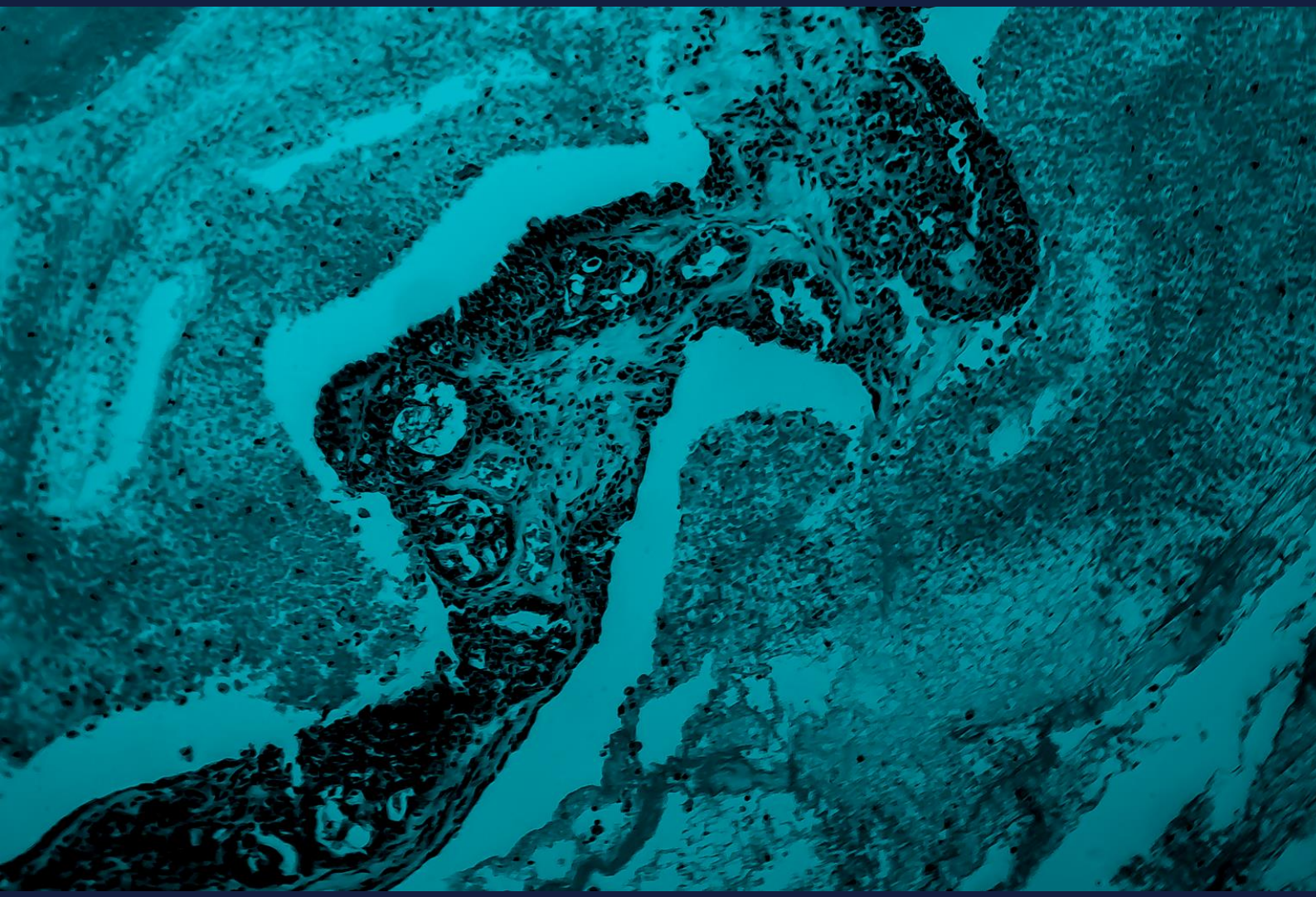
# State of the Nation in Ovarian Cancer: Research Audit

**Final Report to the Ovarian Cancer Research Foundation**

**August 2020**



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# Acknowledgements

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More than 215 people responded to the Survey of Ovarian Cancer Researchers, Clinicians, and Consumers, including 62 researchers and clinicians and 153 consumers, including patients, survivors, and their families. We also thank the Australia New Zealand Gynaecological Oncology Group, the National Cancer Research Institute Gynaecological Group (UK), Cancer Voices Australia, and the Consumer and Community Health Research Network for their support in the launch of the survey.

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# Foreword

This landmark *State of the Nation in Ovarian Cancer: Research Audit* report brings together a roadmap for saving tens of thousands of women's lives. This report is the first ever national audit focused on ovarian cancer research, incorporating views from clinicians, researchers and consumers nationally.

Every major research institute and university in Australia has generously supported the audit through either the contribution of historical research data, or participating in a survey or interview. This has ensured that the audit is truly reflective, and provides a clear and informed view on the future research priorities and urgent need for investment.

As the country's leading funder of early detection research, the Ovarian Cancer Research Foundation has worked tirelessly for 20 years to fill the breach. But historic and current funding levels are inadequate, and we are calling for more to be done.

Ovarian cancer remains one of the most lethal and least understood gynaecological cancers affecting women in Australia and around the world. The five-year survival rate has stagnated at 46% and remains lower than the 5-year survival rates achieved back in 1975 for all cancers. Critically, this low survival rate likely overstates the survival rate for women diagnosed with the most common form of ovarian cancer (high grade serous carcinoma). A recent overview reported that 95 per cent of advanced stage disease diagnoses relate to serous carcinoma, which has only a five-year survival rate of 29 per cent. This is a bleak picture for women diagnosed with ovarian cancer today.

The modern cancer era has shown that investment in cancer research translates into outstanding improvements in survival. The successes in survival outcomes have been realized through significant and sustained funding for high impact research since the 1970s. History shows that where communities, governments and industry come together, big improvements in survival can be realized and countless lives saved. While ovarian cancer has been left behind in the last 45 years of modern cancer research, with a similar focus and funding uplift, it can be the success story of the next generation.

The State of the Nation audit reveals that while Australia is a significant performer of ovarian cancer research globally, funding has been limited compared to the total potential funding for medical research available in Australia. An increase in ovarian cancer's share of the total funding envelope, or an increase in giving overall by the wider community, has the potential to significantly expand on historic trends in funding for this rare and low survival cancer.

This report calls for an ambitious but achievable program of work to improve the lives of women diagnosed with ovarian cancer today, and for the next generation of women.

With a focus on the outlined priorities and funding required, we believe that together we can:

- Improve survival rates to 50 per cent for women today through implementation of existing knowledge and clinical best practice
- Improve survival rates beyond 50 per cent for women tomorrow through developing and testing new and innovative personalised treatments
- Improve survival rates towards 90 per cent for future generations through the development of novel technologies for early detection and diagnosis.

We know that the provision of enhanced treatment options equates to saving the lives of more than 680 Australian women over the 2025-2035 horizon, and more than 110,000 women globally.

Similarly, a focus on early detection has the potential to save the lives of more than 8,000 Australian women over the 2035-2045 horizon, and more than 1.3 million women around the world.

If we want to achieve the same improvements in survival in ovarian cancer that have been seen for so many cancers; if we want to see the major breakthroughs in early detection and prevention that have been realised in breast cancer and cervical cancer, then we must close this gap over the next 10-15 years.

Now is the time for greater investment in outcomes that will save women's lives.

***Julie Toop***

***Chairperson***
***Ovarian Cancer Research Foundation***

***Dr Jane McNeilage***

***Chair, Scientific Advisory Committee***
***Ovarian Cancer Research Foundation***

# A Message from Women Impacted by Ovarian Cancer

This *State of the Nation in Ovarian Cancer: Audit Report* is our lived experience. As women diagnosed with ovarian cancer, women undergoing treatment, and family and friends of loved ones with ovarian cancer this is our story.

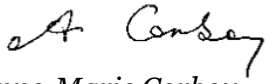
Research for us is vital. We absolutely value the gains that have been made through research conducted to date, but so much more needs to be done. We can see what a difference research has made to other cancer survival rates particularly those cancers that affect women – breast cancer and cervical cancer – both have early detection tests, better treatment options and cervical cancer has a vaccine. These are the things we wish for with ovarian cancer.

A concerted funding effort is required to improve the outcomes for women with ovarian cancer and those that are likely to contract it in the future. We certainly do not want our daughters and granddaughters to have the same limitations that currently apply to us.

We are absolutely delighted that the Ovarian Cancer Research Foundation has commissioned this study which so coherently outlines where we are at and what research funding support is needed.

We want to be part of the solution, and greater funding support is a must.

Please invest in research so that our lives and the lives of our loved ones can be saved and we can make a difference to the women who follow us with early detection, prevention and improved treatment options.



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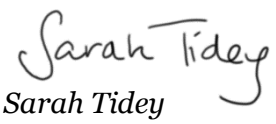

*Sarah Tidey*

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# Executive Summary

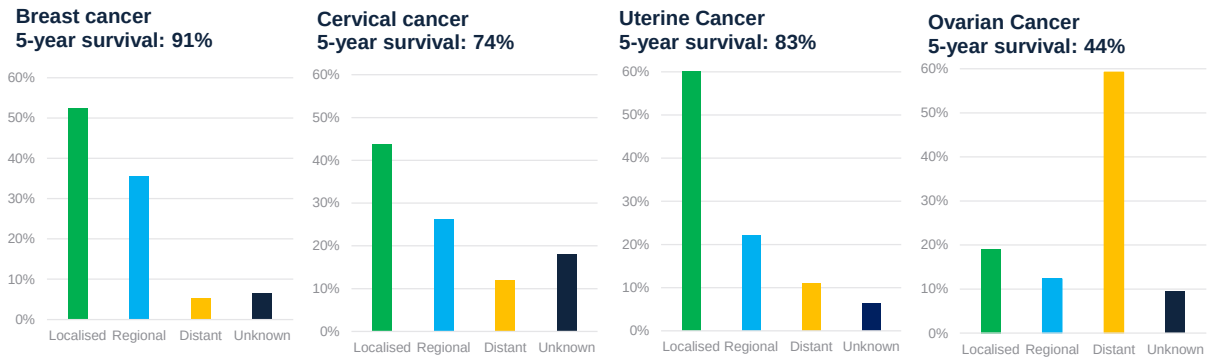
Ovarian cancer is one of the most lethal and least understood cancers affecting women in Australia and around the world. Women with ovarian cancer face a challenging outlook, with 5-year survival rates of only 46 per cent today. Sadly, this survival rate is lower than the 5-year survival rate for all cancers in 1975, when the modern cancer research era began.

## Late diagnosis and a lack of treatment options contribute to poor outcomes

The poor survival outlook for women with ovarian cancer is a function of the advanced stage diagnosis and fewer treatment options compared with other cancers.

While a majority of breast, uterine and cervical cancers are diagnosed while the cancer is still localised (Figure 1), most ovarian cancers are diagnosed once the cancer has spread.

**Figure 1: Stage of diagnosis and survival outcomes — ovarian cancers are diagnosed at advanced stages**




Source: Cancer Institute NSW, 2020, Cancer Statistics, accessed at: https://www.cancer.nsw.gov.au/data-research/access-our-data/cancer-statistics-nsw#//analysis/incidence/

Women with ovarian cancer are treated with surgery and chemotherapy regimens that are initially successful in achieving remission. However, for more than 80 per cent of women the cancer comes back. After multiple rounds of treatment, the cancer typically becomes resistant to treatment.

## More than 2.2 million women will die from ovarian cancer over next 10 years

In Australia today more than 1,800 women are diagnosed each year and more than 1,100 of those women will die as a result of this diagnosis. Globally, ovarian cancer is estimated to impact more than 322,000 women every year. Over the next 10 years alone it is estimated 14,000 Australian women will lose their lives to ovarian cancer; worldwide, mortality from ovarian cancer is expected to exceed 2.2 million women between today and 2030.

**Figure 2: Global ovarian cancer incidence**

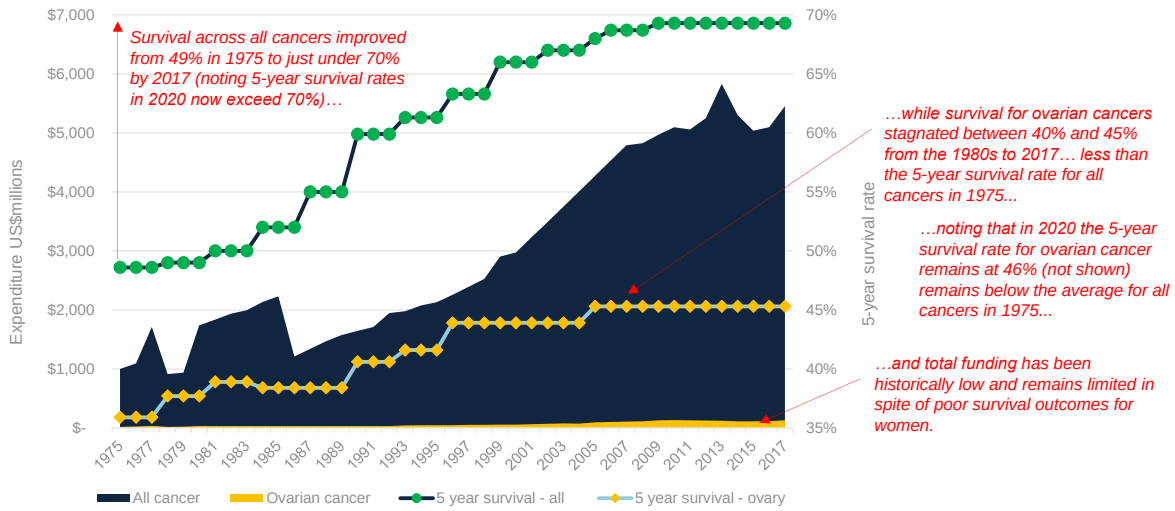

Source: International Agency for Research on Cancer, 2018, WHO, Cancer Today, C56 data reported by continent and selected countries, rounded to the nearest hundred. Data for C57 was not reported. Note Australian data based on aggregate of AIHW data for C56 and C57 in 2018 was 1,700 new cases; 2020 figures are included here due to confusion arising from current AIHW statistics and 2018 data.

## Limited funding for ovarian cancer has slowed research breakthroughs

The lack of breakthroughs for ovarian cancer is largely a product of an inadequate understanding of the underlying biology, which in turn is associated with a history of underfunding of research relative to other major cancers. Historically, low levels of funding can be attributed to the relative rarity of ovarian cancer and also to the lack of patient advocates to sustain campaigns for research funding.

As a consequence, while many cancers have seen survival rates substantially improve over the modern cancer research era, ovarian cancer has not (Figure 3).

**Figure 3: Limited funding for ovarian cancer in the modern cancer era has stifled breakthroughs ($US)**




Source: NCI Budget Factbook Archives 1975-2017, accessed at www.cancer.gov.au/about-nci/budget/factbook/archive. NCI SEER, 2016, Age-Adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival (Percent), https://seer.cancer.gov/archive/csr/1975_2016/results_merged/topic_survival.pdf.

The need for increased research funding to address low-survival cancers has been increasingly recognised by developed nation governments. In the United States, for example, the federal government passed legislation in 2012 mandating investment to improve survival for so-called 'recalcitrant' cancers. This action was echoed in Australia in 2017 with the

Senate Select Committee similarly calling for urgent investment to increase survival outcomes for low-survival cancers to 50 per cent by 2027.

## State of the Nation in Ovarian Cancer: Research Audit objectives and approach

Following the calls for more research funding for low-survival cancers, the Ovarian Cancer Research Foundation (OCRF) commissioned this research audit. As the largest non-government funder of ovarian cancer research in Australia, the OCRF sought to develop an evidence-based roadmap for improving outcomes for women with ovarian cancer. This report brings together:

- Funding data from funders and ovarian cancer researchers across Australia and New Zealand from 2010 to 2020
- Historical time-series analysis of Australian and international funding across a range of cancers, including National Cancer Institute (US) budget analysis from 1975 to 2017 and National Health and Medical Research Council (Australia) and Australian Research Council funding from 2005 to 2020
- A Survey of Ovarian Cancer Researchers, Clinicians and Consumers
- Consultations with Australian and international researchers, patient support organisations, Medicines Australia's Oncology Industry Taskforce, governments and allied charitable foundations.

The *State of the Nation in Ovarian Cancer: Research Audit* brings these data together to highlight the challenges facing women with ovarian cancer today, the barriers to improving survival and future directions for research.

## Research Audit findings: major funders of ovarian cancer research

The data collected through the audit shows that the majority of funding for ovarian cancer research has originated in the United States, with the National Cancer Institute and National Institutes of Health being the largest funder. Combined, United States government departments and agencies invest more than $180 million per annum in ovarian cancer research (Figure 4).

The data also shows that the global biopharmaceutical industry and non-government organisations, including charitable foundations, have been important partners in ovarian cancer research. The global biopharmaceutical industry is estimated to invest about $770 million in clinical research annually, with the majority of studies originating in the United States.

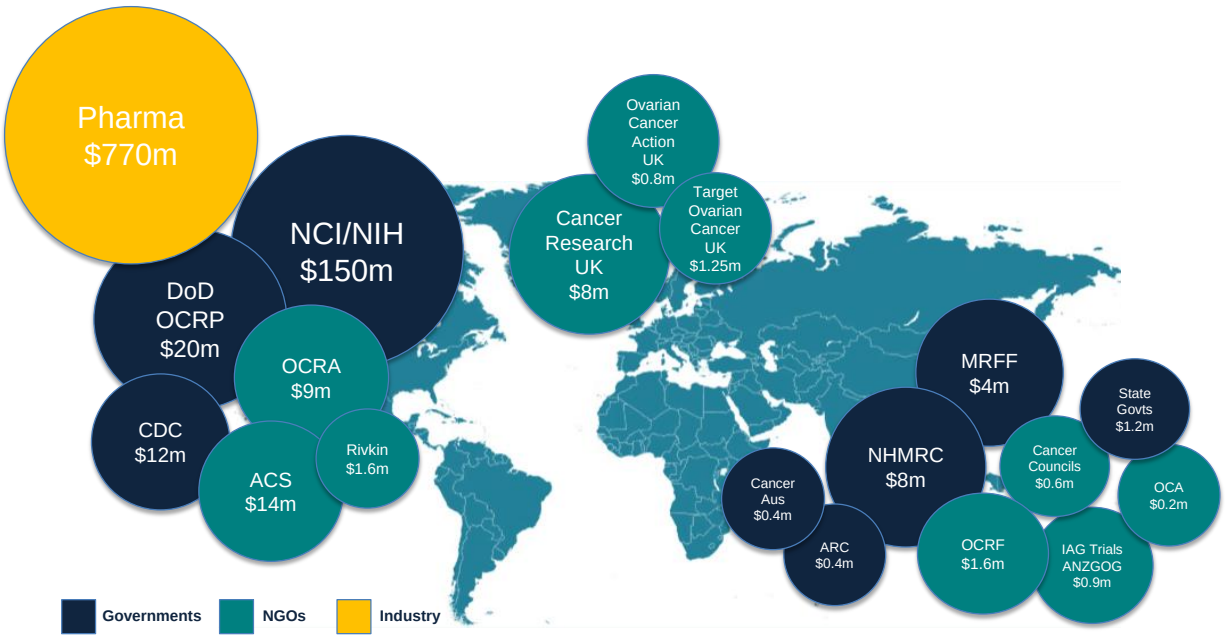
Australia represents only 0.3 per cent of the world's population, but the data show it has been a major funder and performer of ovarian cancer research globally.

Within Australia the Federal Government has been the major funder of ovarian cancer research, accounting for approximately 60 per cent of all Australian funding from 2010 to 2020. Since 2010, the Federal Government has funded $107 million in ovarian cancer research, at an historical average of about $8 million per annum. In 2020, the Federal Government announced an increase on historic funding levels of $4 million per annum through the Medical Research Future Fund over the next five years.

After the Federal Government, the Ovarian Cancer Research Foundation has been the largest funder of ovarian cancer research in Australia and New Zealand, accounting for 10 per cent of all funding across all phases of research between 2010 and 2020. Since 2010, the OCRF has funded more than $17 million in ovarian cancer research, and more than $25 million

since it was founded 20 years ago. The OCRF has funded research at an average of $1.6 million per annum from 2010 to 2020, with funding in the past three years increasing to $1.8 million per annum.

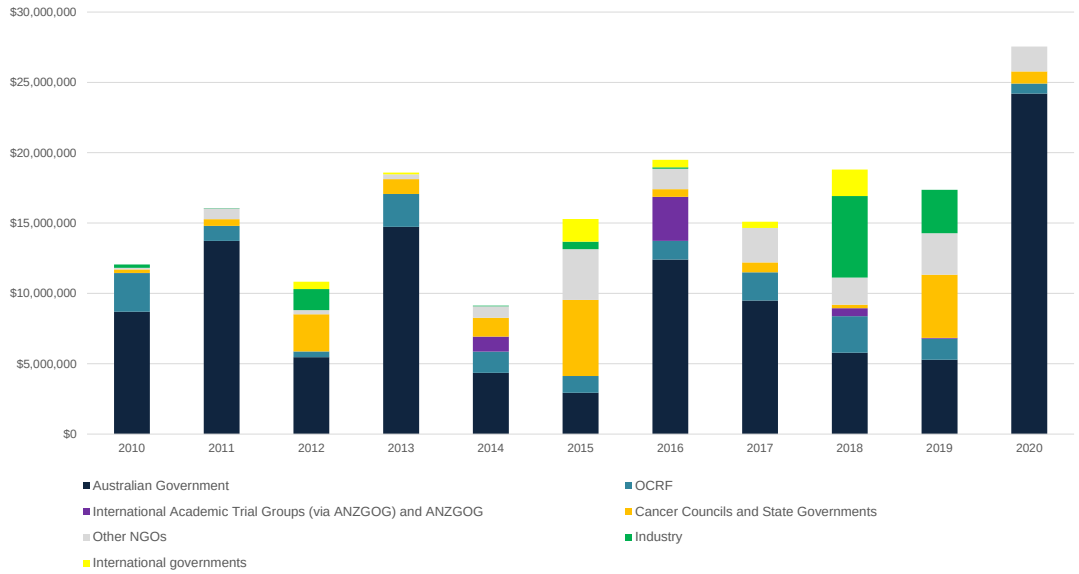
**Figure 4: Average annual funding for ovarian cancer research by funder**




Source: Latest available budgets and annual reports for international funders including National Cancer Institute and National Institutes of Health (NCI/NIH), US Department of Defence Ovarian Cancer Research Program (DoD OCRP), Centres of Disease Control and Prevention (CDC), American Cancer Society (ACS), Ovarian Cancer Research Alliance (OCRA), Rivkin Center, Cancer Research UK, Ovarian Cancer Action UK, Target Ovarian Cancer, Insight Economics analysis of clinical trials data for industry-led clinical trials by phase of research in 2019 published at Clinicaltrials.gov, National Health and Medical Research Council (NHRMC) reporting 2003-2016 accessed at https://www.nhmrc.gov.au/funding and supplemented with data from Australian Government Grants Connect 2016-2020, Medical Research Future Fund (MRFF) data accessed through Grants Connect, Australian Research Council (ARC) data accessed at https://www.arc.gov.au/grants and Grants Connect. Cancer Australia based on audit of ovarian cancer research performers. OCRF and ANZGOG based data shared by organisations and audit of ovarian cancer research performers. Ovarian Cancer Australia (OCA) estimate based on Australian Charity and Not-for-profits (ACNC) AIS reporting in 2017 and the audit of ovarian cancer research performers. See Appendix A for further details about responding organisations.

Following the OCRF, the next major funder of ovarian cancer research has been Cancer Councils and state governments, which often co-ordinate investments to optimise the allocation of scarce research funding dollars across potential projects, as well as international academic trial groups through the Australia New Zealand Gynaecological Oncology Group (ANZGOG). State governments combined fund an average of $1.2 million in ovarian cancer research each year, while Cancer Councils combined account for roughly $0.6 million in funding for ovarian cancer research per annum.

**Figure 5: Historical funding for research in Australia and New Zealand by funding source (2010-2020)**

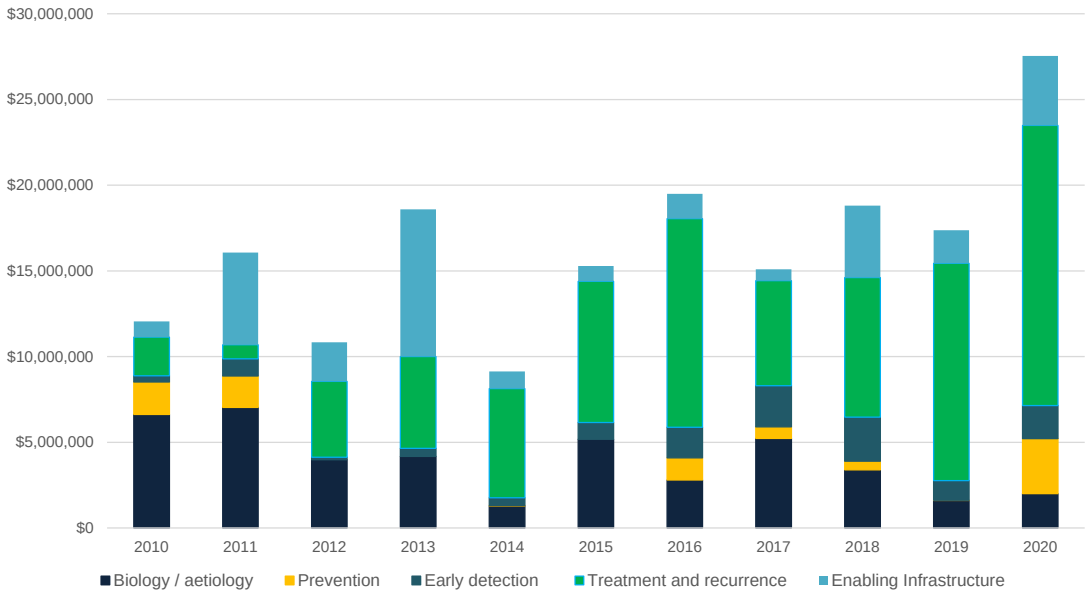



Source: Audit of Ovarian Cancer Research Institutes, See Appendix A.

## Research Audit findings: funding by research phase

By research phase, the majority of funding for research in Australia has been allocated to improve the understanding of disease biology and to develop new treatments. Excluding industry-led trials, funding for research into treatment has accounted for nearly half of all funding (46 per cent) while one quarter of all funding (24 per cent) was directed into research into the biology of the disease. Funding for research into early detection has accounted for only seven per cent of all research funding, the majority of which (81 per cent) has been funded by the NGO sector. Five per cent of funding has supported research into disease prevention, with the balance (18 per cent) directed to enabling infrastructure including biobanking capabilities and fellowships.

**Figure 6: Historical funding for ovarian cancer research by research phase (2010-2020)**

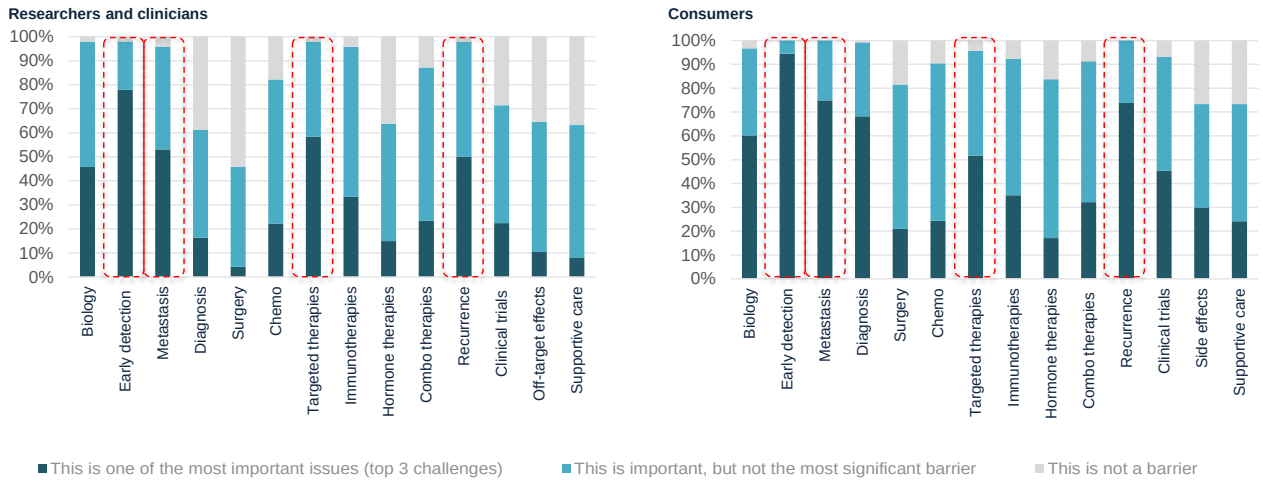



Source: Audit of Ovarian Cancer Research Institutes, See Appendix A.

## Barriers to improving survival and priority areas of research

The Survey of Researchers, Clinicians and Consumers indicates that the major barriers to improving survival outcomes for women with ovarian cancer include a lack of means for early detection, a paucity of treatment options, and an inability to prevent metastasis and disease recurrence (Figure 7).

**Figure 7: Barriers to improving survival: researcher, clinician, and consumer perspectives**




Source: Survey of Ovarian Cancer Researchers, Clinicians, and Consumers, See Appendix B. Note: Chemo is abbreviated for chemotherapy and combo is abbreviated for combination therapies.

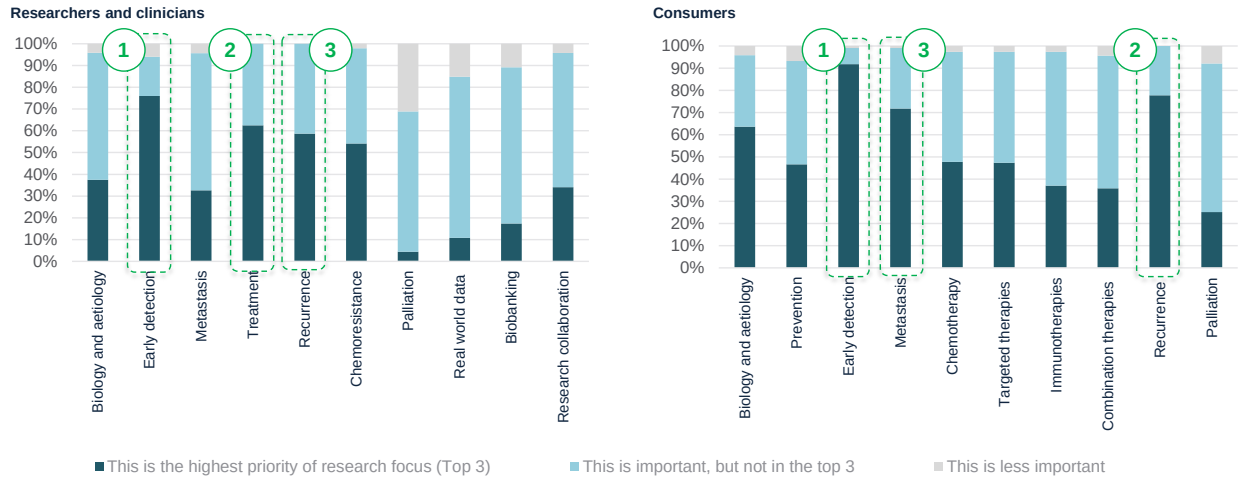
To address these barriers to survival, survey respondents indicated there was an urgent and significant need for a comprehensive program across all phases of research. Areas of research need included:

- *Increased investment in fundamental biology and aetiology*, including in particular to identify ovarian cancer stem cells and to better understand disease progression
- *Increased investment in early detection research*, including the identification of novel biomarkers of disease and diagnostic approaches to enable early detection, particularly among high risk cohorts
- *Increased research to expand treatment options*, including increasing the use of precision medicine capabilities in ovarian cancer and a better understanding of preventing disease recurrence
- *Increased investment in prevention* research to better understand the protective effects of lifestyle and environmental factors on ovarian cancer development and opportunities for intervention.

Importantly, while investment is needed across all areas of research, researchers, clinicians and consumers most frequently identified early detection research as one of the highest priority areas to improve survival. Roughly 80 per cent of researchers and clinicians and 95 per cent of consumers indicated this was one of the top three priorities for research to improve survival outcomes for women (Figure 8).

Following early detection, research to expand treatment options and prevent disease recurrence were most commonly identified as the most urgent priorities among researchers and clinicians. Consumers more frequently identified preventing metastasis and recurrence, and early detection as priority research areas.

**Figure 8: Priorities for research to improve survival: researcher, clinician and consumer perspectives**




Source: Survey of Ovarian Cancer Researchers, Clinicians, and Consumers, See Appendix B.

## A vision to improve survival for women with ovarian cancer

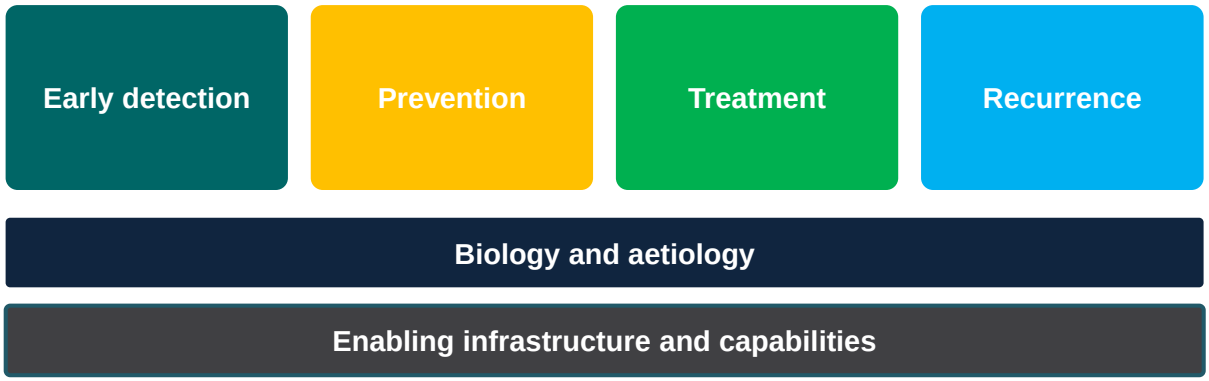
Based on the results of the research audit, the OCRF has set out a vision for a future where women live without ovarian cancer. To achieve this vision, the OCRF proposes pursuing a stepped improvement in survival outcomes over the short, medium, and longer term:

- Improve 5-year survival rates to 50 per cent for women today by rapidly implementing recent advances in knowledge in clinical practice nationally
- Improve 5-year survival rates beyond 50 per cent for the next generation of women through the development of and access to novel, personalised treatments
- Improve 5-year survival rates towards 90 per cent by developing novel technologies for early detection and diagnosis.

These are ambitious but achievable goals if underpinned by increased funding for a strategic program of research and supported by collaboration between governments, researchers and the wider community.

To achieve this vision, the *State of the Nation in Ovarian Cancer: Research Audit* report sets out a comprehensive summary of future research directions by research area (Figure 9). The report calls for an increase in funding across all phases of research to enable the strategic and comprehensive program of work needed to address the low survival rates for ovarian cancer.

