PROGRAMME

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

“Familial Aspects of Cancer 2014 Research and Practice”

Tuesday 12th August

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

Supported by:

9.00 – 9.15 Welcome: Nicola Poplawski

FCC Session 1 Rare cancers
Chairperson: Gillian Mitchell

9.15 - 9.45 Fanconi anaemia
Kathy Tucker

9.45 - 10.15 Familial haematological cancer
Hamish Scott

10.15 - 10.30 Medulloblastoma associated with SUFU mutations
Ingrid Winship

10.30 - 10.45 SMARCA4 – a “new” familial ovarian cancer gene
Nicola Poplawski

10.45 – 11.15 Morning tea

"Familial Cancer 2014: Research and Practice"
FCC Session 2  
**BRCA-associated prostate cancer – the clinical issues**  
Chairperson: Judy Kirk

11.15 - 11.20  Setting the scene: Prostate cancer risk in male **BRCA1** and **BRCA2** mutation carriers  
**Judy Kirk**

11.20 - 11.25  The changing face of prostate cancer pathology  
**Renea Taylor**

11.25 - 11.45  Clinical implications of the unique pathology of **BRCA** associated prostate cancer  
**David Clouston**

11.45 - 12.05  The changing face of prostate cancer pathology, clinical implications of the unique pathology of **BRCA** associated prostate cancer, surveillance and treatment  
**Damien Bolton**

12.05 - 12.30  **Panel discussion**  
Renea Taylor, David Clouston, Damien Bolton

**12.30 - 1.30**  Lunch

FCC Session 3  
**Genomics – what can we translate to the clinic?**  
Chairperson: Graeme Suthers

1.30 - 1.50  Tumour genomics – Insights into targeted cancer therapy from **BRCA2**  
**Ashok Venkitaraman**

1.50 - 2.10  Germline genomics - cancer panel testing; practical implications for clinical practice  
**Judy Garber**

2.10 - 2.30  Personal genomics – contemporary challenges for ethics and the law  
**Margaret Otlowski**

2.30 - 3.00  **Panel discussion**  
Ashok Venkitaraman, Judy Garber, Margaret Otlowski, Susan Shanley

3.00 - 3.30  Afternoon Tea
FCC Session 4  Germline CDH1 mutations: managing gastric and breast cancer risk  
**Chairperson:** Mary-Anne Young

3.30 - 3.50  “Life Changing” The lived experience of risk reducing gastrectomy in people at risk of Hereditary Diffuse Gastric Cancer  
**Chris Butler**

3.50 - 4.10  What is family focused predictive testing? Lessons from CDH1 testing in New Zealand  
**Caroline Lintott**

4.10 - 4.30  Lobular neoplasia, CDH1 mutations and breast cancer risk management in germline CDH1 carriers  
**Vanessa Blair**

4.30 - 5.00  Panel discussion  
**Chris Butler, Caroline Lintott, Vanessa Blair**

5.15 - 6.30  CONFIRM investigators meeting  
Plantation room
Wednesday 13th August

8.30 - 8.40  Welcome: Stephen Fox

Session 1 – Pancreatic Cancer
Plantation Room
Chairperson: Ian Campbell

8.40 - 9.15  Pathogenesis and therapy of familial cancers: Insights from BRCA2
Ashok Venkitaraman

9.15 - 9.35  Sequencing of >350 pancreatic ductal adenocarcinomas for the ICGC project – findings from the germline
Ann-Marie Patch

9.35 - 9.55  Microsatellite Instability in Pancreatic Cancer
Jeremy Humphris

9.55 - 10.15 Novel candidate genes associated with pancreatic neuroendocrine tumours
Nicola Waddell

10.15 - 10.35 Returning individual results in genome-scale research: Impact, outcomes and demands on researchers
Amber Johns

10.35 – 11.05 Morning Tea

Session 2  Colorectal Cancer
Plantation Room
Chairperson: Ingrid Winship

11.05 - 11.40 The Jeremy Jass Memorial Lecture
Chemo prevention in familial bowel cancer - mounting the evidence. An aspirin a day keeps the cancer away?
Finlay Macrae

11.40 - 12.00 Short term risk of colorectal cancer for Lynch syndrome
Mark Jenkins

12.00 - 12.25 Lifestyle factors and risk of colorectal cancer for people with germline mutations in DNA mismatch repair genes
Aung Ko Win and Driss Ait Ouakrim
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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>12.25 - 12.45</td>
<td>Decliners of hereditary colorectal cancer genetic tests: Diverse decision-making and clinical challenges</td>
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<td>Louisa Flander</td>
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<td>12.45 - 1.45</td>
<td>Lunch</td>
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<td><strong>Session 3 –</strong> The influence of technology on genetic counselling**</td>
<td><strong>Plantation Room</strong></td>
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<td><strong>Chairpersons: Mary-Anne Young and Linda Patrick-Miller</strong></td>
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<tr>
<td>1:45 - 2:00</td>
<td>Rethinking service delivery in cancer genetic counselling</td>
<td><strong>Bronwyn Cook and Sharne Limb</strong></td>
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<td>2:00 - 2:25</td>
<td>Stretching the envelope in genetic counselling practice</td>
<td><strong>Linda Patrick-Miller</strong></td>
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<td>2:25 - 2:40</td>
<td>Current evolution of the ovarian familial cancer clinic: Challenging the model of genetic counselling</td>
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<td><strong>Maira Kentwell</strong></td>
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<td>2:40 - 2:55</td>
<td>The psychosocial impact of receiving treatment-focused genetic testing results: The role of family history</td>
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<td><strong>Margaret Gleeson</strong></td>
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<td>2.55 - 3.20</td>
<td><strong>Panel Discussion</strong></td>
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<td>3.20 - 3.50</td>
<td><strong>Afternoon Tea</strong></td>
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<td><strong>Session 4 –</strong> The role of common risk variants on cancer risk**</td>
<td><strong>Plantation Room</strong></td>
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<td><strong>Chairperson: John Hopper</strong></td>
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<tr>
<td>3.50 - 4.25</td>
<td>The Role of Common Risk SNPs on the Risk of Breast Cancer in the Familial Setting: Data from the BCFR and kConFab resources</td>
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<td><strong>David Goldgar</strong></td>
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<td>4.25 - 4.45</td>
<td>The contribution of Common Genomic Variants to the incidence of Breast Cancer Phenocopies in $BRCA1$ and $BRCA2$ families</td>
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<td><strong>Paul James</strong></td>
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<td>4.45 - 5.05</td>
<td>Variants in Practice Study (VIP): High risk women’s responses to receiving genetic test results for genomicvariants associated with breast cancer risk</td>
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<td><strong>Mary-Anne Young</strong></td>
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5.05 - 5.25  Do we know enough about SNPs to influence screening recommendations for colorectal cancer?  
Mark Jenkins

5.30 - 7.00  Poster Session + Wine and Cheese in the main foyer

6.00  Plantation Room: The following selected posters will give a 3 minute oral presentation.

Chairperson: Tess Schenberg
Order of presentation:

**Poster # 27, Jacqie Raison**
Molecular differences between interval and screen detected breast cancer.

**Poster # 33, Michelle Wong-Brown**
Low prevalence of germline PALB2 mutations in Australian triple negative breast cancer.

**Poster # 24, Sarah Sawyer**
Health professional views on the use of common genomic variant breast cancer risk in the assessment and management of high-risk women.

**Poster # 26, Kristy Brown**
Prostaglandin E2 inhibits p53 in human breast adipose stromal cells; A novel mechanism for the regulation of aromatase in obesity and breast cancer.

**Poster # 32, Risha Zia**
Anecdotally noted breast cancer in Chinese women younger than age 35

**Poster # 18, Mei Sim Lung**
Germline WES in patients with a suspected genetic predisposition to colorectal cancer (CRC) or colonic polyposis.

**Poster # 16, Lyn Schofield**
Population-based screening for Lynch Syndrome in Western Australia.

Delegates organise their own dinner
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<tr>
<td>8.45 - 9.00</td>
<td>Integration of microarray meta-analysis with RNASeq and genome-wide genetic data to identify variants associated with endometrial cancer histological subtype</td>
<td>Tracy O'Mara</td>
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<td>9.00 - 9.15</td>
<td>Endometrial cancer panel testing - what genes should be on the panel?</td>
<td>Michael Bowman</td>
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<td>9.15 - 9.30</td>
<td>Bi-allelic somatic mutations are a cause of tumour mismatch repair- in colorectal and endometrial cancer cases with no germline mismatch repair gene mutations</td>
<td>Daniel D. Buchanan</td>
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<td>9.30 - 9.45</td>
<td>Lifestyle factors and risk of endometrial cancer for women with germline mutations in DNA mismatch repair genes</td>
<td>Aung Ko Win</td>
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<td>9.45 - 10.00</td>
<td>Optimal triage of endometrial cancer patients for MMR mutation testing – updated results from ANECS and comparison to published findings</td>
<td>Yen Tan</td>
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<td>10.00 - 10.15</td>
<td>Australian Clinicians' opinions about screening endometrial cancers for Lynch Syndrome in 2014. Where are we now?</td>
<td>Shona O'Connell</td>
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<td>10.15 - 10.45</td>
<td>Panel Discussion</td>
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<td>10.45 - 11.15</td>
<td>Morning tea</td>
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### Session 6 – Rare breast cancer mutations and risk prediction

**Plantation Room**  
Chairperson: David Thomas

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<tr>
<td>11.15</td>
<td>Characterising cancer risks for carriers of mutations in <em>BRCA1</em>, <em>BRCA2</em>, <em>PALB2</em> and <em>RAD51C</em> genes</td>
<td>Antonis Antoniou</td>
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<tr>
<td>11.50</td>
<td>Mutations in <em>BRIP1</em> and breast cancer risk: implications for gene panel testing</td>
<td>Georgia Chenevix-Trench</td>
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<td>12.10</td>
<td>Penetrance of <em>BRCA1</em> and 2 Specific Gene Mutations for Breast and Ovarian Cancers in Asian population</td>
<td>Byoung Park</td>
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<tr>
<td>12.20</td>
<td>Identification of new familial breast cancer susceptibility genes: Are we there yet?</td>
<td>Ian Campbell</td>
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<td>12.50</td>
<td>BRCA1 and BRCA2 mutation prediction algorithms: Argument for the inclusion of ductal carcinoma <em>in situ</em> and other histopathological criteria</td>
<td>Claire Michel</td>
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**1.10 - 2.10**  
Lunch

