UPDATES IN OVARIAN CANCER RESEARCH
WHAT IS OVARIAN CANCER?
The ovaries are two small oval organs, each about 2–4cm across, that sit on either side of the uterus and produce eggs (ova). The ovaries also produce the hormones oestrogen and progesterone, which regulate the menstrual cycle and the development of female physical characteristics.

We now know that ovarian cancer is not a single disease, but is in fact a variety of cancers that share a location in or near the ovaries and that many of these cancers arise from cells outside the ovary. For example, high-grade serous ovarian cancer (HGSC), which accounts for up to 80% of ovarian cancer deaths, mostly arises from cells of the fallopian tube and then spreads to the ovary.

Ovarian cancer is rarely diagnosed and treated in the early stages and around 75% of patients present with advanced cancer at diagnosis. Of these women, only 35–40% are likely to survive for five years, compared with around 90% for women with breast cancer.

RISKS AND SYMPTOMS
Because the ovaries are located deep in the abdomen, it is possible for a cancer to grow to a substantial size without obvious symptoms. When symptoms do develop, they are ones that many women experience from time to time – abdominal or pelvic pain, increased abdominal size or persistent abdominal bloating, needing to urinate often or urgently, or feeling full after eating – making it difficult for a woman to be aware of the development of ovarian cancer.

The risk for ovarian cancer increases with age and it is most common in women over 50 or who have gone through menopause. Other risk factors include reaching puberty before 12 and menopause after 50; not having had children or having them over the age of 30; endometriosis (a common gynaecological condition); or being overweight. The use of oral contraceptives, however, can reduce the risk of developing ovarian cancer by almost half.

Recent research has shown that the major risk genes, BRCA1 and BRCA2, are primarily associated with the HGSC type of ovarian cancer, as well as with breast cancer. Not all women with these mutations will develop ovarian cancer, but the chances are high. For women with a BRCA1 or BRCA2 mutation who have not yet developed ovarian cancer, risk-reducing surgery to remove the ovaries and fallopian tubes can reduce the risk of developing ovarian cancer by 80–90%.

DIAGNOSIS AND TREATMENT
Ovarian cancer is typically diagnosed by a combination of imaging, such as CT scan or ultrasound, biopsy, and blood tests. Often, a definite diagnosis and understanding of the type and extent of the cancer requires surgery, which is also aimed at removing as much of the cancer as possible.

Did you know?
- Symptoms of ovarian cancer can be mistaken for other less serious conditions and most cases are diagnosed when the cancer is already advanced.
- Ovarian cancer is diagnosed annually in around 250,000 women globally and is responsible for 140,000 deaths each year.
- The majority of women with high-grade serous cancer (HGSC), the most common form of ovarian cancer, die within five years of diagnosis, killing over 100,000 women globally each year.

Following surgery women receive chemotherapy, typically with carboplatin and a type of drug called a taxane. These kill cancer cells in different ways and in combination are more effective than either alone. While some women will be cured with this combined treatment, over time many cancers can recur and become resistant to chemotherapy.

The radical shift in understanding of the origins and types of ovarian cancer is resulting in the development of more targeted chemotherapy and greater use of personalised therapies, where treatment is matched to the underlying cellular type of the person’s cancer. This new focus on genetics and the subtypes of ovarian cancer has led to clinical trials for new treatments and new combinations of treatments.

OVARIAN CANCER RESEARCH AT GARVAN
Professor Bowtell leads the Ovarian Cancer Program at the Garvan Institute and also holds a joint appointment at the Peter MacCallum Cancer Centre. He is a world-leading researcher in ovarian cancer and his team have contributed substantially to an improved understanding of the diversity and biology of ovarian cancer. Professor David Bowtell is also leader of the Australian Ovarian Cancer Study (AOCs), one of the largest and most sophisticated studies of ovarian cancer in the world.

PERSONALISED MEDICINE FOR OVARIAN CANCER
Garvan recently became one of the first medical research institutes in the world to acquire technology that can sequence a whole human genome at high throughput and low cost. Using whole-genome sequencing to research deeply into our DNA has led to the discovery that all disease is linked to harmful genetic variants so that instead of trying to treat disease symptoms, we can now target the genetic variants causing them. This is the basis for personalised medicine. The ovarian cancer research teams have an unparalleled ability to undertake whole-genome sequencing of ovarian tumours, vastly increasing our understanding of this disease and leading to better, safer, more effective personalised therapies.
Collaborations

- Australian New Zealand Gynaecological Oncology Group, Sydney, Australia
- BC Cancer Agency, Vancouver, Canada
- Broad Institute, Boston, USA
- Dana Farber Cancer Institute, Boston, USA
- Genentech, San Francisco, California, USA
- Hammersmith Hospital, London, UK
- Lausanne University Hospital, Lausanne, Switzerland
- Memorial Sloan Kettering Cancer Centre, New York, USA
- Peter MacCallum Cancer Centre, Melbourne, Australia
- Prince of Wales Hospital, Sydney, Australia
- Princess Margaret Cancer Center, Toronto, Canada
- QIMR Berghofer Medical Research Institute, Brisbane, Australia
- Royal Women’s Hospital, Melbourne, Australia
- University of Michigan, Ann Arbor, USA
- University of Pennsylvania, Pittsburgh, USA
- University of Southern California, Los Angeles, California, USA
- University of Utah, Salt Lake City, Utah, USA
- Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia
- Westmead Millennium Institute for Medical Research, Sydney, Australia