**Figure 9: Roadmap for ovarian cancer research**



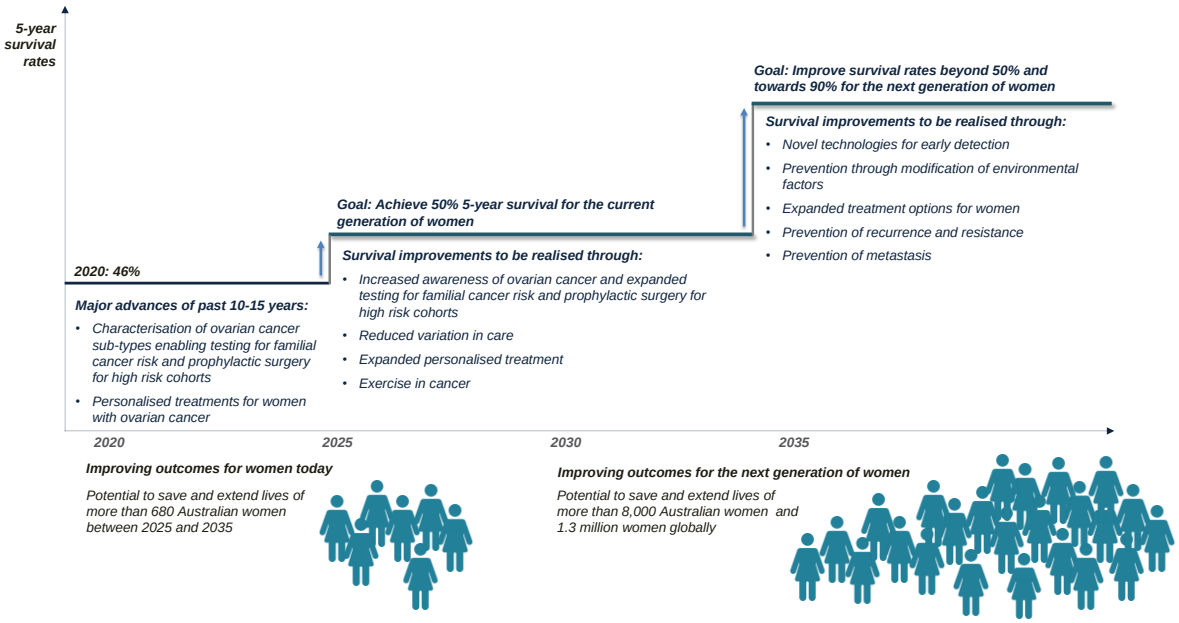

As part of this comprehensive research agenda, the OCRF is calling for new investment in:

- The rapid implementation of current best practice knowledge nationally, building on the commitments through the Medical Research Future Fund to reduce variation in care
- Expanding access to personalised treatment options for women nationally
- The establishment of an Australian Centre of Excellence for Early Detection in Ovarian Cancer
- Establishing an Ovarian Cancer Mentorship Program to attract, retain and develop Australia's next generation of ovarian cancer researchers.

Realising the goals in this report would extend and save the lives of women in Australia and around the world (Figure 10). For example:

- *Benefits of achieving 50 per cent 5-year survival nationally by 2025* — Between now and 2035, nearly 14,000 Australian women are expected to die from ovarian cancer. While the national 5-year survival rate is 46 per cent, there is variation in outcomes by state and territory, and some jurisdictions have reported 5-year survival rates above 50 per cent. By rapidly implementing current clinical best practice nationally and reducing variation in care, more than 680 lives could be extended and saved between 2025 and 2035.
- *Benefits of increasing 5-year survival towards 90 per cent* — Striving to develop an early detection test for the next generation of women has the potential to substantially improve the survival rate for women with ovarian cancer and save the lives of more than 8,000 Australian women over a decade. Importantly, this estimate conservatively assumes ovarian cancer is detected early in only half of the women that would otherwise have died from ovarian cancer. Improving technologies and understanding of ovarian cancer biology could see this estimate increase further. Globally, the development of technologies for early detection could save the lives of more than 1.3 million women.

**Figure 10: A vision for saving women's lives today and tomorrow**




History shows that where communities, governments and industry come together major improvements in survival can be realised and countless lives can be saved. While ovarian cancer has been left behind in the past 45 years of modern cancer research, with appropriate investment it can be the success story of the next generation.

> *"I want to know what hope I can give my daughter… I share lots of things with her and, unfortunately, I've shared these cancer genes with her. I want to know what will be available for our daughters. We need to keep all of the mothers around as long as we can, but that's what keeps me going, what gives me hope… that we can make things different for our daughters."*
>
> *- Ovarian cancer patient*

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## Chapter 1

# Understanding ovarian cancer: the most lethal and least understood gynaecological cancer

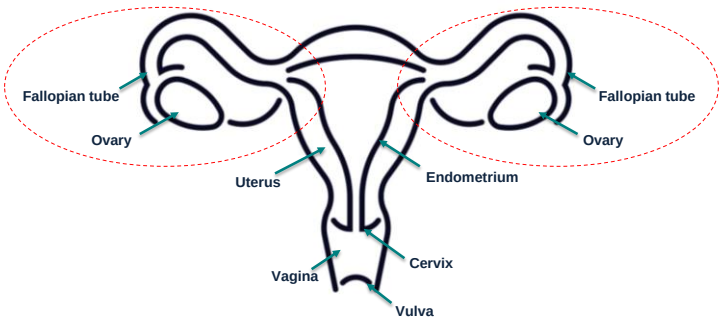
*Ovarian cancer is one of the most fatal forms of cancer affecting women today. In 2020 more than 1,800 Australian women will be diagnosed with ovarian cancer and by 2025 only 830 of these women will still be alive. Globally, more than 2 million women will lose their lives to ovarian cancer over the next 10 years. Despite these figures, ovarian cancer remains a poorly understood condition that is typically detected and diagnosed at a late stage.*

*This chapter explains what ovarian cancer is, where it originates in a woman's body, future incidence and mortality expectations, current diagnosis and treatment pathways and the underlying funding challenges contributing to a poor survival outlook for women diagnosed with ovarian cancer.*

## 1.1 What is ovarian cancer?

Ovaries are small glands, approximately the size of an almond, in which eggs (ova) are produced and released into a woman's uterus (womb) for conception via the fallopian tubes (Figure 1.1). Ovaries also secrete hormones that regulate a woman's fertility and menstrual cycle.

**Figure 1.1: Basic female reproductive anatomy**




**Uterus:** The organ in a woman's body where offspring are conceived and in which they gestate before birth.

**Endometrium:** The lining of the uterus.

**Cervix:** The cervix is a cylinder-shaped neck of tissue that connects the vagina and uterus.

**Vagina:** The vagina is an elastic, muscular tube connecting the cervix of the uterus to the vulva and exterior of the body.

**Vulva:** The vulva is the outer part of the female genitals. The vulva includes the opening of the vagina, labia, and the clitoris.

**Ovary:** Female reproductive organ (glands) in which eggs (ova) are produced and released. Ovaries also secrete hormones that regulate fertility and menstruation.

**Fallopian tubes:** Fallopian tubes connect the ovaries to the uterus. Ova (egg cells) produced by the ovaries are carried to the uterus through the fallopian tubes following ovulation.

**Peritoneum:** The peritoneum is a thin layer of tissue surrounding the abdominal organs, including female reproductive organs.

Ovarian cancer is a cancer that originates in a woman's ovaries, fallopian tubes or endometrial tissues adjacent to the ovaries (Figure 1.1). Ovarian cancer occurs when cells in these tissues become abnormal and start growing and multiplying out of control. Because a woman has ovaries and fallopian tubes on either side of her uterus, ovarian cancer can be found in just one ovary or fallopian tube or in both.

Ovarian cancer is one of seven gynaecological cancers and is often confused with a number of them, including:

- *Cervical cancer* — Cervical cancer is a cancer that originates in a woman's cervix. While there are other known risk factors, almost all cervical cancer is caused by a viral infection, the *human papillomavirus* (HPV). Cervical cancer can be prevented by vaccination against this virus, and screened through a cervical screening test that has recently replaced the Pap smear.[1]

- *Uterine or endometrial cancer* — Ninety five per cent of all uterine cancers originate in the lining of the uterus (the endometrium). More rarely, cancers can originate in the muscle layer of the uterus (sarcomas) or the connective tissue (stroma) that supports the endometrium.

Confusion between ovarian cancer and cervical cancer in particular gives rise to misconceptions that HPV vaccines and regular Pap smears protect against ovarian cancer. Unlike cervical cancer, ovarian cancer cannot be prevented through a vaccine or detected through current screening tools.

## 1.2 Risk factors for ovarian cancer

According to the US Surveillance, Epidemiology, and End Results (SEER) Program, the lifetime risk of ovarian cancer is approximately 1.2 per cent across all women.[2]

A number of genetic factors, medical conditions and lifestyle factors, however, can increase a woman's risk of ovarian cancer. These include:

- BRCA *genetic mutation* — Although *BRCA* genes get their name from the 'breast cancer genes', *BRCA* genes are also closely tied to ovarian cancer. The *BRCA1* and *BRCA2* genes are responsible for repairing damage to DNA. If either of these genes is mutated or altered, DNA damage may not be repaired properly. This can cause additional genetic alterations that can lead to cancer. Women who inherit a *BRCA* genetic mutation are at higher risk of developing both breast and ovarian cancer. It is estimated about 44 per cent of women who inherit a *BRCA1* mutation and about 17 per cent of women who inherit a *BRCA2* mutation will develop ovarian cancer by the age of 80.[3] *BRCA* germline mutations are associated with 10 to 15 per cent of high-grade serous ovarian cancers.

- *Ashkenazi Jewish descent* — *BRCA* genetic mutations are more common among Ashkenazi Jewish women. Ashkenazi Jews are Jews of central or eastern European descent and comprise 80 per cent of the Jewish population today. *BRCA* gene mutations occur in one in 40 in the Ashkenazi Jewish community[4] compared to one in 500 of the general population.[5] As a result, Ashkenazi Jewish women will have an

[1] Cervical screening is the process of looking for cancer or precancerous changes in women who don't have any symptoms. The cervical screening test detects cancer-causing types of human papillomavirus (HPV) in a sample of cells taken from the cervix. Historically, the Pap smear has been used to screen for cervical cancer. In December 2017, the Cervical Screening Test replaced the Pap test in Australia. Through the National Cervical Screening Program the two-yearly Pap test for people aged 18 to 69 has been replaced by a human papillomavirus (HPV) test every five years for people aged 25 to 74. People are due for their first Cervical Screening Test at the age of 25 or two years after their last Pap test. See: Australian Government, 2020, National Cervical Screening Program.

[2] National Cancer Institute, SEER Program, 2020, Cancer Stat Facts: Ovarian Cancer, accessed at: seer.cancer.gov/statfacts/html/ovary.html.

[3] National Cancer Institute, 2020, BRCA Mutations: Cancer Risk and Genetic Screening, accessed at: https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#how-much-does-having-a-brca1-or-brca2-gene-mutation-increase-a-womans-risk-of-breast-and-ovarian-cancer.

[4] CDC Centres for Disease Control and Prevention, 2020, Jewish Women and BRCA Gene Mutations, accessed at: https://www.cdc.gov/cancer/breast/young_women/bringyourbrave/hereditary_breast_cancer/jewish_women_brca.htm#:~:text=Mutations%20in%20BRCA%20genes%20raise%20a%20person%E2%80%99s%20risk,50%25%20chance%20of%20having%20the%20same%20gene%20mutation.

[5] CDC Centres for Disease Control and Prevention, 2020, BRCA Gene Mutations, accessed at: https://www.cdc.gov/cancer/breast/young_women/bringyourbrave/hereditary_breast_cancer/brca_gene_mutations.htm

elevated lifetime risk of developing breast and ovarian cancer over and above the general population.

- *Lynch syndrome* —Lynch syndrome is a rare inherited genetic mutation that increases the risk of a range of cancers in the abdominal cavity, including ovarian cancer. Lynch syndrome is caused by a mutation in one of the following mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[6] The lifetime risk of ovarian cancer in women with Lynch Syndrome is estimated to be between 7-12 per cent.[7]

- *Peutz-Jeghers syndrome* — Peutz-Jeghers syndrome is a very rare, inherited disorder that affects approximately 1 in 160,000 to 1 in 280,000 people.[8] People with the disorder develop polyps in the digestive tract and are at higher risk of a range of cancers, including ovarian cancer. About 21 per cent of women with Peutz-Jeghers syndrome develop ovarian cancer aged 15-64 years old.[9]

- *Endometriosis and infertility* — Endometriosis is defined as the presence of endometrial glands and stroma outside the uterus. It is a relatively common condition affecting between two to eight per cent of all reproductive-age women, and present in approximately 30 per cent of women who are infertile. Although endometriosis itself is not fatal, endometriosis-induced inflammation and hormone production can contribute to the development of ovarian cancer, including, in particular, the clear cell and endometrioid sub-types (See Section 1.2: Ovarian cancer sub-types). Epithelial ovarian cancer risk is 27-80 per cent higher in women with endometriosis, with the risk being higher among infertile women.[10] Ovarian cancer associated with endometriosis, however, usually presents in younger women and is likely to be of a lower grade.[11]

- *Diabetes* — Ovarian cancer risk is 24 per cent higher in type 2 diabetics compared with non-diabetics and 17-83 per cent higher in people with type 1 diabetes compared to people without type 1 diabetes.[12]

- *Obesity* — Ovarian cancer risk is eight per cent higher per 5-unit body mass index (BMI) increase.[13]

Conversely, a number of factors can also reduce a woman's risk of developing ovarian cancer. Lifestyle and environmental factors that reduce a woman's risk of ovarian cancer include:

- *Oral contraceptives* — Among all women the risk of ovarian cancer is reduced by 25-28 per cent for women who have used oral contraception compared to women who have never used birth control. Among women with a *BRCA* mutation the risk of ovarian cancer is reduced by 50 per cent. Across all women the protective benefit of

[6] Lynch Syndrome Australia, 2020, *What is Lynch Syndrome?*, https://lynchsyndrome.org.au/the-facts/what-is-lynch-syndrome/
[7] Crispens MA, 2012, Endometrial and ovarian cancer in lynch syndrome. Clinics in colon and rectal surgery, 25(2): 97–102, doi: 10.1055/s-0032-1313780; Watson, P, Vasen, HF, Mecklin, JP, et al. 2008, The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer, 123(2):444-9.
[8] Cancer Institute NSW, *Peutz-Jeghers syndrome*, accessed at: https://www.cancer.nsw.gov.au/understanding-cancer/cancer-in-nsw/hereditary-cancers/peutz-jeghers-syndrome
[9] Cancer Research UK, 2020, Ovarian cancer, Risk factors from medical conditions.
[10] Wei, JJ, William, J, & Bulun, S, 2011, Endometriosis and ovarian cancer: a review of clinical, pathologic, and molecular aspects. International Journal of Gynecological Pathology, 30(6), 553–568, doi: 10.1097/PGP.0b013e31821f4b85.
[11] Bassiouny, D, El-Baz, MA, Tawakol M, et al, 2019, Endometriosis-associated Ovarian Cancer is a Subset With a More Favorable Outcome and Distinct Clinical-pathologic Characteristics, International Journal of Gynecological Pathology, 38(5):435-442 doi: 10.1097/PGP.0000000000000533.
[12] Sona M, Myung S, Park K, et al., 2018, Type 1 diabetes mellitus and risk of cancer: a meta-analysis of observational studies. Japanese Journal of Clinical Oncology, 48(5):426-433; Zhang D, Li N, Xi Y, et al., 2017, Diabetes mellitus and risk of ovarian cancer. A systematic review and meta-analysis of 15 cohort studies. Diabetes Research and Clinical Practice, 130:43-52; Gapstur, SM, Patel, AV, Diver, WR, et al. 2012, Type II diabetes mellitus and the incidence of epithelial ovarian cancer in the cancer prevention study-II nutrition cohort., Cancer Epidemiol Biomarkers Prev., 21(11):2000-5
[13] Kyrgiou, M, Kalliala, I, Markozannes, G, et al. 2017, Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ, j477.

oral contraception increases with the length of birth control use, with women seeing a 50 per cent reduction in risk after five years of use.[14]

- *Pregnancy and breastfeeding* — Pregnancy reduces the risk of ovarian cancer by approximately 30 per cent.[15] Ovarian cancer risk is 24-30 per cent lower in women who have ever breastfed compared to those who have never done so, and the risk decreases further with longer and more frequent breastfeeding duration.[16] The protective effect is estimated to last for 30 years. Breastfeeding and having more children is also thought to have a combined effect on decreased ovarian cancer risk.[17]

Prophylactic surgery involving the removal of ovaries and fallopian tubes can significantly reduce the risk of cancer for women with high genetic risk. A large international study known as the Hereditary Ovarian Cancer Clinical Study found women with *BRCA1* and *BRCA2* mutations who underwent prophylactic surgery experienced a 77 per cent reduction in their overall risk of death by age 70.[18]

## 1.3 Incidence and mortality

Projections of Australian Institute of Health and Welfare (AIHW) data for ovarian cancer (ICD-10 codes C56 and C57[19]) indicate that in 2020 more than 1,800 Australian women will be diagnosed with some form of ovarian cancer. By 2030, this is projected to grow to more than 2,200 per annum (Figure 1.2).

Nationally, the 5-year relative survival rate for ovarian cancer was reported by the AIHW to be 46 per cent. Within this there is variation by state and territory. For example, the latest Queensland cancer registry data indicated a statewide 5-year survival rate of 50 per cent (2017) and the Queensland Centre for Gynaecological Cancer (QCGC) reported 5-year survival rates of 52 per cent over the 2003-2012 period.

Based on national survival rates nearly 1,200 women will lose their lives to ovarian cancer this year, and by 2030 this is projected to rise to approximately 1,400 women each year.

[14] See: Havrilesky, LJ, Gierisch, JM, Moorman, PG, et al. 2103, Oral contraceptive use for the primary prevention of ovarian cancer. Evid Rep Technol Assess, 212:1-514; Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral, V, Doll, R, Hermon C, et al. 2008, Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls, Lancet, 371(9609):303-14; Moorman, PG, Havrilesky, LJ, Gierisch, JM, et al., 2013, Oral Contraceptives and Risk of Ovarian Cancer and Breast Cancer Among High-Risk Women: A Systematic Review and Meta-Analysis, J Clin Oncol., 31(33):4188-98.Oct 21; Cook, LS, Pestak, CR, Leung, ACY, et al, 2016, Combined oral contraceptive use before the first birth and epithelial ovarian cancer risk, British Journal of Cancer, doi: 10.1038/bjc.2016.400.

[15] Modugno, F, Goughnour, SL, Edwards, RP, Odunsi, K., et al, 2019, Breastfeeding factors and risk of epithelial ovarian cancer, Gynecol Oncol., 153(1): 116–122. doi:10.1016/j.ygyno.2019.01.017; Sung, HK, Ma, SH, Choi, JY, et al, 2016, The effect of breastfeeding duration and parity on the risk of epithelial ovarian cancer: a systematic review and meta-analysis, J Prev Med Public Health, 49:349-366, doi: 10.3961/jpmph.16.066

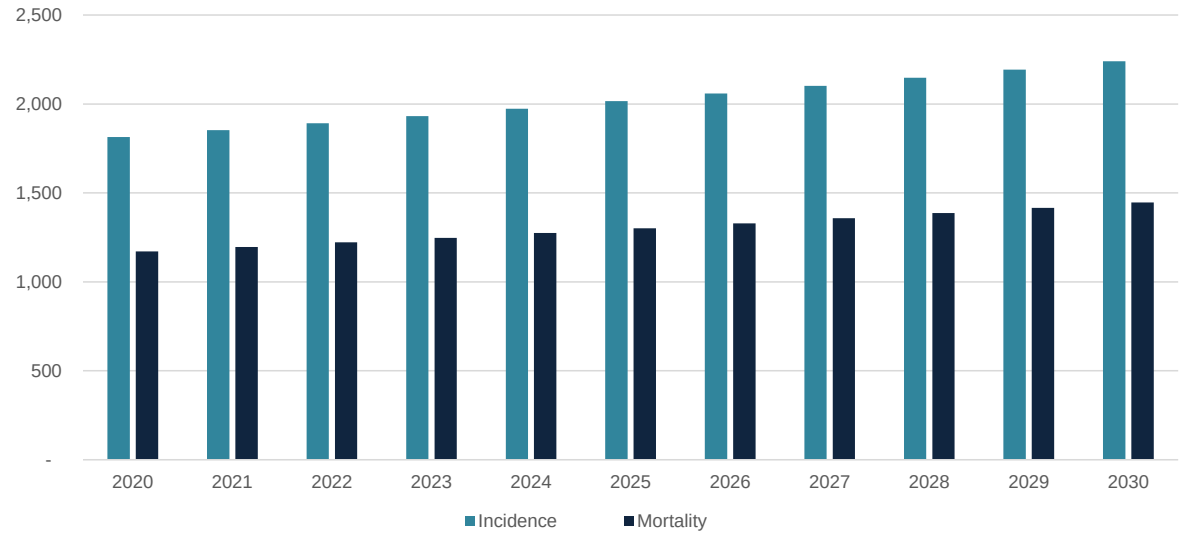
[16] Babic A, Sasamoto N, Rosner BA, et al. 2020, Association Between Breastfeeding and Ovarian Cancer Risk. JAMA Oncol., 6(6):e200421, doi:10.1001/jamaoncol.2020.0421

[17] Li, DP, Du, C, Zhang, ZM, et al. 2014, Breastfeeding and ovarian cancer risk: a systematic review and meta-analysis of 40 epidemiological studies. Asian Pac J Cancer Prev, 15(12):4829-37. Luan, NN, Wu, QJ, Gong, TT, et al. 2013, Breastfeeding and ovarian cancer risk: a meta-analysis of epidemiologic studies. Am J Clin Nutr, 98(4):1020-31. Chowdhury, R, Sinha, B, Sankar, MJ, et al. 2015, Breastfeeding and maternal health outcomes: a systematic review and meta-analysis, Acta Paediatr. 104(467):96-113. Sung, HK, Ma, SH, Choi, JY, et al. 2016, The Effect of Breastfeeding Duration and Parity on the Risk of Epithelial Ovarian Cancer: A Systematic Review and Meta-analysis, J Prev Med Public Health, 49(6):349-366.

[18] Finch, AP, Lubinski, J, Moller, P, et al., 2014, Impact of Oophorectomy on Cancer Incidence and Mortality in Women in with a BRCA1 or BRCA2 Mutation, J Clin Oncol, doi: 10.1200/JCO.2013.53.2820.

[19] ICD-10 refers to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), which is a medical classification list by the World Health Organization (WHO). C56 is the code used to report ovarian cancer statistics and C57 is the code used for fallopian tube cancer. Incidence for C57 increased more than threefold from 2005 to 2015 while C56 has increased by approximately nine per cent. This reflects the improved understanding of cells of origin for ovarian cancer in that time.

**Figure 1.2: Forward projections of ovarian cancer incidence and mortality 2020-2030**



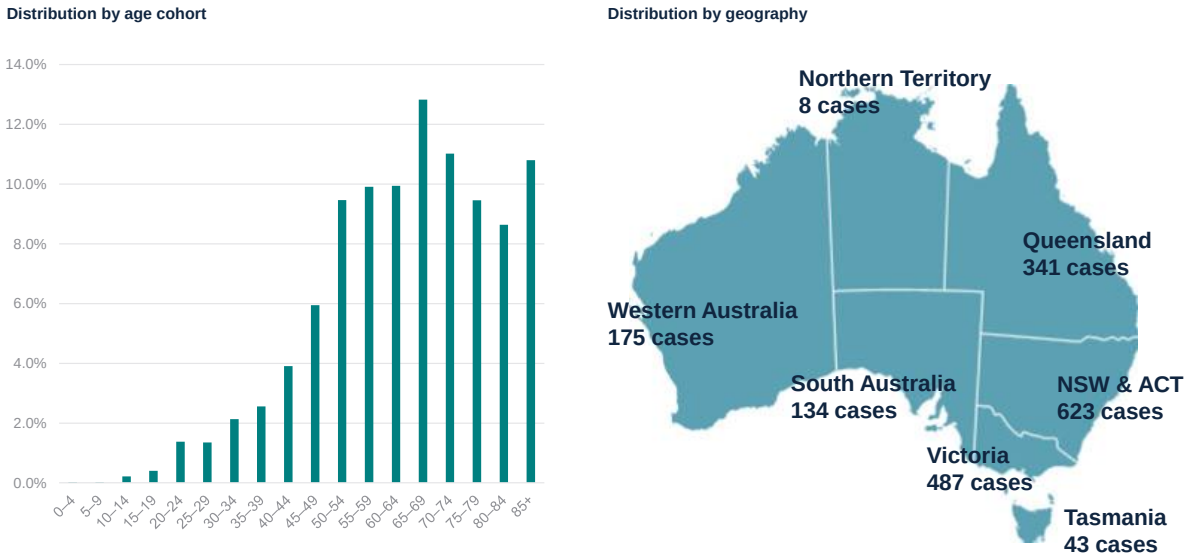

Source: Insight Economics projections based on Australian Institute of Health and Welfare data from 2019. 2015 Australian Cancer Database pivot table, ICD-10 C56 and C57. Canberra: AIHW. http://www.aihw.gov.au/cancer-data. 1-year survival estimated to be 76 per cent, 5-year survival estimated to be 46 per cent and 10-year conditional survival for women already survived 5 years was estimated to be 77 per cent.

Ovarian cancer affects women of all ages, although the risk of ovarian cancer increases from age 50 and the median age of onset is 65. Younger women diagnosed with ovarian cancer face additional challenges around fertility. Because treatment usually requires the removal of the uterus and both ovaries, women will be unable to have children, and may also experience severe side effects associated with the early onset of menopause.

Women are diagnosed in every state and territory in Australia. NSW reports the highest number of new cases each year (620 women) while fewer than 10 are typically diagnosed in the Northern Territory.

Figure 1.3 shows the distribution of incidence by age and geography.

**Figure 1.3: Distribution of incidence by age and geographic location (2020)**




Source: Insight Economics projections based on Australian Institute of Health and Welfare data from 2019. 2015 Australian Cancer Database pivot table, ICD-10 C56 and C57. Canberra: AIHW. http://www.aihw.gov.au/cancer-data.

Taken together, these data show that over the next 10 years more than 22,000 Australian women are expected to be diagnosed with some form of ovarian cancer, and based on current mortality rates nearly 14,000 of these diagnoses are expected to be fatal.

Globally, World Health Organization 2018 data for ovarian cancer based on ICD-10 C56[20] indicate that global incidence of ovarian cancer today likely exceeds 322,000 new cases per annum (Figure 1.4).

**Figure 1.4: Global incidence of ovarian cancer by region**


Source: International Agency for Research on Cancer, 2018, WHO, Cancer Today, C56 data reported by continent and selected countries. Data for C57 was not reported. Note Australian data based on aggregate of AIHW data for C56 and C57 in 2018 was 1,700 new cases; 2020 figures are included here due to confusion arising from current AIHW statistics and 2018 data.

Over the next 10 years more than 3.6 million women will be diagnosed with ovarian cancer worldwide, and more than 2.2 million of those women will lose their lives to ovarian cancer.

## 1.4 Ovarian cancer sub-types

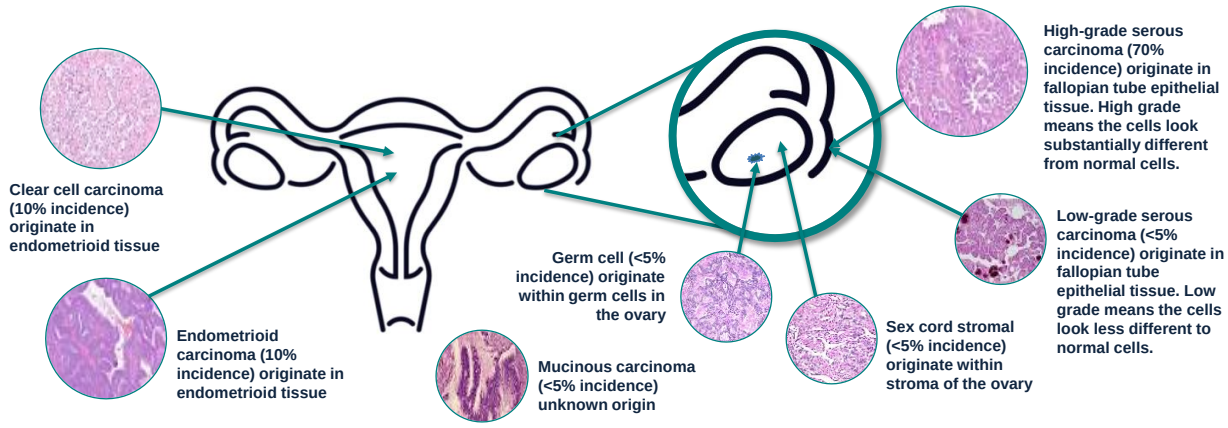
Like many cancers, ovarian cancer is now understood to represent a spectrum of disease, with seven major sub-types being characterised in the last decade alone.

Whilst gaps in the understanding of ovarian cancer biology remain, it is currently estimated that about 85 to 90 per cent of all ovarian cancers arise from mutations in epithelial[21] cells. Over many cycles of ovulation, the ovarian surface epithelium undergoes repeated disruption and repair, as the ovary ruptures to release an ovum (egg) each month. This causes the proliferation of cells and increases the probability of mutation (cancer). Epithelial cells may also become trapped in tissue around the ovaries, leading to cysts, DNA damage and a risk of mutation.

[20] Data reporting for ovarian cancer is challenged by new definitional issues, with ovarian cancer originating in the fallopian tubes increasingly coded as C57. Within Australia, for example, ovarian cancer originating in the fallopian tubes now accounts for approximately 15 per cent of all new cases, increasing from only 5 per cent of cases just 10 years ago.

[21] Epithelium is one of the four basic types of tissue with the other three types of tissue being connective tissue, muscle tissue and nervous tissue. Epithelial tissues line the outer surfaces of organs and blood vessels throughout the body, as well as the inner surfaces of cavities in many internal organs. Examples of epithelial tissues include the epidermis, the outermost layer of the skin, cells lining the intestinal tract, and alveoli (air sacs) in our lungs. All glands are made up of epithelial cells. Functions of epithelial cells include secretion, selective absorption, protection, transcellular transport, and sensing. Epithelial cells are categorised by their shape (squamous, columnar, cuboid) and the extent of layering (simple, stratified). Epithelial cells of the ovaries are classified as simple cuboidal and fallopian tubes are simple columnar epithelial cells. Epithelial layers contain no blood vessels, so they must receive nourishment via diffusion of substances from the underlying connective tissue.

**Figure 1.5: Major ovarian cancer sub-types**




Source: Insight Economics

The major sub-types of epithelial ovarian cancer, shown in Figure 1.5, include:

- High-grade serous carcinomas
- Low grade serous carcinomas
- Clear cell carcinomas
- Endometrioid carcinomas
- Mucinous carcinomas.

Ovarian cancers that do not arise in epithelial cell tissues include germ cell and sex cord stromal ovarian cancers. These sub-types originate from within the ovary and combined are estimated to account for approximately five per cent of all ovarian cancers.

## 1.5 How is ovarian cancer diagnosed and treated?

Ovarian cancer rarely causes symptoms until it is at an advanced stage. Women with ovarian cancer often present to a GP with non-specific symptoms of abdominal pain and bloating. Suspicion of cancer may result in referral to a specialist, either a gynaecological oncologist or a medical oncologist for diagnosis and treatment. This may involve blood tests and imaging diagnostics and, when the diagnosis is confirmed, surgery and chemotherapy.

The following sections provide a short summary of a patient's cancer experience from presentation to the GP to treatment, disease management and survivorship based on current clinical practice in Australia.

### *Presentation to a GP*

Women with ovarian cancer will typically present to their GP with symptoms including:

- Feeling bloated
- Indigestion or heartburn
- Pain in the abdomen
- Trouble eating, feeling full fast
- Feeling the need to urinate often.

These symptoms will be new (experiencing these symptoms for less than a year) and frequent (occurring more than 12 days per month). A woman may experience other symptoms if the cancer mass becomes large or there is fluid build-up in the abdomen.

The GP may perform a series of general health and blood tests. These tests may include:

- Family and medical history
- Abdominal and pelvic exam
- Blood chemistry with liver function tests and serum protein
- Medical imaging with computed tomography (CT) scans or ultrasound imaging.

***Referral to a specialist for diagnosis through clinical and surgical staging***

If cancer is suspected, the GP will refer the patient to an oncologist, who may order further tests to establish the diagnosis of cancer and estimate the stage.

These tests could include:

- Blood and tumour marker tests for CA-125 and sometimes other markers such as inhibin, β-hCG, Alpha-fetoprotein, LDH, CEA, Ca19-9, and HE4
- Imaging of the abdomen and pelvis using ultrasound, CT, positron emission tomography (PET), and/or MRI
- Biopsy of suspected cancer mass, or drainage of ascites fluid from the abdomen.

Due to the non-specific nature of the symptoms caused by ovarian cancer, and notably a lack of symptoms in early stages, most women are diagnosed with advanced stages of the disease. This late stage diagnosis contributes majorly to their subsequent poor overall survival. Table 1.1 provides a summary of the major stages of ovarian cancer based on International Federation of Gynecology and Obstetrics (FIGO) stage descriptions and their frequency, as well as the expected 5-year survival based on the stage of diagnosis.

**Table 1.1: Ovarian cancer stages – descriptions, proportion of cases and 5-year survival by stage**

| | Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|---|
| **Stage Description** | The cancer is in one ovary, and the tumour is confined to the inside of the ovary; or the cancer is in one fallopian tube, and is only inside the fallopian tube (IA)<br>The cancer is in both ovaries or fallopian tubes but not on their outer surfaces (IB)<br>The cancer is in one or both ovaries or fallopian tubes and the tissue surrounding the tumour broke during surgery (IC1)<br>The cancer is on the outer surface of at least one of the ovaries or fallopian tubes or the capsule (tissue surrounding the tumour) has ruptured (IC2)<br>Cancer cells are found in the fluid (ascites) or washings from the abdomen and pelvis. (IC3) | Cancer has spread to uterus and surrounding ovary, fallopian tube tissue but not the lymph nodes (IIA)<br>Cancer has spread to other pelvic organs including bladder, sigmoid colon or rectum but not the lymph nodes (IIA) | Cancer is present in ovaries and/or fallopian tube tissue OR there is primary peritoneal cancer<br>– AND it has invaded other pelvic tissues and lymph nodes only (IIIA1)<br>– AND it has spread or grown into organs outside the pelvis (IIIA2) but cancer is not visible to surgeon<br>– AND the deposits of cancer are large enough for the surgeon to see, but are no bigger than 2cm across (IIIB)<br>– AND the deposits of cancer are larger than 2cm across and may be on the outside (the capsule) of the liver or spleen (IIIC). | Cancer cells are found in the fluid around the lungs (called a malignant pleural effusion) with no other areas of cancer spread such as the liver, spleen, intestine, or lymph nodes outside the abdomen (M1A).<br>The cancer has spread to the inside of the spleen or liver, to lymph nodes other than the retroperitoneal lymph nodes, and/or to other organs or tissues outside the peritoneal cavity such as the lungs and bones (M1B). |
| **% of new cases** | **19%** | **12%** | **59%** | |
| **5-year survival** | **92%** | **75%** | **29%** | |

Source: Stage descriptions based on International Federation of Gynecology and Obstetrics; 5-year survival based on American Cancer Society statistics accessed in March 2020 and % of new cases based on Cancer Institute NSW data accessed in March 2020.

Critically, while the five-year survival rate for ovarian cancer overall is 46 per cent, this likely overestimates the survival rate for women diagnosed with the most common sub-type, high-grade serous carcinoma. An overview of ovarian cancer sub-types reported:[22]

- Approximately 95 per cent of patients diagnosed with advanced stage (III-IV) disease have serous carcinomas, which have an average five-year survival rate of only 29 per cent.
- Approximately 50 to 66 per cent of mucinous carcinomas are diagnosed in stage I.
- Endometrioid carcinoma is the most common sub-type diagnosed at stage I, probably constituting at least 50 per cent of such cases. Most endometrioid carcinomas are diagnosed in stage I or II.
- Between 20 and 50 per cent of low-stage ovarian carcinomas are clear cell carcinomas and, unlike serous carcinomas, these are rarely disseminated at presentation.

[22] Soslow, Robert A. M.D. Histologic Subtypes of Ovarian Carcinoma: An Overview, International Journal of Gynecological Pathology: April 2008 - Volume 27 - Issue 2 - p 161-174 doi: 10.1097/PGP.0b013e31815ea812

### *Treatment*

Once the diagnosis of ovarian cancer is confirmed, a woman may have a range of treatments, which usually include surgery and chemotherapy. Less commonly, women may be candidates for a targeted therapy or immunotherapy, which may be administered after surgery and chemotherapy. The specialist will also identify supportive care treatments for the management of side-effects of the cancer and treatment. In addition, following the confirmation of diagnosis, genetic testing for *BRCA* gene mutations may be done. These tests may involve a blood test or, in some cases, the tumour cells themselves may be tested for *BRCA* gene mutations. In some cases, DNA mismatch repair (MSI-H, dMMR) may also be undertaken.

