocrine cancers (eg pituitary)
- Mesothelioma
- Urinary cancers – kidney, renal pelvis, ureter, bladder, other urinary organs
- Oesophageal, liver, stomach, gallbladder, small intestine, pancreatic, anal cancers
- Blood cancers – Hodgkins lymphoma, non-Hodgkins lymphoma, multiple myeloma and plasma cell cancers, acute and chronic leukaemias
- Male and female reproductive cancers
- Kaposi's sarcoma
- Cancers of connective tissue (eg bone, soft tissue sarcoma)
- Unknown primaries

Advances in medical research and genomic technology have improved our understanding of the individuality of cancer. Where once a cancer was defined by its anatomical location, such as breast or skin, or cell type, such as 'ductal' and 'lobular' breast cancer or melanoma, cancers may now be categorised according to their genetic changes or 'molecular pathology'. We now know that common cancers are actually composed of multiple molecular subtypes.

This molecular-level understanding of cancers now enables clinical researchers and pharmaceutical companies to target specific medicines to these genetic abnormalities to better treat individual patients.

Although molecular and immunological cancer research has made great strides in recent years, research into rare cancers is underfunded compared with breast, prostate and bowl cancer research. The increasing cost of drug development and the challenges of conducting clinical trials with small patient groups has meant that rare cancers are neglected and under-represented in clinical trials.

This neglect has fatal consequences as a key factor in the high mortality rates is the lack of approved (and reimbursable) treatments. Treatments are approved on the basis of evidence of clinical trials, but it is not feasible to conduct standard clinical trials for rare cancers – there aren't enough cases to build the necessary clinical evidence. Innovations in clinical trial design (and their acceptance by government) are essential to accelerate the development of new treatments for rare cancer patients.

WHO IS AT RISK?

Cancer is usually considered a disease of older people, with mortality rates increasing with age for most cancers. One of the key characteristics of rare cancers is that these cancers place a great burden on children and young families. In every age group (Baby Boomers, Gen X, Gen Y, and even children) rare cancers are the most common cause of disease-related death in Australia.

DIAGNOSIS & TREATMENTS

While significant advances in screening, diagnosis and treatment have been made for common cancers, this is not the case for rare cancers, which present major diagnostic and therapeutic, challenges.

Our clinical ability to recognise new patients when they present with a rare cancer remains limited. As a result, rare cancer patients are commonly misdiagnosed and may face long delays before receiving the correct diagnosis and the most appropriate treatment from among the limited treatment options. Unfortunately, this leads to a very poor prognosis.

With recent advances in genomics (the study of an individual's genes) we can now identify the genetic changes responsible for cancer growth and molecular information from tumours can be used to match individual patients with targeted treatments.

The advent of cancer immunotherapies, which harness the body's own cancer-killing mechanisms, has further increased the range of therapeutic options available.

Mortality rates for common cancers have dropped over the last two decades, but rare cancer incidence and mortality rates are actually rising. Due to difficulties in diagnoses, less effective standard treatments and reduced access to new therapies, a patient with a rare cancer is almost twice as likely to die as a patient with a common cancer.

GARVAN – A WORLD CLASS CENTRE FOR RARE CANCER RESEARCH

Garvan's rare cancer research is diverse, focusing on translating basic scientific discoveries into the clinic. These include defining the genetic characteristics of rare cancers, developing biomarkers of prognosis and therapeutic responsiveness and understanding the molecular mechanisms of resistance in order to develop novel therapeutic strategies.

