NATIONAL ACTION PLAN FOR OVARIAN CANCER RESEARCH: THE COMPREHENSIVE REPORT

Working together to change the ovarian cancer story
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This report was developed and funded by Ovarian Cancer Australia, the peak national body for ovarian cancer. Ovarian Cancer Australia acknowledges the input from participants in stakeholder consultations, workshops, the members of the working group, and key opinion leaders who made this report possible.
What women want

A cure.
To us, it’s that simple.

We know it’s very hard and complex but nonetheless that’s what we want. And what, in the depths of our hearts, we dream of.

We’d also like a future where no women develop ovarian cancer. We’d like it to stop with us, if it has to affect us at all. It’s awful knowing other women will follow us on this path.

And in the meantime we’d like a test so, in the future, women can pick it up early and not have to face what we’re facing.

And until you’ve solved all of that we’d like to take better care of those of us diagnosed with and living with ovarian cancer. So we’d like more trials available here. We see lots going on overseas and to us it seems those opportunities aren’t here for us.

We want something better than one size fits all. Because as you know, perhaps even better than we do, it doesn’t.

We want our doctors to tell us about what is available, even if it’s only available at another hospital down the road or interstate or overseas. We want to consider it all and then choose the best course for us with you.

Of course some of us just want to hide under the covers and never come out. But those women too need your help. Just more quietly.

And some of us also want to help you do all of this. Just ask.

So – really, what do we want right now?
We want your help. To live as long as we can, as well as we can.

Best of luck.

Bridget Whelan, consumer
A CALL TO ACTION

This National Action Plan for Ovarian Cancer Research (the Plan) marks a significant milestone for the ovarian cancer community in Australia. The Plan provides a strategic blueprint for how Australia can best contribute to the global ovarian cancer research effort. This is an ambitious and future-facing plan that takes account of progress to date and opportunities ahead, and builds on the expertise and skills available to us in Australia.

The Plan discusses the scientific, clinical and patient care issues relating to ovarian cancer; it then identifies the research priorities and actions that address these issues and highlights the enablers that will facilitate their implementation. At the heart of the Plan are the women living with ovarian cancer today, those who will be diagnosed tomorrow, and all those who have been and will be touched by the disease. These women, and their partners and families, demand and deserve the best: the best ways to find and treat the disease, the best approaches to providing care and support, and the best ways to use available resources to work towards a world in which outcomes from ovarian cancer are better than they are today.

We have come a long way in our understanding of ovarian cancer. Progress in genomics and proteomics has radically changed our understanding of the behaviour of cancer cells. We now know that ovarian cancer is not just one disease but a range of diseases with different cellular appearances, different molecular characteristics, and different trajectories. However, this new knowledge has not yet translated into new treatments or improved outcomes. In 2014, ovarian cancer remains a poor prognosis cancer with limited treatment options available.

Our challenge is not unique. However, it could be said that the tools we have available to address the challenge are. We have the benefit of a highly engaged clinical and scientific research community, internationally recognised leaders in key areas of research, and a platform for consumer engagement that allows women’s voices to be heard.

We acknowledge that the research environment is highly competitive and resources are finite. This highlights the need for a strategic approach that makes the best use of available human and fiscal resources. Our intent in developing the Plan is to set an agreed direction and approach that will maximise our chances of success.

Setting a new strategic direction refers not only to the identification of research priorities, but it also involves changing the way we plan, fund and report our research. Through this Plan we aim to highlight the importance of transparency, accountability and collaboration, as well as the need to communicate progress in a way that is meaningful to clinicians, researchers, the public and to women with ovarian cancer and their families.

I am proud to present this National Action Plan for Ovarian Cancer Research. I believe that progress is infinitely achievable through collaborative, strategic efforts, and I ask all organisations and individuals involved in and with an interest in ovarian cancer research to commit to taking the plan forward.

Paula Benson, Chair, Ovarian Cancer Australia

Development of the National Action Plan for Ovarian Cancer Research

The Plan has been developed through a rigorous approach that has included:

- a desktop audit of funding, publications and research outputs over the period 2008–2013
- broad consultation through interviews and two workshops with stakeholders (researchers, clinicians, consumers and representatives from industry, funding and government organisations)
- input from a multidisciplinary Working Group to review research priorities and enablers
- feedback on the draft Plan through a process of targeted consultation
- final sign-off by the Ovarian Cancer Australia Board.

More detail about the methodology is provided in Appendix I.
ACKNOWLEDGEMENTS

Ovarian Cancer Australia acknowledges the input of all of the individuals and organisations who contributed to this National Action Plan for Ovarian Cancer Research. A full list of contributors is provided in Appendix II.

WORKING GROUP MEMBERS

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OVARIAN CANCER AUSTRALIA STAFF AND BOARD

Board members: Paula Benson (Chair), Stephanie Alvarez, Simon Lee, Carolyn Reynolds.

Staff members: Alison Amos (CEO), Katherine Nielsen (Director, Research and Advocacy), Amanda Purdie (Director, Communications and Fundraising) and Imogen Baratta (Communications Officer).

ZEST Health Strategies conducted and reported on the stakeholder consultations and workshops that are referred to in this report. This report was designed and produced by ZEST Health Strategies.
THE CASE FOR ACTION

OVARIAN CANCER: A GLOBAL DISEASE, A LOCAL PRIORITY

Ovarian cancer is a disease with almost 1500 women in Australia and over 250,000 women worldwide newly diagnosed each year (1, 2). Mortality is high. Around 1000 women die from the disease each year in Australia. Only 43 out of every 100 women diagnosed are still alive 5 years after diagnosis (3, 4).

Behind these statistics are the faces of ovarian cancer: the women affected and their families and loved ones. We need to improve outcomes for the approximately 8900 women living with ovarian cancer in Australia (5), and reduce the number of women who will die from this disease in the future. But our aim is not just survival, we also need to see vast improvements in care and quality of life.

What is ovarian cancer?
Ovarian cancer was once thought to be a single disease, but we now know it is highly complex. There are three main kinds of ovarian cells that can form different types of tumours: epithelial, germ and stromal cells. About 85% to 90% of ovarian cancers are epithelial ovarian carcinomas (EOC), which are comprised of serous, mucinous, endometroid and clear cell subtypes. Upon diagnosis, EOC is further classified by grade and staged according to the American Joint Committee on Cancer (AJCC) and International Federation of Gynecology and Obstetrics (FIGO) staging system, based on the findings of exploratory laparotomy (a surgical diagnostic procedure that involves abdominal exploration). Of the four EOC subtypes, serous cancer is most common and can be high grade or low grade. This is where ovarian cancer has another added layer of complexity: we now know that high grade serous cancer (HGSC) can be separated into yet another four subtypes, each with a different prognosis.
Thus, rather than being one disease, ovarian cancer actually comprises several different cancers: germ

Ovarian cancer statistics

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<tr>
<th>OVARIAN CANCER WORLDWIDE</th>
<th>Low survival rates</th>
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<tr>
<td>3rd most commonly diagnosed gynaecological cancer</td>
<td>2nd most common cause of gynaecological cancer death worldwide</td>
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<tr>
<td>238,719 estimated new cases in 2012</td>
<td>151,905 estimated deaths in 2012</td>
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<tr>
<td>255,660 projected new cases in 2015 (2)</td>
<td>163,752 projected deaths in 2015 (2)</td>
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<td>5-year relative survival 45% (6)</td>
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<tr>
<th>OVARIAN CANCER IN AUSTRALIA</th>
<th>Low survival rates</th>
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<tr>
<td>2nd most commonly diagnosed gynaecological cancer</td>
<td>Most common cause of gynaecological cancer death in Australia</td>
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<tr>
<td>1305 new cases in 2010 (3)</td>
<td>903 deaths in 2011 (7)</td>
</tr>
<tr>
<td>1470 projected new cases in 2014 (1)</td>
<td>5-year relative survival 43% between 2006 and 2010 (8)</td>
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cell tumours, stromal cell tumours, EOC mucinous tumours, EOC endometriod tumours, EOC clear cell tumours, and four types of EOC high grade serous tumours. It is becoming increasingly clear that cellular origins play an important role in cancer progression and development. In fact, EOC was historically thought to originate from the ovaries but new evidence has revealed that the majority of EOC cancers arise in the fallopian tubes and spread into the ovaries.

A more fulsome description of the current understanding of the classification of ovarian cancers is provided on page 46. But it is important to highlight here that this diversity in ovarian cancers is important to future outcomes; by understanding the underlying biology of all forms of ovarian cancer and by discovering the mechanisms driving the most aggressive forms, we can improve diagnosis as well as identify and target each cancer’s weak points.

HGSC, the most common ovarian cancer subtype, is aggressive, presents at an advanced stage at diagnosis and although initial chemotherapy is effective, almost all patients relapse and progress to platinum-resistant disease, for which the prognosis is poor. We need to determine why a cancer that arises from one cell type rarely becomes malignant, while a cancer arising from a nearby cell type rapidly progresses and becomes resistant to treatment. Finding that answer could lead to new therapies, for which there is an urgent need.

The treatment regimen for ovarian cancer has changed little in decades. It involves tumour debulking surgery followed by administration of platinum and taxane-based chemotherapy. Platinum-resistant or refractory patients need more treatment options. In recent years, some progress has been made. The monoclonal antibody, bevacizumab, has been approved in several countries, including Australia, for the treatment of ovarian cancer, however, although there has been a significant improvement in progression-free survival demonstrated, no improvement in overall survival has been reported (reviewed in (9)). There is an urgent need for more effective therapies for ovarian cancer, for first line treatment, maintenance and for more effective treatment options in women with platinum-resistant or refractory disease.

The new insights into the underlying biology and heterogeneity of ovarian cancer has transformed the research field, forming the basis for better understanding of the molecular profiles of the different HGSC subtypes and the development of improved models of disease. These in turn are leading to the development of better methods of diagnosis and disease monitoring, and in the redesign of clinical trials to enable targeted therapies to be tested in the appropriate patient subpopulations (the use of which lags behind that in other cancer types).

According to one market source (10), the ovarian cancer drug pipeline currently consists of 335 drug candidates linked to 253 different targets under development by 242 companies. There is a wide range of novel targets distributed amongst these drug candidates, including growth factors, serine/threonine protein kinases and tumour associated antigens. The bulk of the clinical trials are in early stage clinical development (~87% preclinical-phase II), but nevertheless signify a large international effort to deliver new treatments. Notwithstanding this clinical effort, the high rate of attrition of clinical candidates necessitate exploration of clinical development that takes into account the heterogeneity of ovarian cancer. Molecular profiling techniques are now being developed to help classify tumours and identify which patients will benefit best from which treatments, ushering in an era of precision medicine. This is a field poised for change, but achieving that change will require a concerted effort, an alignment of strategies, and a focus of resources to ensure the greatest advantage for women.

**TERMS USED IN THIS DOCUMENT**
A Glossary of acronyms used in this document is provided in Appendix III.
A woman living with ovarian cancer

I was diagnosed with Stage III ovarian cancer in May 2008. Extensive surgery was followed by chemo. I was fortunate enough to be part of the Avastin trial and the cancer did not return till May 2010.

Once again, surgery removed the tumour which was sitting on the surface of the liver, followed by chemo. In May 2012 the tumour returned again to the surface of the liver and again was removed by surgery but this time with no chemo follow up.

Last year in November a tumour appeared in the abdomen and again it was cut out with no chemo ensuing. A PET scan in March this year was clear, and though my CA 125 went up in May, it has now gone back down to a reading of 9, so I am here to live another day.

“ "
My goal is to be the little fish that swims through the net."

Where would I like to see research heading?

• More research into the molecular malfunctions as we all know it is several diseases and yet it is still being treated on a collective rather than an individual basis. How ghastly to realise you may have suffered severely with a chemo treatment, which was never going to be effective with the type of ovarian cancer you have.

• More education of General Practitioners (GPs) who are too often missing the symptoms, as has been the case with several of my friends.

• While realising how unlikely and difficult this is, I yearn for the day when a simple blood test will indicate the presence of the disease, and oh how marvellous it would be to have a vaccine. Yes, I know, but this is a Wish List so I shall include it.
When my mother was diagnosed with ovarian cancer in 1982 the outlook for her was bleak. It seemed that little had improved by 1999 when my wife Sheila was diagnosed with her ovarian cancer. The treatments were essentially the same and the survival statistics had improved only slightly.

It is fifteen years since Sheila and I started to engage the clinical and research communities in Melbourne with a belief that collaboration, a plan and commitment from the Government could bring about a change in the outlook for women with ovarian cancer.

Since then we have seen some great initiatives and some significant gains in knowledge – predominantly resulting from researchers, clinicians and consumers working together to ensure investment, focus and commitment to unravelling the complex issues that challenge us in the field of cancer research.

Each year far too many women die, their families and friends left bereft and frustrated by disease that is highly aggressive, difficult to treat and overwhelming for many.

Ovarian Cancer Australia’s leadership in the development of this Plan is a critical step in addressing the real needs of the community and further enhancing the effectiveness of ovarian cancer research in Australia. I know it is the one thing that Sheila wanted to see come to fruition – research, collaboration, and outcomes that will make a genuine difference to the lives of thousands of women throughout Australia and the rest of the World.

Through joining together in the implementation of this Plan, we will be responding Sheila’s heartfelt plea:

“LET’S SAVE SOME LIVES!”

Sheila Lee, advocate
THE BROADER CANCER PERSPECTIVE: HOW DOES OVARIAN CANCER COMPARE?

Outcomes from ovarian cancer are poorer than for other cancers in women. In Australia, ovarian cancer is the sixth most common cause of cancer death. The burden of disease for women diagnosed is high, and the long-term impacts on women, their partners and families are significant. The aim of the National Action Plan for Ovarian Cancer Research is to change this picture.

Figure 1: Change in 5-year survival from ovarian cancer over the period 1982-87 to 2006-2010: comparison with other cancers in women (11).

Figure 1 shows how the 5-year survival rate for ovarian cancer has shifted only marginally compared to other cancers in women since 1982, and falls well below the average across all cancers. The improvements may be attributable to the cumulative effects of improved surgical methods, chemotherapeutic formulations and regimens, patterns of care, diagnosis and awareness. Despite this, the prognosis for women diagnosed with ovarian cancer remains relatively poor. This is mainly due to the fact that the most aggressive forms of ovarian cancer, which comprise the majority of cases, are diagnosed at an advanced stage, when the cancer has spread to other parts of the body and is difficult to treat successfully (12). Yet, because so little is known about the latency period and the rate and nature of progression of the aggressive forms, it is not yet clear how earlier diagnosis will be achieved and whether it will improve outcomes in these cases. What is profoundly clear is that women need better treatments. With only 43 out of every 100 women diagnosed with ovarian cancer likely to be alive five years after their diagnosis, the five-year survival rates for ovarian cancer fall far behind those of other cancers affecting women in Australia, including breast cancer (89%), uterine cancer (82%), cervical cancer (72%) and bowel cancer (67%) (4). Improvements in prevention, early detection and/or treatment account for increased survival in these cancer types.
**Burden of disease**

Ovarian cancer is the leading cause of burden of disease from gynaecological cancers, and accounts for 5% of all the female burden of disease attributed to cancer in Australia. In 2012, ovarian cancer resulted in 12,100 years of life lost (YLL) due to premature mortality (6). Figure 2 depicts how ovarian cancer compares with other cancers in terms of burden (as measured by disability-adjusted life year (DALY) score), incidence and mortality – it falls in a poor prognosis/high burden cluster demonstrating a high degree of unmet need.

The high burden of disease, poor prognosis and current paucity of available targeted treatments pose a significant challenge to the Australian and international research communities. Yet there is cause for hope. The new insights into the pathogenesis and heterogeneity of ovarian cancers and the advances in high throughput molecular profiling set the stage for a concerted international effort to advance precision therapy. This has the potential to provide better treatment options and to improve outcomes for women living with ovarian cancer.

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**Figure 2**: Correlation of 5-year survival with incidence and burden of disease as measured by DALY score (size of bubble) compared with other cancers
THE CASE FOR INVESTMENT

Funds invested from public sources (government, philanthropic and public/private investment) in ovarian cancer research have increased, from $6.5m in 2008 to $10.2m in 2013, with the greatest contribution from the National Health and Medical Research Council (NHMRC)\(^1\).

The intent of the Plan is to provide a strategic framework for transparent and accountable investment in ovarian cancer research to ensure available funds are used to optimal effect and act as a catalyst to drive further, much needed investment.

Sources of funding for ovarian cancer research

There are various sources of funding for ovarian cancer research in Australia, including funding schemes from international sources, national and state government organisations and councils, not-for-profit organisations (including cancer councils, charities and foundations associated with research institutions), as well as public and private investment. Table 1 lists the organisations that were identified in the audit process as having funded ovarian cancer research in Australia over the period 2008–2013, together with a description of the type of funding and how the funding is reported. It is notable that several organisations, in particular several not-for-profits, do not adopt regular reporting mechanisms that provide both the amount and nature of research funding in sufficient detail to undertake an adequate analysis.

The limited information creates difficulties in determining financial inputs into ovarian cancer research. For example, inadequate disclosure can lead to underestimates of the total funds expended over the period. This highlights the need for adopting a higher standard of reporting. It would be desirable for donors to obtain information on the inputs into the research they are supporting.

The case for improved financial reporting

Many of the organisations listed in Table 1 have searchable registers, or at least an annual report that details information about research funding, such as recipient, project title and description, and the amount funded. This is consistent with Australian Government Financial Management and Accountability Regulations 1997 for grant reporting.

However, several organisations do not provide sufficient information to undertake a quantitative analysis of funds invested. For example, while recipients may be named, the amounts funded are often not recorded, or the program is not described adequately. In some cases, organisations were unable to provide funding data, citing confidentiality limitations, despite the funds being publicly sourced.

\(^{1}\)This audit of research funding did not examine research funds from commercial/industry sources.
Funding for ovarian cancer research by year

Based on available data, a total of $54.8m was invested in ovarian cancer research over the period 2008–2013, increasing from $6.5m in 2008 to $10.2m in 2013 (approximately a 1.6-fold increase) (Figure 3). The single greatest contributor to funding was NHMRC, with $26m accounting for approximately 48% of the total, while all other organisations combined contributed $28.8m (52%). NHMRC funded areas of basic science, clinical research and public health. Across the funding period, Australian government agencies funded approximately 69% of research, with 25% contributed by not-for-profit organisations and 6% by international funding sources. These numbers indicate that not-for-profit organisations are contributing significantly to the research effort in ovarian cancer.

A recent audit into cancer research funding conducted by Cancer Australia reports funding of $18.9m into ovarian cancer for the six year period 2006-2011 (14). The differences in levels of funding reported reflect differences in audit methods including: different time periods and the exclusion of funding types such as infrastructure and equipment funding, individual fellowships and scholarships and funding for projects across multiple tumour streams, from the Cancer Australia audit. The audit here captures multiple tumour stream funding data, where ovarian cancer was a focus. However, proportional adjustments were made to account for the number of tumour streams and in some cases, based on the estimated proportion of funds allocated to ovarian versus other tumour streams (see Appendix I for methodology). The audit undertaken for this Plan was designed to capture the most comprehensive picture as possible of research investment in ovarian cancer in Australia.
Table 1: Funding sources for ovarian cancer research in Australia 2008–2013*

<table>
<thead>
<tr>
<th>Name/website</th>
<th>Funding scheme and affiliations</th>
<th>Reporting - research funding</th>
<th>Stage or focus</th>
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<tr>
<td><strong>Australian Government agency or council</strong></td>
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<tr>
<td>Australian Research Council (ARC)</td>
<td>National competitive grant scheme open to Australian researchers and approved research institutions</td>
<td>Searchable grants register, annual reports</td>
<td>Research projects, programs, fellowships</td>
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<td><a href="http://www.arc.gov.au">www.arc.gov.au</a></td>
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<tr>
<td>Cancer Australia</td>
<td>Funds via NHMRC process; co-funds with other funding organisations via Priority-driven Collaborative Cancer Research Scheme (PdCCRS)</td>
<td>Searchable grants register, annual grant - reporting since 2009</td>
<td>PdCCRS (Projects, Fellowships, other), clinical trials networks</td>
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<td>canceraustralia.gov.au</td>
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<td>Cancer Institute NSW</td>
<td>Competitive grant scheme open to NSW based universities, cancer services, hospitals, Area Health Services and other relevant agencies</td>
<td>Searchable grants register, annual report</td>
<td>Fellowships, equipment, translational/clinical research</td>
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<tr>
<td><a href="http://www.cancerinstitute.org.au">www.cancerinstitute.org.au</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHMRC</td>
<td>National competitive grant scheme open to Australian researchers and approved research institutions</td>
<td>Searchable grants register, reports grants and amounts</td>
<td>Early stage research, project, programs, clinical</td>
</tr>
<tr>
<td><a href="http://www.nhmrc.gov.au">www.nhmrc.gov.au</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Victorian Cancer Agency (VCA)</td>
<td>Competitive grant scheme open to Victorian researchers and research institutions</td>
<td>Searchable listing of funding recipients and project summaries in latest rounds</td>
<td>Fellowships, infrastructure, research projects (translational, clinical)</td>
</tr>
<tr>
<td><a href="http://www.victoriancanceragency.org.au">www.victoriancanceragency.org.au</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not-For-Profit organisations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australian Gynaecological Cancer Foundation (renamed from National Gynaecological Cancer Foundation)</td>
<td>Not disclosed</td>
<td>nil</td>
<td>Funding of gynaecological cancer research</td>
</tr>
<tr>
<td><a href="http://www.agcf.org.au">www.agcf.org.au</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name/website</td>
<td>Funding scheme and affiliations</td>
<td>Reporting - research funding</td>
<td>Stage or focus</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ANZGOG <a href="http://www.anzgog.org.au">www.anzgog.org.au</a></td>
<td>&gt;51 member organisations nationally</td>
<td>Annual report details grants and funding</td>
<td>Research fund initiated in 2013 to develop research ideas</td>
</tr>
<tr>
<td>Cancer Council Australia <a href="http://www.cancer.org.au">www.cancer.org.au</a></td>
<td>Members include: Cancer Council ACT; Cancer Council NSW; Cancer Council of the Northern Territory; The Cancer Council Queensland; The Cancer Council South Australia; Cancer Council Tasmania; Cancer Council Victoria; The Cancer Council Western Australia Inc. Each member has its own competitive funding scheme</td>
<td>Annual reports; CCV has searchable register; variations across states in process and reporting standards</td>
<td>A range of competitive grant schemes including research, fellowships, clinical trials</td>
</tr>
<tr>
<td>Cure Cancer Australia Foundation <a href="http://www.cure.org.au">www.cure.org.au</a></td>
<td>Competitive funding scheme; Co-funds with other organisations (Cancer Australia via PdCCRS scheme)</td>
<td>Annual report – doesn’t detail amounts to individual recipients</td>
<td>Research project grants and fellowships</td>
</tr>
<tr>
<td>The Eggtober Foundation <a href="http://www.eggtober.com.au">www.eggtober.com.au</a></td>
<td>not disclosed</td>
<td>nil</td>
<td>Research initiatives, details not disclosed</td>
</tr>
<tr>
<td>Fight Cancer Foundation <a href="http://www.fightcancer.org.au">www.fightcancer.org.au</a></td>
<td>Rotary</td>
<td>Annual report</td>
<td>OvCare (detection); fellowships</td>
</tr>
<tr>
<td>GO Foundation website n/a</td>
<td>Royal Hospital for Women, NSW</td>
<td>nil</td>
<td>No longer active</td>
</tr>
<tr>
<td>Gynaecological Cancer Foundation Ltd trading as Cherish Women’s Cancer Foundation cherishfoundation.com.au</td>
<td>In partnership with Queensland Centre for Gynaecological Cancer and other research partners</td>
<td>nil</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>Name/website</td>
<td>Funding scheme and affiliations</td>
<td>Reporting - research funding</td>
<td>Stage or focus</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ladybird Foundation</td>
<td>Gynaecological research in WA</td>
<td>nil</td>
<td>Not disclosed</td>
</tr>
<tr>
<td>ladybirdfoundation.org.au</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Breast Cancer Foundation</td>
<td>National competitive funding scheme</td>
<td>Searchable register, annual report</td>
<td>Several fellowship, scholarship, project and other schemes; focus on breast cancer, but funding for multi-tumour stream projects can include other cancers</td>
</tr>
<tr>
<td><a href="http://www.nbcf.org.au">www.nbcf.org.au</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer Australia</td>
<td>nil</td>
<td>Annual report</td>
<td>Research fellowship</td>
</tr>
<tr>
<td><a href="http://www.ovariancancer.net.au">www.ovariancancer.net.au</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer Research Foundation (OCRF)</td>
<td>Prince Henry’s Research Institute (Vic); funding scheme open to other applicants</td>
<td>nil</td>
<td>Fellowships, projects, infrastructure, clinical</td>
</tr>
<tr>
<td>ocrf.com.au</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women’s Cancer Foundation trading as Ovarian Cancer Institute</td>
<td>Women’s Cancer Institute (Royal Women’s Hospital, Vic); funding scheme open to other applicants</td>
<td>nil</td>
<td>Research, clinical</td>
</tr>
<tr>
<td><a href="http://www.womenscancerfoundation.org.au">www.womenscancerfoundation.org.au</a></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### International funding agencies

<table>
<thead>
<tr>
<th>Name/website</th>
<th>Funding scheme and affiliations</th>
<th>Reporting - research funding</th>
<th>Stage or focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institute of Health (NIH)</td>
<td>Competitive funding scheme</td>
<td>Searchable grants register</td>
<td>Research, project, fellowships, resource grants</td>
</tr>
<tr>
<td>USA government</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="http://www.nih.gov">www.nih.gov</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Department of Defense</td>
<td>Congressionally directed competitive medical research grants scheme</td>
<td>Searchable grants register provides grant but not funding information</td>
<td>Range of infrastructure and research programs and projects</td>
</tr>
<tr>
<td>USA Government</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cdmrp.army.mil/funding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marsha Rivkin Centre for Ovarian Cancer Research</td>
<td>Competitive funding scheme</td>
<td>Annual report</td>
<td>Pilot Study Awards, Scientific Scholar Awards</td>
</tr>
<tr>
<td><a href="http://www.marshalrivkin.org">www.marshalrivkin.org</a></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Other funding organisations not listed in detail here include The Australia and New Zealand Breast Cancer Trials Group (clinical research), The Association for International Cancer Research, Queensland Community Foundation and foundations associated with Medical Research Institutes (for example, The Garvan Research Foundation and Peter MacCallum Cancer Foundation) and those associated with several Australian universities.*
Funding for ovarian cancer research by Common Scientific Outline

Table 2 summarises the percentage of funds invested in ovarian cancer research in Australia over the period 2008–2013 across Common Scientific Outline (CSO) categories (see page 19 for definitions), compared with expenditure via the International Cancer Research Partnerships (ICRP) consortium (15). The ICRP has an extensive database providing publically available information on international funding from participating organisations across tumour stream and CSO categories and which can be used to benchmark funding allocations here.