Current Australian clinical practice for first line treatment generally involves the following:

- *Surgery* — Surgery will usually include:
  - Unilateral salpingo-oophorectomy, which is the removal of only one ovary and fallopian tube. This is fertility-sparing surgery intended to enable women to start or complete their families, and almost never performed except in rare circumstances
  - Bilateral salpingo-oophorectomy, which is the removal of both ovaries and fallopian tubes
  - Total abdominal hysterectomy to remove the uterus, including the cervix
  - Cytoreductive surgery or 'debulking' surgery, which is the removal of any visible cancer within the abdomen. Sometimes this will require removal of part of the bowel.

  Cancer removed at the time of surgery will be examined by a specialist pathologist, who will report on the type of cancer, the extent of spread, and the effect of pre-operative chemotherapy. The cancer will also be assigned a grade, which reflects how aggressively the cancer is growing. Low-grade cancer cells may appear similar to normal cells and may be slow growing, while high-grade cancer cells may look different to normal cells.
- *Chemotherapy* — Women with ovarian cancer are treated with chemotherapy, which is typically administered intravenously to kill cancer cells. In about 50 per cent of cases, chemotherapy is given before surgery to reduce the amount of cancer present. Chemotherapy drugs include:
  - Platinum chemotherapy agents, which directly damage the DNA in the cancer cell. These include carboplatin, or less commonly, cisplatin
  - Taxanes prevent cancer cell division, and the major taxanes used are paclitaxel and docetaxel.

  Chemotherapy is generally administered intravenously, but less commonly can be injected into the peritoneal cavity.
- *Targeted therapies* — Some sub-types of ovarian cancer may have features that allow for the use of drugs that target certain features of the cancer cell.
  - *Angiogenesis inhibitors* — Angiogenesis inhibitors are targeted therapies that limit the growth of blood vessels that 'feed' the cancer. Angiogenesis inhibitors can be monoclonal antibodies or small molecule inhibitors. Bevacizumab, a monoclonal antibody, is an example of an angiogenesis inhibitor, and is sometimes administered if surgery was not successful at removing all of the cancer.

  - *PARP inhibitors* — Normally, *BRCA1* and *BRCA2* gene products repair DNA damage in cells. If the *BRCA* genes are mutated, however, then cancer cells use poly(ADP-ribose) polymerase (PARP) proteins for this repair. PARP inhibitors are drugs that block the PARP protein from repairing damage in the cancer cell's DNA, thereby causing the cancer cell to die. PARP inhibitors can improve outcomes for women with *BRCA1* or *BRCA2* germline mutations, or those with a *BRCA* mutation in the tumour. The major PARP inhibitor available in Australia is olaparib. PARP inhibitors are not yet available as a first line therapy in Australia.

- *Immunotherapies* — Immunotherapies are a class of therapies that take advantage of a woman's own immune system to help kill cancer cells. The role of immunotherapies in ovarian cancer is not fully established; however, pembrolizumab, an immune checkpoint inhibitor, has shown promise among gynaecological cancers that exhibit deficiencies in certain repair proteins (MSI-H or dMMR). Research continues to investigate the role of immunotherapies in the treatment of ovarian cancer.

### *Disease recurrence*

First line therapy with surgery and chemotherapy results in complete remission in more than 80 per cent of cases, meaning there is no evidence of cancer on imaging or in blood tests. Despite this, more than 80 per cent of women experience a recurrence of cancer.[23] If recurrence of ovarian cancer (relapse) is suspected, blood and imaging tests will be conducted to determine the extent of cancer and develop a treatment plan. While sometimes surgery may be possible, most commonly chemotherapy is re-administered.

If more than 12 months has passed since treatment finished then the cancer is termed 'platinum-sensitive', meaning that the cancer will likely respond again to platinum chemotherapy. If the cancer returns less than six months after initial treatment, the cancer is termed 'platinum-resistant' and alternative chemotherapy drugs will be tried. If the interval is 6-12 months, then treatment may include a combination of platinum and non-platinum drugs.

With repeated relapse and chemotherapy treatments, the cancer will change and will eventually become resistant to chemotherapy (chemoresistant). Chemoresistance is responsible for treatment failure and mortality for more than 90 per cent of patients with advanced stage cancer.[24] While different chemotherapy agents can be used, cancers will generally become resistant to all chemotherapy drugs.

Occasionally, hormone therapy is used to slow cancer growth. These include drugs such as anti-estrogens (tamoxifen), aromatase inhibitors, which lower estrogen levels (anastrolzole, exemestane, or letrozole), LHRH agonists (leuprolide acetate) or progestins (megestrol acetate) and are most useful in low-grade cancers.

In addition to considering standard chemotherapy options, women may consider participation in a clinical trial of new drugs or drug combinations.

### *Supportive care, survivorship and long-term follow-up care*

Supportive care is care given to improve the quality of life of patients diagnosed with and treated for ovarian cancer.

[23] Bowtell, DD, Böhm, S, Ahmed, AA, Aspuria, PJ, et al, 2015, Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer, Nat Rev Cancer, 15(11):668-679, doi: 10.1038/nrc4019.
[24] Brasseur, K., Gévry, N., & Asselin, E. (2017). Chemoresistance and targeted therapies in ovarian and endometrial cancers. Oncotarget, 8(3), 4008–4042. https://doi.org/10.18632/oncotarget.14021; Agarwal R, Kaye SB. Ovarian cancer: strategies for overcoming resistance to chemotherapy. Nature Reviews Cancer. 2003;3:502–16.

The goal of supportive care is to prevent or treat as early as possible:

- The symptoms of a disease and side effects caused by treatment
- Any physical, psychological, social, financial and/or spiritual problems related to a disease or its treatment.

The Cancer Council and National Cancer Expert Reference Group have underlined the importance of supportive care services planning and delivery through the development and endorsement of optimal care pathways for cancer.

Survivorship care is closely related to supportive care. Technically, a woman is a survivor of ovarian cancer from the moment she is diagnosed but in practice a survivorship care plan refers to a detailed plan given to a patient after active treatment ends.

Following the completion of active treatment, women will receive follow-up care in the form of check-ups every 2-4 months for the first two years, every 3-6 months for the following three years and once a year after five years. Follow-up tests may include physical and pelvic exams, and blood tests, including tumour markers. In addition, a woman's ongoing supportive care needs should be assessed. The long-term supportive care needs of ovarian cancer survivors will be different for every woman and may include support for managing the fear of recurrence, financial support, and/or referrals to specialists and recommendations for a healthy lifestyle, such as changes in diet and exercise and quitting smoking.

## 1.6 Ovarian cancer is a low-survival cancer with limited funding for research

Without tools for prevention or early detection, and with the limitations of current treatment, ovarian cancer remains one of the most lethal cancers affecting women today. This is inextricably linked to the limited research funding in recent decades.

The nexus between poor survival outcomes and funding limitations comes into sharpest relief when considered against the backdrop of research breakthroughs and funding trends in the wider cancer research landscape. This section contextualises ovarian cancer survival outcomes relative to other cancers and illustrates why research funding is so critical.

### *Understanding the wider cancer research landscape*

Unquestionably, investment in cancer research translates into significant improvements in survival. Survival rates across all cancers improved 44 per cent between 1975 and 2015, transforming many cancers from terminal illnesses into chronic diseases or preventing the occurrence of cancer altogether. In particular, a number of major cancers have seen significant improvements in the modern era of cancer research:[25]

- Breast cancer five-year survival rates improved from 74.8 per cent in 1975 to 91.3 per cent in 2015
- Prostate cancer five-year survival rates improved from 67.8 per cent in 1975 to 98.6 per cent in 2015
- Colon cancer survival rates improved from 49 per cent in 1975 to 66.2 per cent in 2015

[25] NCI SEER, 2016, Age-Adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival (Percent), accessed at: https://seer.cancer.gov/archive/csr/1975_2016/results_merged/topic_survival.pdf

- Leukaemia survival rates collectively almost doubled from 34.1 per cent in 1975 to 65.8 per cent in 2015
- Non-Hodgkin lymphoma survival rates improved from 46.5 per cent in 1975 to 74.7 per cent in 2015
- Melanoma survival rates improved from 81.9 per cent in 1975 to 94.2 per cent in 2015.

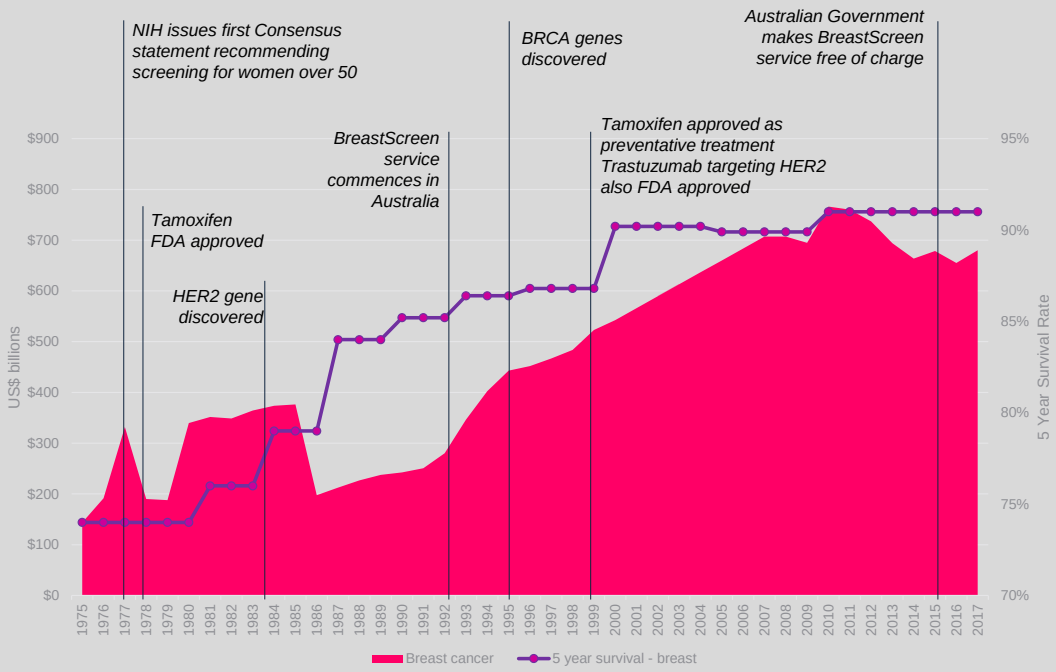
In addition, the survival outcomes for many cancers have been improved by the development of screening programs, including programs for breast cancer, skin cancer, colorectal cancer and cervical cancer.

These advances have been realised through significant and sustained funding for high-impact research since the 1970s. For example, more than $106 billion in research funding has been committed to cancer research through NCI and the NIH since 1975. Box 1.1 highlights some of the significant research success stories that have been realised through the modern era of cancer research.

**Box 1.1: Research funding success — case studies in cancer research breakthroughs made possible by sustained programs of work**

**Case study: Breast cancer breakthroughs**

Breast cancer is the most common cancer impacting women in Australia and globally. The chance of a woman developing breast cancer up to age 85 is 1 in 8. In 2020, AIHW estimates nearly 20,000 Australians will be diagnosed with breast cancer. When breast cancer is detected early, women have a much greater chance of being treated successfully and for most women the cancer will not come back after treatment. The 5-year relative survival rate is 99 per cent when detected and treated while the tumour is localised. If the cancer is not detected early and has spread to the lymph nodes (regional) or to other parts of the body (distant) the survival rate is 86 per cent and 27 per cent respectively. Today the 5-year survival rate for breast cancer is 91 per cent. The breakthroughs in breast cancer are no accident; rather they are the product of a decades-long campaign to fund high-impact research and drive health service practice changes.




Beginning in the 1970s, the breast cancer community rallied to raise significant funding for research that led to the first NIH Consensus recommendation in 1977 for routine mammographies for women. Research for breast cancer successively expanded its understanding of the underlying biology of the disease, including the discovery of the *HER2* gene in rats in 1984 and in humans in 1986, and the *BRCA* genes in 1994. Following this improved understanding of disease biology, treatment options expanded, from Tamoxifen in 1978 to FDA approval of Anastrozole in 1996, the use of Tamoxifen as a preventative therapy in 1998 and Trastuzumab as

an *HER2* targeted therapy in 1998. Radiology and lumpectomies were found to be as effective as mastectomies, but as genetic risk testing related to the *BRCA* gene has improved the use of prophylactic surgery in women with *BRCA* mutations has also increased.

The survival improvements have been realised on the back of a sustained research effort supported by significant funding from governments and the wider community. Roughly 15 per cent of all NCI and NIH funding alone has been allocated to breast cancer since 1975.

**Case study: Cervical cancer breakthroughs**

Cervical cancer stands out as another significant success story of cancer research. Cervical cancer is a cancer arising from the growth of abnormal cells in a woman's cervix (Figure 1.1). It is estimated that the risk of a female being diagnosed with cervical cancer by her 85th birthday is 1 in 494. In 2020, the AIHW estimated just under 1,000 Australian women will be diagnosed with cervical cancer.

Cervical cancer was among the first cancers where early biology research identified the potential for population screening to identify the cancer early, although this research breakthrough was not implemented in clinical practice until the 1990s. A national cervical cancer screening program was introduced at the same time as a breast cancer screening program in 1991.

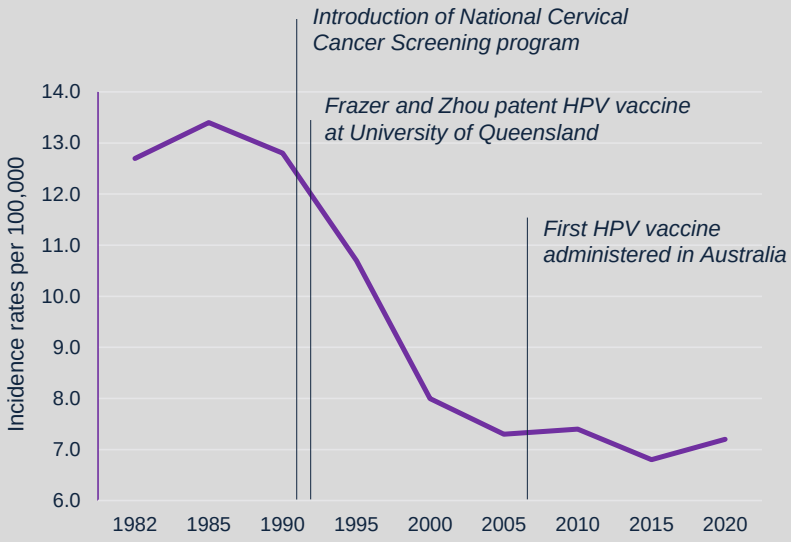
Cervical cancer is also distinguished as the first cancer for which a vaccine was developed to prevent its occurrence. Research leading to the development of the vaccine began in the 1980s, when Professor Ian Frazer began his work in viral immunology, focused on exploring associations between the human papillomavirus (HPV), the human immunodeficiency virus (HIV) and dysplastic changes in men with an autoimmune deficiency illness. This helped to confirm in 1984 that HIV was the cause of AIDS, but it also led to a discovery that the presence of an HPV infection appeared to be inducing pre-cancerous cells.

In 1991, Professor Ian Frazer and Jian Zhou developed and patented the basic technology behind the HPV vaccine against cervical cancer at the University of Queensland. The HPV vaccine was the first vaccine designed to prevent a cancer.

Fifteen years later, following extensive development by industry, the first vaccine against cervical cancer was administered in Australia in 2006. Since 2006, more than 23 million people have been vaccinated in more than 70 countries.

The introduction of screening to detect precursor lesions of disease has seen the incidence of cervical cancer more than halve since the 1980s. The recent introduction of the HPV vaccine into clinical practice will continue to reduce the incidence of this cancer and improve outcomes for women who might otherwise have been diagnosed with this disease. AIHW has reported the HPV vaccine has already contributed to a decrease in pre-cancerous cervical lesions in young women and from 2013 Australian schoolboys were made eligible for the vaccine free of charge.

Looking forward, the World Health Organization has drafted a strategic plan for the progressive elimination of cervical cancer through a global scale-up of screening and vaccination from 2020.

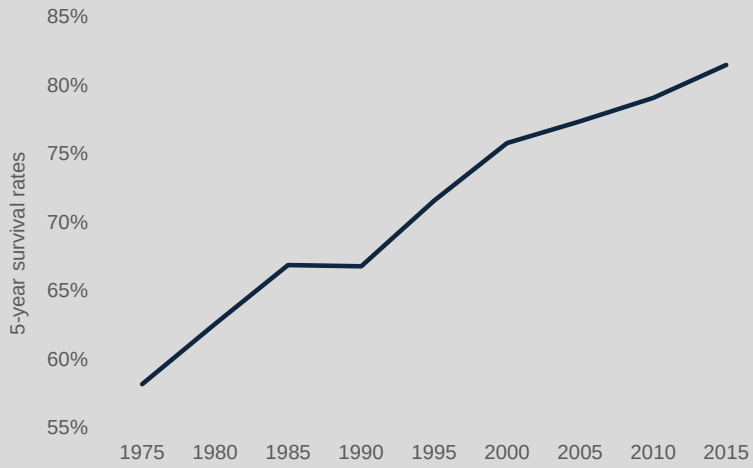



**Case study: Paediatric cancer breakthroughs**

The impact of sustained, high-impact research on cancer survival outcomes is perhaps most evident among paediatric cancers. For children, research is the standard of care, in part because many cancer therapies are developed for adults and therefore provided off-label to children, adolescents and young adults. Children are

treated at highly-specialised centres that work together as part of international research consortia. This research as a standard of care approach has delivered significant improvements across many childhood cancers, with many children achieving long-term cure rates from their cancer. In the past 40 years, the overall survival rate for children's cancer has increased from 10 per cent to nearly 90 per cent today. Research shows that the average per annum reduction in the mortality rate for children diagnosed with cancer was 2.6 per cent per year from 1975 to 1995.

While there is still much work to be done to improve outcomes for children diagnosed with cancer, and many children suffer from rare sub-types that cut their lives down far too soon, the fact that many children go on to lead productive lives is one of the major achievements of the modern cancer research era and is a product of sustained investment in collaborative, high impact research.



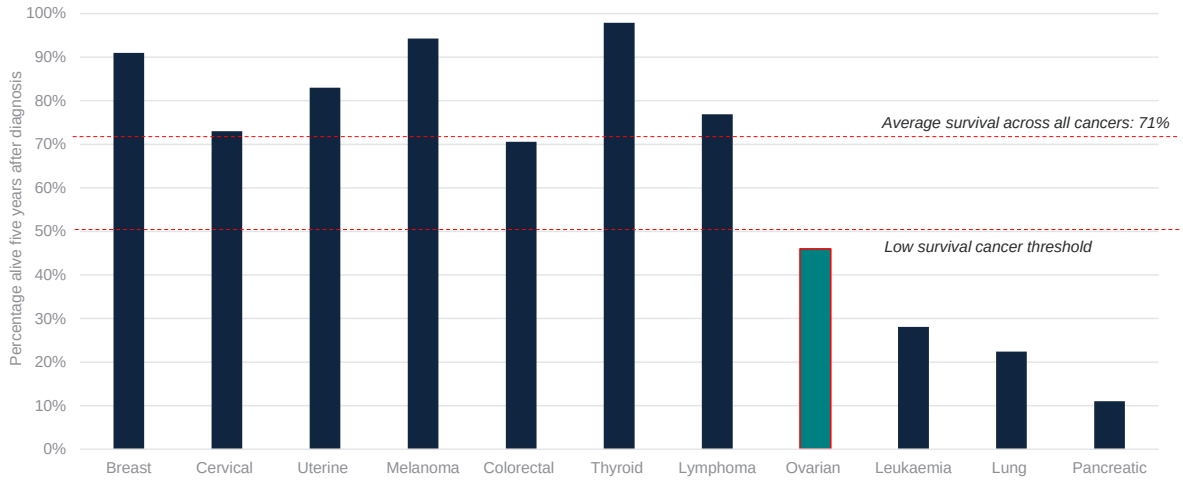

Source: NCI SEER, 2016, Age-Adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival (Percent), https://seer.cancer.gov/archive/csr/1975_2016/results_merged/topic_survival.pdf; American Cancer Society, 2020, Survival Rates in Breast Cancer, accessed at: https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html; Breast Cancer Screening. NIH Consensus Statement 1977 Sep 14-16;1(1):5-8. https://consensus.nih.gov/1977/1977BreastCancer001html.htm; Breast Cancer Screening for Women Ages 40-49. 1997 January 21-23;15(1):1-35. https://consensus.nih.gov/1997/1997BreastCancerScreening103html.htm; Cancer Institute NSW, 2019, A history of global cancer breakthroughs, https://www.cancer.nsw.gov.au/learn-about-cancer/cancer-breakthroughs; Unger, JM, Cook, E, Tai, E, and Bleyer, A, 2016, The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies, ASCO Educational Book, accessed at: https://ascopubs.org/doi/full/10.1200/EDBK_156686; Frazer, IH, Crapper, RM, Medley, G., Brown, TC, and Mackay, IR, 1986, Association between anorectal dysplasia, human immunodeficiency virus infection in homosexual men, The Lancet, 328(8508):657-660, doi: 10.1016/S0140-6736(86)90168-6; Australian Institute of Health and Welfare (AIHW) 2020 Cancer Data in Australia; Canberra: AIHW. https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/, Cervical cancer, age-specific rates (per 100,000); Smith, MA, Lew, JB., Soerjomataram, I, Castle, PE, Bray, F, and Canfell, K, 2019, Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. The Lancet. Oncology, 20(3), 394–407, doi: 10.1016/S1470-2045(18)30836-2; Cancer Council NSW, 2020, CISNET Model Profile, https://cisnet.flexkb.net/mp/pub/CISNET_ModelProfile_CERVICAL_CCNSW_20200406.pdf#pagemode=bookmarks; Canfell K., 2019, Towards the global elimination of cervical cancer. Papillomavirus research, 8, 100170. Doi: 10.1016/j.pvr.2019.100170; Brotherton, JML, and Bloem, PN,, 2018, Population-based HPV vaccination programmes are safe and effective: 2017 update and the impetus for achieving better global coverage, Best Pract Res Clin Obstet Gynaecol.,47: 42-58.

### *Ovarian cancer remains a low-survival cancer with limited research funding*

While survival rates for other cancers have improved since 1975, for women diagnosed with ovarian cancer today, the 1-year relative survival remains at 78 per cent, with a 5-year relative survival of only 46 per cent.[26] Many of those surviving five years are still fighting recurrent disease. This compares to 5-year survival rates of 91 per cent for women diagnosed with breast cancer, 83 per cent for uterine cancer, and 74 per cent for cervical cancer (Figure 1.6), making ovarian cancer the most fatal of all gynaecological cancers, and one of the most fatal of all forms of cancer affecting women today.

[26] AIHW, 2020, Cancer data in Australia, updated 2 June 2020, accessed at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data; Cancer Council Australia, Ovarian cancer, https://www.cancer.org.au/about-cancer/types-of-cancer/ovarian-cancer.html.

**Figure 1.6: 5-year survival rates for women across commonly diagnosed cancers in women**

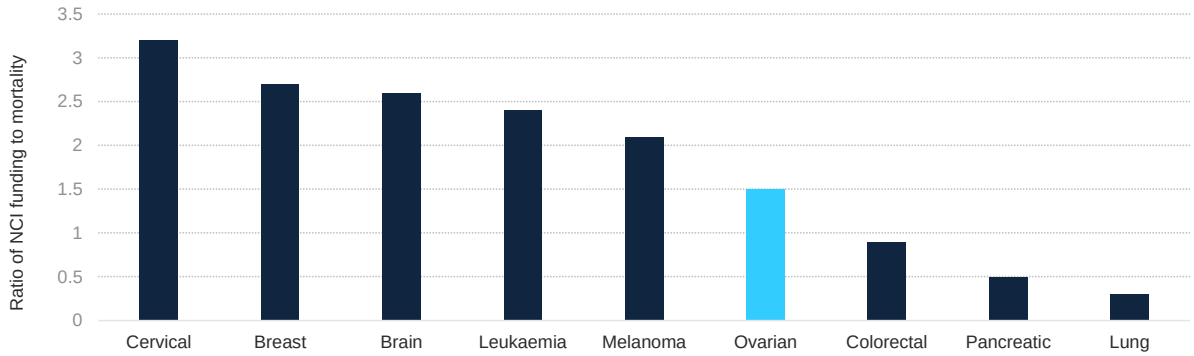



Source: AIHW, 2020, Cancer data in Australia, Relative 5-year survival, updated 2 June 2020, accessed at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data. Note leukaemia survival rates reported here ae the five-year relative survival rates for AML and lymphoma survival rates are survival rates reported here ae the five-year relative survival rates for Non-Hodgkin lymphoma. Low cancer survival threshold based on AIHW and Cancer Australia submissions to the Select Committee into Funding for Research into Cancers with Low Survival Rates.

As a result, ovarian cancer was identified in 2017 by Cancer Australia as one of eight key 'low-survival' cancers impacting Australian communities today.[27]

This persistent low survival rate is explained in large part by a history of limited funding. For example, in 2012, analysis of NCI funding highlighted the challenges related to underfunding of some cancers given their poor survival outcomes (Figure 1.7). Breast cancer, for example, has received funding from NCI/NIH at seven times the rate of ovarian cancer since 1992. Given the significant volume of community giving alongside government funding it is likely this substantially underestimates the difference in funding levels observed.

**Figure 1.7: NCI funding relative to mortality rates for selected cancers (2012)**

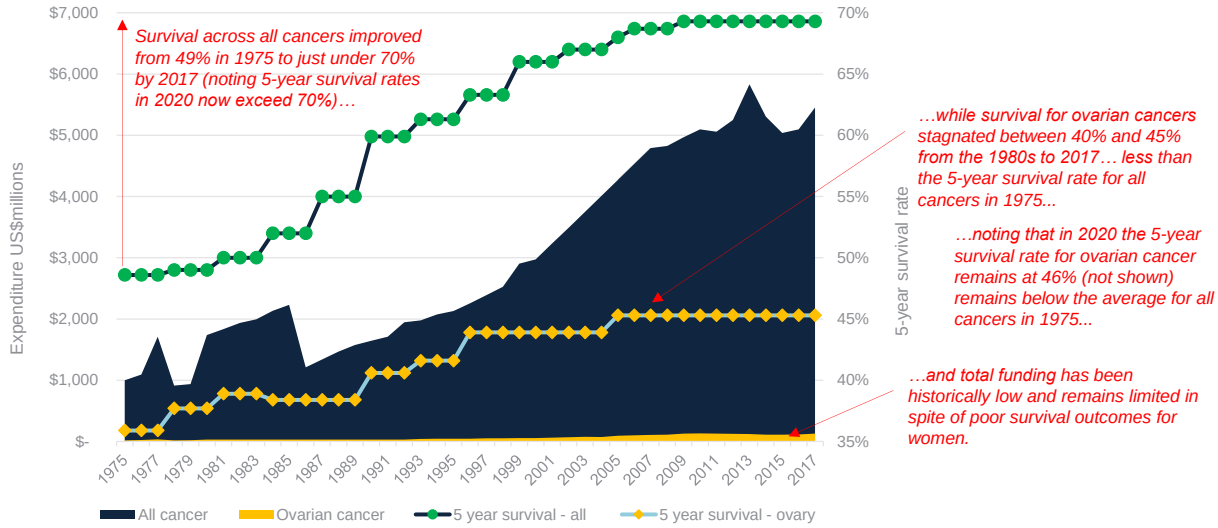



Source: Carter, AJ, and Nguyen, CN, 2012, A comparison of cancer burden and research spending reveals discrepancies in the distribution of research funding, BMC public health, 12, 526. doi: 10.1186/1471-2458-12-526.

[27] Commonwealth of Australia, 2017, Select Committee into Funding for Research into Cancers with Low Survival Rates, p2, accessed at: https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Funding_for_Research_into_Cancers/FundingResearchCancers/Report.

As a result, the 5-year survival rate of 46 per cent for ovarian cancer in Australia in 2020 is still lower than the average 5-year survival rate from all cancers observed in 1975 (Figure 1.8).

**Figure 1.8: Benchmarking funding and survival outcomes for ovarian cancer against all cancers ($US, 1975-2017)**




Source: NCI Budget Factbook Archives 1975-2017, accessed at www.cancer.gov.au/about-nci/budget/factbook/archive. NCI SEER, 2016, Age-Adjusted SEER Incidence and U.S. Death Rates and 5-Year Relative Survival (Percent), https://seer.cancer.gov/archive/csr/1975_2016/results_merged/topic_survival.pdf.

Notably, in 2012, the USA Congress implemented legislation to require the National Cancer Institute to develop a scientific framework for research on 'recalcitrant cancers', defined as a cancer with a 5-year survival rate below 50 per cent.[28] Similarly, the Senate Select Committee recommended in 2017 that the Australian Government develop a comprehensive, Australia-wide strategy to address low-survival cancers, with the explicit goal of increasing the 5-year survival rates for those cancers to above 50 per cent by 2027.[29]

There is an urgent need to review research funding for ovarian cancer and to identify key areas of funding need going forward to support the development of an improved strategy to reduce the significant mortality from this cancer impacting women in Australia and around the world.

[28] Congress.gov, H.R.733 - Recalcitrant Cancer Research Act of 2012, https://www.congress.gov/bill/112th-congress/house-bill/733
[29] Senate Select Committee, 2017, *Funding for Research into Cancers with Low Survival Rates*.

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## Chapter 2

# The research landscape for ovarian cancer

*Ovarian cancer research is a globally collaborative endeavour bringing together governments, industry, NGOs and individuals.*

*Major funding for ovarian cancer research originates in the United States, with the National Cancer Institute and National Institutes of Health, alongside the US Department of Defense's Ovarian Cancer Research Program accounting for the majority of funding for ovarian research each year across all phases of research.*

*Charitable foundations are important investors alongside governments and substantially expand total research funding for ovarian cancer, while industry is the major funder of new therapy development.*

*This chapter maps the Australian and international research landscape for ovarian cancer over time and by research phase. It identifies funding by research phase and benchmarks total funding for ovarian cancer globally against a range of cancers to demonstrate the need for an increase in funding to deliver similar improvements in survival outcomes.*

## 2.1 Who funds ovarian cancer research? Mapping the major funders of ovarian cancer globally

The vast majority of funding for ovarian cancer research originates in the United States, and is comprised of significant funding by governments, US-based biopharmaceutical companies and the non-government sector, which includes charitable foundations and other philanthropy.

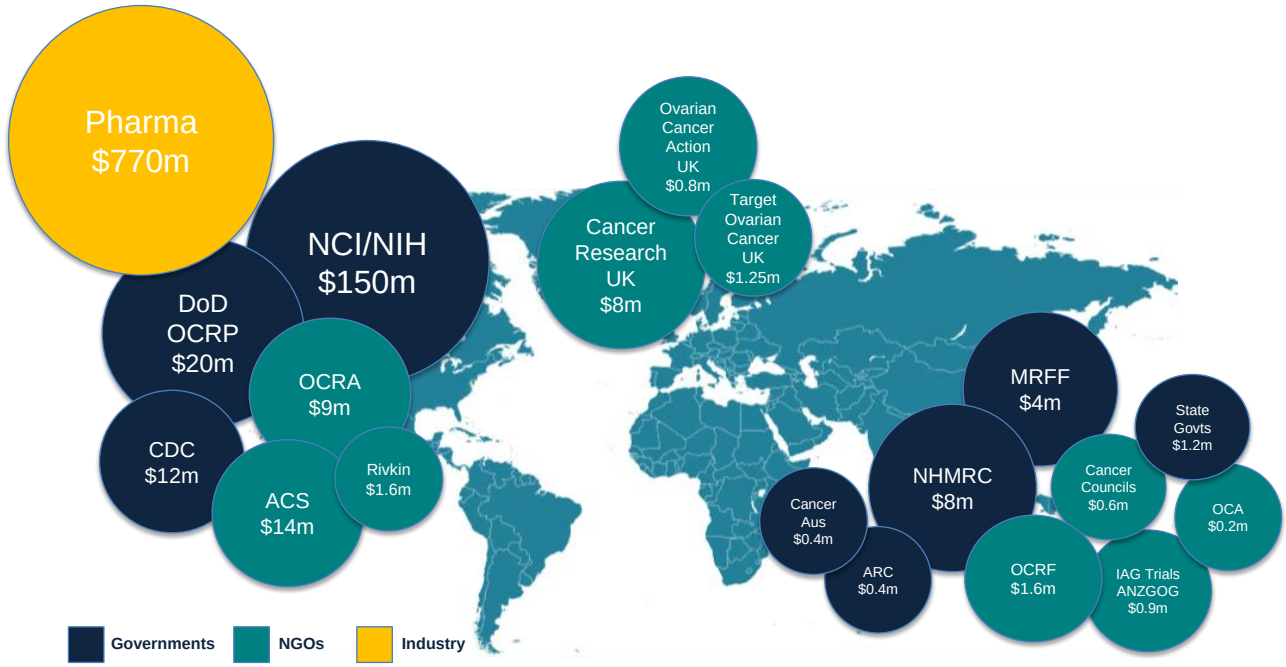
For example, on average, the US government commits more than $180 million to ovarian cancer research each year, with budgets of:

- $150 million per annum through the National Cancer Institute and National Institutes of Health
- $20 million per annum through the Department of Defense's Ovarian Cancer Research Program
- $12 million through Centers for Disease Control and Prevention programs.

Alongside governments, major US NGOs funding ovarian cancer research include the Ovarian Cancer Research Alliance, which provides annual funding of $9 million, the American Cancer Society, which provides annual funding of $14 million, and the Rivkin Center, which provides funding of about $1.6 million per annum.

The biopharmaceutical sector is a global industry but analysis of industry-led clinical trials in 2019 showed the majority of studies were conducted in the United States, followed by Europe. Based on the phase of research of current trials it was estimated the biopharmaceutical industry would have invested $770 million in industry-led clinical trials around the world in 2019.

**Figure 2.1: Average annual funding for ovarian cancer research in selected markets (latest data)**




Source: Latest available budgets and annual reports for international funders including National Cancer Institute and National Institutes of Health (NCI/NIH), US Department of Defence Ovarian Cancer Research Program (DoD OCRP), Centres of Disease Control and Prevention (CDC), American Cancer Society (ACS), Ovarian Cancer Research Alliance (OCRA), Rivkin Center, Cancer Research UK, Ovarian Cancer Action UK, Target Ovarian Cancer, Insight Economics analysis of clinical trials data for industry-led clinical trials by phase of research in 2019 published at Clinicaltrials.gov, National Health and Medical Research Council (NHRMC) reporting 2003-2016 accessed at https://www.nhmrc.gov.au/funding and supplemented with data from Australian Government Grants Connect 2016-2020, Medical Research Future Fund (MRFF) data accessed through Grants Connect, Australian Research Council (ARC) data accessed at https://www.arc.gov.au/grants and Grants Connect. Cancer Australia based on audit of ovarian cancer research performers. OCRF and ANZGOG based data shared by organisations and audit of ovarian cancer research performers. Ovarian Cancer Australia (OCA) estimate based on Australian Charity and Not-for-profits (ACNC) AIS reporting in 2017 and the audit of ovarian cancer research performers. See Appendix A for further details about responding organisations.

The data also illustrates that Australia is an important performer of ovarian cancer research. The Australian Government has historically funded ovarian cancer research through the National Health and Medical Research Council (NHMRC), Australian Research Council (ARC), and Cancer Australia, at an average of approximately $8 million, $0.4 million and $0.4 million per annum respectively over the past 15 years. In early 2020, the Australian Government announced more than $16 million funding for eight new projects and a clinical trial focused on ovarian cancer research.

Similar to international markets, the NGO sector has been an important partner in funding ovarian cancer research. The OCRF is the largest charitable organisation focused on ovarian cancer research and commits funding of approximately $1.6 million to ovarian cancer research each year.

