PROGRAMME

A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study

“Familial Aspects of Cancer 2017 Research and Practice”

Tuesday 29th August

COSA-HGSA Familial Cancer Clinics
Clinical Professional Day – Plantation Room

Supported by:

9.00 - 9.10   Welcome: Nicholas Pachter

FCC Session 1.
9.10 – 10.30   Genetic testing of tumour and tissue: when, why and how
                Chairperson: Helen Marfan

9.10 – 9.40   Mac Gardner
               Mosaicism: a clinical perspective

9.40 - 9.55   Mike Field
               Treatment focused tumour testing in ovarian cancer

9.55 – 10.15   Lesley Rawlins
               Tumour genetic testing in the diagnosis of familial cancer syndromes

10.15 – 10.30  Expert panel for discussion

10.30 – 11.00  Morning tea

FCC Session 2.
11.00 – 12.30  Update on the Genetics of Phaeochromocytoma
                Chairperson: Nicholas Pachter

11.00 – 11.25   Rory Clifton-Bligh
                Genetics of Hereditary Endocrine Neoplasms: moving forward with Bayes

"Familial Cancer 2017: Research and Practice"
11.25 - 11.50  Emma Duncan  
**Gene testing for PCC and phaeochromocytoma in the 21st century, and implications for clinical management.**

11.50 – 12.15  Anthony Gill  
**Pathology perspective**

12.15 – 12.30  Panel Discussion

12.30 – 1.30  **Lunch**

**FCC Session 3.**  
**Hereditary Renal Cancer: Syndromes, Signs and Surveillance**  
**Chairperson:** Margaret Gleeson

1.30 – 1.55  Ingrid Winship  
**Heritable Renal Cancer Syndromes**

1.55 – 2.20  Anthony Gill  
**Pathology perspective**

2.20 – 2.45  Simon Wood  
**Urologist perspective**

2.45 – 3.00  Panel discussion

3.00 – 3.30  **Afternoon Tea**

**FCC Session 4.**  
**Mainstreaming and models of service delivery**  
**Chairperson:** Lucinda Salmon

3.30 – 3.40  Simone Busija  
**Families Ties Foundation**

3.40 – 4.10  Marc Tischkowitz  
**How can we best integrate genetic testing into routine oncological practice?**

4. 10 – 4.40  Beth Crawford  
**Strategies for delivery of clinical cancer gene testing and genetic counselling to Cancer Center Clinics, Community Hospitals and Remote Patients**

4.40 – 4.55  Laura Forrest  
**Evaluation of a centralised national telephone genetic counselling service that facilitates BRCA1/2 testing for women with relapsed high-grade serous ovarian cancer**

4.55 – 5.15  Panel discussion
### Wednesday 30th August

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<tr>
<th>Time</th>
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<td>9.00–9.05</td>
<td><strong>Welcome:</strong></td>
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</table>
| 9.05–9.35 | Hanne Meijers-Heijboer                         | **Prophylactic mastectomy because of increased genetic risk and**  
|          | **What to do about low risk alleles?**        | **What to do about low risk alleles?**  |
| 9.40–10.00 | Terri McVeigh                                  | **The role of genomic profiling in adolescents and young adults (AYAs) with advanced cancer participating in Phase I clinical trials**  |
| 10.00–10.20 | Simone Rowley                                  | **Population genetic testing for breast and ovarian cancer susceptibility**  |
| 10.20–10.40 | Susan Ramus                                    | **Prognostic signature for high grade serous ovarian cancer**  |
| 10.40–11.10 | Morning Tea                                    |                                  |
|          | **Session 2**                                  | **Plantation Room**              |
| 11.10–11.40 | Mary Beth Terry                                 | **Risk-reducing oophorectomy and breast cancer risk across the spectrum of familial risk using a prospective family study cohort (ProF-SC)**  |
| 11.40–12.00 | Kelly Phillips                                  | **Acceptability and usability of iPrevent, a web-based decision support tool for assessment and management of breast cancer risk**  |
| 12.00–12.15 | Paul James                                     | **Common genomic variants modify the effect of Moderate risk breast cancer genes and can improve clinical interpretation.**  |
| 12.15–12.30 | Tatiane Yanes                                  | **Uptake of polygenic risk information among women at potentially high breast cancer risk**  |
| 12.30–12.45 | Alina Stoita                                   | **Pancreatic cancer screening in high risk individuals: A five-year update**  |
| 12.45–1.50 | Lunch                                         |                                  |

*ABCFS, ACCFS, kConFab and the International Sarcoma Kindred Study - Plantation Room*
Session 3  
**Plantation Room - New Projects**  
Chairperson: Lucinda Salmon

1.50 – 2.00  
Geoff Lindeman  
‘BRCA-P’: A randomized, double-blind, placebo-controlled, multi-centre, international phase 3 study to determine the preventive effect of denosumab on breast cancer in women carrying a BRCA1 germline mutation

2.00 – 2.10  
Kelly-Anne Phillips  
STICs and STONes: A Randomised Phase II Double-Blind Placebo-Controlled Trial of Aspirin in Chemoprevention of Ovarian Cancer in Women with BRCA1 and BRCA2 Mutations

2.10 – 2.20  
Rachel Delahunty  
TRACEBACK: Finding BRCA1 and BRCA2 mutations in women with ovarian cancer that predate changes to genetic testing guidelines

2.20 – 2.30  
Margaret Kelaher  
Better Indigenous Genetic health services (BIG health services)

2.30 – 2.40  
Mandy Ballinger  
The Genetic Cancer Risk in the Young Study (RisC Study)

2.40 – 2.50  
Nicole Cousens  
A new population BRCA 1/2 testing program offered to the Jewish community in Australia

2.50 – 3.00  
Laura Forrest  
National Australian online survey of women aged 18–40 years with a BRCA1/2 mutation: how are they managing their breast and ovarian cancer risk and how does this impact their young adulthood?

3.00 – 3.30  
**Afternoon Tea**

Session 4  
**Plantation Room**  
Chairperson: Melissa Southey

3.30 – 4.00  
Jos Jonkers  
Genetic dissection of BRCA-associated breast cancer in mouse models

4.00 – 4.20  
Laura Porter  
High-risk pathological and genomic features of BRCA2-mutant prostate cancer

4.20 – 4.40  
Peter Savas  
The sub-clonal architecture of metastatic breast cancer: Results from a prospective community-based rapid autopsy program “CASCADE”
4.40 – 5.00  Peter Simpson  
*Mutation Landscape of Familial Breast Cancer*

5.00 – 5.20  Georgia Chenevix-Trench  
*A large transcriptome-wide association study in nearly 230,000 women of European descent identifies novel breast cancer susceptibility loci and genes, including PIDD1*

6.00 – 7.30  Poster Session + Wine and Cheese in the main foyer

6.15  
*Plantation Room*  
Chairperson: Bruce Hopper  
*Order of Abstract Presentation: 3 minute rapid oral presentations*

Thomas Green.  Hi-Plex Origin for high-throughput screening of disease genes.

Kylie Gorringe.  Copy number alterations associated with the progression of premalignant breast lesions to breast carcinoma.

Tu Nguyen-Dumont.  BRA-STRAP BrCa Refined Analysis of Sequence Tests: Risk And Penetrance

Somayeh Ahmadloo.  Analysis of RAD51C as breast cancer susceptibility gene in breast cancer families

Shona O’Connell.  Screening Victorian women with endometrial cancer for Lynch Syndrome - Final results

Meera Warby.  The TARGET pilot study initial results: A model for informing the PRISM Precision Medicine Trial in Paediatric Cancer

Krystal Barter.  Pink Hope – Know Your Risk Tool

**Delegates organise their own dinner**
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**9.00 – 9.05**

The Jeremy Jass Memorial Lecture
Introduction: Mark Jenkins

**9.05 – 9.35**

John Hopper
Reflections on a generation of work on familial aspects of cancer

**9.35 – 9.55**

Mark Jenkins.
Revision of the Colorectal Cancer Screening Guidelines: Family History

**9.55 – 10.15**

Aung Ko Win
Potential Difference in Colorectal Cancer Risk for Lynch Syndrome by Geographic Location of Mutation Carriers: Preliminary Result from the International Mismatch Repair Consortium (IMRC)

**10.15 – 10.30**

Elise Cannan
A risk management clinic model of care improves adherence to screening colonoscopy in patients with Lynch syndrome

**10.30 - 11.00**

Morning tea

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**11.00 – 11.30**

James Flanagan
Epigenome-Wide Association Studies for breast and ovarian cancer risk using whole genome and target captured bisulphite sequencing

**11.30 – 11.50**

Ifrah Khalid
Heritable methylation risk factors for familial breast cancer

**11.50 – 12.10**

Ee Ming Wong
Aberrant DNA methylation marks in mutation-negative early-onset breast cancer

**12.10 – 12.30**

Lez Burke
Bioinformatic and functional evaluation of rare variants in the 5’ region of *BRCA1, BRCA2* and non-*BRCA* breast cancer susceptibility genes
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<tr>
<td>12.30 – 12.50</td>
<td>Logan Walker</td>
<td>Nanopore sequencing of full-length BRCA1 mRNA transcripts reveals co-occurrence of known exon skipping events</td>
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<td>12.50 – 2.00</td>
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<td>Lunch</td>
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<tr>
<td>2.00 – 2.30</td>
<td>Beth Crawford</td>
<td>Web-Based Preference-Tolerant Randomized Trial of Risk-Based vs. Annual Breast Cancer screening: WISDOM study</td>
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<td>2.30 – 2.50</td>
<td>Carolyn Nickson</td>
<td>Toward Tailored Screening: prospective validation of personalised breast cancer risk stratification in a cohort of 53,000 Australian women</td>
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<tr>
<td>2.50 – 3.10</td>
<td>William Crozier</td>
<td>Identifying high-risk predisposition genes for childhood cancer</td>
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<td>3.10 – 3.25</td>
<td>Tess Schenberg</td>
<td>The range of BOADICEA scores in women eligible for MRI Breast Screening at the Peter MacCallum Familial Cancer Centre</td>
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<td>3.25 – 3.40</td>
<td>Fiona Bruinsma</td>
<td>Penetrance of FLCN Mutations in Birt-Hogg-Dubé Syndrome</td>
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<td>3.40 – 4.10</td>
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<td>Afternoon Tea</td>
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<td>6.00 – 8.00</td>
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<td>Conference Cocktail drinks pool side @ Peppers All delegates welcome</td>
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Delegates organise their own dinner
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<tr>
<td>9.10 – 9.40</td>
<td>Sharon Savage</td>
<td>The Potential of Cancer Screening in Li-Fraumeni Syndrome</td>
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<tr>
<td>9.40 – 10.00</td>
<td>Cristina Fortuno</td>
<td>Investigating ACMG rules and quantitative methods for TP53 missense variant classification</td>
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<tr>
<td>10.00 – 10.20</td>
<td>Dane Cheasley</td>
<td>Interval Breast Cancer versus Screen-Detected Cancer: Genomic comparison of germline predisposing genetic variants and acquired somatic aberrations</td>
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<td>10.20 – 10.40</td>
<td>Khalid Mahmood</td>
<td>Colorectal cancer susceptibility genes: findings from whole exome, genome and targeted sequencing of multiple-case families</td>
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<td>10.40 – 11.10</td>
<td>Morning Tea</td>
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**Session 9**  
**Plantation Room**  
Chairperson: Georgia Chenevix-Trench

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<tr>
<td>11.10 – 11.40</td>
<td>Marc Tischkowitz</td>
<td>Cancer Gene Panels – Panacea or Pandora’s box?</td>
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<tr>
<td>11.40 – 12.00</td>
<td>Alison Trainer</td>
<td>Balancing clinical excellence with clinical equity: maximizing the minimum gain (maximin)</td>
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<td>12.00 – 12.10</td>
<td>Ian Campbell</td>
<td>The contribution of rare variants in novel candidate genes to the hereditary risk of breast cancer</td>
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<tr>
<td>12.10 – 12.20</td>
<td>Na Li</td>
<td>Targeted sequencing in large cohorts of breast cancer families and population controls identify NTHL1 as novel breast cancer predisposition gene</td>
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<tr>
<td>12.20 – 12.30</td>
<td>Marie Lorans</td>
<td>The role of RNF43, NTHL1, POLE and POLD1 in Serrated Polyposis</td>
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**End of Meeting:** Lunch will be served
Programme

Tuesday 29th August

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“Familial Cancer 2017: Research and Practice”

FCC Session 1:

Plantation Room

Chairperson: Helen Marfan
Mosaicism: a clinical perspective

Mac Gardner

Mosaicism – a mix of cells of different genetic make-up – is a concept familiar to anyone working in genetics. In all probability, every one of us is a mosaic; for most, that doesn’t matter, but for a few it does. I will focus in particular upon mosaicism involving mendelian mutation, or chromosomal status, and will illustrate with several examples. I will emphasise the clinical relevance of mosaicism, and reflect on the distinction between somatic, somatic-gonadal, and gonadal mosaicism. It is surprising (or perhaps it isn’t) how often an understanding of mosaicism will inform advice given in the genetic counselling clinic.

Mac Gardner is a Medical Geneticist of long standing, who retired from full-time practice at Victorian Clinical Genetics Services in 2007, but has continued in part-time work, and presently for Genetic Health Services NZ. He has particular interests in chromosomal disorders, and in neurogenetics. Back in the day, he was involved in setting up several of the familial cancer clinics in Melbourne. He agrees with English geneticist Sir Cyril Clarke, who once defined genetics as “almost anything interesting”.

Treatment focused tumour testing in ovarian cancer

Michael Field¹, Ashley Crook¹, Ellenore Martin¹, Diana Neilson², Jayne Maidens³, Sally Baron-Hay⁴

¹Family Cancer Service RNSH, St Leonards NSW; ²AstraZeneca Pharmaceuticals, Macquarie Park NSW; ³Dept Gynaecology RNSH, St Leonards NSW; ⁴Cancer Services RNSH, St Leonards NSW

Since January 2015, all high grade serous ovarian cancers of patients referred to the family cancer clinic at Royal North Shore Hospital have been forwarded to Myriad genetics for BRCA1 and BRCA2 tumour testing on FFPE slides. At the time of consent, a parallel germline DNA sample was collected and stored. The potential for targeted treatments for both somatic and germline variants makes knowledge of these mutational events potentially useful for clinical care. To date 40 patients have undergone testing, with 66 being the average age of ovarian cancer diagnosis. Two germline and three somatic events were identified (12% of cases). Three tumour samples were unable to be analysed completely because of sample quality issues. Germline mutation rates by age are in keeping with the AOCS data (age 50-60 2/14 (14.3%), age 60-70 0/14, age >70 0/10)¹. Two of the somatic variants occurred in the over 70 patient group. To assess the likelihood of missing germline mutations in somatic tissue, we have performed germline DNA testing for selected individuals with a significant family or personal history diagnosed before 70. This quality control data will also be presented.

We suggest that given the potential therapeutic benefits and the potential for a simplified consent process, selection of tumour tissue for testing at diagnosis may offer an alternative approach for mainstreaming of genetic testing.

Tumour genetic testing in the diagnosis of familial cancer syndromes

Lesley Rawlings BSc (Hons) PhD. Head, Familial Cancer Section, Genetic Pathology

For cancers arising from the loss of function of tumour suppressor genes, both alleles of the gene must be disabled. This can manifest either as a ubiquitous, potentially heritable, “germline” mutation, with a second mutation occurring in differentiated tissue-specific cells, or as two de novo hits in the tissue, depending on the timing when a mutation occurs. The separation of localised, somatic acquired mutations from ubiquitous “germline” mutations, as well as from low level mosaic mutations, is important for genetic counselling in terms of inheritance risk and on-going surveillance.

Diagnostic testing for the underlying genetic causes of cancers presenting in multiple members of a family has become consolidated as standard practice since the late 1980’s/early 90’s as new tumour suppressor genes have been identified, and is expanding exponentially as technology advances our ability to explore the genome in ever greater breadth and depth. Traditionally, disorders such as unilateral retinoblastoma, neurofibromatosis type II and von Hippel Lindau disease have been the classic scenarios for tumour testing to aid in the assessment of the probability of mosaic germline variants predisposing to familial cancer.

This talk will use case studies to present a laboratory perspective on the role of tumour testing in the assessment of familial cancer syndromes, the challenges involved and potential new advancements.
Programme

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“Familial Cancer 2017: Research and Practice”

\textit{FCC Session 2:}

\textit{Plantation Room}

\textbf{Chairperson: Nicholas Pachter}
Rory Clifton-Bligh. Head, Department of Endocrinology and Co-Head, Cancer Genetics Unit Kolling Institute Royal North Shore Hospital, St Leonards NSW 2065
Gene testing for PCC and phaeochromocytoma in the 21st century, and implications for clinical management.

Emma Duncan.
Eminent Senior Staff Specialist, Department of Endocrinology and Diabetes, Royal Brisbane and Women's Hospital. Adjunct Professor, Institute of Health and Biomedical Innovation, Faculty of Health, Queensland University of Technology. Professor of Medicine, Faculty of Medicine, University of Queensland.
Anthony Gill.
Professor of Surgical Pathology, University of Sydney
Programme

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“Familial Cancer 2017: Research and Practice”

FCC Session 3:

Plantation Room

Chairperson: Margaret Gleeson
Heritable Renal Cancer Syndromes

Ingrid Winship\textsuperscript{1,2}

\textsuperscript{1}Genetic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Australia; \textsuperscript{2}Department of Medicine, University of Melbourne, Parkville, Victoria, Australia

The majority of kidney cancers are renal cell carcinoma (RCC), of which 3-5\% are heritable. These are predominantly of the clear cell histological subtype (ccRCC); other less frequent histological subtypes are chromophobe (chRCC) and papillary (pRCC). Heritable renal cancers are considered when cancers are bilateral, occur at an early age, or where there is a relevant family history. Mutations in multiple genes are recognised in renal cancer or RCC-associated syndromes, including \textit{VHL}, \textit{FLCN}, \textit{FH}, \textit{MET}, \textit{PTEN}, \textit{SDHB}, \textit{SDHC}, \textit{SDHD}, \textit{TSC1}, \textit{TSC2}, \textit{CDC73} and \textit{BAP1}. Penetrance estimates of these genes vary greatly. Early evidence is emerging for a wider group of genes by further delineating the cancer phenotypes associated with other known cancer predisposition genes.

Individuals with first-degree relatives with RCC are estimated to have a two-fold increase in RCC risk. Genome-wide association studies have identified new potential risk loci, which justify continuing studies of the potential for genetic susceptibility to RCC. Rare familial renal cancer syndromes including von-Hippel Lindau disease (VHL), Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC), Tuberous Sclerosis (TSC) and Birt-Hogg-Dubé Syndrome (BHD) have clinical phenotypes with indicative histologic subtypes of RCC. There may be associated non-malignant renal features, such as oncocytoma, angiomyolipoma and renal cysts. Consistent extra-renal, non-cancer clinical features are important diagnostically. Furthermore, recognition of these phenotypic features which may precede the onset of RCC and often have higher penetrance than RCC, will provide the opportunity for investigation in advance of malignancy for the individual and the family, in a preventive approach to renal cancer and its potential complications.
Anthony Gill.
Professor of Surgical Pathology, University of Sydney
Urologist Perspective

Simon Wood
Programme

Tuesday 29th August

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“Familial Cancer 2017: Research and Practice”

FCC Session 4:

Plantation Room

Chairperson: Lucinda Salmon
Simone Busija

About:

Family Ties Foundation is an online resource that has been developed to support families in sharing information with their own children and other relatives about their genetic cancer risk.

Family Ties have a wide range of resources including conversation fact sheets developed by genetic counsellors and personal stories.
How can we best integrate genetic testing into routine oncological practice?

Marc Tischkowitz
Department of Medical Genetics
University of Cambridge
East Anglian Medical Genetics Service

The introduction of Next Generation Sequencing years has resulted in cheaper and faster genetic testing for hereditary cancer predisposition. The challenge we currently face is how best to incorporate these advances into routine oncological practice, while at the same time maintaining the necessary support and counselling for affected individuals and their families. In this presentation I will use results from The Genetic Testing in Epithelial Ovarian Cancer (GTEOC) Study to highlight how such integration can be achieved. This showed that population-based genetic testing is acceptable to newly diagnosed patients with ovarian cancer and is less resource-intensive than historical practice where all patients have a full assessment by the genetics team prior to testing. The study necessitated a close working relationship between cancer genetics and oncology, and I will describe how we implemented the study findings using the existing resources and infrastructure of a public healthcare system. I will also provide an update on related efforts in other cancers.
Strategies for Delivery of Clinical Cancer Gene Testing and Genetic Counseling to Cancer Center Clinics, Community Hospitals and Remote Patients

Beth Crawford LCGC, Liane Abrams LCGC, Amie Blanco LCGC, Nicola Cadenas LCGC, Dena Goldberg LCGC, Robin Lee LCGC, Julie Mak Ms, LCGC, Lisa Mar LCGC, Miya Frick LCGC, Megan Myers LCGC, Christina Pedley LCGC, Lara Reichman LCGC, Robert Nussbaum MD

Purpose: Ascertainment of patients and families at high hereditary risk for cancer by overcoming barriers to timely genetic counseling services, risk assessment and gene testing. We designed interventions to address delayed referral rates of newly diagnosed patients, distances to clinical services, access to services for a multiethnic, low income patient population and risk communication within the family.

Method: A number of strategies developed over 20 years of clinical genetic counseling at UCSF in the Cancer Genetics and Prevention Program to address patient identification and communication including a consult service, clinic embedded genetic counselors, satellite clinics, tele-video visits and a patient web site created and curated by a genetic counselor. Strategy design and implementation by a team of genetic counselors and a geneticist was used to address the need for a timely response to patients who may need genetic counseling and gene test results to make surgical or chemotherapy decisions.

Results: Presentation will summarize the increase in referrals and access to gene testing for patients at high risk for hereditary cancers. Six satellite clinics, tele video clinic visits and an outreach clinic in a public hospital addressed barriers for low income multi-ethnic patients and those challenged by geographical distance to care. Genetic counselors available as part of the team in disease specific clinics addressed timely response for newly diagnosed patients. The Hereditary Cancer Syndrome Clinic with a geneticist and genetic counselors is available for patients with complex diagnostic and follow up needs. The majority of cases in other clinics are seen by a genetic counselor only with case discussion at a weekly tumor board.

Conclusion: Provision of cancer genetic services requires continued study and use of technology to address patient communication for education, genetic panel testing and to share updated screening guidelines with high risk families. Additional innovations for providing cancer genetic services are needed.
Evaluation of a centralised national telephone genetic counselling service that facilitates BRCA1/2 testing for women with relapsed high-grade serous ovarian cancer

Laura Forrest,1,2 Joanne McKinley,1 Rowan Forbes Shepherd,1,2 Victoria Rasmussen,1 Paul James,1,2 Bettina Meiser,3,4 Mary-Anne Young5

1Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; 2Sir Peter MacCallum Department of Oncology, The University of Melbourne, Victoria, Australia; 3Prince of Wales Clinical School, The University of New South Wales, Sydney, New South Wales, Australia; 4Psychosocial Research, Hereditary Cancer Clinic, Prince of Wales Hospital, Sydney, New South Wales, Australia; 5Genome One, The Garvan Institute of Medical Research, Sydney, New South Wales, Australia

Women with recurrent high-grade serous ovarian cancer (HGSOC) who have a germline BRCA1/2 mutation benefit from treatment with poly (ADP-ribose) polymerase (PARP) inhibitors. In order to guide treatment decisions for these women, prompt access to genetic testing is essential. However, the rates of genetic testing for such women in Australia remain low despite recent changes to BRCA1/2 genetic testing criteria and efforts to mainstream BRCA1/2 testing. In an attempt to address barriers to genetic testing, in 2016 a national centralised telephone genetic counselling service was established in the Parkville Familial Cancer Centre at Peter MacCallum Cancer Centre. Women with recurrent HGSOC are referred by their medical oncologist and the genetic counselling process, including facilitation of BRCA1/2 testing and delivery of results, occurs via telephone with a genetic counsellor.

A mixed-methods evaluation of the telephone genetic counselling service commenced in August 2016. The aim of the evaluation is to examine the acceptability and feasibility of the telephone genetic counselling to facilitate BRCA1/2 testing in women with recurrent HGSOC. The evaluation consists of three stages: 1) a survey of women who received the telephone genetic counselling service; 2) interviews with the referring medical oncologists; and 3) a measurement of the cost effectiveness of the telephone genetic counselling compared with face-to-face genetic counselling. This presentation relates to the first stage only: women’s experiences of receiving telephone genetic counselling to facilitate BRCA1/2 testing.

The survey was available to complete in paper-based form or online. Women who completed the telephone genetic counselling process were mailed a survey package including a link to an online version of the survey. The survey examines the accessibility of genetic services, acceptability of the telephone genetic counselling service, decision-making about having BRCA1/2 testing, and experience of receiving telephone genetic counselling. Two hundred and thirteen women were invited to participate in the first round of recruitment, and invitations will continue as women continue to receive their results. Preliminary results from the survey will be presented.
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“Familial Cancer 2017: Research and Practice”

Session 1:

Plantation Room

Welcome and Chairperson: Judy Kirk
Prophylactic mastectomy because of increased genetic risk and
What to do about low risk alleles?