Ovarian cancer researchers: Dr Swetansu Pattnaik and Professor David Bowtell.
UNLOCKING OVARIAN CANCER

Ovarian cancer (OC) is the fifth most common cause of cancer deaths in Western women, but despite extensive research efforts survival has little improved over the last 20 years. OC is still largely treated as a single disease with surgery to remove as much of the tumour as possible, followed by six cycles of platinum-based chemotherapy. An early detection test remains elusive, evidence shows that screening is unlikely to be effective, and there are very few practical ways to reduce risk, apart from the use of the oral contraceptive pill.

By contrast, the discovery of the role of genetic mutations offers substantial opportunities for improving treatment for women with ovarian cancer, as well as reducing risk in their female relatives.

Professor David Bowtell leads Garvan’s ovarian cancer research and his work has already revealed that the most common type of ovarian cancer, high-grade serous cancer (HGSC) itself has distinct subsets, both in terms of molecular characteristics and outcomes. His lab focuses on the analysis of genetic mutations and the associated development of new therapies to resolve the most significant issues in OC treatment – primary and acquired chemoresistance and risk reduction.

HGSC primary and acquired resistance – new therapies

‘Over the last 5–10 years the view of OC has changed radically’, said Professor Bowtell. ‘It was previously believed that the great majority of ovarian cancers were derived from changes in the outer surface of the ovaries (epithelium), but we now understand that OC is a collection of distinct diseases, with different cellular origins and molecular characteristics, which simply share an anatomical location.

‘Within high-grade serous cancer (HGSC), the most common type of OC and the cause of 70-80% of all OC deaths, we have identified four new molecular subtypes, each with distinct clinical outcomes – C1 (mesenchymal – a type of stem cell that can change into other cells, such as bone marrow), C2 (immunoreactive), C4 (differentiated – a cell that has already become specialised, like a skin cell), and C5 (proliferative – high growth).

When DNA is damaged, cells are able to repair themselves using a process called homologous recombination (HR). Approximately 50% of HGSC cancers have defective HR mechanisms and so these patients respond well, initially at least, to the platinum-based chemotherapy that attacks the cancer cells as they are unable to properly repair themselves. Around 20% of patients, however, fail to respond to this treatment and the cancer continues to develop. These patients generally only survive for 1–2 years.

For the women with ovarian cancer who do respond to platinum-based chemotherapy, the development of acquired resistance is common. While women may respond to further treatment, following a relapse, most still die with drug-resistant disease within five years. Globally an estimated 100,000 women die each year from recurrent HGSC. This is one of the most important clinical issues in OC, along with the lack of biomarkers to guide further drug selection following relapse.

Professor David Bowtell holds joint appointments with the Garvan Medical Research Institute in Sydney, the Peter MacCallum Cancer Institute, Melbourne, and is a Visiting Professor at Dana Farber Cancer Institute, Boston. Professor Bowtell’s work has led to the development of Australia’s first NHMRC Ovarian Cancer Program. His work is also supported by the US Department of Defense Ovarian Cancer Research Program, the US National Institutes of Health and Ovarian Cancer Australia.

Groundbreaking research by Professor Bowtell and his team has shown that these cancers can evolve different mechanisms to defeat the effect of chemotherapy, including restoration of an ability to repair DNA damage. For the first time in decades, not only do we have a new understanding of how the cancer evades treatment, but importantly, the findings suggest a way to defeat the cancer’s resistance to chemotherapy.
‘Primary and acquired resistance is a major focus of our work. To better understand acquired resistance we are sequencing recurrent and end-stage tumour samples and we have already identified a mechanism of resistance to the chemotherapy drug doxorubicin. Overcoming this resistance will add another important therapy to the options for treating ovarian cancer.’

Making use of unique samples collected during disease recurrence and through a rapid autopsy program, Professor Bowtell’s team is performing whole-genome sequencing and other genomic analyses to comprehensively map the cancer’s evolution. This work will help to identify resistance mechanisms and may provide a route to circumventing them and developing biomarkers of resistance will provide clinicians with tests that can guide drug selection in recurrent disease.

**Long Term Survivors**

Only some 35–40% HGSC patients survive five years, but a small number of patients – exceptional responders – survive much longer to become long-term survivors (LTS). Led by researchers in the US, Canada, UK and Australia, the Multidisciplinary Ovarian Cancer Outcomes Group (MOCOG) was formed in 2013 to share data and identify women who would benefit from targeted immune therapy, as well as understanding genetic features associated with LTS that may lead to new treatments. MOCOG also looks at behavioural changes that may have had an impact on survival.

‘Some HGSC patients exhibit profound tumour shrinkage or complete clearance on initial chemotherapy with little or no recurrence, whereas others survive despite multiple cycles of recurrence and response to treatment. Rapid responses to first line chemotherapy are likely to be driven by aspects of tumour biology that result in hypersensitivity to chemotherapy. In other women, effective immunological responses may result in relatively slow tumour growth.