## 2.2 Australia and New Zealand leaders in ovarian cancer research

Australia and New Zealand are home to some of the world's leading researchers in ovarian cancer (Figure 2.2), including:

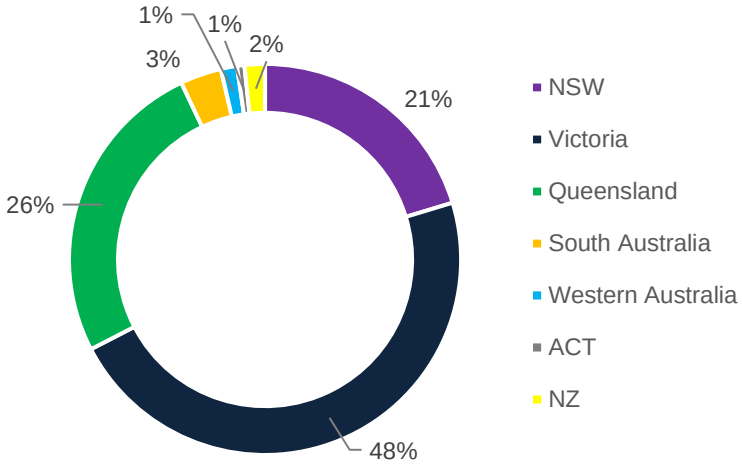
- In Victoria, the Peter MacCallum Cancer Centre, the Hudson Institute of Medical Research, the University of Melbourne, the Walter and Eliza Hall Institute of Medical Research, the Fiona Elsey Cancer Research Institute and RMIT University
- In Queensland, the QIMR Berghofer Medical Research Institute, the University of Queensland, Mater Research and Griffith University

- In NSW, The Westmead Institute for Medical Research, UNSW, the Hunter Medical Research Institute, the University of Newcastle, Kolling Institute of Medical Research and the University of Sydney.
- In Western Australia and South Australia, the University of Adelaide and University of Western Australia
- In New Zealand, the University of Otago.

**Figure 2.2: Research institutes and universities focused on ovarian cancer research in Australia and New Zealand**


Australia's major research centres are based predominantly in Eastern Australia, with more than 90 per cent of all research being undertaken in Melbourne, Sydney or Brisbane (Figure 2.3). Within this, in dollar terms, Victoria accounts for nearly half (48 per cent) of all ovarian cancer research undertaken in Australia, followed by Queensland, which accounts for a quarter (26 per cent) and NSW which accounts for one fifth (21 per cent). The balance of activity is distributed in the main across Western Australia, South Australia and New Zealand.

**Figure 2.3: Distribution of research expenditure by State 2010-2020**




Source: Audit of Australian and New Zealand Ovarian Cancer Research Performers, see Appendix A.

Many Australian researchers have attracted international funding from the US, UK and Europe. These include the Hudson Institute of Medical Research, the University of Melbourne, the Walter and Eliza Hall Institute of Medical Research, Griffith University, QIMR Berghofer Medical Research Institute and the University of Otago. Funding has spanned all phases of research with the majority of funding coming from the US National Cancer Institute and National Institutes of Health.

## 2.3 Funding for Australia and New Zealand research by phase

The audit of Australian ovarian cancer research performers reveals that since 2010, but excluding the Australian Government's recent MRFF commitments to ovarian cancer research announced in 2020, Australian research institutes have received funding of $164 million for research into ovarian cancer, at an average of roughly $15 million per annum.[30] Including the recent MRFF commitments, total ovarian cancer research funding commitments from 2010 to 2020 increased to $180 million.

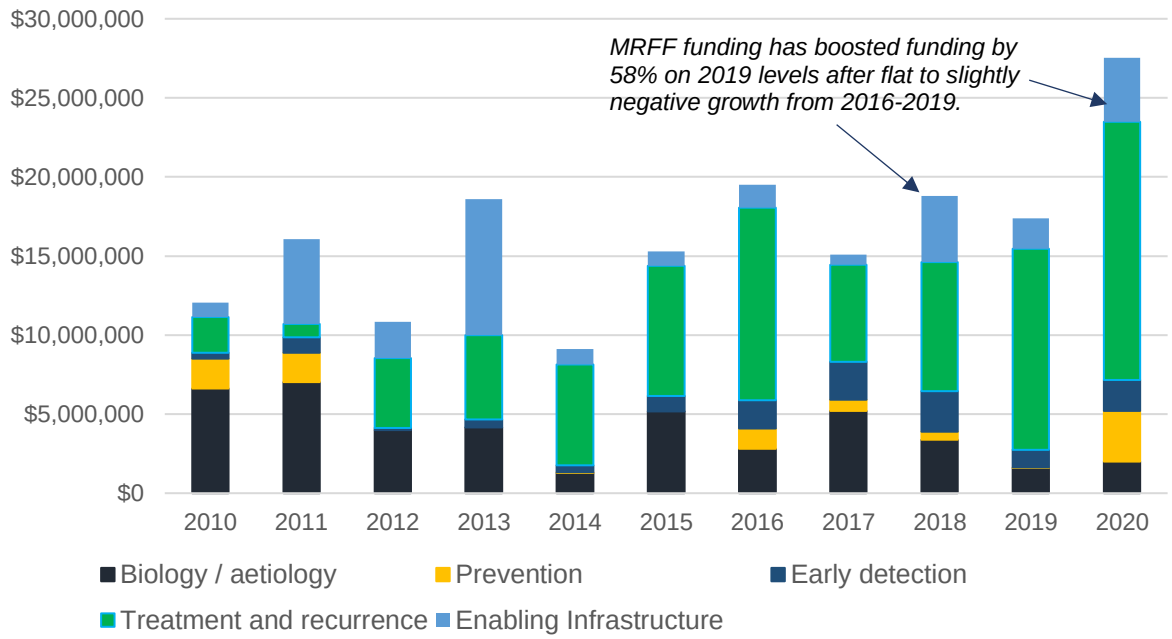
Based on the Common Scientific Outline which provides a standardised approach to the classification of research by research phase,[31] the audit of ovarian cancer research performers shows that excluding industry-led clinical trials funding has been distributed across all phases of research but with significant expenditure in the areas of biology, aetiology and treatment. For example, as shown in Figure 2.4, over the 2010-2020 period:

- Research into biology and aetiology has accounted for 24 per cent of all research funding, with expenditure over the period totalling $43 million at an average of approximately $3.9 million per annum.

[30] The Australian government also committed to $28 million of funding for the International Cancer Genome Consortium funding in 2008 but this has been excluded because a range of cancers were included in this research project and it was not specific to ovarian cancer, although this supported improvements in understanding ovarian cancer biology.
[31] The Common Scientific Outline or 'CSO', a classification system organised into six broad areas of scientific interest in cancer research: biology; aetiology;, prevention; early detection, diagnosis, and prognosis; treatment; cancer control, survivorship, and outcomes research. The CSO is complemented by a standard cancer type coding scheme. Together, these tools lay a framework to improve co-ordination among research organisations, making it possible to compare and contrast the research portfolios of public, non-profit, and government research agencies. In this report we have combined biology and aetiology into a single category and we have included cancer control, survivorship and outcomes research under the heading of enabling infrastructure, in which we also count expenditure on ovarian cancer biobanks, equipment and fellowships not otherwise categorised.

- Research into prevention has accounted for five per cent of all research funding, with expenditure over the period totalling $9.4 million at an average of approximately $1.2 million per annum.
- Research into early detection and diagnosis has accounted for seven per cent of all research funding, with expenditure over the period totalling $13.3 million at an average of approximately $1.2 million per annum
- Research into treatment and recurrence has accounted for 46 per cent of all research funding, with expenditure over the period totalling $82.9 million at an average of approximately $7.5 million per annum
- Funding for enabling infrastructure, which includes cancer control, survivorship, outcomes research, biobanking and fellowships, has accounted for 18 per cent of all research funding, with expenditure over the period totalling $31.3 million at an average of approximately $2.8 million per annum.

**Figure 2.4: Funding by research phase (2010-2020)**

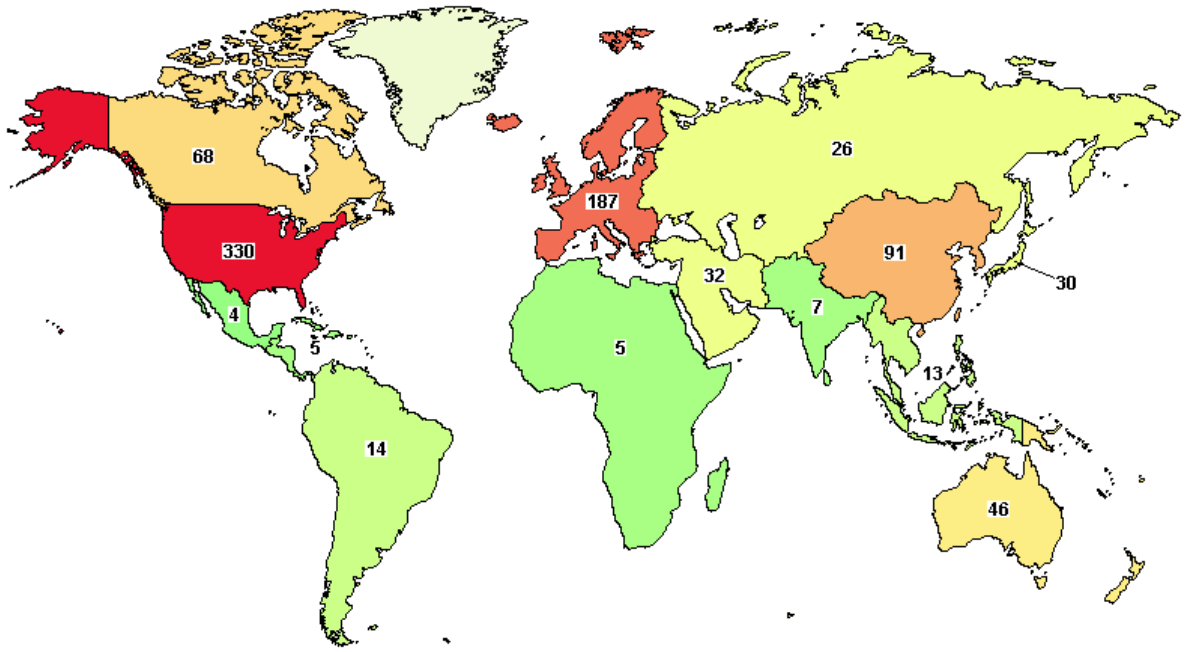



Source: Audit of Australian and New Zealand Ovarian Cancer Research Performers, see Appendix A.

Figure 2.4 also shows funding for ovarian cancer has been increasing over time, at an average annual rate of 13 per cent from 2010 to 2019. The Australian Government's commitment to ovarian cancer research of $16 million in 2020 has contributed to a 58 per cent increase in total funding on 2019 levels, reversing a downward trend of -1.0 per cent growth from 2016 to 2019.

In addition, the biopharmaceutical industry has invested in industry-led clinical trials in ovarian cancer in Australia. Based on analysis of Clinicaltrials.gov and the Australia New Zealand Clinical Trials Registry data from 2010 to 2020, globally the biopharmaceutical industry has completed 507 industry-led clinical trials and Australia has participated in approximately nine per cent (44 trials) (Figure 2.5).

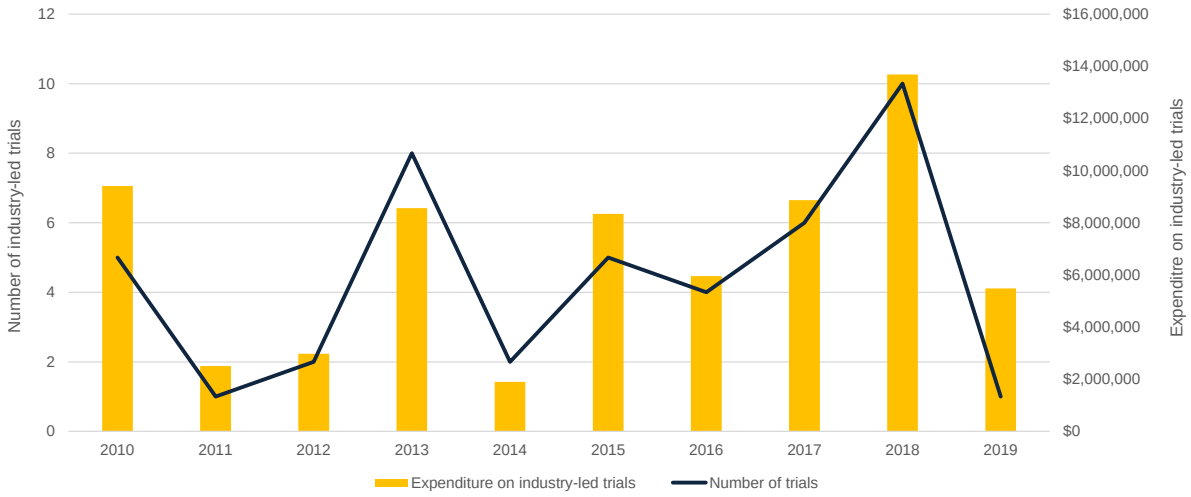
**Figure 2.5: Clinical trials in ovarian cancer 2010-2020**




Source: Clinicaltrials.gov register. Note some trials may have sites in more than one jurisdiction.

These data suggest Australia has hosted or participated in approximately four industry-led ovarian cancer trials per annum, with an estimated average expenditure of about $6.7 million per annum (Figure 2.6). This compares to total industry-led clinical trial expenditure in Australia of $930 million in 2015 across *all conditions* of 437 industry-led clinical trials.[32]

**Figure 2.6: Industry-led clinical trials activity in Australia 2010-2020**




Source: Analysis of Clinicaltrials.gov and commercial-in-confidence trial expenditure data.

## 2.4 Funding for Australia and New Zealand research by funder type

Analysis of funder sources shows that like international markets (excluding industry-led clinical trials), the Australian Government has been the major funder of ovarian cancer

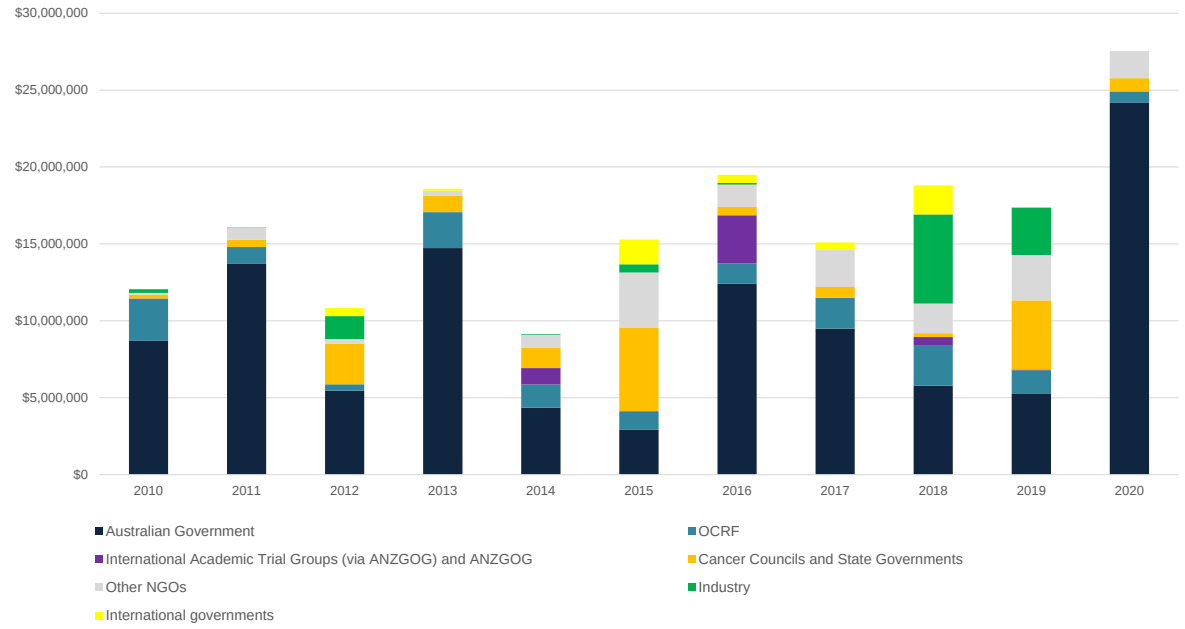
[32] MTP Connect, 2015, Clinical Trials in Australia, accessed at: https://www.mtpconnect.org.au/clinicaltrials.

research, followed by the OCRF and Cancer Councils and State Governments, which often work in close collaboration with respect to research funding by State (Figure 2.7):

- The Australian Government invested more than $107 million in ovarian cancer research over the 2010-2020 period, at an average of about $8 million per annum before MRFF commitments. The recent MRFF commitments translate into a 50 per cent uplift in government spending per annum. In total, the Australian Government accounts for approximately 60 per cent of all funding (59 per cent).
- The OCRF has invested more than $17.4 million in ovarian cancer research over the 2010-2020 period, at an average of about $1.6 million per annum, which is similar to the Rivkin Center in the US as well as Ovarian Cancer Action UK and Target Ovarian Cancer in the UK. The OCRF has been the largest funder of ovarian cancer research after the Australian Government, accounting for 10 per cent of all funding.
- State Governments have collectively invested $11.8 million in ovarian cancer research over the 2010-2020 period, representing approximately seven per cent of total funding and contributing an average of about $1.2 million per annum.
- Cancer Councils[33] have collectively invested nearly $7 million in ovarian cancer research over the 2010-2020 period, representing approximately four per cent of total funding and contributing an average of about $0.6 million per annum.
- Other NGOs and philanthropy, comprised of more than 90 unique donors, have invested $16.5 million in ovarian cancer research, accounting for a further nine per cent of funding from 2010-2020.
- Industry was reported to have funded a further $11 million in research over this period, representing six per cent of total funding.
- International academic groups have funded just over $5 million in investigator-led clinical trials through ANZGOG and account for three per cent of total funding.
- International government funders, being predominantly the US NCI/NIH and Department of Defense, have contributed nearly $5 million to Australian ovarian cancer research, accounting for about two per cent of all funding nationally.

[33] Noting that the Cancer Councils are a federated model and each state Cancer Council operates independently but sometimes (not always) co-ordinates with State Governments to enable optimal application of funds across researchers within each state.

**Figure 2.7: Ovarian cancer research by funding source (2010-2020)**



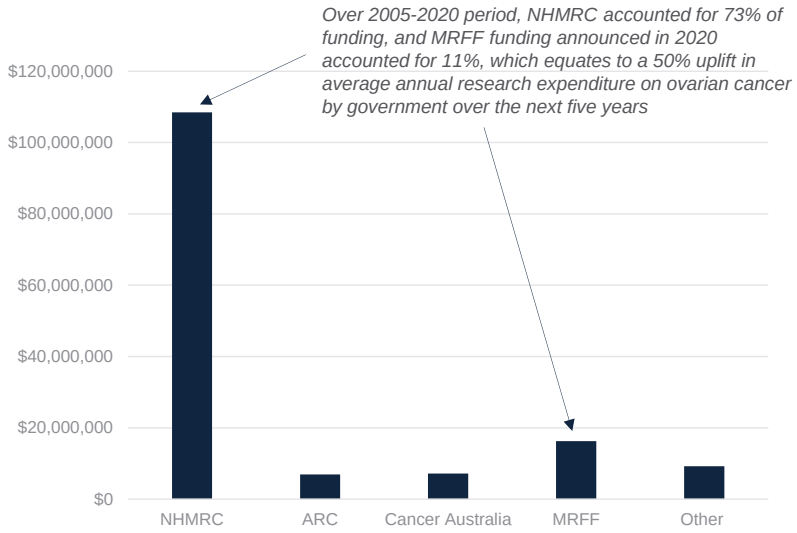

Source: Audit of Australian and New Zealand Ovarian Cancer Research Performers, see Appendix A.

### *In focus: Australian Government funding breakdown and benchmarking*

Australian Government funding has been comprised of funding from the National Health and Medical Research Council (NHRMC), the Australian Research Council, Cancer Australia, the Medical Research Future Fund (MRFF) and other Department-directed funding. Because data is available over a longer period, we have considered Australian Government investment from 2005 to 2020, as shown in Figure 2.8:

- The NHMRC has been the primary mechanism by which government has funded ovarian cancer research, with 73 per cent of funding ($108 million) being allocated through NHMRC grants and fellowships over the 2005-2020 period. NHMRC funding has been strongly focused on better understanding of ovarian cancer biology and aetiology.
- Following the NHMRC, the MRFF represents the next largest source of funding for ovarian cancer research at $16 million in committed funds from 2020. MRFF funding was allocated across all phases of research.
- Cancer Australia has supported $7 million in research funding, mainly towards treatment research through the Priority-driven Collaborative Cancer Research Scheme.
- The Australian Research Council has similarly provided approximately $7 million in funding, focused strongly on biology and aetiology research.
- Department-directed funding has included $5 million in funding to support cancer control though Ovarian Cancer Australia as well as some direct support for Cooperative Research Centre (CRC) programs and industry and innovation research.

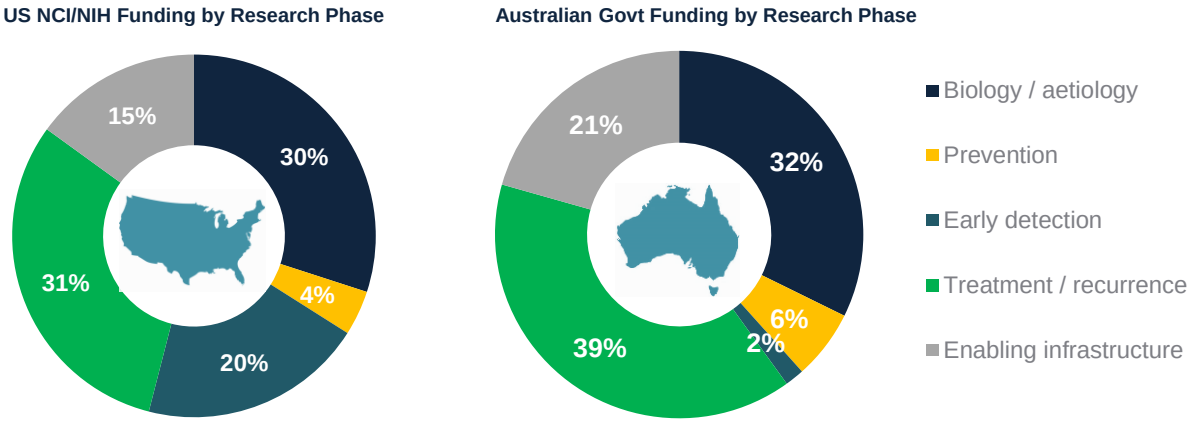
**Figure 2.8: Breakdown of Australian Government funding for ovarian cancer research by program**




Source: Audit of Australian and New Zealand Ovarian Cancer Research Performers, see Appendix A.

Australian Government funding across all programs has been strongly weighted to treatment and biology/aetiology research, with these two categories accounting for more than 70 per cent of total funding. Australian Government investments in ovarian cancer research broadly follow a similar distribution to the US National Cancer Institute and National Institutes of Health in large part, with the exception of funding for early detection and diagnosis research. As shown in Figure 2.9, NCI and NIH have allocated 20 per cent of total funding to early detection and diagnosis compared to only 2 per cent across Australian Government funders.

**Figure 2.9: Breakdown of US and Australian Government funding for ovarian cancer research by program**

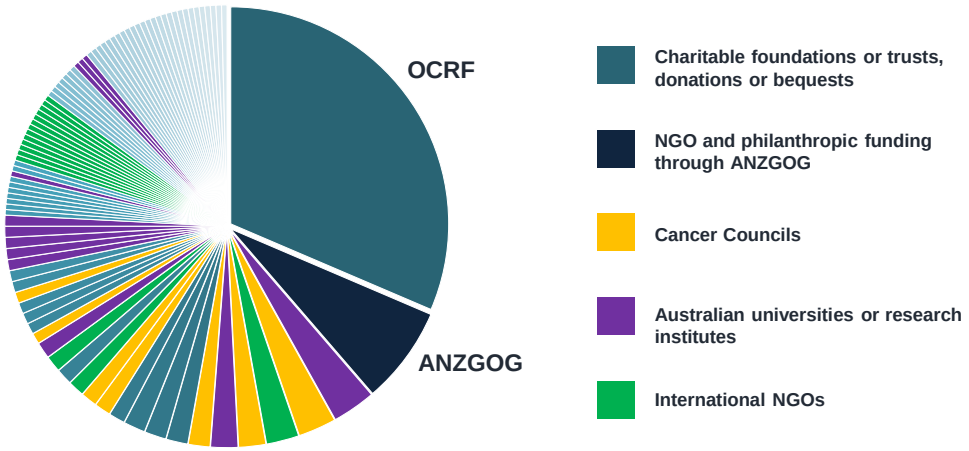



Source: NCI/NIH budget breakdown from National Academies of Science, 2016, *Ovarian Cancers: Evolving Paradigms in Research and Care*. Australian Government data based on data collected through the Audit of Australian and New Zealand Ovarian Cancer Research Performers, see Appendix A.

### *In focus: Non-Government Organisations breakdown*

Philanthropic funding for ovarian cancer from charitable foundations, trusts, Cancer Councils, universities and other NGOs was comprised of more than 90 unique funders over the 2010-2020 period (Figure 2.10).

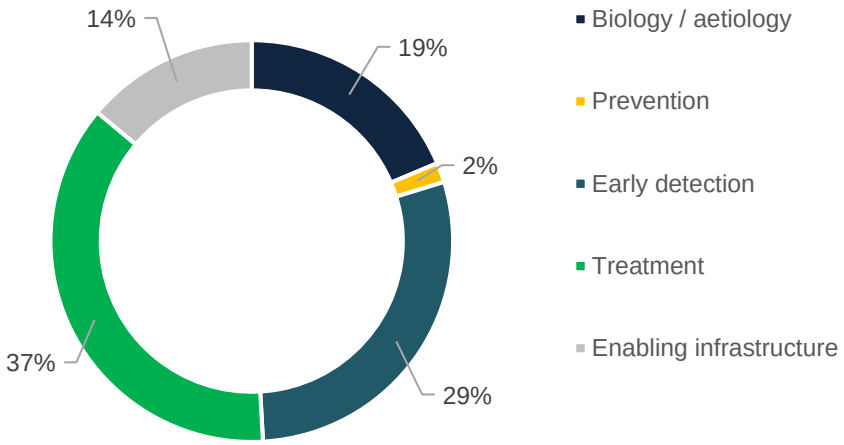
**Figure 2.10: Ovarian cancer NGO ecosystem based on number of projects funded**




Source: Audit of Australian and New Zealand Ovarian Cancer Research Performers, see Appendix A.

Collectively, NGOs, including charitable organisations, universities and other philanthropy, have funded approximately $70 million in ovarian cancer research. This funding has been relatively evenly distributed across all phases of research, with 19 per cent funding biology and aetiology research, two per cent funding prevention research, 29 per cent allocated to early detection and diagnosis, 37 per cent supporting treatment and recurrence research and 14 per cent going towards enabling infrastructure (Figure 2.11). Support for biobanking represents a significant proportion of enabling infrastructure funded by the NGO and philanthropic sector.

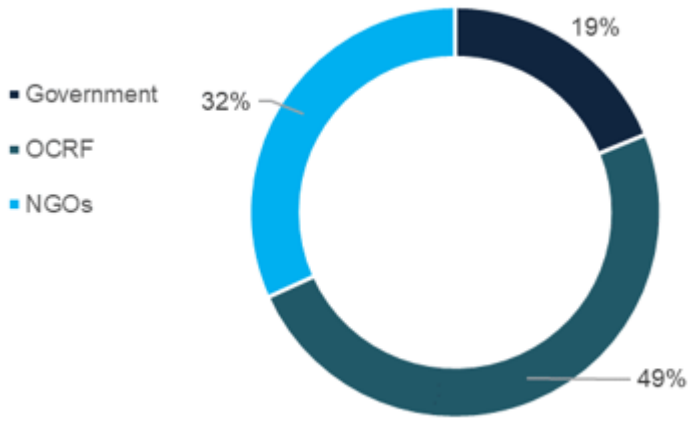
**Figure 2.11: Breakdown of NGO funding for ovarian cancer research by research phase**




Source: Audit of Australian and New Zealand Ovarian Cancer Research Performers, see Appendix A. Figures have been rounded to nearest percentage.

The OCRF has been the major funder of research into early detection and diagnosis in Australia, accounting for 49 per cent of funding into this phase of work across all funders, with the balance coming from the NGO sector (32 per cent) and the Australian Government's recent commitment to early detection and screening through the MRFF program, boosting its share to 19 per cent (Figure 2.12).

**Figure 2.12: Breakdown of funding of early phase and diagnosis research**




Source: Audit of Australian and New Zealand Ovarian Cancer Research Performers, see Appendix A.

## 2.5 Australian research funding potential: sector benchmark analysis

Benchmarking 'bottom up' data against a 'top-down' evaluation of Australia's total funding for medical research reveals that funding of ovarian cancer research represents a small fragment of total public and private funding for medical research in Australia.

There is significant and increasing funding potential for health and medical research by 'mass market' community campaigns, high net worth individuals, and private and public ancillary funds, as well as co-funding of research with other charitable trusts and foundations. To date, however, ovarian cancer has attracted only a very small proportion of these potential funding sources. The following sections provide some insight into philanthropic funding for medical research, and then benchmarks the share of public and private funding pools devoted to ovarian cancer.

### *Community giving and high net worth individual giving*

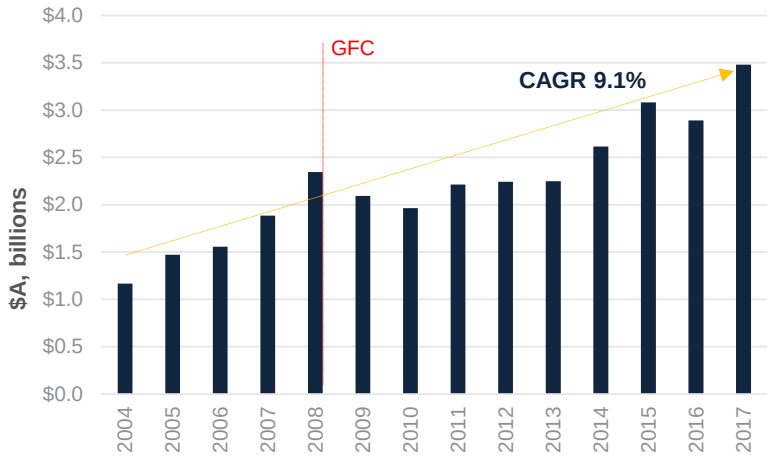
Australian Tax Office data show that approximately 35 per cent of Australians donate, and in the 10 years to 2016 the average value of a donation has increased from just over $300 per person to just over $600 per person.[34]

Since the implementation of taxation policies to promote philanthropy in 1999 there has been strong growth in large and visible giving by high net worth individuals. ATO data shows the number of high net worth individuals claiming large donations of more than $25,000 has increased from 5,190 claims in 2012 to 6,964 in 2017 (latest data).[35] Previous analyses have indicated that compared to their international peers, however, Australian high net worth individuals donate at a lower rate, with their US and Canadian counterparts donating at nearly twice the rate of their pre-tax income.[36]

In 2017, the total value of giving by individuals in Australia was reported to be $3.5 billion, increasing at a compound annual growth rate (CAGR) of 9.1 per cent from 2004 levels ($1.1b) (Figure 2.13).

[34] See ATO timeseries taxation statistics for donations and giving, accessed at: https://data.gov.au/data/dataset/taxation-statistics-2016-17/resource/530b8e7b-d6c7-4779-a35c-656c8267a594
[35] ATO timeseries taxation statistics for donations and giving
[36] Philanthropy Australia, 2011, Strategies for Increasing High Net Worth and Ultra High Net Worth Giving, prepared for the Commonwealth Department of Families, Housing, Community Services and Indigenous Affairs, Final Report.

**Figure 2.13: Gifts and donations by individuals in Australia**




Source: ATO, Taxation statistics, Donation claims by individuals, 2004-2017.

The second-round effects of the COVID-19 pandemic may have a similarly adverse impact on the forward growth of individual donation potential, similar to the effects observed in 2009 and 2010 following the impact of the Global Financial Crisis.

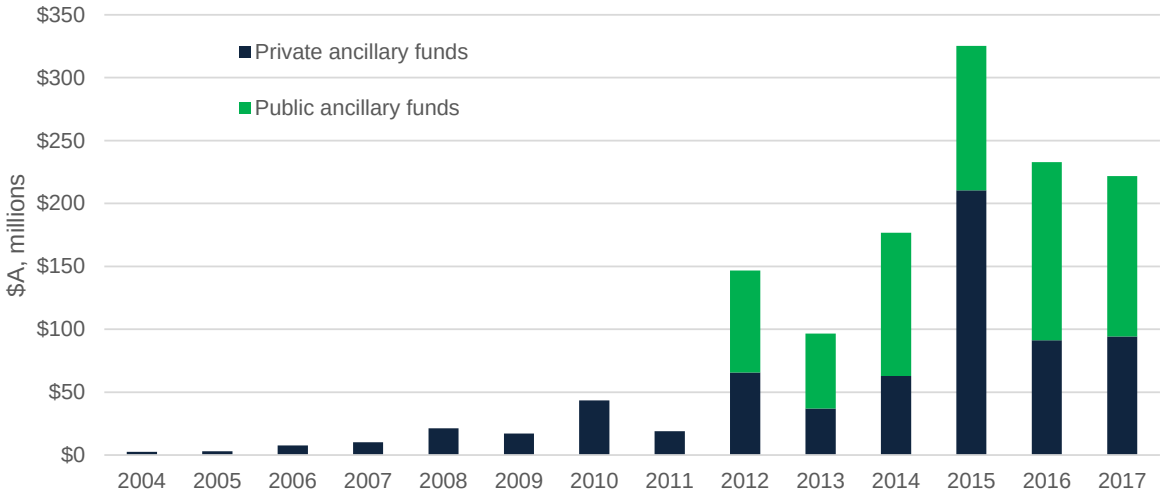
### *Private and Public Ancillary Funds*

There has also been strong growth in structured giving through private and public ancillary funds, which were established to encourage private giving. Philanthropy Australia projects that grants made through private and public ancillary funds are expected to grow to around 17 per cent of all giving by 2036, up from 7 per cent in 1996.[37] ATO data shows that in 2017 giving through private and public ancillary funds exceeded $1.5 billion, which was distributed to a range of causes including health, education, research, welfare, environment, sports and recreation and cultural causes.

Distributions to heath and research causes accounted for 11 per cent of private ancillary fund giving between 2007 and 2012, and 18 per cent of public ancillary fund giving between 2012 and 2013. Applying these shares to the total private and public ancillary fund distributions from 2014-2017 indicates potential funding of more than $200 million per annum for health and research causes (Figure 2.14).

[37] McLeod, J, 2018, The Support Report: The changing shape of giving and the significant implications for recipients, JBWere, report to Philanthropy Australia.

**Figure 2.14: Public and Private Ancillary Funds – Health and Research Distributions (2004-2017)**

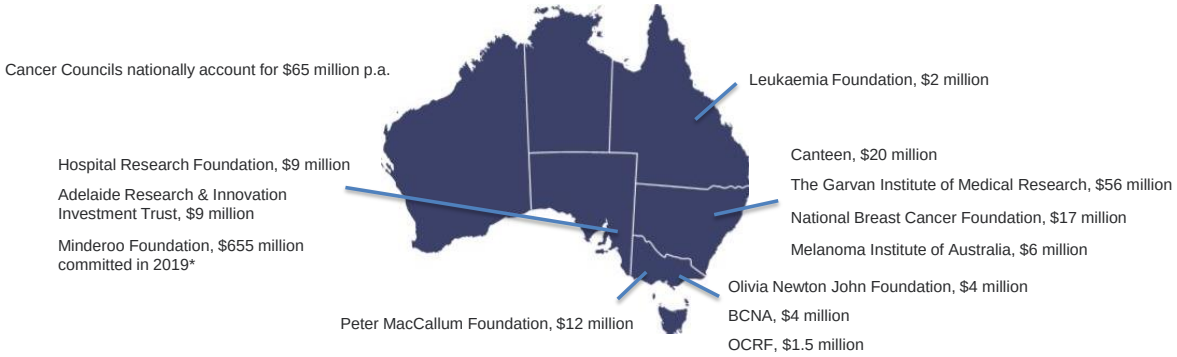



Source: ATO, Public and Private Ancillary Funds, 2004-2017.