Since the identification of high-risk breast cancer risk genes in the nineties of the last century, prophylactic bilateral/contralateral mastectomy (BPM/CPM) has increasingly become accepted as a mode to reduce risks by carriers and medical professionals throughout the western world.

In this talk I will give an overview of the literature on the uptake of BPM/CPM in different countries since the identification of BRCA1 and BRCA2, and the evidence for breast cancer risk reduction achieved by this intervention. A summary will be presented on data published on the psychosocial impact of this procedure.

Further, I will discuss clinical practice with respect to requests for BPM/CPM when dealing with the moderate-risk alleles like mutations of CHEK2.

The current focus on precision medicine well fits to breast cancer risk assessment for each individual women, aiming at benefit for those women at increased risk from risk-reducing interventions. Breast cancer risk is caused by both non-inherited and inherited – genetic - factors. Risk prediction has become more accurate in both domains last decade due new knowledge.

With respect to genetic risk factors, at present many more risk factors have been validated since the identification of BRCA1 and BRCA2, including some moderate-risk genes and many low-risk alleles.

In view of this, the medical community is now at the brink of including additional genetic risk factors apart from mutations of BRCA1 and BRCA2. I will particularly focus on our clinical practice related to CHEK2 c.1100delC, a moderate risk allele in the Dutch population with a population frequency of 1%.
The role of genomic profiling in adolescents and young adults (AYAs) with advanced cancer participating in Phase I clinical trials

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**Introduction:** Patients aged between 15-39 at cancer diagnosis (adolescents and young adults) represent a challenging cohort of patients, with unique psychological and socio-economic considerations. There is also increasing evidence that certain cancers in such individuals may have distinct genetic profiles. Genetic mutations in the soma or the germline represent putative therapeutic targets, and tumour molecular profiling is becoming increasingly utilised in the personalisation of therapy for such individuals, particularly in determining eligibility for novel agents as part of early phase clinical trials. Furthermore, hereditary cancer predisposition syndromes confer increased risks of cancers at young ages. In our unit, diagnosis of certain cancers under the age of 40 will immediately render individuals eligible for germline genetic testing (e.g. breast, non-mucinous ovarian cancer, renal, diffuse gastric). Patients diagnosed with breast or non-mucinous ovarian cancers under the age of 40 can avail of germline BRCA1/2 analysis through the mainstreaming pathway.

**Aim:** The aim of this study was to investigate the actual and potential utility of germline and somatic genomic assessment of AYAs with advanced solid tumours managed in a specialist drug development unit (DDU) in the United Kingdom.

**Methods:** AYAs treated in the DDU at the Royal Marsden Hospital between 2002 and 2016, were identified from departmental databases. Data regarding clinicopathological features, clinical assessments, and germline and tumour genetic testing were retrieved by electronic chart review.

**Results:** 218 AYA patients were managed in our unit over the study period. Common cancer types included sarcoma (41, 19%); cervical (27,12%); breast (25; 11%); ovarian (23,10%) and colorectal (21,10%) cancers. Tumour Molecular Characterisation (MC) was performed using custom-designed multigene panels in 45 cases. Mutations were detected frequently in TP53 (12,31%), PIK3CA (8,18%); KRAS (4, 9%) and MET (4,9%). Twenty-two (10%) patients had been previously diagnosed with a cancer predisposition syndrome. Using current guidelines, a further 18 patients would be eligible for mainstream BRCA1/2 testing, and 7 for TP53 testing based on their personal history alone. In 108 (50%) cases, no family history was taken.

**Discussion:** A proportion of AYAs presenting with advanced cancer may have targetable mutations in the soma or the germline. Thorough assessment of familial risk factors, and inclusion of germline testing in appropriate circumstances can complement tumour testing to help optimize patient management and inform management of their at-risk relatives.
Population genetic testing for breast and ovarian cancer susceptibility

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Germline mutations in a small number of genes account for a large proportion of inherited risk for breast and ovarian cancer. The identification of mutation carriers can significantly reduce the incidence of these diseases as the high risks of cancer in these individuals can be reduced with active management and surgery. The predominant model of familial breast and ovarian genetic testing involves identifying high-risk individuals based on their family history. However, current data suggests that a large proportion of women who carry a BRCA1 or BRCA2 mutation may not have a remarkable family history of cancer in close relatives, although this has not been thoroughly ascertained in a cancer-free population. This study represents the first population-based approach at genetic testing for high risk mutations in hereditary breast and ovarian cancer (HBOC) genes in a general Western population where the results are communicated back to participants. Study participants were drawn from the LifePool study (n>54,000), which recruits women predominantly through BreastScreen Victoria, a population-based mammographic screening program. Germline DNA from a random subset of cancer-free LifePool participants (n=5,577) was sequenced for 11 HBOC predisposition genes (BRCA1, BRCA2, PALB2, ATM, TP53, PTEN, STK11, CDH1, BRIP1, RAD51C, RAD51D) using a custom next-generation sequencing panel to detect clinically actionable mutations. Women with an actionable mutation were notified of a clinically significant finding via a letter from LifePool, which provided a contact number for the PeterMac telephone genetic counselling service and an invitation for formal genetic counselling at a Familial Cancer Centre (FCC). Among the 5,577 cancer-free women, 40 (0.72%) were carriers of mutations in genes that are currently clinically actionable in Australia (BRCA1 n=7, BRCA2 n=15, PALB2 n=15, ATM n=3). Following notification, all 40 women subsequently attended a FCC for genetic counselling and confirmatory predictive testing. Only 8 of the 40 women would have met the minimum threshold for clinical genetic testing under current guidelines. A further 16 participants (0.29%) carried loss of function mutations in BRIP1, RAD51C and RAD51D but were not notified of their result as these genes are not currently actionable in Australia. In summary, a relatively large proportion of cancer-free women from an Australian population of western European descent carry high-risk mutations in HBOC genes and subsequent uptake of clinical genetic testing was very high. Our study shows that population-based genetic testing is well accepted and can identify a much larger proportion of the at-risk population than contemporary family history based approaches.
Prognostic signature for high grade serous ovarian cancer

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High grade serous ovarian cancer (HGSOC) is the most common and aggressive epithelial ovarian cancer. The five-year survival is less than 40%, as it is often diagnosed at a late stage. There is no clinical prognostic signature for ovarian cancer. The Ovarian Tumor Tissue Analysis (OTTA) consortium performed NanoString expression profiling of 518 genes for 5,376 formalin fixed paraffin embedded (FFPE) ovarian tumour cases to identify prognostic markers. Two hundred of the genes were selected from a meta-analysis of survival from available data from fresh frozen tumours. An additional 96 genes were selected from a survival genome wide association study (GWAS) or potential drug targets or key ovarian cancer genes from the literature. Five genes were used for data normalisation. There were 3,696 HGSOC cases with clinical data for the overall survival analysis, after removal of cases with missing data. Cox regression, using the Efron method, was used to test for an association between log-transformed gene expression and overall survival right-censoring at 10 years. The model used left-truncation to account for any survival bias due to delays in recruitment. A likelihood ratio test was conducted to evaluate the statistical significance of each gene in a separate model, adjusting for age, race, stage, grade, and stratifying on study site. For overall survival, 120 of these genes were significant \( P < 10^{-4} \) and using a Benjamini–Hochberg (BH) false discover rate (FDR), 249 genes were significant, \( P < 0.05 \). In a preliminary analysis to develop a multi-gene prognostic signature, the data set was randomly split into a model development data set (2/3) and a model validation data set (1/3). The model was based on expression data for 291 gene selected from the meta-analysis, literature and survival GWAS. All genes with an association at \( P < 0.05 \) were then included in a multi-variable stepwise regression model. Twenty genes were retained in the final regression model. The prognostic index (PI) was strongly associated with all-cause mortality at ten years in the validation data (HR per unit increase in risk score = 2.13, 95% CI 1.82 – 2.51, \( P = 10^{-19} \)). Kaplan Meier plots of the survival probability by quintile of prognostic group, showed that at 5 years the worst quintile had \(~15\%) survival and the best quintile had \(~55\%) survival. Further analysis, using all genes, is ongoing to identify a prognostic signature for clinical use.
Programme

Wednesday 30\textsuperscript{th} August

\textbf{A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.}

"Familial Cancer 2017: Research and Practice"

\textit{Session 2:}

\textit{Plantation Room}

\textbf{Chairperson: John Hopper}
Risk-reducing oophorectomy and breast cancer risk across the spectrum of familial risk using a prospective family study cohort (ProF-SC)

Mary Beth Terry 1 2, Kelly-Anne Phillips3 4 5, Mary B Daly6, Irene L Andruleis9, Yuyan Liaoi, Xinran Ma, Nur Zeinomar, Robert J. MacInnis4, Gillian S. Dite4, Esther M John7 8, Saundra S Buys10, and John L Hopper4

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Background: Whether risk-reducing salpingo oophorectomy (RRSO) reduces breast cancer risk in addition to reducing ovarian cancer risk is controversial with some arguing that the previous evidence of a reduction in breast cancer risk from RRSO was due to bias. Evidence from independent prospective cohorts of high-risk women is needed to resolve this controversy.

Methods: Using a prospective family study cohort of 17,810 women unaffected with breast cancer at baseline, we examined the association between RRSO and breast cancer risk using Cox Proportional Hazards models. We compared results estimating RRSO as a non-time-dependent variable to results treating RRSO as a time-dependent variable, because failing to account for the time-varying nature of a covariate person-time prior to RRSO, should it exist, will incorrectly attribute the cancer-free person-time to RRSO. We separately examined the association with RRSO in BRCA1 and BRCA2 mutation carriers and non-carriers, and further performed gene-stratified analyses in women with BRCA1 and BRCA2 only. We also assessed multiplicative interactions with underlying familial risk profile (FRP), defined as total lifetime risk estimated from the Breast Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model.

Results: During a median 10.7 years of follow-up (maximum 23.7 years), we observed 1,040 incident cases of breast cancer with an average age at diagnosis of 55.8 years and average age at enrolment into the cohort of 46.8 years. A total of 2434 (14%) women reported a RRSO at baseline having a RRSO. We observed decreased risk of breast cancer associated with RRSO for both BRCA1 (N= 650) and BRCA2 (N=557) mutation carriers when RRSO was treated as a fixed covariate (HR= 0.60, 95% CI=0.40-0.92 and HR= 0.40, 95%CI = 0.23-0.69, respectively). In contrast, when we treated RRSO as a time-varying covariate, for both BRCA1 and BRCA2 carriers, we no longer observed a decreased risk for BRCA1 and BRCA2 carriers (HR= 1.67, 95% CI=1.05-2.67 and HR= 0.97, 95%CI = 0.53-1.80, respectively). There was no association between RRSO and breast cancer risk for non-carriers (N=16,603), whether we treated RRSO as a fixed or time varying covariate (HR= 0.88, 95% CI=0.72-1.08 and HR= 1.06, 95%CI = 0.85-1.30, respectively).

Conclusions: Our findings provide an independent replication that the reduced risk of breast cancer previously observed in BRCA1 and BRCA2 mutation carrier women may be from bias in counting person-time. Clinical management of high-risk women should counsel based on the reduced risk of ovarian cancer from RRSO, but not breast cancer.
Acceptability and usability of iPrevent, a web-based decision support tool for assessment and management of breast cancer risk

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Background: iPrevent estimates an individual's personal BC risk, using either the IBIS or BOADICEA algorithms, and provides tailored risk management information on screening, lifestyle modifications, risk-reducing surgery and risk-reducing medication. It is designed to be used collaboratively by women and their clinicians. The purpose of this pre-implementation pilot study was to assess the clinical usability and acceptability of the iPrevent prototype, and to identify barriers to clinical implementation. Exploratory aims investigated patients' BC worry, anxiety, risk perception and knowledge before and after using iPrevent.

Methods: Eligible clinicians worked in primary care (PC), breast surgical (BS) or genetics clinics (GC). Their female patients were eligible if aged 18-70 years with no personal cancer history. Clinicians were familiarized with iPrevent using hypothetical cases, then actor scenarios, and lastly iPrevent was trialed with patients. All participants completed the System Usability Scale (SUS) and an acceptability questionnaire 2 weeks after using iPrevent. Patients also completed the Lerman BC Worry Scale, Spielberger State-Trait Anxiety Inventory, and BC risk perception and prevention knowledge questionnaires before and 2 weeks after using the tool. Data were summarized using descriptive statistics.

Results: 63 participants comprising 20 clinicians (median age 47 years, 8 PC, 6 BS, 6 GC) and 43 patients (median age 38 years, 16% high risk, 51% moderate risk, 33% average risk) were recruited. Usability was rated above average (SUS score >68) by most clinicians (68%) and patients (76%). Most (79% of clinicians, 81% of patients) agreed iPrevent was 'easy to use', although 10 (53%) clinicians and 10 (27%) patients reported that it was too long. Most clinicians (84%) and patients (86%) found iPrevent 'very' or 'somewhat' helpful. 89% of participants reported that it was too long. Most clinicians (84%) and patients (86%) found iPrevent 'very' or 'somewhat' helpful. 89% of participants reported that iPrevent provided the right amount of information. 5% reported to 'rarely' or 'not at all' worry about BC before iPrevent, and 29% after use. 25% of patients reported less impact of worrying about BC after iPrevent, 47% were unchanged and 28% reported more impact of worrying about BC after iPrevent use. State anxiety remained the same. 87% of patients correctly reported their risk category after using iPrevent compared with 40% before. BC prevention knowledge improved for most questions.

Conclusions: iPrevent has high usability and acceptability. Exploratory analyses suggest that iPrevent may also improve patients' BC risk perception and knowledge without adversely affecting anxiety or BC worry. Because concerns about length could be a barrier to implementation, data entry has been abbreviated in the modified version of iPrevent that will be publically available.
Common genomic variants modify the effect of Moderate risk breast cancer genes and can improve clinical interpretation

Paul James¹, Li Na², Simone McInerny¹, Simone Rowley², David Goode², Rodney Scott⁴, Lisa Devereux⁵, Norah Grewal¹, ViP Study Investigators, LifePool Study, Ian Campbell²,³

¹Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital; ²Cancer Genetics Laboratory, Peter MacCallum Cancer Centre; ³Sir Peter MacCallum Department of Oncology, Melbourne University; ⁴Hunter Area pathology Service, Newcastle; ⁵LifePool Study, Peter MacCallum Cancer Centre

A large number of ‘new’ breast cancer risk genes and variants have been described that fall into the moderate risk category; typically rare coding variants with an increased risk in the range of 1.5 to 4 fold. Clinical translation of these findings has been limited by the moderate nature of the described risk and frequent findings of inconsistent segregation in high risk families. We used sequence data from a familial breast cancer case-control study to examine the influence of common genomic variants on the moderate risk alleles to determine whether the combined effects could better identify women at an actionable level of breast cancer risk.

Method: 4139 women affected by breast cancer, with no mutation in BRCA1/BRCA2, from the Variants in Practice Study and the Hunter Area Pathology Service, and 4244 healthy, screened controls from the LifePool study were screened for coding variants in 160 genes and 74 common genomic variants (SNPs) with a reported or potential association with breast cancer risk. More than 600 rare variants in either established moderate risk genes (e.g. CHEK2, ATM, FANCM) or reported candidates, such as NBN, MRE11A, RAD51C etc., were analysed in conjunction with each individual’s polygenic risk score (PRS).

Results: Individual moderate risk variants and the PRS distribution both showed the expected association with breast cancer; average OR for LoF variants 3.3 (95% CI 2.7-3.9). For many of the rare variants analysed the risk was significantly modified by the PRS, with no risk observed when associated with a low PRS background and clinically high risk for the same variant when associated with a high PRS e.g. CHEK2 1100delC: High PRS (quartile) OR=8.5 (2.8-25.9). The same strong modification was found for some candidate genes e.g. RAD51B: average OR = 1.0, but High PRS OR 4.7 (1.9-11.9). We examined interaction with hormone receptor status and co-segregation of the PRS and rare variants in families.

Conclusion: There is evidence of a significant SNP-modifying effect for many reported and potential moderate risk breast cancer genes, potentially contributing to the current conflicting reports in the literature for many of these genes. Combined interpretation of PRS data with rare variants has the potential to significantly improve the clinical utility of this data and allow the accurate identification of truly high risk individuals.
Background: Despite increasing evidence for the utility of polygenic risk in families at high risk of breast cancer, research findings are yet to be integrated into clinical practice. This reflects the status of polygenic risk as an emerging technology and the limited evidence base on the psychosocial and behavioural outcomes of offering such testing.

Aim: To ascertain the important psychosocial and behavioural implications of testing for polygenic breast cancer risk in the existing cohort the “Variants in Practice” (ViP) study.

Methods: 400 women enrolled in ViP, who have either a high or low polygenic risk score (PRS), and whose personal and/or family history breast cancer remained unexplained after genetic testing for known cancer predisposition genes are being invited to participate in this study. Participants complete a baseline questionnaire assessing their knowledge of hereditary breast cancer, current breast cancer screening behaviours, psychological well-being, and intention to receive personal PRS results. A genetic counselling framework was also developed to support the return of polygenic results.

Results: As of June 2017, 91/99 (92%) participants reported interest in receiving their PRS, with 28/91 (31%) having received their results. Primary reasons given by participants to receive their results included: helping research (92%), helping family members (86%), and to get information to manage personal breast cancer risk (83%). The mean baseline knowledge score among participants was 6.6 (out of 10), and 8.7% and 26.1%, of participants scored over the cut-offs for cancer-specific distress and general anxiety scores.

Conclusion: While, there is strong interest in receiving personal PRS result among women at high risk of breast cancer, the psychosocial and behavioural implications should be carefully considered. Data collection is ongoing, with additional data regarding uptake of results and short-term impact of receiving results to be presented.
Pancreatic cancer screening in high risk individuals: a five-year update

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**Background:** Surveillance of high-risk pancreatic cancer (PC) groups may facilitate detection of precursor lesions or early-stage malignancy and improve prognosis. The PC screening trial at St Vincent’s Hospital, Sydney, has been operational for over 5 years and interim screening outcomes will be presented.

**Methods:** Prospective screening outcomes have been collected for a high-risk PC Australian cohort. Baseline demographic and psychological data is collected, along with feedback regarding the prerequisite genetic counselling session. Pancreatic cancer risk estimates are calculated using the PancPRO Bayesian model¹. The surveillance program consists of endoscopic ultrasound (EUS) assessment, at least on an annual basis. Psychological questionnaires are readministered 1 month, 1 year and 5 years post baseline EUS.

**Results:** 102 high-risk individuals from 63 families have undergone at least one EUS assessment, and an average of 3-4. The median age at enrolment is 56 (35 – 78 years), 68% of participants are female, 99% are Caucasian and 12% report Ashkenazi Jewish ancestry. The majority are from familial PC kindreds (77%), 22% carry a BRCA2 mutation and one participant has a clinical diagnosis of PJS. BRCA2 carriers have a higher baseline median cancer worry score of 4 compared to the familial PC cohort score of 3 (p=0.003). The median lifetime PancPRO PC risk for the cohort is 8.5% (1.2 – 14.4%). 82% of participants (63/75) found the genetic counselling session to be helpful, and would recommend to other relatives. A subset of participants (32%) have required more intense screening intervals or additional investigations due to suspicious or abnormal EUS findings. Of this subset, 2 participants have undergone pancreatic resection of histopathologically confirmed tumours. One 55yr old female BRCA2 carrier with one first-degree relative (FDR) diagnosed with PC at 77yrs had an early stage pancreatic ductal adenocarcinoma detected at her third EUS. A 62yr old male with 2 FDR diagnosed with PC at 38 and 60yrs, had a pancreatic neuroendocrine tumour identified at his baseline EUS.

**Conclusion:** Interim data suggests that participants perceive the current PC screening protocol to be beneficial, and that screening does not create psychological harm. Regular surveillance in a high-risk PC Australian population detects a significant rate of suspicious or abnormal EUS findings and successfully stratifies to identify early-stage operable malignancies. Further longitudinal data is needed to determine the true diagnostic yield and the long term psychological impact of PC screening programs.

**References:**
Programme

Wednesday 30th August

A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.

“Familial Cancer 2017: Research and Practice”

Session 3:

Plantation Room

Chairperson: Lucinda Salmon
BRCA-P: A randomized, double-blind, placebo-controlled, multi-centre, international phase 3 study to determine the preventive effect of denosumab on breast cancer in women carrying a BRCA1 germline mutation

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Women who carry a germline mutation in the BRCA1 gene are at high lifetime risk of developing breast and ovarian cancer. A subset of progenitor cells in histologically normal breast tissue from BRCA1 mutation carriers has been identified as the likely ‘cell-of-origin’ that lead to breast cancer in BRCA1 mutation carriers. This population expresses the receptor of RANK ligand (RANK). RANK⁺ progenitors are highly proliferative, prone to DNA damage, and appear to be hyper-responsive to progesterone through paracrine signalling mediated by RANK ligand (RANKL). Importantly, inhibition of RANKL curbs progenitor activity in vivo in BRCA1 mutation carriers and inhibition of RANKL curtails mammary tumorigenesis in mouse models. These and other findings have led to an international breast cancer prevention study in BRCA1 mutation carriers to evaluate the safety and efficacy of the RANKL inhibitor denosumab as a chemoprevention agent.

BRCA-P is a randomised, double-blind, placebo controlled, phase 3 trial in adult women with a pathogenic germline BRCA1 mutation. Women (aged 25-55 years) unaffected by breast or ovarian cancer with a pathogenic BRCA1 mutation will be recruited. Subjects will be stratified by menopausal status at study entry. In total, 2,918 subjects will be recruited; up to 50% will be pre-menopausal at enrolment. Women will be randomised (1:1 ratio) to receive either denosumab 120 mg or placebo s.c. every 6 months for 5 years. They will also be provided with Calcium and Vitamin D supplements and advised to take them for the study duration. The study, which is being led by the ABCSG, will be conducted in Australia through the ANZ Breast Cancer Trials Group in collaboration with kConFab. It is hoped that the study will open in early 2018.

Translational studies:
- QoL
- Bone turnover and bone mineral density
- Mammographic density, MRI Brads
- SNPs and serum biomarkers
- Biobanking for tumour and normal breast tissue analysis
STICs and STONes: A Randomised Phase II Double-Blind Placebo-Controlled Trial of Aspirin in Chemoprevention of Ovarian Cancer in Women with BRCA1 and BRCA2 Mutations

Kelly-Anne Phillips - Peter MacCallum Cancer Centre

**Background:** Women with BRCA1 or BRCA2 mutations are at increased risk of high grade serous gynaecologic cancer (HGSC). These are thought to mostly arise from precursor lesions in fallopian tube fimbriae (serous tubal intraepithelial carcinoma -STIC). HGSCs are usually advanced at presentation and have a poor prognosis. Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is a highly effective prevention method but, despite recommendations for RRBSO after childbearing or before age 40, a third of Australian mutation carriers delay RRBSO until after age 50. At RRBSO some women already have STICs or occult cancer (serous tubal occult neoplasia -STONe). Epidemiological studies suggest aspirin as a potential chemoprevention agent. If confirmed, aspirin would provide an interim measure to reduce risk of HGSC and STIC in women who delay RRBSO.

**Aims:** The primary aim of this study is to compare the frequency of STICs and/or STONes in the fallopian tube, at the time of RRBSO, in BRCA1 and BRCA2 mutation carriers randomised to daily aspirin vs placebo for a period of between 6 months and 2 years. Secondary aims include assessing the acceptance of the aspirin intervention, characterising the effect of aspirin on tumorigenesis, and biobanking for future research.

**Methods:** This is an international 3 arm, randomised, double-blind, placebo controlled, window of opportunity, Phase II trial in women with BRCA1 or BRCA2 mutations, scheduled to undergo RRBSO within 6 months to 2 years after randomisation. Aspirin, either 81mg (low dose) or 325mg (high dose), or placebo will be given daily until RRBSO. Frequency of STICs and/or STONes will be assessed at RRBSO using the SEE-FIM protocol. The study sample size is 414 women over 3 years, with 70 of those expected to be recruited in Australia. This investigator-initiated trial will be led by the Canadian Cancer Clinical Trials Group, with involvement of the Gynecologic Cancer Intergroup including the Australia and New Zealand Gynaecologic Oncology Group.

**Conclusion:** Demonstrating a signal of efficacy of aspirin chemoprevention in this well-defined high-risk sample would be an important prelude to a Phase III population prevention trial.
TRACEBACK: Finding $BRCA1$ and $BRCA2$ mutations in women with ovarian cancer that predate changes to genetic testing guidelines


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**Background and Aims:** Women with deleterious germline $BRCA1$ or $BRCA2$ ($BRCA1/2$) mutations have an increased risk of developing breast cancer (BC) and ovarian cancer$^1$ (OC). The identification of a germline $BRCA1/2$ mutation is critical for implementation of risk-reducing strategies. In the absence of population screening, testing patients with ovarian cancer, a sentential BRCA cancer, provides a cost effective and efficient mechanism to detect unaffected germline carriers.$^2$

Australian guidelines recommending $BRCA1/2$ testing for the majority of patients with high grade non-mucinous epithelial ovarian cancer have been in place since 2013. Despite this, it estimated that less than 50% of patients receive an appropriate referral$^3$ and more than 1100 $BRCA1/2$ carriers in Australia have been diagnosed with ovarian cancer over the last 15 years but not tested. Given that the majority of these untested patients are now deceased, there are many family members in the community who remain unknowing at risk with no current means in which to be found or tested.