### Session 7a - Concurrent session

**Plantation Room**  
Chairperson: Gillian Mitchell

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<tr>
<td>2.10</td>
<td>Randomized controlled trial of a telephone-based peer support program for female carriers of a <em>BRCA1</em> or <em>BRCA2</em> mutation: Impact on psychological distress</td>
<td>Mary Anne Young</td>
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<td>2.30</td>
<td>Understanding and Improving Dissemination in <em>BRCA1/2</em> families with a Family Communication Tool</td>
<td>Emma Healey</td>
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<td>2.50</td>
<td>Barriers and motivators for the communication of genetic information by <em>BRCA</em> carriers to relatives in multiracial Malaysia</td>
<td>Sook-Yee Yoon</td>
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**12th -15th August 2014**  
**Mantra Resort, NSW**

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| 3.10 - 3.30 |         | Health literacy in the Hereditary Cancer Clinic; what do our patients understand?  
**Rachel Williams and Sian Greening** |
| 3.30 - 3.50 |         | Health professional views on the use of common genomic variant breast cancer risks in the assessment and management of high-risk women.  
**Sarah D Sawyer** |
| 3.50 - 4.10 |         | Development and implementation of a molecular multi-disciplinary review process for return of individual research results  
**Skye Simpson** |

**Session 7b**  
**Genome Wide Association Studies**  
**Pavilion Room**  
**Chairperson: Rodney Scott**

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| 2.10 - 2.30 | Multiple variants in regulatory regions of the 6q25.1 (ESR1) breast cancer risk locus target ESR1, RMND1/c6orf211 and CCDC170  
**Stacey Edwards** |
| 2.30 - 2.50 | DEPTH: A Novel Algorithm for Feature Ranking with Application to Genome-Wide Association Studies Identifies that Variation in the ESR1 Gene Region is Associated with Risk of Estrogen Receptor Negative Breast Cancer from a Small Study  
**E. Makalic** |
| 2.50 - 3.10 | Functional characterisation of the 19p13 breast and ovarian cancer risk locus identifies ABHD8 as a novel candidate breast-ovarian cancer susceptibility gene  
**Jonathan Beesley** |
| 3.10 - 3.30 | Returning genetic research results to participants: How are we doing in Australia and where to in the future?  
**Mary Anne Young** |
| 3.30 - 3.50 | Prospective Family Study Cohort (ProF-SC) for Breast Cancer: Rationale and design, and conduct and analysis of the Australian and New Zealand components  
**John Hopper** |
| 3.30 - 4.30 | Afternoon Tea                                                                 |
| 5.00 - 8.00 | Conference Cocktail drinks pool side @ Peppers.  
All delegates welcome.  
Delegates organise their own dinner |

**Friday, 14th August**  
**ABCFS, ACCFS, kConFab, Australian Pancreatic Genome Initiative and International Sarcoma Kindred Study-Plantation Room**
Session 8 – TP53 and other matters of interest
Plantation Room
Chairperson: Judy Kirk

8.30 - 9.05 Title to be announced
Judy Garber

9.05 - 9.25 A surveillance study in TP53 mutation carriers utilizing whole body MRI: the experience to date
Mandy Ballinger

9.25 - 9.45 Mammographic density is associated with breast cancer risk in BRCA mutation carriers
Gillian Mitchell

9.45 - 10.05 Rare germline copy number deletions of likely functional importance are implicated in endometrial cancer predisposition
Gemma Moir-Meyer

10.05 - 10.25 Functional evaluation of breast cancer case-associated non-coding variants in BRCA1/2
Jan Sevcik

10.25 - 11.00 Morning Tea

Session 9 – Epigenetics and Stress
Plantation Room
Chairperson: Melissa Southey

11.00 - 11.35 Epigenetic mechanisms of breast cancer risk
James Flanagan

11.35 - 11.55 Constitutional BRCA1 methylation is a major predisposition factor for high-grade serous ovarian cancer
Alex Dobrovic

11.55 - 12.15 BRCA2 male breast cancers show elevated methylation
Siddhartha Deb

12.15 - 12.50 Psychosocial stress remolds the tumor microenvironment: Novel points of leverage to halt cancer
Erica Sloan

12.50 - 1.10 Does stress increase breast cancer risk? Initial results from the kConFab psychosocial study
Phyllis Butow

End of Meeting: Lunch will be served
PROGRAMME

Tuesday 12th

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“Familial Cancer 2014: Research and Practice”

FCC Session 1:

Plantation Room

Chairperson: Gillian Mitchell
Fanconi anaemia
Dr Kathy Tucker
Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, New South Wales, 2031, Australia

Introduction:
Fanconi anaemia is a (usually) autosomal recessive DNA repair deficiency syndrome that has a variable phenotype with the key features being physical features bone marrow failure and an increased risk of malignancy. There is a rare X-linked recessive subtype. Previously 60-70 % had physical abnormalities such as short stature, abnormal pigmentation, malformations of the thumb, forearm, skeletal system, eyes, kidney and urinary tract, ears, hypogonadism and developmental delay, decreased hearing, abnormalities of the heart, gastrointestinal system, central nervous system. Penetrance of bone marrow failure is 90% by age 40-50yrs. Acute myeloid leukaemia is present in 15-30% and solid tumours especially head and neck, skin, GI and GUS. As there are many genes (16 at last count) that cause FA, historically complementation has been used to narrow down which gene to look for. With massively paralleled sequencing the option of testing all genes at once becomes feasible. Diagnosis is by demonstrating chromosome fragility by diepoxybutane DEB/ mitomycin C MMC testing. Although the management is by the oncologist clinical geneticists have a role in managing the genetic testing and the wider family. FANCD1 FANCN and FANCJ cause an increased risk of breast cancer in female heterozygotes.

There is a suspicion that the incidence is increasing as a wider phenotype is being recognised especially the early onset head and neck SCC and Gynaecologic SCC.
Familial haematological cancer
Hamish Scott, Centre for Cancer Biology, SA Pathology, Adelaide.
Medulloblastoma associated with SUFU mutations
Kirsty Mann¹, Jessica Duffy², Kathy Tucker², Ingrid Winship³
¹Family Cancer Clinic, Royal Melbourne Hospital
²Hereditary Cancer Clinic Prince of Wales Hospital
³Genetic Medicine, Royal Melbourne Hospital

Medulloblastoma tumours may arise sporadically or as part of an inherited syndrome. A subset of children with medulloblastoma carry germline mutations in the SUFU tumour suppressor gene. Medulloblastoma is the main feature associated with SUFU mutations described to date; penetrance is currently estimated to be around 30%. We propose that macrocephaly, and possibly skin manifestations are part of the spectrum and describe two cases that are consistent with this notion.

The first is a 55 year old woman referred for investigation of skin lesions and a family history of two children from different unions with medulloblastoma. Examination revealed facial papules (classified as benign folliculosebaceous harmartomatous lesions) and dysmorphology (macrocephaly, hypertelorism and prognathism). Her father and son are reported to share the same dermatological features. Cowden and Gorlin syndromes were excluded before a SUFU splice-site mutation, predicted to lead to exon skipping, was identified.

The second case is an 18 month only child born to non-consanguineous parents and diagnosed with nodular medulloblastoma at 7 months. Examination revealed macrocephaly and hypertelorism with no other features of Gorlin or Cowden syndromes. The unaffected mother and maternal grandmother also have macrocephaly. SUFU mutation analysis identified a mutation in the proband; cascade testing confirmed the mutation was inherited from his mother, who is now considering pre-implantation genetic diagnosis.

We concur with earlier reports that the emerging SUFU phenotype should include macrocephaly, and suggest that hamartomatous skin lesions are also part of the syndrome. Presence of these features in combination with medulloblastoma may alert clinicians to the syndrome, affording the opportunity for genetic counselling of at-risk families.
SMARCA4 – a “new” familial ovarian cancer gene
Nicola Poplawski, South Australian Clinical Genetics Service, SA Pathology at the Women’s and Children’s Hospital, 72 King William Road, North Adelaide, SA 5067
nicola.poplawski@health.sa.gov.au

The SMARCA4 gene encodes the protein BRG1, a subunit of the SWI/SNF ATP-dependent chromatin-remodelling complex. Paediatric geneticists are familiar with SMARCA4 as mutations that are predicted to have gain-of-function or dominant negative effects are associated with Coffin-Siris syndrome (a congenital syndrome characterised by intellectual disability, growth deficiency, microcephaly, coarse facial features and hypoplastic/absent first fingernails and/or toenails).

As the SWI/SNF complex has an important role in transcription, cell differentiation, DNA repair and tumour suppression it is no surprise that somatic SMARCA4 mutations that are predicted to result in loss-of-function are associated with a range of different cancers including malignant rhabdoid tumours, medulloblastoma, lung and pancreatic cancer.

Germline SMARCA4 mutations that are predicted to be truncating have also been described in rhabdoid tumour predisposition syndrome type 2.

More recently germline SMARCA4 mutations that are predicted to be truncating were identified in women with small-cell carcinoma of the ovary, hypercalcaemic type (SCCOHT). This is a rare aggressive ovarian cancer subtype (most likely a sarcoma) which affects children and young women (mean age 23 years) and is refractory to standard chemotherapy. Immunohistochemical loss of BRG1 protein in SCCHT is a marker for SMARCA4 mutations, in a similar way to loss of MMR proteins being a marker for Lynch syndrome, and loss of SDHB being a marker for familial paraganglioma.

This short paper presents the key clinical aspects of the cancer predisposition thought to be due to germline mutations in the SMARCA4 gene – and a number of important questions and caveats related to the potential clinical utility of genetic testing for SMARCA4 mutations in women with SCCOHT.

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“Familial Cancer 2014: Research and Practice”

FCC Session 2:

Plantation Room

Chairperson: Judy Kirk
The changing face of prostate cancer pathology, clinical implications of the unique pathology of BRCA associated prostate cancer, surveillance and treatment.

Gail P. Risbridger, Renea A. Taylor, David Clouston, Ania Sliwinski, Heather Thorne, Sally Hunter, Jason Li, kConFab, Gillian Mitchell, Declan Murphy, Mark Frydenberg, David Pook, John Pedersen, Roxanne Toivanen, Hong Wang, Melissa Papagiris, Mitchell G. Mitchell, Damien M. Bolton.