This analysis shows that around 86% of funding for ovarian cancer research has focused on the areas of Biology, Detection, Treatment and Aetiology (Table 2, Figure 4a). There has been little expenditure in the categories of Models, Control and Prevention. Using ICRP data as a benchmark, Australia has allocated far greater funds proportionally in Detection, but the categories of Treatment and Prevention are comparatively under-funded.

Table 2: Breakdown of funding for ovarian cancer research in Australia across CSO categories compared with ICRP

<table>
<thead>
<tr>
<th>Category</th>
<th>Biology</th>
<th>Detection</th>
<th>Treatment</th>
<th>Aetiology</th>
<th>Prevention</th>
<th>Control</th>
<th>Model</th>
<th>unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>31%</td>
<td>29%</td>
<td>13%</td>
<td>13%</td>
<td>&lt;1%</td>
<td>7%</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>ICRP</td>
<td>35%</td>
<td>17%</td>
<td>23%</td>
<td>14%</td>
<td>6%</td>
<td>1%</td>
<td>4%</td>
<td>-</td>
</tr>
</tbody>
</table>

94% of funding (ICRP)

About the ICRP

Established in 2000, the ICRP is an alliance of cancer organisations from Australia, Canada, France, Japan, the Netherlands, United Kingdom, and United States, working together to enhance global collaboration and strategic coordination of research.

The ICRP aims to improve access to information about cancer research and enable cancer organisations to maximise the impact of their independent efforts, for the benefit of researchers and cancer patients worldwide.

The ICRP database contains information on 63,051 grants, totalling some $14,711,405,919 in cancer research from 81 organisations.
Overall, Government sources provide the majority of funding in Australia (69%), however this is not consistent across CSO categories. The category of ovarian cancer research receiving the most funding was Biology, with government sources providing 84% and with the majority from NHMRC (74% of the total allocated to Biology). Similarly, Aetiology, Prevention and Treatment received 73%, 100% and 80% of funding through government sources, respectively. In contrast, Detection research received 53% of funding through ‘Other’ organisations including not-for-profits and institutional funding.

The Australian funding profile exhibits a departure from the pattern of expenditure in the areas of Detection, Prevention and Treatment, and pinpoints a deficiency of funding in the latter two categories. This trend was also identified in a recent audit of cancer funding by Cancer Australia, where ovarian cancer funding for Detection was found to be 43% of total funding over 2009-2011, an observation which was considered to relate to targeted research initiatives in this area of ovarian cancer research (14). Similarly, funding allocations for Treatment and Prevention were reported to be significantly lower than ICRP funding. These differences are highlighted in Figure 4b.

This analysis raises the question as to whether future funding in Australia should be reallocated to better align with international expenditure patterns, for example by redirecting funding from Detection to Treatment and Prevention areas. It also highlights the need to identify funding priorities and specifically, identifies an opportunity for Government and other organisations to increase funding to underfunded areas.

The Common Scientific Outline (CSO) is a system commonly used to categorise and audit research in cancer (see Appendix IV for further detail):

1. Biology: how cancer starts and progresses, includes research on normal biology relevant to these processes

2. Aetiology: identifying the causes or origins of cancer – genetic, environmental, and lifestyle, and the interactions between these factors

3. Prevention: identifying interventions which reduce cancer risk by reducing exposure to cancer risks and increasing protective factors. Interventions may target lifestyle or may involve drugs or vaccines

4. Early Detection, Diagnosis, and Prognosis (Detection): identifying and testing cancer markers and imaging methods that are helpful in detecting and/or diagnosing cancer as well as predicting the outcome or chance of recurrence

5. Treatment: identifying and testing treatments administered locally (e.g. radiotherapy and surgery) and systemically (treatments like chemotherapy that are administered throughout the body), as well as non-traditional (complementary/alternative) treatments (such as supplements, herbs); also includes research into the prevention of recurrence

6. Cancer Control, Survivorship, and Outcomes Research (Control): includes a broad range of areas including patient care and pain management; tracking cancer cases in the population; beliefs and attitudes that affect behaviour regarding cancer control; ethics, education and communication approaches for patients and health care professionals; supportive and end-of-life care; and health care delivery in terms of quality and cost-effectiveness

7. Scientific Model Systems (Models): development of new animal models, cell cultures and computer simulations and their application.
Figure 4: Kite diagrams of funding for ovarian cancer research across CSO categories showing funding patterns in (a) Australia 2008-2013 identified in the desktop audit (blue shade), compared to (a) patterns of government (dark blue line) and other funding (green dotted line); and (b) patterns of funding reported by Cancer Australia (2009-2011) (green dotted line), and internationally (2008-2013) according to the International Cancer Research Partnership (ICRP) (dark blue line).
THE CASE FOR COLLABORATION

The level of collaboration between clinicians and researchers involved in ovarian cancer research in Australia has been significant and is yielding tangible benefits. However, greater effort is needed to ensure that collaboration between clinicians, researchers, funders and consumers is integral to all aspects of research planning, funding, conduct and reporting.

The Plan sets a strategic direction for ovarian cancer research that encourages collaboration based on the greatest potential to improve outcomes, while respecting the strengths and expertise of individual researchers and organisations.

The current research model

Research is, by its very nature, competitive. Researchers and the groups and organisations with which they are affiliated have their own areas of interest based on their particular expertise. Success relies on being able to compete for funding, resources and publications.

While the competitive nature of research does, in part, drive research quality, it also results in activities being planned and conducted in isolation and can result in duplication and overlap of effort. This fractured approach is not in the best interests of women.

The need for collaboration

The benefits of collaboration in research are well known and leading cancer research organisations around the world recommend increasing collaborative approaches. For example, The American Society of Clinical Oncology presented a blueprint for transforming clinical and translational oncology research over the next decade. This blueprint relies on molecularly-driven, collaborative approaches to cancer diagnostic and therapeutic development.

Examples of the benefits of collaboration

Australia has benefitted from building resources for ovarian cancer research that involve collaboration between scientists and clinicians.

The Australian Ovarian Cancer Study (AOCS) is an excellent example that has demonstrated the value of a collaborative approach (see page 31 for more information).
In the ovarian cancer field, collaboration will yield measurable advantages. A cohesive national strategy reduces research overlap, enables the development of programs that complement one another, and ensures that critical knowledge gaps are identified and are addressed. There is a host of fiscal advantages to collaboration as well. A recurring issue raised by contributors to this Plan is that philanthropic funding is diluted across multiple groups who don’t necessarily work together. Many stakeholders emphasise the critical need to establish a nationally coordinated and collaborative approach to funding and conducting ovarian cancer research across the continuum:

- A collaborative approach to planning ensures that research programs take national research priorities into consideration and focus on the greatest potential for progress
- Collaboration between funders can achieve greater impact, deliver improved transparency and consistency in decision making and optimise the use of available funds
- Shared resources ensure best use of limited funding
- Multi-site studies help to achieve adequate patient numbers for trials – this is particularly important in ovarian cancer given the small patient population and the heterogeneous nature of the disease
- International linkages ensure that the Australian research effort is aligned with global priorities
- Collaboration between clinicians and researchers supports clinically relevant research and helps with the translation of research into practice
- Personalised oncology requires collaborative endeavor to achieve appropriate, accessible datasets and standardisation.

“New, more collaborative research models and trial designs will enable testing of multiple drugs at once, and provide more meaningful insight into what does and doesn’t work, and why (16).”
“Substantially greater progress could be made in alleviating many of our most serious and complex social problems if nonprofits, governments, businesses, and the public were brought together around a common agenda to create collective impact.”

“Consumers, researchers, clinicians, industry and funders need to be engaged at each stage from research planning to the dissemination of findings and translation to practice”

“Community organisations should continue advocating for more funding for cancer research (particularly for priority-driven research and people and infrastructure support), better national coordination and more partnerships between funding agencies”

“Many small medical research charities do not have sufficient economies of scale in fundraising and overheads. Increased collaboration and coalescence between charities in funding health research will assist in leveraging funding to deliver greater impact”
http://www.mckeonreview.org.au/

“International consortia involving large biological datasets must be encouraged, but they require high fidelity and transparency in analytical approaches. Ovarian cancer is a relatively uncommon disease and, together with its histologic diversity, this makes it difficult to collect substantial numbers of samples of specific subtypes. Global collaborations and consortia such as Ovarian Cancer Association Consortium (OCAC), The Cancer Genome Atlas (TCGA), The Australian Ovarian Cancer Study (AOCS), OCTIPS (Ovarian Cancer Therapy – Innovative Models Prolong Survival) and Ovarian Tumor Tissue Analysis Consortium (OTTA) are crucial to furthering our understanding of the molecular biology of ovarian tumors and genetic risk.”

“While many of the pieces for personalized oncology are already in place, the key to a more holistic model is the creation of a standardized, integrated and scaled dataset of longitudinal molecular, clinical and outcomes data that yields associations. This will require investments in tools, infrastructure and training, as well as new ways of thinking, particularly around economic incentives… Since the data is most valuable in aggregate, the lack of incentives for sharing is a major barrier to personalized oncology”

“Reduction, and possibly elimination, of the breast cancer burden is possible if partnerships are formed that take a coordinated and collaborative approach to planning, funding, implementing and monitoring breast cancer research”

“New, more collaborative research models and trial designs will enable testing of multiple drugs at once, and provide more meaningful insight into what does and doesn’t work, and why”
Collaboration in research is essential to maximising the research outcomes. There is a balance to be struck between stimulating research effort through competition and focusing all of the available expertise on the one goal and reducing replication.

In Australia where we compete with the international community, the goal must be to identify projects where the results will lead to important advances yet in areas where we can be competitive despite differences in the scale of funding. The advances for which we aim should not just involve incremental change but disruption of the current status quo. However we should not only seek collaboration across state boundaries but with international partners to make best use of scarce resources including the valuable patient population which will be asked to participate in clinical trials of new treatments or screening tools.

Identifying the most pressing priorities is also an exercise which must bring together multidisciplinary teams spanning basic research, clinical research including diagnosis and treatment and population research including prevention and screening. The input of the patients and their families is vital at this stage of planning. If then the funders could adopt the same research priorities, greater and more sustainable funding would increase the chances of success. They should also adopt similar measurements of the impact of the research to help guide future initiatives.

“**The advances for which we aim should not just involve incremental change but disruption of the current status quo.**”

Collaboration can be fostered, by striking the correct balance in funding between investigator-initiated research and priority driven research where the funding directs the goal and drives researchers to form the strongest possible cross disciplinary teams.
A VISION FOR CHANGE

The National Action Plan for Ovarian Cancer Research has at its heart the need to focus research activity in Australia on what will make the greatest difference for women with ovarian cancer now and in the future. The Plan is positioned in the context of the global research effort but draws on the strengths and expertise of the Australian ovarian cancer research sector.

While we recognise the need to work to better use the available funding and resources, a robust, strategic and collaborative framework will be a key driver in attracting further funding in key priority areas.

“There is an urgent need to bring researchers together. Identify top priorities and actively identify and use opportunities to collaborate.”

— cancer stakeholder
The opportunities in ovarian cancer research and what Australia can contribute

Ovarian, fallopian tube and peritoneal cancer (referred to as ovarian cancer) are the leading causes of death among women with gynaecological cancer. Late presentation with advanced disease is common, with the resulting poor response to maximum interventions such as radical surgery and chemotherapy.

It is no longer sufficient to simply report on survival data, embedded in the studies should be a measure of the cost to the patient of a slightly prolonged overall survival.

From a global perspective it is clear that the majority of women with ovarian cancer do not have access to specialised gynaecological oncology services (even in developed countries) and this is an important contributing factor to poor survival and outcome. The sub-specialisation of gynaecological oncology with the appropriate surgical and medical oncology training needs to be promoted globally through professional organisations, educational institutions and National Departments of Health. As the complexity of ovarian cancer becomes more apparent through genomics, molecular profiling, investigation of biomarkers and sub-classification, collaboration between clinicians, scientists, geneticists, pathologists and the pharmaceutical/diagnostics industry (among many others) has become critical. The global effort to find solutions to ovarian cancer, from prevention to improved treatment and quality of life is currently fragmented and located in silos. The Australian health care community is to be commended for its collaborative work in the field and should serve as a model for international collaboration. One of the key strengths of the Australian system is the very strong lobby from organisations such as Ovarian Cancer Australia who lobby across a broad front of stakeholders to keep the issue of ovarian cancer alive. In addition, there is a strong collaboration between scientists and clinicians, enabling discoveries at the bench to move closer to the bedside.

Prof Lynette Denny, MD PhD
Chair and Professor of Obstetrics and Gynaecology and registered sub-specialist in Gynaecological Oncology at Groote Schuur Hospital & University of Cape Town, South Africa
Women living in poor countries often suffer the most as either surgery and/or chemotherapy are not available and many will die without any treatment intervention. Interestingly ovarian cancer is the sixth commonest cancer among women living in sub-Saharan Africa, although reliable data are lacking. There may also be ethnic differences in the pathogenesis of ovarian cancer and this too needs investigation – historically most ovarian cancer research has focused on Caucasian women and women of colour are poorly represented in clinical and other trials.

Within the next five years the impact of new targeted therapies on overall survival will become available, however, the complex sub-classification of ovarian cancer types may make accrual of patients to clinical trials more difficult. Evaluation of the impact of new treatment interventions, be they surgical or medical should always be accompanied by meaningful quality of life studies. It is no longer sufficient to simply report on survival data, embedded in the studies should be a measure of the cost to the patient of a slightly prolonged overall survival. Outcomes of therapeutic interventions should be carefully constructed in collaboration with women suffering from ovarian cancer.
AUSTRALIA’S R&D LANDSCAPE

With increasing healthcare costs and the finite nature of health funding, it is more important than ever that Australia’s health and medical research community embraces collaboration over competition in order to improve health outcomes. Though the research environment has traditionally been driven by competition, collaboration has a greater potential to improve patient outcomes by enabling strategic access to networks and large scale resources, generating efficiency benefits, and improving opportunities for innovation.

In 2013, in recognition of the value of leveraging research to improve healthcare delivery, the Australian government released a Strategic review of Health and Medical Research (13).

Key outcomes from this review include recommendations to:

- embed research in the health system
- support priority-driven research
- maintain research excellence through the competitive grants system and building enabling infrastructure (including patient databases, registries, a biobank hub and enabling technologies and capabilities)
- enhance the non-commercial pathway to impact through health services research, public health research, accelerating health system innovation and delivering evidence-based health care and policy
- enhance the commercial pathway to impact through increasing funding for translational research and development and through clinical trial reform
- attract philanthropy through strategic alliances and attract new funding sources
- develop a plan to invest and implement recommendations, including review and evaluation.

This Plan aligns strongly with these broad recommendations and relies on collaborative efforts from researchers and funders to provide the resources and investment necessary for its success. Furthermore, the establishment of a cohesive, priority driven Plan in line with the national vision for medical and health research is expected to attract new funding opportunities and generate philanthropic interest.

AUSTRALIA’S STRENGTHS

Australia is a recognised leader in ovarian cancer research worldwide, with international opinion leaders driving research activity with high level exposure and impact. Australia is home to a growing clinical research infrastructure, as well as a unique biospecimen resource that will help address clinically important questions about the causes, risk factors and treatment of ovarian cancer.

The aim of the Plan is to ensure that ovarian cancer research priorities in Australia make best use of the available expertise and skills, build on our areas of great strength and maximise the potential of available resources.
Key stakeholders in ovarian cancer research

We have got the best brains in ovarian cancer research in the world.
- researcher

Ovarian cancer research resources in Australia

Australia has a wealth of ovarian cancer expertise available to drive high-quality research with relevance at a global level (see Table 3).

Key national strengths identified through the consultation process include expertise in:
- biology and genomics
  - Australian Ovarian Cancer Study (AOCS)
- familial risk and genetic counseling
- translational research
- clinical trials infrastructure
  - Australia New Zealand Gynaecological Oncology Group (ANZGOG)
- quality of life (QOL) expertise (including development and validation of tools to measure QOL, design and analysis of QOL research as well as broader supportive care and psycho-oncology research in cancer).

Further details on these areas of expertise are provided in later sections of the Plan.
Table 3: Key resources available to drive ovarian cancer research in Australia

<table>
<thead>
<tr>
<th>Resource</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOCS</td>
<td>A collaboration between Peter MacCallum Cancer Centre (PMCC), The University of Melbourne (UM), Queensland Institute of Medical Research (QIMR) and Westmead Hospital, cited by key opinion leaders as an exemplary model for collaborative research. Provides a platform for high-impact, collaborative research with peer-reviewed access to its biobank, having specimens linked to clinical outcomes and source data on over 2000 women with ovarian cancer. Has demonstrated leadership in the classification of ovarian cancer subtypes and the provision of its biospecimen resources for researchers to use, that can accelerate translational research. Has supported 90 different national and international studies since its inception in 2001 and participated in over 130 publications since 2008.</td>
</tr>
<tr>
<td>ANZGOG</td>
<td>A not-for-profit organisation dedicated to gynaecological cancer clinical research with multicentre institutional involvement by over 51 sites throughout Australia and New Zealand. ANZGOG has been identified by key opinion leaders as an important clinical research enabler, facilitating high quality national and international collaborative research and developing new trial concepts. ANZGOG is reported to have facilitated Australia’s participation in many major ovarian cancer clinical trials internationally.</td>
</tr>
<tr>
<td>Australian Society of Gynaecologic Oncologists (ASGO)</td>
<td>Member organisation for gynaecological oncologists with a remit that includes promotion of research, training and education in gynaecological oncology.</td>
</tr>
<tr>
<td>Resource</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Research hubs</td>
<td>Leading basic science, clinical, epidemiological and quality of life research teams and networks based in clinical and research facilities around the country. Some key hubs include:</td>
</tr>
<tr>
<td>Gynaecological Cancers Group and the Cancer Genetics Laboratory, QIMR Berghofer Medical Research Institute, QLD; <a href="http://www.qimrberghofer.edu.au/page/Lab/Gyn_Cancer">www.qimrberghofer.edu.au/page/Lab/Gyn_Cancer</a></td>
<td></td>
</tr>
<tr>
<td>Gynaecological Oncology Research Group, Westmead Millennium Institute, NSW; wmi.org.au</td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer Research, Garvan Institute, NSW; <a href="http://www.garvan.org.au/research/cancer/ovarian-cancer-research">www.garvan.org.au/research/cancer/ovarian-cancer-research</a></td>
<td></td>
</tr>
<tr>
<td>Ovarian Cancer Biomarkers, Prince Henry’s Institute, Vic; <a href="http://www.princehenrys.org/ovarian-cancer-biomakers-lab">www.princehenrys.org/ovarian-cancer-biomakers-lab</a></td>
<td></td>
</tr>
<tr>
<td>Queensland Centre for Gynaecological Cancer; Royal Brisbane and Women’s Hospital, Herston QLD; <a href="http://www.gyncan.org">www.gyncan.org</a></td>
<td></td>
</tr>
<tr>
<td>Reproductive Cancer Group, Robinson Research Institute, University of Adelaide, SA; <a href="http://www.adelaide.edu.au/robinson-research-institute/researchers">www.adelaide.edu.au/robinson-research-institute/researchers</a></td>
<td></td>
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<tr>
<td>Translational Cancer Research Network, Lowy Institute, NSW; HSA Biobank resource supporting cancer research; <a href="http://www.tcrn.unsw.edu.au/hsa">www.tcrn.unsw.edu.au/hsa</a></td>
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</tr>
<tr>
<td>Women’s Cancer Research Centre; Royal Womens Hospital, Vic; <a href="http://www.thewomens.org.au/research/research-centres/womens-cancer-research-centre">www.thewomens.org.au/research/research-centres/womens-cancer-research-centre</a></td>
<td></td>
</tr>
<tr>
<td>Victorian Comprehensive Cancer Centre (VCCC) - a network of research organisations including Peter MacCallum, WEHI and Royal Women’s Hospital with key research groups focusing on gynaecological cancer research, treatment and care; <a href="http://www.vcccproject.vic.gov.au">www.vcccproject.vic.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Significant research is also being conducted at laboratories at Queensland University of Technology (QUT), The University of Adelaide, The University of Melbourne, The University of Queensland, The University of Sydney, The University of WA and The University of NSW (UNSW).</td>
<td></td>
</tr>
</tbody>
</table>
At the Mater Hospital in Brisbane we employ a multidisciplinary team (or MDT) model to care for women with ovarian cancer. In practical terms this means that the collective expertise of multiple healthcare disciplines is used to arrive at the most appropriate treatment choices for each patient. As much as is currently possible, this MDT approach helps to individualise each woman’s therapy, be that surgery, chemotherapy, radiation, supportive care, involvement in trials or a combination of these approaches. But there is still so much more to be done to improve diagnosis and treatment. This is where research is so important.

Building on the effectiveness of the MDT approach, we have used it as the centrepiece of our research efforts. Our “Mater Ovarian Cancer Research Collaborative”, or MOCRC, involves surgeons, pathologists, medical and radiation oncologists, nurses, allied health professionals and scientists working together. To date 226 women have consented to being involved in our studies. Currently, we are using the samples collected from patients for two core purposes. The first is to use them to test whether new compounds can be effective at selectively killing cancer cells over non-cancerous cells. Testing in this way is an essential step in developing the drugs needed to treat the different forms of ovarian cancer.

The second purpose is to define the genetic events that cause each patient’s ovarian cancer.

“The goal here is to move even closer to a truly individualised approach to patient care.”

If we can understand each woman’s disease at a molecular level, we are one step closer to knowing which drugs or other therapies will be best for their treatment.

As MOCRC is maturing we are partnering more and more with national and international collaborators to develop the most effective and appropriate care for each woman with ovarian cancer. Over the coming months and years we are looking to further diversify our research efforts to understand the needs of our patients and to provide them with the most up-to-date treatments.

A/Prof Lewis Perrin
Clinical Director, Mater Gynaecological Oncology Service, Brisbane QLD

A research hub embedded in the health system: The Mater Ovarian Cancer Research Collaboration story….so far
ACHIEVEMENTS AND PROGRESS

Significant progress has been made in recent years in understanding the biological and molecular basis of ovarian cancer. This has led directly to advances in genetic testing for women at high risk of the disease, which in turn may translate into preventative mechanisms. However, these advances have not yet translated into new treatments or early detection of the disease itself. Nevertheless, they hold great promise for future research directions.

The aim of the Plan is to draw on the progress and reap the benefits of the knowledge gained through a coordinated and strategic approach that will not only advance our understanding of the genetic basis of ovarian cancer, but will also ensure further, much needed progress in the areas of diagnosis and treatment.

RESEARCH OUTPUTS

The evaluation of research impact is an area of growing interest to funders, research organisations, government and the general community. Frameworks to evaluate research impact have been developed, for example, the Payback system (17) measures knowledge production and how it is disseminated, the benefits to future research, whether that knowledge contributes to the development of products, policies or clinical guidelines, as well as what health sector, social and/or economic benefits it provides. Given the short timeframe under consideration here, and the early stage of the bulk of research, this review focuses on knowledge production, for example the quantity and impact of publications and, to some extent, on clinical development. While it is also recognised that there has been some development activity, in terms of patent applications and changes in practice, a review that includes such measurements would be more appropriate after a sufficient timeframe post-implementation of the Plan.

How well does publication quantity reflect research output?

Measuring the quantity of publications in isolation is uninformative when assessing research and is best used in the context of the international landscape. While quantity provides an indication of research focus and efficiency, it does not provide an indication of the impact of the research.

Ovarian cancer publications

In exploring ovarian cancer research output, we wanted to gain an understanding of how much ovarian cancer research involves Australian researchers, to consider this in relation to the prevalence of the disease in the Australian community, and to then see how this compares with ovarian cancer research efforts in other nations. To this end, the number of ovarian cancer publications for several countries over the period 2008–2013 was calculated and this was then adjusted for the incidence of ovarian cancer in 2012. This was accomplished by determining the ratio of the percentage of total publications for each country to the percentage of total incidence for each country (see Appendix I for detailed methods). The results demonstrate that Australia has a high research output when adjusted for incidence, exceeding that of other countries measured (Figure 6 and Table 4). Note that this analysis does not distinguish between research in which Australian researchers participate from research which is led by Australian researchers.
Table 4: Number of publications and incidence of ovarian cancer by country

<table>
<thead>
<tr>
<th>Measure</th>
<th>USA</th>
<th>UK</th>
<th>Australia</th>
<th>Canada</th>
<th>Japan</th>
<th>NZ</th>
<th>Total all countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of publications</td>
<td>6,120</td>
<td>1,173</td>
<td>567</td>
<td>846</td>
<td>1,116</td>
<td>56</td>
<td>21,771</td>
</tr>
<tr>
<td>% of total publications (all countries)</td>
<td>28.1</td>
<td>5.4</td>
<td>2.6</td>
<td>3.9</td>
<td>5.1</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Incidence 2012 (18)</td>
<td>20,874</td>
<td>6,638</td>
<td>1,417</td>
<td>2,640</td>
<td>8,921</td>
<td>294</td>
<td>236,859</td>
</tr>
<tr>
<td>% of total incidence</td>
<td>8.8</td>
<td>2.8</td>
<td>0.6</td>
<td>1.1</td>
<td>3.8</td>
<td>0.1</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 6: Number of publications by country over 2008-2013 adjusted for incidence of ovarian cancer in 2012 (% of total publications/% of total incidence from Table 4)
The data also revealed that the Australian ovarian cancer research effort is spread across a wide range of research sub-categories. To better understand the scope, and to identify areas of focus, the publications were grouped across each CSO category as shown in Figure 7(a) (see Appendix IV for further details of subcategories). Further, the funding was compared to publication output (Figure 7(b)) to explore the level of coherency between input and output patterns across the domains. This analysis reveals:

- a high number of publications in Biology, consistent with high funding in this category
- a significantly higher proportion of publications in Control and Treatment categories (25.9% and 22.5% of publications, respectively), compared to the funding allocations
- a low number of publications in Aetiology, Prevention and Models (7.7%, 3.6% and 3.6% of publications, respectively), consistent with low funding in these categories
- the publication output for Detection (12.2% of publications) is low given it represents 29% of funding; an observation which may be indicative of challenges in this domain.