TRACEBACK$^4$ is a project aiming to reduce the number of $BRCA1/2$ related cancers in Australia by identifying undiagnosed germline $BRCA1/2$ mutations in patients with OC that would otherwise be missed, and then return the findings to facilitate cascade testing. TRACEBACK will also gather further information on variants in newer risk genes and return pathogenic results to participants.

**Methods:** Participants will be recruited by 3 methods: 1) current cohort studies, 2) self-referral, 3) national clinic based out-reach program. For deceased patients sequencing will be done on DNA from FFPE assessing 5 genes of interest ($BRCA1$, $BRCA2$, $RAD51C$, $RAD51D$, $BRIP1$) and 42 risk-associated loci. The study will pilot a process of returning results to surviving next of kin, and those with a result of potential significance will be encouraged to seek predictive testing at an FCC.

**Conclusion:** TRACEBACK will allow unaffected $BRCA1/2$ germline mutation carriers and carriers of pathogenic $RAD51C/D$ and $BRIP1$ the opportunity to adopt risk-reducing strategies. Although logistically challenging, the study may provide insight into detection of high risk carriers in other sentinel cancers.

Better Indigenous Genetic health services (BIG health services)

1Margaret Kelaher, 2Emma Kowal, 3Ravi Savarirayan, 4Gail Garvey, 5Gareth Baynam, 6Hugh Dawkins, 7Misty Jenkins, 8Yin Paradies, 9Glenn Pearson.

1The University of Melbourne; 2Deakin University; 3Northern Territory Genetics Service and Victorian Clinical Genetics Services; 4Menzies School of Health Research; 5Genetic Services of Western Australia; 6Western Australia Department of Health; 7Walter and Eliza Hall Institute; 8Deakin University; 9Telethon Kids Institute.

There is evidence of significant unmet need for clinical genetics and genetic counselling in Aboriginal and Torres Strait Islander populations. There is also evidence that where services do exist, considerable gaps persist in the provision of these services and the continuity of care. With an increasing trend of integrating genomics into clinical practice, addressing these issues is crucial to improving provision of effective genetic health care services to Indigenous Australians.

In this project we will assess the quality, acceptability and effectiveness of four different models of genetic health service provision, gaining insights about best practice and feasibility in each. The models are current practice in delivery of genetic health services in the Northern Territory, Western Australia and Queensland. Based on the assessment findings, we will develop, implement and evaluate interventions, focusing in particular on needs required for effective service provision to Indigenous Australians. The interventions will prioritize capacity building, including training for Indigenous health workers, through a series of workshops to support sustainable implementation of the project outcomes. Clinical genetic service providers in each region were involved in initiating the project and are involved in each phase of the project, from development through to data collection. Their commitment to improving genetic services will ensure that the results of the project will translate into improved patient care. Methodology during the assessment phase will include patient journey mapping, health service quality measures and genetic literacy measures.

These data will be complemented with clinical audits, service provider interviews and policy analysis to identify critical enablers and barriers to culturally safe care. The findings will be used to inform genetic health service improvements that will be implemented by the service providers and are likely to have important implications for the management of other complex conditions in Indigenous Australian populations.
Cancer is a genetic disease. It is estimated that heritable elements contribute 30-60% of the aetiology of common cancers such as breast and prostate but there is little information on the heritability of less common cancers. Population level research is loosening the familial patterns traditionally recognised as associated with heritable cancer syndromes. Diagnosis at an early age is also a reliable indicator of heritable factors at play at the population level. The RisC study has been formed to investigate the heritable genetic drivers of early onset cancer and create a resource for future research. A sub-study will also investigate the accuracy of knowledge about whole genome sequencing and attitudes towards this type of testing. The eligible population includes individuals diagnosed with cancer aged 16-40yrs, or >1 primary cancer <50yrs of age or >2 primary cancers at any age with a target sample size of 1000 probands and their families. Whole genome sequencing will be undertaken on the cohort and clinical, epidemiological and family history information collected. Quantitative psychosocial measures will be administered at baseline, 3 and 12 months post recruitment and semi-structured in-depth interviews will be undertaken on a sub-set of participants. Recruitment began in August 2016, to date 168 probands (56% female) and 43 family members have enrolled. Target recruitment is 1000 probands. The mean age at first cancer diagnosis is 30yrs, SD 9yrs. Twenty-two probands (13%) have had multiple primary cancers. The range of malignancies in the cohort include breast (21%), sarcoma (14%), Hodgkin lymphoma (11%), Non-Hodgkin lymphoma (8%), testicular (7%), gastro-intestinal tract (6%), kidney (3%) as well as prostate, ovary, uterine, lung, liver and other rare cancers. The study is currently open at St Vincent’s Hospital and Prince of Wales Hospital in Sydney and will soon extend to Lifehouse. All those identified as being at increased cancer risk will be offered participation in the SMOC+ surveillance study and followed longitudinally. The RisC study will further our understanding of the heritable genetic basis of cancer, facilitate identification of those at increased risk and inform clinical risk management strategies.
A new population BRCA1/2 testing program offered to the Jewish community in Australia

Nicole Cousens¹; Martin Delatycki²;³; Ian Campbell⁴; Simone Rowley⁴; Bettina Meiser⁵; Lesley Andrews¹,⁵

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Approximately 2.5% of the Jewish population in Australia carry a BRCA1/2 mutation, in comparison to only 0.2% of the general population in Australia. Ninety percent of the mutations identified within the Jewish population include one of three mutations (two in BRCA1 (185delAG and 5382insC) and one mutation in BRCA2 (6174delT)). In Australia, BRCA1/2 Jewish founder testing is currently offered to Jewish people with a personal or family history of breast and/or ovarian cancer. Studies in the UK and Canada however, have shown that just over half of BRCA1/2 carriers within the Jewish population are unaware of their family history, therefore they are not being identified through current practice. Population-based BRCA testing offered to Jewish communities in other countries have shown to greatly increase the number of mutation carriers identified. We are therefore developing a BRCA1/2 screening program for the Jewish population in Australia. The current model of pre-test face-to-face counselling used within Familial Cancer Clinics is not financially sustainable for a population screening program, therefore we have developed two methods of providing population screening which will be compared to each other, as well as with usual care. In Sydney, online pre-test consultations will be provided through an interactive website and consent for testing will be provided online. Cheekswabs will be mailed to participants and DNA samples sent to the laboratory. The majority of test results will be provided through an email, however the following groups will receive their results through a post-test consultation with a genetic counsellor: those with a founder mutation identified; those with a significant family history of breast/ovarian cancer but no mutation identified, and a random sample of people with no mutation identified and no known family history. In Melbourne, group pre-test information sessions will be carried out for members of the Jewish community. Written informed consent and DNA cheekswab samples will be obtained at these sessions. Mutation carriers and people with a significant family history of breast and/or ovarian cancer will be informed of their results through a telephone consultation, and the rest of participants will be informed of results through an email. Questionnaires will be completed by all participants after receiving pre-test information, 2 weeks after receiving results as well as 12 and 24 months after receiving results for mutation carriers. Patients receiving “usual care” at the Hereditary Cancer Clinic, Prince of Wales Hospital, for Jewish founder testing will also be asked to complete questionnaires at these times.
Laura Forrest,¹,² Louise Keogh, and Paul James¹,²

¹Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, Australia; ²Sir Peter MacCallum Department of Oncology, The University of Melbourne, Australia; ³Centre for Health Equity, Melbourne School of Population and Global Health, The University of Melbourne

Young women with a BRCA1/2 mutation have a rapidly increasing breast cancer risk throughout their 20’s and 30’s, and an increasing ovarian cancer risk from their 40’s.¹ A qualitative study recruiting 40 women aged 18 – 40 years with a BRCA1/2 mutation was undertaken in 2014 – 2015. The findings from this study demonstrated that many of the women were aware of their young adulthood life stage and chose risk management strategies around normative development tasks.² For example, most of the younger women (≤30 years) in this cohort chose breast screening to manage their risk because they felt ‘too young’ to have a bilateral prophylactic mastectomy (BPM) and wanted to wait until after they had completed childbearing to potentially having a BPM. Likewise, reproductive planning was influential regarding women’s choices about Tamoxifen with most who were offered this medication choosing not to use it so they could conceive if they wanted within the following five year period.

These findings demonstrate the women who participated in these interviews – a predominantly white, educated, metropolitan-based cohort – were exercising choice in managing their breast cancer risk, with an emphasis on and recognition of their young adult life stage. Correspondingly, there were no obvious unmet information and support needs identified within this cohort and any misunderstandings or ‘unknown unknowns’ could be anticipated to be addressed by the clinical team through these women’s engagement with their local Familial Cancer Centre. However, these findings may not be congruent with the experiences of other young Australian women with a BRCA1/2 mutation who may not have as ready access to a Familial Cancer Centre due to their geographic location or through their own unwillingness to engage with such a service.

Therefore, the next stage of research for this study is to conduct a national online survey of young women aged 18 – 40 years with a BRCA1/2 mutation. In order to conduct this survey, we are seeking the assistance of FCCs nationally to distribute information about the survey to patients who meet the inclusion criteria. Information and links to the online survey will also be distributed through a targeted campaign on social media, and through breast and/or ovarian cancer organisations.

Programme

Wednesday 30th August

A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.

“Familial Cancer 2017 Research and Practice”

Session 4:

Plantation Room

Chairperson: Melissa Southey
Heterozygous germline mutations in BRCA1 or BRCA2 strongly predispose to development of breast and ovarian cancer (as well as other cancer types) via loss of the remaining wildtype allele. BRCA1/2-deficient cancers are defective in DNA double-strand break (DSB) repair via homologous recombination (HR) and therefore hypersensitive to DNA-damaging agents, including platinum drugs and poly(ADP-ribose) polymerase (PARP) inhibitors. However, these treatments do not result in tumor eradication and eventually resistance develops. To maximize therapeutic efficacy of these drugs and achieve durable remissions, it is important to unravel the mechanisms by which these tumors acquire resistance to platinum drugs and PARP inhibitors, in order to develop combination therapies that prevent development of resistance or re-sensitize resistant tumors.

To identify cancer drivers and therapy resistance mechanisms in BRCA-associated breast cancer, we have established several genetically engineered mouse models (GEMMs) and patient-derived tumor xenograft (PDX) models. These mice develop mammary tumors that are characterized by genomic instability and hypersensitivity to DNA-damaging agents, including platinum drugs and PARP inhibitors. Using cross-species oncogenomics and reverse genetics, we have identified several cancer genes including p53, MYC and RB as critical drivers in BRCA1-associated breast cancer. In addition, we have used these mammary tumor models for preclinical evaluation of therapy response and elucidation of mechanisms of acquired drug resistance. Using functional genetic screens, reverse genetics and genomic analysis of therapy-resistant tumors, we found that therapy response and resistance of BRCA1-deficient mammary tumors to cisplatin and the clinical PARP inhibitor olaparib is affected by several factors, including drug efflux transporter activity, type of BRCA1 founder mutation and restoration of HR repair via loss of 53BP1 or REV7. Also BRCA1 re-activation via genetic or epigenetic mechanisms contributes to therapy resistance in PDX models of BRCA1-deficient breast cancer. Importantly, pharmacokinetic or HR-related mechanisms underlie olaparib-resistance in only a fraction of BRCA1/2-deficient mammary tumors, indicating the existence of additional, unknown mechanisms.
High-risk pathological and genomic features of BRCA2-mutant prostate cancer

Laura H. Porter1,2, Mitchell G. Lawrence1,2, Carmel Pezaro1, Heather Thorne2, kConFab2, Kohei Hashimoto1, kConFab2, Dragan Ilic1, Hong Wang1, Melissa Papargiris1, Michael Fraser3, Julie Livingstone3, Shadrielle Melijah G. Espiritu4, Ania Sliwinski5, Jason Li2, Declan G. Murphy2, Mark Frydenberg1, Damien Bolton5, Daniel Moon1, Shomik Sengupta3, Andrew Ryan6, Sam Norden6, David Clouston6, Paul C. Boutros7, Robert G. Bristow7, Renea A. Taylor1,2, Gail P. Risbridger1,2

1Monash University, Clayton, Australia; 2Peter MacCallum Cancer Centre, Melbourne, Australia; 3Princess Margaret Cancer Centre, University Health Network, Toronto, Canada; 4Ontario Institute for Cancer Research, Toronto, Canada; 5Department of Urology, University of Melbourne, Austin Hospital, Heidelberg, Australia; 6TissuPath, Mount Waverley, Victoria, Australia; 7University of Toronto, Toronto, Canada

Germline BRCA mutations are associated with an increased risk of developing aggressive prostate cancer with poor clinical outcomes. However, the mechanisms by which BRCA mutations contribute to clinical aggressiveness are not completely understood. Previously, we showed that BRCA2-mutant prostate cancers often have intraductal carcinoma of the prostate (IDC-P), a distinct growth pattern of prostate cancer that is associated with adverse clinical features. Despite this, IDC-P is not routinely reported in pathology and its functional significance remains poorly understood. Thus, we investigated the clinical relevance of IDC-P as well as the underlying molecular features of localised BRCA2-mutant prostate cancers with and without IDC-P.

To define the prevalence of IDC-P across cohorts of sporadic and familial prostate cancer, we conducted a systematic review in accordance with PRISMA guidelines. This analysis of over 7000 patient specimens revealed that the prevalence of IDC-P rises from 2.1% in low-risk cohorts to 56% in cohorts with metastatic/recurrent disease. Since these data showed that IDC-P is a prominent feature of high-risk prostate cancer, we next studied the biological features of IDC-P using patient-derived xenografts (PDXs). PDXs were established from three patients with germline BRCA mutations and compared to PDXs from four high-risk sporadic cases. IDC-P was successfully grown within the PDXs, maintaining its characteristic morphological features for up to 800 days. Using classical castration-hormone regeneration experiments, we showed that IDC-P contains a subset of “castrate-tolerant” cells that persist after androgen deprivation and subsequently regenerate the tumour. Notably, we found that PDXs derived from BRCA-mutant tumours have the same response to androgen deprivation as sporadic cases.

To further investigate the aggressiveness of BRCA2-mutant tumours, we profiled the genomes and methylomes of localised prostate cancers from 14 germline BRCA2-mutation carriers and compared them to 200 sporadic prostate cancers. BRCA2-mutant prostate cancers had elevated genomic instability and global hypomethylation compared to sporadic tumours. In addition, some genomic features of BRCA2-mutant tumours more closely resembled metastatic than localised disease. Importantly, negative prognostic factors were enriched in BRCA2-mutant prostate cancers harbouring IDC-P. Sequencing of macrodissected IDC-P and invasive carcinoma revealed that these two pathologies arise from a common tumour clone and diverge later in tumour evolution.

In summary, this work demonstrates that IDC-P pathology and genomic instability are two high-risk features of localised BRCA2-mutant prostate cancers. Given the high prevalence of IDC-P in high-risk patient cohorts, including BRCA2-mutation carriers, IDC-P warrants greater recognition and reporting as this may improve patient risk stratification.
The subclonal architecture of metastatic breast cancer: Results from a prospective community-based rapid autopsy program “CASCADE”

Peter Šavas, Zhi Ling Teo, Christophe Lefevre, Christoffer Flensburg, Franco Caramia, Kathryn Alsop, Mariam Mansour, Prudence A Francis, Heather A Thorne, kConFab, Maria Joao Silva, Nnennaya Kanu, Michelle Dietzen, Andrew Rowan, Maik Kschischo, Stephen Fox, David D Bostell, Sarah-Jane Dawson, Terence P Speed, Charles Swanton, Sherene Loi.

Division of Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; Sir Peter MacCallum Department of Oncology, the University of Melbourne, Victoria 3010, Australia; The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia; Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Victoria 3010, Australia; kConFab, Division of Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; Cancer Genomics Program, Division of Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; UCL Cancer Institute, CRUK Lung Cancer Centre of Excellence, Paul O’Gorman Building, Huntley St., London, UK; The Francis Crick Institute, Midland Road, London, UK; University of Applied Sciences Koblenz, RheinAhrCampus Remagen, Department of Mathematics and Technology, Joseph-Rovan-Allee 2, D-53424 Remagen; Department of Pathology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; Bioinformatics Division, Walter & Eliza Hall Institute of Medical Research, Parkville, VIC 3052, Australia; Department of Mathematics and Statistics, University of Melbourne, Parkville, VIC 3010.

Background: Understanding the cancer genome is seen as a key step in improving outcomes for cancer patients. The majority of work in this area has targeted primary tumours however, and very few studies have performed comprehensive profiling of advanced disease. Evolution of the cancer genome during the natural history of breast cancer is largely unknown, as is the profile of disease at death. We sought to study in detail these aspects of advanced breast cancers that have resulted in lethal disease.

Methods: Three patients with ER-positive, HER2-negative breast cancer and one patient with triple negative breast cancer underwent rapid autopsy as part of an institutional prospective community-based rapid autopsy program. Cases represented a range of management problems in breast cancer, including late relapse after early stage disease; de novo metastatic disease; discordant disease response and disease refractory to treatment. Between 5 and 12 metastatic sites were collected at autopsy together with available primary tumours and longitudinal metastatic biopsies taken during life. Subclonal architectures were inferred by jointly analysing mutation and copy number data from all samples for each patient.

Results: Between cases, there were significant differences in mutational burden, driver mutations, mutational processes and copy number variation. Within each case, we found dramatic heterogeneity in subclonal structure from primary to metastatic disease and between metastatic sites, such that no single lesion captured the breadth of disease. Evidence of metastatic cross seeding was found in each case and treatment drove subclonal diversification. Subclones displayed parallel evolution of treatment resistance in some cases, and apparent augmentation of key oncogenic drivers as an alternative resistance mechanism. We also observed the key role of mutational processes in subclonal evolution.

Conclusion: This study highlights the variety of mechanisms that shape the genome of metastatic breast cancer, and the value of studying advanced disease in detail. Treatment drives significant genomic heterogeneity which has implications for disease monitoring and treatment selection in the personalised medicine paradigm.
Mutation Landscape of Familial Breast Cancer

Katia Nones*, Julie Johnson*, Xavier De Luca, Sriganesh Srihari, Kaltin Ferguson, Lynne Reid, Amy McCart Reed, Stephen Kazakoff, Ann-Marie Patch, Felicity Newell, The Kathleen Cuningham Foundation Consortium for Research into Familial Aspects of Breast Cancer (kConFab), Australian Breast Cancer Tissue Bank (ABCTB), Brisbane Breast Bank (BBB), Mark Ragan, Georgia Chenevix-Trench, Kum Kum Khanna, Sunil Lakhani, John Pearson, Nicola Waddell*, Peter Simpson*.

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*These authors contributed equally to the study.

To better understand the aetiology of familial breast cancer we are conducting a comprehensive molecular analysis of tumours from BRCA1, BRCA2 and non-BRCA1/2 (including 1 PALB2) germline mutation carriers. Biospecimens and clinical data were obtained from kConFab, the Brisbane Breast Bank and the Australian Breast Cancer Tissue Bank. Whole genome sequencing (WGS) was performed using Illumina Hiseq Xten on 82 matched tumour (60x coverage)/normal (30x coverage) pairs. The complete spectrum of somatic and germline of mutations has been evaluated, including SNPs, indels, copy number changes and structural rearrangements, and somatic mutational signatures. BRCA1, BRCA2 and non-BRCA1/2 tumours exhibited a different burden of mutations and a different spectrum of mutational signatures. We identified candidate variants in genes which may underlie risk and pathogenesis of disease. For example, a BRCA1-associated tumour contained a BRCA somatic mutational signature, but also a prominent signature that has been associated with variants in the MUTYH gene; a pathogenic germline mutation in MUTYH was subsequently identified. A group of the non-BRCA1/2 carriers contained a BRCA mutational signature suggesting that mutations in other members of the Homologous Recombination (HR) pathway might be driving the development of those tumours. The HR index has also been used to confirm tumours with defective HR pathway. A subset of the 82 tumours was also evaluated by whole genome methylation arrays (n=73) and RNAseq (n=46). The integration of these data will provide evidence of mechanisms that may drive non-BRCA1/2 familial breast tumours. The results obtained with this cohort will be compared to data on sporadic breast tumours obtained from the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA).
A large transcriptome-wide association study in nearly 230,000 women of European descent identifies novel breast cancer susceptibility loci and genes, including *PIDD1*

Georgia Chenevix-Trench¹, Lang Wu², Wei Shi¹, Dylan Glubb¹, Kyriaki Michailidou³,⁴, Jonathan Beesley¹, Natasha Tuano⁵, Breast Cancer Association Consortium, Roger L. Milne⁶, Fares Al-Ejeh¹, Stacey L. Edwards¹, Peter Kraft⁷,⁸, Douglas F. Easton⁵, Joseph Rosenbluh⁵ and Wei Zheng²

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Breast cancer risk variants identified in genome-wide association studies explain only a small fraction of familial relative risk, and genes responsible for the associations remain largely unknown. To identify novel risk loci and likely causal genes, we performed a transcriptome-wide association study (TWAS) evaluating associations of genetically predicted gene expression with breast cancer risk in 122,977 cases and 105,974 controls of European ancestry. We used data from the Genotype-Tissue Expression Project to establish genetic models to predict gene expression in breast tissue and evaluated model performance using data from The Cancer Genome Atlas. Of the 8,597 genes evaluated, significant associations were identified for 46 genes at $P < 5.82 \times 10^{-6}$, a Bonferroni-corrected threshold, including ten in regions not yet reported for breast cancer risk. We silenced 13 putative oncogenes identified in the TWAS in normal breast and breast cancer cell lines and showed an effect for 11 on proliferation and/or colony forming efficiency. One of these 11 genes is *PIDD1* (*p53* inducible protein with death domain), in which the latest genome-wide association study for breast cancer recently found promoter polymorphisms associated with risk. We tested these variants in luciferase reporter assays and showed that the risk alleles in the *PIDD1* promoter were associated with increased expression. Over-expression of *PIDD1* in HMLE cells, an immortalised normal human mammary epithelial cell line that can grow in soft agar only upon introduction of an additional oncogenic insult, showed an increase in colony formation. Our study provides new insights into breast cancer genetics and biology.
Thursday 31\textsuperscript{st} August

A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.

“Familial Cancer 2017  Research and Practice”

Session 5:

*Plantation Room*

The Jeremy Jass Memorial Lecture

Introduction and Chairperson: Mark Jenkins
Reflections on a generation of work on familial aspects of cancer

John L. Hopper, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne

It was 30 years ago at the Genetic Analysis Workshop in Paris that I presented my ideas for a population-based case-control-family study to Mary-Claire King. Graham Giles and I had developed these ideas and in 1992 obtained funding from the Victorian Health Promotion Foundation to study Victorian breast and colorectal cancer families. In collaboration with Margaret McCredie, this became the Australian Breast Cancer Family Study (ABCFS) which has been funded since 1995 by the U.S. National Institutes of Health (NIH) as part of the Breast Cancer Family Registry (Breast CFR). Two years later, and led by Jeremy Jass, the Australasian Colorectal Cancer Family Study (ACCFS) was also funded by NIH as part of the Colon Cancer Family Registry (Colon CFR). Each study includes both population-based, clinic-based and community recruitment, and these designs have been extended by other Australian researchers to other cancers, including prostate, melanoma, endometrial and ovarian cancer, as well as sarcomas and paediatric cancers. Importantly, the clinic-based kConFab study has used the same questionnaire as the ABCFS, enabling data to be pooled with the BCFR to create the Prospective Family Study Cohort (ProF-SC). A generation has passed, and in that time new investigators have taken over and recruitment of the next generation of participants is happening.

The population-based families, complemented by the multiple-case families, now being followed in time have proven to be an extraordinarily powerful design. Findings that challenged what was then a simplistic view of cancer genetics rapidly emerged, and brought with them information that could make, and have made, cancer genetics more cost-effective in translating new genetic knowledge into clinical and population health practice. Multiple papers on the clinical implications of colorectal cancer genetics flowed from the Colon CFR. The population-based family design uncovered the important roles of some variants in *ATM* and *PALB2* well ahead of conventional approaches. The controversies over ‘penetrance’ appear to have been clarified by a large family study of DNA mismatch repair carriers and the recent JAMA publication of long term follow-up of *BRCA1* and *BRCA2* carriers. However, both these papers opened up new issues, and made insights which show that knowledge of one risk factor alone is not enough. The ProF-SC is showing that the greater a woman’s overall familial and genetic risk, the more (not less) important are her environmental and lifestyle risk factors.

Using the odds per adjusted standard deviation (OPERA) concept, the abilities of genetic and other risk factors to differentiate cases from controls can be put in perspective. This is proving to be critical for informing plans to change cancer screening programs that could make them substantially more effective in multiple ways.