### *Charitable foundations and trusts*

Charitable foundations are more complex to establish than giving either through simple donations or private and public ancillary funds, but represent a major vehicle for raising and distributing funds for a range of causes. Funding by charitable foundations for research accounts for 20 per cent of all distributions by charitable trusts in Australia, according to analysis by Philanthropy Australia.[38] Many of the largest charitable trusts in Australia today are strongly oriented to supporting medical research, including specifically cancer. Combined, charities with a focus on cancer research within their portfolio accounted for more than $820 million in funding in 2017 (latest data, accessed March 2020, excluding universities).

**Figure 2.15: Analysis of selected major charitable foundations medical research annual budgets**




Source: Australian Charities and Not-for-profits Commission, AIS database, 2017, accessed at: https://data.gov.au/dataset/ds-dga-a1f8626c-fefb-4c4d-86ea-deaa04fb1f6e/details?q=, Cancer Council of Australia, and Brammer, J, 2019, Andrew and Nicola Forrest best own Australian donation record with $655m gift for Minderoo Foundation, The West Australian, May 19, accessed at: https://thewest.com.au/business/andrew-and-nicola-forrest-best-own-australian-donation-record-with-655m-gift-for-minderoo-foundation-ng-b881189239z.

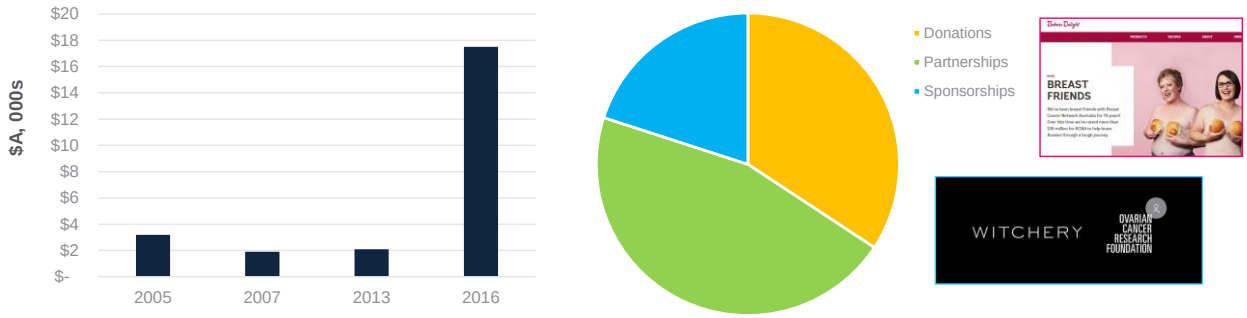
### *Corporate giving*

Australia's corporate sector has also been increasing donations to charitable causes. The total funding potential from Australian corporations is harder to estimate because companies are

[38] McLeod, J, 2018, The Support Report: The changing shape of giving and the significant implications for recipients, JBWere, report to Philanthropy Australia

not required to report donations.[39] Ovarian cancer and breast cancer have been relatively successful in this domain with corporate sponsorships from Witchery and Bakers Delight respectively.

**Figure 2.16: Corporate giving to charitable causes**




Source: McLeod, J, 2018, The Support Report: The changing shape of giving and the significant implications for recipients, JBWere, report to Philanthropy Australia.

For example, Bakers Delight reports having helped raise more than $16 million for the BCNA over the past 19 years through a range of aligned marketing and advertising strategies[40]. The OCRF Witchery White Shirt Campaign raised $13.5 million between 2008 and 2019.[41]

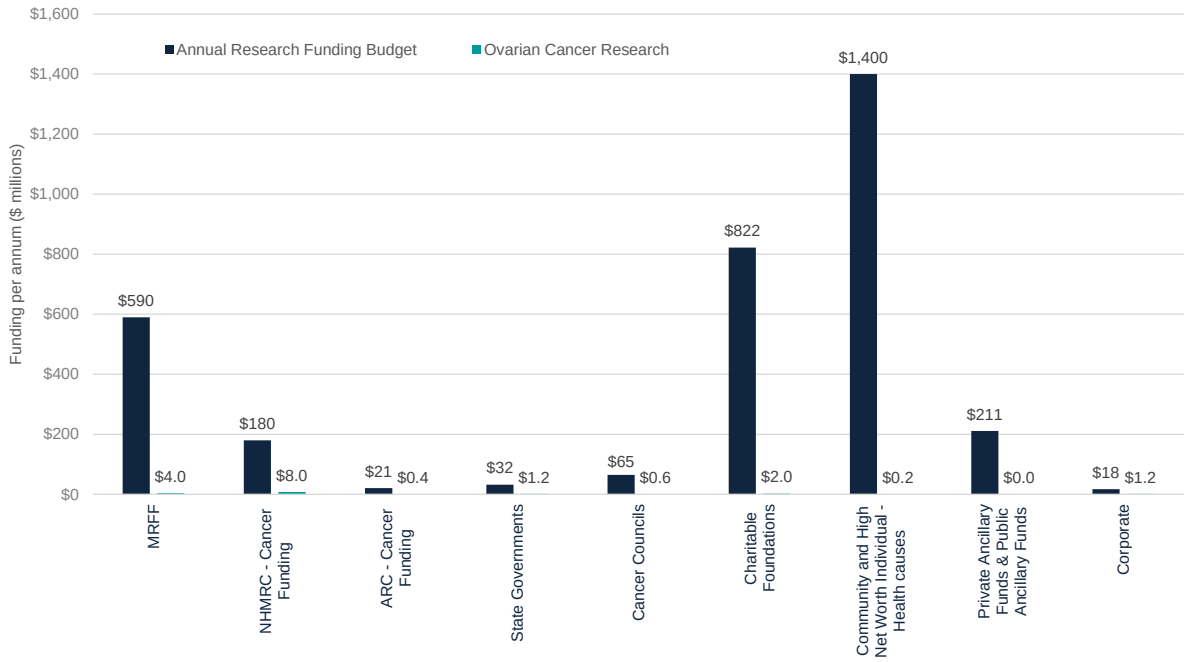
### *Bringing it all together: Benchmarking ovarian cancer funding levels against total public and private funding by sector*

Australian funders, public and private, have the potential to make a significant difference in the outlook for women with ovarian cancer. Funding for ovarian cancer accounts for a small proportion of total funding for cancer and medical research (Figure 2.17).[42]

Even a modest uplift to fund critical research collaborations would provide the step change in funding needed to achieve high-impact research outcomes and close the gap between ovarian and other cancers. For example, a 0.1 per cent increase in ovarian cancer's share of the total funding pool would translate into a 20 per cent increase in annual funding for ovarian cancer research from current levels. A one per cent increase in total funding directed towards ovarian cancer would see total annual funding for ovarian cancer research nearly double.

[39] Ibid
[40] Bakers Delight, 2020, BCNA Breast Friends, https://www.bakersdelight.com.au/occasion/bcna/.
[41] OCRF, 2020, Witchery White Shirt Campaign 2020, https://www.ocrf.com.au/campaign/2/white-shirt-campaign.
[42] Budgets for cancer research are presented for NHMRC, ARC and State Governments based on average of recent budget announcements by organisation and jurisdiction. Charitable foundation, community, high net worth individuals and PuAF/PAF estimates of total giving are based on share of health and medical research causes as cancer was not identified as a category for these sectors.

**Figure 2.17: Benchmarking funding for ovarian cancer research against public and private funding potential**




## 2.6 Research audit: key findings

The audit of ovarian cancer research reveals Australia to be a significant performer of ovarian cancer research globally. However, funding has been limited relative to the total potential funding for medical research available in Australia. Even a small uplift in the share of the total funding envelope, or an increase in giving overall by the wider community, has the potential to significantly expand funding for this low-survival cancer.

While the Australian Government has been the major funder of ovarian cancer research within Australia, most funding has been directed towards research into biology, aetiology and treatment. For the past 20 years the OCRF has been the largest funder of ovarian cancer research in Australia after the Australian Government, and the primary driver of research into early detection and diagnosis. Notably, the recent allocation of MRFF funding offers a roughly 50 per cent uplift on historic Federal Government funding levels and diversifies government investment into early detection and diagnosis.

To meet the goal of improved survival set by the Senate Select Committee for Research Funding for Low Survival Cancers, however, will require a continued uplift in funding, directed at the areas of greatest need and highest impact. These issues and opportunities are explored in the subsequent chapters.

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Chapter 3

# Barriers and priorities in ovarian cancer: researcher, clinician, and consumer perspectives

*As part of the audit of ovarian cancer research, a Survey of Ovarian Cancer Researchers, Clinicians and Consumers was undertaken to identify the major barriers to improving survival outcomes for women and the priority areas of research to address these barriers. The audit also sought views from women with respect to the importance of survival and other quality of life outcomes, including reducing major symptoms and side effects of cancer and treatment.*

*This chapter presents the results of that survey. There was a strong congruence between researchers, clinicians and consumers about the major barriers and opportunities for research in ovarian cancer. Both researchers and consumers identified the major barriers to improving survival to be the lack of an early detection test, lack of treatment options and inability to prevent recurrence. Researchers and consumers were also aligned in the identification of research priorities, with the need for research to identify an early detection test being identified as the top area of research need. Researchers identified the second priorities for research to be expansion of treatment options and prevention of recurrence, while consumers identified the second priorities to be the prevention of metastasis and prevention of recurrence.*

*Nearly all consumers identified improvements in survival to be the major priority for research (98 per cent), but 40 per cent also indicated a need to develop better services for the prevention and management of anxiety and one in three said reduction of side effects should also be a top priority.*

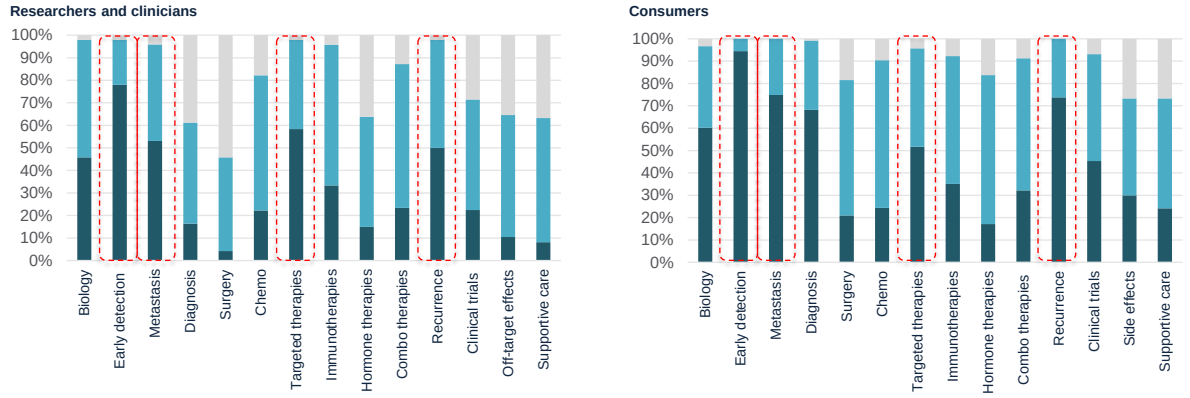
*In addition to comments provided through the survey, this chapter also presents stakeholder perspectives on the barriers to and opportunities for improving survival obtained through consultations.*

*Appendix B provides data on the Survey of Ovarian Cancer Researchers, Clinicians and Consumers and Appendix D provides the consultation brief used to guide semi-structured interviews with researchers, clinicians and consumers.*

## 3.1 What are the barriers to improving outcomes for women?

Researchers, clinicians and consumers alike agreed that the most significant barrier to improving survival outcomes for women with ovarian cancer was the lack of an early detection test (Figure 3.1). The next biggest barriers to improving survival were identified as preventing metastasis and recurrence, and lack of targeted therapies. An interesting point of diversion can be seen around diagnosis with consumers rating this as a critical issue.

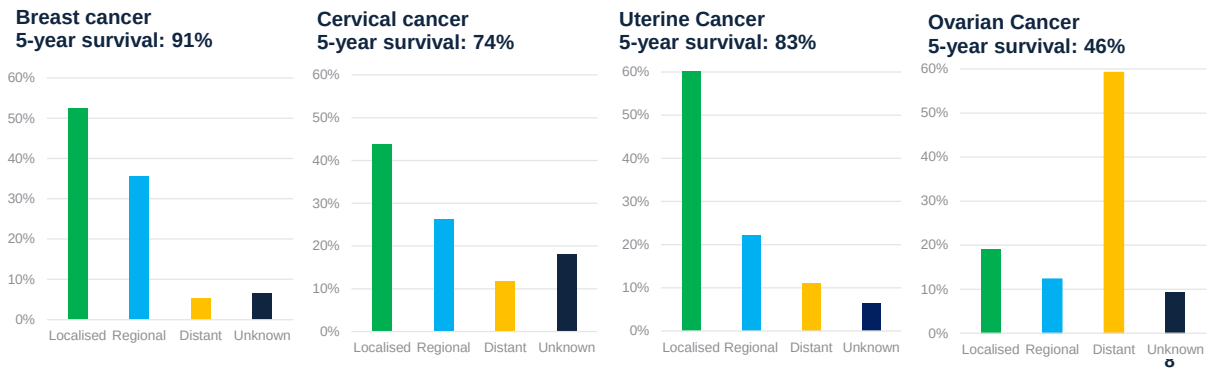
**Figure 3.1: What are the major barriers to improving survival for women with ovarian cancer?**




Source: Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B.

This prioritisation reflects that the significant improvements in 5-year survival rates for breast and cervical cancer have resulted from effective screening programs for early detection. Ovarian cancer is distinguished by a lack of tools for screening and early detection (Figure 3.2).

**Figure 3.2: Benchmarking survival outcomes and stage of diagnosis**




Source: Cancer Institute NSW, 2020, Cancer Statistics, accessed at: https://www.cancer.nsw.gov.au/data-research/access-our-data/cancer-statistics-nsw#//analysis/incidence/

The prioritisation also reflects that poor outcomes from late stage diagnoses have been compounded by a lack of treatment options, with frequent disease recurrence and high mortality rates. More than 80 per cent of women relapse following first-line treatment and eventual resistance to chemotherapy is typical.

Stakeholder feedback through the survey and consultations underscored the complexity of the barriers to improving survival. Inadequate understanding of disease biology, issues arising from variation in clinical care across Australia, barriers to research impact arising from failures to collaborate, and challenges in retaining high quality researchers were highlighted. Overarching all of these issues, many stakeholders indicated a lack of research funding was among the most significant barriers to improving survival (Figure 3.3).

**Figure 3.3: What are the major barriers to improving survival for women with ovarian cancer?**


Note: Researcher and clinician perspectives in dark blue, consumer perspectives in teal.

Consumers further identified a lack of awareness of ovarian cancer by the Australian community in general and among primary care providers specifically, as barriers to improving survival (Figure 3.4). Consumers shared stories of misdiagnosis, overlooked symptoms and feeling like they were not being taken seriously. Concerns were also raised about risks of inequitable access to services and research for Australians outside capital cities.

**Figure 3.4: What are the major barriers to improving survival for women with ovarian cancer? Consumer perspectives**


## 3.2 Research priorities to improve outcomes for women

The Survey of Researchers, Clinicians and Consumers identified a range of research areas as important priorities for improving survival going forward, which reflects the significant work required to improve ovarian cancer survival outcomes.

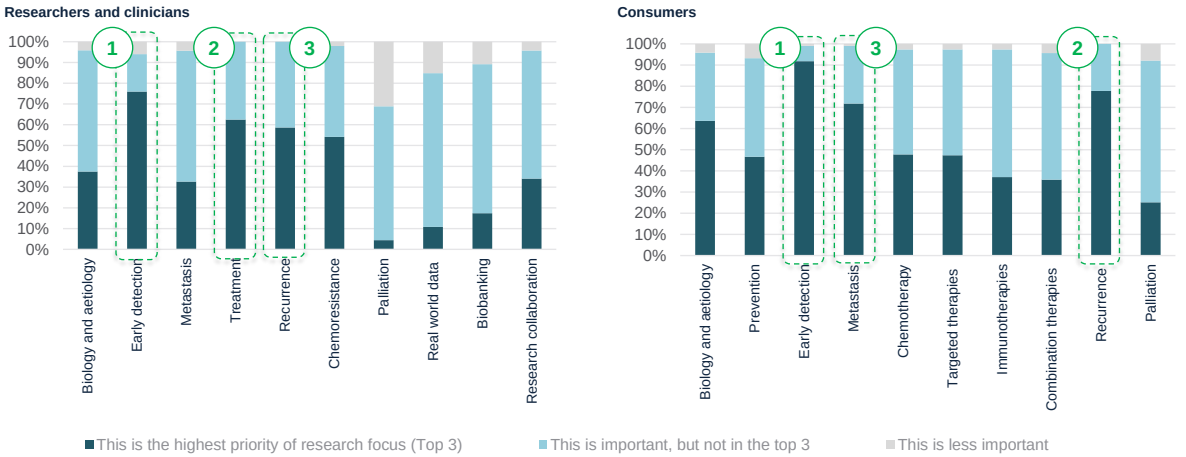
Researchers, clinicians, and consumers reported that one of the highest priority areas for research to improve survival for women with ovarian cancer is early detection and diagnosis, which likely reflects the source of survival improvements realised in other cancers (Figure 3.5). Nearly 80 per cent of researchers and clinicians and 95 per cent of consumers identified early detection and diagnosis to be one of the top three areas for ovarian cancer research.

After early detection research, there was some divergence between researchers, clinicians and consumers:

- Among researchers and clinicians, the next most commonly identified area identified as a top three priority for ovarian cancer research was research into new approaches to treatment and prevention of recurrence, followed closely by research into the prevention of chemoresistance.

- After early detection and diagnosis, consumers most commonly identified top priorities to be prevention of recurrence and metastasis.

**Figure 3.5: Priorities for research: perspectives from researchers, clinicians, and consumers**

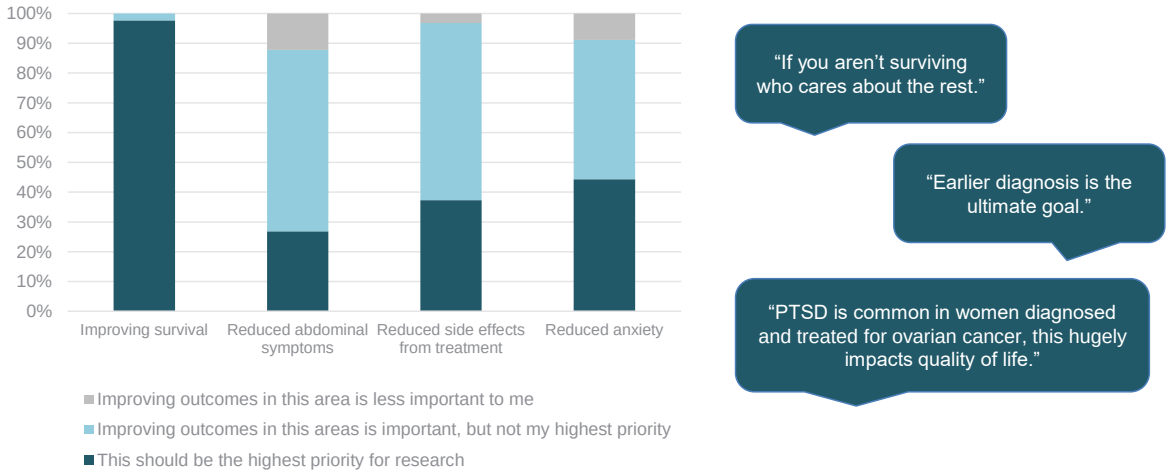



Source: Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B.

Stakeholders highlighted that there is significant work to be done within each area of research. They also highlighted the significant interconnectedness of research, with breakthroughs in biology and aetiology supporting the potential for gains in early detection, prevention and treatment (Figure 3.6, page 39).

The survey also asked women what were the most important outcomes to address from their perspective. Overwhelmingly, 98 per cent said the outcome of most importance was improving survival, but significantly 40 per cent also indicated that reducing anxiety was an important priority for research, and one in three women also wanted to see reduced side effects from treatment (Figure 3.7)

**Figure 3.7: Priorities for research: perspectives from researchers, clinicians, and consumers**




Source: Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B.

**Figure 3.6: What are the major opportunities for improving survival for women with ovarian cancer?**


Note: Researcher and clinician perspectives in dark blue, consumer perspectives in teal.

## 3.3 Implications for the ovarian cancer research agenda

The Survey of Ovarian Cancer Researchers, Clinicians and Consumers illustrates significant priorities for ovarian cancer research. Improving survival was identified to be the most important outcome from a consumer perspective, and researchers, clinicians and consumers agreed that the primary barriers to improving survival were the lack of an early detection test and lack of treatment options. While early detection, treatment, prevention, and recurrence were identified as key research priorities, stakeholders indicated that realising gains in these domains will require substantial work across a range of research areas. The next chapter brings these ideas into a framework for future research in ovarian cancer and identifies the major directions for future research.

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## Chapter 4

# Improving survival outcomes for women: future directions in research

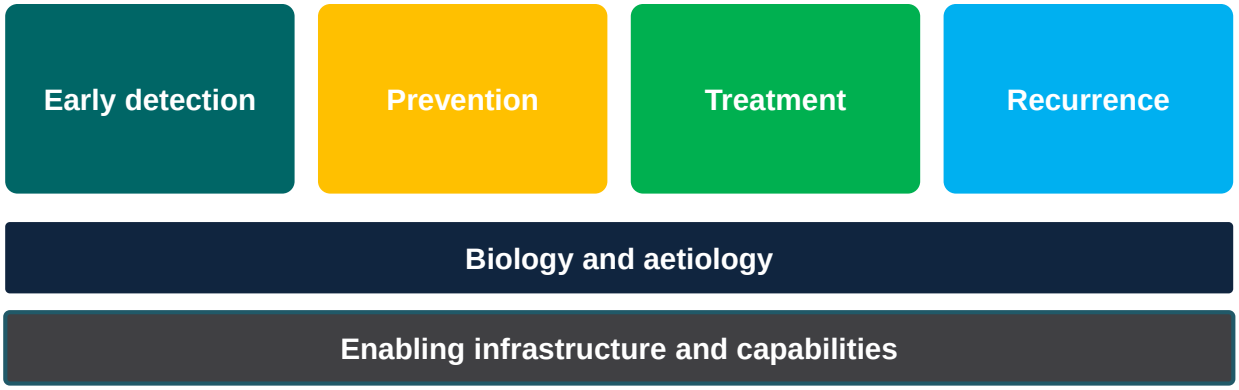
*In 2020, the 5-year survival outcomes for ovarian cancer are poorer than the average across all cancers in 1975. Developed nation governments have recognised the need to increase funding for low-survival cancers to address significant survival disparities across cancers. Case studies in other cancer research success show that realising improvements in survival outcomes requires a comprehensive program of high-impact research across a range of research areas, leading to improvements in the understanding of disease biology, reductions in disease incidence, expansion of treatment options and capacity to detect cancer early, when it is easiest to treat.*

*This chapter presents a roadmap for future research, including a summary of future directions for research by research phase and key enabling infrastructure required to support these research activities.*

## 4.1 Overview: future directions for ovarian cancer research by research phase

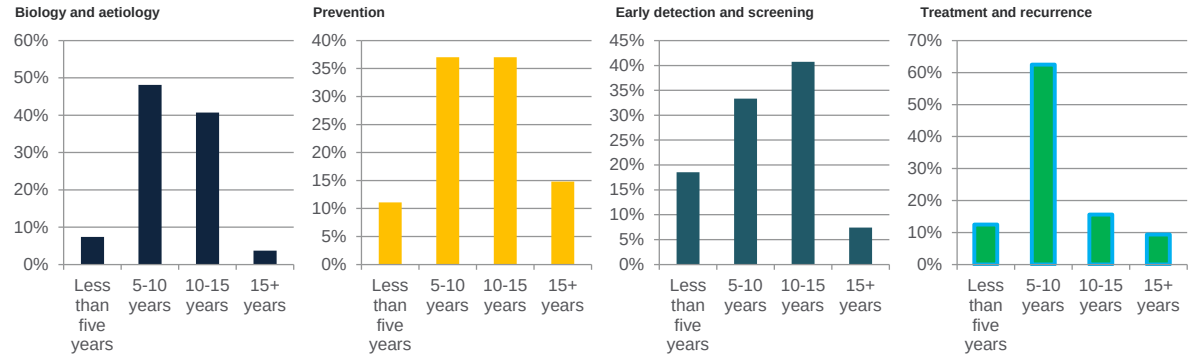
There is an urgent need to increase funding in ovarian cancer, with significant research questions remaining across all phases of research. Even with limited funding to date, major advances have been made over the past 10-15 years, which have the potential to enable further breakthroughs over the next funding horizon.

**Figure 4.1: Research roadmap for ovarian cancer**




Significant opportunities exist to improve outcomes for women today as well as the next generation of women. There was an expectation among researchers that funding new research into treatment and recurrence could deliver benefits within five to 10 years (Figure 4.2). Research into the areas of early detection and diagnosis, biology and prevention were expected to have a longer horizon for benefits realisation, of between five and 15 years, but had the potential to deliver benefits for the next generation of women (Figure 4.2).

**Figure 4.2: Indicative timeline for benefits realisation: researcher and clinician survey responses**




Source: Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B.

## 4.2 Future directions for research: early detection and diagnosis

Early stage ovarian cancer (Stage I and II) can be cured with currently available surgery and chemotherapy in around 90 per cent and 70 per cent of cases respectively. However, ovarian cancer is difficult to detect at an early stage using current technologies, and symptoms may be vague and non-specific.

A further challenge is the rapid progression of the disease. Statistical analysis of theoretical test capabilities indicates that an annual screening test for ovarian cancer could achieve mortality reductions of 40 to 50 per cent with the potential to be cost effective across all women over age 50. However, because of rapid disease progression, further improvements in mortality would require more frequent testing, which may be desirable to only subsets of women at potentially higher risk of the disease.[43]

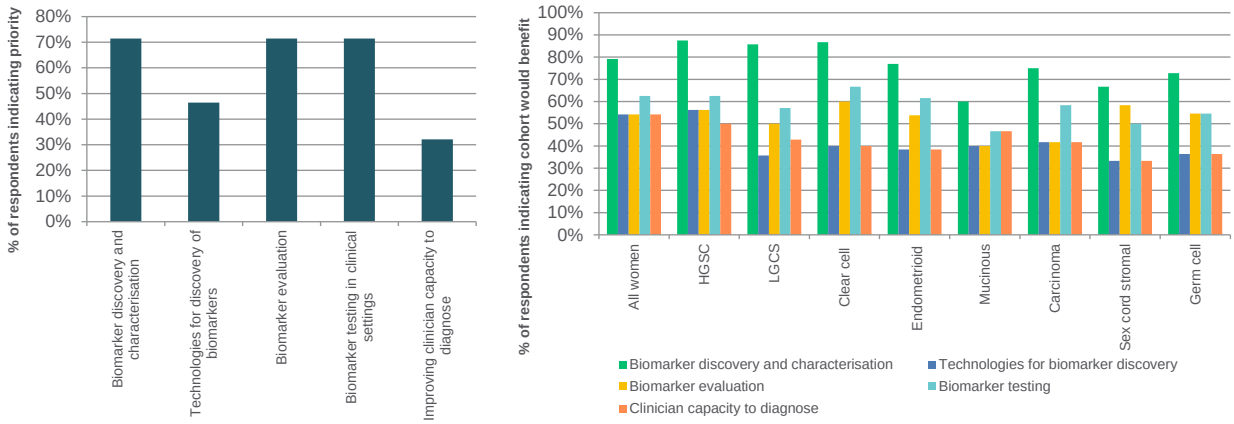
For these reasons, a major focus of research has involved better understanding of genetic risk to identify high risk cohorts, as well as of multi-modal screening approaches that seek to detect ovarian cancer by identifying markers of disease in the blood (biomarkers) and potential malignant masses in the body using transvaginal ultrasound.

In the past 15 years a major focus of research screening globally has examined CA125, a protein biomarker present in the blood, as a potential test for the early detection of ovarian cancer. Several major studies involving more than 200,000 women, including the Normal Risk Ovarian Cancer Screening Study and the United Kingdom Collaborative Trial of Ovarian Cancer, were undertaken to investigate the potential of CA125 to identify early stage ovarian cancer. Although a 28 per cent reduction in mortality was observed in a pre-specified subset of patients after seven years of annual screening,[44] ultimately CA125, either on its own or in combination with an ultrasound, has proved to be insufficiently sensitive and specific to be used as an early detection and screening intervention, and often resulted in unnecessary surgery due to false positive tests.

Subsequently, the focus has shifted to analysis of other biomarkers of disease in the blood (serum biomarkers) and also to cervical secretions, as well as new approaches to imaging. Survey respondents indicated the focus for early detection should be on biomarker discovery, evaluation and testing in clinical settings, especially as this may benefit women across all sub-types of ovarian cancer. (Figure 4.3).

[43] Havrilesky, LJ, Sanders GD, Kulasingam S, Myers ER, 2008, Reducing ovarian cancer mortality through screening: Is it possible, and can we afford it?, Gynecologic Oncology 111:179–187, doi:10.1016/j.ygyno.2008.07.006.
[44] Jacobs, IJ, Menon, U, Ryan A, Gentry-Maharaj, A, et al, 2015, Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial, The Lancet, doi: 10.1016/S0140-6736(15)01224-6.

**Figure 4.3: Research priorities in early detection and diagnosis – survey results**




Source: Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B.

The next phase of biomarker research has involved the detection of circulating tumour DNA (ctDNA), which can be found when cancer cells are shed from ovarian tumours or pre-cursor lesions,[45] and the detection of autoantibodies, which are the body's immune response to the presence of cancer. Recent research reported the detection of ctDNA in 47 per cent of early stage ovarian cancers with a specificity of 100 per cent, and the detection of ctDNA in the blood in 35 per cent of early stage ovarian cancers. Combining tests of ctDNA in cervical secretions and blood identified early stage ovarian cancer in 54 per cent of patients.[46] Similarly, diagnostics based on a combination of autoantibody biomarkers have also been found to improve the predictive power of early detection tests (Box 4.1).

**Box 4.1: Case studies in current biomarker research**

**Case study: The Multiplex Active Ratio Test (mART test)**

The immune system plays a large role in the development and progression of epithelial ovarian cancer. Cells in the ovarian tumour send out signals to the immune system. One of these signals is a molecule called CXCL10, and when the cancer is developing CXCL10 is converted to a different form called antagonistic CXCL10 (Ag-CXCL10). This change is cancer-specific so the detection of this cancer-specific change can potentially be utilised as an early detection test. Using cervicovaginal swabs in a procedure similar to a pap smear, the test has been found to detect ovarian cancer in early clinical trials. Researchers at the Hudson Institute of Medical Research, in partnership with researchers from Israel, are conducting a larger trial involving the recruitment of 300 Australian women to explore the potential for a cervicovaginal swab to identify cancer in high-risk cohorts. The trial is currently recruiting and is expected to conclude in 2021.

**Case study: Novel biomarkers for early detection**

The ability to distinguish cancer from other benign masses in the body is crucial for accurate diagnosis and treatment. High-grade serous ovarian cancers are associated with local and systemic inflammation arising from the patient's immune response.

A collaborative, multidisciplinary research effort by immunologists, pathologists, gynaecologists, and biostatisticians at Monash University, the Royal Women's Hospital, the Hudson Institute of Medical Research, and RMIT University has been exploring the inclusion of inflammatory biomarkers in sera with the objective of improving diagnostic test sensitivity and specificity. The team evaluated four existing clinical tests and a panel of 28 immune soluble biomarkers in sera from 66 patients undergoing surgery for suspected ovarian cancer.

Six immune biomarkers were evaluated, both individually and in combination with conventional tests (n=69). One of those biomarkers, a cytokine called IL-6, was found to be significantly higher in women with ovarian

[45] Erickson, BK, Kinde, I, Dobbin, ZC, Wang, Y,et al, 2014, Detection of somatic TP53 mutations in tampons of patients with high-grade serous ovarian cancer. Obstet. Gynecol. 124, 881–885.
[46] Wang, Y, Li, L, Douville, C, et al, 2018, Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers, Science Translational Medicine, 10(433), eaap8793. https://doi.org/10.1126/scitranslmed.aap8793

cancer compared to those with a benign mass (28.3 pg/ml vs 7.3 pg/ml, p<0.0001) or compared to women with normal ovaries (28.3 vs 1.2pg/ml, p<0.0001).

The combination of IL-6 with existing tests therefore further improved the overall predictive probability of the conventional tests. Modelling a two-step triage of women with a suspicious ovarian mass, with IL-6>3.75pg/ml as primary triage, followed by conventional tests (CA125 or RMI score) identified ovarian cancer in patients with a misclassification rate of 4.54–3.03%, superior to the use of CA125 or RMI alone (9.09 to 10.60). The validation cohort demonstrated a similar improvement in the diagnostic sensitivity following addition of IL-6.

IL-6 in combination with conventional tests may therefore be a useful clinical biomarker for triage of patients with suspected ovarian cancer.

**Case study: the PapGene test**

Researchers at the Johns Hopkins University and University of Pennsylvania Specialized Program of Research Excellence (SPORE) in Ovarian Cancer are similarly leading a project focused on the early and low-volume detection of high-grade serous ovarian cancer cells from liquid-based cervical cytology Pap smear samples and/or ctDNA present in blood. As one of four key projects under investigation at the SPORE, researchers are seeking to evaluate the clinical performance of a molecular-based cytology test (PapGene test), alone or in combination with circulating tumor DNA liquid biopsy test (ctDNA test), for early detection of high-grade serous ovarian cancer.

Source: The Hudson Institute of Medical Research; Kampan, N.C., Madondo, M.T., Reynolds, J., et al, 2020, Pre-operative sera interleukin-6 in the diagnosis of high-grade serous ovarian cancer, Nature Research, Scientific Reports, doi: 10.1038/s41598-020-59009; Johns Hopkins University/University of Pennsylvania SPORE of Ovarian Cancer, 2018, Applying PapGene test for early ovarian cancer detection, accessed at: https://trp.cancer.gov/spores/abstracts/johnshopkins_ovarian.htm#h03.

New approaches to imaging are also being explored. This approach supports greater multi-disciplinary research collaborations that bring together expertise in ovarian cancer as well as engineering and devices. One such collaborative project is being led by researchers from the University of Queensland and Mater Research.

In summary, future directions for research in early detection include:

- Discovery and development of novel serum biomarkers
- Research into circulating tumour DNA in blood and cervical secretions
- Development of new approaches to multi-modal screening
- Improve risk prediction algorithms to identify high-risk women
- Novel imaging technologies
- Novel screening approaches exploiting understanding of genomic instability.

## 4.3 Future directions for research: prevention

Ovarian cancer growth and treatment are influenced by both genetic risk and lifestyle factors. Women with mutations of the *BRCA* gene have a high lifetime risk of ovarian cancer. Intergenerational ovarian cancer research studies in Australia and overseas, such as TRACEBACK, have resulted in changes in clinical practice and in government funding for genetic testing. Women with endometriosis have been found to have a higher risk of ovarian cancer. On the other hand, some lifestyle factors may reduce the incidence of ovarian cancer in women, in particular the use of oral contraceptives, breastfeeding and pregnancy.

At the same time, the precise nature of the protective effects is not well understood and further research is needed to understand the underlying mechanisms of these lifestyle factors in order to inform potential future strategies for risk reduction in relevant populations. For example, it has been postulated that these genetic and lifestyle factors may combine to influence the tumour microenvironment, which may aid or impede the cancer's growth and/or resistance to treatment. For example, there is an increasing focus on better

understanding how the microenvironment may influence the cancer's ability to grow by developing new blood vessels (angiogenesis) and treatments to prevent this.[47]

Survey respondents indicated the focus for prevention research going forward was better understanding of both genetic and lifestyle factors (Figures 4.4 and 4.5), which would include a better understanding of the protective effects of some lifestyle factors including why some women are 'exceptional responders' (which intersects with treatment research) and whether lifestyle changes or other interventions have the potential to prevent the occurrence of ovarian cancer or improve response to therapy.[48] For example, key research questions include exploring whether the use of contraceptive pills or hormones in older women could reduce the incidence of ovarian cancer. Non-hormonal factors may also be important, with recent studies indicating that women who reported daily aspirin use had a 20 per cent lower risk of ovarian cancer compared with women who did not take aspirin regularly (Box 4.2).