The high number of publications in the Control category is interesting, given this category has attracted far less funding compared with other categories. The greatest focus in this category is in the area of surveillance which includes epidemiological studies and risk factor analyses based on case-control studies. Other areas of focus within this category include patient care, QOL and survivorship research, as well as behavioural and psychosocial research. The output in Biology is spread over three main subcategories: pathogenesis, signalling and progression of ovarian cancer. In Treatment, the majority of publications focus on preclinical studies, a broad category encompassing target discovery to preclinical validation. Detection focuses primarily on biomarker discovery.
Figure 7: (a) The number and spread of ovarian cancer research publications across CSO categories, detailing the subcategories; and (b) Comparison of pattern of funding input across CSO categories to publication output.

Abbreviation: QC = quality control
Measuring research impact

A commonly used measurement of impact is the Impact Factor (IF), which ranks scientific and medical journals according to the average number of citations received per paper published in that journal. IF values provide an indication of the extent of research dissemination with a benchmark of IF ≥5 signifying publications that are likely to be widely read and cited by peers.

While using IF values to measure impact is subject to criticism for pertaining to the journal, rather than the individual publication, it is still considered a reasonable indicator in the absence of a better system of measurement.

Impact can also be measured by Citation Index, which is the number of citations per publication. However, this is considered more prone to misinterpretation for recent datasets due to the fact that older publications are more likely to be cited than newer ones.

Correlations between IF and citation number were poor when data from 2012–2013 were included. Therefore, IF values are primarily relied upon here.

To better understand the impact of these research findings, we looked at the IF of each publication where available. The majority of IF values for ovarian cancer research articles published between 2008 and 2013 are <5 (Figure 8), indicating that the bulk of research output has not been widely disseminated into the international community. In order to enable benchmarking of certain research areas and to help assess areas of expertise and weakness, the mean and median IF values were then calculated. Of note, the median values appear to be more informative than the mean, as the latter tends to be skewed by the extremely high IFs of a few journals, creating an outlier effect. The results indicate that the median value is well below the IF threshold of 5, which represents an overall rating of low impact (Table 5). While this may indicate weakness or challenges in some research areas, this is tempered by the observation that in some specialty areas, for example health care delivery, the gynaecological oncology journals have lower IF values but are the source of choice for ovarian research given the specialist readership.
Figure 8: Waterfall graph showing IF values for ovarian cancer research publications involving Australian researcher(s) for the period 2008–2013

Table 5: Average and median IF values and % publications by recognised IF intervals (19)

<table>
<thead>
<tr>
<th>IF</th>
<th>Average</th>
<th>Median</th>
<th>&gt;20</th>
<th>10–20</th>
<th>5–10</th>
<th>2–5</th>
<th>&lt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.43</td>
<td>3.73</td>
<td>4.2%</td>
<td>3.0%</td>
<td>20.3%</td>
<td>52.9%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Impact</td>
<td>Moderate</td>
<td>Low</td>
<td>V High</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>V Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Analysis of IF values by year shows a steady growth in the number of publications but with no corresponding improvement in average or median IF values. However, there was noticeable improvement in number of publications in high impact journals (IF > 5) over this period, from 15 in 2008 to 36 in 2013.

In order to see how IF varied between research areas, and thus identify areas of high impact research, each CSO category was ranked based on a composite score that included both quantity and impact measurements:

- number of publications
- average IF
- median IF
- number of publications with an IF > 5.

The outcome: the areas of Biology, Treatment, Aetiology and Control represent the highest ranking categories (Table 6).
Table 6: Summary of values for number of publications and IF factor measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Biology</th>
<th>Aetiology</th>
<th>Prevention</th>
<th>Detection</th>
<th>Treatment</th>
<th>Control</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. publications</td>
<td>113</td>
<td>36</td>
<td>17</td>
<td>57</td>
<td>105</td>
<td>121</td>
<td>17</td>
</tr>
<tr>
<td>Median IF</td>
<td>4.4</td>
<td>4.8</td>
<td>3.2</td>
<td>3.3</td>
<td>3.9</td>
<td>2.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Average IF</td>
<td>7.5</td>
<td>5.5</td>
<td>3.5</td>
<td>4.3</td>
<td>6.5</td>
<td>3.7</td>
<td>4.0</td>
</tr>
<tr>
<td>No. IF &gt; 5</td>
<td>36</td>
<td>16</td>
<td>2</td>
<td>11</td>
<td>38</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Score</td>
<td>13</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>RANK</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Top 4 in each category scored 4–1, with highest number representing highest rank; overall Rank = sum of scores

Factors driving high-impact research

We reviewed some of our top publications in ovarian cancer research to determine what factors were driving high impact research. These publications were identified by determining the 15 publications with (i) the highest IF values; and (ii) by citation index. This resulted in a list of 19 notable publications (Appendix VI). Analysis of these revealed the following:

- 12 of the 19 resulted from large collaborations involving more than 10 collaborating institutions
- 14 of the 19 resulted from international collaborations
- 10 of the 19 cited the use of Australian biobanks (tissue sample collections).

Analysis of all publications with IF ≥ 5 shows that just as many publications are the result of a small, national effort as are the result of a large international collaboration with a cited biobank. However, the average and median IF values are markedly higher for the latter, in fact they are 200% greater than the national average value over all publications, significantly outperforming the impact of those publications resulting from national/small collaborations (Table 7(a)).

This provides a compelling case that high-impact research is driven by international collaboration and that accessibility of Australian biobanks is an important enabler for such collaborations.

This finding is consistent with the cancer research field in general. The Cancer Research Leadership Forum (CRLF) recommended increasing international collaboration as a means to improving research outcomes (20). Ovarian cancer comprises a range of low prevalence subtypes, so it is particularly important to collaborate internationally in order to achieve access to the large datasets required to produce statistically meaningful results.

The above methods of research impact analysis can be used to benchmark performance of Australian organisations or consortia involved in the funding or conducting of research or related activities. This approach to measuring research impact is exemplified by two cases studies, the AOCS and ANZGOG. The results are summarised in Table 7(b).

Case study 1 - Biobank: The AOCS is a collaborative research initiative between several Australian research organisations that provides peer reviewed, collaborative access to its biospecimen collection. AOCS has facilitated over 90 collaborations since its inception in 2001, and key opinion leaders have cited it as an exemplary model for a collaborative research approach. Analysis of the publication output (21) over the review period shows performance 62% above the national average.
benchmark for ovarian cancer research in Australia over the same period, providing arm’s length validation of its position as a leading research enabler. See Table 7(b).

Case Study 2 – Clinical research organisation: ANZGOG is a not-for-profit organisation dedicated to gynaecological cancer clinical research with multicentre institutional involvement by over 51 sites throughout Australia and New Zealand. ANZGOG has been identified by key opinion leaders as a key clinical research enabler, facilitating high quality national and international collaborative research and developing new trial concepts. We applied the IF analysis method to ANZGOG publications cited in their annual reports. In the area of clinical research into ovarian cancer, ANZGOG was involved in high impact publications that are 59% above the national average benchmark (Table 7(b)) providing validation to the key opinion leader endorsements offered in the consultations.

Table 7: Impact drivers

(a) Median and average IF for publications with IF ≥ 5

<table>
<thead>
<tr>
<th></th>
<th>% Total IF ≥ 5</th>
<th>Average (Median)</th>
<th>Change from national benchmark (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large collaboration / Biobank</td>
<td>47.7</td>
<td>16.3 (8.6)</td>
<td>+200 (131)</td>
</tr>
<tr>
<td>National/small collaboration</td>
<td>52.3</td>
<td>7.8 (6.2)</td>
<td>+44 (66)</td>
</tr>
<tr>
<td>Benchmark (national)</td>
<td>n.a.</td>
<td>5.43 (3.7)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

(b) Benchmarking performance

<table>
<thead>
<tr>
<th>Group/Organisation</th>
<th>No. publications</th>
<th>Average (Median)</th>
<th>Change from national benchmark (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biobank - AOCS</td>
<td>130</td>
<td>8.8 (5.1)</td>
<td>+62 (+36)</td>
</tr>
<tr>
<td>Clinical - ANZGOG</td>
<td>36</td>
<td>8.6 (5.1)</td>
<td>+59 (+36)</td>
</tr>
</tbody>
</table>
A clear understanding of the biology of ovarian cancer is central to the research effort, as it underpins the research strategies in all other domains.

As part of the consultation process to inform the Plan, we asked participants to reflect on the ‘game-changing’ research that has been undertaken in the field of ovarian cancer nationally and internationally in recent years. Views have been captured in Table 8. Of note, these views align with the areas of expertise identified from the desktop audit process.

The majority of participants agreed that one of the most important advancements in recent years is the improved understanding of the heterogeneity of ovarian cancer – both at a histological and molecular level. This understanding of the basic biology of the disease is seen to be the foundation for future research questions around risk reduction, detection and treatment of ovarian cancer.

“We have got the edge and need to keep on improving.”
– academic researcher
<table>
<thead>
<tr>
<th>Area of research</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity of ovarian cancer</td>
<td>Recognition that ovarian cancer is not just one disease but a range of diseases with different histological and molecular subtypes. Classification of subtypes has led to better animal models that can be used as the basis for research.</td>
</tr>
<tr>
<td>Understanding of the aetiology of ovarian cancer</td>
<td>Discovery of the fallopian tube as the origin of high-grade serous ovarian cancer has led to new thinking about preventive strategies for women at high risk.</td>
</tr>
<tr>
<td>Genetic risk factors</td>
<td>Discovery of the links between BRCA mutations and ovarian cancer has led to changes in guidelines for genetic testing and the potential for preventive strategies.</td>
</tr>
<tr>
<td>Treatments</td>
<td>There have been few notable advances in systemic treatments, but identification of sub-types and new molecular targets holds promise for the development of new therapies. Reductions in surgical volume through use of laparoscopic surgery. Role of intraperitoneal chemotherapy.</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Greater understanding of the benefits of reducing symptoms in improving quality of life for women with ovarian cancer.</td>
</tr>
<tr>
<td>Importance of specialisation</td>
<td>Identification of improved outcomes when ovarian cancer surgery is undertaken by a gynaecological oncologist.</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Understanding of patterns of care and disease progression.</td>
</tr>
</tbody>
</table>

**Ensuring that progress continues**

Key opinion leaders and consumers agree that the best way to move forward is via a priority-driven research plan that leverages Australia’s strengths through collaboration.

There is an urgent need to bring researchers together, identify top priorities and actively identify and use opportunities to collaborate.
- cancer stakeholder

We need the signatures on the page – the ovarian cancer research community needs to step up... and feel ownership of the plan and see a role for everyone in driving it and taking it forward.
- consumer
In order to optimise our chances of success, a comprehensive Australian strategy for ovarian cancer research must align with and complement international research efforts. International research priorities have been identified in a recent publication entitled “Rethinking Ovarian Cancer: Recommendations for Improving Outcomes” (22). This publication summarised the 2011 Helene Harris Memorial Trust meeting whereby an international group of researchers, including Australian researchers, considered actions that should be taken to improve outcomes for women with ovarian cancer. Nine major recommendations for action were reported as follows:

- **Biology:** further classification of individual ovarian cancer ‘histotypes’ into sub-categories based on genomic analysis, gene expression profiles, and studies that explore signal activation pathways
- **Biology:** understanding the genetic differences between tumour cells and the mechanisms by which tumours adapt, including the acquisition of resistance
- **Biology/Treatment:** targeting the local ‘microenvironment’ around a tumour as an adjunct to other molecular therapeutics and chemotherapy
- **Aetiology:** identifying patients at increased genetic risk of ovarian cancer in order to provide the most effective measure for prevention and early detection
- **Treatment:** identification of new targets
- **Treatment:** improved clinical trial design and implementation
- **Collaboration:** international consortia involving large biological datasets must be encouraged, having high fidelity and transparency in analytical approaches
- **Experimental Models:** speed the development of more appropriate experimental models to improve understanding of ovarian cancer and facilitate preclinical testing
- **Control:** Inclusion of QOL and symptom benefit with response and survival rates as a primary endpoint in clinical trials investigating palliative treatment.

We undertook a series of consultations and workshops with clinicians, scientists and consumers in order to best identify the research and patient care needs in the field of ovarian cancer to inform the Plan. From this, we have identified a series of potential future research priorities with a strong focus on building on existing strengths and networks. In addition, we identified areas where there is opportunity to generate significant improvements both in the short and longer terms. The international recommendations outlined above were validated through these processes, either as research priorities or as enablers. The following sections review the international and national landscape over the review period and summarise a series of research goals across each CSO category. The research goals identified are diverse and span the research continuum. Amongst stakeholders, it was recognised that many of these were longer term goals, some were considered of greater priority than others, while others desirable but high risk. For example, some priorities have the potential to transform the field but have inherently high barriers to success. Therefore, where relevant, we have assigned descriptors to specific goals to mark whether something is of high importance relative to other goals (H), is for immediate/short term implementation (I), leverages a key strength (K), or is associated with a high level of risk (R), or some combination of these.

We will now discuss the issues relevant to the following research domains: Biology and Aetiology, Experimental Models, Epidemiology, Prevention, Detection, Treatment and Control.
Our understanding of the biology and aetiology of ovarian cancer has undergone a transformational change. Biological research, including stratification of subtypes at the molecular level is critical to inform development of targeted treatments and improved methods of diagnosis. Biological research has thus far bolstered our understanding of the different genetic and epidemiological risk factors across the subtypes. This, in turn, widens the opportunity to investigate mechanisms of cancer recurrence and treatment resistance and will help guide the development of preventive strategies.

**What we know: the international landscape**

Our understanding of ovarian cancer as a collection of diseases has driven research efforts to characterise the different subtypes of the disease. This has led to new knowledge about the genetic and molecular traits unique to each subtype and is enabling scientists and clinicians to establish a standard classification system that can be used both for diagnosis and for guiding treatment decisions.

A summary of the current understanding of ovarian cancer subtypes is depicted in Figure 10 (23,24), in particular, highlighting the molecular complexity of HGSC. Defects in two different DNA repair pathways have been found to promote genomic instability and tumour progression. At least 50% of HGSCs have defects in the homologous recombination (HR) pathway, which includes BRCA1/2 dysfunction, while approximately 30% have defects in the Rb pathway or genes involved in Rb-mediated DNA repair and cell cycle control, including amplification of CCNE1 (25).

Gene expression profiling and subsequent cluster analysis studies have identified that HGSC comprises four distinct subtypes associated with distinct clinical outcomes (26-28): C1 (Mesenchymal), C2 (Immunoreactive), C4 (Differentiated) and C5 (Proliferative). While this is the general consensus, it should be noted that another study (29) provides a slightly different (but overlapping) categorisation and nomenclature. This highlights the need for a standard system of classification. Notwithstanding these differences, there has clearly been a paradigm shift in the way ovarian cancer is viewed, and this has the potential to impact on potential treatment options, prevention measures and detection research. Indeed a preliminary report linking responses to targeted treatment to tumour subtypes, demonstrated that C1 and C5 HGSC subtypes were more responsive to bevacizumab treatment than other subtypes (30).

This knowledge is also leading to better experimental models and is driving efforts to develop subtype-specific therapies as well as predictive biomarkers to guide those treatments. It has also led to improvements in our understanding of the different genetic and epidemiologic risk factors across the subtypes, and offers the opportunity to better understand mechanisms of recurrence and resistance. While the heterogeneity and complexity of ovarian cancer imparts great challenges, the stratification approach offers new prospects for developing targeted treatments that will pave the way forward to better outcomes for women.
Figure 10: Summary of ovarian cancer subtypes, with a breakout of the key genes involved in HGSC subtypes and the different subtypes identified by gene profiling studies.

Abbreviations: HR = homologous recombination; MC = mucinous cancer; EC = endometroid cancer; LGSC = low grade serous cancer; CCC = clear cell carcinoma; TCGA = The Cancer Genome Atlas

Australia’s contribution

Australian researchers have assumed a leading position in biology and aetiology research; 12 of the 19 top Australian research publications are in these two categories. A summary of these is provided in Table 9. A major contributor to this expertise is through the AOCS, a collaborative research cohort that has been instrumental in the stratification and classification of ovarian cancer subtypes, as described above. Key Australian research highlights include the discovery of different molecular subtypes of HGSC in concert with improved understanding of how ovarian cancer initiates and evolves. In addition, Australian research has revealed how BRCA mutation status affects survival and how a range of other genetic changes also influence ovarian cancer susceptibility and progression. Moreover, Australian researchers have shown how cancer cells manipulate certain cellular mechanisms in order to become resistant to chemotherapy. Australian immunologists and cancer biologists are also making progress in the understanding of how the local ‘microenvironment’ immediately surrounding a tumour influences the immune system.

Australian research has been at the forefront because of access to specimens through AOCS – cancer stakeholder
Table 9: Summary of key Australian biology and aetiology research findings and their implications for practice

<table>
<thead>
<tr>
<th>WHAT WE HAVE FOUND OUT</th>
<th>WHY IT’S IMPORTANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery of molecular subtypes of HGSC (26,27)</td>
<td>Identification of novel treatment strategies</td>
</tr>
<tr>
<td>Understanding of the role of BRCA mutation status in determining survival from ovarian cancer (32)</td>
<td>Has resulted in changes to genetic testing guidelines in Australia and other countries (32)</td>
</tr>
<tr>
<td>Identification of mutations, common susceptibility alleles and other molecular changes associated with ovarian cancer (33)</td>
<td>Provide possible targets for early detection and / or treatment</td>
</tr>
<tr>
<td>Identification of amplification of cyclinE1 as a key event in primary chemotherapy resistance (39)</td>
<td>Assists in understanding what drives response to treatment</td>
</tr>
<tr>
<td>Increased understanding of the genesis and evolution of ovarian cancer (31)</td>
<td></td>
</tr>
</tbody>
</table>
A new understanding of ovarian cancer biology

In the last five to ten years the view of epithelial ovarian cancer has changed radically. It was previously believed that the four main types of ovarian cancer were derived from cells that covered the surface of the ovary.

Noting these relationships is important as it provides clues about treatments that could translate between these anatomically distinct but molecularly related cancers.

The prevailing view now is that ovarian cancer is a collection of distinct diseases, with different cellular origins and molecular characteristics, which share an anatomical location but individually are more closely related to other solid cancers, such as breast or renal cancer. These findings are important for several reasons.

Parallels with other cancers. The new classification strongly indicates that ‘ovarian cancer’ as a collective term, suggesting one disease, is misleading. The different types of ovarian cancer have distinct clinical behaviours including their response to drugs, the chances of survival, and their association with genetic risk factors. For example, we now know that BRCA1 or BRCA2 mutations are predominantly associated with HGSCs. We can now see that an anatomically based classification of ovarian cancer is misleading and we should look to other classification approaches – just because these different types of ovarian cancer cluster in the pelvic space doesn’t mean they are molecularly related.

Indeed, through genetic studies it is apparent that there are close similarities between triple negative breast cancer, small cell lung cancer and HGSC. There are also molecular similarities between ovarian clear cell cancer and renal cancer. Noting these relationships is important as it provides clues about treatments that could translate between these anatomically distinct but molecularly related cancers.

Implications for risk reduction. We now know that the most common types of epithelial ovarian cancer arise from cells that are separate to the ovary. For example, clear cell cancers derive from cells associated with endometriosis, and high grade serous cancers appear to derive from the distal fallopian tube. This improved understanding is needed to develop better preventative strategies, as well as more accurate animal models of the different types of ovarian cancer. For example, knowing that the fallopian tubes are an important starting point for high grade serous cancer has implications for risk reducing surgical approaches in women who carry BRCA1 or BRCA2 mutations – certainly the fallopian tubes should be removed during risk-reducing surgery. Whether it is sufficient to just remove the fallopian tubes and leave the ovaries in high risk women undergoing surgery is unclear at the moment since the fallopian tubes can seed cells into the ovary that may later develop into a cancer.
Personalised treatment. We are beginning to move away from a one-size-fits-all approach to treatment with platinum-taxane based drugs used in all ovarian cancer patients receiving chemotherapy to specific clinical trials for the different types of epithelial ovarian cancer. For example, trials are underway to test MEK inhibitors in certain types of serous ovarian cancers and other trials that exploit the similarities between clear cell and kidney cancer. If these trials are positive it will begin the process of a more nuanced approach to ovarian cancer treatment.

For other solid cancers it has become the standard of care to test for certain mutations in an individual patient’s cancer thereby directing them to specific molecularly based treatments – this is well developed in lung and breast cancer. In this sense ovarian cancer lags behind. As a first step, we have made good progress on developing a complete ‘parts list’ of all the mutations that drive the different types of ovarian cancer. In some cases this information is very useful in suggesting a new treatment approach but for many patients it doesn’t change care because a target isn’t as yet found or if one has been found, a specific drug to it is not yet available. In order to take a personalised (molecular) approach to treatment for more patients, we need to improve our ability to understand the logic of a given tumour, that is, explain how the mutations work together. For example, when you take apart a mobile phone and identify all the electronic components, the parts list doesn’t tell you how the phone works – for that you need to understand how all the components fit together.

Acquired resistance. One of the greatest challenges for the field lies in understanding how a cancer that was once sensitive to treatment has evolved to become resistant. The development of acquired resistance is a major challenge – an estimated 80,000 women die each year around the world with recurrent resistant HGSC\(^2\). We need a systematic effort to map the changes that occur to allow the cancers to resist therapy. This is technically possible but will require international collaboration, funding, and a willingness of clinicians and patients to collect samples during recurrence.

National and international collaboration. We now understand that epithelial ovarian cancer is a heterogeneous and evolving disease. Ovarian cancer is less common than lung or breast cancer, and the stratification into subtypes makes it even more challenging to recruit meaningful numbers of patients to research studies and to conduct clinical trials. We therefore need a national collaborative approach to make substantial progress. The AOCS and ANZGOG are examples of two powerful, internationally recognised collaborative networks that have a strong track record in enabling laboratory research and clinical trials that can be used as a foundation for future collaboration.

\(^2\)Author estimate based on data from the International Agency for Research on Cancer (http://www.iarc.fr/) using the number of deaths per year and the proportion of HGSC at diagnosis.
Biology and Aetiology Research Priorities

Australia clearly has a strong research record in the fields of ovarian cancer biology and aetiology, and this in turn is helping to guide further advancements both nationally and internationally. However, it is crucial that ongoing research efforts align with international research strategies and that current and future resources are focused on areas that will generate the greatest level of benefit for patients. As such, experts identified the following priorities in biology and aetiology research:

• Basic science:
  • Continue research on the biology of ovarian cancer to inform diagnosis, early detection, treatment pathways and research translation (H,I,K)
  • Continue the classification of disease subtypes both in terms of their molecular profiles and their histology, with the aim of identifying and validating new therapeutic targets for identifying and validating targets to use for treatment (H,I,K)
  • Explore the tumour immune microenvironment to identify potential targets for therapy (H,I,K).

• Mechanisms of resistance and recurrence:
  • Explore the ways in which tumours respond to their environment and to treatment, with particular focus on the mechanisms tumours employ in treatment response and resistance (H,I,R)
  • Compare recurrent disease with initial disease with a view to understanding factors that influence resistance to treatment (experts note that it will be challenging to get samples for this research) (H,I,R).

• Aetiology:
  • Understand the natural history and latency of HGSC to identify precursors for earlier detection and treatment (H,I,K).

EXPERIMENTAL MODELS

High-quality research with the potential to improve clinical outcomes depends on access to validated experimental model systems. This includes: (i) in vitro models for rapid screening of large molecular libraries, and (ii) animal models of disease that enable proof-of-concept research in target validation, biomarker validation and drug discovery programs.

Precision medicine critically depends on the use of laboratory-based animal models that can accurately predict which patients will benefit from a targeted therapy.

Experimental models are both a focus for research priorities and a fundamental enabler for an effective ovarian cancer research effort.

What we know: the international landscape

High quality research has the potential to improve clinical outcomes, but this depends on access to validated experimental model systems. At the drug discovery and early preclinical stage, in vitro models involving ovarian cancer cell lines are needed for rapid screening of large datasets. A landmark study assessing ovarian cancer cell lines used by researchers internationally found that many of the most commonly available cell lines were poorly predictive of HGSC (40). This is a critical issue having the potential to compromise research directed towards detection and treatment and underscores the importance of having appropriate models of disease.

In preclinical research, clinically relevant animal models are needed for accurate target validation, biomarker validation and to demonstrate efficacy in drug discovery programs. An area of growing importance is the development of patient-derived xenografts (PDXs) from women with HGSC to capture the complexity and genetic heterogeneity
of ovarian cancer subtypes and thereby facilitate drug and biomarker research programs.