All this leads me to optimistically predict that the future will involve integration between cancer genetics services, government-funded cancer screening programs, and commercial interests in risk prediction, so as to realise the full potential of using familial aspects for cancer control.
Revision of the Colorectal Cancer Screening Guidelines: Family History

Mark A. Jenkins\textsuperscript{1}, Driss Ait Quakrim\textsuperscript{1}, Alex Boussioutas\textsuperscript{2}, John Hopper\textsuperscript{1}, Hooi Ee\textsuperscript{3}, Jon Emery\textsuperscript{4}, Finlay Macrae\textsuperscript{5}, James St. John\textsuperscript{6}.

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\textbf{Background:} The clinical practice guidelines for the prevention, early detection and management of colorectal cancer provide information and recommendations to guide practice across the continuum of cancer care including colorectal cancer prevention, screening and diagnosis, clinical aspects of surgery, radiotherapy and chemotherapy, follow-up and psychosocial care. The guidelines also provide an evidence base for the National Bowel Cancer Screening Program. These guidelines are a revision and update of the 2005 clinical practice guidelines. One of the sections is dedicated to \textit{risk and screening based on family history of colorectal cancer}.

\textbf{Methods:} Guidance in this section is based on: the 2005 edition of this guideline; a systematic review of colorectal cancer risk according to family history; a systematic review of benefit of population screening; selected subsequent articles and international guidelines; and adaptations based on consensus. Draft guidelines were assessed by NHMRC following a public consultation phase, and final versions are due for release in 2017.

\textbf{Results:} The following guidelines are for people not known or suspected to have an inherited colorectal cancer risk syndrome (separate sections have been written for high risk familial syndromes). For people with a family history of colorectal cancer who are assessed as having category 1 risk (one or less first-degree relatives with colorectal cancer over age 55), iFOBT should be offered every 2 years from age 50 to age 74. For people in category 2 risk (one first-degree relative with colorectal cancer before age 55 or two first degree relatives with colorectal cancer over age 55), iFOBT should be offered every 2 years starting at age 40, then colonoscopy every 5 years starting at age 50. For people in category 3 risk (three or more first degree relatives with colorectal cancer), iFOBT should be offered every two years starting at age 35, then colonoscopy every five years starting at age 45.

\textbf{Conclusions:} Since the last guidelines, the National Bowel Cancer Screening Program has been funded with a phased roll-out (complete by 2019) offering all Australians free colorectal cancer screening from age 50-74 by biennial iFOBT. These guidelines recommend that all people in Category 1 avail themselves of this screening program which will be sufficient given their risk of colorectal cancer. The main changes from the 2005 guidelines are: some additional family history inclusion criteria for category 2; the removal of the specification for relatives from the same-side of the family to be affected; the genetic syndromes have been removed from category 3, and as a consequence, colonoscopy screening for category 3 is now five yearly; and for category 2 and category 3, screening to begin with iFOBT before age 50, prior to transitioning to colonoscopy at a later age.
Potential Difference in Colorectal Cancer Risk for Lynch Syndrome by Geographic Location of Mutation Carriers: Preliminary Result from the International Mismatch Repair Consortium (IMRC)

Aung K. Win,1,2 Jeanette C. Reece,1 Grant Lee,1 James G. Dowty,1 Robert W. Haile3, Gabriela Moslein,4 Finlay A. Macrae,2,5 Mark A. Jenkins1 on behalf of the IMRC investigators

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Background: Lynch syndrome is a cancer predisposition caused by inherited mutations in mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2, or EPCAM. Accurate cancer risk estimates are needed to develop genetic counselling guidelines, and are of importance for the clinical management of mutation carriers and their family members. Cancer risks for Lynch syndrome may differ not only by age, sex and the mutated gene but also by the genetic variant, country, and ethnicity of the carrier.

Methods: We analysed self-reported age, sex, cancer histories and mutation status of 59,704 first- and second-degree relatives (on average, 14 per family) from 4,146 families submitted to the International Mismatch Repair Consortium (IMRC), worldwide consortium of investigators and experts in research and/or clinical treatment of Lynch syndrome (http://www.sphinx.org.au/imrc). We estimated the hazard ratios (HRs) of colorectal cancer incidence for mutation carriers relative to the general population (based on age-, sex- and country-specific cancer incidences), and hence the age-specific cumulative risks (penetrance) using a modified segregation analysis that incorporated both genotyped and ungenotyped relatives and conditioned on ascertainment to produce unbiased estimates. HRs and penetrance of colorectal cancer were estimated by MMR gene (MLH1, MSH2, MSH6 and PMS2) and by continent (Australasia, Europe, North America, South America and East Asia).

Results: HR (95% confidence interval) of colorectal cancer appeared to be higher for MLH1 mutation carriers from Australasia and North America (32 [22-46] and 32 [26-38], respectively) compared with those from Europe, South America and East Asia (19 [14-26], 5.6 [1.4-22] and 7.4 [3.6-15], respectively). Similarly, HRs for MSH2 mutation carriers from Australasia and North America (62 [24-54] and 33 [28-40], respectively) appeared to be higher than those for Europe and East Asia (14 [12-17] and 8.4 [4.1-17], respectively). HRs for MSH6 mutation carriers from Australasia and North America (5.9 [3.1-11] and 7.6 [5.0-11], respectively) were also higher than those for Europe (3.7 [2.4-5.6]). However, there was no evidence for difference in HRs for PMS2 mutation carriers by continent. Accordingly, the penetrance of colorectal cancer appeared to differ by continent for MLH1, MSH2 and MSH6 mutation carriers. For example, penetrance to age 70 years for female MLH1 mutation carriers: 55%, 48%, 32%, 14% and 10% for Australasia, North America, Europe, East Asia and South America, respectively.

Conclusions: For Lynch syndrome, colorectal cancer risk might differ by geographic location of mutation carriers in addition to the mutated gene. This finding highlights the importance of environmental (and genetic) modifiers of cancer risks for Lynch syndrome.
A risk management clinic model of care improves adherence to screening colonoscopy in patients with Lynch syndrome

Elise Cannan¹, Lucinda Hossack², Dr Driss Ait Ouakrim³, Professor Mark Jenkins³ and Professor Alex Boussiouta²

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**Background:** Lynch syndrome is the most common form of hereditary colorectal cancer. Surveillance colonoscopy has been proven to reduce the colorectal cancer risk in Lynch syndrome, however the benefit is contingent upon patients adhering to the recommendation for annual colonoscopy. Even in high-risk populations adherence to invasive and time-consuming screening procedures is often less than ideal. The primary aim of this study was to evaluate the impact of a specialised risk management clinic on screening adherence in a large population of confirmed mismatch repair gene mutation carriers.

**Methods:** A retrospective analysis of a prospective cohort study at the Peter MacCallum Familial Cancer Centre between 1 January 2006 and 31 December 2016. To investigate screening adherence, patients with a confirmed mutation in *MLH1*, *MSH2*, *MSH6* or *PMS2* genes who underwent clinically-verified screening colonoscopy in the community (non-RMC) or through the Peter MacCallum Risk Management Clinic (RMC) were included. Data was gathered on date, quality and outcome of screening. Patients were considered adherent if they met a threshold of 80% for annual colonoscopy. Adherence was measured as a categorical variable and assessed by Fisher’s Exact test. A logistic regression analysis was used to investigate the association between RMC attendance and adherence to screening colonoscopy.

**Results:** A total of 157 Lynch syndrome mutation carriers were included in the study. We assessed 804 colonoscopies for adherence, quality and outcome. Adherence to annual colonoscopy at a threshold of 80% was 29% for community-screened patients and 62% for RMC patients (p<0.001). RMC patients were five times more likely to be adherent annual colonoscopy than non-RMC patients (OR 5.1, 95% CI 2.4-10.5). Incident CRC was diagnosed in 10% of community-screened patients compared to 0% of RMC patients (p=0.012). Polyp number in the RMC group was significantly reduced over time (p=0.002). There were 18 incident extra-colonic cancer diagnoses over the study period, including 5 gastric, 4 small bowel and 3 urinary tract cancers.

**Conclusions:** The Peter MacCallum Risk Management Clinic model of care improves adherence to annual colonoscopy in patients with Lynch syndrome and improves screening related outcomes. Our results suggest greater adherence to annual colonoscopy and reducing polyp burden may contribute to lowering the risk of colorectal cancer in patients with Lynch syndrome. It is likely extra-colonic Lynch syndrome cancers will present a greater clinical challenge in the future and further research is needed.
Programme

Thursday 31st August

A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.

“Familial Cancer 2017 Research and Practice”

Session 6:

Plantation Room

Chairperson: David Thomas
Background: The field of epigenetic epidemiology has rapidly advanced and recent work has discovered epigenetic markers of breast cancer risk in white blood cell (WBC) DNA. There have been six epigenome-wide association studies (EWAS) for breast cancer risk using blood DNA from prospective cohorts published thus far, and the only consistent finding is a global loss of methylation observed in breast cancer cases compared with controls, with no individual CpG sites passing validation across studies. In contrast, a more successful approach has been the identification of EWAS signatures of cancer risk factors such as smoking, body mass index, age and alcohol use with numerous validated CpG sites. These signatures may be used as a molecular test to quantify cancer risk associated with these factors. We have proposed a mechanism that involves cancer risk exposures, lifetime and environmental events, that alter the epigenome and stably modifies an individual’s cancer risk. Our overall aim is to identify epigenetic traits within the epigenome that are associated with the risk of developing breast and ovarian cancer.

Methods: We have recently conducted EWAS using whole genome bisulphite sequencing (WGBS) of WBC DNA from incident breast cancer cases (n=548) compared with matched controls (n=548) and from ovarian cancer cases (n=78) compared with matched controls (n=78) using a pooled DNA approach. We used Agilent target capture bisulphite sequencing (TCBS) for technical validation in a subset of breast cancer cases (n=48) and matched controls (n=48).

Results: Interrogation of specific genomic regions showed that gene-body methylation averages tended to be hypomethylated in both breast and ovarian cancer cases, while CpG island averages identified both hypo- and hypermethylation. We identify significant increase in “accelerated methylomic aging” in breast cancer cases and show epigenetic risk is independent of polygenic risk scores for breast cancer.

Conclusions: Epigenome-wide hypomethylation and methylation in specific sites, particularly gene bodies, measured in pre-diagnostic blood samples may be predictive of breast and ovarian cancer risk, and may thus be useful to incorporate into risk models. Further validation in larger cohorts using a TCBS based approach, targeting the variable epigenome, is warranted.
Heritable methylation risk factors for familial breast cancer

Ifrah Khalid, Jihoon E. Joo, James G. Dowty, Roger L. Milne, Ee Ming Wong, Pierre-Antoine Dugué, kConFab, ABCFR, Dallas English, John L. Hopper, David E. Goldgar, Graham G. Giles, Melissa C. Southey

Currently, only approximately 50% of breast cancer cases occurring in multiple-case breast cancer families are associated with mutations in the known breast cancer susceptibility genes. We have previously developed an innovative statistical genetic method, based on genetic segregation analysis, that uses data generated from a high-density methylation array (Infinium HumanMethylation450; HM450K) and a multiple-case family design to identify heritable methylation marks associated with breast cancer risk. We identified two peripheral blood DNA methylation marks located at the promoter regions of VTRNA2-1 and GREB1 genes. While the HM450K allows the measurement of DNA methylation on a genome-wide scale, it is a low-resolution technique and each region requires further characterisation using loci-specific detection techniques.

In the present study, we aimed to (i) assess DNA methylation levels of the VTRNA2-1 and GREB1 promoter regions using targeted bisulfite sequencing with blood DNA samples from 126 members from 20 multiple-case breast cancer families; (ii) sequence the 2kb flanking regions of these CpG sites to identify potential genetic variants responsible for the aberrant methylation marks observed in these individuals; (iii) examine the corresponding breast tumour methylomes (n=26), using the HM450K, to assess the role of these methylation marks in the tumourigenic process. We will present new data to illustrate how the study of heritable DNA methylation marks can improve breast cancer risk management for all women by improving risk prediction models, identifying potentially modifiable risk factors and providing new targets for epigenetic therapeutics in breast cancer prevention and treatment.
Aberrant DNA methylation marks in mutation-negative early-onset breast cancer

Ee Ming Wong\textsuperscript{1,2}, JiHoon Eric Joo\textsuperscript{1,2}, Tu Nguyen-Dumont\textsuperscript{1,2}, Cameron M. Scott\textsuperscript{1}, Neil O’Callaghan\textsuperscript{1}, ABCFS, kConFab, ViP, Graham G. Giles\textsuperscript{3,4}, Paul James\textsuperscript{5,6}, John L. Hopper\textsuperscript{3}, Melissa C. Southey\textsuperscript{1,2}

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Early-onset breast cancer (EOBC; diagnosed before the age of 40 years) accounts for less than 5\% of all breast cancers in Australia. Many affected young women face a poor prognosis as their tumours tend to be at a more advanced stage at diagnosis, with limited treatment options. Previous work has shown that mutations in the known breast cancer predisposition genes account for ~10\% of EOBC.

\textit{BRCA1} provides an example of a breast cancer predisposition gene that increases the risk of breast cancer when mutated or when methylated in the germline. A high level of \textit{BRCA1} promoter methylation is also a feature of some breast cancer tissues (including those arising in women with \textit{BRCA1} constitutional methylation) and associated with the same morphological features as breast cancers arising in \textit{BRCA1} germline mutation carriers. This study explores the possibility of other, yet to be identified genes, involved in breast cancer predisposition via multimodal silencing such as in the \textit{BRCA1} example.

Using genome-wide technology, several regions of aberrant methylation have been identified in breast cancers and shown to be associated with copy number, hormone receptor status, intrinsic molecular subtypes, gene expression, mutation status and/or overall survival. DNA methylation has been described as an early event in breast cancer and these marks provide new opportunities for targeted therapy. To date, few studies have examined the EOBC methylome. Here, we have measured genome-wide methylation using the Infinium HumanMethylation450 Beadchip array on EOBC tumour-enriched DNA. Our study includes women who carry mutations in \textit{BRCA1} (n=5), \textit{BRCA2} (n=12), \textit{PALB2} (n=12) and women who carry no germline mutation in these genes (n=47).

Conditional logistic regression analysis will be used to identify differentially methylated probes (DMPs) (false discovery rate (FDR) adjusted p-value<0.01) between \textit{BRCA1}, \textit{BRCA2}, \textit{PALB2} and mutation-negative tumours. We will specifically test for adjacent FDR\textsubscript{adj} DMPs in the same genomic region. We will present data focussed on the association of these DMPs with i) carrier status; ii) germline DNA methylation status; iii) family history; iv) tumour histological features and v) hormone receptor status.

A new class of risk factor for EOBC (DNA methylation) could increase the precision of tools developed to identify young women at greatest risk of breast cancer, enabling them to engage in risk management and cancer prevention strategies. This is an exciting area of work given the potential for methylation marks to be modifiable and for these findings to capitalise on developing epigenetic therapeutics and chemoprevention.
Bioinformatic and functional evaluation of rare variants in the 5’ region of BRCA1, BRCA2 and non-BRCA breast cancer susceptibility genes

Lez Burke1*, Jan Sevcik1,2,3*, Gaetana Gambino1,5*, Emma Tudini1,4 , Philip Whitey1,4 , Michael Parsons4, Kim De Leeneer6, Sara Gutiérrez-Enríquez7, Marta Santamaría Pena8, Sandrine Caputo9,10, Elizabeth Santos dos Santos9,10, Stacey Edwards1*, ENIGMA consortium, Rien Blok11, Thomas van Overeem Hansen12, Orland Diez7, Ana Vega8, Kathleen Claes6, Etienne Rouleau9,10, Peter Rogan13 Paolo Radice14, Paolo Peterlongo14, Maria Caligo5, Amanda Spurdle3, and Melissa A. Brown16

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Germline mutations in non-coding regions of a significant number of genes have been shown to alter gene regulation and be associated with increased cancer risk. An escalating number of these variants are being identified by next generation sequence analysis of early onset and familial breast cancer cases, the vast majority of which are of unknown clinical significance. These ‘unclassified variants’ present a major clinical challenge as they complicate test reporting and genetic counseling, limit patient eligibility for intensive surveillance and gene-targeted therapies and prevent gene testing and guided management of relatives. We have screened the 5’ non-coding regions of BRCA1 and BRCA2 for sequence variants in a large set of early-onset breast cancer cases collected by the ENIGMA consortium that carry no known pathogenic mutations in BRCA1 or BRCA2 coding regions or splice junctions. We have identified 128 rare non-coding single nucleotide variants and small indels from multiple cohorts over different geographical sites. Through a comprehensive pipeline of bioinformatic analyses, 23 single nucleotide high priority rare variants were selected for functional analyses. Luciferase reporter assays in breast cancer cells demonstrated altered promoter activity in 6 of these variants. Electrophoretic mobility shift assays further showed that 5 of these 6 variants alter the binding of proteins to BRCA1 and BRCA2 promoter regions showing that bioinformatic-based prioritization of variants enable a reliable estimation of potential impact of sequence alteration of promoter activity. These data suggest that single nucleotide variants in the 5’ region of BRCA1 and BRCA2 may contribute to breast cancer susceptibility by altering the expression of these genes, and forms the basis of further studies to determine the contribution such variants may make to breast cancer risk. These data, along with preliminary studies to characterize the promoter regions of the non-BRCA breast cancer susceptibility genes PTEN, PALB2, RAD51C/D and TP53 will be presented.
Nanopore sequencing of full-length BRCA1 mRNA transcripts reveals co-occurrence of known exon skipping events

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*These authors jointly supervised this work

Accurate interpretation of DNA sequence variants in the breast and ovarian cancer susceptibility gene, BRCA1, is essential for clinical management of patients and their families. Laboratory assays evaluating the effect of these variants on splicing of the 7.2 kb BRCA1 mRNA transcript can contribute to classification by providing molecular evidence. However, our knowledge of normal and aberrant BRCA1 splicing events to date has been limited to data derived from assays targeting partial transcript sequences. The ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) Splicing Working Group recently reported a comprehensive analysis of numerous ‘naturally occurring’ mRNA splice isoforms for BRCA1. This ENIGMA-based study identified more than 60 BRCA1 mRNA isoform events occurring in breast and/or blood cells. However, it remains unclear whether these individual splicing events can co-occur in the same BRCA1 transcript. For the first time, we resolve the exon structure of full-length BRCA1 transcripts using MinION nanopore sequencing of long-range PCR amplicons. We analysed RNA from a lymphoblastoid cell line, used previously by ENIGMA, and identified 32 BRCA1 isoforms, including 18 novel isoforms which comprised multiple individual splicing events. Furthermore, we show that known BRCA1 exon skipping events, such as Δ(9,10) and Δ21, can co-occur in a single transcript, with some isoforms containing four or more alternative splice junctions. Our results highlight BRCA1 has a complexity in transcript structure that has not previously been described and has key implications for predicting in-frame and out-of-frame events, which are important for interpreting the clinical significance of spliceogenic variants. Our study also demonstrates the utility of nanopore sequencing to characterize the exon structure of whole transcripts and the potential of this technology to overcome limitations of PCR-based techniques. Future research is warranted to quantitatively assess full length BRCA1 transcript levels and assess potential correlations between co-occurring exon skipping events.
Programme

Thursday 31\textsuperscript{st} August

A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.

“Familial Cancer 2017  Research and Practice”

Session 7

*Plantation Room*

Chairperson: Rachel Williams
Beth Crawford¹, Irene Acerbi¹, Katherine Abihider², Jennie Ling¹, Tracy Layton², Diana DeRosa², Lisa Madlensky², Jeffrey Tice¹, Yiwey Shieh¹, Elad Ziv¹, Setareh Sarrafan¹, Roxanna Firouzian¹, Barry Tong¹, Miya Frick¹, Liane Abrams¹, Amie Blanco¹, Deborah Goodman⁴, Erica Silver⁵, Vivian Lee, advocate¹, Diane Heditsian, advocate¹, Susie Brain, advocate¹, Celia Kaplan¹, Alexander Borowsky³, Hoda Anton-Culver⁴, Arash Naeim⁵, Thomas Cink⁶, Allison Stover Fiscalini¹, Barbara Parker², Laura van ’t Veer¹, Andrea LaCroix⁵, Laura Esserman¹, Wisdom Study and Athena Breast Health Network Investigators and Advocate Partners¹

¹University California San Francisco; ²Univ California San Diego; ³Univ California Davis; ⁴Univ California Irvine; ⁵Univ California Los Angeles; ⁶Sanford Health, Sioux Falls, South Dakota

Purpose: Women Informed to Screen Depending on Measures of risk (WISDOM) trial is a pragmatic study comparing two real world approaches to clinical care for breast screening: annual screening versus personalized screening. The novelty of the personalized arm of the study is that we are combining known risk factors (age, family history, history of breast disease, ethnicity, BIRADS breast density, and genetics) into a single risk assessment model. All components of the model have been tested and established, but have never been used jointly. The goal of the WISDOM study is to examine the effectiveness of personalized breast cancer screening and to bring objective recommendations to the current mammography screening debate.

Methods: The WISDOM trial will enroll 100,000 women with a preference-tolerant design that will determine if risk-based screening vs. annual screening, is as safe, less morbid, enables prevention, and is preferred by women. Women 40 - 74 years of age with no history of breast cancer or DCIS, and no previous double mastectomy can join the study from the WISDOM Study website (wisdomstudy.org). All participants sign up, elect randomization or self-select the study arm, provide electronic consent using DocuSign (eConsent), and sign a Medical Release Form. For all participants, 5-year risk of developing breast cancer is calculated according to the Breast Cancer Screening Consortium (BCSC) model. For participants in the personalized arm, the overall 5-year risk BCSC score is combined with a Polygenic Risk Score (based on a panel of 75 common single nucleotide polymorphisms known to increase breast cancer risk), and genetic testing including mutations in 9 genes (BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, ATM, PALB2, and CHEK2). Risk stratification will determine frequency of screening. The study is registered on ClinicalTrials.gov as NCT02620852 and funded by PCORI PCS-1402-10749.

Results: As of June 12th 2017, the WISDOM study is live at all UC medical centers and recruitment is open to all eligible women in California. Up to date 4,769 eligible women registered at all sites. 2,823 women have consented in the trial. 64% were randomized and 36% chose their screening arm. A pilot was conducted to test the logistics of online participation and examine the acceptance of the study design and approach. We are partnering with health insurance companies and self-insured companies to reach our recruitment goal.

Conclusions: Enrolment will be completed by end of 2018.
Toward Tailored Screening: prospective validation of personalised breast cancer risk stratification in a cohort of 53,000 Australian women

Carolyn Nickson\textsuperscript{1}, Paul James\textsuperscript{2,4}, Lisa Devereux\textsuperscript{7}, Sarah Carr\textsuperscript{1}, Pietro Procopio\textsuperscript{1}, Bruce Mann\textsuperscript{5}, Yulia Arzhaeva\textsuperscript{6}, LifePool Study, Ian Campbell\textsuperscript{3,4}

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Targeting mammography and other measures aimed at improving breast cancer (BC) outcomes to women in the population at the highest level of risk has the potential to significantly improve screening effectiveness. Epidemiological and lifestyle factors, family history, mammographic density (MD) and genetic variation have all been found to predict breast cancer risk. The LifePool study is a large cohort of Australian women, healthy at enrolment, undergoing breast screening with ongoing follow up. The study began enrolling in 2010 and allows direct assessment of the performance of risk stratification tools in the Australian population.

After exclusions, NCI Breast Cancer Risk Assessment tool (Gail model) and AutoDensity mammographic density measurements were applied to 38,762 LifePool participants aged 50-69 at enrolment who completed their questionnaire within ± 60 days of a baseline BreastScreen screening episode. Incident cancer diagnoses (and deaths) were identified by report and through cancer registry linkage (median follow-up 4.1 years since baseline screen) and included 423 invasive BC (1.1%) (56 confirmed interval cancers) and 85 DCIS, with median diagnosis age of 63 years.

The median 5-year BC risk estimated by the Gail model was 1.5% (range 0.6-19.4) with increasing numbers of BC observed from the lowest to the highest quintile of predicted risk (HR=2.3 (1.6-3.1)). Receiver operator curve analysis demonstrated moderate ability to predict invasive BC (AUC 0.59) and interval cancers (AUC 0.58) and a lower performance for DCIS (AUC 0.54). AutoDensity MD ranked by 5-year age group generated an inter-quintile HR of 1.8 (1.3-2.5) for invasive breast cancer and HR=7.5 (1.7-32.8) for interval cancers; ROC analyses showed MD could help discriminate women at risk of future invasive BC (AUC 0.55), DCIS (AUC 0.55) and interval cancers (AUC 0.66). Genotyping for 74 breast cancer associated SNPs was performed in a subgroup of 5,000 women and a polygenic risk score (PRS) calculated. The average PRS in women diagnosed with BC was significantly increased, (0.23 SD), with a similar increase in BC diagnoses across the quintiles of risk (IQ OR 1.8 (1.3-2.4)). Pairwise correlation between Gail scores, AutoDensity MD and PRS was weak (r≤0.02).