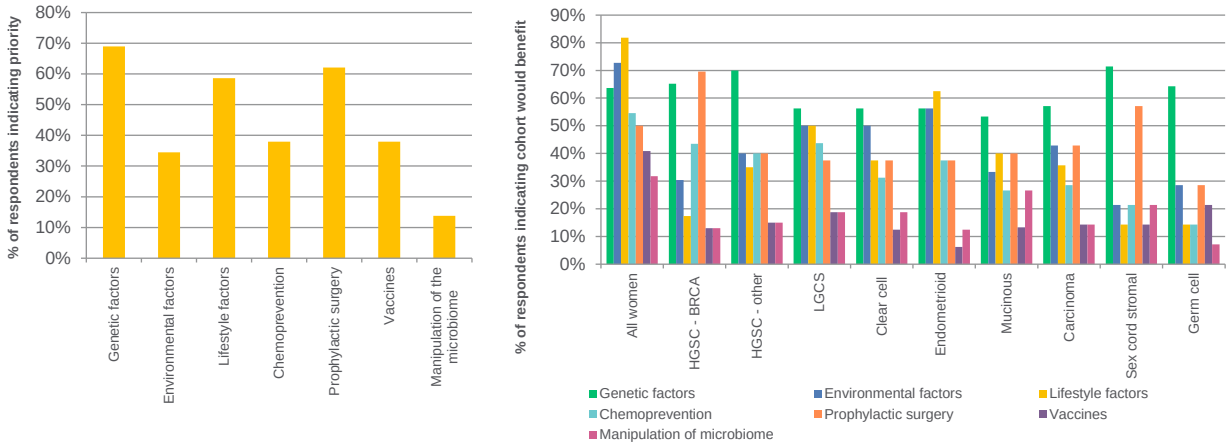
Survey respondents indicated there was also a need to explore the potential for expanded use of prophylactic surgery, particularly for women with an identified high risk. One approach is to research the benefits and risks of salpingectomy, which is the removal of the fallopian tubes only, as a prophylactic intervention, since many ovarian cancers actually originate in the fallopian tubes. This may avoid the early onset of menopause in young women caused by removing the ovaries, which may then be removed following natural menopause.[49]

**Figure 4.4: Researcher and clinician perspectives on priorities in prevention research**


Survey respondents indicated that different areas of research were likely to benefit specific sub-types of ovarian cancer (Figure 4.5). For example, while research into lifestyle factors was expected to benefit all women, further research into genetic factors was likely to benefit some of the rarer sub-types to a greater extent, including in particular sex cord stromal ovarian cancers. Similarly, research into potential for prophylactic surgery was identified to be important for women with *BRCA* mutations and sex cord stromal ovarian cancers.

[47] Bast, RC, Matulonis, UA, Sood, AK, Ahmed, AA, et al, 2019, Critical Questions in Ovarian Cancer Research and Treatment: Report of an American Association for Cancer Research Special Conference, Cancer, doi: 10.1002/cncr.320004.
[48] Saner, F.A.M., Herschtal, A., Nelson, B.H. et al. 2019, Going to extremes: determinants of extraordinary response and survival in patients with cancer. Nat Rev Cancer 19:339–348, doi: 10.1038/s41568-019-0145-5.
[49] Bowtell, DD, Böhm, S, Ahmed, AA, Aspuria, PJ, et al, 2015, Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer, Nat Rev Cancer, 15(11):668-679, doi: 10.1038/nrc4019

**Figure 4.5: Research priorities in prevention – survey results**




Source: Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B.

In conclusion, future directions for prevention research include:

- Work to move 'beyond *BRCA*' and develop better models for predicting the risk of ovarian cancer based on polygenic risk scoring
- Understand the underlying protective mechanisms of key lifestyle factors, including the potential use of hormones, contraceptive pills, and aspirin in at-risk groups
- Understand the influence of the microenvironment on cancer growth and resistance, and the potential to prevent this
- Continue to explore the impact of modifiable risk factors, including reductions in obesity, physical inactivity, diet and smoking, on survival outcomes.

**Box 4.2: Case studies in current prevention research**

**The STICs and STONEs clinical trial**

The regular use of aspirin has been associated with a reduced risk of cancer, particularly of the gastrointestinal tract, and a number of recent studies have consolidated the role of aspirin as a chemopreventive drug.

The STICs and STONEs trial builds on these findings and is currently investigating if aspirin reduces the risk of developing ovarian cancer in high-risk women with abnormalities in their *BRCA1* or *BRCA2* gene (or both). The trial is a randomised Phase II double-blind placebo-controlled trial, and is targeting the recruitment of 70 women over the 2019-2024 period.

The primary outcome measure of this study is measuring the frequency of precursor lesions, serous tubal intraepithelial carcinomas (STICs), and malignant lesions, serous tubal occult neoplasias - early (STONEs), in in the fallopian tube/ovary, at the time of risk-reducing surgery (bilateral salpingo-oophorectomy or bilateral salpingectomy inclusive of fimbria), in women carriers of *BRCA1/2* mutations who have been treated with a minimum of 6 months and a maximum of 2 years of daily aspiring or a placebo.

The study will also seek to improve on the understanding of how high-grade serous ovarian cancers form (tumourigenesis) and examination of the link between tumour formation and the microenvironment, as well as explore the feasibility of using ctDNA/cfDNA as a detection method for precursor and malignant tubal and ovarian lesions and will biobank samples for future correlative studies.

**Better understanding the role of hormones in ovarian cancer**

Researchers at the Hunter Medical Research Institute and University of Newcastle are investigating if a hormonal pill, similar to the contraceptive pill, might be developed to prevent ovarian cancer. The protective effects of oral contraceptive use and pregnancy against ovarian cancer are due to high levels of progesterone hormone, which inhibits oestrogen.

The research is seeking to further define the role of ovarian hormones in the initiation, progression and spread of ovarian cancer, and determine the effectiveness of drugs that mimic the anti-cancer activity of formulations

contained in oral contraceptives. Their work has shown that oestrogen promotes and progesterone suppresses the growth of precursor lesions by influencing important cell signalling (Wnt signalling) in fallopian tube cells. The aim is to develop an ovarian cancer prevention pill that is differentiated from birth control.

Source: ANZGOG, 2020, Clinical trials, accessed at: https://www.anzgog.org.au/research/trials/. ANZCTR, ACTRN12619000520134, accessed at: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376759&isReview=true; OCRF, 2019, Defining the roles of hormones in the pathogenesis of ovarian cancer, accessed at: https://www.ocrf.com.au/page/80/our-research-projects; Nagendra, PB, Goad, J, Rassam, L, Neilsen, S, et al, 2016, Ovarian hormones through Wnt signalling regulate the growth of human and mouse ovarian cancer initiating lesions, Oncotarget, 7(40): 64836-64853.

## 4.4 Future directions for research: treatment

For the past 30 years there has been a 'one size fits all' approach to treatment for women with ovarian cancer. While chemotherapy has resulted in improved progression-free survival and overall survival, most women experience relapse and subsequent disease resistance to chemotherapy, leading to poor survival outcomes.

The characterisation of the ovarian cancer sub-types may lead to a wider range of therapies, which can be tailored to the patient and her individual cancer (Table 4.1).

**Table 4.1: Potential expansion in treatment options by ovarian cancer sub-type**

| **Cellular Origin** | **Fallopian tube Epithelium** | **Fallopian tube Epithelium** | **Endometrium** | **Endometrium** | **Unknown** | **Ovary** | **Ovary** |
|---|---|---|---|---|---|---|---|
| | **Epithelial ovarian cancer (90% of all ovarian cancers)** | | | | | **Non-epithelial ovarian cancers** | |
| **Sub-type (histology)** | **High-grade serous** | **Low-grade serous** | **Clear cell carcinoma** | **Endometrioid carcinoma** | **Mucinous carcinoma** | **Germ cell** | **Sex cord stromal** |
| **% of all ovarian cancers** | **70-75%** | **3-5%** | **10%** | **10%** | **2-6%** | **3-5%** | **2-3%** |
| **Common mutations and molecular aberrations** | *TP53* (90%)<br>*BRCA 1/2* mutations (germline: 14%, somatic 7%, *BRCA1* methylation 11%)<br>*HRD* (10%)<br>*NF1* loss (17%)<br>*PTEN* loss (6%)<br>*RB1* loss (15%)<br>*CCNE1* amp (20%)<br>*AKT, PIK3CA, MYC* amp<br>Chromosomal instability<br>Aneuploidy<br>mTOR | *KRAS*<br>*NRAS*<br>*BRAF*<br>*EIF1AX*<br>*USP9X*<br>*FFAR1*<br>*NF1*<br>*HRAS* | *ARID1A*<br>*PIK3CA*<br>*PTEN*<br>*CTNNB1*<br>*KRAS*<br>*TP53*<br>*RPL22* | *ARID1A*<br>*PIK3CA*<br>*TERT* | *CDKN2A* (76%)<br>*KRAS* (64%)<br>*TP53* (64%)<br>*ERBB2* (26%)<br>*RNF43* (8-12%)<br>*BRAF* (8-12%)<br>*PIK3CA* (8-12%)<br>*ARID1A* (8-12%) | - | *FOX2L (87%)* |
| **Familial risk** | *BCRA1, BRCA2, BRIP1, PALB2, RAD51c, RAD541D* | | *Lynch Syndrome* | *Lynch Syndrome* | - | - | *Peutz-Jeghers Syndrome* |

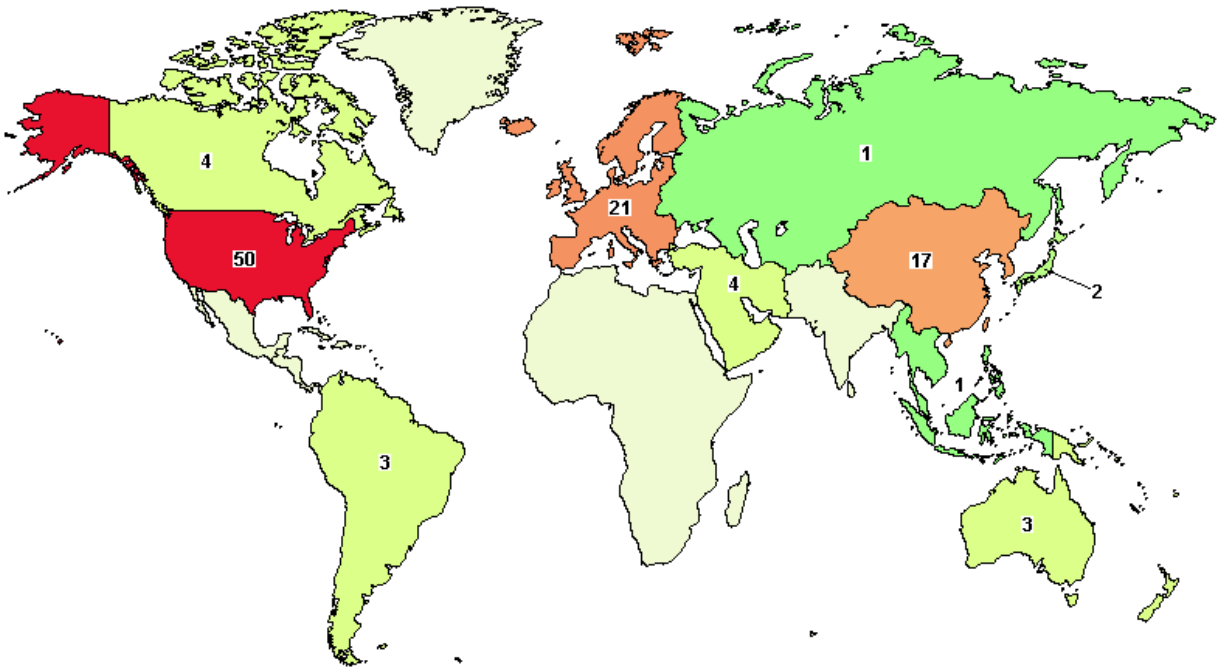
Source: High Grade Serous - Bowtell, DD, Böhm, S, Ahmed, AA, Aspuria, PJ, et al, 2015, Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer, Nat Rev Cancer, 15(11):668-679, doi: 10.1038/nrc4019; Mucinous - Cheasley, D., Wakefield, M.J., Ryland, G.L. et al. The molecular origin and taxonomy of mucinous ovarian carcinoma. Nat Commun 10, 3935 (2019). https://doi.org/10.1038/s41467-019-11862-x. Clear cell, Endometriod, Sex cord – Testa, U, Petrucci, E, Pasquini, L, Castelli, G., Pelosi, E, 2018, Ovarian Cancers: Genetic Abnormalities, Tumour Heterogeneity and Progression, Clonal Evolution and Cancer Stem Cells.

An example is the use of PARP inhibitors, which can improve outcomes for women with *BRCA* mutations and/or homologous recombination deficiency (HRD), a condition of genomic instability of an individual cancer arising from copy variations in DNA. Identification of other genetic mutations may lead to the development of treatments targeted to the specific mutation.

Such advances in the understanding of ovarian cancer biology have spurred investment in industry-led clinical trials as well as investigator-led trials. For example, in 2019, the Pharmaceutical Research and Manufacturers of America's *Medicines in Development* report listed 62 therapies in development for ovarian cancer, up from 49 reported in 2013. In contrast, there was reported development of 91 new therapies for breast cancer in 2013, nine for cervical cancer and a total of 139 medicines to treat cancers affecting women (2013 data).

Data from Clinicaltrials.gov indicates that in the 2019 calendar year 74 clinical trials were open globally; but of this, only three studies were hosted at Australian sites (Figure 4.6).

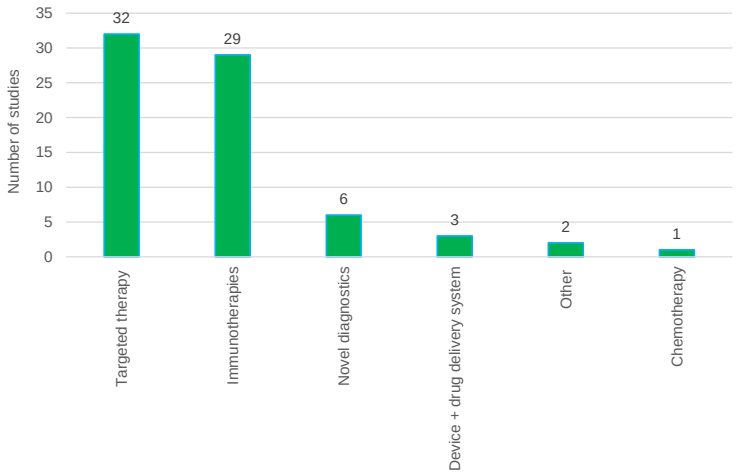
**Figure 4.6: Industry-led clinical trials — 2019 snapshot**




Source: Clinicaltrials.gov. Some trials may be open in more than one jurisdiction.

These clinical trials were investigating a range of new therapies including targeted therapies, such as TKI inhibitors, immunotherapies, novel diagnostics and novel device and drug delivery systems. Many of these therapies are proposed to be delivered in combination with chemotherapy agents (Figure 4.7).

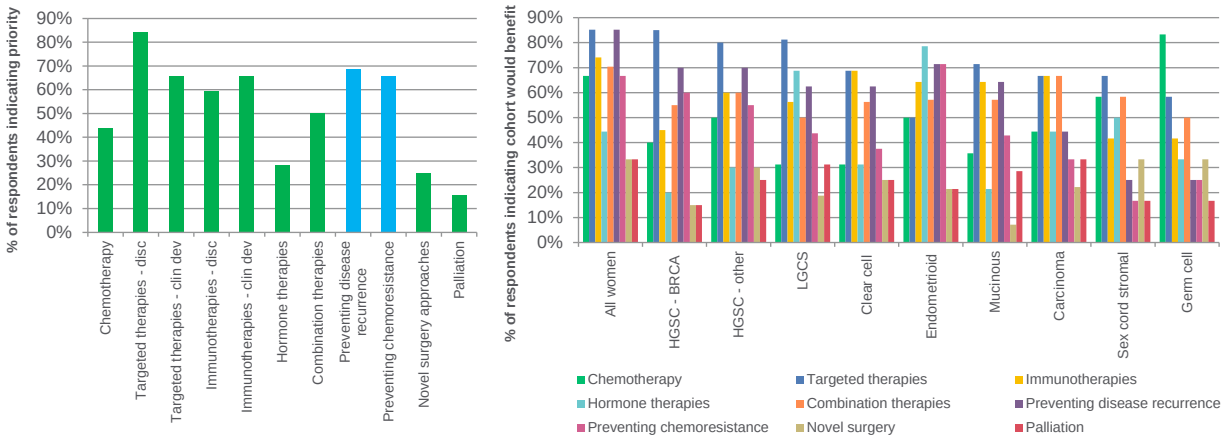
**Figure 4.7: Therapies in development — 2019 snapshot**




Source: Clinicaltrials.gov

This pattern of therapy development aligns with the Survey of Ovarian Cancer Researchers, Clinicians and Consumers. Researchers and clinicians highlighted targeted therapies as particularly important for serous sub-types (high-grade and low-grade), while hormone therapy research may be important for endometrioid cancers. In contrast, germ cell tumours are usually cured with chemotherapy (Figure 4.8).

**Figure 4.8: Areas of research priorities within treatment and recurrence**




Source: Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B. Notes: Disc is short for 'Discovery', Clin dev is short for clinical development.

Important research foci include the concept of moving 'beyond *BRCA*' to expand treatment options, most importantly where cancer has become 'chemotherapy resistant'. In contrast some women experience very long remissions following platinum-based chemotherapy and are classified as 'exceptional responders'. What differentiates cancer in these women from patients with poorer responses is an important research question.

As recurrence and therapy resistance can be increasingly predicted with precision, some women could be stratified and triaged for clinical trials as part of first-line therapy, rather than waiting for relapse/recurrence and subsequent drug resistance.

Critical research includes understanding the individual patients' immune responses to ovarian cancer. Some patients have immunologically 'cold' cancers, which means that their immune responses to the ovarian cancer are muted. New studies are exploring the potential

to develop 'personalised vaccines' for these patients, and early results have shown some improvement in survival.[50]

New approaches to improving cytoreductive surgery in order to get a woman to zero residual disease or as close as possible were also highlighted by stakeholders. In some jurisdictions additional training is undertaken to improve outcomes from surgery, and novel approaches are being trialed including the use of radioactive agents to better highlight disease (See Box 4.3) and hyperthermic (or heated) intraperitoneal chemotherapy (HIPEC) to intensify and better target the chemotherapy.[51]

Supportive care is also increasingly identified as a core component of treatment; in particular, research continues to develop the evidence base for exercise and understand its impact on overall survival in order to inform practice change and government funding for services.[52] There have been very few studies on the effects of pre-diagnosis physical activity and post-diagnosis physical activity on all-cause mortality for ovarian cancer; the American College of Sports Medicine Roundtable Report identified only two studies in ovarian cancer, compared to 30 in breast cancer, 15 in colorectal cancer, and 10 in prostate cancer.[53] Importantly, exercise medicine in cancer has been shown to benefit patients across a range of symptoms, including not only cancer-specific mortality and all-cause mortality, but also reduced anxiety, fewer depressive symptoms, less fatigue, better quality of life, and improved physical function.[54]

In summary, future directions for research into treatments include:

- Molecular profiling and histology to identify and validate new therapeutic targets for treatment
- Evaluate use of combination therapies to overcome drug resistance in some sub-types (e.g., PARP inhibitors)
- Evaluate synthetic lethality of novel agents and/or a combination of agents
- Understand exceptional responders
- Enhancing the immune response to ovarian cancer
- Stem cell-directed therapeutics
- Develop limited evidence base with respect to potential for supportive care (e.g., exercise) to improve survival outcomes.

[50] Bast, RC, Matulonis, UA, Sood, AK, Ahmed, AA, et al, 2019, Critical Questions in Ovarian Cancer Research and Treatment: Report of an American Association for Cancer Research Special Conference, Cancer, doi: 10.1002/cncr.320004.
[51] van Driel, WJ, Koole, SN, Sikorska, K, et al. 2018, Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N Engl J Med., 378(3):230-240. doi:10.1056/NEJMoa1708618
[52] Jones, T, Sandler, C, Spence, R, and Hayes, S, 2020, Physical activity and exercise in women with ovarian cancer: a systematic review, Gynaecologic Oncology.
[53] Patel, AV, Friedenreich, CM, Moore, SC, Hayes, SC, et al, 2019, American College of Sports Medicine Roundtable Report on Physical Activity, Sedentary Behaviour and Cancer Prevention and Control, Medicine & Science in Sports & Exercise, doi: 10.1249/MSS.0000000000002117.
[54] Schmitz, KH, Campbell, AM, Stuiver, MM, Pinto, BM, et al, 2019, Exercise is Medicine in Oncology: Engaging Clinicians to Help Patients Move through Cancer. Strong evidence for reduced anxiety, fewer depressive symptoms, less fatigue, better quality of life, improved physical function. Moderate evidence for improvement in sleep and bone health. Insufficient evidence for cardiotoxicity, chemo-induced peripheral neuropathy, cognitive function, falls, nausea, pain, sexual function, and treatment balance. See also Hayes, SC, Newton, RU, Spence, RR, Galvao, DA, 2019, The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management, Journal of Science and Medicine in Sport, doi: 10.1016/j.sams.2019.05.003.

**Box 4.3: Case studies in treatment**

**Precision medicine with the INOVATe program**

Precision medicine aims to improve patient outcomes by moving treatment from the traditional "one-size-fits-all" approach to one that takes individual differences into account. INOVATe (Individualised Ovarian Cancer Treatment Through Integration of Genomic Pathology into Multidisciplinary Care) is a research program that has been established to develop strategies to better define ovarian cancer patient subsets, based on tumour genomic profiling in conjunction with conventional histological subtyping, to optimise the selection of patients for novel molecularly-targeted clinical trials and ultimately to individualise treatment.

INOVATe is a multi-centre, collaborative research program being conducted in the major gynaecological oncology treatment and research centres across Sydney. All women with ovarian, fallopian tube and primary peritoneal cancers are eligible for inclusion.

In the INOVATe trial, next generation multi-gene mutation testing and whole genome copy number profiling is conducted and women are then given standard first-line treatments. Using the multi-gene mutation testing and whole genome copy number tests, a predictive logistic regression model is used to determine the patient's homologous recombination repair deficiency (HRD) status based on three genomic lesion scores (HRD score) obtained from single nucleotide polymorphisms (SNP) array data. In the event of relapse or disease progression, the patient may be enrolled in a biomarker-based clinical trial based on the results of the molecular test.

**The Precision Medicine Program in Ovarian Cancer at the Hudson Institute of Medical Research**

The Precision Medicine Program in Ovarian Cancer (PMPOC) was established as a way to develop individualised, targeted therapeutic strategies for every patient. Each individual responds differently to treatment and over time the PMPOC allows clinical research teams to examine and predict individual patient responses and specifically tailor their treatments for improved outcomes.

Using the PMPOC, clinical research teams can assess patient responses to ~2000 different drugs in the lab, and identify the therapies that will be most effective for that individual. This information is obtained over a period of a few weeks, providing valuable treatment information in a relevant time frame for clinical use. The patient-specific model is also analysed at the molecular level, and the information combined to assist in identifying markers for responsiveness to the drugs. Over time, this information can be used to further refine treatments and predict when treatment should be adapted to continue its effectiveness.

The PMPOC platform has been developed and validated, and is now functional. Patient tumour samples are taken at primary diagnosis, and a specific cellular model (a "patient avatar") is created that defines their disease at that point in time. At present, the PMPOC program is in its "pilot" phase, screening a small group of ovarian cancer patients to establish the potential impact of predictive screening on clinical outcomes.

At the broadest level, the program has successfully demonstrated the potential to accurately predict individual patient responses to standard chemotherapy and identify patients who may benefit from different approaches for initial disease management. The program is also identifying potential new therapeutic combinations that provide more effective disease suppression, and thus a greater likelihood for successful treatment. This ongoing work, on conclusion of the pilot phase, will proceed into formal clinical trials.

**New directions in imaging for diagnosis and treatment**

The goals of primary surgery for ovarian cancer are proper staging (in early disease) and optimal cytoreduction/debulking (in advanced disease). Optimal debulking surgery is defined as surgery that results in no macroscopic residual disease.

Fluorescence image-guided surgery represents a promising intraoperative guidance technique to improve debulking completeness and detect recurrent disease. A number of contrast agents have been used in clinical trials for intraoperative fluorescence imaging but there is a demand for the development of more tumor-selective contrast agents.

Researchers at the University of Queensland and Mater Research are seeking to revolutionise care of advanced ovarian cancer. Supported by new funding from the MRFF program in 2020, the research team is seeking to develop a new radio-imaging agent (10D7) to guide diagnosis and targeted therapy for epithelial ovarian cancer. Researchers have both discovered and patented this new agent and, in this study, will label it with a radioactive particle to determine its biodistribution in patient tumours and normal organs, and its safety. The study results have significant potential to increase options for advanced ovarian cancer not responsive to current treatments.

**Exercise is medicine: the ECHO and ECHO-R trials in ovarian cancer**

The benefits of physical activity and exercise pre-diagnosis and post-diagnosis have been progressively demonstrated for a range of cancers, with strong evidence (Level 1 evidence) being developed that exercise substantially improves survival outcomes as well as a range of other physical, social and wellbeing outcomes, including reduced anxiety, reduced depression, reduced fatigue, improved quality of life and improved physical

function. Very few studies have been undertaken in ovarian cancer leading to limited evidence of benefit for or against exercise programs. Moreover, like medicine, exercise programs are not 'one-size-fits all' prescriptions; programs must be developed that allow for appropriate interventions depending on a person's personal circumstances.

ECHO is a multi-centre, randomised trial funded by Cancer Australia in 2020. The ECHO trial will recruit 500 women to determine if an individually-tailored exercise program during chemotherapy for ovarian cancer can:

- Improve progression-free survival
- Improve overall survival
- Improve physical wellbeing and function
- Quality of life at 6 and 12 months post-randomisation
- Improve chemotherapy adherence
- Lead to fewer and less severe adverse events during chemotherapy
- Lower health care costs for complications of ovarian cancer treatment.

The ECHO trial represents one of only four trials worldwide seeking to address evidence gaps for the benefits of exercise in ovarian cancer. Once completed, we will know to what extent women may benefit from exercise following diagnosis with ovarian cancer, and what exercise treatment should look like (that is, what women should do, how and when).

Similarly, the ECHO-R trial is a Phase II trial designed to evaluate the feasibility, safety and potential efficacy of an individually-tailored exercise intervention during chemotherapy for recurrent ovarian cancer. Funded by the MRFF in 2020, the ECHO-R trial will begin recruiting patients in July 2020 through 2022.

Source: Westmead Institute for Medical Research, 2020, INOVATe, Program overview, accessed at: https://www.westmeadinstitute.org.au/research/featured-projects/inovate-(1)/overview; Cancer Institute NSW, 2020, Individualised Ovarian Cancer Treatment through Integration of Genomic Pathology into Multidisciplinary Care – An Analysis of Initial Recruitment to the INOVATe Study, accessed at: https://www.cancer.nsw.gov.au/getmedia/b112bc6d-5127-4406-8f8e-43e06847350c/Anna-deFazio-Individualised-Ovarian-Cancer-Treatment-through-Integration-of-Genomic-Pathology-into-Multidisciplinary-Care.pdf; Di Lorenzo, G, Ricci, G, Severini, GM, Romano, F, and Biffi, S. 2018, Imaging and therapy of ovarian cancer: clinical application of nanoparticles and future perspectives, Theranostics, 8(16):4279-4294. doi:10.7150/thno.26345; Basu S, Rubello D, 2008, PET imaging in the management of tumors of testis and ovary: current thinking and future directions, Minerva Endocrinol., 2008;33(3):229-256; Grant Connect, 2020, Grant Award View - GA79774, accessed at: https://www.grants.gov.au/?event=public.GA.show&GAUUID=18A0446C-B465-1F9F-0EFAE25C7661AC5B; ANZGOG, 2020, Principal Investigator Professor Sandi Hayes comments on ECHO, the first ever exercise intervention clinical trial run by ANZGOG, accessed at: https://www.anzgog.org.au/sandi-hayes-echo/. Grants Connect, 2020, The ECHO trial: Exercise during CHemotherapy for Ovarian cancer, Grant Award View - GA52649.

## 4.5 Future directions for research: recurrence

For many years, the standard of care for women with advanced ovarian cancer has been a combination of surgery and chemotherapy with carboplatin and paclitaxel. Despite a high initial response rate, most women experience recurrence of cancer. Recurrent cancer will frequently develop resistance to chemotherapy leaving few therapeutic options and subsequent high mortality.

Beyond an increased understanding of the inherent genomic instability of ovarian cancers, the mechanisms of why ovarian cancers recur and become resistant to therapies are poorly understood. Additionally, resistance is not limited to chemotherapies, and has also been observed among women previously treated with PARP inhibitors.

Resistance to chemotherapy is observed across a variety of cancers types giving rise to new theories of cancer initiation and progression. For example, research focused on the stem cell theory of cancer and the identification of 'leader cells' postulates that small numbers of cells may evade treatment and ultimately recur in a more resistant form. Identifying and better understanding these specific cells and their mechanisms of action may support new treatment approaches that mitigate disease recurrence and resistance, and improve overall survival.

Thus, future directions for research into recurrence include:

- Understand intrinsic and acquired chemoresistance

- Understand how the microenvironment contributes to recurrence and resistance
- Understand response and resistance to PARP inhibitors among *BRCA* and HRD cohorts
- Understand cancer stem cells, leader cells and their role in disease recurrence.

**Box 4.4: Case study in recurrence**

**Understanding the role of 'leader cells' in metastasis and recurrence**

Epithelial ovarian cancer metastasis is driven by spheroids, which are heterogeneous cancer cell aggregates released from the primary tumour mass that passively disseminate throughout the peritoneal cavity to promote tumour spread, disease recurrence, and acquired chemoresistance.

Despite their clinical importance, the molecular events that control spheroid attachment and invasion into underlying healthy tissues remain poorly understood. A recent study at the Hudson Institute of Medical Research identified a sub-population of highly motile, invasive cells which were termed 'leader cells'.

The study team found these leader cells expressed the basal epithelial marker KRT14 and the loss of KRT14 completely abrogated the invasive capacity of these cells, although they had no impact on cell viability or proliferation, suggesting these leader cells play an invasion-specific role in cancer spread. These leader cells could be clinically relevant targets in directed anti-tumour therapies.

KRT14 expression was negatively associated with progression-free survival and response to therapy in ovarian cancer patients. Similar correlations have been observed in other tumour types, where the KRT14-expressing cell subset is increased in urothelial cancers in response to chemotherapy. However, the restricted occurrence of KRT14 expression to a sub-population of cells likely masks their overall influence in publicly available datasets; thus, the influence of KRT14 expression may be more significant than is currently understood.

Source: Bilandzic, M, Rainczuk, A, Green, E, Fairweather, N, Jobling, TW, Plebanski, M, and Stephens, AN, 2019, Keratin-14 (KRT14) Positive Leader Cells Mediate Mesothelial Clearance and Invasion by Ovarian Cancer Cells. Cancers, 11(9), 1228, doi: 10.3390/cancers11091228.

## 4.6 Future directions for research: biology and aetiology

The past 15-20 years of research have led to significant changes in the understanding of ovarian cancer biology.

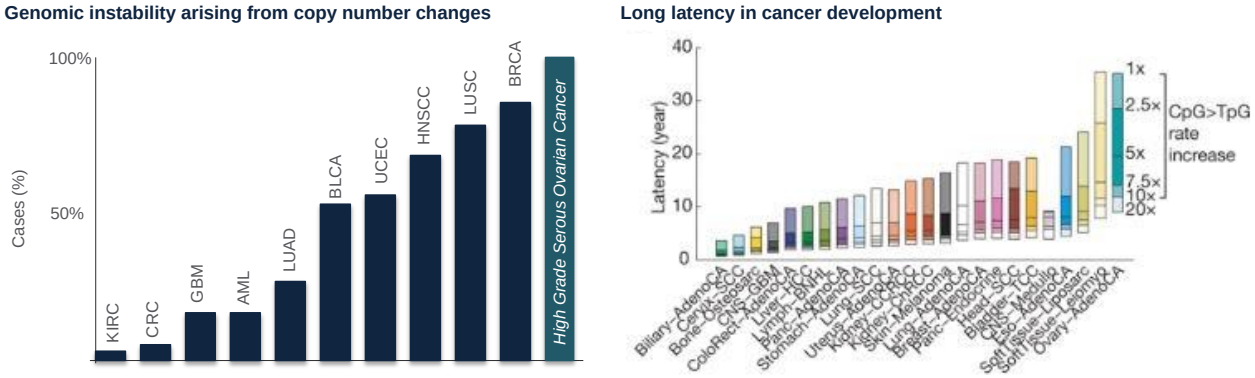
It is now understood that ovarian cancers can arise not only out of the ovary, but also from the fallopian tubes and other tissues. Major international studies, such as the Cancer Genome Atlas, have enabled the characterisation of seven major histological sub-types in ovarian cancer and have also revealed unique characteristics of ovarian cancer as distinct from other cancers including:

- Long latency in ovarian cancer development, with studies indicating for many women the genetic changes leading to cancer may have been occurring over a woman's entire adult lifetime (Figure 4.9)
- Significant genomic instability typified by a high number of copy changes in the cancer genome, which present unique challenges for treatment and may limit the capacity to repurpose therapies that have 'worked' in other cancers (Figure 4.9).[55]

Recent studies have also identified an average time of 6.5 years between the development of pre-cursor lesions, termed serous tubal intraepithelial carcinomas (STICs), and the initiation of ovarian cancer, with a range of between 1.4 years to 10.7 years, indicating a very rapid onset for many women.[56]

[55] Gerstung, M, Jolly, C, Leshchiner, I, Dentro, SC, et al, 2020, The evolutionary history of 2,658 cancers, Nature, 578, doi: 10.1038/s41586-019-1907-7.
[56] Labidi-Galy, S, Papp, E, Hallberg, D, et al, 2017, High grade serous ovarian carcinomas originate in the fallopian tube, Nature Commun, 8:1093, doi: 10.1038/s41467-017-00962-1.

**Figure 4.9: Ovarian cancer distinguished by significant genomic instability and long latency compared to other cancers**




Source: Bowtell, D, Böhm, S, Ahmed, A, et al., 2015, Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer, Nat Rev Cancer 15:668–679, doi: 10.1038/nrc4019; and Gerstung, M, Jolly, C, Leshchiner, I, et al. 2020, The evolutionary history of 2,658 cancers, Nature, 578:122–128; doi: 10.1038/s41586-019-1907-7. Notes: AML = acute myeloid leukaemia; BLCA = bladder urothelial carcinoma; BRCA = breast invasive carcinoma; CRC = colorectal carcinoma; GBM = glioblastoma; HNSCC = head and neck squamous cell carcinoma; KIRC = kidney clear-cell carcinoma; LUAD = lung adenocarcinoma; LUSC = lung squamous cell carcinoma; UCEC = uterine carcinoma. Image reproduced with permission.