**Australia’s contribution**

In our analysis of Australian ovarian cancer research studies published between 2008 and 2013, we found that 95 articles reported use of ovarian cancer cell lines primarily to investigate the effects of drugs. To a lesser extent, cell lines were used in investigations into ovarian cancer biology and detection. Of these 95, 23 abstracts did not cite which ovarian cell lines were used and were excluded from the analysis. The remaining 72 abstracts cite a total of 153 ovarian cell line experiments using 30 different ovarian cell lines. Of these, A2780, A2780(cisR), OVCAR-3 and SKOV-3 were the most common, having each been cited in >20 publications. While many of the cell lines cited were not rated by the landmark paper discussed above (40), and some were not relevant to HGSC (eg those used in GCT studies), it is evident that a large proportion of studies (50%) utilised cell lines that are unlikely to be predictive of HGSC, with 19% possibly and only 3% likely to be predictive of ovarian cancer (Figure 11). Thus, it is feasible that the use of poorly predictive models have hindered the progression of Australian preclinical research. While this is a retrospective analysis, it highlights the importance of enabling access to the most current and predictive experimental models, or, where they don’t yet exist, developing new predictive models appropriate to the range of ovarian cancer subtypes to be studied. Indeed, this was the consensus amongst the participants in consultations and the workshops to inform this Plan.

Australian researchers have developed expertise in the development of PDX models. These provide an invaluable resource in the development of personalised cancer therapy and the pursuit of more effective treatment for patients with recurrent ovarian cancer. PDX models also assist with drug screening and biomarker development and validation (41). There is a need to expand this resource, to gain access to or develop and maintain a range of PDX-models that encompass the spectrum of ovarian cancer subtypes to accelerate progress into targeted clinical research.

**Experimental Model Research Priorities**

The use of clinically relevant biological models is crucial to the advancement of ovarian cancer research. These models are a core component of research into our understanding of the biological basis of the disease. They aid in the identification of new drug targets, guide the development of accurate biomarkers and sit at the core of proof-of-concept research that reveals whether or not a new therapy holds promise. If a cell line or an animal model cannot give a reasonably accurate representation of the disease state, then consequences can be severe both in terms of misdirected time and resources, and in terms of missed opportunities. The following priorities aim to ensure Australian researchers use the most appropriate models in their studies:

- Further develop clinically relevant PDX models that are consistent with ovarian cancer subtypes in order to facilitate targeted treatment (H,I,K)
- Further develop and enable access to clinically relevant cell lines (H,I,K).
Research to identify new experimental models

It is possible to implant a piece of ovarian cancer tissue at the time of surgery into laboratory mice and over time study the cancer and its response to various treatments. This is called a “Patient-Derived Xenograft” or “PDX”.

There have not been many reports until recently and previous examples were often made after growing cancer cells in tissue culture in between surgery and implantation into the mouse, creating similar problems to those described for cell lines. However, those few PDX models generated from tumours that were not manipulated and were rigorously analysed, were shown to retain pathological features of the primary tumour (42). Few papers have reported the response of these PDX to conventional or targeted therapeutics (43) and none have been considered in the context of detailed gene analysis and patient outcomes until recently (43,44). Australian researchers and some from overseas are now developing highly informative PDX, of as many different types of ovarian cancer as possible. This is a large task, as not all ovarian cancers are the same and it is important to “group” the PDX (and women’s tumours from which they came) in the same way that we are trying to group patients into relevant groups for clinical trials.

The main difference is that with PDX, very detailed analysis can be performed in the mouse, which is not possible in the clinic – and evidence so far suggests that this will be very informative for future clinical trial design.

A/Prof Clare Scott MBBS PhD FRACP
Head, Ovarian Cancer Laboratory, Walter and Eliza Hall Institute of Medical Research; Medical Oncologist, Royal Melbourne Hospital, Vic

“Women should benefit by having available to them clinical trials based on more precise genetic and treatment response data than ever before.”
Epidemiology is an area of expertise in the Australian research community, particularly with regard to the role environmental risk factors play in the causation and prognosis of ovarian cancer. An AOCS supported study into the molecular epidemiology of ovarian cancer used a questionnaire as well as blood and tumour samples to explore the relationship between environmental factors (family history of disease, reproductive history, medical history, diet, alcohol, smoking etc) and risk of the different subtypes of ovarian cancer. The OPAL (ovarian cancer prognosis and lifestyle study) initiated in 2012, is currently examining lifestyle factors that may improve survival and QOL for women with ovarian cancer. Little is currently known about the patterns (incidence, genetics) and experience (care and outcomes) in key population subgroups such as the elderly, women from culturally and linguistically diverse backgrounds, Aboriginal and Torres Strait Islanders and women who live in rural and remote Australia.

Epidemiology Research Priorities
• Risk factors:
  • Continue to explore genetic risk factors for ovarian cancer subtypes (histological and molecular) (H,I,K)
    - Identify high risk sub groups for developing new genetic or other biomarker tests
  • Conduct population studies to further explore the relationship between non-genetic risk factors and ovarian cancer aetiology and survival (H,I,K)
    - Explore the potential to reduce risk of ovarian cancer by modification of lifestyle factors
    - Understand how modifiable aspects of lifestyle influence chemotherapy completion and response, QOL, recurrence and survival
  • Conduct studies to understand the patterns and experience of disease in population subgroups (the elderly, women in rural and remote areas, Aboriginal and Torres Strait Islanders and those from culturally and linguistically diverse backgrounds) (I,K).
Advancements in ovarian cancer research have improved our understanding of the different genetic and epidemiologic risk factors across the subtypes. This provides an opportunity to better understand mechanisms of recurrence and resistance and to consider preventive strategies.

In recent years it has become clear that BRCA mutations are prevalent in women with ovarian cancer, regardless of whether or not there is a family history of the disease. This has led to changes in the guidelines for genetic testing in ovarian cancer and presents significant opportunities with regard to prevention and risk reduction. If every woman with ovarian cancer in Australia received genetic testing, this would reveal many families for whom there are opportunities to modify risk. Recent findings of the significant reduction in all cause mortality in BRCA mutation carriers who had their ovaries removed as young as 35 years further supports the potential for impact in this area (45). This of course requires a balanced approach in relation to life stage and age.

Recent discoveries have also revealed the involvement of the fallopian tube in HGSC. Routine hysterectomies usually do not involve a salpingectomy (fallopian tube removal), but these new findings provide an opportunity to explore the potential of routine incorporation of salpingectomies as a means to reduce ovarian cancer risk in those women who undergo the surgery.

Prevention Research Priorities

Our picture of the risk factors for ovarian cancer is not yet complete, and further strategic research is required to develop comprehensive prevention strategies. Nevertheless, while this work is underway, recent advances in biological and epidemiological research are able to provide highly valuable guidance for prevention strategies that can be put in place in the near term. The following priorities with regard to ovarian cancer prevention are recommended:

- The adoption of risk reducing surgical methods to reduce mortality in high risk women
  - Surgical methods for BRCA1/2 carriers and post-menopausal women – patterns of care, linking to survival, ensuring adoption of best practice methods (H,I,K)
  - Developing the evidence-base for supporting, or otherwise, the adoption of salpingectomy alone versus bilateral salpingo-oophorectomy (BSO) (H,I)

- Research relating to preventive measures that extend from knowledge of the biology of the disease. It is crucial to explore preventative measures that do not reduce women’s quality of life (including sexual and reproductive lives).
Any discussion of ovarian cancer must include the related fallopian tube and primary peritoneal cancers and the term ovarian cancer will be used here to cover all three tumour types. It is also important to note that many so-called ovarian cancers almost certainly arise in the fallopian tube and spread to the ovary. Surgery to remove the ovaries and fallopian tubes will prevent ovarian and tubal cancer, but it will not prevent development of primary peritoneal tumours. It is also a radical intervention that induces menopause in premenopausal women and is not a practical method for risk reduction for any but those at very high risk of cancer. What is less clear is the extent to which salpingectomy (without oophorectomy) might protect women and how this compares to the ~20% reduction in risk of ovarian cancer seen among women who have undergone tubal ligation. Furthermore, while early studies consistently reported reduced risks of ovarian cancer among women who had undergone hysterectomy, this has not been seen in more recent studies and the reasons for this are unknown. These are all questions that need to be answered.

The greatest known risk factor for ovarian cancer is carriage of a BRCA mutation. Enhanced identification of mutation carriers and clarification of the optimum methods for risk reduction in this group, while recognising the desires of younger women who wish to have a family, thus has the potential to reduce rates of familial cancers. Non-genetic factors that confer protection against ovarian cancer risk include pregnancy and use of the oral contraceptive pill (OCP), with a possible additional benefit of breastfeeding. Ovarian cancer rates would almost certainly be higher if women did not use the OCP, but use is not without risk and cannot be recommended solely for cancer prevention. There is less evidence regarding the potential benefits (and risks) of newer contraceptive methods such as the levonorgestrel-releasing intra-uterine devices (LNG-IUD) where the hormone is delivered directly to the uterus. This is of relevance because, while the OCP greatly reduces risk of ovarian (and endometrial) cancer, recent users are at slightly increased risk of breast, cervical and liver cancer. It is therefore important to understand the potential impact of LNG-IUD use on cancer risk at different sites. Greater understanding of the mechanisms underlying all of these hormonally-driven associations may also allow development of novel hormone preparations that retain the ovarian (and endometrial) function conferred by the OCP, without the current risks associated with OCP use.

Other known risk factors have more modest effects and/or only seem to affect risk of some subtypes of ovarian cancer. Thus, while standard health recommendations regarding increasing breastfeeding, not smoking (mucinous cancers) and maintaining a healthy body weight may prevent some ovarian cancers, the overall effects of changing behaviour in these areas are likely to be modest. Avoidance of the use of talcum powder in the perineal region is a simple message but again likely to have limited impact, while other factors such as a history of endometriosis (endometrioid and clear cell cancers) are not easily modified. Greater understanding of the role of these factors in relation to the different molecular subtypes of ovarian cancer may, however, shed further light on their aetiology.

"Any discussion of ovarian cancer must include the related fallopian tube and primary peritoneal cancers..."
DETECTION

Ovarian cancer has non-specific symptoms and diagnosis is often late-stage, which requires aggressive treatment and is associated with high mortality. As such, there have been public calls for a simple low-invasive test for asymptomatic women, a perceived “holy grail” of early detection. Increased capability in biomarker detection has indeed encouraged efforts towards developing biomarker panels for screening. Yet despite prolific studies, there are no biomarkers currently approved for population-based screening in ovarian cancer.

The field is controversial. In theory, a population-based screening test would have the potential for great impact in the field of ovarian cancer, but many experts believe this is the least realistic target given the heterogeneity of the disease, the difficulties in achieving sensitivity and specificity criteria and the high regulatory challenges to market approval.

Internationally, population-based screening in asymptomatic women is seen as an unlikely near-term goal. Earlier detection in high-risk or symptomatic women is considered a more realistic near-term goal than a population-based screening test. Other areas of biomarker research focus are prognostic and companion diagnostics, and for monitoring disease progression.

What we know: the international landscape

Biomarkers can be used clinically to screen for a wide range of diseases. They aid in diagnosis and prognosis, and can also help monitor disease progression. They can guide clinical decisions, particularly when targeted therapies are available, and can help assess therapeutic responses. In the field of ovarian cancer, several types of biomarkers are under investigation including DNA-based markers (SNPs, chromosomal aberrations, changes in DNA copy number and methylation), RNA-based markers such as microRNAs, and protein markers including post-translational modification of proteins. While there has been intense research effort, financial investment and significant technological advances in high throughput technologies with regard to all these areas, few novel biomarkers have been adopted into clinical practice. This has been attributed to a long, uncertain and difficult path from discovery to commercialisation including the lack of coherent and comprehensive pathways for biomarker development and regulatory approval and to economic considerations (46).

Biomarker development in ovarian cancer over 2008-2013 has been the subject of much debate and there is great uncertainty as to whether biomarker panels will be utilised in population screening. Currently the best known non-invasive method for ovarian cancer detection is a combination of elevated CA 125 and trans-vaginal ultrasound (TVUS). CA 125 is a protein produced by ovarian cancer cells that can be found in the blood, and elevated levels are found in women with ovarian cancer. However, high levels of CA 125 can also occur as a result of endometriosis, menstruation, or ovarian cysts, so it is not specific to cancer. Moreover, CA 125 (using a simple cut off at 35 U/ml) has limited specificity and sensitivity and is only detected in ~50% of early stage ovarian cancer cases. It is not recommended for screening at present, even in combination with TVUS. There has been a large effort internationally to identify and develop improved biomarker panels, but there has been limited progress despite the market anticipation (47).

“

The least realistic target but has the potential for the greatest impact.

- academic researcher

“
There’s been an enormous amount of hype and promise. But after 10 or 15 years of intense work in these fields, there’s simply not a lot to show for it. It’s important for the whole field to step back and look at what is wrong (47).

Some key issues related to biomarker development in ovarian cancer are described below:

- OvaSure®, a biomarker panel that was marketed in the USA to assess cancer risk in women with an ovarian mass, was withdrawn after the FDA issued a warning relating to unvalidated marketing claims (48).
- The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial reported that of six biomarker panels tested (including OvaSure®), none performed well in pre-diagnostic specimens from asymptomatic women, challenging the assumption that markers for early-stage disease are good screening markers (49, 50).
- The standard approach to undertaking studies for both early detection and population-based screening using samples obtained from symptomatic patients at the time of diagnosis was criticised for introducing a systematic bias, leading to exaggerated reports of biomarker performance (47).
- Progress has been made towards clarifying the clinical pathway for biomarker development. Frameworks incorporating prospective, blinded clinical evaluation of biomarkers for the relevant population (ie prediagnostic samples for population screening tools) are now recommended (49, 51, 52). Such programs will entail challenging clinical investigations of many years duration and require international collaboration to access sufficient specimens.

The PLCO Trial reported that screening with CA 125 testing and TVUS did not improve cancer-specific or overall mortality compared with usual care and confirmed the risk of potential harms associated with false-positive screening test results.

In 2012, the US preventative task force re-affirmed a previous D recommendation for screening, stating that the potential harms may outweigh the benefits (53). Cancer Australia published a position statement in 2009, stating that screening for ovarian cancer in the general population is not recommended (54).

WHO guidelines recommend a screening test requires a strong evidence base for benefit outweighing the harm, with stringent test criteria of sensitivity, specificity and positive predictive value (55).

Currently there are no approaches to screening which can achieve the required test criteria (>99.9% specificity and a sensitivity >85%) for ovarian cancer in asymptomatic women. Due to the low prevalence of disease, assessment of the impact of screening in prospective trials requires large samples sizes (to capture sufficient numbers of women who go on to develop ovarian cancer), for example the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) (56) recruited over 200,000 participants (see ‘screening versus early detection’). Given the heterogeneity of ovarian cancer, a single test may not be able to detect all early stage ovarian cancer subtypes. Several other factors must be taken into consideration with regard to early stage screening in the wider population: we have a poor understanding of the latency of aggressive ovarian cancer subtypes, there is a lack of efficacious treatments that demonstrably result in reduced mortality and morbidity, and false positives have the potential to harm if they lead to unnecessary surgery. Consequently, the overall benefit of a population-based screening program has not yet been
demonstrated. The field awaits the outcomes of UKCTOCS (56) expected in 2015 to better assess the balance between a measurable benefit versus the potential harm of screening in average-risk, asymptomatic women. This will greatly inform the feasibility of general population screening.

It has been reported that the majority of biomarker studies in ovarian cancer have not progressed beyond early stage (47). However this is primarily in regard to the use of biomarkers for screening the general, asymptomatic population. The picture is more promising for the use of biomarkers in screening high-risk women and those at the point of diagnosis and beyond. There have been technological advances in profiling and analysis enabling better research into the use of biomarkers in diagnosis, prognosis, treatment guidance and monitoring recurrence. Examples of biomarker products and services in development include:

- OvaDx (Avant Diagnostics Inc), a panel of ~100 biomarkers under development in USA as a diagnostic aid for high-risk or symptomatic women; in early 2014, the company sought funds to undertake a pilot clinical trial
- FDA-approved Ova1 (Vermillion Inc), a test comprising five biomarkers to measure the likelihood of malignancy in women with a pelvic mass for whom surgery is planned
- OvPlex (Healthlinx Ltd), a biomarker panel developed as an aid to diagnosis in high-risk women – approved for marketing in some countries, but not in USA or by TGA in Australia. There is limited information on the marketing status available
- ROCA, an algorithm for longitudinal measurement of CA 125 over time (Abcodia, UK) which is currently being tested as part of the UKCTOCS trial
- Caris Molecular Intelligence Service (Caris Life Sciences Inc, USA) – a tumour molecular profiling service linking tumour information with data from clinical studies to inform personalised treatment options
- Foundation One - a tumour molecular profiling service linking tumour information with data from clinical studies to inform personalised treatment options.

The progression and market uptake of these products should be monitored to understand the market appetite for these diagnostic products, their adoption into clinical practice, and to further clarify regulatory approval and reimbursement requirements.

### Screening vs early detection

No professional body currently recommends screening for ovarian cancer in the general population.

Research in ovarian cancer has tended to combine concepts of screening and early detection, leading to confusing terms such as ‘early diagnosis screening’. It is not clear whether this refers to a screening test for the general population in advance of symptoms or to a diagnostic marker test for symptomatic, clinically presenting or high-risk women already on the path to diagnosis.

The results of a large international cohort (UKCTOCS) examining the benefits of screening in 202,000 women are expected in 2015, which will greatly inform the feasibility of general population screening (56).

In the meantime, the current focus of research on early detection in ovarian cancer is biomarker development as an aid to diagnosis in high-risk women – less challenging, but a much smaller market size.
Australia’s contribution

While research into the detection of ovarian cancer has attracted a major portion of funding in Australia over 2008-2013, to date this has produced only moderate output. This may reflect the challenging development and regulatory hurdles for biomarkers described above, and the complexities of ovarian cancer, which may not lend itself well to simple, blood-based biomarker tests. Furthermore, ovarian cancer detection was not identified as an area of expertise within the Australian research community through the consultation process.

Of the 57 Australian publications coded under Detection, eight involved investigation of imaging methods or symptom awareness, and five were not able to be assigned, whereas the bulk of research was focused on biomarker analysis, particularly the identification of biomarkers (gene microarrays, proteins) in biological samples. Very few studies had reached the stage of preclinical evaluation. Only a minority were retrospective biomarker clinical studies, and none were prospective (Figure 12). In accordance with international findings, there is a significant gap between exploratory work and clinical validation in early detection.

Publications relating to preclinical evaluation and clinical studies reported that their purpose was to aid diagnosis in high risk women, assist in prognosis, measure a response to therapy and/or monitor for recurrence. Given the challenges, it is not surprising that this review did not identify a single example of a biomarker panel being on a genuine development path towards a general population screen in Australia. This appears to be an area where the public perception is not in alignment with the research progress, and it is incumbent on research organisations and funders to clarify research goals and provide a more realistic picture of the challenges and hurdles faced on the pathway to market. Alongside the need for research is the need for education of health professionals and women about symptoms of ovarian cancer and about the complexities of the ‘early detection’ message.

With this in mind it is important to emphasise that biomarker profiles are of significant use in the field of ovarian cancer and there has been progress in research into their use in diagnosis, prognosis and clinical decision making. The molecular profiling of tumours to guide patient treatment options are beginning to be tested in small trials in Australia with encouraging results (57, 58) but these methods are still early stage and the regulatory frameworks are uncertain. There remain a number of areas where more work is needed, as identified in the research priorities (page 64).
Figure 12: Types of publications in the area of detection, diagnosis and screening and the stage of development

<table>
<thead>
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<th>Method</th>
<th>Discovery</th>
<th>Evaluation</th>
<th>Retrospective</th>
<th>Prospective</th>
<th>Reviews &amp; case studies</th>
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<td>10</td>
<td>3</td>
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No. Publications

- **Biomarker**
- **Other**
Detection in ovarian cancer: controversies, opportunities and challenges

The current status of screening for ovarian cancer

The majority of women who develop cancer of the ovary have cancer which has spread outside the ovaries by the time of diagnosis. For those with extensive disease the long-term results of treatment remain poor despite advances in surgery and chemotherapy.

For these reasons there has been a concerted focus on efforts to screen for early detection of ovarian cancer over the last 30 years. This has eventually led to two large randomised controlled trials, one of which has already reported (the ovarian arm of the PLCO study in the USA) and the other the UKCTOCS which will report in 2015. Until the full results of these trials are available it will remain uncertain whether or not screening can detect ovarian cancer early enough to save lives. The PLCO and UKCTOCS trials used two tests to screen for ovarian cancer – the CA 125 blood test and ultrasound scanning.

CA 125 is a marker produced by ovarian cancers and some normal cells, which is elevated in the circulation of approximately 90% of women who already have a diagnosis of ovarian cancer. It is easily measured in a standard blood sample. In addition to ovarian cancer, CA 125 can be raised in a variety of other situations such as pregnancy, fibroids, endometriosis, heart or renal failure and in advanced stages of other cancers. This means that false positive results can occur in women who do not have ovarian cancer. To reduce the frequency of false positives a “Risk of Ovarian Cancer Algorithm” (ROCA) has been developed which looks at the pattern of CA 125 levels over time. This decreases the false positive rate as women with ovarian cancer have a rising CA 125 pattern whereas women with other conditions usually have a flat or falling pattern, even if CA 125 is raised. The ROCA also increases the sensitivity (detection rate) for ovarian cancer, as women with ovarian cancer who have low levels of CA 125 usually have a rising CA 125 pattern. Women who have a persistently raised CA 125 or ROCA go on to have an ultrasound scan. Current evidence suggests that the ROCA can detect 85%-90% of women who have ovarian cancer, on average approximately two years before they develop symptoms. This is encouraging but does not necessarily mean that screening with the ROCA can save lives (the answer will be provided by UKCTOCS).

Ultrasound scanning measures changes in the size and texture of the ovaries, which occur in ovarian cancer. Ultrasound to view the pelvis and ovaries can be performed with a probe placed on the abdomen, as in pregnancy but for the purpose of ovarian cancer screening a vaginal probe is used, as a clearer picture of the ovary is obtained. As with CA 125 there is a
false positive rate. In the case of ultrasound this is because some non-cancer changes in the ovary or other pelvic organs can be difficult to distinguish from ovarian cancer. These include normal cyclical ovarian changes which cause cysts as well as benign ovarian tumours, fibroids and endometriosis. The false positive rate is reduced by repeating scans at intervals but is still higher than for CA 125 or the ROCA in combination with ultrasound. In general when used to screen postmenopausal women in the general population, ultrasound results in 10-15 false positive results requiring surgery per case compared to 3-5 for the ROCA followed by ultrasound. The sensitivity of ultrasound screening seems to be a bit less than screening using CA 125 and the ROCA – in the range of 75%-85%.

The PLCO trial in the USA used CA 125 and ultrasound in combination in 39,000 women and compared the outcome with a similar number of women who did not have screening. Unfortunately the PLCO study did not find any reduction in deaths or increase in survival from ovarian cancer as a result of screening. The UKCTOCS trial involves 202,000 women in the UK randomly allocated to three groups: a control group who are not screened; a group screened with ultrasound; and a group screened with CA 125 using the ROCA with ultrasound as a secondary test for those with elevated levels. Information about the impact of screening on survival and mortality in UKCTOCS will be available in 2015. The results of UKCTOCS may, like the PLCO study, be disappointing but there is reason for some hope. The sensitivity of the CA 125/ROCA arm is over 85% and higher than the sensitivity of screening in the PLCO trial. This is partly due to the use of the ROCA and partly due to the rigorous protocol for managing screen positive cases in UKCTOCS. Hopefully this will be sufficient to achieve a significant reduction in the number of deaths and/or an increase in survival. At this point I should note that having persisted with the quest for an effective screening test for ovarian cancer for 30 years as the director of UKCTOCS, I am the eternal optimist!

Others are more sceptical and doubt that screening will be able to detect ovarian cancer early enough to be effective. We don’t have long to wait as UKCTOCS will report within the next year.

For the time being screening for ovarian cancer is not recommended for women in the general population who are at average or low risk of ovarian cancer because the downside (false positive results leading to anxiety and unnecessary surgery) may outweigh the upside (uncertain survival or mortality benefit of screening). The situation is rather different for women who have a high risk of ovarian cancer because of a strong family history of ovarian and/or breast cancer. For women in this category referral for cancer genetics advice is a sensible step. Women who are at more than a 1 in 10 lifetime risk of ovarian cancer (compared to the general population risk of less than 1 in 70) are usually offered the option of surgery to remove their ovaries (and tubes) to eliminate the risk of ovarian cancer. For those who do not want to proceed with this option or want to delay until they have completed their families or reached the menopause, screening can be considered. It is important to emphasise that screening, unlike surgery to remove the ovaries, will not prevent ovarian cancer and that the impact of screening on survival/mortality is not known. The UK Familial Ovarian Cancer Screening Study (UKFOCSS) is a national study to assess screening in women with a strong family history of ovarian cancer. The study involved a CA 125 blood test every four months interpreted with the ROCA and a yearly ultrasound scan. The results will be published in 2015 and will identify how effective screening is at detecting ovarian cancer early in women at high risk. UKFOCSS will not answer the question as to whether screening saves lives as it is not a randomised trial.

So in summary:

- Screening tests for ovarian cancer are able to detect the cancer before any symptoms occur in a large proportion of affected women
- The most sensitive test at present seems to be CA 125 in the ROCA followed by ultrasound
- All screening strategies have a false positive rate, which can cause anxiety and/or lead to unnecessary surgery
- We do not yet know whether screening can detect ovarian cancer early enough to save lives
- The results of the UKCTOCS randomised trial will be available in 2015 and will establish whether or not screening can increase survival and/or save lives
- For now, general population screening is not recommended and screening is limited to women at high risk as an alternative to preventative surgery.