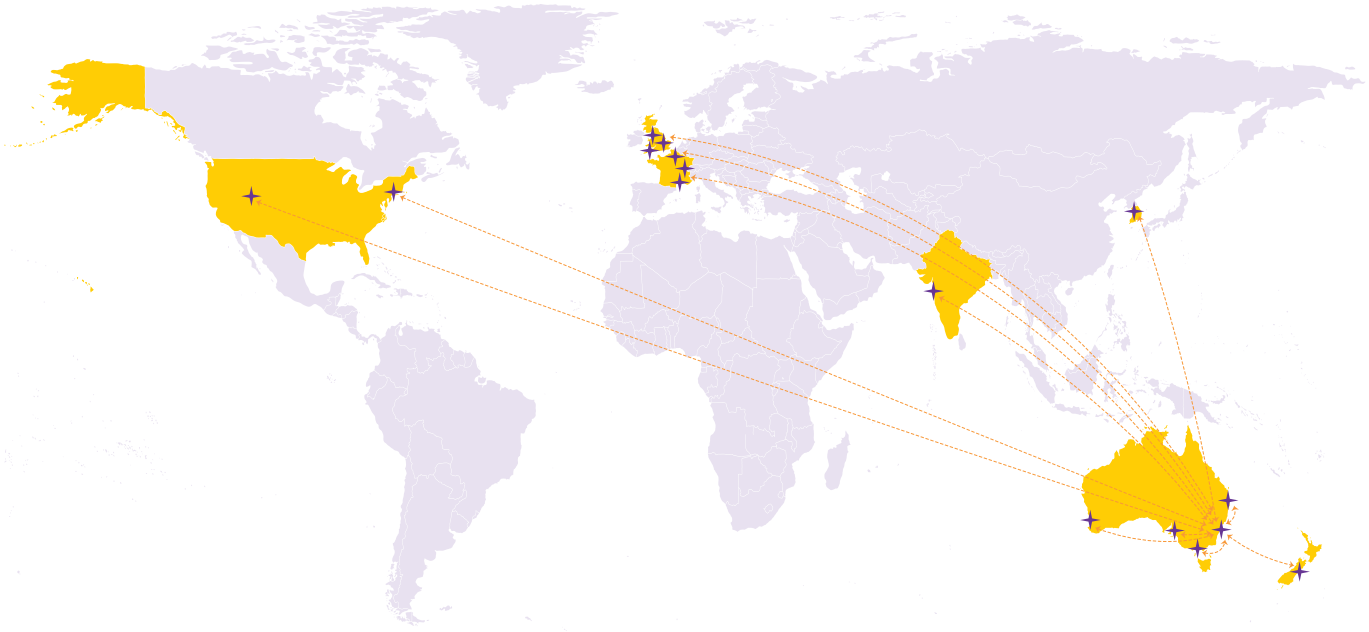
WORLD FIRST WHOLE GENOME SEQUENCING OF RARE CANCERS

The Garvan Institute recently became one of the first in the world to acquire technology that can sequence a whole human genome at high throughput and low cost. This gives the rare cancer research teams the unparalleled ability to undertake whole genome sequencing on cancerous tumours, vastly increasing our understanding and leading to safer, more effective personalised therapies.

Professor David Thomas and his team: L–R: Professor David Thomas, Dr Dominique Hess and Dr Ann McCormack.

National and international collaborators

- Asan Medical Center, Seoul, Korea
- AstraZeneca, Cambridge, UK
- Centre Georges François Leclerc, Dijon, France
- Centre Régional de Lutte Contre le Cancer Léon Bérard, Lyon, France
- Centre Régional de Lutte Contre le Cancer Oscar Lambret, Lille, France
- Chris O'Brien Lifehouse, Sydney, Australia
- Christchurch Hospital, Christchurch, New Zealand
- Derriford Hospital, Plymouth, UK
- Garvan Institute of Medical Research, Sydney, Australia
- Hollywood Private Hospital, Perth, Australia
- Hospitaux de Marseille, Marseille, France
- Huntsman Cancer Institute, University of Utah, Utah, USA
- Institut Gustave Roussy, Villejuif, France
- Mt Sinai Hospital, New York, USA
- NHMRC Clinical Trials Centre, Sydney, Australia
- Peter MacCallum Cancer Centre, Melbourne, Australia
- Pfizer, New York, USA
- Prince of Wales Hospital, Sydney, Australia
- Princess Alexandra Hospital, Brisbane, Australia
- Royal Adelaide Hospital, Adelaide, Australia
- Royal Liverpool and Broadgreen University Hospital, Liverpool, UK
- Royal Marsden Hospital, London, UK
- Royal Prince Alfred Hospital, Melbourne, Australia
- Sydney Children's Hospital, Sydney, Australia
- Tata Memorial Hospital, Mumbai, India
- The Kinghorn Cancer Centre, Sydney, Australia
- University College London Hospital, London, UK
- Victorian Comprehensive Cancer Centre, Melbourne, Australia
- Walter and Eliza Hall Institute, Melbourne, Australia



IMPROVING THE ODDS FOR RARE CANCERS

Recent advances in medical research have led to a shift in understanding the molecular and immunological biology of cancers, leading in turn to the creation of new therapies. Many treatments developed in common cancers have been shown to work in rare cancers. We no longer have to think about cancer treatment anatomically and can ultimately treat patients according to their genetic and molecular features. For the first time we have a real opportunity to improve the outcomes for rare cancer patients across Australia. Where targeted approaches aim to inhibit molecular pathways that are crucial for tumour growth and maintenance, immunotherapies endeavour to stimulate a host immune response that delivers long-lived tumour destruction. These medicines, which work on differing cancer mechanisms, offering new opportunities for patients.