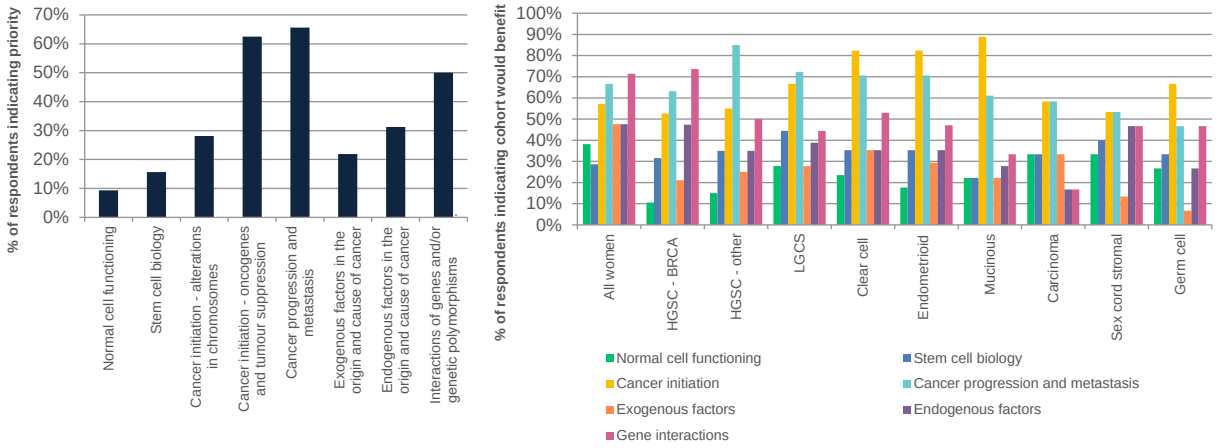
In spite of these significant advances, however, stakeholders indicated there is still much about ovarian cancer that is not well understood.[57] For example, there remains relatively significant debate with respect to the specific cells of origin and still limited understanding of how the different sub-types progress (Figure 4.10).

**Figure 4.10: Researcher perspectives on future biology and aetiology research priorities**


[57] Nikitin, AF, Hwang, C, Cheng, C, et al, 2013, Ovarian surface epithelium at the junction area contains cancer-prone stem cell niche, Nature 495(7440), doi: 10.1038/nature11979; Auersperg, N, 2013, The Stem-Cell Profile of Ovarian Surface Epithelium Is Reproduced in the Oviductal Fimbriae, With Increased Stem-Cell Marker Density in Distal Parts of the Fimbriae, Int J Gynecol Pathol, 32(5):444-53. doi: 10.1097/PGP.0b013e3182800ad5.

Stakeholders indicated that a better understanding of cellular origins of cancer, cancer initiation and progression for all sub-types would support advances across research areas including early detection and screening, prevention, treatment and recurrence. In particular, survey respondents indicated the focus for biology and aetiology going forward is cancer initiation, progression and metastasis, and gene interactions (Figure 4.11). Understanding cancer initiation was identified to be particularly important for some of the rarer ovarian cancer sub-types, including clear cell, endometrioid and mucinous ovarian cancers.

**Figure 4.11: Areas of research priorities within biology and aetiology**




Source: Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B.

In summary, future directions for research include:

- Follow-up studies to understand the initiation, progression and metastasis of all ovarian cancer sub-types to enable screening, early detection and precision medicine, including improving the understanding of specific cells of origin and disease progression for all sub-types
- Understand cancer stem cell biology, their role in metastasis and potential for therapeutic targeting
- Understand DNA methylation, gene expression and ovarian cancer risk
- Identify and genetically characterise early markers of cancer formation and progression (precursor lesions in fallopian tubes, ovaries and peritoneum)
- Improve risk prediction algorithms
- Translate fundamental biology discoveries to the clinic.

**Box 4.5: Case study in biology research**

**Practice change resulting from understanding cancer biology – the TRACEBACK program**

Data show that 44 per cent of women with non-mucinous ovarian cancer positive for *BRCA1/2* mutations did not report a family history of breast or ovarian cancer.

In May 2016, the Division of Cancer Prevention and the Division of Cancer Control and Population Sciences at the National Cancer Institute convened a workshop to discuss a conceptual framework for identifying and genetically testing previously diagnosed but unreferred patients with ovarian cancer and other unrecognised *BRCA1* or *BRCA2* mutation carriers to improve the detection of families at risk for breast or ovarian cancer.

The concept, designated TRACEBACK, was prompted by the recognition that although *BRCA1* and *BRCA2* mutations are frequent in women with ovarian cancer, many women have not been tested, especially if their diagnosis predated changes in testing guidelines.

The failure to identify mutation carriers represents a lost opportunity to prevent cancer in unsuspecting relatives through risk-reduction intervention in mutation carriers and to provide appropriate reassurances to noncarriers. The TRACEBACK program has provided an important opportunity to reach families from racial, ethnic and socioeconomic groups who historically have not sought or been offered genetic counselling and testing and thereby contribute to a reduction in health disparities in women with germline *BRCA* mutations.

Source: Samimi, G, Bernardini, MQ, Brody, LC, et al, 2017, Traceback: A Proposed Framework to Increase Identification and Genetic Counseling of BRCA1 and BRCA2 Mutation Carriers Through Family-Based Outreach, Journal of Clinical Oncology, 35:20, 2329-2337.

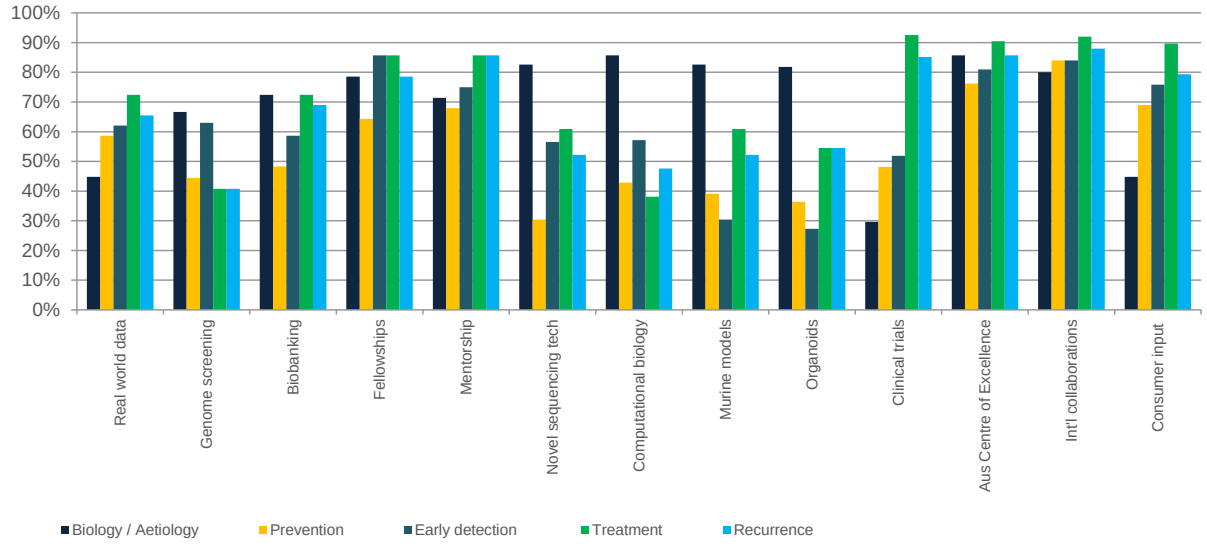
## 4.7 Key enabling infrastructure

Improving survival through high-impact research will depend on the right infrastructure and capabilities being brought together. While Australia is a small country, it has many advantages and has been able to punch above its weight due to the calibre of its research community, its participation in leading international consortia and clinical trials, and strategic investments in key infrastructure such as biobanking capabilities. Continued support for enabling infrastructure is critical to support a more rapid improvement in outcomes for women with ovarian cancer. Stakeholder comments provided through the survey regarding key enabling infrastructure are shown in Figure 4.12.

**Figure 4.12: Critical enabling infrastructure for ovarian cancer research to drive improvements in survival – researcher and clinician perspectives**


Investments in enabling infrastructure were identified to be important for all phases of research, with some notable variations observed in the responses (Figure 4.13). For research into biology and aetiology for example, sequencing technologies, computational biology capabilities and experimental models (murine models and organoids) were identified as crucial. Researchers and clinicians consistently and strongly emphasised the importance of mechanisms to support high-impact collaborations through the establishment of an Australian Centre of Excellence and international collaboration. Fellowships were also identified to be important enabling infrastructure to all phases of research.

**Figure 4.13: Criticality of key enabling infrastructure by research phase**




Survey of Ovarian Cancer Researchers, Clinicians and Consumers, See Appendix B.

These ideas, combined with stakeholder consultations, were distilled down to five key areas of enabling infrastructure needed to support a comprehensive program of high-impact research (Figure 4.14):

- Expansion of biobanking linked to real world data
- Pre-clinical models and sequencing capabilities
- Support for collaboration
- Support for Early and Mid-Career Researchers through mentorship and fellowships
- Health services implementation research and policy action to improve awareness of ovarian cancer risks and symptoms and access to quality and safe care.

**Figure 4.14: Enabling infrastructure needs**

**Biobanking linked to outcome data**

- ✓ Ensuring specimens annotated and linked to real world data
- ✓ Invest in platforms that are easy to interrogate and share
- ✓ National real world data linkage projects

**Pre-clinical models & sequencing**

- ✓ Development of new mouse and organoid models
- ✓ Access to cell lines, organoids
- ✓ PDX to inform treatment
- ✓ Sequencing capabilities

**Collaboration**

- ✓ Leverage universal healthcare system
- ✓ Reduce competition for patients
- ✓ Improve data and sample sharing
- ✓ Consortia efforts have supported breakthroughs

**Early & Mid-Career Mentorship and Fellowships**

- ✓ Attract, retain and develop best scientists through secure employment and mentorship

**Awareness and Access**

- ✓ 45% of women unable to identify *any* symptom
- ✓ Poor understanding of risk factors
- ✓ Educating GPs on symptoms
- ✓ Referral to gyn-onc specialists, supportive care

### *Biobanking and linked real world outcome datasets*

Across Australia there are a range of biobanks collecting ovarian cancer samples in operation, including:

- The OCRF biobank in Victoria and South Australia
- The Australian Ovarian Cancer Study Biobank in Victoria
- The Gynaecological Oncology Biobank at Westmead biobank in NSW
- The Hunter Medical Research Institute biobank in NSW
- Kolling Institute Biobank in NSW
- Mater Institute Biobank in Queesland
- Western Australian Gynaecologic Oncology Biospecimen Bank
- kConFab Biobank.

Stakeholders indicated that while these Australian biobanks are a key foundational infrastructure for research their capabilities could be improved to support accelerated research outcomes. A particular challenge is the ongoing funding for biobanks, since many operate via the support of charitable foundations rather than governments, and ensuring ready access to samples.

Notably, a national system for collecting and biobanking human tissue samples was a recommendation of the 2016 National Research Infrastructure Roadmap for low survival cancers. Specifically, it recommended establishing standards for data gathering and sample curation to assist in both the sharing of materials and support of research collaborations. Minimum data standards for genomics, proteomics and metabolomics should be articulated, as well as relevant health, lifestyle and clinical data, to maximise the potential for data linkage.

With respect to high quality, real world data, the Federal Government has committed in its recent MRFF announcements to developing a National Clinical Quality Registry at Monash University and funding health services implementation research into variation in gynaecological outcomes through the OVARIAN study at QIMR Berghofer Medical Research Institute. Expanding real world datasets for research through the AIHW remains an important and ongoing priority.

Opportunities to accelerate research capabilities:

- Support expansion and improvement of biobanking capabilities
  - Nationally-standard annotation
  - Improve interrogation and sharing of data across biobanks nationally
  - Real world data linkage
- Develop a National Clinical Quality Registry for ovarian cancer
- Expand availability of real-world data for research through the AIHW.

### *Pre-clinical models and sequencing capabilities*

Improvements in the understanding and treatment of a range of cancers has depended on the use of animal models and the development of advanced genomic sequencing technologies.

To improve the understanding of ovarian cancers better pre-clinical mouse models are needed. Mice are often used as *in vivo* models for understanding human disease, due to the similarity of the mouse and human genomes. Traditionally, pre-clinical research has relied on the use of immunologically-compromised mice into which cell lines are injected. Because the immune system plays such an important role in the development of ovarian cancer, however, these traditional mouse models fail to meet the needs of ovarian cancer research. As a result, only 5% of potential ovarian cancer therapies that have been evaluated in mice have demonstrated sufficient clinical activity in phase III clinical trials to eventually be licensed. These limitations highlight the need for improved pre-clinical mouse models for ovarian cancer.

In addition, while cell lines remain important, new cell culture platforms are in development and use to better capture the heterogeneity and complexity of ovarian cancer, including patient-derived xenografts (often referred to as PDX) or 3D organoid cultures. Patient derived xenografts can provide more reliable information about tumour biology than traditional cell lines, including recapitulating the three-dimensional structure of the cancer and the interaction of cancer cells with stroma and blood vessel infiltration. However, xenografts require significant investment to maintain, are poorly suited for large-scale drug screening or for genetic manipulation, and undergo rapid mouse-specific tumour evolution. Organoid cultures can be clonally established from single cells derived from tumour tissue, which allows for the study of tumour heterogeneity; a recent *Nature Medicine* article identified 56 different organoid cultures in use. Organoids allow rapid assaying of phenotype-genotype correlations and drug sensitivity.

These research requirements will further keep upward pressure on demand for sequencing capabilities across research sites, including in particular single cell sequencing, and the computational biologist workforce to expand analytical throughput.

Opportunities to accelerate research capabilities:

- Fund research to support development of animal models, cell lines, patient-derived xenographs, and organoids
- Invest in advanced sequencing capabilities.

### *Collaboration*

While research remains in many respects a competitive endeavour, the importance of collaboration is significant, especially for rarer cancer types such as ovarian cancer. The absence of collaboration sees slower patient recruitment into trials, increasing competition for patients and the risk of reduced statistical power or delays in study completion. Critically, Australia has the potential to use its smaller size and comparatively universal health care system to the advantage of women with ovarian cancer, and is placed to support greater collaboration both domestically and internationally.

In the United States, for example, there are four major Specialised Programs for Ovarian Cancer Research Excellence (SPOREs) funded by the National Cancer Institute through its Translational Research Program today. These include:

- The Johns Hopkins and University of Pennsylvania SPORE
- The Mayo Clinic
- The Roswell Park Comprehesive Cancer Institute and University of Pittsburgh Hillman Cancer Center
- The University of Texas at Austin.

Each of these Ovarian SPOREs has a defined set of projects backed by administrative, biobanking, and biostatistics capabilities, with the goal of accelerating research outcomes. Most recently, a new SPORE was announced last year to support a research collaboration focused on early detection research (Box 4.6).

**Box 4.6: US Government investing in collaboration for an early detection research breakthrough**

The US Department of Defense is funding an initiative that brings together top ovarian cancer researchers in an effort to better enable the early detection and prevention of the disease.

The program, known as the DoD and SPORE Ovarian Cancer Omics Consortium, includes researchers from both government and academic centers. It is led by teams from:

- The Roswell Park Comprehensive Cancer Center in Buffalo, New York
- The Inova Health System, a non-profit organization based in Falls Church, Virginia
- The Mayo Clinic Cancer Center located in Rochester, Minnesota
- The University of Texas MD Anderson Cancer Center in Houston, Texas
- The US Department of Defense.

Survivors of ovarian cancer, patient advocates, and physicians will also offer guidance with, among other things, a 6-member patient advisory council.

The effort's overriding goal is to identify serous tubal intraepithelial carcinoma precancerous lesions (STICs) at their earliest stages. The DoD's developmental grant is funding research based on recent discoveries regarding the origin of ovarian cancers and "omics," a term that refers to new sequencing-based methods that provide a deep characterization of various types of molecules that play crucial roles in human biology.

The first phase of the initiative is financed by a grant for $544,360 from the DoD. Those funds support building the infrastructure and teams to launch the program. The next phase will include gathering biospecimens and validating biomarkers to further develop screening and early detection methods.

Dr Larry Maxwell, Chair of Obstetrics and Gynecology at Inova Fairfax Women's Hospital, is co-PI of the new effort as well as co-PI for the Department of Defense (DoD) Gynecologic Cancer Center of Excellence (GYN-COE):

> *"I don't believe there has ever been such a united effort in medical science among researchers from both government and academic research organizations. This project will rely on expertise and resources that could only be realized through such a cooperative and collaborative effort. We're able to set our sights much higher by working together and creating a force multiplying synergy."*

This initial phase of work, funded by an initial $544,360 grant from the DoD (award number W81XWH-19-1-0183), will focus on setting up the infrastructure and teams to enable this ambitious effort. Longer-term goals focus on gathering and harmonizing biospecimens and discovering and validating biomarkers to inform early detection and screening for STIC and ovarian cancer.

Source: Printz, C., 2020, Research teams unite to develop an early detection test for ovarian cancer, *Cancer*, ACS Journals, 28 April 2020, doi.org/10.1002/cncr.32917

The International Genome Consortia project supported by Australian Governments delivered significant advances in the understanding of genomics which has benefitted a range of cancers, including ovarian cancer. Major international consortia focused on ovarian cancer have included the Ovarian Cancer Association Consortium, the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), the Ovarian Tumour Tissue Analysis consortium, the Ovarian Cancer Cohort Consortium, the Collaborative Group on Epidemiological Studies of Ovarian Cancer (The Oxford Collaborative Group), and the Ovarian Cancer in Women of African Ancestry consortium.

As evident in Figure 4.13 above, supporting the creation of an Australian Centre of Excellence and/or supporting international collaborations has the potential to support research across all phases and substantially accelerate research outcomes, particularly focused around significant disease priorities such as early detection, precision medicine and recurrence.

Opportunities to accelerate research:

- Establish an Australian Centre of Excellence in Ovarian Cancer focused around disease priorities
- Support international collaboration.

### *Early and mid-career researcher development*

Developing and retaining high calibre researchers in ovarian cancer depends on career security and progression. Many stakeholders highlighted the risks of losing quality candidates to other fields with overall higher funding levels, which can limit future research potential for the field.

The US Department of Defense's Ovarian Cancer Research Program leadership identified a similar challenge in the US and developed a mentorship program called The Academy which seeks to develop and retain high-quality early career researchers and support a 'team based' approach to science supported by a capacity to engage with consumers.

Stakeholders indicated that supporting fellowships and mentorship models could be expanded across Australia.

Opportunities to accelerate research:

- Develop and implement a formal mentorship model in ovarian cancer
- Fund fellowships to support high-calibre researchers to remain in ovarian cancer.

**Box 4.7: A formalised approach to early and mid-career mentorship: The OCRP Academy**

The OCRP Ovarian Cancer Academy, initially created in 2009, is a unique, interactive virtual academy providing intensive mentoring, national networking, and a peer group for junior faculty. The overarching goal of the Ovarian Cancer Academy is to develop successful, highly productive ovarian cancer researchers in a collaborative research training environment. The Ovarian Cancer Academy is a virtual career development and research training platform that consists of Early-Career Investigator/Designated Mentor pairs from different institutions and an Academy Dean and Assistant Dean. The Academy Leadership serves as a resource for the Early-Career Investigators and Mentors, assessing the progress of the Early-Career Investigators, and facilitating communication and collaboration among all of the Early-Career Investigators and Mentors, as well as with national research and advocacy communities.

Source: DoD Ovarian Cancer Academy 2016, About the OCRP Ovarian Cancer Academy, accessed at: http://ovariancanceracademy.org/about/overview/

### *Access and awareness*

In 2015, Cancer Australia conducted a survey of more than 600 women and found 45 per cent of women surveyed were unable to identify any symptom of ovarian cancer, with women aged 60 years and over the least likely to know. Additionally, almost half of the women surveyed incorrectly responded that the age group most at risk of ovarian cancer was 35-50.[58] OCRF-supported research conducted by the University of Melbourne similarly found that women most at risk of ovarian cancer (women over the age of 65) were least likely to be aware of ovarian cancer risk. The research also found that two thirds of women incorrectly believed there was an early detection test for ovarian cancer, and that Pap smears and/or cervical tests screened for ovarian cancer.[59]

This is consistent with stakeholder consultations which indicated that many women were unaware of the risks of ovarian cancer, including in particular the association of endometriosis and familial breast cancer (See Chapter 3). This frustration was amplified by

[58] Cancer Australia, 2015, *Lack of awareness of ovarian cancer symptoms*
[59] University of Melbourne, 2020, *Ovarian Cancer Awareness Landscape*, report to the OCRF.

the lack of awareness among their GPs which resulted in delays in several cases to the investigation of symptoms, and limited knowledge of gynaecological oncology specialists.

The issue of GP awareness of rare cancers was similarly raised with the Senate Select Committee, which recommended in 2017 that the Australian Government work in collaboration with the medical profession via the RACGP and Australian Medical Association to improve awareness of low-survival cancers amongst GPs, including through continuing professional development (Recommendation 10).

Stakeholders indicated there is a clear need to improve information to consumers about oncologist choice and the availability of gynaecological oncologists, as well as ensure access to supportive care services to enable the better management of anxiety and other effects of ovarian cancer and its treatment. Ovarian Cancer Australia is the major support services provider and critical partner with government to improve equitable access to supportive care services nationally.

Opportunities:

- Community education and awareness campaigns for ovarian cancer risks and symptoms
- Invest in GP education
- Improved information to consumers and GPs at diagnosis about gyn-oncology specialists
- Improved referrals to supportive care, especially exercise and psychosocial support.

## Chapter 5

# Vision to improve survival for women with ovarian cancer

*The OCRF, together with Governments, ANZGOG, Cancer Councils, industry and other charities, have been long-term partners in the efforts to improve survival outcomes for women with ovarian cancer.*

*Where governments and the community have come together to sustain meaningful funding for research, dramatic improvements in survival have been seen. This is the goal for ovarian cancer: to realise the same significant improvements in survival that have been seen for so many cancers over the past 45 years.*

*These improvements in survival will come by finding breakthroughs in early detection and screening, preventing the occurrence of ovarian cancer, and expanding and personalising treatment options, including treatments that reduce disease recurrence and resistance.*

*This chapter sets out a vision for improving survival for women today through expanded access to treatment and for the next generation by pursuing a strategic research program focused on accelerating the path to early detection testing.*

## 5.1 A vision for women living without ovarian cancer

Based on the results of the research audit, the OCRF has set out a vision for a future where women live without ovarian cancer, and proposes the pursuit of a stepped improvement in survival outcomes over the short, medium, and longer term:

- Improve 5-year survival rates to 50 per cent for women today by rapidly implementing recent advances in knowledge in clinical practice nationally
- Improve 5-year survival rates beyond 50 per cent for the next generation of women through the development of and access to novel, personalised treatments
- Improve 5-year survival rates towards 90 per cent by developing novel technologies for early detection and diagnosis.

These are ambitious but achievable goals, if supported by funding for a strategic, high-impact program of research, supported by collaboration between governments, researchers and the wider community.

Importantly, within the Australian context, this goal is in line with the recommendations of the Senate Select Committee for Funding Research into Low Survival Cancers. These goals are also in line with the Survey of Researchers, Clinicians and Consumers, which identified expanding treatment options as one of the top three priorities for ovarian cancer research, with the potential to deliver survival benefits within five to 10 years, and early detection as the top priority for ovarian cancer research, with the potential to deliver benefits over the next 10-15 years.

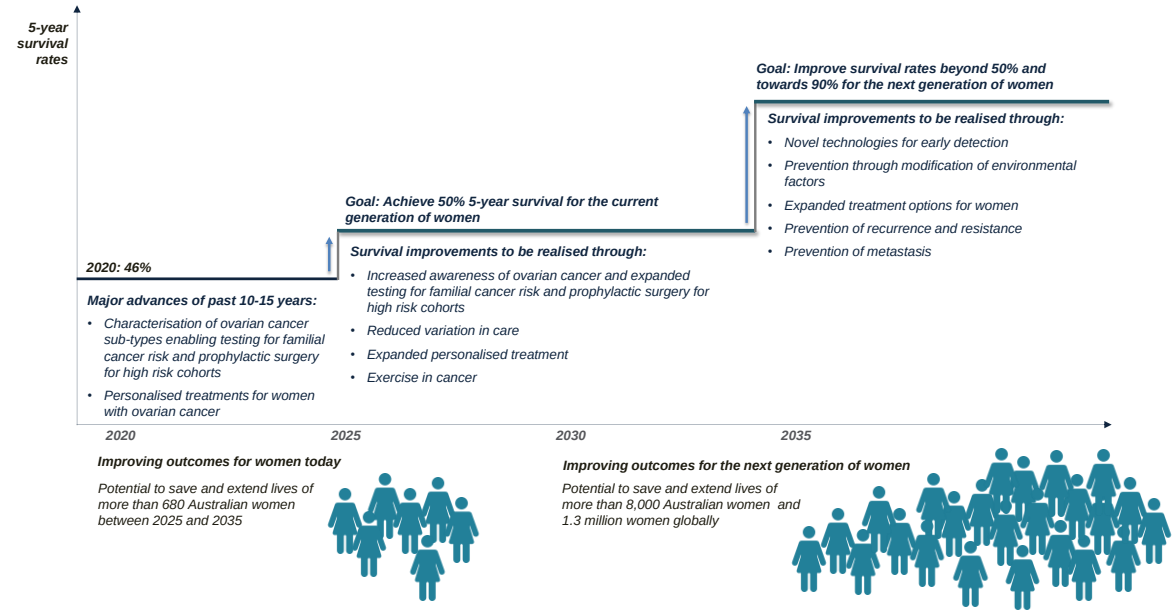
To achieve this vision, the *State of the Nation in Ovarian Cancer: Research Audit* calls for an increase in funding across all phases of research and critical enabling infrastructure to make possible the execution of the strategic and comprehensive program of work needed to

address the low survival rates for ovarian cancer. This would build on and extend the important and welcome first steps made by the Federal Government to improve survival for women with ovarian cancer through its recent Medical Research Future Fund commitments.

Realising the goals set out by this report would see the lives of women in Australia and around the world extended and saved (Figure 5.1):

- *Benefits of achieving 50 per cent 5-year survival nationally by 2025* — Between now and 2035, nearly 14,000 Australian women are expected to die from ovarian cancer. While the national 5-year survival rate is 46 per cent, there is variation in outcomes by state and territory, and some jurisdictions (Queensland) have reported 5-year survival rates above 50 per cent. By rapidly implementing current clinical best practice nationally and reducing variation in care, more than 680 of those lives could be extended and saved.
- *Benefits of increasing 5-year survival towards 90 per cent* — Striving to develop an early detection test for the next generation of women has the potential to substantially improve the survival rate for women with ovarian cancer and save the lives of more than 8,000 Australian women over a decade. Importantly, this benefit estimate conservatively assumes ovarian cancer is detected early in only half of the women that would otherwise have died from ovarian cancer due might have their cancer detected early. Improving technologies and understanding of ovarian cancer biology could see this estimate increase further. Globally, an early detection test could save the lives of more than 1.3 million women.

**Figure 5.1: A vision for saving women's lives today and tomorrow**




## 5.2 How can we get there? High-impact research collaboration

To realise this vision, as a community Australia must invest in a strategic program for high-impact ovarian cancer research. In addition to continued investment across all phases of research, there are potential opportunities to accelerate research outcomes through a nationally collaborative approach to key research priorities. Specific opportunities include:

- Support the rapid implementation of recent advances in ovarian cancer clinical best practice nationally
- Expand access to personalised treatment options for women nationally

- Establish an Australian Centre of Excellence for Early Detection in Ovarian Cancer
- Establish an Ovarian Cancer Mentorship Program to attract, retain and develop Australia's next generation of ovarian cancer researchers.

### *Support rapid and consistent implementation of best practice*

Nationally, as of June 2020, the 5-year survival rate for ovarian cancer was reported by the AIHW to be 46 per cent. State cancer registry data, however, indicate outcomes vary nationally. For example, 5-year survival outcomes in Queensland are already reported to be 50 per cent statewide. Within this, the Queensland Centre for Gynaecological Cancers reported a survival rate of 52 per cent over the 2003-2012 period. The Australian Government has made important investments in health services implementation research through the Medical Research Future Fund to better understand and reduce variation in care nationally. Significant investment to support the implementation of the findings from these studies and any needed policy reforms should be a high priority for all Australian governments.

In addition, it is recommended that the Australian Government fund programs to improve awareness and understanding of ovarian cancer in the community and among GPs. These programs should improve awareness of available tests for genetic risk to enable increased uptake of prophylactic surgery where appropriate.

Further investment should also be made to support the full enrolment in the ECHO clinical trial evaluating the impacts of individually-tailored exercise on survival and quality of life outcomes for women with ovarian cancer. Completing the trial would provide for the recruitment, randomisation and data collection for 200 additional women; intervention delivery for an additional 100 women; evaluation of all primary (survival) and secondary outcomes (health resource use, quality of life, function, treatment-related side effects, chemotherapy adherence); and reporting and dissemination of study outcomes nationally and internationally, as well as activities to facilitate the integration of exercise into standard care for women diagnosed with ovarian cancer.

### *Expand access to personalised treatment*

The characterisation of ovarian cancer sub-types has enabled clinical practice in ovarian cancer to move from an historical 'one size fits all' model of care to increasingly individualised treatment. This work, however, has only begun and critical research in the development of novel treatments for ovarian cancer is needed and identified to be a top three priority by researchers and clinicians.

A national program for clinical trials research in ovarian cancer is needed to support the improved personalisation of treatment of women across Australia. Every woman should be considered as an individual, with molecular profiling undertaken to enable treatment specific to her own genetic and tumour profile. This approach has been piloted in NSW and Victoria through the INOVATe and Precision Medicine programs at Westmead Institute for Medical Research and at the Hudson Institute of Medical Research respectively. Expanding access to these clinical research programs has the potential to deliver a step change improvement in 5-year and longer-term survival outcomes for a number of cohorts over the 2020-2030 horizon. In particular, a nationally oriented trials program should expand access to PARP inhibitors as first-line therapy for women with *BRCA* mutations and homologous recombination deficiencies (HRD) and invest in research for novel therapies and combination therapies for women with other prospective tumour targets. This national program should be supported by funding for a nationally co-ordinated approach pathology, biobanking and health outcomes analysis.

***Establish an Australian Centre of Excellence in Early Detection***

Early detection was the most frequently identified area of priority research by the ovarian cancer research community, including researchers, clinicians, and consumers.

Globally, the need for collaboration to accelerate high-impact discovery research in early detection has been recognised through a number of initiatives including most recently the establishment of the US Ovarian Cancer Omics Consortium which brings together leading centres of excellence in ovarian cancer research to focus on breakthroughs in early detection.

Given Australia's acknowledged global leadership in ovarian cancer research and its small population size, there is a clear opportunity to pull together a 'Team Australia' approach to this research challenge. Such an approach would maximise the value of Australia's research assets, including in particular the value of Australia's biobanking assets, and could make a valuable contribution to global efforts in this research area.

***Establish a mentorship program to attract, retain, and develop Australia's next generation of ovarian cancer researchers***

The challenges to recruiting and retaining researchers within the field of ovarian cancer are significant given historical funding challenges for the sector.

With Australia boasting global-leading ovarian cancer clinical practice and playing host to some of the world's leading ovarian cancer researchers across a range of disciplines and fields of research, there is an untapped opportunity to improve recruitment and retention through the development of an early and mid-career researcher mentorship program.

The Australian Ovarian Cancer Mentorship Program could be designed as a competitive program in which successful candidates received a three-year fellowship supported by formal mentoring at their home institution, as well as structured engagement with inter-institution and inter-discipline mentors and multi-disciplinary teams. The program could be open to clinical and non-clinical research candidates.

## 5.3 Australia can make a difference in ovarian cancer for women everywhere

The ovarian cancer community is calling for an increase in funding to support breakthroughs in ovarian cancer research that have been seen for so many other cancers.

This report identifies key funding needs based on historical funding trends and research priorities identified by the ovarian cancer research community. Specifically, the report recommends expanded funding for early detection and treatment research.

Australian researchers have proven themselves to be high-performing leaders in gynaecological cancer research globally, pushing knowledge forward across a range of research specialisations. Australians attract international funding and are consistent collaborators with high-impact international research consortia.

Australians are also major funders of medical research, however, funding for ovarian cancer has been limited and needs to be increased to meet the requirements for future research and to address low survival outcomes. Even small uplift funding from across governments, industry and the community combined has the potential to support a substantial expansion in research capabilities and breakthrough potential.

Increasing funding to meet the ovarian cancer research agenda has the potential to improve outcomes for women today but also must be urgently pursued if we are to improve survival outcomes for the next generation.

## Appendix A

# Audit of Ovarian Cancer Research Funding in Australia and New Zealand

### A.1 Methodology

From February to June 2020, Insight Economics contacted more than 50 organisations and invited them to provide details of funding for ovarian cancer research projects, programs and key enabling infrastructure.

Information was requested to be supplied in the form of an electronic spreadsheet or text document which would include:

- Year of award or funding allocation
- A summary or abstract of the research funded
- Details of the Chief Investigator and named collaborators
- Amount of funding granted to each funded cancer research project or fellowship
- The source of funding, be it government programs, charitable foundations or trusts, other philanthropy, industry, or individual donations.

All data received from performers of ovarian cancer was reviewed to ensure that the data focused on ovarian cancer within the scope of the research audit.

In parallel to the research request, a desktop review of publicly available data reporting of ovarian cancer was also undertaken. This included grants reporting by the Australian Government, State Governments, Cancer Councils, the Australian Charities and Not-for-Profits Commission and relevant annual reports by organisations and institutes.

All data received was consolidated and coded based on a Common Scientific Outline framework developed by the International Cancer Research Partnership to enable analysis by state, phase of research and funder type over time.

### A.2 Sources of data

The Audit of Ovarian Cancer Research brings together responses and data from the following organisations nationally:

- Australia New Zealand Gynaecological Oncology Group
- Australian National University
- Cancer Council Australia
- Curtin University
- Deakin University

- Edith Cowan University
- Fiona Elsey Cancer Research Institute
- Griffith University
- Harry Perkins Institute of Medical Research
- Hudson Institute of Medical Research
- Kolling Institute of Medical Research
- La Trobe University
- Mater Research
- Monash University
- QIMR Berghofer Medical Research Institute
- RMIT University
- St Vincent's Institute of Medical Research
- The John Curtin School of Medical Research
- The University of Adelaide
- The University of Melbourne
- The University of Newcastle
- The University of Queensland
- The University of Sydney
- The University of Western Australia
- The Westmead Institute for Medical Research
- University of Otago
- University of South Australia
- UNSW
- Victoria University
- Walter and Eliza Hall Institute of Medical Research

Data was received from performers of ovarian cancer research for the years 2010-2020. In addition, publicly available databases provided information on ovarian cancer from 2003. Data is presented from 2005-2020 in Section A.4 but report analysis is based on the 2010-2020 period as this is a more complete dataset.

## A.3 Classification and analysis of cancer research projects, programs and key enabling infrastructure

All cancer research projects and research programs were classified based on the Common Scientific Outline, which is classification system specific to cancer research that uses cancer-related research terminology. Specifically, the Research Audit classified projects, programs or fellowships into one of the following categories:

- Biology and aetiology
- Prevention
- Early detection and diagnosis
- Treatment and recurrence
- Enabling infrastructure, which comprised projects or programs aimed at biobanking, cancer control, survival and outcomes research, scientific model systems or research fellowships.

## A.3 Ownership and access to the data

The data supplied by participants is held in confidence by Insight Economics. Access to identifiable information is limited to Insight Economics staff involved in the audit. Details of individual research projects and research programs, and individual levels of funding, will not be published or accessible unless agreement is obtained in advance from the organisation(s) supplying the data.