Finally, it is worth noting that exciting work is ongoing in laboratories around the world to try and identify new markers for ovarian cancer, using mass spectrometry and other new technologies. The hope is that markers will be discovered which can detect ovarian cancer earlier and more reliably than CA 125. So even if UKCTOCS, like PLCO does not achieve a mortality benefit, there is still room for hope.
**Detection Research Priorities**

In light of the progress and challenges with regard to detection of ovarian cancer, the contributors to this Plan have highlighted the following research priorities as a means to make the best use of Australian expertise and resources:

- **Pathways to earlier diagnosis:**
  - Develop better biomarker-based diagnostic tools:
    - To identify high risk women based on genetic or other molecular risk factors (H,I,K)
    - To aid in the diagnosis of symptomatic women
    - To aid in the differentiation of benign or tumours of low malignant potential (LMP) from malignant tumours
    - For screening – this will depend on outcomes of UKCTOCS study and will require prospective study design (watching brief).
  - **Diagnosis of disease subtypes:**
    - Develop biomarkers for (i) identifying disease subtypes (ii) as prognostic indicators, (iii) for guiding treatment (companion diagnostics), and (iv) monitoring disease recurrence
      - Identification and validation of biomarkers relating to more aggressive subtypes, particularly low volume HGSC (H,I)
    - Continue and expand research into the molecular profiling of tumours in order to guide treatment choices (H,I).

**TREATMENT**

More effective agents are needed to treat ovarian cancer, prevent relapse and improve overall survival and patient outcomes. This includes: (i) treatment of newly diagnosed advanced ovarian cancer; (ii) treatment of platinum-resistant and refractory ovarian cancer; and (iii) improvements in toxicity profile, such as in previously treated advanced ovarian cancer where QOL is an important parameter of therapy. Advancements in our understanding of the molecular basis of ovarian cancers, coupled with knowledge of other cancers with similar molecular changes, provides hope for the development of treatments optimised for each subtype and stage of the disease. The promise of such molecular targeted therapies (MTTs) is driving the transition towards precision medicine, where biomarker detection could guide the tailored use of MTTs on a patient-by-patient basis. But further work is needed in the development of those new therapies. Other new areas of treatment are immunotherapy and antibody drug conjugates.

While the heterogeneity and complexity of ovarian cancer present a range of challenges, the improved understanding of ovarian cancer subtypes provides opportunities for developing new treatments with better outcomes.
What we know: the international landscape

The standard treatment for advanced ovarian cancer is a combination of debulking surgery and cytotoxic chemotherapy. While initial responses are often good, recurrence and resistance is common and the prognosis is poor. It is clear that the limits of cytotoxic chemotherapy are being reached, or that reformulations and new drug delivery approaches are not likely to result in further marked improvements in patient outcomes. Because of this, the cancer field is transitioning towards molecular targeted and immunological therapies. Whereas cytotoxic chemotherapy broadly disrupts actively dividing cells, whether or not they are cancer cells, MTTs are typically drugs that specifically interfere with the function of molecules known to be involved in pro-cancer pathways. Examples of MTTs include drugs that target specific molecules involved in new blood vessel formation around tumours (anti-angiogenesis); drugs that target cell types that support the development and growth of tumours (such as stromal therapies); and drugs such as PARP inhibitors that target aberrant cell cycle control in cancer cells. These are just a few of many promising MTT developments. Cancer immunotherapy refers to treatments that cause the body’s own immune system to identify and destroy cancer cells. This therapeutic approach is making progress in a range of cancers, including lung cancer, melanoma, and even pancreatic cancer.

Of clinical trials registered internationally with ovarian cancer as a therapeutic indication over 2008–2013 (59), 57% were for MTTs, 19% were for immunotherapy and 17% for cytotoxic therapies (Figure 13(a)). The majority of these trials (57%) have focused on new molecular entities (small molecules, antibodies, antibody-drug conjugates, proteins, peptides), 18% on cell therapies or vaccines, and 24% have tested re-profiled drugs (drugs already marketed for other therapeutic indications). The move towards more targeted treatments for ovarian cancer is consistent with the shift towards precision therapy across the field of cancer research.

Figure 13: Ovarian cancer treatment pipeline showing breakdown of treatment type for (a) international clinical trials; (b) Australian preclinical research; and (c) clinical trials with sites registered in Australia.

Abbreviations: UK = unknown, IM = immunotherapy, AH = anti-hormonal therapy, Gene = gene therapy
Advances in molecular profiling offer opportunities for developing MTTs that target specific ovarian cancer subtypes. Figure 14 depicts some of the potential treatment options for different classes of ovarian cancer. Molecular profiling has already identified key biomarkers that show an association with drug therapies, thus indicating whether a patient may benefit from a particular MTT and can also help identify drugs that are unlikely to have a clinical benefit for a patient. This approach, being championed by US company, Caris Life Sciences Inc, is being applied across different ovarian cancer subtypes. A retrospective analysis of patients with ovarian, primary peritoneal and fallopian tube carcinomas provides early support that tumour molecular profile-directed treatment has the potential to improve survival (60). This approach is integral to the implementation of “umbrella” type clinical trials (see page 77).

**Figure 14:** Potential treatment options under investigation for different ovarian cancer subtypes (23, 25, 72)

**Australia’s contribution**

**Preclinical research**

In Australia, there is a significant amount of preclinical research in the field of ovarian cancer. This is a broad category, encompassing target validation, new drug discovery/screening, re-profiling of drugs, testing new drug combinations, formulations, delivery options, treatment regimens and drug resistance (see Appendix V for descriptions of CSO category 5.3 subcategories). Of these, the predominant effort (based on publication output) is on drug discovery and target validation, with least on drug delivery and resistance.

Target validation research is a logical consequence of ovarian cancer having been reclassified into multiple subtypes. From this, new targeted drug discovery and development programs are likely to be undertaken in the future. There is a possibility that some therapies could be re-profiled as a result. For example, some drugs may have previously performed poorly in trials simply because they were used on a broad group of patients when they are only active on one subtype. A new trial targeting only that subtype could potentially renew and fast track their development. There is also scope for novel drug discovery programs.

Of the published Australian preclinical studies that relate to drug testing (ie excluding target research), 85% were very early stage and confined to in vitro testing across ovarian cancer cell lines. Only 15% of preclinical studies tested drugs in animal models of disease (proof-of-concept stage). Thus, the rate of progression along the drug development continuum is low. The recent finding that many ovarian cancer cell lines available internationally were poorly predictive of HGSC (40) would indicate that research using these cell lines may not be as informative as once thought. This has also been the case in Australia where only a minority of studies utilised cell lines that were likely, or even possibly predictive of HGSC (see Figure 11). This is likely to be a contributing factor to the low rate of transition from early stage discovery to proof-of-concept.

Figure 13(b) provides a snapshot of how Australian preclinical research efforts compare with Australian
and international clinical efforts in terms of which therapy types are receiving the most attention. Our analysis shows that Australian research focuses heavily on cytotoxic therapies with ~75% of publications reporting early stage studies on novel or re-profiled cytotoxic compounds. This emphasis on cytotoxic compounds, particularly novel metallo-complexes, is not consistent with the international trend towards MTT and immunotherapy clinical research and may indicate a need for future re-prioritising.

Clinical studies

A review of the international clinical pipeline was conducted (61) to see how Australian clinical trial efforts align with the international clinical trial landscape (Figure 15). Australia is clearly undertaking clinical testing at a rate comparable with major pharmaceutical markets based on incidence of ovarian cancer. While this is encouraging, further information is required to understand the direction of clinical research and how Australia is positioned.

Figure 15: Clinical trials adjusted for incidence by country. The percentage of clinical trials of the total conducted in ovarian cancer is divided by the percentage of total worldwide incidence by country (see Appendix I for reference sources)
MTTs are the predominant focus of clinical trials which include sites registered in Australia. This aligns well with the international focus (Figure 13(c)), but may be attributable to the fact that most (but not all) clinical trials conducted in Australia are part of larger international industry sponsored or collaborative trials where the Australian involvement is as participants rather than primary innovators. Nevertheless, stakeholders considered that continued participation in large international trials was important to enable patient access to investigative drugs. Notable publications on international clinical trials for which Australian researchers have made significant contributions include:

- Phase II clinical study of Olaparib, a PARP-1 inhibitor, as maintenance treatment demonstrated significantly improved progression-free survival among patients with platinum-sensitive, relapsed, HGSC (62).
- Phase II clinical study providing positive proof-of-concept of efficacy and tolerability of Olaparib in advanced ovarian cancer in women with BRCA mutations (63).

Immunotherapy is considered to have potential for the treatment of at least some ovarian cancer subtypes. However, Australia produces little research output and participates in few clinical trials in the field of immunotherapy. This trend needs to be reversed and more resources made available to immunotherapy programs in Australia, in order to come into line with international research efforts. This is considered an area of high priority by key opinion leaders in ovarian cancer research.

One Australian-linked immunotherapy in clinical trials is CVac (PrimaBioMed Ltd), a novel immunotherapeutic drug that is being tested in a recently launched 210-patient Phase II clinical trial in patients with relapsed platinum-sensitive disease who enter second remission. CVac has received fast track designation from the FDA.

Other innovative drug development programs originating from Australia or sponsored by Australian companies include:

- BNC105P (Bionomics Ltd) a vascular-disrupting agent in Phase I/II, tested in combination with gemcitabine-carboplatin in platinum-sensitive ovarian cancer patients in first or second relapse, conducted by ANZGOG.
- Trx-1 (Novogen Ltd/ CanTx Inc), a novel chemotherapeutic in preclinical development.

A further initiative, sponsored by US company Caris Life Sciences and which has involved Australian researchers, uses molecular profiling to guide treatment, as discussed previously (57, 58). These related studies provide preliminary support for the use of molecular profiling in identifying therapeutic interventions for advanced refractory and rare solid tumours that have limited treatment options and poor prognosis.
Table 10: Summary of the focus of published Australian research on ovarian cancer treatments

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<thead>
<tr>
<th>Type of study</th>
<th>Focus</th>
<th>Reflections</th>
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<tr>
<td>Drug discovery</td>
<td>Strong focus on cytotoxic therapies 75% of publications report early stage studies on novel or reprofiled cytotoxic compounds</td>
<td>Focus on cytotoxic compounds, particularly novel metallo-complexes, is not consistent with the international trend and may indicate a need for future re-prioritising</td>
</tr>
<tr>
<td>Pre-clinical studies</td>
<td>85% early stage (in vitro testing) 15% testing in animal models (proof-of-concept)</td>
<td>Rate of progression along the drug development continuum is low Progress may be hindered by poorly predictive models</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Predominantly MTTs Molecular profiling</td>
<td>Aligns with international focus May be attributable to the fact that most (but not all) clinical trials in Australia are part of larger international industry-sponsored or collaborative trials Australia produces little research output and participates in few clinical trials on immunotherapy Australian researchers are participating in studies exploring how molecular profiling of tumours can help guide clinical decisions</td>
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New treatments for ovarian cancer

After 20 years of research and multiple clinical trials, the standard of care for women with advanced ovarian cancer remains surgery (concerted attempt to achieve complete resection) and chemotherapy with carboplatin and paclitaxel.

Although response rates to platinum based chemotherapy are high, particularly in women with HGSC, the majority of women with advanced ovarian cancer will still relapse and ultimately die. It is very likely that this treatment paradigm will change over the next decade due to the radical advances in our understanding of the biology of epithelial ovarian cancer (EOC) and the increasing availability of a large number of molecular targeted therapies and we expect that this will result in better outcomes.

There is an urgent need to identify and validate predictive biomarkers that could help identify which patients will benefit from treatment.

It is now clear that EOC is not a single disease entity as was previously thought but is essentially a collection of distinct diseases, with different cellular origins and molecular characteristics, which share a similar anatomical location and clinical presentation, but little else. There are five different histological subtypes of EOC which differ with respect to risk factors, clinical behaviour and response to chemotherapy as well as potentially actionable molecular targets. HGSC is the most common histological subtype, but there are at least four different molecular subtypes of HGSC, based on mRNA expression profiles and which probably should be treated differently. It is time to capitalise on these observations and investigate the potential role of immune modulators, angiogenesis and stromal targeted therapies, PARP inhibitors as well as novel chemotherapeutic agents. There are also a number of different molecular targets in clear cell, mucinous and low grade serous cancers which all need to be investigated. It is very clear that treating all patients in the same way and with the same drugs will not result in any substantial improvement in outcomes, but this brings new challenges.

This paradigm shift in the understanding of the biology of ovarian cancer has created real challenges in how we design clinical trials for all these rare/uncommon subtypes and underscores the need for international collaboration as we move towards more selective and molecularly targeted trials. The translational component of all these trials is critically important and integral to their interpretation and success. There is an urgent need to identify and validate predictive biomarkers that could help identify which patients will benefit from treatment.

This has been elusive in EOC to date, but this is an area of intense research activity. It will be important to develop companion diagnostics to predict response and select appropriate patients for treatment.

There are many exciting opportunities with the new knowledge and all the new agents but there are also many challenges ahead with clinical trial design and endpoints. There are also many barriers to trial participation including geographic access, funding, ethics and regulatory issues amongst others. ANZGOG are now well positioned to take up this challenge and work collaboratively to improve the outcomes of women with ovarian cancer.

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Treatment Research Priorities

In summary, Australian drug discovery research in ovarian cancer focuses heavily on cytotoxic therapies, which is not in keeping with international research strategies. Australian pre-clinical research is primarily in vitro and relies heavily on the use of ovarian cancer cell lines that are no longer considered good models for HGSC. The progress into animal models of ovarian cancer is relatively low. Clinical trials of ovarian cancer therapeutics are more consistent with the international research strategies, with a particular emphasis on MTTs. This may be due to the international collaborations associated with these trials. Finally, more immunotherapy programs are needed. In light of these issues, the following priorities are identified:

- Develop new treatments for ovarian cancer:
  - Preclinical studies:
    - Identify and validate new subtype-specific therapeutic targets (H,I)
    - Identify which experimental models are the most informative and clinically relevant; establish recommendations for cell lines and facilitate access to those cell lines
    - Identify and develop to proof-of-concept new or re-purposed drugs using clinically relevant experimental models of disease
    - Focus on early stage development of novel, immune-modulatory agents and MTTs.
  - Design and conduct clinical trials: Explore novel and efficient trial designs that provide quicker answers with fewer patients. This will likely require adopting a ‘precision medicine’ approach, where biomarker based diagnostics, including molecular profiling, are used to guide the testing of new or re-purposed targeted treatments
    - Early stage clinical research adopting small, SMART approach for targeted therapies in patients selected on the basis of the molecular characteristics of disease (H,I,R)
    - Initiate or participate in (i) umbrella trials (where different treatments are used based on ovarian cancer subtype) or (ii) basket trials (where the same treatment is used against the same target across different cancers) with patient selection determined by molecular subtype (H,I,R)
    - Improve the incorporation of patient reported outcomes and QOL measures into clinical trial endpoints (H,R).
  - Explore ways to improve response to existing treatments: understand what subgroups of patients respond to treatments, why some patients do not respond, and what factors are associated with recurrence (H,I).
  - Managing side effects: undertake research that focuses not only on new treatments but also on finding ways to help women get through treatment by reducing and/or managing side effects.
  - Radiotherapy: identify the sub-groups of women who may benefit from radiation therapy.
  - Translational research: find ways to ensure novel and existing molecular and tumour-specific targeted therapies are progressed as rapidly as possible through clinical development and made available to patients as soon as possible.
Control covers a wide range of topics including survival, patterns of care, risk factor surveillance over large populations, psychosocial issues, education and epidemiology. These studies facilitate our understanding of how well research findings are adopted into clinical practice and whether they improve outcomes such as quality of life and survival. These studies also address investigations into the economic benefits of new treatments, behaviours related to cancer control and how information about ovarian cancer is communicated. Despite their importance, these research areas are poorly funded both internationally and in Australia.

**Australia’s contribution**

In Australia, the area of Control ranked highest across all research domains according to the number of publications and while this encompasses a great breadth of topics, specific expertise areas were identified: health care delivery, behaviour (psychosocial), patient care (QOL, survivorship) and epidemiology. In order to get a better sense of the Australian research output in these areas, we first examined impact factors. The average impact factors for the Australian publications are modest, however this may be a reflection of the highly specialised fields, rather than the quality of work. For example, research into patterns of care and communication might be of national interest, or field specific, whereas epidemiological studies into survival may reach more general oncology journals. Therefore, it was considered more appropriate to measure research output by journal type, rather than journal impact.

Analysis revealed that 121 research articles were published in 52 different journals, a wide spread indicative of the diversity of subject matter. However, the most popular journals were indeed topic specific, with 16% in *International Journal of Gynecological Cancer*, 7.5% in *Gynecologic Oncology*, 5.8% in *Australian and New Zealand Journal of Obstetrics and Gynaecology* and 5% each in *Psychooncology*, *Annals of Oncology* and *Familial Cancer*, capturing ~44% of the total publications in this research domain. The remaining publications were spread over 46 different journals.

Key findings in this area include:

1. Research demonstrating that reducing time from symptoms to diagnosis would not greatly alter stage of disease at diagnosis or survival rates (64)
2. A study that measured relative survival during 1995-2007 for breast, ovarian, colorectal and lung cancers in Australia, Canada, Denmark, Norway, Sweden, and the UK using population-based cancer registry data. Survival was persistently higher in Australia, Canada, and Sweden, intermediate in Norway, and lower in Denmark, England, Northern Ireland, and Wales, particularly in the first year after diagnosis and for patients aged 65 years and older (65)
3. An analysis of pooled case control studies that establish a link between endometriosis and clear-cell, low-grade serous and endometrioid invasive ovarian cancers (66).

In addition to important findings with regard to epidemiology, particularly those relating to factors affecting disease initiation and survival, the area of Control also deals with some very critical issues relating to patient care and QOL.
Health service models for ovarian cancer

As highlighted in this National Action Plan for Ovarian Cancer Research, ovarian cancer has a significant impact on women and their families across Australia. While all Australians have access to health care, there are many factors that can cause delay or reduce access to health services, leading to a disparity in clinical outcomes and access to ongoing support. Geographical location (living in rural, remote or regional areas of Australia), cultural and linguistic barriers, and decreased socioeconomic resources have all been found to be factors in poorer overall health. This has also been identified for women diagnosed with ovarian cancer. How to achieve sustainable improvements in delivery of ovarian cancer care for all Australian women is the central focus of health services research. The focus for health service research is on developing new and improved approaches to integrating all aspects of care; diagnosis, treatment, psychological support and rehabilitation. This is achieved in several ways; identifying barriers, facilitating rapid implementation of new treatments, and examining how the health system can improve services for women and their families.

Health services research enables the optimal implementation of new approaches to treatment, through developing a better understanding of system, local and individual barriers to the diagnosis and treatment of ovarian cancer, and approaches to overcoming these. Integration of new advances in any aspect of diagnosis and treatment for ovarian cancer cannot be achieved without a better understanding of barriers to changes, and testing the best approaches to address them.

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Professor Cancer Nursing, Cancer Nursing Research Unit, Sydney Nursing School, University Sydney, NSW

Similarly, improvements in the delivery of care of women diagnosed with ovarian cancer needs to be sustainable and equitable. Health service research provides an avenue to develop new models of delivering high quality care adapted to address common barriers to equitable health care such as geographical location, cultural, language and socioeconomic factors. The development of cancer nurse coordinators to provide a single point of support and guidance throughout the different treatment modalities is an example of a new health service model. Research has shown these positions have led to improved coordination and access to support for individuals diagnosed with cancer.

Perhaps most importantly, health service research provides an avenue to better understand the experience for women and their families as they navigate through the system, and develop new and improved health care models that better meet the women’s needs.
Health service models

Patient care does not only rely on the development of informative diagnostics and effective therapeutics. Patients need adequate access to effective health services. However, there is currently a lack of information about service delivery and limited evidence on the relationship between surgical volume and mortality and clinical outcomes. Other service model considerations include how best to optimise QOL during and after treatment. Routine data collection and benchmarking are crucial to informing service improvements that can impact on outcomes.

“Accessing appropriate and timely data to undertake linkage of 50-80% of patients for follow up could be a game changer” – cancer stakeholder

Quality of life

“Investment in science will take a while to come to fruition – in the meantime, it is important not to forget the women who are currently being diagnosed and treated and to ensure that their quality of life is optimal” – consumer

While our understanding of the biological basis of ovarian cancer holds great promise for the development of new treatments, it is important that the benefit of these treatments is not solely measured in terms of progression-free and overall survival. Trials of new treatments should incorporate QOL measures, including quantitative and qualitative exploration of patient-reported outcomes (PROs). In other words, it is important to also measure patients’ subjective improvement during and following treatment.

Mounting evidence indicates that psychosocial factors play a role in survival outcomes for women with ovarian cancer, with psychosocial wellbeing considered the most important contributing factor to QOL. There is much debate on the shortcomings of methods used to date, leading to a proposal for a general framework for the use of PROs as end points to improve clinical trial design and analysis. Australian researchers are examining how such a framework can be adapted for use in ovarian cancer clinical trials (67).

Research into QOL and psychosocial predictors of outcome indicate high levels of unmet supportive care needs for women living with ovarian cancer and their supporters, particularly in rural areas. Interventions are required to reduce stress, assist in decision-making and improve the QOL of women with ovarian cancer and their supporters.
Ovarian cancer affects the quality of a person’s life in many ways. The initial diagnosis can cause fear, uncertainty, anger, anxiety and depression. The cancer itself may cause symptoms – abdominal bloating, discomfort and pain, nausea and vomiting, sleep disturbance and fatigue, poor appetite, bowel disturbance, urinary symptoms, shortness of breath, weight changes. Treatment to control the cancer also has effects, some adverse and some beneficial. Some of these will be short-lived while some will last longer. For example, hair lost during chemotherapy will grow back, but tingling and numbness of fingers and toes caused by neurotoxicity may be permanent. Debulking surgery may have a major impact on functional ability initially, but recovery is usually rapid, and should leave patients with fewer abdominal symptoms.

Thus the effects of ovarian cancer and its treatment are many and varied, not only physical but also psychological, with the immediate effects of diagnosis, disease and treatment in turn affecting functional abilities and everyday activities across a range of function - physical, role, social, emotional and sexual. When one can no longer do the things one once enjoyed and which brought meaning to one’s life, whether it be playing a game of golf, playing with the grandkids, or enjoying a meal, quality of life is diminished.

Thus the effects of ovarian cancer and its treatment are many and varied, not only physical but also psychological...

Quality of life means different things to different people at different times of their lives. But in order to assess something in a standard way, it must first be defined in a standard way. To avoid this conundrum, a new term, patient reported outcomes, is increasingly used in health research. Several excellent questionnaires have been developed to assess the impact of ovarian cancer from the patient’s perspective. The content of each one provides a specific operational definition of quality of life. Each has been developed in a comprehensive and scientific way, starting with interviews with patients and clinicians to determine the relevant issues, followed by rigorous psychometric assessment to ensure validity and reliability, despite the subjective nature of the subject matter. Some cover a wide range of issues – disease symptoms, treatment side-effects, a multi-dimensional array of aspects of functioning and well-being, plus one or two global questions about perceived quality of life. Others are confined to symptoms – these are commonly called symptom indexes. All have a place in ovarian cancer research, providing candidate measures from which investigators can select the most appropriate to match their study objectives.

Quality of life and other patient-reported outcomes have been assessed in many but not all ovarian cancer trials, and typically have been secondary to the more traditional endpoint of disease-free survival. Often they are not reported in great detail, nor fully integrated with other outcomes in framing the implications and conclusions of the trial. So there is scope for improvement in the way patient-reported outcomes are integrated into future studies of treatments for ovarian cancer. Arguably, symptom benefit (assessed by the patient) should be the primary outcome in trials of new treatments for platinum resistant/refractory recurrent ovarian cancer, where symptom palliation is the treatment goal. Survivorship studies are also needed, to assess the long-term impacts of treatment and other aspects of quality of life. The robust methods now used to assess patient-reported outcomes in clinical trials may also have a role in the management of individual patients, to monitor disease symptoms in a standardised way. Such information may augment other sources now used in diagnosis and treatment decision making.
Control Research Priorities

The research topics relating to Control are valuable and diverse. There is a significant research effort underway in Australia, and while the impact factors for the publications tend to be low, this is likely due to the high level of field specialisation. Based on an analysis of the Australian research efforts in the area of Control, particularly with regard to multidisciplinary care, service delivery, QOL and palliative care, it is believed we can develop best-practice approaches to patient care by addressing the following priorities:

- **Best-practice health service delivery models and patterns of care (H,I,K):**
  - Understand why differences in clinical outcomes and mortality exist between facilities and geographic regions and how this relates to patterns of care, service delivery models, and adherence to best-practice guidelines (where relevant)
  - Describe the extent of access to and use of specialist cancer treatment and services (genetic testing, multidisciplinary care) as a way of highlighting service / treatment gaps
  - Explore ways to pro-actively support women and their families during and post-treatment. This could be achieved via routine screening for psychological distress, and by focusing on wellness and survivorship.

- **Quality of Life:**
  - Identify ways to improve outcomes for women living with ovarian cancer (H,I,K) including:
    - how to optimise functioning and QOL when the burden of disease is significant
    - how to best support women experiencing psychosocial concerns (including psychosexual issues) as a result of their treatment for ovarian cancer
    - how to ensure women have the support they need from diagnosis
    - how to help women get through treatment by reducing and/or managing side effects
    - explore links between QOL and time to recurrence and survival outcomes.
  - Explore the experience of survivorship of women with ovarian cancer and identify areas for focus and unmet needs.

- **Palliative care:**
  - Identify how best to meet the specific palliative care needs of women living with ovarian cancer in a way that moves beyond curative and end-of-life paradigms
  - Identify ways to improve the process of informed decision making by women and their carers about ovarian cancer treatment, particularly when the intent of treatment is not curative.

Progress in key priority areas will depend on appropriate research design. This may require exploration of new research paradigms and consideration of which types of research can best be led by Australian researchers.
Progress in key priority areas will depend on appropriate research design. This may require exploration of new research paradigms and consideration of which types of research can best be led by Australian researchers.