BRCA1 and BRCA2 are tumour suppressor genes associated with increased risk of developing cancer, predominantly breast, ovary and prostate cancer. Male BRCA2 mutation carriers, and men from high-risk breast cancer families with no identified BRCA mutation (BRCAx), have an increased risk of prostate cancer and a higher rate of prostate cancer-specific mortality. High Gleason Score (GS) disease is also more prevalent in BRCA2-associated prostate cancer. The precise mechanism by which BRCA2 mutations contribute to highly aggressive prostate cancer is not completely understood. Serum PSA levels, GS and clinical staging are commonly combined to predict prostate cancer outcomes using the D’Amico risk grading. However, these routinely used discriminators are less predictive of treatment outcomes in BRCA2 carriers with prostate cancer and they fail to predict the poorer outcomes in BRCA2 carriers compared to non-carriers, even when matched for GS.

In order to study the biology of tumours from men with high-risk familial prostate cancer our group employed a number of strategies: a) xenographs were established using fresh prostate cancer tumours sourced from BRCA2 and BRCAx kConFab men and b) a review of the original radical prostatectomy specimens from 33 BRCA2 carriers and 62 BRCAx patients from kConFab was performed. Histopathological examination of the xenographs and their original radical prostatectomy samples derived from the kConFab BRCA mutation carriers revealed an unexpected finding of prominent areas of intraductal carcinoma (IDC-P), a distinct clinico-pathologic entity known to be associated with aggressive prostate cancer and also predicts poor treatment response. IDC-P has previously been under-diagnosed and under-reported in routine prostate biopsy and radical prostatectomy specimens, thus the true incidence of IDC-P has been difficult to estimate. Of note, IDC-P was not specifically noted in any of the original kConFab associated pathology reports (33 BRCA2 carriers and 62 BRCAx participants) but was observed in XX on specimen review. For all kConFab BRCA-associated prostate cancer cases, statistical analysis of survival outcome and other diagnostic features linked to the presence or absence of IDC-P was performed and will be presented.

This study reports for the first time the high prevalence of IDC-P in BRCA2 and BRCAx patients with prostate cancer and its association with poor overall survival. This might identify patients who may benefit from immediate multi-modality treatment with curative intent rather than active surveillance. If active surveillance strategies are used, our data suggest that there should be a low threshold for repeat biopsy and/or imaging to identify tumour upstaging. Although there is uncertainty about the optimal management of BRCA2 carriers and BRCAx patients with IDC-P, an appreciation of the poor overall survival of this unique cohort is useful for treating clinicians and patients when discussing the optimal management of prostate cancer.
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“Familial Cancer 2014: Research and Practice”

FCC Session 3:

*Plantation Room*

Chairperson: Graeme Suthers
Tumour genomics: Insights into targeted cancer therapy from BRCA2
Genomics: What can we translate to the clinic?

Ashok Venkitaraman, The Ursula Zoellner Professor of Cancer Research, University of Cambridge Director, Medical Research Council Cancer Unit Hutchison/MRC Research Centre, Hills Road, Cambridge CB2 0XZ, United Kingdom.

• The development of targeted therapy
• Currently available targeted therapy
• The role of combined therapies
• Future possibilities in targeted therapy
Germline genomics - Cancer panel testing; practical implications for clinical practice
Judy Garber, Director, Center for Cancer Genetics and Prevention, Dana Farber Cancer Institute, Professor of Medicine Harvard Medical School
Personal genomics – contemporary challenges for ethics and law
Margaret Otlowski, Faculty of Law, University of Tasmania

This paper will explore key ethical and legal challenges presented by next generation sequencing, with particular regard to the context of clinical cancer genetics and the capacity for cancer panel testing. It will focus on the role that patient consent plays in navigating some of the ethical and legal challenges, including the issue of results back and potential for incidental findings. It will also examine the extent of the clinicians’ duty of disclosure to their patients, particularly into the future as more is understood about currently unknown mutations. The paper will seek to highlight that the initial consent process is crucial in negotiating the terms of engagement with this powerful form of genetic technology. This, in turn, underscores the importance of the role of genetic counselling in supporting patients to ensure that they understand the implications of the genetic testing that is being proposed and also the significance of any findings for them and their genetic relatives.
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“Familial Cancer 2014: Research and Practice”

FCC Session 4:

Plantation Room

Chairperson: Mary-Anne Young
“Life Changing” The lived experience of risk reducing gastrectomy in people at risk of Hereditary Diffuse Gastric Cancer.
Butler C¹,², A McEwen³, Wake S¹,², M.A Young⁴

1. Department of Paediatrics, The University of Melbourne, Parkville, VIC, Australia
2. Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Royal Children’s Hospital, Parkville, VIC, Australia
3. Genetic Health Service NZ (Central Hub), Wellington Hospital, Wellington South, New Zealand
4. The Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia

Background:
Hereditary Diffuse Gastric Cancer (HDGC), a rare familial cancer syndrome, is caused by mutations in the gene CDH1. Individuals who inherit a CDH1 mutation have a high lifetime risk of developing stomach cancer. Women have a significantly increased risk of developing breast cancer. There are no proven methods of screening for diffuse gastric cancer so mutation carriers are urged to consider complete surgical removal of the stomach or risk-reducing gastrectomy (RRG). RRG is medically effective in reducing cancer risk but carries risks of surgical complications and long-term morbidity. Those who have RRG are a unique group of often young, otherwise healthy individuals. Little is known of the long-term psychosocial outcomes of RRG.

Aims and methodology:
We have conducted an exploratory qualitative study into the lived experiences of eight individuals who have undergone RRG. In-depth semi-structured interviews were conducted with individuals who are known to carry a CDH1 mutation and who had chosen to undergo RRG asking specifically about information and support. Thematic analysis of verbatim transcripts was used to generate results.

Results:
Information gathering, support strategies and the recovery process all emerged as themes from the analysis. Participants used a variety of information sources to explore the meaning of their experiences including family history, peer support, medical staff and the Internet. The most important source of support was family, supplemented by social networks, professional support and online resources. Recovering emerged as a theme that included an educational process of learning to eat again and coming to terms with a new sense of self. Despite varying experiences of recovery time, physical and psychological effects, all participants expressed satisfaction in their decision to undergo RRG. Participants reported that RRG was “life-changing” but this was off-set by the sense that they had made a life-saving decision.
What is family focused predictive testing? – Lessons from CDH1 testing in New Zealand
Caroline Lintott, Alison McEwen. Genetic Health Service NZ – South Island and Central Hubs.

Autosomal dominant diffuse gastric cancer in an NZ Maori family was first reported in the NZ Medical Journal in 1964. In 1998, the molecular basis for hereditary diffuse gastric cancer was described in a large NZ Maori family with early onset multigenerational diffuse gastric cancer (CDH1 G>T of exon 7). Appropriate clinical management of asymptomatic individuals with a CDH1 mutation includes curative surgical resection, with timing of surgery recommended around age 20 years, before the signet ring adenocarcinomas apparently present in almost all patients have become invasive. Genetic counselling is considered an essential component of predictive testing for familial CDH1 mutations. The Eurocentric model of genetic counselling is based on the principles of informed choice, individual autonomy, and privacy of the individual. This Eurocentric model of decision-making, focused on the individual, does not necessarily deliver a culturally acceptable genetic counselling service for Maori, where collective whanau-focused (extended family) decision-making is fundamental to Kaupapa Maori. Pre-test genetic counselling to facilitate decision-making, may become a process through which a consensus decision by whanau is achieved. Recognition and validation of family focused genetic counselling, and the barriers a Eurocentric model favouring individual autonomy may present to this, are discussed in relation to predictive testing for CDH1 mutations.
Lobular neoplasia, CDH1 mutations and breast cancer risk management in germline CDH1 carriers
Vanessa Blair, FRACS, PhD.

The two most common types of breast cancer are invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), at 70-80% and 5-10% of cases respectively. In IDC malignant cells display varying amounts of gland formation, whereas in ILC small clusters/ribbons of malignant cells show absent gland formation. CDH1 is the gene which codes for E-cadherin, a cell-to-cell adhesion molecule. Loss or reduced expression of E-cadherin parallels cancer invasion and metastasis and E-cadherin immunostaining is absent in most ILCs, but present in IDC. Somatic mutations occur in the E-cadherin gene (CDH1) in sporadic ILCs but are rare in IDCs.

Germline CDH1 mutation carriers from Hereditary Diffuse Gastric Cancer (HDGC) kindred have a 60% risk of ILC by 80y, along with an 80% lifetime risk of stomach cancer. Rare families with multiple ILCs but no gastric cancer have been identified with germline CDH1 mutation. Loss of E-cadherin explains the divergent morphologic phenotype between ILC and IDC, and diffuse versus intestinal gastric cancer. A better name for ILC might be ‘diffuse breast cancer’, one advantage being it avoids the misconception that ILC arises in breast lobules and IDC the ducts.

There is no established model describing how loss of E-cadherin function might be related to initiation and/or progression in carcinogenesis, however a model has been proposed in HDGC suggesting a long indolent phase for early stomach lesions. There are some similar themes in the natural history of ALH (atypical lobular hyperplasia) and LCIS (Lobular carcinoma in-situ), together referred to as lobular neoplasia (LN). Whether LN is purely a marker of increased risk or the precursor lesion of ILC has been a controversial issue in breast pathology. Recent molecular evidence suggests it is both.

This talk will review breast cancer risk management in E-cadherin mutation carriers. Results from pathological mapping of a mastectomy from a CDH1 mutation carrier will be presented: Mapping revealed 4 ILC, 11 foci of ALH and 16 foci of LCIS.
Programme

Wednesday 13th

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

"Familial Cancer 2012: Research and Practice"

Session 1:

Plantation Room

Welcome: Stephen Fox

Chairperson: Ian Campbell
Pathogenesis and therapy of familial cancers: Insights from BRCA2
Ashok Venkitaraman, Medical Research Council Cancer Unit, University of Cambridge, UK.

Genetic alterations associated with early-onset familial cancers offer powerful insights into sporadic cancer pathogenesis and therapy. Several cancer-susceptibility syndromes have been identified in which familial cancer predisposition is associated with instability in the structure and number of chromosomes in the cells of cancer-prone tissues. An important example concerns germline mutations affecting BRCA2, which predispose to cancers of the breast, ovary, pancreas and other organs. We demonstrated some years ago that BRCA2 inactivation triggers chromosomal instability in dividing cells. We have since studied hereditary cancer predisposition associated with BRCA2 inactivation as a powerful model system in which to elucidate the connections between chromosome instability and cancer pathogenesis (reviewed in 1). Here, I will discuss our recent work linking the cellular functions of BRCA2 to familial cancer pathogenesis and therapy. In particular, we have identified functions for BRCA2 in the control of the RAD51 recombinase during homologous DNA recombination, and in the coordination of cell division by cytokinesis, which are perturbed by cancer-associated mutations (eg., 2-5). An autochthonous mouse model for Kras-driven pancreatic cancers associated with BRCA2 inactivation offers fresh insights into cancer evolution in the setting of chromosomal instability, and its implications for therapy (eg., 6-7).