There is excellent evidence to show that participation in clinical trials is associated with better outcomes for people with rare cancers. Governments also use the information from trials in their decisions to fund new drugs. But until now it has not been feasible to run clinical trials for the small numbers of people with one rare cancer or another and so many patients are being left to self-fund expensive medical treatments simply because statistically they have been deemed insignificant.

At Garvan, Professor David Thomas, Director and Division Head of Genomic Cancer Medicine and his colleagues are devising new types of clinical trials and other innovative studies to try to improve the treatment options for people with rare cancer. The research team includes Dr Dominique Hess (MoST Program Coordinator), Dr Mandy Ballinger (ISKS Study Coordinator), Dr Maya Kansara, Dr Arcadi Cipponi, Dr Mark Pinese, Dr Mark Cowley, Dr Anne McCormack, Dr Min Ru Qiu, Gary Pan and Associate Professor Anthony Joshua (Head of Medical Oncology – St Vincent's Hospital and Director of Oncology, Garvan).

Molecular Screening and Therapeutics (MoST) Program

Professor David Thomas and his team have developed the innovative MoST program of clinical trials designed specifically to evaluate the effectiveness of new treatments and help patients with advanced rare cancers. The MoST program builds on partnerships across multiple academic research organisations and cancer centres, the public health sector, and the pharmaceutical industry. Major partners include the Garvan Institute of Medical Research, the NHMRC Clinical Trials Centre (University of Sydney), the Peter MacCallum Cancer Centre, the Kinghorn Cancer Centre, Chris O'Brien Lifehouse, AstraZeneca and Pfizer.

Professor David Thomas
Director and Division Head Genomic Cancer Medicine

'There are new medicines with applications across a range of cancers, many of which are sufficiently rare that there is neither the patient population nor the commercial opportunity for extensive traditional clinical trials to be conducted or funded,' explained Professor Thomas. 'This has led to the emergence of 'basket trials' where, rather than focusing on a tumour's anatomical location, such as the ovaries, patients say with ovarian cancer, pancreatic cancer, sarcoma and other cancers, but who have a shared rare mutation, are treated with a drug that may target the mutated pathway.'

In the MoST program, tumour samples from patients undergo genomic/molecular screening. Patients are then assigned to clinical substudies of targeted therapies based on specific genetic alterations. The MoST program looks to understand how targeted therapies work and find new biomarkers that can predict which patients will benefit from these treatments.

'The type of trial developed in the MoST program represents an important step forward in how we conduct trials for small patient populations. For example, we are treating a small group of 16 patients with genetic changes in the CDK4 and CDK6 pathway with a selective inhibitor of this pathway. These genetic changes are thought to make the tumours sensitive to the drug and treatment should block tumour growth.

'Clinical trials into effectiveness of novel, targeted therapies, in small patient populations, require collaborative trial development and research which crosses traditional boundaries of trials currently being undertaken in Australia, and the evidentiary requirements for regulators must also be made to be more flexible for rare and super rare cancers. Equally important is that with research we build up centres of knowledge and clinical excellence that are critical to providing the best possible standard of care for patients with specific rare cancers.

Precision Cancer Immunotherapy

The MoST program is also conducting clinical studies to test novel immunotherapy drugs in patients with rare cancers. The first MoST immunotherapy substudy tests a combination of so-called 'immune checkpoint inhibitor' drugs that take the brakes off the anti-tumour immune response, enabling immune cells to attack cancer cells. This three-year clinical trial is open to patients who cannot be matched with a targeted treatment. A second immunotherapy study will combine a targeted treatment with a checkpoint inhibitor and will recruit patients with specific genetic abnormalities in their tumour.

Although immunotherapies are proving to be effective in many cancer types, they do not work in all patients. Professor Thomas and his team are looking to find biomarkers that can predict which patients will benefit from specific treatments targeting the immune system and to better understand how immunotherapies work to fight cancer. With this knowledge, the team aims to develop a more precise approach that tailors treatment with immunotherapy to individual patients based on the characteristics of their immune system and its interactions with tumour cells.