Data from this population-based cohort provides large-scale prospective validation of the Gail model and AutoDensity MD scores for risk stratification in the Australian population as well as evidence for independent approaches such as polygenic risk. The study aims to establish an algorithm combining these scores to help optimise approaches to tailored screening.
Identifying high-risk predisposition genes for childhood cancer

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Approximately 650 children are diagnosed with cancer in Australia every year, but the aetiologies of these rare diseases are not known. Only 10% of all childhood cancer cases are associated with known cancer predisposition genes. Furthermore, the role of adult cancer predisposition syndromes in childhood cancer is not well understood. The Victorian Paediatric Cancer Family Study (VPCFS) is a population-based sample of 379 children diagnosed with cancer before the age of 15 years, and their families, recruited from the two paediatric cancer hospitals in Victoria. Cancers in the probands comprised 165 haematological malignancies, 47 brain tumours and 67 childhood solid tumours. Of 960 cancers observed in the family members, 39, 64 and 106 were diagnosed before the ages of 30, 40 and 50 years, respectively. We first performed whole genome sequencing (WGS) for 30 highly-selected probands using blood-derived DNA. Germline DNA was then extracted for all remaining VPCFS participants who had provided a blood sample (n=745). Further screening of 292 genes of interest, identified from the WGS analysis and from the literature, was performed for all these VPCFS participants using the HaloPlex enrichment system. Preliminary analysis of known cancer predisposition genes including BRCA1, BRCA2, APC, DNMT3A, CTR9, NSD1, PMS2, NF1, RB1 and RUNX1 revealed 83 heterozygous (30%) and 5 rare homozygous (2%) proband carriers of genetic variants defined as pathogenic in ClinVar. No pathogenic variants were observed in TP53. We will report on further comprehensive analysis of the genetic variation identified by the targeted sequencing, and assess the possible association of these genetic variants with predisposition to childhood cancer. We anticipate that this dataset will reveal important insights into childhood cancer aetiology and lead to improved cancer prevention, more effective cancer screening and impact clinical care.
The range of BOADICEA scores in women eligible for MRI Breast Screening at the Peter MacCallum Familial Cancer Centre

T Schenberg, P James, A Trainer

Background/Aims: Medicare Benefit Schedule Criteria for MRI breast screening are out of date and do not accurately determine women whom are at high risk of breast cancer. Ours (and many other) centres now use the breast cancer risk calculator BOADICEA to assess womens’ lifetime risk of breast cancer.

The aim of this study is to describe the range of BOADICEA lifetime risk scores in women whom are eligible for MRI Breast Screening. We would like to clarify what percentage of women eligible for MRI breast screening do not achieve a lifetime risk score of 30% as this has traditionally been considered the definition of high risk in Australia. We hope to demonstrate that a large amount of women not at high lifetime risk of breast cancer are eligible for MRI Breast screening.

Methods: Patients eligible for MRI Breast Screening were found by performing a keyword search of the Familial Cancer Centre (FCC) database. Their progeny pedigree was converted to a Boadicea Web Application data file. These files were then run as a bulk batch through BOADICEA.

Results: A total of 212 patients were included in the audit. The range of BOADICEA scores can be seen in Graph 1.

75.5% of women eligible for MRI breast screening did not achieve a BOADICEA lifetime risk score of 30%.

Graph 1. Range of BOADICEA scores

Conclusion
At our centre, most women eligible for MRI Breast Screening do not have a BOADICEA score compatible with a high lifetime risk of breast cancer.
Penetrance of FLCN Mutations in Birt-Hogg-Dubé Syndrome

Fiona Bruinsma and Laura Goddard

**Background:** Birt-Hogg-Dubé (BHD) is a rare genetic predisposition caused by germline mutations in *FLCN* and associated with renal carcinoma and lung and skin manifestations. Previous penetrance estimates of these diseases for BHD have been unprecise or biased.

**Methods:** A systematic literature review was performed by searching studies that reported pedigree and disease data of families with at least one person with a *FLCN* mutation through PubMed MEDLINE, and contacting corresponding authors for required data if possible. A modified segregation analysis was conducted incorporating both genotyped and ungenotyped relatives, and conditioning on ascertainment to produce unbiased estimates. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) of incidence of renal cell carcinoma, lung and skin manifestations, and colorectal cancer for mutation carriers compared with the general population, and hence the age-specific cumulative risks (penetrance) were estimated.

**Results:** A total of 678 first-degree relatives and 713 second-degree relatives from 165 families entered into the penetrance analysis. We observed 14 renal cell carcinomas, 89 lung manifestations, 12 skin lesions and 6 colorectal cancers amongst first- and second-degrees, with a mean age at diagnosis of 49.7 (standard deviation [SD] 17.5), 40.4 (18.1), 40.3 (16.2) and 59.8 (18.4) years, respectively. The HRs (95% CI) were: renal cell carcinoma, 7.43 (2.26-24.5) for males and 7.22 (1.37-38.2) for females; lung manifestations, 115 (4.51-2965) for males and 19.9 (4.90-81.1) for females; skin manifestations, 11.21 (4.35-28.9) for males and 14.2 (5.89-34.2) for females; and colorectal cancer, 0.69 (0.06-7.35) for males and 1.66 (0.09-29.48) for females. The cumulative risks to age 70 years (penetrance) were estimated to be: renal cell carcinoma, 8.3% (2.6-25%) for males and 4.3% (0.8-21%) for females; lung manifestations, 1% (0.1-23%) for males and 0.1% (0.02-0.4%) for females; and skin manifestations, 9.3% (3.7-22%) for males and 11.7% (5-26%) for females.

**Conclusions:** These unbiased penetrance estimates from our large study will be useful for genetic counselling and clinical management for BHD families.
Programme

Friday 1st September

A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.

“Familial Cancer 2017 Research and Practice”

Session 8:

Plantation Room

Chairperson: Mandy Ballinger
The Potential of Cancer Screening in Li-Fraumeni Syndrome

Sharon A. Savage, M.D.
Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Patients with Li-Fraumeni syndrome (LFS) are at very high risk of bone and soft tissue sarcoma, premenopausal breast cancer, brain tumors, adrenocortical carcinoma, leukemia, and many other cancers. The primary cause of LFS is autosomal dominant inheritance of pathogenic variants in the TP53 tumor suppressor gene. As more individuals with cancer undergo clinical genetic testing, the LFS cancer spectrum has expanded to include most major cancer types, such as melanoma, lung, gastrointestinal, thyroid, and ovarian cancers. Early detection of cancer in LFS is challenging because of the wide-range of cancers occurring over the entire lifespan. Two studies using 18F-PET/CT found an asymptomatic cancer in 10 to 20% of TP53 mutation carriers but concerns about radiation exposure have limited its use. Recently, 10-year follow-up was reported on 89 children and adults with LFS who underwent a comprehensive cancer surveillance strategy using annual whole body MRI (WB MRI), brain MRI, breast MRI (for women), quarterly blood tests, and quarterly abdominal ultrasound for children. This approach showed significant reduction in cancer-related mortality and higher overall survival for patients undergoing cancer surveillance.

In 2011, we opened a longitudinal cohort study of LFS at the US National Cancer Institute (NCI) to further quantify the cancer risk in these families, identify cancer risk modifiers, evaluate psychosocial challenges associated with LFS, and establish a cancer screening regimen for individuals with TP53 mutations. We recently reported on cancer occurrence in 286 TP53 mutation carriers from 107 families in this cohort. The cumulative cancer risk in women with germline TP53 mutations was 50% at 31 years of age, predominantly due to very high incidence of pre-menopausal breast cancer. Men with germline TP53 mutations had a cumulative cancer incidence of 50% by age 46 years. Almost half of patients with one cancer developed a second cancer. We recently evaluated baseline cancer screening studies of 116 TP53 mutation positive individuals in this cohort. The median age of the participants was 37.6 years (range 3-68 years) and 77 were female (66.4%). Forty participants (34.5%) had a finding on screening evaluation requiring additional studies and 32 of those were incidental, benign, or normal findings. The baseline screening led to the diagnosis of eight new malignancies (6.9% of the screening cohort) via WB MRI, brain MRI, or breast MRI. Baseline abdominal ultrasound, mammography, or blood tests did not lead to any cancer diagnoses.

In collaboration with investigators in the Li-Fraumeni syndrome Exploration (LiFE) consortium, we combined data from 13 cohorts in six countries and conducted a meta-analysis of baseline WB MRI findings. Of the 578 TP53 mutation positive individuals, the mean age was 33.2 years (+/-17.1 years) and 376 were female (65.1%). 173 participants required follow-up for 225 WB MRI lesions. A total of 42 new primary malignancies were diagnosed in 39 individuals resulting in 7% detection rate (95% confidence interval 5-9%) for new cancers in this cohort.

In summary, the data suggest that a comprehensive cancer surveillance program for TP53 mutation carriers has the potential to improve survival given the high detection rate for new malignancies.
Investigating ACMG rules and quantitative methods for TP53 missense variant classification

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Background: TP53 pathogenic germline variants are related to Li-Fraumeni Syndrome (LFS). The increasing use of multi-gene panel testing has led to identification of many TP53 variants in cancer patients outside LFS. Further, the majority of variants identified are missense alterations, complicating assessment of their clinical relevance. Methods commonly used to evaluate variants include qualitative criteria such as the American College of Medical Genetics (ACMG) guidelines, or statistical quantitative methods such as multifactorial likelihood analysis.

Aims & Methods: Using a reference set of pathogenic (n=351) and benign (n=166) TP53 missense variants defined by both clinical and functional evidence, this work aimed to: (i) optimize performance of the Align-GVGD missense prediction tool by modification of the existing multi-sequence alignment datasets; (ii) compare the performance of different bioinformatic prediction methods to address ACMG computational rules (PP3; BP4); (iii) establish benign frequency cut-offs in order to address ACMG population rules (BS1; BA1); (iv) investigate other information sources that could be used as evidence in quantitative modelling: a) duplicated amino acid residues (ACMG PM5); b) somatic to germline ratio.

Results & Discussion: Increasing the average number of substitutions per position in the multi-sequence alignments used by Align-GVGD improved performance, with ROC analysis AUC 0.909 for the new optimized alignment compared to 0.891-0.900 for existing alignments. The Matthews correlation coefficient (MCC) was then used to compare the prediction quality for several tools: optimized Align-GVGD, SIFT, Polyphen2, REVEL, and BayesDel. Prediction was more reliable when using a combination of tools (MCC = 0.84 for optimized Align-GVGD and REVEL; MCC = 0.85 for optimized Align-GVGD and BayesDel) than when using any tool alone (MCC = 0.55 – 0.81). Regarding population data, the gnomAD dataset included 699 unique TP53 variants. The highest population-specific frequency (excluding Ashkenazi Jewish) of a single variant from the missense pathogenic reference set was 9.75e-5 for c.848G>A (p.Arg283His). This observation supports using ACMG frequency cut-offs of 0.03% (strong) and 0.1% (stand-alone) as evidence against pathogenicity. For the reference sets, co-location of missense substitutions was observed for 88.1% of the pathogenic variants and 58.4% of the benign variants, with only 16 unique amino acid residues shared between both sets. This observation indicates that finding a new variant in a known pathogenic residue could be used as qualitative evidence for pathogenicity (ACMG PM5), and also has potential to be included as quantitative evidence in multifactorial modelling. The somatic to germline count ratio in the IARC TP53 database was highly correlated for pathogenic (R² = 0.8052), but not benign (R² = 0.0706) reference set variants, and has demonstrated value for use in quantitative modelling.

Conclusion: We provide evidence to define gene/syndrome-specific data sources suitable for TP53 variant classification using ACMG criteria, and/or quantitative statistical modelling.
Interval Breast Cancer versus Screen-Detected Cancer: Genomic comparison of germline predisposing genetic variants and acquired somatic aberrations

Dane Cheasley, Kylie L Gorringe, David Byrne, Lisa Devereux, Simone M Rowley, Siobhan Hughes, Kenny Elder, Rhonda Huynh, Kenji Fujihara, Hugo Saunders, Bruce Mann, Stephen B Fox, Ian G Campbell

1Cancer Genetics Laboratory, Peter MacCallum Cancer Centre, Melbourne; 2Dept of Pathology, Peter MacCallum Cancer Centre, Melbourne; 3Lifepool, Peter MacCallum Cancer Centre, Melbourne; 4Royal Melbourne and Royal Womens Hospitals, Melbourne.

Breast cancers diagnosed after a negative mammogram but prior to the next screening episode are termed “interval cancers” and account for ~25% of women diagnosed with breast cancer attending population-based screening programs. The high interval cancer (IC) rate is a major problem affecting the effectiveness of mammographic screening. Many ICs are diagnosed at later stages and have a worse prognosis in comparison to screen detected (SD) cancers, indicating the aggressive nature of the tumour. Whether ICs possess unique therapeutic vulnerabilities is unknown, since remarkably little is known about the molecular changes that contribute to this aggressive phenotype. Whilst large databases of genomic data are available for breast cancer, this data is rarely linked to mammographic screening status. In addition to understanding the molecular drivers of ICs, equally important is determining which women are at risk of developing an IC as it could be used to devise more appropriate and targeted screening.

Using an Australian prospective population-based cohort of over 54,000 women (LifePool), 1294 cases of breast carcinoma (in situ and invasive breast cancer) were identified, of which 1003 had known screening status at time of diagnosis. Pathology reports, mammographic density data, germline DNA and tumour tissue were available for analysis. ICs had increased tumour size (P < 0.001), higher proportion were node positive (P < 0.001), higher proportion of ER and PR positive staining (P < 0.001), had a higher proliferative index (P < 0.001), and higher grade (P < 0.001). There was a trend towards a higher proportion of HER2 positive cases, younger age at diagnosis, and occurrence in mammographically dense breasts in ICs; however these differences were not significant.

Analysis of germline DNA was performed using a panel sequencing approach of known breast cancer predisposition genes as well as lower-penetrance breast cancer SNPs. Pathogenic mutations in BRCA1, BRCA2, TP53 and PALB2 were identified in 13/62 ICs (in BRCA2), and 5/309 SD cases. SD cancers may thus have a reduced contribution from high-penetrance predisposing variants. Somatic mutation and copy number analysis was performed on a subset of invasive SD and IC cases using panel sequencing and OncoScan MIP arrays. No differences in mutations profile, overall copy number aberrations or fraction of the genome altered was observed. However specific differences were noted between IC and SD cases, including copy number changes on chromosomes 8 and 11. Together with published epidemiological studies, genomic analysis points towards ICs having a different molecular etiology.
Colorectal cancer susceptibility genes: findings from whole exome, genome and targeted sequencing of multiple-case families


1Melbourne Bioinformatics, The University of Melbourne, Parkville, Victoria, Australia; 2Colorectal Oncogenomics Group, Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Parkville, Victoria, Australia

Only a small proportion of the heritable risk for colorectal cancer (CRC) can be attributed to mutations within known CRC-associated genes, suggesting that additional CRC-predisposition genes are yet to be discovered. The aim of this study is to develop a mutational landscape of CRC predisposition from a family based cohort using a mixture of whole genome, exome and targeted sequencing. 200 CRC-affected individuals were selected for whole genome and exome sequencing from 100 Australasian Colorectal Cancer Family Registry (ACCFR) families (criteria: Familial Colorectal Cancer Type X (FCCTX), multiple-case families not meeting clinical criteria or had Oligopolyposis). Another set of 830 early-onset CRC cases from ACCFR were screened using multiplexed PCR-based target-enrichment (Hi-Plex).

Software pipelines were developed to identify variants from all sequencing platforms (available from https://github.com/khalidm). Variant calls were filtered on quality metrics such as depth of coverage and genotype qualities. Individual variants were prioritized as being likely pathogenic based on the criteria: (1) rare variants (ExAC MAF < 0.05%), (2) variants annotated as being protein truncating (stop gained, frameshifts and splice sites), (3) non-synonymous mutations with predicted impact on protein function derived from CADD score > 20 or REVEL score > 0.5. Gene level prioritization was performed by comparing frequencies of likely pathogenic variants observed in cases compared to the general population described in ExAC.

Sequencing analysis has identified 3 likely pathogenic \textit{FAN1} variants in 4 multi-case CRC families. The variant (\textit{FAN1}:p.Arg952*) was found in 4 individuals from a family (3 CRC and 1 bone marrow cancer case). We have identified additional likely pathogenic variants in \textit{NT HL1}, \textit{POLE} and \textit{POLD1} genes using the WGS/WES and Hi-Plex data from these cohorts. We will also present novel likely pathogenic variants and genes as well as a complete landscape of likely pathogenic variants and genes across the cohorts. These data suggests that WES/WGS and targeted sequencing together are important tools for studying the underlying genetic causes for CRC-predisposition.
Programme

Friday 1st September

“A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.

“Familial Cancer 2017: Research and Practice”

Session 9:

Plantation Room

Chairperson: Georgia Chenevix-Trench
Cancer Gene Panels – Panacea or Pandora’s box?

Marc Tischkowitz
Department of Medical Genetics, University of Cambridge, East Anglian Medical Genetics Service, UK

Over the last five years cancer gene panels have rapidly taken over from gene-specific testing in cancer genetics practice. However, the evidence base for many of the genes on panels is weak and management guidelines are lacking. I will give an in depth update on one these genes, PALB2, based on the latest data on >500 families from the PALB2 Interest Group www.palb2.org. I will look at some of the other more controversial genes included on panels and describe the UK consensus-based approach to developing standard panels for use across the country.
Balancing clinical excellence with clinical equity: maximizing the minimum gain (maximin)

Trainer AH¹, Widdowson H², Farrugia H²,

¹Parkville Familial Cancer Center, Parkville, Melbourne; ²Victorian Cancer Registry, Cancer Council Victoria

The two principles underlying a socially-funded health care system are 1) cost-effectiveness, and 2) equity of access according to need. Issues of cost-efficiency are being increasingly addressed in the familial cancer, whilst equity of access studies, arguably more important for a cancer-prevention specialty, are limited.

With recognition that specific subtypes of breast and ovarian cancer are strongly associated with germline BRCA mutations irrespective of family history, comes the ability to clearly define a population of women with cancer who warrant BRCA testing based on tumour-pathology alone and therefore a group that can be defined on clinical grounds as at equal need of familial cancer referral. This group of women can be identified on any state cancer registry (CR).

In Victoria, we assessed 1) how effective our FCC referral pathways are for women who develop a triple negative breast cancer (TNT) diagnosed ≤ 50yrs, or a high grade serous ovarian cancer at any age (HGSO), and 2) what epidemiological, socio-economic and geographic factors impact on the probability of FCC Referral.

We performed a retrospective data cross-match of all women with either a TNT diagnosed ≤ 50yrs or HGSO diagnosed ≤ 80yrs (defined by ICD –O 3 codes and ER / PR receptor immunohistochemistry and HER2 expression result where appropriate) held on the Victorian cancer registry from 1st January 2008 to 31st December 2014 with the subset of women seen at the Victorian FCCs. Using this approach, all women reported to the VCR with an incident TNT or HGSO in this period were categorized as either “FCC referred” or “FCC non-referred”. Parameters relating to year of diagnosis, age at diagnosis, time from diagnosis to death, socio-economic index for area codes (SEIFA) codes, Accessibility/Remoteness Index of Australia (ARIA) codes, region of birth and integrated cancer service region were supplied for all women: in de-identified form for women in the “FCC Non-referred category”.

A univariate and multivariate logistic regression (LR) analysis was undertaken using “FCC non-referred” as the outcome variable.

The results indicate that there was a significant increase in both single and multivariate analysis in FCC referral for TNT in years 2011-2014 compared to 2008 (base year). In 2014, 77% of all TNT cases diagnosed ≤ 50 were referred. In comparison, the FCC referral of HGSO cases all ages has not changed significantly from 65% between 2009 - 2014. Age at Diagnosis, tumour grade, time from diagnosis to death, and socio-economic index (SEIFA code) significantly impact on FCC referral of HGSO in the multivariate analysis, whilst age of diagnosis, year of diagnosis, grade, time to death and ARIA code impact on FCC referral for TNT. These data and their implication on clinical service provision will be discussed in more detail.
The contribution of rare variants in novel candidate genes to the hereditary risk of breast cancer

Na Li¹, Simone Rowley¹, David Goode¹, Lisa Devereux¹, Simone McInerny², Norah Grewal², Amanda Lee¹, Alison Trainer¹,², Michelle Wong-Brown³, Rodney Scott³, Kylie Gorringe¹, Paul James¹,², Ian Campbell¹.

¹Cancer Genetics Laboratory, Peter MacCallum Cancer Centre, Melbourne, Australia; ²Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, Australia; ³Division of Genetics, Hunter Area Pathology Service, Newcastle, Australia.

Background: About 20-40% of breast cancer patients are diagnosed less than 50 years old and/or have a family history of breast/ovarian cancer suggesting a considerable proportion of cases are caused by inherited factors. BRCA1 and BRCA2 mutations account for about 20 to 25 percent of hereditary breast cancers and other high to moderate penetrance genes such as account for a further 5 to 10 percent. However, in approximately half of high-risk families the causative genetic factor remains unknown (so called BRCAx families). Identifying the full repertoire of breast cancer predisposition genes could have a major and immediate impact on reducing breast cancer risk in these family members.

Methods: We identified candidate breast cancer predisposition genes through whole exome sequencing of BRCAx families and subsequently sequenced up to 1325 genes, along with 76 common low penetrance variants associated with breast cancer, in index cases from 6,000 BRCAx families and 6,000 cancer free women from the lifepool study (www.lifepool.org).

Results: The role of recently described (PALB2) or suspected (MRE11A) moderately penetrant genes was confirmed. Conversely, the size of the cohort means that the absence of enrichment for loss of function (LoF mutations) provides strong evidence against other reported breast cancer genes (BRIP1, RINT1, RECQL). Novel candidate genes were identified based on LoF mutations and this identified a large number of candidates where the ratio of LoF mutations in cases versus controls indicates that they may convey an actionable level of risk; 46 genes (in 519 families) meet the basic criteria of multiple LoF variants and an OR >2 for cases versus controls – including previously proposed breast cancer genes MRE11A, BLM, MLH1, MUTYH, FANCD2 and functionally plausible candidates such as MLH3, PARP2 and ATR. Collectively the OR of breast cancer for LoF mutations in this group of genes is 3.3 (95% CI 2.7-3.9, P=3.5x10^-41). Principal Component Analysis using 74 Ancestry Informative Markers showed the study subjects were predominantly European ancestry (more than 96%) with significant overlap of ancestry distributions between cases and controls, strongly suggesting our findings are not due to major differences in ancestry between our cohorts.

Conclusion: Our data shows that the effect of rare variation in established and novel breast cancer genes explain a substantial component of the heritable risk of breast cancer in our cohort.
Targeted sequencing in large cohorts of breast cancer families and population controls identify \textit{NTHL1} as novel breast cancer predisposition gene

Na Li$^1$, Simone Rowley$^1$, Simone McInerny$^2$, Lisa Devereux$^1$, Michelle Brown$^3$, Amanda Lee$^1$, Norah Grewal$^2$, Alison Trainer$^2$, Rodney Scott$^3$, Kylie Gorringe$^1$, Paul James$^2$, Ian Campbell$^1$

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\textbf{Objectives}: Identifying the missing hereditary factors underlying the familial risk of breast cancer could have a major and immediate impact on managing the breast cancer risk for these families.

\textbf{Methods}: We identified candidate breast cancer predisposition genes through whole exome sequencing of BRCAx families, and validated up to 1325 genes in index cases from 5,000 BRCAx families and 4,800 cancer free women (confirmed ethnically matched by principal component analysis).

\textbf{Results}: Novel candidate genes were identified based on \textit{loss-of-function} (LoF) mutations; missense variants were analysed separately and a series of \textit{in silico} prediction tools were used to predict the likelihood of pathogenicity. From the 1325 genes that were successfully sequenced, \textit{NTHL1}, which encodes a key glycosylase in the base excision repair (BER) pathway, showed the strongest enrichment of LoF mutations (38 cases versus 15 controls, OR 2.5, $p=0.003$) including one homozygous LoF carrier diagnosed with multiple primary cancers, including breast cancer. In addition, missense variants also showed significant enrichment in the cases, either on the basis of rarity (allele frequency MAF<0.5%) (77 cases versus 46 controls, OR 1.6, $p=0.008$) or predicted pathogenic by any of the \textit{in silico} tools (e.g. CADD score $>15$; 51 cases versus 30 controls, OR 1.7, $p = 0.033$). If loss of NTHL1 function drives breast cancer development in carriers of LoF mutations this may impart a specific mutation signature in the tumour. To assess this, we sequenced breast cancer DNA from 17 heterozygous \textit{NTHL1} mutation carriers and this revealed a strong bias towards a C:G$\rightarrow$T: A (C$\rightarrow$T) transitions. This signature was not evident in breast cancers without germline \textit{NTHL1} mutations and consistent with the signature identified in colorectal cancers with bi-allelic \textit{NTHL1} mutations. The pattern of segregation of \textit{NTHL1} LoF mutations in 9 families where DNA samples from family members were available was consistent with that expected for a moderate penetrance gene.