- **Leverage existing expertise**: use existing expertise in the stratification of ovarian cancer subtypes, identification of biomarkers and targets to facilitate the transition from early stage research to human proof-of-concept. This should be done using existing infrastructure (AOCS, ANZGOG).

- **Use innovative clinical trial design**:
  - proof-of-concept “SMART” trials: these are relatively small Phase I/IIa trials (<$500K for two years) with 30–40 patients; these will be good for testing targeted treatment on specific patient groups such as potential responders identified through analysis of molecular subtypes. SMART trials are innovative, quick to implement and flexible with integration between laboratory and clinical practice. They can be implemented nationally
  - umbrella trial designs: the patient is classified using molecular profiling and directed to a particular targeted treatment appropriate for the subtype.

- **Join international trials**: international collaboration on Phase II-III trials will be important so that Australian patients can benefit from research at a global level.

- **Reprofiling**: it is important to fund research that re-profiles existing drugs on the market or in development for other indications.

- **Translational research**: researchers have a fundamental responsibility to produce policy- and practice-ready research.

- **Experimental models**: ensure the availability of preclinical models (cell line and PDX-models) that are predictive of ovarian cancer subtypes.

- **Molecular profiling**: ensure availability of profiling capacity to progress research and clinical testing of targeted treatments.

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**Realising precision therapy for ovarian cancer: changing the clinical research paradigm**

The American Society of Clinical Oncologists (ASCO) has recently called upon patients, advocates and clinical investigators to collectively raise the bar in expectation of benefits for new therapies and to better design clinical trials to achieve this.

The aspirational aim is to enable well-conducted Phase II trials to demonstrate clear benefits to patients and thereby possibly avoid large Phase III studies.

Critical to this are: (i) an improved understanding of the drug target; (ii) development of a companion diagnostic to guide patient selection; (iii) comprehensive bio-specimen banks linked to patient registries; and (iv) determining meaningful outcomes, including overall survival, target hazard ratio, 1-year survival and progression-free survival.

While this report was aimed at other cancers (pancreatic, breast, lung), the principles are highly applicable to ovarian cancer (68).
The aim of the Plan is to articulate the approaches that will assist in overcoming funding, resource and administrative barriers with a view to progressing ovarian cancer research as efficiently and effectively as possible.

WHAT’S HOLDING US BACK?

The prior chapters have given an overview of the current state of Australian ovarian cancer research, including what scientific issues are most pressing, how they align with international research efforts, and where the gaps in our knowledge lie. We now have a comprehensive list of recommendations addressing each of the major research areas relating to ovarian cancer. This is a critical step forward, but in order to optimise our chances of success, we must address the primary barriers that have faced ovarian cancer research thus far (Table 11). Many of these are common not only to the broader field of cancer research but also to clinical and scientific research in general, particularly a lack of funding, lack of infrastructure, bureaucracy, and the risk of a fragmented approach. Ovarian cancer research also faces some specific challenges, such as a small patient population and the nature of the advanced disease. The small patient population hampers access to samples and poses limits on clinical trials. The asymptomatic nature of the early stage disease means that women are often diagnosed at an advanced, aggressive stage where their options are limited and their prognosis poor. While these are all significant challenges, the Australian ovarian cancer research field does have the benefit of a small and well-connected research community, making communication and collaboration easier. This, in turn, means that we are well positioned to establish a cohesive, synergistic framework that makes optimal use of resources and expertise. Furthermore, we have identified a set of factors that address and help off-set each of the major barriers facing ovarian cancer research. These ‘Enablers’ form a crucial part of the Plan.
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<thead>
<tr>
<th><strong>BARRIERS</strong></th>
<th><strong>ENABLERS</strong></th>
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<tr>
<td><strong>LACK OF FUNDING</strong></td>
<td>Funding is increasingly competitive&lt;br&gt;Clinical trials are expensive in Australia; funding for early stage clinical testing is difficult to obtain&lt;br&gt;Philanthropic funds do not necessarily go to priority areas or high impact research&lt;br&gt;As important as the research is raising awareness of the need for the research so that funding becomes available</td>
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<tr>
<td><strong>LACK OF INFRASTRUCTURE</strong></td>
<td>Limited funding available for infrastructure&lt;br&gt;Limited experimental models (animal and other) that are clinically predictive&lt;br&gt;Access to tissue can be difficult in the absence of biobanks with open access programs&lt;br&gt;Lack of a standardised national registry</td>
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<tr>
<td><strong>FRAGMENTED APPROACH</strong></td>
<td>Researchers and funders have a tendency to concentrate on their own priorities and areas of interest&lt;br&gt;Need to plan the common areas in which greatest progress is likely to be made&lt;br&gt;Multiple tissue repositories makes access to biospecimens difficult</td>
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<tr>
<td><strong>BUREAUCRACY</strong></td>
<td>Ethics processes and research governance are cumbersome and cause delays&lt;br&gt;While a lot of states have centralised ethics review, additional layers of governance approval and the requirement for agreements with individual hospitals makes multisite research challenging&lt;br&gt;Consent for acquisition of biospecimens from patients is relatively easy but governance approval is complex and time-consuming&lt;br&gt;Data linkage issues due to privacy concerns</td>
</tr>
<tr>
<td><strong>SMALL POPULATIONS</strong></td>
<td>Ovarian cancer is a low volume cancer&lt;br&gt;Identification of subtypes has further reduced the numbers of women available for research&lt;br&gt;Multiple sites are needed for research</td>
</tr>
<tr>
<td><strong>RESEARCH TIMEFRAME</strong></td>
<td>Research findings typically take a long time to result in changes in practice</td>
</tr>
<tr>
<td><strong>NATURE OF ADVANCED DISEASE (PALLIATIVE CARE)</strong></td>
<td>Knowing how to approach people with advanced disease to take part in research&lt;br&gt;Knowing how to discuss research in the space between treatment with curative intent and palliation</td>
</tr>
</tbody>
</table>

A range of enablers will be important to progress the research priorities in the Plan.
Collaboration Goals

Collaboration at a national and international level is seen as central to the success of the Plan.

- Foster international collaborations: continue to collaborate and participate in high-profile international research activity and expand international collaborations (including Asia)
- Strengthen national collaborations: AOCS, ANZGOG, ASGO, KConFab
- Develop an integrated model: researchers, clinicians and funders should work together towards a collective national ovarian cancer research agenda
- Develop forums for idea generation: foster big picture and innovative thinking through idea exchange
- Develop mechanisms for information sharing: foster regular sharing of information through established and well-supported forums and communication mechanisms.

“...The brain power in the room would light up New York – they are amazing researchers and they put their egos aside to get on for the common good... it [AOCS] was really the first project where everyone joined forces for the common good. ...” – academic researcher

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3 A consortium of geneticists, clinicians, surgeons, genetic counsellors, psychosocial researchers, pathologists and epidemiologists to make data and biospecimens widely available to researchers for use in peer-reviewed, ethically-approved funded research projects on familial aspects of breast and breast/ovarian cancer. http://www.kconfab.org/Index.shtml
Funding Goals
Funding is a key enabler for research activity and lack of funding the biggest barrier to progression of research activity.

- **Consolidation:** develop collaborative or consolidated approaches to fund ovarian cancer research to reduce duplication of effort and cost, focus investment on priorities and amplify capacity for impact
- **Prioritisation:** make decisions on low-risk, safe and steady returns by investing in research strengths, while setting funding aside to divert towards more innovative projects of higher risk but potentially transformational returns
- **Investment models:** explore funding models such as syndication to facilitate collaborations (national and international) and build investment streams to fund priority-driven research projects, including clinical trials, and infrastructure, and fellowships and provide funding for other opportunities across the research and development continuum
- **Innovation:** find and test different models of investment such as venture philanthropy to cover funding needs to translate research outcomes to human proof-of-concept; adopt project-focused, milestone-based industry models for development activities
- **Leverage:** combine resources to establish collaborative models and leverage government, philanthropic and other funding in priority areas
- **Transparency:** develop a more transparent approach to how funding for ovarian cancer research is allocated by all funders, including what funding is available, how decisions are made, what funds are allocated and what outcomes are achieved. This would ensure that funders and researchers are more accountable for overall research direction and would translate to increased public, government and investor confidence in supporting research
- **Increase competitiveness:** seek to increase the success rate of ovarian cancer research funding applications through a better understanding of the requirements for research funding, developing appropriate performance indicators and impact measurement tools, aligning applications with the most appropriate funding streams and with international research priorities
- **Build track records:** given the strong relationship between track record and grant success, look for ways to strengthen the track records of early and mid-career researchers who may be applying for funding.

Research Infrastructure Goals
The approach to collecting, storing and accessing tissue for the purposes of ovarian cancer research is seen as a critical enabler for driving progress. Resource and administrative issues and the growth in the number of small organisation-level biobanks, are currently barriers to progress in this area.

Key areas of focus were identified as utilising existing research infrastructure such as AOCS to establish a nationally co-ordinated biobank and the development and provision of predictive animal and cell models to support research.

- **Biobank:** establish a nationally co-ordinated biobank facility using:
  - **Common approach:** developing a uniform way of managing tissue samples and consistency in producing high quality data
  - **Competent procedures:** establishing competent and efficient mechanisms for collection, annotation, storage and access to tissue and other samples to support operations and access by multiple researchers
  - **Leverage existing infrastructure and expertise:** opportunity to expand and sustain AOCS
  - **Molecular profiling:** increase capacity, such as next generation sequencing, to conduct tumour and other biospecimen profiling
  - **Experimental Models:** develop a national resource to enable researcher access to validated and predictive cell and PDX-models to facilitate new drug development programs.
Clinical Trials Infrastructure Goals
Participating in large clinical trials with dedicated resources such as research nurses and specialists in the field is key to the development of new treatments and approaches to care.
Clinical testing in proof-of-concept “SMART” trials will provide a rapid method to test targeted therapies and validate new clinical targets.
It is recommended that we utilise existing clinical trial infrastructure - networks such as ANZGOG to access large trials and develop innovative trial concepts.

- ANZGOG: this should be sustained and expanded to enable access and participation in large trials and to develop innovative trial concepts.

Database Goals
Infrastructure, such as information platforms and IT tools are critical to the sharing of information and data as well as enabling real-time access to data.

- Clinical registry: establish a national ovarian database to allow us to know where the deficiencies in current management are so that these can be a priority for future research to allow us to know where the deficiencies in current management are so that these can be a priority for future research
- Consolidate data collection through centralised or linked datasets, with guidance on how to implement and collect consistent data (including coding) across centres
  - further develop systems to link biospecimen data with clinical registries and clinical outcomes
  - overcome governance issues around data custodianship and privacy
- Develop systems for routinely capturing patient reported outcomes in clinical trials.

Communication Goals
Communication will be essential in the planning, conduct and reporting of research priorities under the Plan.

"Doesn't matter how good the plan is if the messaging around it is wrong – people won’t use it or contribute to it if they have the wrong view of its intent - consumer"
• Communicating priorities:
  - managing the expectations of the community to effectively broker funding opportunities and provide a better understanding of research outcomes, development pathways and timelines
  - communicating a cultural change to drive collaboration and demonstrate its benefits
  - include senior nurses, allied health providers and consumers
• Communicating outcomes: finding a better way of communicating issues around ovarian cancer research that is fair, balanced and transparent; this includes:
  - messaging around the value of investing in research that has the potential to make a difference to the longevity and quality of women’s lives
  - addressing the misconceptions around the likelihood of a population-based screening test
  - communicating the real benefits of new treatments
  - more realistic communication around ‘breakthrough’ discoveries, the translation to new treatments and the pathways and timelines involved
  - what the community should expect in terms of reporting outcomes against funding provided.

CONSUMER PARTICIPATION
All participants in consultations to inform the Plan recognised the importance of meaningful and active involvement of people affected by ovarian cancer. This includes incorporating consumer voices in the construction of research objectives and in considering how research findings will eventually be used and/or translated back to the treatment and management of women with ovarian cancer.

Consumers can play a very strong role in raising public awareness about the need for ovarian cancer research as well as taking a position to government about the need for funding.

The National Framework for Consumer Involvement in Cancer Control (69) provides a useful frame for the roles that consumers can and should play in ovarian cancer research as described in Table 12.

“Would be good to look for more formal ways for consumer voices to be heard as part of research”
– academic researcher
Table 12: Framework for consumer involvement in ovarian cancer control

<table>
<thead>
<tr>
<th>Level of participation</th>
<th>How defined</th>
<th>Application in ovarian cancer research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informing</td>
<td>Provide information, seek feedback, build awareness, improve health literacy</td>
<td>Provide information to consumers about ovarian cancer research activities and impact through a range of mechanisms – consumer forums, newsletters or other channels (oral, electronic, print and web-based)</td>
</tr>
<tr>
<td>Consulting</td>
<td>Seek information, provide feedback</td>
<td>Seek information from consumers about their experience, and what’s important to them to guide research priority setting and to guide the conduct and communication of research through individual interviews, surveys, focus groups and consultation workshops</td>
</tr>
<tr>
<td>Involving</td>
<td>Involved in information, support, cancer services, policy, research and spanning the patient pathway</td>
<td>Build consumer involvement into the planning and conduct of research through: consumer representation on research management groups, working parties or project teams; inclusion of ‘consumer reviewer’ roles and steps into the research pathway</td>
</tr>
<tr>
<td>Partnership</td>
<td>Work equally with health professionals, administrators, researchers, policy makers</td>
<td>Consumer Advisory Groups at organisational and jurisdictional levels as a formal advisory mechanism. Inclusion of consumer representation (at least two consumers) in research management groups, working parties and research review and funding panels</td>
</tr>
<tr>
<td>Consumer-led</td>
<td>Set priorities, lead major activities</td>
<td>Grass roots, consumer-based organisational involvement - consumer involvement in setting or informing priorities and strategic directions, in reviewing progress and outcomes and in advocating for improvement</td>
</tr>
</tbody>
</table>

Consultation and workshop participants recognised the need for the voices of consumers to be considered across all areas of research activity, and indeed across the broader domain of advocacy. Fundamental to the effective integration of consumer involvement in ovarian cancer research in Australia is a consumer-focused mindset. The consideration of ‘what would this mean for women?’ from our earliest research planning conversations, ensuring that research objectives consider consumer perspectives, through to the development of measures and the conduct of, and reporting on, research outcomes. Integral to this is seeking input into measuring what matters, for example by the inclusion of PROs via QOL and psychosocial measures as a key component of research and clinical methodologies to gather information about disease management as part of routine practice. This could also potentially inform other research areas like enabling better biological targeting through understanding patient-reported symptoms of toxicity.

A further priority in relation to consumer involvement is to ensure that the diversity of women and their experiences are considered carefully – the geographic, cultural and social factors that will influence their experience and outcomes and their capacity to participate in research or access best practice care. Additionally, it was considered important to establish mechanisms, such as surveys, to inform important issues such as genetic testing, for example, to ensure that every woman with ovarian cancer who is reviewed and treated is asked whether they have been referred for genetic testing and to understand what messages about genetic testing are being conveyed and to whom, particularly in rural settings.
The National Action Plan for Ovarian Cancer Research aims to provide strategic direction for ovarian cancer research activity in Australia. This is not about a new start, or a different direction, but rather about continuing the job that has been started and fostering a renewed spirit of collaboration that will allow us to achieve far loftier goals than would otherwise be possible, and in a more timely way. The women living with ovarian cancer now and those who will be diagnosed tomorrow are at the heart of this Plan. These women urgently need this Plan and need the collective efforts and impact that its successful implementation will facilitate.

“Ensuring that funding in Australia goes to the areas that are likely to have the greatest impact and drawing on Australia’s strengths – academic researcher”

The Plan is not designed to be static, but will be monitored and reviewed over time to ensure that the path it sets continues to be relevant and appropriate and to keep all of those who are involved accountable for their individual and our collective contributions.

OUR POTENTIAL FOR ADVANCEMENT

Australia has a small research community in the field of ovarian cancer, nevertheless we have a high level of research output per incidence of ovarian cancer and have actively participated in high impact research. This research has played an important role in advancing our understanding of the biological basis of ovarian cancer, and due to the high level of expertise, access to resources such as AOCs and ANZGOG, and the close networks of researchers, the Australian research community is well positioned to build on the progress made to date. Nevertheless, a great deal of work remains to be done to improve outcomes for women, and while Australian ovarian cancer research has the potential to generate significant advances in the field, there are barriers that can and must be addressed as soon as possible.

THE ACTIONS: RECOMMENDED STRATEGIC ACTIVITIES AND RESEARCH PRIORITIES

Research priorities alone cannot affect change unless acted upon in a coordinated manner. The Strategic Activities considered essential to support the successful implementation of the Plan are described in Table 13. The Research priorities themselves are then outlined in Table 14. Many of the research priorities are ranked high in importance, for near term implementation, and represent an area of existing expertise. Many of these priorities are part of a broad continuum from basic biology (understanding the disease) to translational research (therapy development), and beyond (patient care).
### Table 13: Recommendations for strategic activities to support the successful implementation of the Plan

<table>
<thead>
<tr>
<th>Theme</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Funding the research</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Consolidate** | Develop collaborative or consolidated approaches to fundraising for ovarian cancer research to reduce duplication of effort and cost, focus investment on priorities and amplify capacity for impact.  
Facilitate discussion by not-for-profits about coordinated approaches for funding ovarian cancer research in Australia and internationally. |
| **Communicate** | Develop a transparent, accountable approach to funding ovarian cancer research that includes knowledge of what funding is available, how decisions are made, what funding has been allocated and the outcomes and impact of the research resulting from such funding.  
Manage the expectations of the community to effectively broker funding opportunities and provide a better understanding of research outcomes, development pathways and timelines. |
| **Innovate** | Find and test different models of funding and investment. |
| **Raise the bar** | Increase the success rate of ovarian cancer research funding applications through a better understanding of the requirements for research funding and aligning applications with the most appropriate funding streams. |
| **Capacity build** | Strengthen the track records of early and mid-career researchers in ovarian cancer. |
| **Invest in collaboration and bridge current gaps** | Develop funding models to facilitate collaborations (national and international) and build investment streams to fund infrastructure and priority-driven research across the research and development continuum including dedicated funding for early stage clinical trials. Provisions should also be made for investigator-led research opportunities and for scholarships and fellowships. |
| **Seed/Development funding** | Adopt project-focused, milestone-based industry models for progressing relevant research outcomes to proof-of-concept, including appropriate resourcing for development activities. |
| **Conducting the research** | |
| **Prioritise** | Continually review and prioritise research activities based on the potential for greatest impact on women’s QOL and survival.  
Make decisions on low-risk, safe and steady returns by investing in research strengths, while setting funding aside to divert towards more innovative projects of higher risk but potentially transformational returns. |
<p>| <strong>Leverage</strong> | Build on existing expertise in stratification, biomarker and target identification and existing infrastructure and associated networks (AOCS, ANZGOG) to facilitate the transition from early stage research to human proof-of-concept. |
| <strong>Innovate</strong> | Use innovative clinical trial designs, such as SMART or umbrella trial designs, to achieve rapid proof-of-concept in humans. |
| <strong>Collaborate internationally</strong> | Continue to participate in high-profile international research and clinical activity, including Phase III trials, and expand international collaborations (including Asia). |</p>
<table>
<thead>
<tr>
<th>Theme</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Translate</td>
<td>Ensure that research is policy- and practice-ready to facilitate rapid translation to the bedside and dissemination across the field.</td>
</tr>
</tbody>
</table>

**Supporting the research**

<table>
<thead>
<tr>
<th>Collaborate nationally and invest in our strengths</th>
<th>Facilitate a cultural change and establish national standardised resources to drive collaboration and demonstrate its benefits across the clinical, research and consumer spectrum.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strengthen national collaborations and infrastructure such as AOCS, ANZGOG &amp; ASGO.</td>
</tr>
<tr>
<td></td>
<td>Foster big picture and innovative thinking through ideas exchange, networking and professional development opportunities within the broader frame of innovation, collaboration, leadership and commercialisation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Establish a consistent approach to managing data, biospecimens and clinical registries</th>
<th>Establish competent and efficient mechanisms for collection, annotation, storage and access to tissue and other samples with access by multiple researchers.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Establish a national ovarian database – this would enable investigations into the deficiencies in current management so that these can be a priority for research.</td>
</tr>
<tr>
<td></td>
<td>Create linkages between biobanks and clinical registries and overcome governance issues around data custodianship and privacy.</td>
</tr>
</tbody>
</table>

**Communicating the research and priorities**

<table>
<thead>
<tr>
<th>Share</th>
<th>Foster regular sharing of information through established and well-supported forums and communication mechanisms.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educate</td>
<td>Educate health professionals and women about symptoms of ovarian cancer.</td>
</tr>
<tr>
<td>Clarify</td>
<td>Clearly communicate the complexities of early detection and screening to women and the community.</td>
</tr>
<tr>
<td></td>
<td>Communicate the value of investing in research that can make a difference to quality of life and survival for women, including more realistic communication of research ‘breakthroughs’.</td>
</tr>
<tr>
<td>Inform</td>
<td>Communicate research priorities to other funders (NHMRC, ARC etc.) to inform on key issues relating to ovarian cancer research.</td>
</tr>
</tbody>
</table>

**Evaluating the research**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Adopt a core suite of evaluation measures by all funders to raise the bar on transparency and accountability to support investment decisions and public reporting.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Routinely review and monitor progress of investments – establish improved and additional mechanisms to measure performance and impact e.g. social return on investment methodology.</td>
</tr>
</tbody>
</table>

| Review and update | Regularly revisit the Plan to ensure relevance, and revise and reprioritise as required. |
Table 14: Research priorities for ovarian cancer showing core priorities and specific, non-limiting examples of these, where identified.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Core priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIOLOGY &amp; AETIOLOGY</strong></td>
<td></td>
</tr>
<tr>
<td>Basic science</td>
<td></td>
</tr>
<tr>
<td>Core priorities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continue research on the biology of ovarian cancer to inform diagnosis, early detection, treatment pathways and research translation.</td>
</tr>
<tr>
<td></td>
<td>Continue the classification of disease subtypes both in terms of their molecular profiles and their histology, with the aim of identifying and validating new therapeutic targets.</td>
</tr>
<tr>
<td></td>
<td>Explore the tumour immune microenvironment to identify potential targets for therapy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mechanics of resistance and recurrence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Core priorities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Explore the ways in which tumours respond to their environment and to treatment, with particular focus on the mechanisms tumours employ in treatment response and resistance.</td>
</tr>
<tr>
<td></td>
<td>Compare recurrent disease with initial disease with a view to understanding factors that influence resistance to treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aetiology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Core priorities</td>
<td>Understand the natural history and latency of disease subtypes, particularly HGSC, to identify precursors for earlier detection and treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXPERIMENTAL MODELS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical models</td>
<td></td>
</tr>
<tr>
<td>Core priorities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Further develop and assess clinically relevant preclinical models, such as PDX-models, that are consistent with the various ovarian cancer subtypes in order to facilitate research into targeted treatments.</td>
</tr>
</tbody>
</table>

| In vitro models             |                 |
| Core priorities             |                 |
| | Further develop and enable access to clinically relevant cell lines. |

<table>
<thead>
<tr>
<th>EPIDEMIOLOGY &amp; PREVENTION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td></td>
</tr>
<tr>
<td>Core priorities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continue to explore genetic risk factors for ovarian cancer subtypes (histological and molecular).</td>
</tr>
</tbody>
</table>

| Epidemiology               |                 |
| Core priorities            |                 |
| | Conduct population studies to explore the relationship between non-genetic risk factors and ovarian cancer aetiology and survival. |
| | Conduct studies to understand the patterns and experience of disease in population subgroups (the elderly, women in rural and remote areas, Aboriginal and Torres Strait Islanders and those from culturally and linguistically diverse backgrounds). |

| Surgical methods           |                 |
| Core priorities            |                 |
| | The adoption of risk reducing surgical methods to reduce mortality in high risk women. |