Sequencing of >350 pancreatic ductal adenocarcinomas for the ICGC project – findings from the germline

Ann-Marie Patch1, Jeremy Humphris2, Amber L. Johns2, Nicola Waddell1, David K. Chang2,3,4,5, Karin S. Kassahn1, David Miller1,5, Katia Nones1, Michael C. J. Quinn1, Conrad Leonard1, Lorraine A. Chantrill2, Ilse Rooman2, Australian Pancreatic Cancer Genome Initiative6, Anthony J. Gill2,7, Ralph H. Hruban8, Christian Pilarsky9, Aldo Scarpa10,11, John V. Pearson1,12, Andrew V. Biankin2,3,4,5 and Sean M. Grimmond1,5.

1Queensland Centre for Medical Genomics, Institute for Molecular Bioscience, The University of Queensland, St Lucia, Brisbane, QLD, 4072, AUSTRALIA; 2The Kinghorn Cancer Centre, Cancer Division, Garvan Institute of Medical Research, University of New South Wales, 384 Victoria St, Darlinghurst, Sydney, NSW 2010, AUSTRALIA; 3Department of Surgery, Bankstown Hospital, Eldridge Road, Bankstown, Sydney, NSW 2200, AUSTRALIA; 4South Western Sydney Clinical School, Faculty of Medicine, University of NSW, Liverpool NSW 2170, AUSTRALIA; 5Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Garscube Estate, Switchback Road, Bearsden, Glasgow, Scotland G61 1BD, United Kingdom; 6Australian Pancreatic Cancer Genome Initiative, for full list of contributors see http://www.pancreaticcancer.net.au/apgi/collaborators; 7University of Sydney, Sydney NSW 2006, AUSTRALIA; 8Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, the Johns Hopkins University School of Medicine, Baltimore, Maryland 21231, USA; 9Departments of Surgery and Pathology, TU Dresden, Fetscherstr. 74, 01307 Dresden, Germany; 10ARC-NET center for applied research on cancer, University and Hospital Trust of Verona, Verona 37134, Italy; 11Department of Pathology and Diagnostics, University of Verona, Verona 37134, Italy; 12Queensland Institute of Medical Research, Berghofer Medical Research Institute, Genomic Biology Laboratory, 300 Herston Road, Herston, 4006, AUSTRALIA.

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer with a median survival of 6 months. It has been estimated that approximately 10% of patients have an inherited predisposition to PDAC. Genes which have been associated with an increased risk in PDAC include those which are linked to known pancreatic genetic syndromes such as STK11, APC, CDKN2A, BRCA1/2 and PRSS1, as well as a variety of other DNA repair genes PALB2, TP53 and ATM.

As part of the International Cancer Genome Consortium (ICGC) we have performed exome or whole genome sequencing of >350 PDACs and matched normal DNA. Within the cohort we identified approximately 5 million germline non-silent coding variants. We find germline changes in the known pancreatic cancer genes including frameshift mutations in BRCA1, BRCA2, ATM and PALB2. In addition we also find a large number of rare or novel (not in dbSNP) missense and splice site changes, however without knowing the clinical relevance of these variants caution must be taken in interpretation of these findings. We have used a variety of tools to predict the likely pathogenicity of these variants. We have also used the somatic mutation data to predict the likely significance of these variants eg looking for a ‘second hit’ in the gene or in the case of BRCA and DNA repair genes looking for an association with the BRCA mutational signature. Our findings show that even ‘sporadic’ PDACs have a significant genetic germline component.
Microsatellite Instability in Pancreatic Cancer

Jeremy L. Humphris1, Nicola Waddell2, Ann-Marie Patch2, Amber L. Johns1, Skye H. Simpson1, Mark Pinese1, Anthony J. Gill3, David K. Chang4, Australian Pancreatic Genome Initiative5, R. Scott Mead1, Sean M. Grimmond2,4, Andrew V. Biankin1,4.

1The Kinghorn Cancer Centre, 370 Victoria Street, Darlinghurst, and the Cancer Research Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, Sydney
2Queensland Centre for Medical Genomics, Institute for Molecular Bioscience, University of Queensland, St Lucia, Brisbane, QLD, AUSTRALIA
3Department of Anatomical Pathology, Royal North Shore Hospital, St Leonards. Sydney NSW 2065, AUSTRALIA;
4Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland United Kingdom.
5Australian Pancreatic Cancer Genome Initiative (APGI), http://www.pancreaticcancer.net.au/apgi/collaborators

Purpose: Inherited genetic factors play an important role in the predisposition to pancreatic cancer (PC). One such hereditary predisposition syndrome is Lynch syndrome, resulting from a germline mutation in DNA mismatch repair genes (MMR), with tumour DNA showing microsatellite instability (MSI) following the loss of the wild type allele. The prevalence of pathogenic germline MMR mutations and the contribution of MSI to neoplastic progression in PC are not well defined.

Methodology: The cohort examined comprised 296 consecutive patients with PC from 12 tertiary referral centres associated with the Australian Pancreatic Genome Initiative. Germline and tumour DNA underwent whole-genome (WGS, n = 132) or whole-exome (WES, n = 164) sequencing. Germline and tumour copy number variants were assessed with SNP arrays. Germline DNA was assessed for mutations in MLH1, MSH2, MSH6 and PMS2. Tumour DNA was assessed for hypermutation, including increased frameshift indels, as a marker of defective MMR. Where available immunohistochemistry (IHC) for MMR protein expression was performed on tumour tissue.

Results: In the 296 PC patients, 25 (8.4%) met the criteria for familial PC (FPC). A further 10 had previous colorectal (CRC) or endometrial cancer (EC) and 25 had at least one FDR with CRC or EC. Only one pathogenic germline MMR mutation was identified (PMS2:c.1738A>T, p.Lys580*). This patient had no personal or family history of malignancy and tumour showed normal PMS2 expression on IHC and no hypermutated signature with WGS (count = 6491). Two PCs showed hypermutation (mean indel count = 43,926) consistent with defective MMR. Tumour DNA in both cases showed bi-allelic somatic mutations in MSH2 (homozygous deletion or complex structural re-arrangements). One of these patients had tissue for IHC, which confirmed absent MSH2 protein expression. Two additional tumours showed absent expression on IHC for MMR proteins. The first was a tumour with absent PMS2, but we could not detect germline or somatic mutations in the gene and the tumour did not show hypermutation (indel count = 6351). The second was a PC with absent MSH2 MMR protein expression, in this case a germline change could not be detected but there was a somatic splice-site mutation predicted to be damaging.

Conclusion: In our cohort 1.4% (4/296) of PC patients showed evidence of defective MMR based on either hypermutation or absent protein expression. In the majority (3/4) of these cases this was the result of somatic MSH2 inactivation. Inherited pathogenic MMR mutations were found in 0.3% (1/296) and do not appear to play a major role in PC predisposition in our cohort.
Novel candidate genes associated with pancreatic neuroendocrine tumours

Nicola Waddell\textsuperscript{1}, Amber L. Johns\textsuperscript{2}, Katia Nones\textsuperscript{1}, Jeremy Humphris\textsuperscript{2}, David K. Chang\textsuperscript{2,3,4,5}, David Miller\textsuperscript{1,5}, Michael C. J. Quinn\textsuperscript{1}, Ann-Marie Patch\textsuperscript{1}, Conrad Leonard\textsuperscript{1}, Lorraine A. Chantrill\textsuperscript{2}, Ilse Rooman\textsuperscript{2}, Australian Pancreatic Cancer Genome Initiative\textsuperscript{6}, Anthony J. Gill\textsuperscript{2,7}, Marie-Claude Gingras\textsuperscript{8}, Richard Gibbs\textsuperscript{8}, Aldo Scarpa\textsuperscript{9,10}, John V. Pearson\textsuperscript{1,11}, Andrew V. Biankin\textsuperscript{2,3,4,5} and Sean M. Grimmond\textsuperscript{1,5}.

\textsuperscript{1}Queensland Centre for Medical Genomics, Institute for Molecular Bioscience, The University of Queensland, St Lucia, Brisbane, QLD, Australia;
\textsuperscript{2}The Kinghorn Cancer Centre, Cancer Division, Garvan Institute of Medical Research, University of New South Wales, 384 Victoria St, Darlinghurst, Sydney, NSW, Australia;
\textsuperscript{3}Department of Surgery, Bankstown Hospital, Eldridge Road, Bankstown, Sydney, NSW, Australia;
\textsuperscript{4}South Western Sydney Clinical School, Faculty of Medicine, University of NSW, Liverpool NSW, Australia;
\textsuperscript{5}Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Garscube Estate, Switchback Road, Bearsden, Glasgow, United Kingdom;
\textsuperscript{6}Australian Pancreatic Cancer Genome Initiative, for full list of contributors see http://www.pancreaticcancer.net.au/apgi/collaborators;
\textsuperscript{7}University of Sydney, Sydney NSW, AUSTRALIA;
\textsuperscript{8}Baylor College of Medicine, Houston, TX, USA;
\textsuperscript{9}ARC-NET center for applied research on cancer, University and Hospital Trust of Verona, Italy;
\textsuperscript{10}Department of Pathology and Diagnostics, University of Verona, Italy;
\textsuperscript{11}Queensland Institute of Medical Research, Berghofer Medical Research Institute, Genomic Biology Laboratory, 300 Herston Road, Herston, Australia.

Pancreatic neuroendocrine tumours (PanNET) represent approximately 2\% of tumours of the pancreas and are an uncommon tumour with two to four people per million affected annually worldwide. The rare genetic syndromes multiple endocrine neoplasia type 1 (MEN1) and Von Hippel-Lindau (VHL) syndrome are associated with an increased risk of PanNET. PanNETs are known to harbour frequent somatic mutations in the \textit{MEN1} gene as well as genes involved in telomere length (\textit{DAXX}/\textit{ATRX}) and members of the mTOR pathway.

We have performed whole genome sequencing of 100 PanNETs and matched normal DNA. Within the cohort we identified 1 patient with a novel missense germline variant in the \textit{VHL} gene and two additional patients with a rare missense variant (p.P25L, c.74C<T) which the literature suggests is not pathogenic. Four patients contain germline frameshift mutations of the \textit{MEN1} gene, and a single patient had a novel germline splice site variant.