\textbf{Conclusions}: Our data implicates rare mutations in \textit{NTHL1} as moderate penetrance breast cancer susceptibility alleles and is consistent with the observation that over 50\% of female bi-allelic \textit{NTHL1} LoF mutation carriers develop breast cancer (manuscript submitted).

The role of RNF43, NTHL1, POLE and POLD1 in Serrated Polyposis

Marie Lorans¹, Khalid Mahmood, Mark Clendenning, Bernard Pope, Harindra Jayasekara, Christophe Rosty, Sharelle Joseland, Sonja Woodall, Julie Arnold, Neil O’Callaghan, Susan Preston, Daniel J. Park, Fleur Hammet, Tu Nguyen-Dumont, Melissa C. Southey, Kara Semotiuk, Melyssa Aronson, Spring Holter, Steven Gallinger, Aung K. Win, Mark A. Jenkins, Kevin Sweet, Finlay A. Macrae, Ingrid M. Winship, Susan Parry, Daniel D. Buchanan for the Genetics of Colonic Polyposis Study

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Background: Serrated polyposis (SP) is characterised by the presence of multiple serrated polyps in the large intestine and associated with an increased risk of colorectal cancer (CRC). Recent studies have reported germline pathogenic variants in RNF43 in individuals with SP. The association between the polyposis-associated genes, NTHL1, POLE and POLD1, has not been previously investigated in SP. The aim of this study was to determine the clinical utility of testing for germline mutations in RNF43, NTHL1, POLE and POLD1 in individuals with SP.

Methods: 67 probands and 8 first-degree relatives with SP from the Genetics of Colonic Polyposis Study (GCPS) were selected for whole exome sequencing (WES, n=58) or whole genome sequencing (WGS, n=17) based on clinical criteria (young age at diagnosis, high polyp burden and family history of SPS and/or CRC). A further 351 SP probands were screened using a PCR-based target-enrichment platform (Hi-Plex) covering the coding regions of RNF43, NTHL1, POLE and POLD1. Single nucleotide variants and short indels were considered likely pathogenic if they satisfied the following two criteria: 1) novel or present in ExAC at <0.2% minor allele frequency (NTHL1) and <0.005% (RNF43, POLE and POLD1); and 2) resulting in loss of protein function (LoF: truncating, frameshift or splice site) or a non-synonymous change predicted to have deleterious effect on protein function as determined by a CADD (>20) or a REVEL (>0.5). Likely pathogenic variants were confirmed by Sanger sequencing.

Results: The combined WGS/WES and Hi-Plex datasets identified six (1.4%) likely pathogenic variants in RNF43 among the 418 SP probands. Compared with the ExAC dataset, individuals with SP exhibited an enrichment for likely pathogenic RNF43 variants (odds ratio [OR] 18.3, 95% confidence interval [CI] 7.8-42.9, p=1.3E-06). A total of 10 RNF43 carriers from these 6 families were identified, with 7 fulfilling WHO criteria for SP; one carrier was diagnosed with CRC, at age 27 years. We identified six (1.7%) NTHL1 carriers: five heterozygote carriers; and a single compound heterozygote carrier who was diagnosed with 30 serrated polyps and 20 adenomatous polyps as well as CRC and breast cancer at age 61 and 62 years, respectively. A carrier of a likely pathogenic missense variant within the exonuclease domain of POLE was also identified. No variants within the exonuclease domain of POLD1 was identified.

Conclusions: We found a substantial enrichment of likely pathogenic variants in RNF43 among individuals with SP, although such variants were present in only a small fraction of individuals affected by this syndrome. Our findings of NTHL1 and POLE likely pathogenic variants in individuals that fulfil the criteria for SP suggests that the phenotype associated with germline mutation in these genes includes both adenomatous and serrated polyps.
Programme

Wednesday 30th September

A combined meeting of kConFab, Australian Breast Cancer Family Study, Australasian Colorectal Cancer Family Registry, Family Cancer Clinics of Australia and New Zealand and the International Sarcoma Kindred Study.

“Familial Cancer 2017: Research and Practice”

Poster Session

6.00 – 7.30 pm

In the main Foyer of Mantra
Challenges with MEN: experiences from the Parkville Familial Cancer Centre

K Storey, C Beard, A McLauchlan, E Wright, M Kentwell, M Walsh, C Yates, N Sachithanandan, A Trainer

Multiple Endocrine Neoplasia Type 1 (MEN1) is a highly-penetrant, autosomal dominant condition caused by mutations in the \textit{MEN1} gene. MEN1 is characterized by parathyroid, pancreatic islet, and pituitary tumours. A clinical diagnosis of MEN1 can be made if an individual has two or more of these tumours. Some patients may also develop carcinoid tumours, adrenocortical tumours, meningiomas, facial angiofibromas, collagenomas, and lipomas. Detection rates of inherited \textit{MEN1} mutations are high in those with a clinical diagnosis, especially if there is family history, however scenarios where isolated features are seen are less predictive of a mutation. Limiting genetic testing to those with a clinical diagnosis poses the risk of missing clinical cases, however a broad approach to testing also reduces specificity for this rare condition. To assist with this, EviQ provides a summary of detection rates reported in the literature based on some clinical presentations.

To learn from our own experiences of testing for this condition, we conducted an audit of referrals for MEN1 and genetic testing outcomes at the Parkville Familial Cancer Centre. We assessed our findings compared with expected detection rates from the literature based on clinical presentation, and identified cases that did not fit the classic MEN1 presentation.

As biochemical and radiological investigations can assist in identifying suitable individuals for genetic testing, a multidisciplinary approach is recommended for these patients. We also present experiences from collaboration with Endocrinologists affiliated with our service, and optimal referral pathways that incorporate input from both genetics and endocrinology teams.
The Australasian genetic counsellor workplace: 15 years on

B. Massey¹; R. Fleischer², J. Fleming¹, A. Colley³ and K Barlow-Stewart¹

¹Discipline of Genetic Medicine, Sydney Medical School – Northern, University of Sydney, St Leonards, NSW; ²Department of Medical Genomics, Royal Prince Alfred Hospital Camperdown, NSW; ³Department of Clinical Genetics, Liverpool Hospital, Liverpool NSW

National and international discussion highlights the importance of the genetic counselling workforce. This study therefore aimed to establish a snapshot of the current Australasian genetic counselling workforce and workplace and explore changes over the last 15 years. Invitations to participate in an anonymous online survey (RedCAP) were disseminated via genetic counsellor list-serves and promotion at relevant meetings. The survey was a repeat of that by James et al (2003), with additional questions relevant to current and future practice. All 111 respondents to date reported they are employed as a genetic counsellor. Preliminary analysis shows respondents work in all states, territories and NZ in traditional public genetics services, subspecialties, private practice and other settings; 44% employed for >5 years in current setting. Compared to 2002, more genetic counsellors working in research and private practice completed a survey. 55% work full-time; qualifications include Graduate Diploma (28%) and Masters (56%); and 38% are HGSA certified and 56% in training. Respondents reported increases in workload (85%) and changes in roles (76%); such as use of genome databases (~70%) and undertaking variant interpretation (~65%). Free text comments include ‘more autonomy/responsibility’; ‘manage increased complexity in information’; and ‘implement new technologies’. Overall, 24% have considered changing roles including decreasing their clinical contact. HGSA certification was valued, though lack of career path and level of salary/awards remain a concern. Analysis and recruitment is continuing. The findings will inform development of the profession, future workforce planning, and state and federal health policies related to genetic counselling service provision.
Patient experiences of consenting to a rapid autopsy study: The CASCADE-PIPS (Participant Interview Psychosocial Study) proposal

Laura Forrest,1,2 Lisa Devereaux,2,3 Heather Thorne,2,4 Odette Spruyt,5 Mary-Anne Young,6 Philomena Horsley,7 Robin Anderson,2,8 Kathryn Alsop,9 Matthew Ryan,10 and David Bowtell2,9

1Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, Australia; 2Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville Australia; 3BROCADE-CASCADE, Research Department, Peter MacCallum Cancer Centre, Melbourne, Australia; 4kConFab, Research Department, Peter MacCallum Cancer Centre, Melbourne, Australia; 5Pain and Palliative Care, Peter MacCallum Cancer Centre, Melbourne, Australia; 6Genome One, The Garvin Institute of Medical Research, Sydney, Australia; 7Centre for Women's Health, Gender and Society, The University of Melbourne, Parkville Australia; 8Translational Breast Cancer Programme and Metastasis Research Laboratory, Olivia Newton-John Cancer Research Institute; 9Cancer Genomics and Genetics Program, Peter MacCallum Cancer Centre, Melbourne, Australia; 10Consumer Representative

Abstract

CASCADE is a research program enrolling patients with advanced metastatic disease who consent to undergo rapid autopsy following death. CASCADE was initiated at the Peter MacCallum Cancer Centre to enable research into treatment resistant cancers, including: melanoma, ovarian, breast, prostate, and lung cancer. Individuals with metastatic disease are consented to CASCADE when they reach the end of life, and understand that there are no further curative options available. We are not aware of any empirical evidence describing participants’ experiences of consenting to a rapid autopsy cancer study at the end of life. Therefore, this psychosocial study aims to examine CASCADE participants’ motivations and experiences of consenting to a rapid autopsy study.

A descriptive qualitative approach using phenomenology is being undertaken to examine the experiences of individuals who have consented to the CASCADE program. CASCADE participants will be invited to take part in a semi-structured interview that will explore different facets of their decision-making process, the personal and familial impact of this decision, and explore their motivation for taking part in CASCADE.

This presentation will describe the development of the CASCADE-Participant Interview Psychosocial Study (CASCADE-PIPS). This will include a brief review of the literature that provided a foundation to the development of CASCADE-PIPS, describe the research protocol that guides the recruitment and interviewing processes, consider the ethical implications of conducting this qualitative research with participants who are at the end of life, and outline the expected outcomes of CASCADE-PIPS. Finally, preliminary findings from interviews with CASCADE participants will be described if data have been collected to date.
A Centralised National Telephone Genetic Counselling Program for Woman with Ovarian Cancer to Access BRCA1/2 Mutation Testing: Referral Patterns, Uptake and Patient Characteristics

Linda Cicciarelli,¹ Alexandra Lewis,¹ Alisha McLauchlan,¹ Sharne Limb,¹ Mary-Anne Young,² and Paul James¹,³

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This program is supported by AstraZeneca

Background: Recurrent high-grade epithelial ovarian cancer has been shown to respond to poly (ADP-ribose) polymerase (PARP) inhibitors offering survival benefit specifically to women with germline BRCA1/2 mutations. The availability of this treatment necessitates prompt access to genetic testing for women with this type of ovarian cancer. However, the rates of genetic testing for women with ovarian cancer remain low despite recent changes to the clinical genetic testing criteria and efforts to mainstream BRCA1/2 testing. A centralised national telephone genetic counselling program was implemented in 2016 by the Familial Cancer Centre at the Peter MacCallum Cancer Centre to improve access to BRCA1/2 testing for women with recurrent high-grade epithelial ovarian cancer.

Clinical Pathway: Patients with recurrent high-grade epithelial ovarian cancer throughout Australia are referred by a member of their oncology team via telephone or email to the telephone genetic counselling program. The patients are contacted within 24 hours by a genetic counsellor via telephone for a genetic counselling appointment. Patients who wish to proceed with genetic testing after their telephone genetic counselling appointment are mailed a pathology request slip and have blood collected locally and processed by a centralised laboratory. The genetic counsellor provides the test results by telephone 4-6 weeks afterwards to most patients, except those whose oncologist wishes to return the results.

Outcome: Two hundred and forty seven women from all States and Territories in Australia have been referred for genetic testing via the telephone genetic counselling program between January 2016 and July 2017. 15 were ineligible as they either had undergone BRCA testing previously, or did not have high-grade epithelial ovarian cancer. One hundred and ninety five women proceeded with BRCA1/2 mutation testing, with pathogenic BRCA1 or BRCA2 mutations identified in 13 women (6.7 per cent) and variants of unknown significance in 11 women (5.6 per cent). Eighty Seven oncology services referred patients to this program from all States and Territories in Australia, of whom 5 elected to mainstream the genetic testing by consenting and deliver the test results to their patient themselves.

The uptake of this program by women with ovarian cancer from all States and Territories in Australia and their referring oncologists indicates that this program may make genetic counselling and testing more accessible to patients who previously may have experienced barriers to conventional genetic testing pathways. An independent evaluation using a mixed methods approach is currently being conducted to examine the accessibility, acceptability, and feasibility of offering this telephone genetic counselling program to women with ovarian cancer and their oncologists.
The lived experiences of adolescents and young adults with Li-Fraumeni Syndrome: are their psychosocial needs being met?

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**Background:** Adolescents and young adults (AYAs: aged 15-29 years) with Li-Fraumeni Syndrome (LFS) have significantly increased risks of developing primary malignancies at multiple sites from an early age. AYAs with LFS experience their transitional life stage of emerging adulthood concurrently with increased cancer risk and the potential of a reduced lifespan. The prospect of intensive life-long surveillance and, for some, cancer treatment may create a complex and unique set of psychosocial needs that remain inadequately understood.

**Aim:** To explore the lived experiences and identify the psychosocial support needs of AYAs who live with, or at risk of, LFS.

**Methods:** Thirty participants aged 15-29 years with, or at 50\% risk of having, a \textit{TP53} germline mutation are being recruited across Victoria. Participants complete semi-structured interviews examining the psychosocial impact of LFS for AYAs. Data analysis is ongoing, and informed by interpretive phenomenology.

**Results:** We present preliminary data from six interviews collected during the first three months of this ongoing qualitative interview study. All young participants understood their high cancer susceptibility but possessed a varied understanding of which cancers were associated with LFS. Females were able to detail their age-specific breast cancer risk. All participants felt their identity was not defined by LFS, and that genetic testing and comprehensive screening provided them control over their future. Two participants reported LFS-related distress and had sought out professional support. Four were enrolled in research-based or personalised comprehensive screening programs and felt that screening offered them a sense of control over LFS. One was concerned about potential screening fatigue associated with longitudinal comprehensive screening and one did not engage in MRI-based screening due to anxiety of confined spaces. One young female had sought consultation to undergo bilateral prophylactic mastectomy.

**Conclusion:** These preliminary data suggest young people with, or at risk of, LFS have a range of genetic and health literacy. Some experience LFS-related distress, and this may be addressed by active risk management strategies and seeking professional support. The experiences of AYAs in this context are still under exploration to develop a better understanding of their ongoing psychosocial support needs.

**Key Words:** Li-Fraumeni Syndrome; adolescents and young adults; psychosocial; lived experiences
“Just another straw on the stack” – Men with Lynch Syndrome’s experiences of re-contact about potential increased risks of prostate cancer

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**Introduction:** In cancer genetics, efficacious risk management strategies are available to individuals who carry a high-risk germline mutation. However, we know little of how these individuals experience being notified of newly associated cancer risks, especially when corresponding effective risk management strategies are yet to be established.

**Aim:** To explore how men with Lynch Syndrome understand and experience the return of uncertain prostate cancer risk information and its influence on their health behaviours.

**Methodology:** Using a modified grounded theory approach sixteen men with Lynch Syndrome were purposively recruited from the Australian IMPACT study (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in men at a higher genetic risk and controls) to undergo a semi-structured interview. At the time of the interview, the mean age of participants was 51 years and the mean time since genetic testing for Lynch Syndrome was 9 years.

**Results:** The majority of men acknowledged they may be at above population risk of prostate cancer and recognised that evidence linking Lynch Syndrome and prostate cancer was still emerging. They felt their risk of prostate cancer was overshadowed by the diagnosis of Lynch Syndrome; a potential prostate cancer risk was “just another straw on the stack” to be added to their already high-risk status. Consequently, the emotional experience of being notified of their prostate cancer risk was characterised by low cancer worry and acceptance. Overall men were highly engaged in personal and familial health.

**Conclusion:** These findings suggest men integrate new prostate cancer risk information into their pre-existing understanding of Lynch Syndrome such that it has limited emotional impact, and that they are highly engaged in screening, which plays a critical role in their perceived sense of cancer risk control. Optimally, new cancer risk information from research should be returned in tandem with the offer of research-based or clinically available cancer-specific screening.

**Key Words:** Lynch Syndrome; prostate cancer; recontact; experiences; male
Male breast cancer survivors: Psychosocial experiences and needs

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Abstract

Background: In contrast to the widespread awareness, support and research on breast cancer in women, little is known about male breast cancer and how the condition affects men psychologically, physically and socially.

Objective: This study aimed to explore the experiences of Australian male breast cancer survivors.

Methods: A mixed-methods approach using a sequential explanatory model, integrating data from both quantitative and qualitative collection phases. Phase 1: Participants completed a self-reporting questionnaire in order to investigate experiences and perceptions. Phase 2: To further explore and elaborate on domains identified from the questionnaire responses, semi-structured interviews were conducted with a purposive sample of respondents.

Results: Data from 38 questionnaires and five interviews revealed various experiences and perceptions, with many participants experiencing a delay in their diagnostic pathway. Participants also identified a lack of relevant and accurate information in relation to male breast cancer, and a need for gender-specific peer support resources.

Conclusions: This study is the first Australian investigation into the experiences of male breast cancer survivors and reveals that compared to reports from other countries, Australian men were more open with family and friends about their diagnosis. Findings indicate that an increase in awareness of male breast cancer could contribute to the improvement of outcomes and experiences for Australian men diagnosed with the disease in the future.

Implications for Practice: Despite men’s mostly positive experience, tailored resources and healthcare services for male breast cancer patients, including gender-specific informational resources and male peer support services are needed.
Heightened risk perception and the influence on decision-making in younger women undergoing bilateral prophylactic mastectomy

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Background: The way women perceive their risk of developing BC could have a strong influence on the decision to undergo a bilateral prophylactic mastectomy (BPM). Many women overestimate their risk of developing BC and their fear of this risk is often a deciding factor to undergo BPM. However, there is a dearth of literature focusing on younger women (<40) in relation to BPM.

Methods: Qualitative interviews guided by interpretative phenomenological analysis (IPA) were conducted with women who had a strong family history of BC (or a BRCA1/2 mutation) and had either undergone (n=26) or were considering (n=20) BPM. Participants were recruited from Australia and New Zealand.

Results: Five themes were identified: underlying fear and anxiety, screening anxiety and fatigue, children, personal experiences with BC and death, information that increases fear of BC. A further two themes: relief following surgery and confusion about residual risk following surgery were identified. The decision to undergo BPM for younger women (<35) was multifaceted, however, it appeared that fear and anxiety were the main influence. Younger women (<35) appeared to have heightened and sometimes inaccurate perceptions of their BC risk. They appeared less relieved of anxiety and fear of developing BC by BPM surgery, in comparison to previous research with older women (>40). Those who had undergone BPM seemed more anxious about their risk of developing BC than those who were still considering surgery.

Conclusions: These findings have important practice implications, particularly improving communication of accurate risk statistics, especially to those with no known BRCA1/2 mutation. Health professionals need to take into account the way younger women perceive information given to them when discussing risk. Emphasis should be placed on communicating the residual risk of developing BC post BPM. Future research should examine why some women interpret information differently.
Australian Genomics Health Alliance (AGHA) Survey of Current Genetic Testing Practices in Australia

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The Australian Genomics Health Alliance (AGHA) proposes to integrate genomic medicine into Australian healthcare. Program Two – A National Approach to Data Federation and Analysis – aims to co-ordinate curation, storage and secure sharing of genomic data nationally.

To inform project implementation, we surveyed Australian NATA-accredited self-nominated genetic testing laboratories to assess current practices around germline and somatic variant testing. These laboratories were invited to participate by email, and 22/30 (73%) eligible labs completed the survey online or by telephone interview. General findings were:

- Germline testing ranged from single variant to whole genome, with single-gene and in-house/commercial gene panels most commonly performed.
- 13/16 (81%) responding laboratories use American College of Medical Genetics and Genomics (ACMG) criteria alone, or in combination, for variant classification.
- 12/14 (86%) respondents report variants of uncertain significance in genes relevant to the condition.
- 9/13 (69%) respondents report incidental/secondary findings.
- Reasons stated for selecting “actionable” genes varied greatly, and included: use of a standard lab gene list (4/14, 29%); genes requested by a clinician (3/14, 21%); ACMG or other clinical guidelines (3/14, 21%); literature (2/14, 14%); a combination (3/14, 21%).
- 11/13 (85%) respondents re-evaluate variant classifications, but only 3/11 (27%) re-evaluate periodically, and only 5/9 (55%) re-issue reports.
- Somatic testing appeared to vary considerably with regard to testing services and processes for variant classification and reporting.

This survey identified several areas for further investigation that, in consultation with HGSA, RCPA, NPAAC and NATA, are required to reach national consensus in genetic variant evaluation and reporting in Australia.
Pink Hope – Know Your Risk Tool

Krystal Barter, Sue Jones, Jowveria Muffi and medical experts from Peter MacCallum Cancer Centre. Pink Hope, PO Box 725, Narrabeen, NSW 2101.

Pink Hope is a preventative health organisation working to ensure every individual can assess, manage and reduce their risk of breast and ovarian cancer, while providing personalised support for at risk women.

In 2015, in collaboration with Peter MacCallum Cancer, Centre Pink Hope developed an online breast and ovarian cancer risk assessment tool; Know Your Risk. The tool provides an assessment of a women’s family history of breast and ovarian cancer risk so together with their doctor women can formulate a plan to manage their risk and, if they are eligible, seek a referral to a Family Cancer Clinic. The tool was launched October 2015.

The Know Your Risk Tool is based on the national EViQ guidelines. Early in 2016 the EviQ guidelines were updated so changes to the tool were made to reflect these amendments. At this time the tool was also given a refreshed look.

Pink Hope launched the updated version of the Know Your Risk tool at the beginning of February 2016. The marketing campaign featured models, actors and influencers with videos, testimonials and photos using the tool. This material was rolled out across Facebook, Instagram and Twitter. During February and March 2016 4,763 people took the tool.

In February 2017 an online marketing campaign to encourage people to take the Know Your Risk tool was expanded to include clinicians and high risk women.

The tool is currently being updated to include more information for those with a cancer diagnosis and better reporting tools. The design of the tool is also being refreshed. A launch and marketing campaign will be held in August 2017.

Since October 2015 nearly 17,000 people have taken the tool. The number of people in each category is as follows:

- Gene Mutation in Family - 3099
- Strong fhx Ovarian Cancer - 253
- Fhx Male Breast Cancer - 371
- Mod/High Risk - 2878
- Mod Risk Breast – 1091
- Low Risk Breast & Ovarian - 2641
- Low Risk (no fhx) - 5162
- Phx Cancer - 1112
- Slightly higher ovarian LR breast - 68
Website review for an online BRCA 1/2 community testing program offered to the Sydney Jewish community

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Background: About 2.5% of the Ashkenazi-Jewish population within Australia carry a mutation in BRCA1 and BRCA2, compared with 0.2% of the general Australian population. Unlike the general population, 90% of mutations identified within the Jewish population consist of three “founder” mutations (two in BRCA1 (185delAG and 5382insC) and one in BRCA2 (6174delT)). Therefore, testing for these specific “founder” mutations, within the Jewish population, is relatively simple. Currently in Australia, testing is offered to Jewish people with a personal or family history of breast and/or ovarian cancer; however studies in the UK and Canada have shown that just over half of BRCA1/2 carriers within the Jewish population are unaware of their family history and are therefore not identified through current practice. Population-based testing in other countries has shown to greatly increase the number of mutation carriers identified, compared to targeted testing of people with a family history. The current model of pre-test face-to-face counselling used within the Familial Cancer Clinics is financially unsustainable and inefficient within a population screening program however. Therefore an interactive website was developed by a cancer genetics clinician, in consultation with genetic counsellors, to provide all information that would normally be presented at a pre-test Jewish Founder Mutation (JFM) consultation. This website will be used in a large study comparing a new online population BRCA1/2 testing program with usual care. Before this study begins however, the website needs to be reviewed.

Aim: To assess the attitudes of a small sample of Sydney Jewish community members towards the website before it is made available to the entire community for an online BRCA1/2 testing program.

Method: A previewed version of the website was emailed to 20 members of the Jewish community. These people were also asked to complete an online questionnaire. The sample included: Rabbis, medical practitioners, geneticists, people who have undergone BRCA testing previously, as well as others who are involved in the community who do not have any previous experience with BRCA testing personally or within their family. The questionnaire asked people about the information presented on the website, including amount of information, how clear the information was, whether the information was well balanced, whether it allows you to make an informed decision regarding undergoing the BRCA1/2 test or not, as well as any suggestions for improvements. Results will be presented at the conference.
PREXIT-Paper Records Exit into an Electronic Era- the birth of CHOCgene

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\textbf{Background:} With the move to the new Bright Alliance premises, the Hereditary Cancer Centre (HCC) was required to become paper-light. No accommodation was provided for patient paper records. The HCC was required to adopt an electronic record appropriate for family genetics records and provide for electronic storage and access of old files. Typically hospital electronic medical records deal with the record of one individual. Genetics records are family records, which need to comply with a secure level of privacy separate from main hospital medical records, and cannot be destroyed. The NSW state genetics database (Trakgene) is not compliant as an electronic medical record (EMR), nor does it allow for the scanning of documents into the database. A cost effective, secure and medical records compliant EMR was needed, which would also minimise duplication of data entry.