## A.4 Summary data: 2010-2020

**Table A.1: Research funding 2010-2020 ($ millions)**

| | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | Total | Average | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Total** | **$12.1** | **$16.1** | **$10.8** | **$18.6** | **$9.1** | **$15.3** | **$19.5** | **$15.1** | **$18.8** | **$17.4** | **$27.5** | **$180.3** | **$16.4** | **100%** |
| **By research area:** | | | | | | | | | | | | | | |
| Biology / aetiology | $6.6 | $7.0 | $4.0 | $4.2 | $1.3 | $5.2 | $2.8 | $5.2 | $3.4 | $1.6 | $2.0 | $43.3 | **$3.9** | **24%** |
| Prevention | $1.9 | $1.8 | $0.0 | $0.0 | $0.0 | $0.0 | $1.3 | $0.7 | $0.5 | $0.0 | $3.2 | $9.4 | **$1.2** | **5%** |
| Early detection | $0.4 | $1.0 | $0.1 | $0.5 | $0.4 | $1.0 | $1.8 | $2.4 | $2.6 | $1.1 | $1.9 | $13.3 | **$1.2** | **7%** |
| Treatment and recurrence | $2.3 | $0.8 | $4.4 | $5.3 | $6.4 | $8.2 | $12.2 | $6.1 | $8.1 | $12.7 | $16.3 | $82.9 | **$7.5** | **46%** |
| Enabling Infrastructure | $0.9 | $5.4 | $2.3 | $8.6 | $1.0 | $0.9 | $1.4 | $0.7 | $4.2 | $1.9 | $4.1 | $31.3 | **$2.8** | **17%** |
| **By funder type:** | | | | | | | | | | | | | | |
| Australian Government | $8.7 | $13.7 | $5.5 | $14.7 | $4.4 | $2.9 | $12.4 | $9.5 | $5.8 | $5.3 | $24.2 | $107.1 | **$9.7** | **59%** |
| OCRF | $2.7 | $1.1 | $0.4 | $2.3 | $1.5 | $1.2 | $1.3 | $2.0 | $2.6 | $1.5 | $0.7 | $17.4 | **$1.6** | **10%** |
| International Academic Trial Groups (via ANZGOG) and ANZGOG | $0.0 | $0.0 | $0.0 | $0.0 | $1.1 | $0.0 | $3.1 | $0.0 | $0.6 | $0.1 | $0.0 | $4.8 | **$1.0** | **3%** |
| Cancer Councils and States | $0.2 | $0.5 | $2.6 | $1.1 | $1.3 | $5.4 | $0.5 | $0.7 | $0.3 | $4.5 | $0.9 | $18.0 | **$1.6** | **10%** |
| Other NGOs | $0.1 | $0.8 | $0.3 | $0.3 | $0.8 | $3.6 | $1.5 | $2.4 | $1.9 | $2.9 | $1.8 | $16.5 | **$1.5** | **9%** |
| Industry | $0.2 | $0.0 | $1.5 | $0.0 | $0.1 | $0.5 | $0.1 | $0.0 | $5.8 | $3.1 | $0.0 | $11.3 | **$0.0** | **6%** |
| International governments | $0.0 | $0.0 | $0.5 | $0.1 | $0.0 | $1.6 | $0.5 | $0.4 | $1.9 | $0.0 | $0.0 | $5.1 | **$0.0** | **3%** |

## A.5 Summary data: Australian Government and OCRF data 2005-2020

**Table A.2: Australian Government and OCRF research funding 2005-2020 ($ millions)**

| | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Australian Government | $7.6 | $5.2 | $13.9 | $8.7 | $5.6 | $8.7 | $13.7 | $5.5 | $14.7 | $4.4 | $2.9 | $12.4 | $9.5 | $5.8 | $5.3 | $24.2 | **$148.2** |
| OCRF | $0.1 | $5.1 | $0.8 | $0.1 | $0.8 | $2.7 | $1.1 | $0.4 | $2.3 | $1.5 | $1.2 | $1.3 | $2.0 | $2.6 | $1.5 | $0.7 | **$24.4** |

## Appendix B

# Survey of Ovarian Cancer Researchers, Clinicians and Consumers

### B.1 Survey Approach

The Survey of Ovarian Cancer Researchers, Clinicians and Consumers was open between 29 April and 23 May 2020, with the support of ANZGOG, National Cancer Research Institute, Gynaecological Group UK, Cancer Voices, and the Consumer and Community Health Research Network. The survey was also posted on social media to allow responses from the general public via the OCRF. Electronic copies of the survey were also made available on request and responses were received by email to Insight Economics.

Drafts of the survey were piloted with two researchers and two consumers and revised according to pilot results feedback.

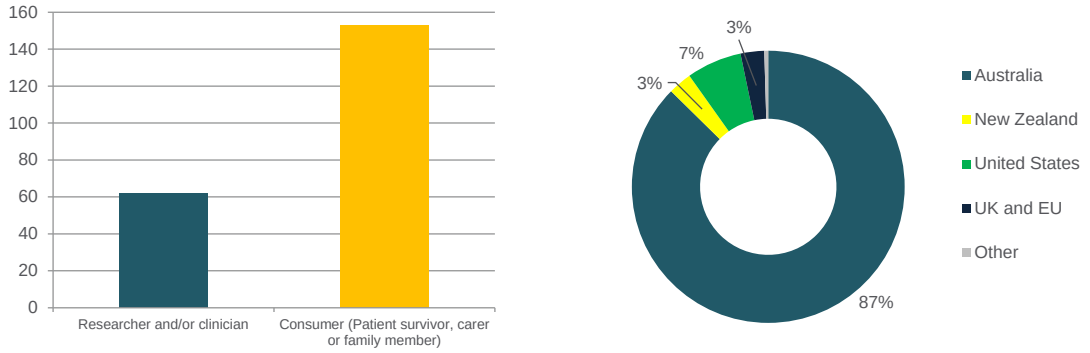
The survey was multiple-choice and designed using a page-logic format so that respondents only answered questions based on their experience. To that end, consumers received a consumer survey, which utilised to a greater extent layperson language and included some questions specific to the consumer experience. Researchers and clinicians received a longer survey that adopted Common Scientific Outline categories and language, and included specific questions by research phase aimed at identifying specific research priorities. Importantly, however, researchers, clinicians and consumers all received the same questions with respect to barriers to research and priorities for research to enable comparisons across the two groups.

The survey took approximately 10-15 minutes to complete. Responses were confidential and analysed by Insight Economics.

### B.2 Survey response

In total, 216 people responded, of which 62 identified themselves as researchers and/or clinicians (only five people identified as exclusively as a treating clinician), and 154 of respondents identified as consumers (Figure B.1).

**Figure B.1: Who responded? Survey response statistics**

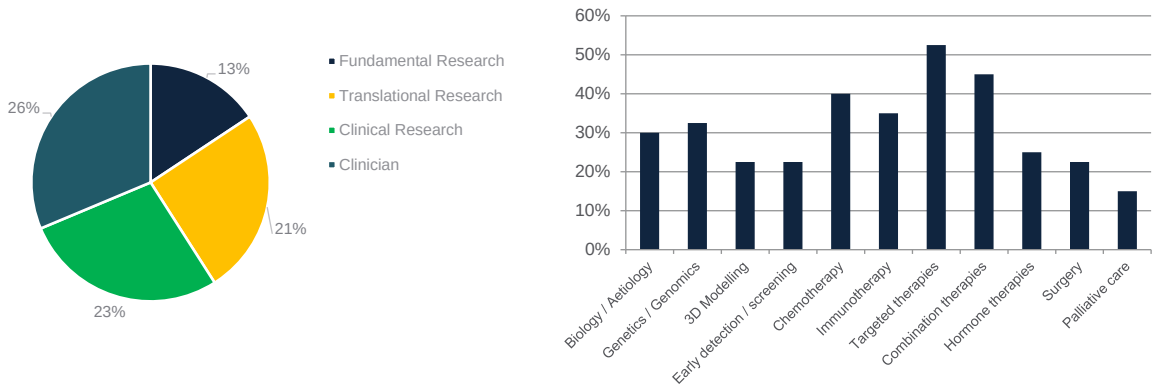



Most respondents were based in Australia (87 per cent), with the balance of respondents coming from the US (7 per cent), the UK and Europe (3 per cent), and New Zealand (3 per cent).

A 'bottom up' analysis of unique lead researchers identified in ovarian cancer research projects based on the Audit of Ovarian Cancer Research Funding and ANZGOG ovarian tumour group members was undertaken in order to estimate the indicative population of ovarian cancer researchers in Australia and New Zealand. This analysis identified 158 unique lead researchers between 2005 and 2020. The response by Australian researchers therefore translates into a response rate of roughly 39 per cent, which is equivalent to the high end of an internal survey response rate that typically has 30-40 per cent response rates (external surveys of general public typically have 10-15 per cent response rates).

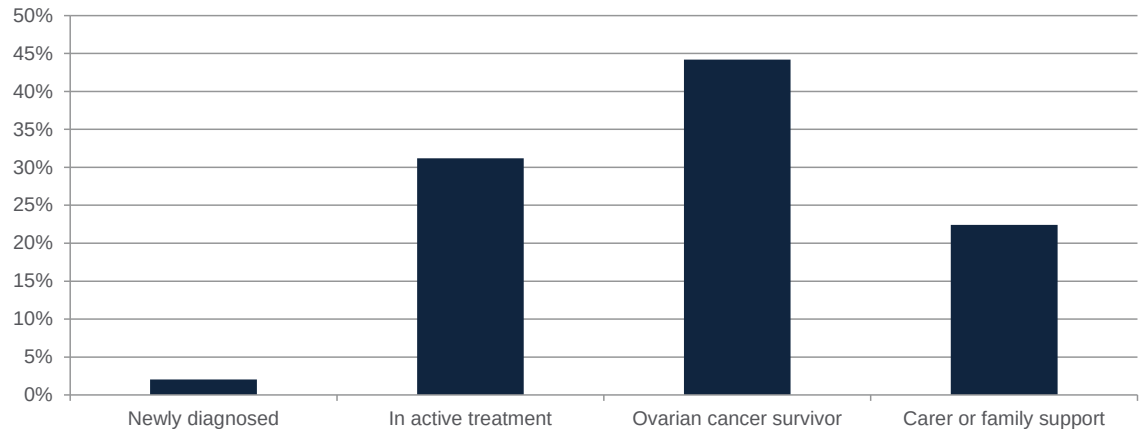
Of equal importance, among researchers there was a balanced distribution of specialisation across areas of research focus (Figure B.2).

**Figure B.2: Researcher and clinician response profiles**




There was also a balanced distribution of consumer respondents. One in five respondents was a carer or family support person. Nearly half of consumer respondents were ovarian cancer survivors (45 per cent) and one in three was in active treatment, which really serves to highlight how critical and important research is to patients.

**Figure B.3: Consumer respondent profiles**



## Appendix C

# Care pathway for ovarian cancer

### Symptoms

Common symptoms of ovarian cancer include:

- Feeling bloated
- Indigestion or heartburn
- Pain in the abdomen
- Trouble eating, feeling full fast
- Feeling the need to urinate often

These symptoms will be new (experiencing these symptoms for less than a year) and frequent (occurring more than 12 days per month).

Other symptoms may be experienced if the cancer mass becomes large or there is fluid build up in the abdomen.

### Diagnosis

**Presentation to GP**

Women will present to the GP who may perform a series of general health and blood tests. These tests include:

- Family and medical history
- Nutritional status
- Abdominal and pelvic exam
- Complete blood count
- Blood chemistry with liver function tests and serum protein.

**Referral to an oncologist**

If ovarian cancer is suspected, the patient is referred to an oncologist, who may order further tests to enable a clinical staging of the suspected cancer. This will include:

- Blood and tumour marker tests for CA-125 and other markers such as inhibin, β-hCG, Alpha-fetoprotein, LDH, CEA, Ca19-9, HE4
- Imaging of the abdomen and pelvis using ultrasound, CT, PET, and/or MRI
- Imaging of the chest (chest x-ray)
- Gastro-intestinal evaluation.

Ovarian cancer is then surgically staged to determine the spread of cancer and diagnosis confirmed through pathology of tissue biopsies taken during surgery. Biopsy sites may include the lymph nodes, pelvis, abdomen, diaphragm, omentum, peritoneum and ascites. The cancer will also be graded, with Grade 1 cancer cells looking similar to normal cells and Grade 3 (High Grade) cancer cells looking very different to normal cells. Following surgery, genetic testing for BRCA genes, DNA mismatch repair (MSI-H, dMMR).

### First line treatment

Depending on the staging, grading and sub-type of ovarian cancer, a woman may have a range of treatments, including surgery and chemotherapy. Some sub-types of ovarian cancer may allow for the use of a targeted therapy or immunotherapy, which may be administered after surgery and chemotherapy. The specialist will also identify supportive care treatments for the management of side-effects of the cancer and treatment.

**Surgery**

Depending on their age and the spread of the cancer, the following surgeries may be performed:

- Unilateral salpingo-oophorectomy (USO), which is the removal of only one ovary and fallopian tube, however this is very rarely performed
- Bilateral salpingo-oophorectomy (BSO), which is the removal of both ovaries and fallopian tubes
- Total abdominal hysterectomy (TAH) is surgery to remove the uterus, including the cervix
- Cytoreductive surgery or 'debulking' surgery.

USO is fertility sparing surgery intended to enable women to start or complete their families, but is only available if the cancer is in one ovary. BSO and TAH are performed together, along with debulking surgery to reduce the risk of recurrence.

**Chemotherapy**

Women with ovarian cancer are administered some form of platinum chemotherapy and taxane based chemotherapy following surgery. These medicines are given in combination:

- Platinum agents damage the DNA in the cancer cell, and major platinum agents used include carboplatin, cisplatin, and oxaplatin.
- Taxanes prevent cancer cell division, and the major taxanes used are paclitaxel, paclitaxel aluminum bound, and docetaxel. Chemotherapy is traditionally administered via IV, injected into the peritoneal cavity.

**Targeted therapies**

Some sub-types of ovarian cancers may have features that allow for the use of drugs that target certain features of the cancer cell.

- Angiogenesis inhibitors are targeted therapies that limit the growth of blood vessels to 'feed' the cancer. Bevacizumab is an example of an angiogenesis inhibitor.
- Poly ADP-ribose polymerase (PARP) inhibitors are a new type of targeted therapy that stops the PARP protein from repairing damage in cancer cell DNA. Normally the *BRCA1* and *BRCA2* genes would also repair DNA damage in cells, and so these therapies can improve outcomes for women with BRCA1 or BRCA2 germline mutations or a mutation in the tumour. Examples of PARP inhibitors include olaparib, rucaparib, and niraparib.
- Tyrosine kinase inhibitors (TKIs) are also therapies that interrupt protein functioning needed for cancer cell growth. Tyrosine kinase are proteins that send signals tell cancer cells to grow and divide, of for blood vessels to grow to feed the cancer cells. TKIs stop these proteins from sending these signals.

**Immunotherapies**

Immunotherapies use a woman's own immune system to identify and fight the cancer.

A type of immunotherapy to right ovarian cancer is checkpoint inhibitors. Checkpoint inhibitor immunotherapies use important disease-fighting cells called T-Cells, which are a type of white blood call, to attack the cancer. T-cells are have a protein on the surface of their cells called PD-1. Cancer cells have a different protein on the surface of their cells, called PD-L1. T-cells roam around looking for disease. When the protein on the surface of the T-Cell, PD-1, meets with the protein on the surface of the cancer cell, PD-L1, this is called an 'immune checkpoint'. At this immune checkpoint the T-cell is 'told' by the cancer cell to leave it alone, instead of attacking it. Immune checkpoint inhibitors stops these two proteins from meeting, and as a result T-cells attack the cancer cells. Pembrolizumab is an example of a checkpoint inhibitor, and can be used if a woman has tested positive for chromosomal defects (MSI-H or dMMR).

### Disease recurrence & management

Most women have a good intiial response to platinum therapy, but in a majority of cases women experience refractory or relapsed disease. If the cancer returns more than six months after treatment the cancer is termed 'platinum-sensitive' if the cancer returns les than six months after initial treatment, the cancer is termed 'platinum-resistant'.

When the disease returns the cancer has often changed substantially and may resistant to chemotherapy. A different chemotherapy agent will typically be administered.

If relapse is suspected, further blood, tumour marking, and imaging tests will be conducted to determine a treatment plan.

In addition to recurrence therapy with chemotherapies and potentially targeted or immunotherapies, women in a relapsed setting may be administered a hormone therapy to slow the cancer growth, such as anti-estrogens (tamoxifen), aromatase inhibitors which lower estrogen levels (anastrolzole, exemestane, or letrozole), LHRH agonists (leuprolide acetate) or progestins (megestrol acetate).

If the cancer has spread women may be enrolled in a clinical trial.

### Supportive care, survivorship and long-term follow-up

From diagnosis, women with ovarian cancer should be supported to develop plans for the management of symptoms and side effects associated with the cancer and its treatment.

Supportive care is care given to improve the quality of life of patients diagnosed with and treated for ovarian cancer. The goal of supportive care is to prevent or treat as early as possible:

- The symptoms of a disease and side effects caused by treatment
- Any physical, psychological, social, financial and/or spiritual problems related to a disease or its treatment.

The Cancer Council and National Cancer Expert Reference Group have underlined the importance of supportive care services planning and delivery through the development and endorsement of optimal care pathways for cancer.

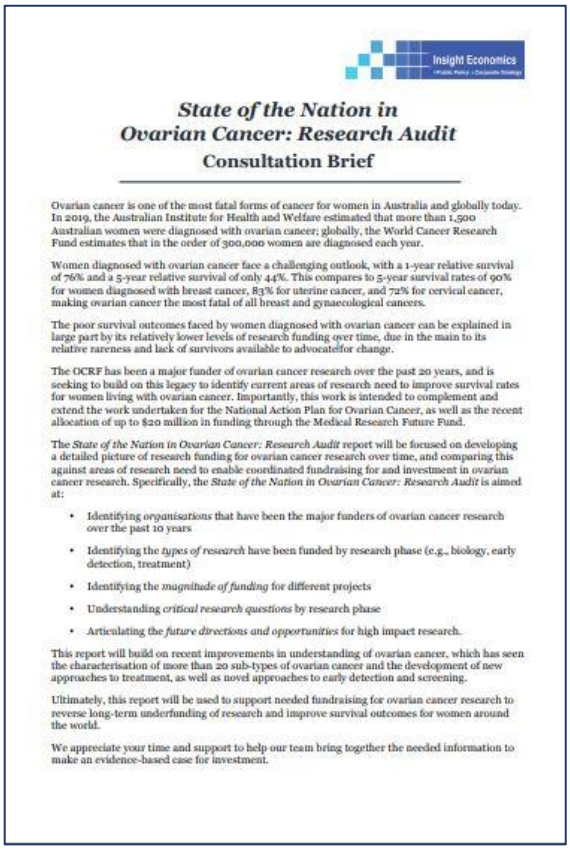
Survivorship care is closely related to supportive care. Technically a woman is a survivor of ovarian cancer from the moment she is diagnosed. In practice, a survivorship care plan is a detailed plan given to a patient after treatment ends, that contains a summary of the patient's treatment, along with recommendations for supportive care and follow-up care, including plans for regular health and wellness check-ups.

Following the completion of active treatment, women will receive follow-up care in the form of check-ups every 2-4 months for the first two years, every 3-6 months for the following three years and once per year after 5 years of survival. Follow-up tests may include physical and pelvic exams, imaging of the chest, abdomen and pelvis as needed, blood tests as needed, tumour marker testing as needed (especially in cases where tumour markers were originally high), and genetic testing.

A woman's long-term supportive care needs to enable a high quality of life should also be assessed. While the long term supportive care needs of ovarian cancer survivors will be different for every woman, but are likely to include support for managing the fear of recurrence, financial support, and/or referrals to specialists and recommendations for a healthy lifestyle, such as changes in diet and exercise and quitting smoking.

## Appendix D

# Consultation brief



Insight Economics

***State of the Nation in Ovarian Cancer: Research Audit***

**Consultation Brief**

Ovarian cancer is one of the most fatal forms of cancer for women in Australia and globally today. In 2019, the Australian Institute for Health and Welfare estimated that more than 1,500 Australian women were diagnosed with ovarian cancer; globally, the World Cancer Research Fund estimates that in the order of 300,000 women are diagnosed each year.

Women diagnosed with ovarian cancer face a challenging outlook, with a 1-year relative survival of 76% and a 5-year relative survival of only 44%. This compares to 5-year survival rates of 90% for women diagnosed with breast cancer, 83% for uterine cancer, and 72% for cervical cancer, making ovarian cancer the most fatal of all breast and gynaecological cancers.

The poor survival outcomes faced by women diagnosed with ovarian cancer can be explained in large part by its relatively lower levels of research funding over time, due in the main to its relative rareness and lack of survivors available to advocatefor change.

The OCRF has been a major funder of ovarian cancer research over the past 20 years, and is seeking to build on this legacy to identify current areas of research need to improve survival rates for women living with ovarian cancer. Importantly, this work is intended to complement and extend the work undertaken for the National Action Plan for Ovarian Cancer, as well as the recent allocation of up to $20 million in funding through the Medical Research Future Fund.

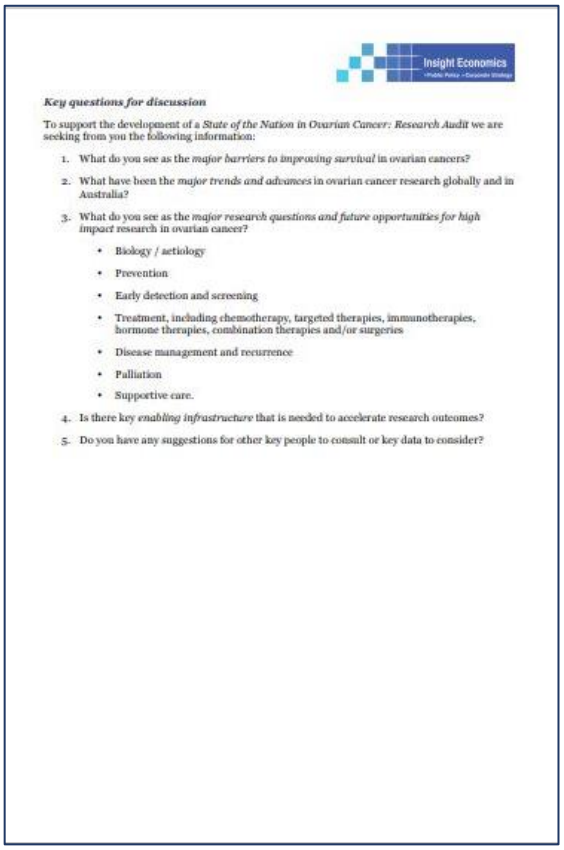
The *State of the Nation in Ovarian Cancer: Research Audit* report will be focused on developing a detailed picture of research funding for ovarian cancer research over time, and comparing this against areas of research need to enable coordinated fundraising for and investment in ovarian cancer research. Specifically, the *State of the Nation in Ovarian Cancer: Research Audit* is aimed at:

- Identifying *organisations* that have been the major funders of ovarian cancer research over the past 10 years
- Identifying the *types of research* have been funded by research phase (e.g., biology, early detection, treatment)
- Identifying the *magnitude of funding* for different projects
- Understanding *critical research questions* by research phase
- Articulating the *future directions and opportunities* for high impact research.

This report will build on recent improvements in understanding of ovarian cancer, which has seen the characterisation of more than 20 sub-types of ovarian cancer and the development of new approaches to treatment, as well as novel approaches to early detection and screening.

Ultimately, this report will be used to support needed fundraising for ovarian cancer research to reverse long-term underfunding of research and improve survival outcomes for women around the world.

We appreciate your time and support to help our team bring together the needed information to make an evidence-based case for investment.



Insight Economics

***Key questions for discussion***

To support the development of a *State of the Nation in Ovarian Cancer: Research Audit* we are seeking from you the following information:

1. What do you see as the *major barriers to improving survival* in ovarian cancers?
2. What have been the *major trends and advances* in ovarian cancer research globally and in Australia?
3. What do you see as the *major research questions and future opportunities for high impact* research in ovarian cancer?
    - Biology / aetiology
    - Prevention
    - Early detection and screening
    - Treatment, including chemotherapy, targeted therapies, immunotherapies, hormone therapies, combination therapies and/or surgeries
    - Disease management and recurrence
    - Palliation
    - Supportive care.
4. Is there key *enabling infrastructure* that is needed to accelerate research outcomes?
5. Do you have any suggestions for other key people to consult or key data to consider?

## Appendix E

# Glossary

| Term | Definition |
|---|---|
| **Angiogenesis inhibitor** | Angiogenesis inhibitors are targeted therapies that limit the growth of blood vessels that 'feed' the cancer. |
| **Ascites** | Ascites are the abnormal build-up of fluid in the abdomen that may cause swelling. In late-stage cancer, tumour cells may be found in the fluid in the abdomen. |
| **Biobank** | Biobanks are created to store biological samples for use in research. Tissue samples, such as blood or tumour tissue, are collected from the patient with their consent, annotated with clinical information, and preserved for later evaluation by scientific and medical researchers seeking to understand the causes, development, diagnosis and treatment of disease. |
| **Biomarker** | A biomarker, or tumour marker, is a biological molecule found in blood, other body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. For example, elevated levels of CA125, a protein, biomarker for ovarian cancer (although levels can be elevated as the result of other conditions as well). HE4, inhibin, β-hCG, Alpha-fetoprotein, LDH, CEA, and CA19-9 are other examples of biomarkers for ovarian cancer that have been evaluated in ovarian cancer research and/or may be used in current clinical practice. |
| **BRCA1** | A gene on chromosome 17 that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a BRCA1 gene has a higher risk of getting breast, ovarian, prostate, and other types of cancer. |
| **BRCA2** | A gene on chromosome 13 that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a BRCA2 gene has a higher risk of getting breast, ovarian, prostate, and other types of cancer. |
| **CA125** | CA125 is a protein that is a tumour marker or biomarker, which is a biological substance that is found in greater concentration in tumour cells than in other cells of the body. CA125 is present in greater concentration in ovarian cancer cells than in other cells, but elevated levels of CA125 can also be associated with other conditions or may be benign. CA stands for cancer antigen. CA125 is often measured through blood tests, but it can be measured in other fluids in the abdominal cavity. |
| **Cervical cancer** | Cervical cancer is a cancer that arises in a woman's cervix, which is a small, cylindrical neck of tissue that connects a woman's uterus and vagina. While there are other known risk factors, almost all cervical cancer is caused by a viral infection called the human papillomavirus (HPV). Cervical cancer can be prevented through vaccination against this virus, and screened through a cervical screening test that has recently replaced the Pap smear. |
| **Charitable foundation or trust** | A charitable foundation is a type of not-for-profit organisation or charitable trust that will typically provide funding and support for other charitable organisations through grants or other charitable activities. Charitable foundations or trusts can be set up to support a variety of charitable purposes. Charitable trusts and foundations can offer a range of taxation concessions, benefits or exemptions to donors under Commonwealth law and must register with and adhere to regulations by the Australian Charities and Not-for-profits Commission. Foundations or trusts can be public charitable foundations, such as community foundations. Private foundations are typically endowed by an individual or family. |
| **Chemoprevention** | Chemoprevention is the use of drugs, vitamins, or other agents to try to reduce the risk of, or delay the development or recurrence of, cancer. |
| **Chemoresistance** | Chemoresistance means the cancer cells become resistant to the action of a specific therapeutic agent, in this case the first line platinum-based chemotherapy agent. The drug will no longer be as effective as in previous lines of treatment and so a different agent or combination of drugs must be used. |

| Term | Definition |
|---|---|
| **Clear cell carcinoma** | One of seven major sub-types of ovarian cancer. Clear cell carcinomas account for 10 per cent of ovarian cancers. They originate in ovarian epithelial tissues. |
| **Common Scientific Outline** | Common Scientific Outline, or CSO, is a classification system organised into six broad areas of scientific interest in cancer research: biology; aetiology; prevention; early detection, diagnosis, and prognosis; treatment; cancer control, survivorship, and outcomes research. The CSO is complemented by a standard cancer type coding scheme. |
| **CT scan** | A CT scan, or computed tomography scan (formerly computerised axial tomography scan, or CAT scan) is a medical imaging procedure that uses computer-processed combinations of many X-ray measurements taken from different angles to produce cross-sectional (tomographic) images (virtual "slices") of specific areas of a scanned object, allowing the user to see inside the object without cutting. |
| **Endometrioid carcinoma** | One of seven major sub-types of ovarian cancer. Endometrioid carcinomas account for 10 per cent of ovarian cancers. They originate in ovarian epithelial tissues. |
| **Endometriosis** | Endometriosis is defined as the presence of endometrial glands and stroma outside the uterus. It is a relatively common condition affecting two to eight per cent of all reproductive-age women, and present in approximately 30 per cent of women who are infertile. Although endometriosis itself is not fatal, endometriosis-induced inflammation and hormone production can contribute to the development of ovarian cancer, including in particular the clear cell and endometrioid sub-types |
| **Epithelial cells** | Epithelium is one of the four basic types of tissue with the other three types of tissue being connective tissue, muscle tissue and nervous tissue. Epithelial tissues line the outer surfaces of organs and blood vessels throughout the body, as well as the inner surfaces of cavities in many internal organs. Examples of epithelial tissues include the epidermis, the outermost layer of the skin, cells lining the intestinal tract, and alveoli (air sacs) in our lungs. All glands are made up of epithelial cells. Functions of epithelial cells include secretion, selective absorption, protection, transcellular transport, and sensing. Epithelial cells are categorised by their shape (squamous, columnar, cuboid) and the extent of layering (simple, stratified). Epithelial cells of the ovaries are classified as simple cuboidal and fallopian tubes are simple columnar epithelial cells. Epithelial layers contain no blood vessels, so they must receive nourishment via diffusion of substances from the underlying connective tissue. |
| **High-grade serous carcinomas** | High-grade serous carcinomas account for approximately 70 per cent of all ovarian cancers. Most high-grade serous carcinomas originate in the fallopian tubes. |
| **Hormone therapy** | Hormone therapy can be used to slow cancer growth. These include drugs such as anti-estrogens (tamoxifen), aromatase inhibitors, which lower estrogen levels (anastrolzole, exemestane, or letrozole), LHRH agonists (leuprolide acetate), or progestins (megestrol acetate). |
| **ICD-10** | ICD-10 stands for International Classification of Disease version 10. ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list by the World Health Organization (WHO). It contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases. Work on ICD-10 began in 1983, became endorsed by the Forty-third World Health Assembly in 1990, and was first used by member states in 1994. It remains current until January 1, 2022, when it will be replaced by ICD-11.<br>Ovarian cancer is coded as C56 in ICD-10, and fallopian cancer and cancers of unknown origin are coded under C57. |
| **Immunotherapy** | Immunotherapy is a type of cancer treatment that helps your immune system fight cancer. The immune system helps your body fight infections and other diseases. It is made up of white blood cells and organs and tissues of the lymph system.<br>Immunotherapy is a type of biological therapy. Biological therapy is a type of treatment that uses substances made from living organisms to treat cancer. |
| **Incidence** | The number of newly diagnosed cases of ovarian cancer each year. |

| Term | Definition |
|---|---|
| **Low-grade serous carcinomas** | Low-grade serous carcinomas account for 3-5 per cent of ovarian cancers, and may originate in the fallopian tubes. |
| **Monoclonal antibody** | Monoclonal antibodies are immune system proteins that are created in the lab. Antibodies are produced naturally by your body and help the immune system recognise germs that cause disease, such as bacteria and viruses, and mark them for destruction. Like your body's own antibodies, monoclonal antibodies recognise specific targets.<br>Many monoclonal antibodies are used to treat cancer. They are a type of targeted cancer therapy, which means they are designed to interact with specific targets.<br>Some monoclonal antibodies are also immunotherapy because they help turn the immune system against cancer. For example, some monoclonal antibodies mark cancer cells so that the immune system will better recognise and destroy them.<br>Other monoclonal antibodies bring T cells close to cancer cells, helping the immune cells kill the cancer cells. |
| **Mortality** | A measure of the number of people deceased from ovarian cancer, typically expressed on a per annum basis. |
| **MRI scan** | Magnetic resonance imaging, or MRI, scan is a procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal tissue and cancer. |
| **Mucinous carcinoma** | One of seven major sub-types of ovarian cancer. Mucinous carcinomas account for between 2-6 per cent of ovarian cancers. Their tissue of origin is currently unknown. |
| **Non-governmental organisation** | A non-governmental organisation, or NGO, refers to organisations that are operated independently of any government, typically on a not-for-profit basis and one whose purpose is to address a social or political issue. |
| **Off label** | Off-label use is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration. |
| **PARP inhibitor** | Poly(ADP-ribose) polymerase, or PARP, is a type of enzyme involved in many functions of the cell, including the repair of DNA damage. DNA damage may be caused by normal cell actions, UV light, some anti-cancer drugs, and radiation used to treat cancer.<br>A PARP inhibitor is a drug that blocks the PARP enzyme from repairing DNA damage in the cancer cell. |
| **PET scan** | Positron Emission Tomography (PET) is a nuclear medicine technology that uses short-lived radioisotopes to enable the non-invasive imaging of metabolic functions within the body. A small amount of radioactive glucose (sugar) is injected into the patient's vein, and a scanner is used to make detailed, computerised pictures of areas inside the body where the glucose is taken up. Because cancer cells often take up more glucose than normal cells, the pictures can be used to find cancer cells in the body. While computed tomography (CT) and magnetic resonance imaging (MRI) primarily provide information about anatomical structure, PET can image and quantify biochemical and/or physiological function. This is important because functional changes caused by disease, such as cancer, are often detectable before any structural abnormalities become evident. |
| **Platinum-based chemotherapy** | Platinum-based chemotherapy agents are a form of chemotherapy administered to directly damage the DNA in the cancer cell. Platinum-based agents used in ovarian cancer include carboplatin, or less commonly, cisplatin. |
| **Prevalence** | The number of people diagnosed and living with ovarian cancer; includes newly diagnosed cases plus other survivors. |
| **Private ancillary fund** | A private ancillary fund, or PAF, is a form of charitable trust that can be used for strategic long-term giving. It offers donors tax deductibility and flexibility in their charitable giving. PAFs must have corporate trustees. PAFs must comply with the ACNC Act, which regulates the entire charitable sector, and the requirements of the relevant state trustee legislation (which is broadly consistent across all states) and common law.<br>PAFs differ from public ancillary funds (PuAFs) in that they cannot seek or receive contributions from the public. |

| Term | Definition |
|---|---|
| **Prophylactic surgery** | Surgery to remove an organ or gland that shows no signs of cancer, in an attempt to prevent development of cancer of that organ or gland. Prophylactic surgery is sometimes chosen by people who know they are at high risk for of developing cancer. |
| **Public ancillary fund** | A public ancillary fund, or PuAF, is a form of charitable trust that can be used for strategic long-term giving. Public Ancillary Funds are not-for-profit entities established solely for the purpose of providing money, property or benefits to (and for the establishment of) deductible gift entities not including other ancillary funds. PuAFs must fundraise from the public and all donations are income tax deductible for donors. PuAFs must have corporate trustees. PuAFs must also comply with the ACNC Act, which regulates the entire charitable sector, and the requirements of the relevant state trustee legislation as well as common law. |
| **Real world data** | Real world data or real world evidence is information related to the health status and health care delivered to patients routinely collected through a variety of sources such as clinical registries, electronic medical records (EMRs), patient reported outcome (PRO) platforms, pharmaceutical Benefits Scheme (PBS) and Medical Benefits Scheme (MBS) data. |
| **Sub-type** | More properly termed histological sub-type, the term sub-type refers to the sub-classification of ovarian cancer tumours. There are seven major histological sub-types of ovarian cancer, including high-grade serous, low-grade serous, clear cell, endometrioid, mucinous, sex cord stromal, and germ cell ovarian cancer. |
| **Synthetic lethality** | Synthetic lethality arises when a combination of deficiencies in the expression of two or more genes leads to cell death, whereas a deficiency in only one of these genes does not. The deficiencies can arise through mutations, epigenetic alterations or inhibitors of one of the genes. *BRCA* mutations and PARP inhibitors are an example of synthetic lethality. |
| **Targeted therapy** | Targeted therapy is the foundation of precision medicine. It is a type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread. |
| **Taxane** | Taxanes are a form of chemotherapy used to prevent cancer cell division. The major taxanes used in ovarian cancer are paclitaxel and docetaxel. |
| **Transvaginal ultrasound** | A transvaginal ultrasound, also called an endovaginal ultrasound, is a type of pelvic ultrasound used by doctors to examine female reproductive organs. This includes the uterus, fallopian tubes, ovaries, cervix, and vagina. |
| **Uterine cancer** | Most uterine cancers originate in the lining of the uterus (the endometrium). More rarely, cancers can originate in the muscle layer of the uterus (sarcomas) or the connective tissue (stroma) that supports the endometrium. |

## Appendix F

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