In addition to \textit{MEN1} and \textit{VHL} we found germline variants in several other genes which we hypothesise have a role in PanNET tumourigenesis. These include \textit{MUTYH}, \textit{TERT} and SDH family members. We will show evidence which supports the role of these genes in PanNET. For example \textit{MUTYH} is involved in oxidative DNA damage repair and mutations in the gene are associated with MUTYH-associated polyposis and biallelic inactivation has been shown to confer a risk of colorectal carcinoma. In this cohort 4 of the PanNETs have novel germline alterations (including 1 frameshift, 2 missense and 1 splice site), and an additional 5 patients have rare germline variants (3 missense and 1 splice site). In support of a role for \textit{MUTYH} in PanNET, patients with a germline change and somatic biallelic inactivation were associated with a high somatic mutational signature which is associated with \textit{MUTYH}.
Returning individual results in genome-scale research: Impact, outcomes and demands on researchers

Amber L. Johns¹, Skye H. Simpson¹, Jeremy L. Humphris¹, Mark Pinese¹, Lorraine A. Chantrill¹,², Katherine Tucker², Lesley Andrews², Australian Pancreatic Cancer Genome Initiative³, Sean M. Grimmond⁴,⁵, Nicola Waddell⁵, Nikolajs Zeps⁶,⁷, Andrew V. Biankin¹,⁴

¹Cancer Research Program, Garvan Institute of Medical Research, the Kinghorn Cancer Centre, Sydney Australia.
²Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, Sydney Australia.
³Australian Pancreatic Cancer Genome Initiative (APGI), http://www.pancreaticcancer.net.au/apgi/collaborators
⁴Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland United Kingdom.
⁵Queensland Centre for Medical Genomics, Institute for Molecular Biosciences, University of QLD, St Lucia Australia.
⁶St John of God Subiaco, Perth Australia.
⁷School of Surgery, The University of Western Australia, Perth, Australia
⁸Dept of Medical Oncology, Campbelltown Hospital, Sydney, NSW Australia

Background: The conduct of large-scale genomic studies is accelerating, which has triggered a shift in challenge from data generation to interpretation and implementation. This has intensified the discussion surrounding returning research results, which is currently a complex and well-debated issue. Guidelines, commentaries and case studies have been described to address the return of incidental findings, but very little data exists on the practicality, impact, resource requirements and associated outcomes, on both research investigators and clinical teams, with returning research results in large-scale cancer genomics research.

Methods: The Australian Pancreatic Cancer Genome Initiative (APGI) is an Australian contribution to the International Cancer Genome Consortium (ICGC), which involves prospective sequencing of tumour and normal genomes of study participants with pancreatic cancer in Australia. Through interrogation of germline data from this study we account the methods and practical applications of the return of results framework; including representative time-intervals for key procedures, resource and worker-hours required for interpretation, reporting, disclosing and overall management of the return of results process. Associated actions and preliminary outcomes for each result will also be explored.

Results: From 2009-2013 total of 375 patients were recruited and tumour and normal genomes sequenced with either deep whole exome or whole genome approaches. 13 germline findings were deemed actionable and were returned via a constituted, previously described ethically defensible framework. Findings were validated in an independent, diagnostic grade assay in all 13 cases (100%). 8 cases were actioned (61%), and resulted in an intervention of a therapeutic or surveillance nature. The time taken from result communication to action was on average 222 days, with a range 82 -550 days. The time and resource requirements for ensuring adequate communication with clinical teams and patients, preparation of confirmatory testing, curation and preparation of relevant paperwork and supporting documentation was significant, and specific examples are illustrated.

Conclusion: Returning research results within the context of large-scale genomics research is a labour intensive, highly variable, complex operation. Through the experiences of the APGI, specialised personnel and dedicated infrastructure are required to manage the process to ensure a clinically relevant and useful standard. We hope that these data serve as practical support for those planning large-scale genomic research, and may give empirical insight into the infrastructure and resource requirements likely to be necessary for those intending to return research results.
Programme

Wednesday 13th

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

“Familial Cancer 2014: Research and Practice”

Session 2:

Plantation Room

The Jeremy Jass Memorial Lecture

Introduction & Chair: Ingrid Winship

Presented by: Finlay Macrea
Chemo prevention in familial bowel cancer - mounting the evidence. An aspirin a day keeps the cancer away

Finlay Macrae, International Vice Chair, CAPP; Principal Investigator, AusFAP trial; Secretary InSiGHT; Steering Committee, NIH Colon Family Register; Head, Colorectal Medicine and Genetics, The Royal Melbourne Hospital

Proof in translational medicine usually is firmest with level 1 evidence which is derived from the meta-analysis of randomized controlled trials.

The preventative benefits of aspirin and other NSAIDs from observational epidemiology are, however, very compelling. CAPP2 moved on to provide Level 2 evidence for aspirin’s remarkable ability to prevent cancers, notably in Lynch Syndrome – strong evidence unlikely to be duplicated. The dose in CAPP2 was chosen to thoroughly but reasonably test the hypothesis: 600mg. The question at present is whether the benefits can be secured at a lower dose with lesser side effects: GI toxicity, though often overstated compared with benefit, is dose stated. CAPP3 funded and commencing now in UK addresses this with randomization between 100mg, 300mg and 600mg. As strong participants to CAPP2, we are hopeful that CAPP3 will be funded in the current NHMRC/Cancer Council round of funding. We will need close engagement with all of you to recruit if we achieve funding. Recognizing the importance of the question, RMH has provisionally undertaken to fund CAPP3 at RMH if not funded through the current national cycle. We will invite others to do the same if this is not funded in the current round of funding.

There are other preventative strategies available. AusFAP, funded and recruiting in Melbourne but multi-state poised and funded by most state cancer councils, is testing a modified starch preparation developed by the CSIRO, to prevent polyps in people with familial adenomatous polyposis. Its active ingredient, released through fermentation in the colon, is butyrate. This is a RCT cross over trial with 120 participants projected. It will roll out also in Queensland (RBWH), Sydney (St Vincent’s – Allan Spigelman), Newcastle (John Hunter – Alan Spigelman and Rodney Scott), Adelaide (Flinders- we hope – Peter Bampton) and possibly in WA (Marina Wallace). Other Victorian Centres are Cabrini (Finlay Macrae), Western (Iain Skinner and Alex Boussioutas), Royal Children’s Hospital (Don Cameron). AusFAP is happy to engage your patients in this Australian first.

Other approaches to chemoprevention include resveratrol for which we at RMH are just completing an RCT with mucosal biomarkers as the endpoint. Curcumin and tumoric are attractive agents to trial. In Europe, a multi-national trial to build on the first RCT of Eicosapentaenoic Acid-Free Fatty Acid has secured EU funding and will be the next agent to drive international preventative attention.

Calcium, folate and to some extent, fibre, have fallen from grace.
Short-term risk of colorectal cancer for Lynch syndrome.

Mark A. Jenkins,¹ James G. Dowty,¹ Driss Ait Ouakrim,¹ John D. Mathews,¹ John L. Hopper,¹ Youenn Drouett,²,³ Christine Lasset,²,³ Valérie Bonadona,²,³ Aung Ko Win.¹

¹ Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia.
² Université Lyon 1, Centre National de la Recherche Scientifique (CNRS) UMR 5558 LBBE, Villeurbanne, France.
³ Prevention and Genetic Epidemiology Unit, Centre Léon Bérard, Lyon, France.

Background: For carriers of germline mutations in DNA mismatch repair (MMR) genes, the most relevant statistic for cancer prevention is their risk of colorectal cancer (Lynch syndrome), particularly in the short-term.

Methods: We have conducted a meta-analysis of all the independent published Lynch syndrome studies that reported age- and sex-dependent colorectal cancer risks. We estimated 5-year risks of colorectal cancer over different age groups, separately for male and female mutation carriers, assuming no prior colorectal cancer, and number needed to screen to prevent one death.

Results: We pooled estimates from analyses of 1,114 Lynch syndrome families (508 MLH1, 606 MSH2). On average, 1 in 71 male and 1 in 102 female MLH1 or MSH2 mutation carriers in their 20s will be diagnosed with colorectal cancer in the next 5 years if they do not screen for the disease. These colorectal cancer risks increase with age peaking in their 50s (1 in 7 males and 1 in 12 females), and then decrease with age (1 in 13 males and 1 in 19 females in their 70s). Annual colonoscopy in 16 males or 25 females in their 50s would prevent one death from colorectal cancer over 5 years while resulting in almost no serious complications. In comparison, annual colonoscopy in 115 males or 217 females in their 20s would prevent one death while resulting in approximately one serious complication.

Conclusion: Current guidelines recommend colonoscopy every 1-2 years starting in their 20s for MLH1 or MSH2 mutation carriers. Our findings support this regimen from age 30 years; however, it might not be justifiable for carriers aged in their 20s.
Lifestyle factors and risk of colorectal cancer for people with germline mutations in DNA mismatch repair genes


Joint First Authors
1 Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia.
2 Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Parkville, Victoria, Australia.
3 Department of Veterans Affairs, Eastern Colorado Health Care System, University of Colorado School of Medicine, Denver, Colorado, USA.
4 Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA.
5 Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.
6 School of Public Health, University of Washington, Seattle, Washington, USA.
7 Centre for Public Health Research, Massey University, Wellington, New Zealand.
8 Department of Preventive Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA.
9 Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada.
10 Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University, California, USA.
11 University of Hawaii Cancer Center, Honolulu, Hawaii, USA.
12 Department of Health Science Research, Mayo Clinic Arizona, Scottsdale, Arizona, USA.
13 Molecular Genetics Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA.
14 Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia.
15 Genetic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Australia.

Aim: People with germline mutations in DNA mismatch repair (MMR) genes have a substantially high risk of colorectal cancer; however, the modifiers of this risk are not well established. The aim of this study was to investigate associations between lifestyle factors and risk of colorectal cancer for MMR gene mutation carriers using the largest sample of mutation carriers to date.

Methods: This study comprised 1,903 carriers of a mutation in an MMR gene (695 MLH1, 905 MSH2, 203 MSH6 and 100 PMS2) from the Colon Cancer Family Registry. Using Cox proportional hazards regressions weighted to correct for ascertainment bias, we estimated hazard ratios (HRs) and 95% confidence interval (CIs) for associations between lifestyle factors and risk of colorectal cancer for MMR gene mutation carriers.