\textbf{Methods:} Compliance was achieved with the hospital medical records, ethical and privacy policies for dealing with an individual’s and family genetic record, and state health electronic documentation requirements.

\textbf{Results:} The HCC adapted the existing Cerner hospital medical record for the use for genetics records, using the CHOC (Community Health and Outpatient Care) module. Successful implementation occurred at the HCC in early 2017. Old files were prepared by our department and scanned by an outside provider (ADEC).

Issues faced in this implementation included patient process mapping, dealing with family records in a single patient environment, development and approval of hospital forms and genetic acronyms, and event set hierarchy approval for scanning documents into the record. Regular review was required in the first few weeks to ensure actual patient process flow worked in the anticipated process planned 12 months earlier.

We propose to give a presentation of the CHOCgene solution and describe the hurdles we have faced in processing old files and adapting to the new system.
Determining drivers of self-funded genetic testing demand: Clinical experience at the Parkville Familial Cancer Centre

Abiramy Ragunathan, Alisha McLauchlan, Maie Walsh, Geoff Lindeman, Paul James, Alison Trainer.

Background: An underlying genetic predisposition is seen in a small percentage of all cancers – in breast cancer it is estimated to be approximately 5-10%. However, detecting this group of patients is important as this information is increasingly having an impact on their cancer treatment, as well as being able to predict their risk of other cancers and also allowing the identification of other family members at high risk for developing cancer. In view of the limited public resources, to gain access to publicly funded genetic testing patients need to meet certain criteria. However, as genetic technology has advanced, the costs for testing are no longer prohibitive and many cancer-affected and cancer-naive patients are opting for self-funded genetic testing. Therefore, we have undertaken a retrospective review of patients who elected to self-fund genetic testing through the Parkville Familial Cancer Clinic. The overall aim of the study is to look at the trend of self-funded genetic testing over time, assess the breast and ovarian cancer risk distribution in these women relative to their clinical situation and, assess the impact on clinical decision making, and analyse the mutation rate in this cohort.

Methods: 305 patients were identified who elected to self-fund genetic testing through the Parkville Familial Cancer Centre. Patient characteristics, referring doctor, personal cancer history, pre-test probability (Boadicea mutation risk score), lifetime risk of breast cancer and test results were extracted for all patients.

Results: 305 patients have elected to self-fund genetic testing through Parkville Familial Cancer Centre. 14 (4.6%) patients were male. We have detected 7 (2.3%) pathogenic mutations in this population of patients. 158 (51.8%) patients were affected by cancer. Further analyses to follow.

Conclusion: This study will illustrate the trend in self-funded genetic testing and the driving motivation for patients seeking self-funded genetic testing.
Direct-to-Consumer Genetic Testing: A Cautionary Tale

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Introduction: On the back of the genomic revolution, genetic tests are being marketed by private companies that are largely internet-based and sold directly to consumers without the involvement of a health professional; this phenomenon is referred to as direct-to-consumer genetic testing (DTCGT). Here we present a case of a man who was referred for assistance in interpreting DTCGT results and discuss the issues it raised.

Case Description: A 53-year-old male with no personal history of cancer was referred by his GP for clarification of results received from DTCGT. He had ordered DNA testing through Ancestry.com and used these results to do further analysis through Promethease: a literature retrieval system that creates a report based on SNP data. This result identified the gentleman as having a pathogenic CDH1 variant. Reported family history included his paternal grandmother with breast cancer at 48 years of age and paternal great-grandmother with breast cancer at 73 years of age. However, the state-wide genetics database revealed a more extensive family history that included a confirmed lobular breast cancer and a reported gastric cancer in a 35-year-old, suggestive of a CDH1 mutation. Confirmatory genetic testing for the CDH1 variant performed on two independent samples in an accredited laboratory failed to detect the CDH1 variant.

Discussion Points:
- The role of publically funded FCC’s in interpreting DTCGT results from private companies
- The accuracy and clinical validity of DTCGT results
- The psychological impact of DTCGT on the patient
- The lessons learned from dealing with a DTCGT result
Impact of Privately Funded Genetic Testing in the Austin Familial Cancer Clinic of Genetics in the North East

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Over time, the cost of mutation detection testing has decreased making privately funded testing more accessible to patients. Some of the patients choosing to have privately funded testing are referred for genetic assessment as it may impact their cancer treatment decisions, although the likelihood of identifying a pathogenic mutation is low. Other patients wish to arrange privately funded testing to refine risk assessment advice for themselves or family members.

The number of patients proceeding with privately funded testing at the Austin Familial Cancer Clinic (FCC) has increased. The tests available to patients has also changed over time with single gene or paired gene (e.g. BRCA\textsubscript{1} and BRCA\textsubscript{2}) testing being replaced with routine testing of panels of genes. An audit of privately funded mutation detection testing arranged through the Austin FCC was performed and the results will be presented.

We examined which tests are privately funded by Austin FCC patients and the frequency of these tests over time to assess their impact on the Clinic workload. We also compared the mutation detection frequency of privately funded tests and tests performed when clinical criteria for State funded testing were met.

Uptake of privately funded testing is likely to continue to increase as costs further reduce. By examining these trends we aim to gain insight into the impact this type of testing has on service delivery, risk estimation, and overall management. These results will allow an improved understanding of service provision and facilitate mechanisms through which these patients may potentially be managed by treating specialists outside the Austin FCC. We will also assess the outcome of privately funded testing to better appreciate its utility.
Cost-effectiveness of cancer risk management for BRCA1/2 carriers: Evaluation of the Annual Review Program

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Background: Women with a pathogenic BRCA1/2 mutation have an elevated lifetime risk of breast and ovarian cancer. Clinical guidelines recommend BRCA1/2 carriers undergo intensive breast screening for early detection, and to consider risk-reducing salpingo-oophorectomy and/or prophylactic mastectomy to significantly reduce their risk. These strategies have been shown to be cost-effective in terms of the cost per life year and quality-adjusted live year (QALYs) saved across multiple settings provided there is high to 100% compliance. Existing studies exclude robust consideration of costs associated with the clinical follow-up and resource use required to ensure women undertake these procedures at the optimal risk-appropriate age. An intensive mutation carrier follow-up program (the Annual Review Program, ARP) has been in place at the Peter MacCallum Cancer Centre and Monash Health Familial Cancer Centres from 2009 and 2013 respectively, aiming to improve mutation carrier outcomes by providing long-term support.

Method: A microsimulation model will be developed in Python to analyse costs, life years and QALYs over a lifetime horizon for BRCA1/2 carriers participating in a formal ARP compared to standard care (no organised follow-up program). Data from 591 carriers enrolled through a well-established versus newly instituted ARP will be used to populate the model for uptake of risk management recommendations.

Conclusion: BRCA1/2 risk management interventions are theoretically cost-effective in reducing mortality and morbidity. Unfortunately resource use and costs related to ongoing support and long-term clinical care of these patients is unknown. The proposed evaluation aims to assist in the development of a standard model of health-care service delivery for BRCA1/2 carriers.
Returning results from the BRA-STRAP study

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BRA-STRAP is a nation-wide study of approximately 10,000 women affected with breast/ovarian cancer who have tested negative for mutations in BRCA1 and BRCA2 through Australian FCCs. We have commenced testing for a panel of breast cancer genes*, with the aim of improving Australian population-based prevalence and penetrance estimates and facilitating translation of the panel testing approach into FCCs.

*BRCA1, BRCA2, PALB2, TP53, ATM, MLH1, MSH2, MSH6, PMS2, BARD1, BRIP1, CDH1, CHEK2, MRE11A, RAD50, NBN/NBS1, MUTYH, NF1, PTEN, RAD51C, STK11, FANCN, RECQL, and RAD51D.

Using an analysis framework tailored to high-throughput analysis of Hi-Plex data, the variants detected will be broadly categorised according to their clinical significance. Since few of these genes have established clinical validity, careful consideration was needed when planning return (or non-return) of results.

1. **Clinically relevant variants** - those with clear evidence of breast cancer risk and best practice guidelines (e.g. eviQ). For example, a pathogenic PALB2 variant may warrant breast MRI, with predictive testing enabling more accurate risk assessment for relatives. Because of historical DNA samples, we are also likely to identify previously undetected pathogenic variants in BRCA1/2. Such results will be returned to FCCs who will notify the patient and confirm the result in a NATA accredited laboratory.

2. **Results requiring further study** - UVs in known breast cancer susceptibility genes (e.g. BRCA1 UV), pathogenic variants in genes of unknown significance (e.g. pathogenic variant in RAD51C), and pathogenic variants inconsistent with the FHx (e.g. pathogenic CDH1 mutation with no gastric cancer). These participants (and their relatives) will be invited by their FCC to enrol in KConFab. BRA-STRAP resources will be directed to KConFab to enable recruitment and biospecimen collection and provide important resources for segregation analyses and functional assays. Variants that are later deemed clinically relevant will be managed according to standard KConFab protocol. Although participants previously consented to clinical BRCA1 and BRCA2 testing they did not have the opportunity to consider the potential uncertainty associated with more extensive gene panel testing. This plan enables better data for the patient and community, as well as the opportunity for participants to make an informed choice about receiving (or not receiving) research results.

3. **Likely benign (Class 1 & 2) variants** will not be returned to participants. In the absence of clinical utility, return of these results could potentially result in misinterpretation, anxiety, and unnecessary interventions. In addition to benefiting the broader community by refining prevalence and penetrance estimates for these genes, this approach will also enable improved management of a proportion of women (~200 families participating in BRA-STRAP) in whom a clinically relevant result is obtained (likely to be <2% based on previous data).
The TARGET pilot study initial results: A model for informing the PRISM Precision Medicine Trial in Paediatric Cancer

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Background and rationale: The TARGET pilot study aims to identify novel treatment options for paediatric cancer patients with a poor prognosis. The study, opened at Sydney Children’s Hospital in collaboration with Children’s Cancer Institute, recommends personalised therapies to patients following genomic analysis and in vitro and in vivo drug testing. As part of the work-up, germline genetic testing is performed which may identify cancer predisposition syndromes. Results from TARGET will assist in streamlining logistics and will facilitate the development of a national personalised medicine program, PRISM. The classification, identification and delivery of germline results will have an impact on genetic services Australia-wide and highlights the importance of clinical genetics in a research setting.

We anticipated that TARGET would identify germline mutations in approximately 10% of children [1]. For TARGET, like other experimental high risk cancer trials, genetic counselling is only offered post-test, which differs from standard paediatric clinical genetic testing. Parents have the choice of opting out of receiving these results. Understanding the impact of these results, in the absence of traditional genetic counselling models, is vital to informing the development of appropriate recruitment, improved genetic services and better management.

Methods: Patients aged 2-21 years with an anticipated survival rate of <30% are eligible. Peripheral blood and tumour samples are collected and next generation sequencing arrays performed. A multidisciplinary oncology and molecular genetics panel convenes to determine the significance of genomic analysis.

Preliminary results: Of the 57 patients recruited to date, germline analysis has been completed for 21. Five germline mutations have so far been identified. Germline mutations were confirmed in two patients previously tested clinically:
1. Confirmation of an MSH2 mutation
2. Confirmation of biallelic MSH6 mutations

Three were found to carry germline mutations for which clinical testing was not indicated:
3. An LZTR1 frameshift mutation, the penetrance of which is unknown.
4. A pathogenic PALB2 mutation
5. A novel NF1 variant with uncertain pathogenicity

Conclusions and future directions: The number of germline mutations may be higher than anticipated in this cohort. Psychosocial data will be retrospectively collected from TARGET patients and PRISM patients prospectively, to enable better understanding of family and health professional attitudes towards, and the impact of, personalised medicine in childhood cancer. A sub-aim of this study will be to assess the impact of receiving germline genetic information. The results will impact how germline mutations identified through the PRISM study are disseminated to patients nationally.

Screening Victorian women with endometrial cancer for Lynch Syndrome - Final results

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Purpose: To pilot the use of Mismatch Repair Immunohistochemistry (IHC) as a screening test to detect Lynch syndrome (LS) in women with endometrial cancer (EC) at or before age 70 at three Victorian centres in a 12 month period.

Methodology: IHC was requested by pathologists at three centres between 1/4/2013 and 1/4/2014. IHC results were added to the pathology report as standard. Treating centres referred abnormal IHC results to Familial Cancer Clinics (FCCs). Patients referred to FCCs with abnormal IHC audit results were asked to consent for their clinical information to be released to study follow up. In addition, women with absent MLH1 and PMS2 IHC were invited into a study for MLH1 germline testing on blood samples and MLH1 methylation testing on their EC, with results interpreted by their treating FCC doctors.

Results: Across the three centres 172 women had IHC performed (median age 59y, range 37-70y). Of the 172 ECs tested, 47 (27%) had abnormal IHC (26 absent MLH1 and PMS2, 5 absent PMS2 alone, 7 absent MSH2 and MSH6, and 9 absent MSH6 alone). Seven women were identified as having Lynch Syndrome (6 definite and 1 probable) (4% of the total 172 cases) and one woman was identified as having a constitutional methylation of MLH1. All LS cases were aged 60 and under at diagnosis of EC. Mutations were: PMS2 (n=1), MSH2 (n=2) and MSH6 (n=4). Of the 18 women with absence of MLH1 and PMS2 IHC who had evaluation, all 18 had endometrial tumour MLH1 methylation. Of these, 15 had no MLH1 germline mutation detected, and 3 had no germline testing performed. Eleven of 47 women (23%) who had abnormal IHC declined to attend a FCC.

Conclusion: Four percent of all women whose EC was screened were found to have LS. Our results are concordant with previous literature that suggests screening of EC diagnosed at or before age 60 would detect all those with LS. Exploration as to why many women with abnormal IHC decline FCC evaluation is needed. A cost effectiveness analysis is planned.
New Challenges in Treatment Focused Genetic Testing: A Genetic Counselling Perspective

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Germline mutations in cancer predisposition genes are increasingly being used to inform breast cancer treatment, resulting in an increased number of Familial Cancer Centre referrals for treatment focused genetic testing (TFGT). TFGT requires urgency not typical in genetic testing for familial cancers. This urgency presents psychosocial challenges for our clients and, as genetic counsellors, the necessity to increase our understanding of chemotherapy options and surgical interventions.

A collaboration between genetic counsellors and oncologists at the Parkville Familial Cancer Centre (PFCC) led to the development of an annotated clinical pathway, outlining typical breast cancer treatment options and the key time points where genetic testing may have an impact on treatment.

Through the use of case studies we highlight genetic counselling challenges faced as a result of TFGT, as well as psychosocial and clinical impacts specific to TFGT.

The development of an annotated clinical pathway has informed our intake process for TFGT referrals. We are now better able to understand the possible psychosocial impacts of genetic testing for our patients undergoing TFGT and have an improved understanding of the common medical treatment pathways for breast cancer. Furthermore, the psychosocial challenges that arise during TFGT are important considerations as mainstreaming programs move this type of testing away from the genetics clinic and into an oncological setting.
Hi-Plex Origin for high-throughput screening of disease genes

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Genetic sequencing is a comprehensive method for diagnostic genetic screening in modern medicine, allowing the detection of genetic variants that influence disease susceptibility and progression, and can inform treatment regime and prognosis. In many diagnostic settings, it is unnecessary to sequence the entire genome/exome because clinical guidelines to steer clinical management are available for relatively few genes. To this end, with costs, sequencing depth requirements, potential serial sampling scenarios and expediency in mind, gene region targeted massively parallel sequencing (MPS) can often be the most desirable option.

Hi-Plex Origin is a high-multiplex PCR method of library preparation for targeted MPS that uses only standard laboratory reagents to perform accurate, low-cost screening of genetic regions, without requiring expensive instrumentation, reagents or consumables. In preliminary, proof-of-concept work, we have demonstrated that Hi-Plex Origin is highly effective in the context of sample-by-sample processing, as gauged by on-target mapping and coverage uniformity metrics. This approach is significantly more robust to imperfections in panel design and enables considerably larger target designs than the parent Hi-Plex protocols, from which it is derived, while accepting the same primer design format.

We will present our developing protocols that allow Hi-Plex Origin to be applied to streamlined high-throughput screening of the cancer susceptibility genes \textit{BRCA1}, \textit{BRCA2}, \textit{PALB2} and \textit{TP53}.
Moderate risk ovarian cancer susceptibility alleles

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Epithelial ovarian cancer (EOC) is the most lethal gynecological malignancy and is often diagnosed at a late stage when survival is poor. Germline mutations identified in ovarian cancer susceptibility genes can be used in risk prediction and could have a significant impact on reducing disease mortality. Identification of a mutation has implications for risk management in other family members. We have performed targeted next generation sequencing of the coding regions of 54 candidate genes in 6,000 high grade serous ovarian cancer cases and 6,000 controls of European origin, and 2,000 unaffected high-risk women from a clinical screening trial of ovarian cancer (UKFOCSS). The gene panel included; genes in the FANC pathway, key genes from commercial testing panels, and novel candidate genes selected from several exome sequencing projects comparing ovarian cancer cases to publically available control data. Targeted sequencing was performed using Fluidigm access array and Illumina sequencing, with 1536 barcoded samples per lane. Potentially protein truncating variants with a minor allele frequency >40% were compared in cases and controls. Sanger sequencing confirmation was used to determine the minor allele frequency threshold. This is the largest case control analysis of moderate risk genes for ovarian cancer risk. Preliminary analysis has identified several new potential ovarian cancer susceptibility genes. Accurate risk estimates are required before genes should be used in clinical management.
The newly recognised NTHL1-associated polyposis (NAP) disorder: A case study

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While familial adenomatous polyposis accounts for approximately 1% of all colorectal cancer, the genetic cause underlying the development of multiple colonic adenomas remains unsolved in many patients. Adenomatous polyposis syndromes can be divided into: familial adenomatous polyposis (FAP), MUTYH associated polyposis (MAP), polymerase proofreading associated polyposis (PPAP) and the recently described NTHL1-associated polyposis (NAP). NAP is characterised by recessive inheritance, attenuated adenomatous polyposis, colonic cancer(s) and possible extracolonic malignancies. To date, eleven cases have been reported as having germline homozygous or compound heterozygous mutations in the base excision repair gene NTHL1. We will present a twelfth case involving a male with a history of adenomatous polyposis and bladder cancer, who has a previously described homozygous nonsense variant in the NTHL1 gene.

This case, believed to be Australia’s first known case of NAP, is consistent with the emerging phenotype previously described of multiple colorectal adenomas and at least one primary tumour, adding to the small but growing body of literature about NTHL1-associated polyposis.
Cancer risks for relatives of people with serrated polyposis

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Background: Serrated polyposis, characterised by the formation of multiple colorectal polyps displaying serrated architecture, is associated with an increased risk of colorectal cancer and possibly extracolonic cancers. However, the risk of cancers for relatives of people with serrated polyposis is not well understood.

Methods: A cohort of 2,620 first- and 2,893 second-degree relatives of 412 people with serrated polyposis were recruited, regardless of their family history, from genetic clinics throughout Australia, New Zealand, Canada and the USA. Self-reported age, sex and cancer histories from family pedigree data were analysed to determine standardised incidence ratios (SIR) of colorectal and extracolonic cancers for relatives of people with serrated polyposis compared with age-, sex- and country-specific cancer incidence of the general population.

Results: A total of 421 colorectal cancers were observed in first- and second-relatives (SIR 2.07, 95% confidence interval (CI) 1.85–2.34), with 215 in first-degree relatives (SIR 4.31, 95% CI 3.70–5.04) and 206 in second-degree relatives (SIR 1.35, 95% CI 1.15–1.58). There were 18 pancreatic cancers reported in first-degree relatives (SIR 2.55, 95% CI 1.64–4.18). There was no statistical evidence of increased risk for cancer of the stomach, brain, kidney, bladder, endometrium, ovary, breast, or prostate.

Conclusions: The findings from this international study of serrated polyposis, which is the largest to date, support the existence of underlying genetic aetiology for serrated polyposis. The findings suggest that relatives of people with serrated polyposis might be considered for regular colonoscopic surveillance.
The Clinical Utility of Immunohistochemistry for Mismatch Repair Proteins on Colorectal Polyps: A Retrospective Review of Practice

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Abstract

Background: Immunohistochemistry (IHC) for loss of expression of one or more of the mismatch repair (MMR) proteins is performed on colorectal cancer (CRC) tissue as a screening test to identify individuals with Lynch Syndrome (LS) yet the role of performing MMR IHC on premalignant polyps remains controversial. The aim of this study was to determine the effectiveness of MMR IHC performed on premalignant colorectal polyps for identifying Lynch Syndrome, with a focus on its clinical utility and value.

Methods: A retrospective audit was conducted of MMR IHC performed on non-malignant polyps in patients with a personal or family history of CRC, or other LS-associated malignancy who attended the Family Cancer Clinic at the Royal Melbourne Hospital. Two hundred and six patient records over a 10 year period (2006-2016) were reviewed, identifying 57 patients who underwent MMR IHC testing on their polyp/s. Personal and family history data was collected including results of genetic testing performed.

Results: The family history met Amsterdam II Criteria for 12.3% of patients undergoing polyp MMR IHC, included a history of LS-associated malignancies for 80.7%, and a history of polyps for 8.8%; 10.5% of patients tested had no significant family history. Polyp MMR IHC demonstrated normal protein expression in 94.7% of cases; MMR-deficiency was observed in 3 individuals and concordant germline MMR variants were detected in 2 patients (1 variant of unknown significance and 1 pathogenic mutation). Thirty genetics tests were carried out in 24 patients, 21 of whom had normal polyp MMR IHC and no cases of LS were diagnosed based on polyp MMR IHC which would not have been diagnosed by other standard testing.

Conclusion: The little clinical utility of performing MMR IHC on polyp tissue in our service was low. No additional cases of Lynch Syndrome were identified, and a large proportion of patients went on to germline testing despite normal polyp MMR IHC results. We suggest that there is no justification for this clinical approach.
The Genetic Basis of Unexplained Adenomatous Polyposis: The Genetics of Colonic Polyposis Study

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Abstract

Polyposis of the colon and rectum, that is the development of multiple (>10) polyps throughout the bowel, is associated with an increased risk of developing colorectal cancer (CRC) in the affected individual and their relatives. A number of polyposis susceptibility genes harbouring high risk mutations have been described including APC, MUTYH, SMAD4, BMPR1A, PTEN, and GREM1, and more recently germline mutations in the POLE, POLD1, NTHL1 and MSH3 genes. However, germline mutations in these genes account for only half of the individuals who present with colonic polyposis, suggesting additional high risk genes are yet to be identified.

The Genetics of Colonic Polyposis Study (GCPS) has been established to investigate the clinical phenotype, characterisation of the molecular and pathological features of polyps and CRCs, identifying genetic and environmental risk factors, and establishing evidence-based guidelines for improved clinical management of individuals who present with genetically unexplained colonic polyposis, including Serrated Polyposis Syndrome and Adenomatous Polyposis (Oligopolyposis). To date, we have recruited 20 individuals with unexplained adenomatous polyposis from Family Cancer Clinics across Australia and from the New Zealand Familial Gastrointestinal Cancer Service. Colonoscopy and histology records were collected to establish polyp counts and morphology. Participants provided a blood sample and data on ethnicity, lifestyle and environmental risk factors, and family history of cancer and/or polyposis and, when possible, archival polyp/CRC tissue has been collected for pathological review and molecular characterisation. These first 20 oligopolyposis-affected probands have a mean age at first diagnosis of 44.7yrs ± 19.3yrs, (range 13-78yrs), 55% females, and a mean polyp count=36±28.8, (range 10->100 adenomatous polyps). Recruitment of individuals with oligopolyposis and their relatives is ongoing.

The aim of the study is to perform whole genome sequencing on oligopolyposis-affected probands and affected relatives, to identify novel germline predispositions. The results from recruitment including their personal and family tumour spectrum and the results from germline testing performed to date will be presented.
Disparities in Health Care and the Color Cancer Gene Panel test

Michael Gattas, Wesley Medical Centre, Auchenflower, QLD

Color (www.color.com) is a company founded near Silicon Valley in the USA in April 2015 with the goal of providing high quality, cancer gene tests to everyone, everywhere. Color now offer a 30 cancer gene panel test, cascade testing to other family members, and a telephone genetic counselling service.

The Color company actively tries to overcome the problem of access (or disparity) to cancer gene tests in the USA and elsewhere. For example, Color has partnered with the Pink Hope organisation in Australia to provide a subsidised test.

Brisbane Genetics started using the Color brand test in July 2016. It was not the first cancer gene panel test used by this clinic, but has been the most successful. As of June 2017, about 303 tests have been completed, and 15% had a pathogenic or likely pathogenic result. VOUS are not reported by choice.