<p>| Other                     |                 |
| Core priorities            |                 |
| | Research relating to preventive measures that extend from knowledge of the biology of the disease. It is crucial to explore preventative measures that do not reduce women’s quality of life (including sexual and reproductive lives). |</p>
<table>
<thead>
<tr>
<th>Specific non-limiting examples</th>
<th>Priority description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue research on the biology of ovarian cancer to inform diagnosis, early detection, treatment pathways and research translation.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>Continue the classification of disease subtypes both in terms of their molecular profiles and their histology, with the aim of identifying and validating new therapeutic targets.</td>
<td>High, Immediate, Significant risk</td>
</tr>
<tr>
<td>Explore the tumour immune microenvironment to identify potential targets for therapy.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>Explore the ways in which tumours respond to their environment and to treatment, with particular focus on the mechanisms tumours employ in treatment response and resistance.</td>
<td>High, Immediate, Significant risk</td>
</tr>
<tr>
<td>Compare recurrent disease with initial disease with a view to understanding factors that influence resistance to treatment.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>Understand the natural history and latency of disease subtypes, particularly HGSC, to identify precursors for earlier detection and treatment.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>Further develop and assess clinically relevant preclinical models, such as PDX-models, that are consistent with the various ovarian cancer subtypes in order to facilitate research into targeted treatments.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>Further develop and enable access to clinically relevant cell lines.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>Continue to explore genetic risk factors for ovarian cancer subtypes (histological and molecular). Identify high risk subgroups for developing new genetic or other biomarker tests. Explore the potential to reduce risk of ovarian cancer by modification of lifestyle factors. Understand how modifiable aspects of lifestyle influence chemotherapy completion and response, QOL, recurrence and survival.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>Conduct population studies to explore the relationship between non-genetic risk factors and ovarian cancer aetiology and survival. Explore the potential to reduce risk of ovarian cancer by modification of lifestyle factors. Understand how modifiable aspects of lifestyle influence chemotherapy completion and response, QOL, recurrence and survival.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>The adoption of risk reducing surgical methods to reduce mortality in high risk women. Surgical methods for BRCA1/2 carriers and post-menopausal women – patterns of care, linking to survival, ensuring adoption of best practice methods. Developing the evidence-base for supporting, or otherwise, the adoption of salpingectomy alone versus BSO.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>Theme</td>
<td>Core priorities</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>DETECTION</td>
<td></td>
</tr>
<tr>
<td><strong>Pathways to earlier diagnosis</strong></td>
<td>Develop better biomarker-based diagnostic tools.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis of disease subtypes</strong></td>
<td>Develop biomarkers for (i) identifying disease subtypes (ii) as prognostic indicators, (iii) for guiding treatment (companion diagnostics), and (iv) monitoring disease recurrence. Continue and expand research into the molecular profiling of tumours to guide treatment choices.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>TREATMENT</td>
<td></td>
</tr>
<tr>
<td><strong>New treatments</strong></td>
<td>Preclinical studies: identify and validate new subtype-specific therapeutic targets.</td>
</tr>
<tr>
<td></td>
<td>Preclinical studies: identify and develop to proof-of-concept new or re-purposed drugs using clinically relevant experimental models of disease.</td>
</tr>
<tr>
<td></td>
<td>Explore novel and efficient clinical trial designs that provide quicker answers with fewer patients. This will likely require adopting a ‘precision medicine’ approach, where biomarker based diagnostics, including molecular profiling, are used to guide the testing of new or re-purposed targeted treatments.</td>
</tr>
<tr>
<td></td>
<td>Prevent the incorporation of patient reported outcomes and QOL measures into clinical trial endpoints.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Translational research</strong></td>
<td>Find ways to ensure novel and existing molecular and tumour-specific targeted therapies are progressed as rapidly as possible through clinical development and made available to patients as soon as possible.</td>
</tr>
<tr>
<td><strong>Improve response to existing treatments</strong></td>
<td>Explore what subgroups of patients respond to treatments, why some patients do not respond, and what factors are associated with recurrence.</td>
</tr>
<tr>
<td><strong>Managing side effects</strong></td>
<td>Undertake research that focuses not only on new treatments but also on finding ways to help women get through treatment by reducing and/or managing side effects.</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td>Identify the sub-groups of women who may benefit from radiation therapy.</td>
</tr>
<tr>
<td>Specific non-limiting examples</td>
<td>Priority description</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>To identify high risk women based on genetic or other molecular risk factors.</td>
<td>High, Immediate, Key strength</td>
</tr>
<tr>
<td>As an aid in the diagnosis of symptomatic women.</td>
<td>High, Immediate</td>
</tr>
<tr>
<td>As an aid to differentiate benign or LMP tumours from malignant tumours.</td>
<td>Maintain watching brief</td>
</tr>
<tr>
<td>For screening – will depend on the outcomes of the UKCTOCS study and will require prospective study designs.</td>
<td></td>
</tr>
<tr>
<td>Identifying and validating of biomarkers relating to more aggressive subtypes, particularly low volume HGSC.</td>
<td>High, Immediate</td>
</tr>
<tr>
<td></td>
<td>High, Immediate</td>
</tr>
<tr>
<td>Focus on early stage development of novel, immune-modulatory agents and molecular targeted therapies.</td>
<td>High, Immediate</td>
</tr>
<tr>
<td>Early stage clinical research adopting small, SMART approach for targeted therapies in patients selected on the basis of the molecular characteristics of disease.</td>
<td>High, Immediate, Significant risk</td>
</tr>
<tr>
<td>Initiate or participate in (i) umbrella trials (where different treatments are used based on ovarian cancer subtype) or (ii) basket trials (where the same treatment is used against the same target across different cancers) with patient selection determined by molecular subtype.</td>
<td>High, Immediate, Significant risk</td>
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<td>High, Immediate, Significant risk</td>
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<tr>
<td>Theme</td>
<td>Core priorities</td>
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<td><strong>CONTROL</strong></td>
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<tr>
<td>Health service models /</td>
<td>Understand why differences in clinical outcomes and mortality exist between facilities and geographic regions and how this relates to patterns of care, service delivery models, and adherence to best practice guidelines (where relevant).</td>
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<tr>
<td>Patterns of care</td>
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<td></td>
<td>Describe the extent of access to and use of specialist cancer treatment and services (genetic testing, multidisciplinary care) as a way of highlighting service / treatment gaps.</td>
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<td></td>
<td>Explore ways to pro-actively support women and their families during and post- treatment such as routine screening for psychological distress, with a focus on wellness and survivorship.</td>
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<tr>
<td>Quality of Life</td>
<td>Identify ways to improve outcomes for women living with ovarian cancer.</td>
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<td></td>
<td>Explore the experience of survivorship of women with ovarian cancer and identify areas for focus and unmet needs.</td>
</tr>
<tr>
<td>Palliative care</td>
<td>Identify how best to meet the specific palliative care needs of women living with ovarian cancer in a way that moves beyond curative and end-of-life paradigms.</td>
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<td></td>
<td>Identify ways to improve the process of informed decision making by women and their carers about ovarian cancer treatment, particularly when the intent of treatment is not curative.</td>
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<tr>
<td>Specific non-limiting examples</td>
<td>Priority description</td>
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<td></td>
<td>High, Immediate, Key strength</td>
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<tr>
<td></td>
<td>High, Immediate, Key strength</td>
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<tr>
<td>Determine how to optimise functioning and QOL when the burden of disease is significant.</td>
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<tr>
<td>Determine how to best support women experiencing psychosocial, including psychosexual, concerns as a result of their treatment for ovarian cancer.</td>
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<td>Determine how to ensure women have the support they need from diagnosis.</td>
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<tr>
<td>Help women get through treatment by reducing and/or managing side effects.</td>
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<tr>
<td>Explore links between QOL and time to recurrence and survival outcomes.</td>
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A ROADMAP FOR OVARIAN CANCER RESEARCH

For a more visual overview of the Plan, we provide Figure 17: a concept roadmap to strengthen, focus and fund future ovarian cancer research in Australia. This roadmap:

- is underpinned by collaboration and meaningful, active consumer involvement
- identifies three critical streams of funding: (i) infrastructure funding to support and enable research effort and impact, (ii) research funding for priority-driven research and researcher support, and (iii) development funding to drive the translational effort through to proof-of-concept
- depicts the research priorities along the critical pathways to achieving better outcomes for women.

Collaboration network

Figure 17: A concept roadmap to strengthen, focus and fund future ovarian cancer research in Australia.

Abbreviations: Dx = diagnostic, Gx = genetic
VISION FOR THE FUTURE

Women living with ovarian cancer need and deserve a better future than they currently have. The Plan represents a major step towards giving them that future. Our short to longer term vision for the future is encapsulated by the goals articulated in Figure 18. Implementation of the research priorities identified in this Plan will help achieve this vision. Regular review, evaluation and adaptation of the Plan will be required to face down the current and emerging challenges, and will give us a legitimate chance to make a vital difference.

<table>
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<tr>
<th>2 year vision</th>
<th>5 year vision</th>
<th>10 year vision</th>
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| • Priorities and strategic activities from the Plan (as identified in Tables 13 and 14) have been integrated into local and collaborative research plans. In particular:  
  - progress towards the provision of shared resources to support research including improved experimental models reflective of ovarian cancer subtypes (PDX and cell lines), a national standardised system for managing biospecimens and linking data to clinical registries and increased molecular profiling capacity  
  - targeted drug discovery programs and Australian-led precision-based clinical trials have been initiated  
  - improved integration of patient reported outcomes in trial design  
  - research priorities in Detection have been further developed (informed through clarification of regulatory pathway and the results of UKCTOCS) in relation to population screening  
  • Alliances between research organisations, clinicians, researchers, consumers and funders have been enhanced  
  • Collaborative funding models have been implemented, with appropriate evaluation frameworks in place to measure and report on progress and impact  
  • Growth in investment in ovarian cancer infrastructure, research (clinical, preclinical, other) and development has been demonstrated | • Significant progress in priority areas has been demonstrated including:  
  - the availability and routine use of a range of experimental models reflective of the different ovarian cancer subtypes  
  - a national standardised system for managing biospecimens linked to clinical registries  
  - new targets for different ovarian cancer subtypes have been validated and there has been an increase in drug development programs based on these targets  
  - increased translational research, particularly a demonstrated shift from early stage to proof-of-concept studies involving new treatments, including treatments for resistant subgroups, and studies relating to biomarkers involved in diagnosis, prognosis and measuring response to treatments  
  - expansion of the number Australian-initiated precision-based clinical trials  
  - progress in the identification of risk factors (genetic and environmental) and other population-based studies  
  - QOL studies have identified ways to improve outcomes for women  | • A new standard of care - targeted and immunotherapy treatment options are part of the standard of care for ovarian cancer  
  • The benefits of precision medicine have been realised – molecular profiling, targeted therapies and companion diagnostics are available for women  
  • There are improved tools to support diagnosis, prognosis, treatment and surveillance  
  • Improved clinical outcomes for women diagnosed with ovarian cancer are demonstrated, including reduced incidence of recurrence  
  • A greater understanding of genetic and environmental risk factors has informed new preventive strategies  
  • Survivorship studies assessing the long-term impacts of treatment and other aspects of quality of life have resulted in improved outcomes for women  
  • Improvements in care in alignment with best practice are demonstrated across Australia |

Figure 18: Our vision for the future providing short, medium and longer term goals that can be achieved through the adoption of research priorities and strategic activities outlined in this Plan.
A COMMITMENT TO ACTION

The Australian Charter for Ovarian Cancer Research Excellence articulates a set of principles to underpin the planning, funding, conduct, evaluation and reporting of ovarian cancer research in Australia. Great strides forward will be enabled through the individuals and organisations involved in ovarian cancer research in Australia reviewing their approach to align with these principles, united with our common goals and in the interests of the women we serve.

AUSTRALIAN CHARTER FOR OVARIAN CANCER RESEARCH EXCELLENCE

By developing this Charter we aim to:

• **engage:** through open discussion and setting out stakeholder roles in developing and implementing a national ovarian cancer research agenda
• **guide:** through collective effort, we will promote the efficient use of available infrastructure and resources
• **encourage commitment:** we will seek stakeholder ownership and agreement on planned approaches
• **set out key principles:** we will establish transparency, objectivity, accountability, consistency, collaboration and encourage greater consumer involvement.

These goals are consistent with the philosophy of collective impact (70) which could be applied to ovarian cancer research to encourage collaboration and a common agenda between diverse stakeholders across the ovarian cancer community.

The principles of the Australian Charter for Ovarian Cancer Research Excellence are:

1. **Common Agenda**
   • Develop a shared vision for change and a mutual plan of action involving a joint approach. The plan should be adaptive and responsive to environmental change and should deliver a clear value proposition.
   • Establish and implement national research priorities with the greatest potential to deliver impact in research, translation and development.
   • Participate in regular review and evolution of goals and priorities through established mechanisms.

2. **Collaboration**
   • Explore and develop collaborative approaches amongst funders, research organisations, researchers, clinicians, consumers and the community to appropriately resource, review and deliver high impact research and development programs.
   • Enable sharing of resources, information and outcomes as a fundamental basis for an effective research and clinical effort - a strong basic and applied research base, access to patient populations, and an integrated and standardised dataset of longitudinal molecular, clinical and outcomes data.

3. **Consumer involvement**
   • Increase meaningful engagement across the spectrum, including in advocacy activities and in research planning, review, participation (e.g. the establishment of appropriate quality of life measures), conduct, evaluation and governance.

4. **Consistency**
   • Align efforts to develop a consistent approach towards the collection of specimens and data and the analysis of results.
   • Develop an evaluation framework to span the research and development continuum so as to improve our ability to measure research impact and progress. Research would be assessed to determine what knowledge was produced and how it was disseminated, whether that knowledge contributes to the development of products, policies or clinical guidelines, as well as what health sector, social and/or economic benefits it provides.
5. Transparent communication
- Communicate consistently and openly with funders, research organisations, researchers, clinicians, consumers and the community to engage, build trust, assure shared objectives and to recognise and work to overcome barriers to development.
- Adopt transparent and accountable standards for the public reporting of ovarian cancer infrastructure, research, clinical and development funding and achievements.

6. Backbone support
- Ensure there is adequate resourcing to enable the required support for independent administration, funding, evaluation, reporting and to enable transparent and accountable practice.

Figure 19: The key domains of the Australian Charter for Ovarian Cancer Research Excellence

We commend to you the National Action Plan for Ovarian Cancer Research. This Plan is the first of its kind for ovarian cancer research in Australia. With your support, it will have the potential to make a significant difference in the lives of women at risk of, or living with, ovarian cancer.
FUNDING SOURCES

Funding data for ovarian cancer were obtained over the years 2008–2013. NHMRC funding data were obtained from https://www.nhmrc.gov.au/_files_nhmrc/file/grants/dataset/2014/cancer_nhpa_2000_2013.xlsx. Data accessed March, 2013.

Estimates of funding in ovarian cancer were also obtained, where possible, from searchable registers on the websites of the following organisations: Cancer Australia, ARC, Cancer Council Australia and state-based Cancer Councils, Fight Cancer Foundation, VCA, NBCF and NIH. For some other organisations listed in Table 2, the information was available in annual reports, although for many, it was difficult to find funding information. For example, some state-based government organisations and many not-for-profit organisations had limited public disclosure. Although most (but not all) organisations publish annual reports, they often do not list research grants by both description and funding amount. In some cases, funded grants are listed without the amount, or just aggregate amounts.

Modifications were made to grants that focused on more than one tumour stream. Estimates of the proportion of funding allocated to the ovarian cancer research components of these studies were obtained by dividing the funding by the number of tumour streams identified (from the title, description or key words, when provided) or directly from investigators, where possible. Otherwise the full funding amount was used.

Annual reports for public companies conducting research and development in ovarian cancer were also examined to identify funding sources and track their allocations to research. Only data that was clearly directed towards ovarian cancer research programs was included in the analysis. In general, it was not possible to obtain information from private companies.

To help fill in the funding information gaps, researchers and clinicians involved in leading ovarian cancer research in Australia were identified from publications and contacted directly with a request for information on grants received over 2008-2013. Overall, the rate of response was low (<30%), and some respondents declined to disclose information, citing confidentiality restrictions. However, the level of detail provided by compliant respondents increased the amount of funding information available for this audit.

LITERATURE

The database pubmed (http://www.ncbi.nlm.nih.gov/pubmed) was accessed to identify peer reviewed publications that list one or more Australian authors using the search terms “ovarian cancer and Australia” or “ovarian cancer and Australian” published over the time period 1/1/2008-31/12/2013. Information retrieved from pubmed included the Title, Citation and Abstract. From the resulting dataset, each entry was reviewed manually for coding according to CSO categories (Appendix V). Inclusions from the dataset included publications resulting from original research, with one or more Australian-based authors or where the study was conducted in Australia wholly, or as a part of an international collaboration. Exclusions from the dataset included citations without an abstract, where the subject matter did not relate directly to ovarian cancer or where there was no Australian author or otherwise, no genuine Australian connection. In general, reviews and case studies were excluded from the dataset unless there was a new insight or specific outcome revealed. Where the abstract did not provide sufficient information to make a determination, the full publication was accessed and reviewed.

For comparisons to research output in other countries, the term “Australia” was substituted for the country in question e.g. “USA”.

Journal IF data were obtained from Web of Science listings (71). Each data listing was assigned the IF value for the appropriate year, except for 2013 where values for 2012 were used (2013 values not having been published at the date of the analysis). Where the appropriate year listing was not available, either the 5-year IF for that journal was used, or the closest year if the former was not available. Publications in journals lacking a published IF value were excluded from this analysis.
Pubmed Citation Indices were obtained from the individual Pubmed listings.

**MEASURING OVARIAN CANCER INCIDENCE**

Statistics for ovarian cancer incidence were obtained for several countries to enable comparisons across key metrics. Data was obtained for: Australia, USA, Canada, Japan, UK and NZ. Data for each country was obtained from the Globocan 2012 database (http://globocan.iarc.fr, accessed Aug 2014).

**CLINICAL**

The NIH database, www.clinicaltrials.gov, was used to identify clinical trials in ovarian cancer that were registered over the review period 2008-2013. Search terms included “ovarian cancer” in the trial indication. To measure the number of trials conducted in Australia, search terms included the requirement for one or more clinical trials sites in Australia.

For comparison to other countries, the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) was searched by country for trials conducted with ovarian cancer as the therapeutic indication. It was not possible to specify the timeframe, therefore all trials since 1994 were analysed (data downloaded March, 2014).

For further detail on trials conducted in Australia, the ANZCTR database was used (http://www.anzctr.org.au/).

**STAKEHOLDER CONSULTATION METHODOLOGY**

A number of mechanisms were implemented to engage key stakeholders in the process of developing the Plan. Consultation methods have included the conduct of a series of stakeholder interviews (administered by ZEST Health Strategies as an independent third party) and two multidisciplinary consultation workshops on 28 and 29 March during the ANZGOG 2014 Annual Scientific Meeting in Canberra. The purpose of the stakeholder interviews and workshops were to:

- seek opinions from key stakeholders involved in conducting and funding research on the value of current ovarian cancer research activity in Australia
- assess the impact of ovarian cancer research for individual consumers and health professionals, health services and the healthcare system
- identify future priorities for ovarian cancer research
- identify key international evidence that may inform Australian research priorities.

Over 50 stakeholders representing clinicians, consumers, researchers, and representatives from medical research institutions, industry, not-for-profit and government organisations were invited to participate in the consultation process. Of these, 32 invitees accepted. Consultations were conducted by telephone interview of approximately one hour duration, using a semi-structured interview format.

In addition to this, more than 50 stakeholders (including ASGO members attending ANZGOG 2014) were invited, and 36 stakeholders attended one of two half-day workshops (15 stakeholders on Friday and 21 on Saturday). Note that some stakeholders who attended the workshops also contributed to the telephone interviews prior to or following the workshops. Participants in the consultation and workshops are listed in Appendix II.

Reports outlining key themes from stakeholder interviews (in a de-identified form) and workshops have been produced by ZEST Health Strategies outlining themes and outcomes from the interviews and workshops. These findings have been incorporated into this Plan.
The following people contributed through participation in consultation interviews, workshops or the provision of expert opinion pieces on selected topics, as designated throughout the report. Participation in workshops, consultation interviews, the working group or as a key opinion leader should not be construed as endorsement of the final report by those listed and/or their organisations.

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Mr Richard De Abreu Lourenco</td>
<td>Research organisation</td>
</tr>
<tr>
<td></td>
<td>Centre for Health Economics Research and Evaluation (CHERE)/</td>
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<tr>
<td></td>
<td>Cancer Research Economics Support Team (CREST), University of Technology</td>
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<td></td>
<td>Sydney, NSW</td>
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<td>Ms Sharon Andrews</td>
<td>Industry</td>
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<td></td>
<td>Roche Pharmaceutical Company, Senior Executive</td>
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<td>Ms Jan Antony</td>
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<tr>
<td>Associate Professor Philip Beale</td>
<td>Clinician researcher</td>
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<td></td>
<td>Clinical Director of Cancer Services, Sydney Local Health District, NSW</td>
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<tr>
<td>Ms Paula Benson</td>
<td>Consumer</td>
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<td></td>
<td>Ovarian Cancer Australia Board of Directors, Vic</td>
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<tr>
<td>Dr David Bernshaw</td>
<td>Radiation Oncologist</td>
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<td></td>
<td>Peter MacCallum Cancer Centre, Vic; Director, ANZGOG</td>
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<td>Ms Joy Boulos</td>
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<td>Professor David Bowtell</td>
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<td></td>
<td>Head, Cancer Genomics and Genetics Program, Peter MacCallum Cancer</td>
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<td></td>
<td>Centre, Vic; Principal Investigator, AOCS</td>
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<tr>
<td>Ms Sue Brew</td>
<td>Clinical Trial Coordinator</td>
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<td></td>
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<tr>
<td>Professor Phyllis Butow</td>
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<td></td>
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<tr>
<td>Professor Georgia Chenevix-Trench</td>
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<td></td>
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<tr>
<td>Ms Jenny Chynoweth</td>
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<td></td>
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<td>Professor David Currow</td>
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<td>Professor Margaret Davy</td>
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<td>Professor Lynette Denny</td>
<td>Gynaecological Oncologist</td>
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<td></td>
<td>Chair and Professor of Obstetrics &amp; Gynaecology &amp; registered sub-specialist in Gynaecological Oncology at Groote Schuur Hospital &amp; University of Cape Town, South Africa</td>
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<tr>
<td>Mr Warren Dickens</td>
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<td>Ms Alison Evans</td>
<td>Clinical research organisation</td>
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<td></td>
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<tr>
<td>Professor Anna de Fazio</td>
<td>Researcher</td>
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<tr>
<td></td>
<td>Head of the Gynaecological Oncology Research Group, Westmead Millennium Institute; Head of research (Gynaecological Oncology), Westmead Hospital and Professor of Translational Cancer Research, Sydney West Translational Cancer Research Centre, NSW</td>
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<td>Ms Jane Francis</td>
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<td>Professor Michael Friedlander</td>
<td>Medical Oncologist</td>
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<td>Conjoint Professor of Medicine, University of NSW &amp; Director of Medical Oncology, Prince of Wales Hospital, Sydney NSW</td>
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<tr>
<td>Dr Gregory Gard</td>
<td>Gynaecological Oncologist</td>
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<td>Dr Jeffrey Goh</td>
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<td>Icon Cancer Care, Brisbane, QLD</td>
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<td>Mr Simon Lee</td>
<td>Consumer</td>
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<td></td>
<td>Board Director (and Founder), Ovarian Cancer Australia, Vic</td>
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<tr>
<td>Professor Marion Haas</td>
<td>Researcher</td>
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<td></td>
<td>Professor of Health Economics and Deputy Director CHERE/CREST, University of Technology Sydney, NSW</td>
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<tr>
<td>Professor Neville Hacker</td>
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<td>Royal Women's Hospital, Melbourne, Vic</td>
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<tr>
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<td>Obstetrician and Gynaecologist</td>
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| Professor Ian Jacobs        | Clinician Researcher  
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<td>Nursing</td>
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<td>Cancer Nurse Coordinator, Gynaecological Cancer, WA Cancer and Palliative</td>
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<td>Professor Patsy Yates</td>
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### APPENDIX III: GLOSSARY

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<th>Definition</th>
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<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
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<td>ANZGOG</td>
<td>Australia New Zealand Gynaecological Oncology Group</td>
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<tr>
<td>AOCS</td>
<td>Australian Ovarian Cancer Study</td>
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<tr>
<td>ARIDIA</td>
<td>Tumour suppressor gene</td>
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<tr>
<td>ARC</td>
<td>Australian Research Council</td>
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<tr>
<td>ASCO</td>
<td>The American Society of Clinical Oncologists</td>
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<tr>
<td>Avastin®</td>
<td>US brand name for bevacizumab</td>
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<tr>
<td>bevacizumab</td>
<td>A recombinant humanised monoclonal antibody directed against the vascular endothelial growth factor and used in the treatment of cancers, including ovarian cancer in Australia</td>
</tr>
<tr>
<td>BRCA/BRCA1/BRCA2</td>
<td>Breast cancer, early onset – genes that produce tumour suppressor proteins that help repair DNA. People with mutations in these genes have a higher than normal risk of breast, ovarian, prostate, and other types of cancer</td>
</tr>
<tr>
<td>CA</td>
<td>Cancer Australia</td>
</tr>
<tr>
<td>CA 125</td>
<td>Cancer antigen 125, a biomarker that may be elevated in the blood of some patients with specific types of cancers, including ovarian cancer</td>
</tr>
<tr>
<td>CC</td>
<td>Cancer Council</td>
</tr>
<tr>
<td>CCC</td>
<td>clear cell carcinoma</td>
</tr>
<tr>
<td>CCQ</td>
<td>Cancer Council Queensland</td>
</tr>
<tr>
<td>CC NSW</td>
<td>Cancer Council NSW</td>
</tr>
<tr>
<td>CC SA</td>
<td>Cancer Council SA</td>
</tr>
<tr>
<td>CCT</td>
<td>Cancer Council Tasmania</td>
</tr>
<tr>
<td>CCV</td>
<td>Cancer Council Victoria</td>
</tr>
<tr>
<td>CFWA</td>
<td>Cancer Foundation WA</td>
</tr>
<tr>
<td>CRLF</td>
<td>Cancer Research Leadership Forum (Au)</td>
</tr>
<tr>
<td>CSO</td>
<td>Common Scientific Outline</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life years - a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>EC</td>
<td>Endometrioid cancer</td>
</tr>
<tr>
<td>EOC</td>
<td>Epithelial ovarian cancer</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (USA)</td>
</tr>
<tr>
<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
</tr>
<tr>
<td>FOX2</td>
<td>Also known as RBM9, it is RNA binding motif protein 9, encoded by the RBM9 gene</td>
</tr>
<tr>
<td>GCT</td>
<td>Granulosa Cell Tumour</td>
</tr>
<tr>
<td>HGSC</td>
<td>High grade serous cancer, also known as high grade serous ovarian cancer</td>
</tr>
<tr>
<td>HR</td>
<td>Homologous recombination</td>
</tr>
<tr>
<td>ICRP</td>
<td>International Cancer Research Partnership</td>
</tr>
<tr>
<td>IF</td>
<td>Impact factor</td>
</tr>
<tr>
<td>IM</td>
<td>Immuno-modulatory agents</td>
</tr>
<tr>
<td>INPP4B</td>
<td>Gene encodes the inositol polyphosphate 4-phosphatase type II, one of the enzymes involved in phosphatidylinositol signaling pathways</td>
</tr>
<tr>
<td>KConFab</td>
<td>Kathleen Cunningham Foundation Consortium for research into Familial Breast cancer</td>
</tr>
<tr>
<td>KOL</td>
<td>Key opinion leader</td>
</tr>
<tr>
<td>LNG-IUD</td>
<td>Levonorgestrel-releasing intra-uterine device</td>
</tr>
<tr>
<td>LGSC</td>
<td>Low grade serous cancer</td>
</tr>
<tr>
<td>MC</td>
<td>Mucinous cancer</td>
</tr>
<tr>
<td>MEK inhibitors</td>
<td>A chemical or drug that inhibits the mitogen-activated protein kinase enzymes MEK1 and/or MEK2</td>
</tr>
<tr>
<td>MTT</td>
<td>Molecular targeted therapy</td>
</tr>
<tr>
<td>NBCF</td>
<td>National Breast Cancer Foundation</td>
</tr>
<tr>
<td>NBOCC</td>
<td>National Breast and Ovarian Cancer Centre</td>
</tr>
<tr>
<td>NFP</td>
<td>Not for profit organisation</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institute of Health (USA)</td>
</tr>
<tr>
<td>OCP</td>
<td>Oral contraceptive pill</td>
</tr>
<tr>
<td>Olaparib</td>
<td>A small molecule - inhibitor of the nuclear enzyme poly (ADP-ribose) polymerase (PARP) with potential chemosensitising, radiosensitising, and antineoplastic activities</td>
</tr>
<tr>
<td>OPAL</td>
<td>Ovarian cancer prognosis and lifestyle study</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>p13/AKT</td>
<td>Phosphoinositide 3-kinase and protein kinase B (PKB), both kinases involved in intracellular signalling important in apoptosis and hence cancer</td>
</tr>
<tr>
<td>p53</td>
<td>A tumour suppressor protein encoded by the TP53 gene</td>
</tr>
<tr>
<td>PdCCRS</td>
<td>Priority-driven Collaborative Cancer Research Scheme (Cancer Australia)</td>
</tr>
<tr>
<td>PDX</td>
<td>Patient-derived xenograft</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission topography</td>
</tr>
<tr>
<td>PLCO Cancer Screening Trial</td>
<td>Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial</td>
</tr>
<tr>
<td>PMCC</td>
<td>Peter McCallum Cancer Centre</td>
</tr>
<tr>
<td>POC</td>
<td>Proof-of-concept</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient reported outcome</td>
</tr>
<tr>
<td>QCF</td>
<td>Queensland Community Foundation</td>
</tr>
<tr>
<td>QIMR</td>
<td>Queensland Institute of Medical Research</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>ROCA</td>
<td>Risk of ovarian cancer algorithm</td>
</tr>
<tr>
<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
</tr>
<tr>
<td>TPS3</td>
<td>A tumour suppressor gene</td>
</tr>
<tr>
<td>TVUS</td>
<td>Trans-vaginal ultrasound</td>
</tr>
<tr>
<td>UKCTOCS</td>
<td>UK Collaborative Trial of Ovarian Cancer Screening</td>
</tr>
<tr>
<td>UKFOCSS</td>
<td>UK Familial Ovarian Cancer Screening Study</td>
</tr>
<tr>
<td>UM</td>
<td>The University of Melbourne</td>
</tr>
<tr>
<td>UQ</td>
<td>The University of Queensland</td>
</tr>
<tr>
<td>WARTN</td>
<td>Western Australia Research Tissue Network</td>
</tr>
<tr>
<td>WGOTB</td>
<td>Westmead Gynaecological Oncology Tissue Bank</td>
</tr>
<tr>
<td>WEHI</td>
<td>Walter and Eliza Hall Institute</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>WICR</td>
<td>Westmead Institute for Cancer Research now known as Westmead Millenium Institute, Centre for Cancer Research</td>
</tr>
<tr>
<td>YLL</td>
<td>Years of life lost</td>
</tr>
</tbody>
</table>
APPENDIX IV: DESCRIPTION of CSO CATEGORIES