Results: During 76,380 person-years of observation, 779 carriers (41%) were diagnosed with colorectal cancer. A decreased risk of colorectal cancer was associated with use of multivitamin supplements (for 1-5 years: HR 0.59, 95% CI 0.40-0.89; and for >5 years: HR 0.47, 95% CI 0.31-0.72), calcium supplements (for 1-5 years: HR 0.45, 95% CI 0.26-0.78; and for >5 years: HR 0.33, 95% CI 0.16-0.71), aspirin (for 1-10 years: HR 0.48, 95% CI 0.26-0.89; and for >10 years: HR 0.28, 95% CI 0.26-0.89), oestrogen and progestin hormone replacement therapy (HR per year 0.69, 95% CI 0.48-0.99), and hormonal contraceptive (HR per year 0.94, 95% CI 0.92-0.97) compared with never users. An increased risk of colorectal cancer was found to be associated with over alcohol consumption (for ethanol per 14 g/day: HR 1.05, 95% CI 1.00-1.11) and liquor/spirits consumption (for ethanol per 14 g/day: HR 1.34, 95% CI 1.23-1.46). An increased risk of rectal cancer was found to be associated with beer consumption (for ethanol per 14 g/day: HR 1.19, 95% CI 1.03-1.37).

Conclusion: Lifestyle factors are important modifiers of colorectal cancer risk for MMR gene mutation carriers.
Decliners of hereditary colorectal cancer genetic tests: Diverse decision-making and clinical challenges

Louisa Flander\textsuperscript{1}, Antony Ugoni\textsuperscript{2}, Louise Keogh\textsuperscript{3}, Heather Niven\textsuperscript{1}, Alison Rutstein\textsuperscript{1}, Aung Ko Win\textsuperscript{1}, Driss Ait Ouakrim\textsuperscript{1}, Clara Gaff\textsuperscript{4}, Ingrid Winship\textsuperscript{5}, Mark Jenkins\textsuperscript{1}

Louisa Flander l.flander@unimelb.edu.au Centre for Epidemiology and Biostatistics, The University of Melbourne, VIC 3010, Australia. T +61 3 8344 0739, F +61 3 9349 5815

\textsuperscript{1}Centre for Epidemiology & Biostatistics, The University of Melbourne, VIC 3010, Australia
\textsuperscript{2}School of Physiotherapy, The University of Melbourne, VIC 3010, Australia
\textsuperscript{3}Centre for Health & Society, The University of Melbourne, VIC 3010, Australia
\textsuperscript{4}Departments of Paediatrics & Medicine, The Royal Melbourne Hospital, Parkville VIC 3050, Australia
\textsuperscript{5}Department of Medicine, The Royal Melbourne Hospital, Parkville VIC 3050, Australia

Genetic counselling and/or testing to identify mutation status and risk of colorectal cancer (CRC) is not utilised in approximately half of people from mutation-carrying families. We studied perceived CRC risk and reasons for declining in 26 participants (mean age 43.1 years, 14 women) in the Australasian Colorectal Cancer Family Registry. All were relatives of DNA mismatch repair gene mutation carriers, who had not been diagnosed with any cancer and had declined to an invitation to attend genetic counselling and/or testing. Their risk perception of 10-year risk of CRC, understanding of genetic testing and CRC risk, reasons for declining testing and self-reported colonoscopy screening were elicited during face-to-face interviews. A sub-group of decliners (31\%) unconditionally rejected genetic testing compared to conditional decliners who would consider genetic testing in the future. Mean perceived 10-year risk of CRC was 54\% [95\% CI 37, 71] in unconditional decliners, compared with 20\% [95\% CI 5, 36] in conditional decliners, after adjusting for potential confounding factors (age, gender and reported screening colonoscopy). The unconditional decliner group perceive themselves to be at 3.26 times higher risk than conditional decliners. General practice interventions may increase testing uptake and/or screening for high-risk under-serviced individuals, whose health behaviours appear inconsistent with their risk perceptions.

KEYWORDS
Colorectal cancer, decision making, genetic testing, Lynch syndrome, risk perception
Wednesday 13th

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

“Familial Cancer 2014: Research and Practice”

Session 3:

Plantation Room

Chairperson: Mary-Anne Young and Linda Patrick-Miller
Rethinking service delivery in cancer genetic counselling

Bronwyn Cook, Sharne Limb, Susan Shanley, Paul James and Mary-Anne Young
Peter MacCallum Cancer Centre

Traditionally cancer genetic counselling was designed upon a modified version of the Huntington Disease (HD) model of genetic counselling where a client meets with a genetic health professional face-to-face for an initial consultation and blood collection, then again for results disclosure. This two-visit approach was adopted in cancer genetic counselling as the psychosocial implications of genetic testing in cancer genetics were unknown.

As demand on cancer genetic counselling services continues to increase, the ability to continue to operate in this manner is becoming increasingly difficult. This two visit approach can be resource and time expensive both for genetics services and also for clients.

Newer research suggests that individuals attending for cancer genetic counselling are responsive to alternative more efficient models of service delivery. In addition, the majority of individuals who attend for cancer genetic counselling and undergo genetic testing do not suffer adverse psychological consequences. This emerging evidence indicates it is timely for genetic services to reconsider alternate service delivery models that can improve efficiency of practice whilst maintaining quality of care and client satisfaction.

We will discuss evidence for considering other models of care including tele-health and information aids, highlighting the benefits and potential drawbacks both for clients and genetic counselling providers of utilising these approaches. Research has shown these approaches can increase retention and understanding of information and provide more timely access to services however they are often not used routinely in clinical practice.

We will also address alternative strategies to manage the increase in referrals to genetics services such that those at high genetic risk of developing cancer are identified and supported appropriately. For genetics services, identifying and considering more efficient modes of practice is paramount to providing high quality, timely and effective care that maximises benefits to our clients.
Stretching the envelope in genetic counselling practice
Linda Patrick-Miller
Current Evolution of the Ovarian Familial Cancer Clinic: Challenging the Model of Genetic Counselling.

Kentwell M\textsuperscript{1}, Wrede D\textsuperscript{2}, McNally OM\textsuperscript{2}, Sexton A\textsuperscript{1}, Taylor J\textsuperscript{1}, Bogwitz M\textsuperscript{1}, Hodgkin L\textsuperscript{1}, Mann K\textsuperscript{1}, Beard C\textsuperscript{1}, Higgs E\textsuperscript{1}, Lindeman GJ\textsuperscript{1}, Antill Y\textsuperscript{1}, Scott C\textsuperscript{1,2}

1. Familial Cancer Centre, The Royal Melbourne Hospital, Melbourne
2. Gynaecological Oncology and Dysplasia, The Royal Women’s Hospital, Melbourne

The Ovarian Familial Cancer Clinic (OVFCC) started in November 2009 as a collaborative clinic between The Royal Women’s Hospital (RWH) and The Royal Melbourne Hospital (RMH), bringing together specialities in Gynaec-oncology, Oncology, Menopause, Women’s Psychology, and Genetics.

An audit of the clinical activity from November 2009 to May 2013 suggested that BRCA1/2 genetic testing was emerging as a regular consideration in the gynaec-oncology setting at the RWH. Referral data of the 72 serous ovarian cancer patients referred, showed that approximately 30\% of referrals to the OVFCC were isolated cases, with 86\% of the referrals being gynaec-oncology initiated. The data also showed that 26\% were referred specifically to discuss clinical trials.

The clinical activity audit was repeated for the period of May 2013 to May 2014. The data has suggested the same trend continuing, with an increase in the number of ovarian cancer referrals being received. A total of 55 serous ovarian cancer referrals were received with 55\% being isolated cases of serous ovarian cancer. This increase in volume, in addition to the availability of new PARP inhibitor clinical trials starting early 2014, have brought new challenges to the traditional genetic counselling model, and as a consequence has driven a change in the way genetic counselling is being delivered. Process related changes have become necessary in: processing new referrals, assessing the timing of genetic testing, co-ordination and discussion of genetic testing and consent, communication with the treating team, and the medical discussion with patients.

Since its inception, the overall OVFCC mutation detection rate for a pathogenic BRCA1 or BRCA2 mutation has been 24\% (31/127), the rate of an unclassified variant in BRCA1 or BRCA2 has been 9\% (11/127), and the number of patients who reported a family history of breast and/or ovarian cancer has been 58\% (74/127). These outcomes have continued to generate the need for ongoing family care and follow up by the OVFCC. Genetic Counselling involvement has also been necessary for education and advice for at-risk family members, particularly for those from a family with an apparently isolated case of ovarian cancer, who therefore may have lacked experiential knowledge about cancer.

This presentation will examine the clinical data from the OVFCC, and describe the impact it has had on clinical genetic counselling practice. It will also describe an emerging model of care which has sought to make sense of the philosophies of oncology (treating the individual) and the genetics (managing the risk in the family).
The psychosocial impact of receiving treatment-focused genetic testing results: The role of family history

Gleeson M, 1 Meiser B, 2 Sousa M, 2 Quinn, V, 2 Kirk J, 3 Saunders C, 4 Tucker K, 5Barlow-Stewart K, 6 Mitchell G 7

1Hunter Family Cancer Service, Newcastle NSW; 2Prince of Wales Clinical School, University of New South Wales, Sydney NSW; 3Familial Cancer Service, Westmead Millenium Institute, Sydney NSW; 4School of Surgery, University of Western Australia, Crawley WA; 5Hereditary Cancer Clinic, Prince of Wales Hospital, Sydney NSW; 6Sydney Medical School, Sydney University, Sydney NSW; 7Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne VIC

Background: As the traditional approach of using family history as the major selection criteria for genetic testing is changing, increasingly women with breast cancer without a family history are eligible for treatment-focused genetic testing (TFGT). No studies to date have examined the psychosocial impact of testing on women without a family history of breast/ovarian cancer. This qualitative study aimed to assess the role that family history plays on the psychosocial impact of receiving, and adjustment to, TFGT results.

Methods: In-depth semi-structured interviews were conducted with 18 women who had undergone TFGT as part of a previous randomised clinical trial. Purposive sampling was used to create 4 groups: mutation positive with family history (n=5) and without family history (n=5), and BRCA inconclusive with family history (n=4) and without family history (n=4). NVivo software was used to cross-tabulate emergent themes and facilitate group comparisons.