Several biomarkers have been suggested to predict response to treatment with immunotherapies and will be studied in companion biological studies. These include the presence and change of certain immune cells in the tumour and blood, patterns of immune-related gene expression, proteins released by immune cells, inhibitory proteins displayed on tumour cells, genetic changes in tumour cells and inherited genetic changes in immune genes.

'These findings will then be correlated to patient outcomes to discover predictive biomarkers that better identify patients who may benefit from treatment with immune checkpoint inhibitors or who may develop side effects.

'The immunotherapy trials will allow us to understand how these immune biomarkers influence the anti-tumour response and help develop a precision immunotherapy approach where treatment can be personalised.

'Treatment strategies that select therapies based on immunological and molecular characteristics of tumours, rather than the organ and tissue of origin, create new opportunities for the treatment of rare cancers.'

Sarah-Grace Williams

In her mid-30s, internationally recognised orchestra conductor Sarah-Grace Williams was working hard in her role as Artistic Director and Chief Conductor at The Metropolitan Orchestra, conducting numerous performances and leading a very active life. In the peak of health, Sarah-Grace had given birth to her daughter in January 2014.

Then in the second half of 2014, Sarah-Grace was diagnosed with diffuse pigmented villonodular synovitis (PVNS) – tumours of the joint lining (synovium) of her knee.

'In January 2015 I underwent surgery to remove the tumours behind my leg,' said Sarah-Grace. 'The pain post-op was excruciating, and, worse, the PVNS returned very quickly, at the front of the knee.'

Over the following year and a half while waiting to get into a clinical trial, Sarah-Grace's condition deteriorated. 'My pain levels were through the roof and I was on constant pain relief. I was having my knee drained of around a litre of fluid every 6 weeks or so, but it remained swollen – up to 11cm larger than the other.

'Since being able to trial a new therapy based on mutations identified in my tumour type, my life has turned around. Not only is this the first improvement I have ever had, the speed is mind blowing. In the first 13 weeks, some of my tumours had shrunk up to 50% and my leg is now only 1–2 cm bigger.

'Living with PVNS is awful. My limited mobility and high level of pain meant I had to heavily rely on my very dedicated husband to help me with so many things.

'My career is on stage, on a podium, and requires me to stand for three hours at a time in the exact same position. PVNS made this incredibly difficult and painful for me but in September 2016, with my pain so improved, I was able to conduct my first concert without pain meds!'

'I feel I have my quality of life back, and I'm continually improving. Before this trial I felt lost, without hope. I am eternally grateful for this trial and the research. Without it, my life would have continued to become harder and harder, consumed completely by this horrendous disease.'

Luke Ryan

At 11 Luke Ryan was diagnosed with an osteosarcoma (cancerous bone tumour) in the back of his left knee. He had 12 months of chemotherapy with five different agents, enduring three-to-five-day hospital stays with breaks of 10 days between each one. He remembers the treatment as 'A lot, a long time and just beyond horrendous'.

'Three months in, I had a seven-hour limb salvage operation that left me with a full knee replacement, a slight leg extension and half a dead person's femur, and without most of my quads,' said Luke. 'It was not fun.'

Even in a close and comparatively well-off family, Luke says it's hard to overstate how tough that year was for everyone.

Following treatment Luke was monitored for five years and then the month before he finished school, his doctors told him he was cured. Luke says he cried, not from joy, but because he had survived.

Then when Luke was 22 was diagnosed with sarcoma for the second time – in his right arm. He had just finished an arts degree at Melbourne University and was part way through a law degree.

This time, however, the treatment was much easier to tolerate with two nine-week batches of chemotherapy and six weeks of radiotherapy. Three to five days in hospital became two to three hours. 'I was energetic, healthy and for the first time in months no longer crippled with pain. Chemotherapy made me feel substantially better than I did before. It was really something.'

Luke has been clear of sarcoma for eight years now and his monitoring is being wound down.

Receiving a rare cancer diagnosis not once, but twice, has made Luke acutely aware of the importance of medical research. 'The change in treatment methodologies between my two tumours and the impact that had on my lived experience cannot be overstated – in the first, an intolerable barrage of crippling chemotherapy that almost killed me. In the second, a well-measured regime that allowed me to continue on with my life largely unchanged. That happened in just 11 years. Incredible things can be achieved, so long as we continue to work towards them.'