These description was obtained directly from https://www.icrpartnership.org/CSO.cfm

<table>
<thead>
<tr>
<th>CSO category</th>
<th>Description and examples of science that would fit designated category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Biology</td>
<td>Biology of how cancer starts and progresses as well as normal biology relevant to these processes</td>
</tr>
</tbody>
</table>
| 1.1 Normal Functioning | - Developmental biology (from conception to adulthood)/ biology of ageing  
- Normal functioning of genes, including their identification and expression, and the normal function of gene products, such as hormones and growth factors  
- Normal formation of the extracellular matrix  
- Normal cell-to-cell interactions  
- Normal functioning of apoptotic pathways |
| 1.2 Cancer Initiation: Alterations in Chromosomes | - Abnormal chromosome number  
- Aberration in chromosomes and genes  
- Damage to chromosomes and mutation in genes  
- Failures in DNA repair  
- Aberrant gene expression  
- Epigenetics  
- Genes and proteins involved in aberrant cell cycles |
| 1.3 Cancer Initiation: Oncogenes and Tumour Suppressor Genes | - Genes and signals involved in growth stimulation or repression, including oncogenes (Ras, etc.), and tumour suppressor genes (p53, etc.)  
- Effects of hormones and growth factors and their receptors such as oestrogens, androgens, TGF-beta, GM-CSF, etc. |
| 1.4 Cancer Progression and Metastasis | - Latency, promotion, and regression  
- Expansion of malignant cells  
- Interaction of malignant cells with the immune system or extracellular matrix  
- Cell mobility, including detachment, motility, and migration in the circulation  
- Invasion  
- Malignant cells in the circulation, including penetration of the vascular system and extravasation  
- Systemic and cellular effects of malignancy  
- Tumour angiogenesis and growth of metastases  
- Role of hormone or growth factor dependence/independence in cancer progression |
| 1.5 Resources and Infrastructure | - Informatics and informatics networks  
- Specimen resources; Reagents, chemical standards  
- Epidemiological resources pertaining to biology  
- Education and training of investigators |
<table>
<thead>
<tr>
<th>CSO category</th>
<th>Description and examples of science that would fit designated category</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Aetiology</td>
<td>Identify the causes or origins of cancer - genetic, environmental, and lifestyle, and the interactions between these factors</td>
</tr>
</tbody>
</table>
| 2.1 Exogenous Factors in the Origin and Cause of Cancer | • Lifestyle factors such as smoking, chewing tobacco, alcohol consumption, parity, diet, sunbathing, and exercise  
• Environmental and occupational exposures such as radiation, second-hand smoke, radon, asbestos, organic vapours, pesticides, and other chemical or physical agents  
• Infectious agents associated with cancer aetiology, including viruses and bacteria  
• Viral oncogenes and viral regulatory genes associated with cancer causation |
| 2.2 Endogenous Factors in the Origin and Cause of Cancer | • Free radicals such as superoxide and hydroxide radicals  
• Genes known to be involved or suspected of being mechanistically involved in familial cancer syndromes; for example, BRCA1, Ataxia Telangiectasia, and APC  
• Genes suspected or known to be involved in “sporadic” cancer events; for example, polymorphisms and/or mutations that may affect carcinogen metabolism (e.g., CYP, NAT, glutathione transferase, etc.) |
| 2.3 Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors | • Gene-environment interactions  
• Interactions of genes with lifestyle factors, environmental, and/or occupational exposures such as variations in carcinogen metabolism associated with genetic polymorphisms  
• Interactions of genes and endogenous factors such as DNA repair deficiencies and endogenous DNA damaging agents such as oxygen radicals or exogenous radiation exposure |
| 2.4 Resources and Infrastructure Related to Aetiology | • Informatics and informatics networks; for example, patient databanks  
• Specimen resources (serum, tissue, etc.)  
• Reagents and chemical standards  
• Epidemiological resources pertaining to etiology  
• Statistical methodology or biostatistical methods  
• Centers, consortia, and/or networks; Education and training of investigators |
| 3. Prevention | Identifying interventions which reduce cancer risk by reducing exposure to cancer risks and increasing protective factors. Interventions may target lifestyle or may involve drugs or vaccines |
| 3.1 Interventions to Prevent Cancer: Personal Behaviours That Affect Cancer Risk | • Research on determinants of personal behaviours, such as diet, physical activity, sun exposure, and tobacco use, that affect cancer risk  
• Interventions to change personal behaviours that affect cancer risk |
| 3.2 Nutritional Science in Cancer Prevention | • Quantification of nutrients and micronutrients  
• Studies on the effect(s) of nutrients or nutritional status on cancer incidence  
• Dietary assessment efforts, including dietary questionnaires and surveys  
• Development, characterization, and validation of dietary/nutritional assessment instruments |
<table>
<thead>
<tr>
<th>CSO category</th>
<th>Description and examples of science that would fit designated category</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3 Chemoprevention</td>
<td>• Chemopreventive agents and their discovery, mechanism of action, development, testing in model systems, and clinical testing</td>
</tr>
<tr>
<td>3.4 Vaccines</td>
<td>• Vaccines for prevention, their discovery, mechanism of action, development, testing in model systems, and clinical testing</td>
</tr>
</tbody>
</table>
| 3.5 Complementary and Alternative Prevention      | • Discovery, development, and testing of complementary/alternative prevention approaches such as diet, herbs, supplements, or other interventions that are not widely used in conventional medicine or are being applied in different ways as compared to conventional medical uses  
• Hypnotherapy, relaxation, transcendental meditation, imagery, spiritual healing, massage, biofeedback, etc., used as a preventive measure |
| 3.6 Resources and Infrastructure Related to       | • Informatics and informatics networks; for example, patient databanks  
• Specimen resources (serum, tissue, etc.)  
• Epidemiological resources pertaining to prevention  
• Clinical trials infrastructure  
• Statistical methodology or biostatistical methods  
• Centres, consortia, and/or networks  
• Education and training                                                                                                                                                                                      |
| Prevention                                        |                                                                                                                                                                                                                                                                           |
| 4. Early Detection, Diagnosis, and Prognosis      | Identifying and testing cancer markers and imaging methods that are helpful in detecting and/or diagnosing cancer as well as predicting the outcome or chance of recurrence                                                                                                      |
| 4.1 Technology Development and/or Marker Discovery| • Discovery of markers (e.g., proteins, genes), and/or technologies (such as fluorescence, nanotechnology, etc.) that are potential candidates for use in cancer detection, staging, diagnosis, and/or prognosis  
• Use of proteomics, genomics, expression assays, or other technologies in the discovery of markers                                                                                                                                                                |
| 4.2 Technology and/or Marker Evaluation With      | • Development, refinement, and preliminary evaluation (e.g., animal trials and Phase I human trials)  
• Preliminary evaluation with respect to laboratory sensitivity, laboratory specificity, reproducibility, and accuracy  
• Research into mechanisms assessing tumour response to therapy at a molecular or cellular level                                                                                                                                                                      |
| Respect to Fundamental Parameters of Method       |                                                                                                                                                                                                                                                                           |
| 4.3 Technology and/or Marker Testing in a Clinical| • Evaluation of clinical sensitivity, clinical specificity, and predictive value (Phase II or III clinical trials)  
• Quality assurance and quality control  
• Inter- and intra-laboratory reproducibility  
• Testing of the method with respect to effects on morbidity and/or mortality  
• Study of screening methods, including compliance, acceptability to potential screenees, and receiver-operator characteristics  
• Research into improvements in techniques to assess clinical response to therapy                                                                                                                                                                       |
<table>
<thead>
<tr>
<th>CSO category</th>
<th>Description and examples of science that would fit designated category</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4 Resources and Infrastructure Related to Detection, Diagnosis, or Prognosis</td>
<td>• Informatics and informatics networks; for example, patient databanks&lt;br&gt;• Specimen resources (serum, tissue, images, etc.)&lt;br&gt;• Clinical trials infrastructure&lt;br&gt;• Epidemiological resources pertaining to risk assessment, detection, diagnosis, or prognosis&lt;br&gt;• Statistical methodology or biostatistical methods&lt;br&gt;• Centres, consortia, and/or networks&lt;br&gt;• Education and training of investigators</td>
</tr>
<tr>
<td>5. Treatment</td>
<td>Identifying and testing treatments administered locally (such as radiotherapy and surgery) and systemically (treatments like chemotherapy which are administered throughout the body) as well as non-traditional (complementary/alternative) treatments (such as supplements, herbs). Research into the prevention of recurrence is also included here</td>
</tr>
<tr>
<td>5.1 Localised Therapies - Discovery and Development</td>
<td>• Discovery and development of treatments administered locally that target the organ and/or neighbouring tissue directly, including but not limited to surgical interventions and radiotherapy&lt;br&gt;• Therapies with a component administered systemically but that act locally (e.g., photodynamic therapy, radioimmunotherapy and radiosensitisers)&lt;br&gt;• Development of methods of drug delivery&lt;br&gt;• Localised therapies to prevent recurrence</td>
</tr>
<tr>
<td>5.2 Localised Therapies - Clinical Applications</td>
<td>• Clinical testing and application of treatments administered locally that target the organ and/or neighbouring tissue directly, including but not limited to surgical interventions and radiotherapy&lt;br&gt;• Clinical testing and application of therapies with a component administered systemically but that act locally (e.g., photodynamic therapy and radiosensitisers)&lt;br&gt;• Phase I, II, or III clinical trials of promising therapies that are administered locally&lt;br&gt;• Side effects, toxicity, and pharmacodynamics&lt;br&gt;• Clinical testing of localised therapies to prevent recurrence</td>
</tr>
<tr>
<td>5.3 Systemic Therapies - Discovery and Development</td>
<td>• Discovery and development of treatments administered systemically such as cytotoxic or hormonal agents, novel systemic therapies such as immunologically directed therapies (vaccines, antibodies), gene therapy, angiogenesis inhibitors, apoptosis inhibitors, and differentiating agents&lt;br&gt;• Defining molecular signatures of cancer cells&lt;br&gt;• Molecular targets for drug discovery. Includes mechanistic studies of cellular metabolism, combinatorial chemical synthesis, drug screening, development of high-throughput assays, and testing in model systems&lt;br&gt;• Molecular mechanisms of drug resistance and pre-clinical evaluation of therapies to circumvent resistance&lt;br&gt;• Development of methods of drug delivery&lt;br&gt;• Development of systemic therapies to prevent recurrence</td>
</tr>
<tr>
<td>CSO category</td>
<td>Description and examples of science that would fit designated category</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 5.4 Systemic Therapies - Clinical Applications | • Clinical testing and application of treatments administered systemically such as cytotoxic or hormonal agents, novel systemic therapies such as immunologically directed therapies (vaccines, antibodies), gene therapy, angiogenesis inhibitors, apoptosis inhibitors, and differentiating agents  
• Phase I, II, or III clinical trials of promising therapies administered systemically  
• Side effects, toxicity, and pharmacodynamics  
• Clinical testing of systemic therapies to prevent recurrence |
| 5.5 Combinations of Localised and Systemic Therapies | • Development and testing of combined approaches to treatment  
• Clinical application of combined approaches to treatment such as systemic cytotoxic therapy and radiation therapy  
• Development and clinical application of combined localised and systemic therapies to prevent recurrence |
| 5.6 Complementary and Alternative Treatment Approaches | • Discovery, development, and clinical application of complementary/alternative treatment approaches such as diet, herbs, supplements, natural substances, or other interventions that are not widely used in conventional medicine or are being applied in different ways as compared to conventional medical uses  
• Complementary/alternative approaches to the prevention of recurrence (please note that primary prevention using complementary or alternative approaches should be coded under 3.5) |
| 5.7 Resources and Infrastructure Related to Treatment and the prevention of recurrence | • Informatics and informatics networks; for example, clinical trials networks and databanks; Clinical trial groups  
• Mathematical and computer simulations; Statistical methodology or biostatistical methods  
• Specimen resources (serum, tissue, etc.)  
• Epidemiological resources pertaining to treatment  
• Drugs and reagents for distribution and drug screening infrastructures  
• Centres, consortia, and/or networks; Education & training |
| 6. Cancer Control, Survivorship, and Outcomes Research | This category includes a broad range of areas: patient care and pain management; tracking cancer cases in the population; beliefs and attitudes that affect behaviour regarding cancer control; ethics, education and communication approaches for patients and health care professionals; supportive and end-of-life care; and health care delivery in terms of quality and cost effectiveness |
| 6.1 Patient Care and Survivorship Issues | • Quality of life; Pain management; Psychological impacts of cancer survivorship; Rehabilitation; Reproductive issues; Long-term morbidity  
• Symptom management, including nausea, vomiting, lymphedema, neuropathies, etc.  
• Prevention of treatment-related toxicities and sequelae, including symptom management, prevention of mucositis, prevention of cardiotoxicities, etc. |
| 6.2 Surveillance | • Epidemiology and end results reporting (e.g., SEER)  
• Surveillance of cancer risk factors such as diet, body weight, physical activity, sun exposure, and tobacco use  
• Analysis of variations in risk factor exposure by demographic or other factors  
• Registries that track incidence, morbidity, and/or mortality related to cancer  
• Trends in use of interventional strategies  
• Method development for risk factor surveillance |
<table>
<thead>
<tr>
<th>CSO category</th>
<th>Description and examples of science that would fit designated category</th>
</tr>
</thead>
</table>
| **6.3 Behaviour**                                | • Behavioural medicine research and interventions  
• Influence of social factors such as community, policy, education, and legislation, on behaviours related to cancer control  
• Attitudes and belief systems and their influence on psychological health and on behaviours related to cancer control. For example, how beliefs can alter attempts to seek screening, detection, and treatment  
• Interventions to change attitudes and beliefs that affect behaviour related to cancer control and cancer outcomes  
• Influences of attitudes and beliefs on compliance with treatment and prevention protocols  
• Psychological or educational interventions to promote behaviours that lessen treatment-related morbidity and promote psychological adjustment to the diagnosis of cancer and to treatment effects  
• Burdens of cancer on family members/caregivers and psychological/behaviour issues   |
| **6.4 Cost Analyses and Health Care Delivery**   | • Analyses of the cost effectiveness of methods used in cancer prevention, detection, diagnosis, prognosis, treatment, and survivor care/support  
• Development and testing of health service delivery methods  
• Interventions to increase the quality of health care delivery  
• Impact of organisational, social, and cultural factors on access and quality of care  
• Studies of providers such as geographical or care-setting variations in outcomes  
• Effect of reimbursement and/or insurance on cancer control, outcomes, and survivorship support  
• Access to care issues  
• Health services research, including health policy and practice  
• Analysis of health service provision, including the interaction of primary and secondary care; cost-effectiveness of treatments |
| **6.5 Education and Communication**             | • Development of communication tools and methods  
• Education of patients, health care providers, at-risk populations, and the general population about cancer  
• Communication to patients regarding therapeutic options  
• Educational interventions to promote self-care and symptom management  
• Communicating cancer risk to underserved populations, at-risk populations, and the general public  
• Alternative teaching methods to communicate therapeutic options and risk-reduction behaviour to patients and the general public  
• Communication of lifestyle models that reduce cancer risk, such as communication of nutritional interventions  
• Communicating smoking and tobacco cessation interventions  
• Special approaches and considerations for underserved and at-risk populations  
• Education, information, and prevention/screening/assessment systems for the general public, primary care professionals, or policy makers  
• Training, predictive cancer models, pain management, and surveillance systems for primary care professionals, telehealth/telemedicine applications  
• Communication regarding cancer genetics, managed oncology care, and communicating with survivors  
• Barriers to successful health communication |
<table>
<thead>
<tr>
<th>CSO category</th>
<th>Description and examples of science that would fit designated category</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.6 End-of-Life Care</td>
<td>• End-of-life care issues, including palliative care, psychological interventions with families at end of life, hospice care, and pain management for terminally ill patients</td>
</tr>
</tbody>
</table>
| 6.7 Ethics and Confidentiality in Cancer Research                            | • Informed consent modelling and development  
• Quality of Institutional Review Boards (IRBs)  
• Protecting patient confidentiality and privacy; Research ethics |
| 6.8 Complementary and Alternative Approaches for Supportive Care of Patients and Survivors | • Hypnotherapy, relaxation, transcendental meditation, imagery, spiritual healing, massage, biofeedback, etc., as used for the supportive care of patients and survivors  
• Discovery, development, and testing of complementary/alternative approaches such as diet, herbs, supplements, or other interventions that are not widely used in conventional medicine or are being applied in different ways as compared to conventional medical uses |
| 6.9 Resources and Infrastructure Related to Cancer Control, Survivorship, and Outcomes Research | • Informatics and informatics networks  
• Clinical trial groups related to cancer control, survivorship, and outcomes research  
• Epidemiological resources pertaining to cancer control, survivorship, and outcomes research  
• Statistical methodology or biostatistical methods  
• Psychosocial, economic, political and health services research frameworks and models  
• Surveillance infrastructures; Centres, consortia, and/or networks  
• Education and training of investigators |
| 7. Scientific Model Systems                                                  | Development of new animal models, cell cultures and computer simulations and their application |
| 7.1 Development and Characterisation of Model Systems                        | • Development and characterisation of model systems, including but not limited to:  
- Computer-simulation model systems and computer software development  
- *In vitro* models systems  
- Cell culture model systems  
- Organ and tissue model systems  
- Animal model systems such as drosophila and *c. elegans*, zebra fish, mouse, etc. |
| 7.2 Application of Model Systems                                             | • Research into new ways of applying model systems, including but not limited to systems described in 7.1 |
| 7.3 Resources and Infrastructure Related to Scientific Model Systems         | • Models made available for distribution to the scientific community  
• Centres, consortia, and/or networks; Education and training of investigators |
APPENDIX V: CSO CATEGORY 5.3 BREAKDOWN

Entries coded in 5.3 (preclinical research) were sub-classified into 6 subcategories ranging from discovery to formal preclinical as outlined below.

1. Target identification

Identification and validation of drug targets, including proteins, genes, signals or pathways having the potential to be modulated either by blocking or enhancing activity and that could be used for developing targeting, cytotoxic or other therapies or for improving chemo-sensitivity; includes gene expression signatures.

2. Drug discovery

Testing/screening and validation of new molecular entities as chemotherapy agents, MTTs, biologics etc.

3. Drug reprofile

Testing of existing agents (either approved or in development) for other indications for the treatment of ovarian cancer

4. Combination

Testing combinations of existing agents for example, testing administration patterns, dosages, previously untested combinations

5. Drug delivery

Improved formulations or delivery mechanisms of known agents e.g. micelles, dendrimers, nanotechnology, carriers

6. Resistance

Testing agents for the development of resistance in experimental models

Within CSO 5.3, the stage of development was coded as Early Stage or Proof-of-Concept as follows:

- Early Stage
  - Target: the identification of gene or protein expression or signaling patterns using in vitro or cell-based assays
  - Drug discovery/Reprofile/Combination: screening or identifying agents that modulate a target; testing of samples in ovarian cancer cell lines (or other in vitro tests) for biomarker response, cytotoxicity or other signal

- Proof-of-Concept
  - Target: validation through knock-out studies, animal models of disease or ex vivo using human tumour samples
  - Drug Discovery/Reprofile/Combination: testing samples for efficacy in animal model of disease or ex vivo using human tissues samples; formal preclinical/development studies, for example, toxicology, pharmacokinetics or dosing studies
# APPENDIX VI: NOTABLE PUBLICATIONS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Key Finding</th>
<th>Au participation</th>
<th>AU funding</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Genome Atlas Research Network (2011) <em>Nature</em>: 609-15 CSO: 1</td>
<td>HGSOG characterised by TP53 mutation in 96% of tumours</td>
<td>Au Authors: D. Bowtell (PMCC); Speed, TP (WEHI)</td>
<td>None cited</td>
<td>International, very large collaboration (297 collaborators)</td>
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<td>Audeh MW, Carmichael J, Penson RT et al; (2010) <em>Lancet</em>: 245-251 CSO: 5</td>
<td>Phase II clinical study providing positive proof-of-concept of efficacy and tolerability of genetically targeted treatment with Olaparib in BRCA-mutated advanced ovarian cancer</td>
<td>Au Authors: Friedlander, M (Prince of Wales Cancer Centre, NSW); Scott, C (WEHI &amp; Royal Melbourne Hospital, Vic); Mitchell G (PMCC)</td>
<td>Industry funded (AstraZeneca)</td>
<td>International; large collaboration</td>
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<td>Reference</td>
<td>Key Finding</td>
<td>Au participation</td>
<td>AU funding</td>
<td>Other</td>
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<td>Coleman MP, Forman D, Bryant H et al. (2011) <em>Lancet</em>: 377(9760): 127-38</td>
<td>Estimation of survival, incidence and mortality in Au, Ca, Sweden, Denmark, Norway &amp; UK across breast, colorectal, lung and ovarian cancer</td>
<td>Au collaborators: Hacker, N (UNSW and Royal Women’s Hospital, Sydney); Tracey, E (CI NSW); Coory M &amp; Hill, D. (CCV); Boyager J (Westmead Breast Cancer Institute, NSW); Boyer M. (Sydney Cancer Centre); Spigelman A (UNSW)</td>
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<td>Review on genesis and evolution of HGSC</td>
<td>Au Author: Bowtell DD (PMCC, UM)</td>
<td>n/a</td>
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<td>Song H, Ramus SJ, Tyrer J et al. (2009) <em>Nat Genet</em>., 41(9): 996-1000</td>
<td>A genome wide association study to identify common ovarian cancer susceptibility alleles identified 12 SNPs at 9p22 associated with disease risk. This is the first common susceptibility locus for ovarian cancer to be established</td>
<td>Biobank: AOCS</td>
<td>NHMRC, CCT, CFWA</td>
<td>International, large collaboration</td>
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<td>Gewinner C, Wang ZC, Richardson A et al (2009) Cancer Cell, 16(2): 115-25 CSO: 1</td>
<td>Demonstrating that the phosphoinositide phosphatase INPP4B plays a role similar to that of PTEN in suppressing the PI3K/ AKT signaling pathway, thereby suppressing tumor growth. INPP4B is frequently deleted in a variety of solid tumors, including the majority of basal-like breast cancers. Results suggest that PI3K pathway inhibitors in current clinical trials may be effective in treating cancers where INPP4B is deleted</td>
<td>Biobank: AOCS</td>
<td>Not cited</td>
<td>International, medium size collaboration</td>
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†Collaboration size: Large > 10, medium 5-10, small < 5 collaborators
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