Results: All participants found the experience of TFGT advantageous in allowing them to clarify: surgical decisions, risk of ovarian cancer, and risk of cancer for their family. However, the period before and at the time of receiving a positive TFGT result was complicated for those with no knowledge of a family history by the need for: i) causal explanations for their breast cancer diagnosis, and ii) quick surgical decisions whilst trying to understand the implications of their positive result. In contrast, for mutation positive women with a family history, their result was not unexpected, and a decision regarding risk-reducing bilateral mastectomy (RRBM) had already been made before receipt of their result. Long-term adjustment to a positive result was hindered by a sense of isolation not only by those without a family history, but also those who lacked an affected relative with whom they could identify with. All BRCA inconclusive women reported an immediate relief on receipt of their result. However, those with strong family histories, who had not elected RRBM, reported a lack of closure following TFGT, relating to the possibility of a mutation in another predisposition gene.

Conclusions: The findings suggest that the TFGT process for women without a family history may be complicated by confusion as to the cause of their young diagnosis and the need to make surgical decisions whilst trying to understand the implications of a positive result. Identified support deficits hindering long-term adjustment to TFGT results for both women with and without a family history, highlights an area requiring further investigation within the TFGT process.
Programme

Wednesday 13th

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

"Familial Cancer 2014: Research and Practice"

Session 4:

Plantation Room

Chairperson: John Hopper
The Role of Common Risk SNPs on the Risk of Breast Cancer in the Familial Setting: Data from the BCFR and kConFab resources.

Hongyan Li\(^1\), Bingjian Feng\(^1\), Alex Miron\(^2\), John Hopper\(^3\), Esther John\(^4\), Mary Beth Terry\(^5\), Saundra Buys\(^1\), Mary Daly\(^6\), Irene Andrulis\(^7\), Georgia Chenevix-Trench\(^8\), Xiao Qing Chen\(^8\), Paul James\(^9\), Antonis Antoniou\(^10\), Gillian Mitchell\(^9\), David Goldgar\(^1\).

\(^1\) Huntsman Cancer Institute, Salt Lake City, Utah USA
\(^2\) Dana Farber Cancer Institute, Boston Mass
\(^3\) School of Population Health, University of Melbourne
\(^4\) Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Victoria 3010, Australia
\(^5\) Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY
\(^6\) Cancer Prevention Institute of California, Fremont, CA 94538, USA
\(^7\) Department of Molecular Genetics, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, ON M5G 1X5, Canada
\(^8\) QIMR Berghofer Medical Research Institute, Brisbane, Australia.
\(^9\) Peter MacCallum Cancer Centre, Melbourne Australia
\(^10\) Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK.

**Introduction** While the utility of panels of common SNPs associated with breast cancer risk has been studied extensively through theoretical modeling and case-control studies, much less is known how predictive such panels are in the familial setting, where women are already at elevated risk due to their family history of the disease. Moreover, no studies have looked at the predictive ability of such panels in a prospective fashion. The purpose of this project is to evaluate the effects of 30 common breast cancer susceptibility SNPs on the risk of breast cancer using data from Breast Cancer Family Registries (BCFR) and the kConFab familial cancer resource to explore the utility of such a panel in families.

**Materials and Methods** From the BCFR, a total of 9,137 women from 721 families were eligible for retrospective analysis. To avoid survival bias, prospective analysis was also conducted for a subset of the women in the retrospective analysis which included 2,063 women who were unaffected at the time of enrollment. Two genotype risk scores were generated based on the combined information of the 30 SNPs; one score was simply the number of risk alleles carrier while the other incorporated the per allele OR for each SNP as weights. Missing genotypes at each SNP were imputed based on genotypes of relatives using the MENDEL package and then scores generated for all untyped individuals. Robust Cox regression models adjusting for the family membership on the continuous scores and the quintiles of the scores were performed for both retrospective and prospective analyses to estimate the association between two generated scores and the risk of breast cancer. In kConFab we examined retrospective data from 3295 probands and their female relatives (up to 3rd degree) from 1695 families genotyped for 18 common SNPs.

**Results** In the BCFR data set, the two scores are both associated with increased risk of breast cancer in both retrospective (RR: HR=1.96, 95%CI: 1.748-2.204 vs. NR: HR=1.10, 95%CI: 1.076-1.143) and prospective (RR: HR=2.10, 95%CI: 1.518-2.917 vs. NR: HR=1.11, 95%CI: 1.053-1.161) analyses, especially for RR which is associated with an obvious higher risk of breast cancer. In addition, both scores reveal stronger association in prospective analysis than in retrospective analysis. Analysis of the quintiles estimated women whose score lies in the highest quintile are at much greater risk of breast cancer than those in the lowest quintile in retrospective analysis, both for RR (HR=1.35, 95%CI: 1.214-0.504) and NR (HR=1.44, 95%CI: 1.294-1.610), and this risk increases greatly in prospective analysis (RR: HR=2.75, 95%CI: 1.765-4.293 and NR: HR=2.09, 95%CI: 1.365-3.193). In a preliminary retrospective analysis of the kConFab families, the SNP score was associated with BC risk (HR=1.17; p< 0.0001). Results of a larger number of SNPs and prospective analyses on the kConFab data set will be presented at the meeting.
The contribution of Common Genomic Variants to the incidence of Breast Cancer Phenocopies in BRCA1 and BRCA2 families.

Paul A James¹, Sarah Sawyer¹, Simone McInerny¹, Jonathan Beesley², Marion Harris³, KConFab⁵, AOCS⁶, Geoff Lindeman⁴, Georgia Chenevix-Trench², Gillian Mitchell¹.

¹Peter MacCallum Cancer Institute, ²Queensland Institute of Medical Research, ³Monash Medical Centre, ⁴Royal Melbourne Hospital, ⁵Kathleen Cunningham Foundation, ⁶Australian Ovarian Cancer Study.

Background: A large number of common genomic variants have been associated with breast cancer risk in both the general population and as modifiers in BRCA1 and BRCA2 carriers. It has been suggested that these SNPs may contribute to a residual risk of breast cancer for non-carriers in some BRCA1/2 positive families but the significance of this risk is debated. We examined the degree to which breast cancer risk was influenced by the combined effect of a panel of more than 70 recently described variants identified in population based GWAS, in families segregating a BRCA1 or BRCA2 mutation, including women who tested negative for the family mutation.

Methods and Results: SNP genotyping data from two familial breast cancer cohorts was combined: the KConFab families and the Breast Cancer: Variants in Practice (ViP) study. Analysis included 3445 individuals from 866 families segregating BRCA mutations (830 BRCA1, 533 BRCA2, 2030 Non-carriers, overall 1115 (32%) affected) as well as 897 population based controls. All participants were genotyped for an extended panel of breast cancer associated SNPs selected from high quality GWAS with 98% genotyping success. Polygenic risk scores (PRS) were calculated for each individual using both published and locally calculated ORs. Evidence of a strongly significant effect of the combined risk alleles was found for the 161 women diagnosed with a phenocopy breast cancer; equivalent to the effect of polygenic risk we have previously measured in non-BRCA familial breast cancer. Polygenic risk scores were greater in early onset cases. In contrast breast cancer in a first degree relative that carried the family mutation was not associated with a significant increase in the measurable polygenic risk of breast cancer in their non-carrier relatives.

Conclusions: Results of from this large dataset provides a unique picture of the segregation of polygenic risk in both carriers and non-carriers in BRCA families and confirms that the residual aggregation of genetic risk plays an important role in the occurrence of phenocopies in these families. We found no evidence that this was modified by the distribution of BRCA related breast cancers in the families.
Variants in Practice Study (VIP): High risk women’s responses to receiving genetic test results for genomic variants associated with breast cancer risk

M.A Young¹, P. James¹, Mitchell G¹, Forrest L¹, Sawyer S¹, Forrest L¹, N Hallowell¹

1. The Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia

Results from genome-wide association studies (GWAS) have identified common genomic variants that form an important component of the heritability of breast cancer risk. Data from Victorian high risk breast cancer families demonstrate that testing for these genetic factors identifies a significant aetiological group known as ‘polygenic families’ and provides clinically important information including the risk of a second primary breast cancer and the risk of ovarian cancer.

It is important to investigate lay and professional understandings of novel, complex genetic test information generated by SNP testing to identify the most effective ways for genetic health professionals to communicate complex polygenic risk information to patients and the treating medical team, who may request and need to use it.

Our qualitative study aimed to assess patient and healthcare professionals’ understandings of genomic variant data. This presentation focuses upon women’s experiences of receiving SNP results following their participation in the VIP study.

Forty women who were invited back to the familial cancer clinic to learn their SNP results took part in semi-structured in-depth interviews. The women attended an appointment with a clinical geneticist or genetic counsellor at the familial cancer clinic, Peter MacCallum Cancer Centre, Australia. Participants had previously been diagnosed with breast cancer and assessed as high risk based on their family history. All women had undergone BRCA1/2 mutation testing and no mutation was found. Subsequently they were genotyped for 22 common genomic variants from which breast cancer risks were calculated.

Analysis of interview transcripts has revealed a number of preliminary themes, which suggest that study participation is motivated by feelings of altruism or responsibility for family members, in particular. Receiving SNP information following participation in the VIP study was viewed very positively, particularly by those women who had already undergone risk-reducing bilateral mastectomy, who felt this risk reducing decision was validated by their polygenic result. In conclusion, this study suggests that SNP results are regarded as useful information for both the research participants and their families.
Do we know enough about SNPs to influence screening recommendations for colorectal cancer?

Jenkins MA, Makalic E, Schmidt DF, Win AK, Hopper JL, Buchanan D.
Centre for Epidemiology & Biostatistics, Melbourne School of Population & Global Health, University of Melbourne

Background: Death from colorectal cancer (CRC) can be prevented if detected early by screening. The age at which screening begins should be appropriate to the risk of disease. Common single nucleotide variants (SNPs) in DNA have been associated with CRC risk. While these are unlikely to be causal, they do have potential as risk predictors and for decisions on age of onset for screening.

Methods: We identified all SNPs from published and submitted genome-wide association studies reporting replication of independent associations with CRC risk for people of European descent. For each SNP we extracted the allele frequency of the ‘risk’ allele for CRC and the odds ratio (OR) per allele. Using PLINK we simulated a population of one million people of which 5% developed CRC by age 70 years (equal to the age-specific cumulative risk for the Australian population). The distribution of SNP risk alleles in the simulated population was selected to match risk allele frequencies and per allele ORs of the known CRC associations.