The Color test is using next generation sequencing as part of a service that is very different to traditional pathology providers. The test has been popular for patients who pay for their own cancer gene test.
Genetic analysis of breast tumours in PALB2 germline mutation carriers

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PALB2 is a moderate to high penetrance breast cancer predisposition gene that interacts with BRCA1 and BRCA2 with a central role in homologous recombination-mediated repair of DNA double stranded breaks. Biallelic mutations of PALB2 are linked to Fanconi anaemia while monoallelic germline mutations in PALB2 increases susceptibility to breast cancer. However, from the limited data that exists, it is frequently cited as an example of a predisposition gene that does not require bi-allelic inactivation in the tumour and therefore does not conform to Knudsen’s two hit model. This has important implications for the discovery of new breast cancer predisposition genes as the absence of a “second hit” in a candidate gene is no longer used as an exclusion criteria on the basis of the paradigm of PALB2.

In this study, we analysed 15 breast cancer tumours from individuals with a PALB2 germline mutation whom were referred to familial cancer centres with no pathogenic BRCA1 and BRCA2 variant identified. DNA were extracted from formalin fixed paraffin embedded (FFPE) tumours and ran on a custom made sureselect gene panel targeting known breast cancer genes. Off target sequencing reads were used to generate copy number aberration (CNA) plots across the genome.

Of the 15 tumours sequenced 10 showed clear evidence of bialleic inactivation of PALB2; 6/6 tumours with LOH showed loss of the wild-type allele and 4 had a somatic missense and frame-shift mutations. There was no correlation with the level of genomic alterations and null or heterozygous status of PALB2 but somatic TP53 mutations were more often observed in PALB2 heterozygous tumours compare to PALB2 null tumours (60% versus 30%).

Our findings demonstrate that the majority of breast tumours from PALB2 germline mutation carriers do harbour a “second hit” and therefore PALB2 in general does conform to Knudsen’s two hit model.
Analysis of RAD51C as breast cancer susceptibility gene in breast cancer families

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Introduction: Only ~40% of the familial clustering of breast and ovarian cancer can be explained by mutations in known highly penetrant genes such as BRCA1, BRCA2 and PALB2. Numerous candidate genes have been proposed to explain the missing heritability but the status of many remains unresolved. One such gene, which has been identified through large-scale sequencing of familial breast and ovarian cancer families, is RAD51C. RAD51C is a crucial protein involved in early and late stages of homologous recombination. In 2010, Meindl et al proposed germline RAD51C mutations confer susceptibility to breast and ovarian cancer. While the importance of RAD51C mutations in ovarian cancer had been confirmed the associated risks, if any, for breast cancer remains controversial. In particular, loss of function (LoF) mutations in RAD51C are almost universally only observed in families with both breast and ovarian cancer, suggesting the breast cancers in such families might not be related to the RAD51C mutation. The aim of this study is to assess if breast cancers harboring LoF RAD51C mutations acquire a “second hit” which would support a causative role of RAD51C in those cancers.

Methods and Results: All exons of RAD51C were sequenced in 4500 index cases of breast cancer-affected women referred to specialized Familial Cancer Centres on the basis of a strong family history of breast cancer but who tested negative for pathogenic mutations in BRCA1 and BRCA1 (BRACx). Controls (n = 4500) were cancer-free women from the LifePool study. Sequencing data were filtered for rare (allele frequency <0.005) loss-of-function mutations and missense variants. Predictions on functional relevance of detected missense variants were obtained from different prediction algorithms. 17 LoF mutations were identified in the cases versus 2 in the controls suggesting that RAD51C may indeed predispose to breast cancer. 10 families were participants from the ViP study where full pedigrees were available as well at potential access to tumour blocks. In contrast to previous reports, among the 10 RAD51C families from ViP, 9 had BC but no OC in the pedigree suggesting RAD51C may be driving the BC in these families. Segregation analysis is being performed in family members of these RAD51C index cases. Archival FFPE breast tumour blocks were access for 10 cases and tumour DNA was extracted and using an Agilent targeted sequencing panel which included RAD51C and also enabled genome wide copy number to be derived. Data analysis of 8 samples to date suggests that 5 out of 7 have Loss of wild type allele (LOH), 2 remain heterozygous. One of the samples has borderline ovarian cancer and didn’t show any LOH/somatic mutation. Interestingly, all 5 samples with LOH have TP53 somatic mutations while it doesn’t exist in the rest of the samples.

Conclusion: Although large more samples will be needed, our data consistent with RAD51C being a driver mutation in Breast cancer.
Copy number alterations associated with the progression of premalignant breast lesions to breast carcinoma

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Background: Breast lesions such as atypical ductal hyperplasia (ADH) and papilloma are common findings in the mammographic era, and yet their potential to progress to breast carcinoma (BC) is poorly understood. ADH is thought to be a non-obligate precursor to low grade (LG) BC, but the precursor lesion for high grade (HG) BC is uncertain. Papillomas often co-exist with BC yet are not considered to be precursors. We sought to clarify the molecular taxonomy of these lesions and determine whether genetic changes are associated with BC progression.

Method: Cases of ADH (n=120) and papilloma (n=70) were identified from a hospital database and reviewed by pathologists, followed by micro-dissection and DNA extraction. We assayed genome-wide copy number (CN) in 21 ADH and 24 papillomas (not associated with cancer), as well as 20 ADH and 15 papillomas with synchronous DCIS and/or IDC. Targeted sequencing of BC genes was performed for some papillomas.

Results: Only 40% of ADH diagnoses were confirmed on pathology review. 95% of pure ADH had at least one CN event and the median fraction of the genome altered was 9.8% (0-21%). Surprisingly, while 71% of pure ADH showed 16q loss and 33% had 1q gain (common in LG-BC), 29% of pure ADH showed 8q gain, an event more frequently observed in HG-BC. Analysis of ADH with synchronous BC showed that 70% of ADH was clonally related with both LG (7/9) and, unexpectedly, HG carcinoma (7/11). One HER2+ DCIS and one ER- BC were clonal to their co-existing ADH, all other BC were ER+. Additional CN changes were observed in 10/14 BC compared to their clonal ADH. Clonal and pure ADH had significantly more CN changes than non-clonal ADH (p<0.05). Analysis of the papilloma cohort is ongoing, however to date, 8/18 (44%) pure papillomas showed CN change. Of papillomas synchronous with BC, 2/6 were clonally related (1xHG, 1xG2). All pure papillomas harboured somatic mutations in PIK3CA (8/9) or PIK3RI (1/9) suggesting that papillomas are driven by alterations in the PI3-kinase pathway.

Conclusion: This is the largest genome-wide study of these pre-malignant putative BC precursors. Our observation that 70% of ADH is clonal to co-existing BC suggests that both LG- and HG-BC can evolve from a similar ancestor lesion, with additional CN events required in most cases. Fewer papillomas share CN events with synchronous BC. A biomarker signifying capacity for BC progression is highly desirable for more precise treatment of these lesions.
Invasive Lobular Breast Cancer: Using tumour genome-wide DNA methylation to further subtype and aid in the identification of susceptibility genes

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There is evidence of increased heritability of invasive lobular breast cancer (LBC). We have conducted a whole-genome sequencing project involving 120 early onset and multiple-case LBC cases aimed at identifying susceptibility genes for LBC. The project has identified a vast amount of germline genetic variation but no strong candidate LBC susceptibility gene. Here, we have sought to identify strategies for subtyping LBC in order to more precisely analyse the whole genome sequences.

Epigenetic alterations play a crucial role in the susceptibility and progression of cancers, including breast cancer. There are an increasing number of studies investigating the epigenetic mechanisms involved in breast cancer. Early indications of breast malignancy include coordinated long-range changes in the epigenome that often target loci regulated by key transcription factors. Methylation signatures/clusters have also been reported to have prognostic value for breast cancer and could be valuable biomarkers for early detection and/or disease monitoring for specific breast cancer subtype.

The aim of this study was to assess the genome-wide DNA methylation pattern of the LBCs for the purpose of LBC subtyping.

Formalin-fixed paraffin-embedded (FFPE) tumor-enriched DNA was prepared using macrodissection and run on the Infinium HumanMethylation450 Beadchip (HM450K) array to generate a genome-wide methylation data. The raw methylation data was pre-processed and normalised using \textit{minfi} Bioconductor package in R programming software. Cluster analysis was used to identify subgroups of LBC based on DNA methylation clusters. This dataset was also compared to similar dataset prepared from FFPE samples of invasive ductal carcinoma of the breast.

Identification of LBC subtypes using DNA methylation that increases the homogeneity of disease in each subtype could inform the analysis of our whole-genome sequencing project and lead to the identification of LBC susceptibility genes.
Expression variability is associated with breast tumour subtype

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Inherited mutations in \textit{BRCA1} are associated with greater risk of developing breast and ovarian cancers. \textit{BRCA1} is important for several functions in cells throughout the body, however mutations in \textit{BRCA1} are strongly associated with breast and ovarian cancer, with only minor effects in other tissues. Approximately 70\% of \textit{BRCA1}-related breast tumours display a basal-like phenotype (e.g., enriched for high grade and oestrogen receptor negative), although the gene networks that are critical for the mechanism remain unclear. Gene expression studies have extensively interrogated breast cancers, including tumours from \textit{BRCA1} mutation carriers, however results from these studies lack consensus, with inconsistency in candidate genes and pathways. Importantly, these studies have focused on differentially expressed genes by comparing the mean of each group and determining statistical significance. We demonstrate the application of an alternative approach, which is to assess expression data using differential variability analysis, thereby discovering genes with a significant difference in variance between two sample groups. Expression data from 74 familial breast cancers and a 2116 sporadic breast cancer meta-cohort were interrogated for gene expression variability. We found that basal-like tumours and \textit{BRCA1}-related tumours showed 39.9\% (95\% CI 39.4\%-40.3\%) and 13.2\% (95\% CI 12.6\%-13.7\%) increased global variability, respectively. Differential variability analysis identified gene sets that were enriched in pathways associated with epithelial cell function and development. Furthermore, we identified two genes, \textit{PAX6} and \textit{FOXA1}, involved in these pathways with significantly greater expression variability in basal-like or \textit{BRCA1}-related tumours, in both study cohorts. These findings are novel and suggest epithelial cell development pathways may be more tightly regulated in non-basal and non-\textit{BRCA1} related tumours.
BRA-STRAP
Brca Refined Analysis of Sequence Tests: Risk And Penetrance

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The rapid introduction of massive parallel sequencing into clinical genetics services is enabling the screening of multiple breast cancer susceptibility genes in one assay at reduced cost for women who are at increased risk of breast (and other) cancer. These gene panels now typically include a large number of genes but only a few of these genes have established clinical validity. These tests therefore pose considerable challenge to clinical genetic services, as very little is known about the breast cancer risk associated with any of the observed genetic variation.

Accumulated research on BRCA1 and BRCA2 mutation carriers now means that these women can be offered personalized risk assessment, targeted treatment regimens and informed decision making about the use of chemo-preventive agents, bilateral salpingo-oophorectomy, mammography, risk reducing mastectomy, magnetic resonance imaging (MRI) and other screening modalities. This information is lacking for high-risk women (as defined by family history) who are not found to carry an identifiable mutation in BRCA1 or BRCA2. These women represent about 80% of those tested. Some evidence has been accumulated to enable improved management for women found to carry mutations in PALB2, ATM and CHEK2, and their families.

The community now needs similar information about the larger number of genes that are being tested routinely on gene panels to provide the evidence-base from which clinical management and genetic counselling can be provided.

We are conducting a large nation-wide study of 10,000 Australian women at high-risk of breast cancer who have tested negative for mutations in BRCA1 and BRCA2. We are performing targeted sequencing of BRCA1, BRCA2, PALB2, TP53, ATM, MLH1, MSH2, MSH6, PMS2, BARD1, BRIP1, CDH1, CHEK2, MRE11A, RAD50, NBN/NBS1, MUTYH, NF1, PTEN, RAD51C, STK11, FANCM, RECQL, RAD51D and will present the spectrum of genetic variation observed in these genes. The BRA-STRAP study will enable i) Australian population-based specific estimates of mutation prevalence and penetrance and ii) pooling with similar data from other international efforts including BRIDGES (European Commission) and CARRIERS (NIH). This work will enable the evidence-based translation of new genetic information and a new genetic testing model into clinical practice.
Detecting Genetic Variation in the BRA-STRAP Study: The Analysis Framework

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Gene panel testing for breast cancer predisposition aims to sequence multiple genes in one genetic test in order to provide an individualised risk estimate. As more breast cancer susceptibility genes are identified, gene panel tests are gaining increasing prominence in breast cancer risk assessment and clinical practice. Genetic variants in \textit{BRCA1} and \textit{BRCA2} have been well characterised and successfully translated into the clinic, allowing for personalised risk assessment and risk management options for women identified with pathogenic mutations. However, for other genes included on these panel tests, the estimates and evidence of risk vary significantly, creating difficulties for clinical implementation.

The Brca Refined Analysis of Sequence Tests: Risk and Penetrance (BRA-STRAP) study aims to better define the breast cancer risks associated with mutations in genes included on gene panel tests in order to improve the clinical utility of the results. In this study, 5,460 Australian women at high risk of breast cancer who have tested negative for mutations in \textit{BRCA1} and \textit{BRCA2} have been recruited from Familial Cancer Centres. Their germline DNA was screened for mutations in \textit{ATM}, \textit{BARD1}, \textit{BRCA1}, \textit{BRCA2}, \textit{BRIP1}, \textit{CDH1}, \textit{CHEK2}, \textit{CHEK2}, \textit{FANCM}, \textit{MLH1}, \textit{MRE11A}, \textit{MSH2}, \textit{MSH6}, \textit{MUTYH}, \textit{NBN/NBS1}, \textit{NF1}, \textit{PALB2}, \textit{PMS2}, \textit{PTEN}, \textit{RAD50}, \textit{RAD51C}, \textit{RAD51D}, \textit{RECQL}, \textit{STK11} and \textit{TP53}. Libraries were prepared using the Hi-Plex enrichment system and sequenced on the NextSeq (Illumina). Although highly accurate, the tools traditionally used to analyse Hi-Plex sequencing data (ROVER and UNDROVER) have limitations, such as a lack of compatibility with current annotation tools. In order to determine the most appropriate pipeline for the analysis of this data, we sought to assess the performance of various high-throughput analysis pipelines. We will present the bioinformatics analysis framework used in the BRA-STRAP study resulting from this assessment and comparison.

An optimised analysis framework for assessing genetic variation, tailored to high-throughput analysis of Hi-Plex data, will enable the most accurate assessment of the sequencing data generated in the BRA-STRAP study.

"Familial Cancer 2017: Research and Practice"
The Variants in Practice (ViP) Study: 5 year cohort overview and recruitment update

Simone McInerny¹, Norah Grewal¹, Rebecca Driessen¹, Gillian Mitchell¹, Marion Harris², Geoff Lindeman³, Thomas John⁴, Yoland Antill⁵, Ingrid Winship³, Mary-Anne Young¹, Na Li¹, Ian Campbell¹ and Paul A James¹,³

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The ViP study is a cohort of high-risk breast and ovarian cancer families that aims to offer ongoing genomic research to all families undergoing FCC assessment and testing for an inherited risk of breast or ovarian cancer. Ongoing research includes: 1. the identification of novel risk-associated genomic variants and rare predisposition genes and 2. the integration of testing of these novel variants and genes into the routine clinical management of high-risk hereditary cancer families.

The cohort enrolls individuals and families who have undergone clinical testing for mutations in the genes BRCA1/2 through the Victorian and Tasmanian Familial Cancer Clinics: Peter MacCallum Cancer Centre, Royal Melbourne Hospital, Monash Health, Cabrini Health, Austin Health, Barwon Health and the Tasmanian Clinical Genetics Service.

- Since ViP began in 2012, more than 5800 individuals have been enrolled. Of these, 4200 are index cases (individuals who have undergone BRCA mutation detection testing) and 1600 are family members of participating indexes.
- Recruitment of index participants consists of 1. prospectively enrolling patients undergoing genetic testing through a participating clinic and 2. retrospectively inviting by mail patients who have previously undergone BRCA mutation testing. Enrolment of family members is initiated using invite letters disseminated by the participating index.
- Currently, of indexes invited retrospectively by ‘cold’ invite mailout, approximately 60% have consented. Of the remaining 40%, approximately a quarter responded ‘not interested’ to the invite letter, around the same number responded ‘interested’ to the invite letter but did not consent and finally, half did not respond to the invite letter and were not able to be contacted via followup phone call.
- Index participant group characteristics: 97% female, 11% BRCA1/2 pathogenic mutation carriers, 83% breast cancer affected, 11% ovarian cancer affected, 3% both breast and ovarian cancer affected, age range 22-97 years, 12% current age ≤40 years.
- Family member participant group characteristics: 86% female, 16% breast cancer affected, 1% ovarian cancer affected, 5% ‘other’ cancer affected, age range 20-103 years, 81% live in Victoria/Tasmania.

The cohort collects DNA samples, pedigree data, pathology data and tumour blocks (for a subset of participants). Study activity, undertaken directly by the ViP investigators as well as in collaboration with other groups, includes: genotyping samples for >90 breast and ovarian cancer SNPs, qualitative and quantitative studies exploring participants’ experience of receiving their genotyping results, panel screening for rare novel breast cancer predisposition genes, whole exome sequencing of ovarian cancer affected participant samples and family segregation analysis for novel variants of interest.
kConFab – 20 years of biobanking

Heather Thorne, Eveline Niedermayr, Lynda Williams, Lana Djamjgava, Genna Glavich and the kConFab research nurses on behalf of the Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConFab).

kConFab, Research Department, Peter MacCallum Cancer Centre, St. Andrew’s Place, East Melbourne, VIC 3002.

kConFab, the Australian/New Zealand consortium for research into families at high risk of breast and ovarian cancer, has completed collection & recruitment of 1768 families during the past 20 years. Biological material, genetic, epidemiological, and psychosocial data are collected from affected and unaffected, female and male participants over the age of 18. This material is available to peer reviewed, ethically approved and funded research projects. kConFab has previously and currently supplied biospecimens and/or data to 163 research projects world-wide.

The kConFab biological repository contains blood specimens from a total of 13,829 participants and 234 best friend controls. The standardized blood processing protocol produces plasma, non-lymph, blood pellet and white blood cell fractions. White blood cells undergo EBV transformation which can be used by in functional assays or as a replacement source of DNA/RNA. To date, 2076 unique EBV cell line transformations are available.

As of June 2017, 97% of kConFab families have had genetic testing; identifying 40% of families with a pathogenic, large genomic rearrangement (LGR) or splice site mutation in either BRCA1 or BRCA2. An additional 11% of families carry unclassified variants in BRCA1 or BRCA2; with a further 1% with mutations in the ATM, CHEK2, PALB2 or TP53 genes. Of the 2502 female participants who harbour the germline mutation, 68% are affected with breast or ovarian cancer. Over the past 12 months we have started mutation notification to families that carry a PLAB2 LOF variant and the CHEK2 1100delC variant.

kConFab has collected a total of 1324 fresh tissue collections, including prophylactic mastectomy and oophorectomy specimens; and has a large collection of archival specimens. The tissue bank consists primarily of breast, ovarian and prostate tissue (tumour and normal), with a small proportion of other tissues. Following collection, a full research pathology review is conducted, wherein features such percentage tumour, normal epithelial, lymph and necrotic components are scored. For the past four years we have run a rapid autopsy program to facilitate research into the mechanisms of resistance, metastasis, and cancer evolution using genomic and biological tools.

kConFab has constructed a total of 31 tissue microarrays (TMAs) both sporadic and familial tumours from our tissue biobank. Where possible, tumour is matched to normal from the same archival block.

The kConFab resource enables researchers to answer important questions relating to familial aspects of breast cancer. Information about the kConFab resource and the application process is available on the web site (http://www.kconfab.org)
Predicting breast cancer risk based on information in a mammogram other than conventional mammographic density


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Purpose: To predict breast cancer risk based on information in a mammogram by considering more than the conventional concept of mammographic density.

Methods: We conducted case-control or nested case control studies of Australian, Korean and/or Japanese women using analog or digital mammograms. First, we used the semi-automated CUMULUS software to measure mammographic density. We defined density conventionally as the ‘white or bright’ regions, and called these measures Cumulus. We then measured density at in effect higher pixel brightness thresholds by defining density as the ‘bright’, and then ‘brightest’, areas and called these measures Altocumulus and Cirrocumulus, respectively. Second, we used machine learning, image processing techniques, and Bayesian Lasso regression to combine 20 textural features not based on pixel brightness to create risk measures which we call Cirrus. The ability of measures to differentiate cases from controls on a population basis was assessed by the increase in odds per standard deviation of the risk measure adjusted for all potential confounders in the design or analysis (OPERA).

Results: We consistently found that risk was better predicted by Altocumulus, Cirrocumulus and/or Cirrus than by Cumulus. The Cirrus measures learnt from one data set predicted risk almost as well on other data sets, even across Australian and Japanese women. The OPERAs for our new measures Altocumulus, Cirrocumulus and Cirrus were as high as 1.7, compared with OPERAs of 1.4-1.6 for the Cumulus measures. More importantly, when the different measures were estimated concurrently, the Cumulus measure reduced to the null.

Conclusion: Conventional mammographic density is a surrogate for other mammography-based risk measures which give better discrimination than all currently known genetic and lifestyle risk factors. Combining mammography-based risk measures, especially with risk measures based on multi-generational family history and SNPs, could produce inter-quartile risk ratios of >10-fold. If automated, this could revolutionise breast screening.
The chemopreventative effect of aspirin in Lynch syndrome carriers: Development and evaluation of an educational leaflet

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Background: Carriers of germline mutations in mis-match repair genes associated with Lynch syndrome are at increased risk of developing colorectal, endometrial, ovarian and other cancers. There is now good evidence that daily consumption of aspirin can reduce the cancer risk in these individuals. However there are no educational resources to inform them of the chemopreventative effects of aspirin or to support decision-making for those considering this strategy. The study aimed to develop an educational leaflet, for people with Lynch syndrome, that describes the risks and benefits of taking aspirin that may help them talk to their doctor about this risk reduction strategy.

Methods: The two page leaflet’s content was developed with experts involved in Lynch syndrome. Two health literacy measures - Flesch-Kincaid readability and Flesch reading ease score – guided the content presentation to 8th grade reading level. Lynch syndrome carriers, aged 18 and over and proficient in English, recruited through the Parkville Integrated Familial Cancer Centre, Royal Melbourne Hospital, are being invited to participate in the resource evaluation in regard to its content and clarity, length, relevance and visual appeal as well as understanding.

Results: Most participants to date (n=33) thought the length (97%) and amount of information (90%) was about right. The leaflet was rated as likely helpful in their decision-making by 66% of participants and 70% said they would recommend it to a friend. A number of suggestions have also been made to improve their understanding of the dose and timing of aspirin consumption, which are being explored.

Conclusion: Piloting the leaflet with the target group is guiding improvements and may result in the production of a widely distributed educational leaflet. Such a resource will be useful for patient education and as an aid to discussion between patients and their health care professionals.
AOCS II: THE AUSTRALIAN OVARIAN CANCER STUDY – PART II

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Background

The Australian Ovarian Cancer Study (AOCS) is a unique resource for ovarian cancer research, involving thousands of biospecimens and linked clinical and epidemiological data, created through a national, multidisciplinary collaborative program. AOCS was initially funded by the US Department of Defence (DoD) to recruit participants between 2002 and 2006. During this time, a total of 2456 women from all Australian states had consented to take part in the study, of which 1859 are cases with invasive or borderline disease. Control recruitment is also complete and a total of 1066 women that did not have ovarian cancer were recruited. Clinical details have been recorded at regular intervals for all AOCS patients. We have primary treatment data, including surgery and chemotherapy details on 99% of cases; and 92% of eligible cases have follow-up to five years post-diagnosis. Thus far only 49 patients (2.4%) have been lost to follow-up. Nationwide patient recruitment for the original DoD-funded study ceased on 30 June 2006, however, the study remained active and we continued to collect clinical data on all patients. On a smaller scale, primary surgical patients and women with recurrent disease continued to be recruited.

AOCS II

Given that most patients were collected over a decade ago and some treatment practices have changed, it is timely to ascertain a new cohort of high-grade serous ovarian cancer patients, the most common histotype, and to collect their biospecimens and clinical data. We have also taken this opportunity to revise the patient information and consent document to reflect new capabilities in DNA sequencing, such as the ability to obtain whole genome sequence information. We have called the new cohort AOCS II. The governance of all existing samples and data is transferred to this new ethics application and all future recruitment will be under “AOCS II”.

Aims

- To recruit a cohort of approximately 600 women with primary high grade serous ovarian cancer from the eastern states of Australia (VIC, NSW, QLD, TAS) to create AOCS II
- To collect matched clinical outcome data, epidemiologic data and biospecimens (blood, tumour tissue) on all 600 women recruited to the study
- To continue to make this valuable resource available to projects involving national and international investigators.

Resource

AOCS is an extraordinarily rich and flexible biospecimen repository for national and international studies on ovarian cancer. Researchers can apply to access biospecimens and associated data and these are made available to HREC-approved projects.

The structure of AOCS II parallels the operation of AOCS for the last decade, which has provided samples and data to over 110 approved projects nationally and internationally, and enabled over 240 publications.

Further information can be found at www.aocstudy.org.
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