The International Sarcoma Kindred Study

Sarcomas are rare, devastating cancers that arise anywhere in the body. The two main categories of sarcoma are soft tissue sarcomas, affecting mainly adults, and bone sarcomas, which are much more common in children and young adults. There are more than 50 subtypes of sarcoma that develop in the connective tissues – bone, muscle, tendons, nerves, fat, cartilage and blood vessels –each requiring different treatment and needing highly specialised multidisciplinary care.

The International Sarcoma Kindred Study (ISKS) is an Australian initiative investigating the heritable aspects of adult-onset sarcoma. Recruitment began at six sites in Australia in 2009 and has since expanded to 21 sites globally, including in France, India, New Zealand, USA, UK and Korea, with the global study centre in Australia as a biospecimen storage facility, laboratory and database repository.

Sarcoma patients and their families are asked to complete a family pedigree and questionnaire and give blood samples. There are more than 1700 families involved worldwide, with recruitment aiming for 3000 families internationally.

To date more than 1000 individuals with sarcoma have been screened and the researchers have uncovered numerous new genetic risk factors for the cancer – and, in a world first for any cancer type, they showed how carrying two or more of these rare mutations increases an individual's cancer risk.

The ISKS team looked at a 'gene panel' of 72 genes in each participant. They identified a number of new genes that significantly increase the risk of developing sarcoma, including mutations in the genes ERCC2, ATR, BRCA2 and ATM. Importantly, in individuals carrying mutations in two genes, the risk of developing sarcoma was measurably higher than in those with only a single mutation. And in carriers of three or more mutations, the risk was greater still.

'Until now, we've been limited to single-gene thinking, so we tell patients, for instance, that carrying a BRCA1 mutation means your breast cancer risk is higher, or that your risk of sarcoma and other cancers is higher because you've got a particular p53 mutation.

'The study shows us that the landscape of cancer risk is far more complex than that. We can now see that the risk for developing sarcoma is equally due to the combined effect of multiple genes, and that the more mutations you carry, the earlier the onset of cancer.

'The better we understand the genetic drivers that give a person an increased risk of cancer, the more precisely we can match individuals with the best possible treatment for them.'

Throughout its more than 50-year history, Garvan researchers have been responsible for significant breakthroughs that have improved our understanding and the lives of people living with some of the most common, yet complex diseases affecting society today.

These include:

- Pancreatic cancer
- Hearing loss
- Lupus
- Obesity
- Alzheimer's disease
- Osteoporosis
- Parkinson's disease
- Arthritis
- Asthma
- Breast cancer

We are currently in the midst of the genomic revolution – using the information contained in an individual's DNA to understand the basis of human development, help evaluate the genetic risk of disease, predict outcomes, and determine the most effective treatments for that individual.

I am proud to say that Garvan is one of the leading institutes internationally in the development and application of new genomic technologies to understand human disease and its prevention and treatment. The acquisition of the most advanced sequencing technology in the world has positioned Garvan as the human genomics hub for Australia and the region. It allows massive increases in genome sequencing capacity, accelerating medical research across the spectrum to include cancer, osteoporosis, autoimmune diseases, diabetes and neurological diseases.

Given Garvan's exceptional research talent, combined with its innovative use of leading-edge technology, I am excited by the potential of our work to deliver real benefits to this generation and those to come.

Professor John Mattick AO FAA
Executive Director
Garvan Institute of Medical Research

To sustain Garvan research projects, the Garvan Research Foundation aims to match government funding dollar for dollar.

Philanthropic support not only alleviates some of the financial stress on research teams, it also encourages innovation. It is vital for funding promising novel projects that do not yet have enough basic data behind them to be eligible for government funding.

Donations are also crucial for the purchase of the equipment and technology that is essential to modern day medical research, but is not eligible for government funding.

Your donation can help support these cutting-edge projects and purchase vital equipment to continue achieving life-changing breakthroughs.

Andrew Giles
Chief Executive
Garvan Research Foundation

WHY INVEST IN GARVAN'S RARE CANCERS RESEARCH?

- Better understand the inherited elements of rare cancers
- Develop treatment options for people with rare cancers
- Develop novel immunotherapies to harness the body's ability to fight rare cancers

For information about how you can help Garvan's researchers unravel the puzzle of Rare Cancers, contact:

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Front cover images

Top: Damaged DNA. Courtesy Dr Kate Patterson, Visual Science Communicator and Biomedical Animator, Garvan Institute of Medical Research.

Bottom left: Researcher Dr Dominique Hess looking at tumour sections.