While the extent of residual disease following surgery and chemotherapy is a significant predictor of outcome, approximately 45% of 10-year LTS actually have some residual disease, and approximately one-third have had recurrent disease. This strongly suggests that other factors, such as tumour biology and tumour immunity also contribute to LTS.

As in the women who respond well to platinum-based chemotherapy, in 75% of the HGSC patients who were still alive eight years after diagnosis, the HR DNA repair pathways of their cancer genes were inactivated, highlighting the importance of HR pathway inactivation in survival in HGSC. It is possible that some LTS have more than one HR pathway mutation that could render tumours hypersensitive to chemotherapy, or reduce the likelihood of developing resistance.

‘It is now also recognised that lifestyle, environmental and genetic exposures influence the specific risks of OC subtypes in very different ways. We plan to contact living LTS to collect data on their lives prediagnosis and what they

**Letitia Linke**

In 2014 Letitia Linke was on top of her world. The 34-year-old mother of two little boys, Ollie 9 and Tommy 8, had achieved a personal goal of losing some 30kg through her sheer determination to have a healthier life and was running her online interiors store and decorating business from the farm she runs with her husband Paul on the Yorke Peninsula in South Australia.

‘I was feeling fabulous and the best I had in years. Then I discovered a lump in my abdomen that I couldn’t feel before, but I had no other symptoms’, said Letitia.

During surgery to treat what were thought to be endometriomas and endometriosis, biopsies of the ovaries revealed ovarian cancer. A week later Letitia had a radical hysterectomy.

‘I had five surgeries in all. I underwent 18 weeks of chemotherapy treatment once a week. I tolerated this reasonably well. It was life as normal other than the chemo day. I then underwent five weeks of radiotherapy, five days a week. I felt fine during this but I live two hours from the treatment centre so had to stay away from my family at times and rely on others to help look after them.’

In late 2015, the cancer recurred, and Letitia is now on monthly second-line chemotherapy.

Aside from polycystic ovarian syndrome, like so many others with ovarian cancer, Letitia had no particular symptoms that she felt needed investigating. ‘Lack of general awareness is a major issue in ovarian cancer,’ she said.

‘There is a huge need for an early detection test to discover ovarian cancer before it is too late, which is so often the problem due to the symptoms going undetected. Also identifying genetic risk may help women at higher risk to follow up and be alert for any signs they do notice.

‘There also needs to be more work in molecular profiling and general understanding of the disease which of course is paramount for any successful treatment.’
did to help themselves after diagnosis, especially in terms of meditation, exercise, sleep, supplements, continuing to work and food and alcohol choices. Such behaviours may have helped the patient tolerate therapy such that she was able to receive full course, uninterrupted chemotherapy, or they may affect survival in other ways.’

‘We believe it is important to look at the interactions between the immune, genetic and personal factors associated with LTS, and to specifically look at women who experienced an exceptional response (eg, women who had no recurrences during the 10+ year period), compared to women with more typical disease trajectories.’

**Heritability and management of ovarian cancer**

Women with *BRCA1* or *BRCA2* mutations have 20-70% lifetime risk of developing OC. In 2012 Professor Bowtell’s finding of an unexpectedly high prevalence of *BRCA1/2* mutations in OC completely changed genetic testing guidelines for OC in Australia and elsewhere. With the change in the guidelines, more women are being offered genetic testing than previously, and it is expected that the detection of mutation carriers will more than double. This information is important to other female members of the family, in whom cancers may be prevented by knowledge of their mutation status.

Professor Bowtell’s TRACEBACK study is now seeking those mutation carriers whose diagnosis of ovarian cancer pre-dated the change in the guidelines (2000–2015). Modelling suggests that around 1000 ovarian cancers and 2500 breast cancers could be prevented in family members over a period of a decade or more if TRACEBACK is implemented.

Women who inherit a defective copy of the *BRCA1* or *BRCA2* gene are at increased risk of ovarian cancer because these genes reduce correct DNA repair. While this increases the risk of developing cancer, the cancers that do arise are usually especially vulnerable to the damage caused by therapy. Although most women with *BRCA* mutations have a very good response to chemotherapy, the cancer progresses rapidly in a subset of patients. Study of women with *BRCA1/2* mutations and rapidly progressive disease complements the Long-term Survivor study. Investigating these clinical extremes – short and long term survival – should provide the maximum ability to understand the determinants of clinical response and thereby offer new therapeutic approaches.
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

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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

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**WHY INVEST IN GARVAN’S OVARIAN CANCER RESEARCH?**

- Better understand what drives ovarian cancer
- Deliver new therapies that overcome drug resistance
- Reduce the risk of ovarian cancer for those with high-risk genetics

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For information about how you can help Garvan’s researchers unlock the secrets of ovarian cancer, contact:

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Front cover image:
Tissue section showing the cells of a high-grade serous ovarian cancer, the primary focus of the Bowtell laboratory. Courtesy Dr Elizabeth Christie.