Results: Forty-two SNPs were identified from the literature. Four were highly correlated and substituted by a single haplotype leaving a total of 39 markers. Mean risk allele frequency was 0.42 (range 0.07-0.90). Mean OR per risk allele was 1.14 (range 1.06-1.53). There was a high degree of overlap for the number of risk alleles between CRC affected and unaffected people (affected median = 34 risk alleles, range 15-53; unaffected median = 32 risk alleles, range 14-51). The OR per allele for CRC was 1.8 for people in the highest decile (top 10%) of risk alleles, and 0.4 for people in the lowest decile (compared to the median number of risk alleles). The risk of CRC to age 70 years was 8.9% for people in the highest decile of risk alleles compared with 1.7% for those in lowest decile.

Conclusion: Being in the highest decile of risk alleles is equivalent to having the bowel of someone five years older (in terms of CRC risk), implying screening could begin five years earlier for those people than for the general population. Using only the very few SNPs that reach ‘genome wide threshold significance’ (an extremely insensitive method for identifying risk alleles) provides potentially useful information that could be used to target, and in theory improve the effectiveness of, CRC screening. We plan to develop and apply modern Bayesian sparse regression and ensemble learning techniques to better measure the association with CRC risk across all SNPs so as to provide CRC prediction tools with more useful discriminatory power and predictive value.
Programme

Thursday 14th

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

“Familial Cancer 2014: Research and Practice”

Session 5:

Plantation Room

Chairperson: Marion Harris & Mark Jenkins
Integration of microarray meta-analysis with RNASeq and genome-wide genetic data to identify variants associated with endometrial cancer histological subtype
Tracy A. O’Mara and Amanda B. Spurdle
Genetics and Computational Biology Dept, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

Non-endometrioid endometrial cancer comprises approximately 20% of new endometrial cancer diagnoses, but is responsible for an estimated 50% of deaths from this disease. Microarrays have been successfully used to measure mRNA expression in biological samples to identify differentially expressed genes. However, it is recognized that results from individual microarray studies are often not reproducible. Public availability of gene expression microarray data has facilitated research assessing the increased reliability of combined datasets. Furthermore, the availability of genome-wide scale “-omics” data on the same sample sets, such as that provided by The Cancer Genome Atlas (TCGA), allows for a powerful, integrative approach to identify genes and genetic variants important in cancer initiation and/or progression. We have used patient derived microarray data from multiple datasets to identify differences between endometrioid (EEC) and non-endometrioid (NEEC) histological subtypes of endometrial cancer, and then validated these differences using an independent endometrial cancer set with RNASeq data from the TCGA.

A literature review and repository search conducted in April 2014 identified 15 endometrial cancer microarray studies. Raw microarray data was accessed from publication supplementary data, the NCBI Gene Expression Omnibus (GEO) and the TCGA data portal, or otherwise requested by directly contacting authors.

Overall raw microarray data was accessed for 9 of 15 studies, with a maximum of 79 EEC and 12 NEEC cases in one study. Following QC and meta-analysis using the MetaOmics package in R, 1,910 genes from 6 studies were identified by Fisher’s test as displaying significant differential expression between the two subtypes (FDR < 5%). The expression of these genes was then analyzed using normalized RNASeq data for 328 EEC and 97 NEEC non-overlapping samples from the TCGA. For the 1,186 genes captured by the RNASeq analysis, moderated t-test identified differences in expression for 912 genes at P < 0.05 (77% of genes analysed), of which 261 were at P < 1x10^-19.

These findings demonstrate a strong relationship between microarray meta-analysis and RNASeq results, and identify candidate genes differentially expressed in aggressive endometrial cancer histological subtypes. Future analysis will investigate genetic variation associated with differential gene expression in the TCGA dataset, to prioritize genetic variants for downstream prognostic studies.
Genes that are well established to predispose to a high risk of endometrial cancer cause tumourigenesis by different mechanisms. The Lynch syndrome-associated genes (MLH1, MSH2, MSH6, PMS2, EPCAM deletion) cause a defect to the mismatch repair pathway, the polymerase proofreading-associated polyposis genes (POLD1, POLE) cause loss of polymerase proofreading capability, and the Cowden syndrome-associated gene (PTEN) causes abnormal cell survival. There are also other cancer syndrome genes (including MutYH, TP53, BRCA1, CHEK2) that are reported to contribute to endometrial cancer risk at a population-based level, some which may predispose only to a certain subtype of endometrial cancer.

An endometrial cancer panel offers increased clinical sensitivity compared to testing only for the Lynch syndrome-associated genes, and it is more cost effective than stepwise genetic testing. However, it is important to select the correct genes for analysis. We have conducted a comprehensive literature review to identify the genes that have been reported to increase the risk of endometrial cancer, document the evidence to support their association with high, moderate or low risk of endometrial cancer, and summarise the clinical management sequelae for mutation carriers and their relatives. We also discuss the appropriate content of an endometrial cancer panel.

We conclude that the single existing commercial endometrial cancer panel does not test all known high-risk endometrial cancer genes, and includes others for which genetic counselling and patient management strategies are currently not established.
Bi-allelic somatic mutations are a cause of tumour mismatch repair-deficiency in colorectal and endometrial cancer cases with no germline mismatch repair gene mutations

Mark Clendenning, Christophe Rosty, Aung Ko Win, Rhiannon J. Walters, Belinda N. Nagler, Alex Metcalf, Michael Bowman, Yen Tan, Felicity Lose, Ingrid M. Winship, Graham G Giles, Melissa C. Southey, John L. Hopper, Mark A. Jenkins, Amanda B. Spurdle, Daniel D. Buchanan\textsuperscript{1,2} on behalf of the ANECS and ACCFR investigators

\textsuperscript{1} Oncogenomics Group, Genetic Epidemiology Laboratory, Department of Pathology, and \textsuperscript{2} Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne.

Background: Tumour mismatch repair (MMR) deficiency, determined by microsatellite instability and/or immunohistochemical (IHC) loss of MMR protein expression, is used diagnostically to identify individuals with Lynch syndrome. Combined data from published studies suggest that up to 59% of colorectal cancers (CRC) and 52% of endometrial cancers (EC) that demonstrate tumour MMR-deficiency have no germline MMR gene mutation identified and are, therefore, referred to as “suspected Lynch syndrome” cases. The aim of this study was to determine the proportion and characteristics of suspected Lynch syndrome cases with tumour MMR-deficiency resulting from bi-allelic somatic mutations.

Methods: All samples were derived from the Australasian Colorectal Cancer Family Registry Cohort and the Australian National Endometrial Cancer Study. Somatic mutation detection within the \textit{MLH1, MSH2, MSH6, PMS2, MSH3, MLH3} and \textit{PMS1} genes was performed using AmpliSeq custom capture and sequencing on the Ion Proton for 35 FFPE DNA samples comprising 24 suspected Lynch syndrome cases (n=11 CRC-affected and n=13 EC-affected) and 11xCRC tumours from MMR gene mutation carriers as the reference group. Tumour testing for MSH2 gene promoter methylation was performed on cases with MSH2 IHC loss.

Results: The 24 suspected Lynch syndrome cases demonstrated the following patterns of MMR immunohistochemistry (IHC) loss: 10xCRC and 11xEC with MSH2 & MSH6 loss; 1xCRC and 1xEC with MSH6 only loss; 1xEC case with MLH1 & PMS2 loss. Bi-allelic somatic point mutations were identified in 2/11 (18%) of CRC- and 5/13 (39%) EC-suspected Lynch syndrome cases, while no bi-allelic mutations were observed in CRC tumours from the 11 MMR gene mutation carriers. A single somatic point mutation was identified in 4/11 (36%) of CRC- and 6/13 (46%) EC-suspected Lynch syndrome cases and in 5/11 (46%) of the MMR gene mutation carriers. All somatic mutations identified were consistent with the gene indicated by IHC loss. Sanger sequencing confirmed the presence of somatic point mutations in all 11 samples tested to date. A single suspected Lynch syndrome CRC tumour out of the 20 suspected LS cases tested (1/20; 5%) showed evidence of MSH2 gene promoter methylation and was absent of any somatic point mutations. The mean age at diagnosis of suspected Lynch syndrome cases with bi-allelic somatic mutations was significantly older (56.1 ± 10.9yrs) than both suspected Lynch syndrome cases with no somatic point mutations (41.9 ± 10.1yrs; p=0.03) and MMR gene mutation carriers (43.1 ± 12yrs; p=0.04).

Conclusions: We have shown that bi-allelic somatic mutations are likely to be a significant cause of tumour MMR-deficiency in suspected Lynch syndrome cases, while tumour MSH2 gene promoter methylation may be an infrequent cause of somatic MMR-deficiency. Tumour loss of heterozygosity testing is currently being performed and is likely to identify additional suspected Lynch syndrome cases with a second somatic “hit”. A further 45 CRC- or EC-affected suspected Lynch syndrome cases are currently being tested and if these findings are confirmed, revision of the current triaging and diagnostic testing strategies used to identify individuals and their relatives with Lynch syndrome would be warranted.
Lifestyle factors and risk of endometrial cancer for women with germline mutations in DNA mismatch repair genes

Aung Ko Win,1 Rowena Chau,1 Seyedeh G. Dashti,1 Driss A. Ouakrim,1 Daniel D. Buchanan,1,2 Mark Clendenning,2 Graham Casey,3 Steven Gallinger,4 Robert W. Haile,5 Loïc Le Marchand,6 Noralane M. Lindor,7 Polly A. Newcomb,8 Stephen N. Thibodeau,9 John L. Hopper,1 Mark A. Jenkins.1

1 Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, The University of Melbourne, Parkville, Victoria, Australia.
2 Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Parkville, Victoria, Australia.
3 Department of Preventive Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA
4 Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
5 Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University, California, USA.
6 University of Hawaii Cancer Center, Honolulu, Hawaii, USA.
7 Department of Health Science Research, Mayo Clinic Arizona, Scottsdale, Arizona, USA.
8 Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.
9 Molecular Genetics Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

Aim: A women carrying a germline mutation in a DNA mismatch repair (MMR) gene is at increased risk of endometrial cancer, colorectal cancer and several other cancers. The aim of the study was to investigate associations between lifestyle factors and risk of endometrial cancer for carrier women, adjusting for measured potential confounders using the largest dataset to date.

Methods: This study comprised 1,118 female mutation carriers (419 MLH1, 530 MSH2, 114 MSH6 and 55 PMS2) from the Colon Cancer Family Registry (176 from Canada, 605 from Australia, and 337 from USA). During 47,456 person-years of observation from birth, 144 carriers (14%) were diagnosed with endometrial cancer. Using Cox proportional hazards regression weighted to correct for ascertainment bias, we estimated hazard ratios (HRs) and 95% confidence interval (CIs) for associations between lifestyle factors and risk of endometrial cancer for carrier women, adjusting for measured potential confounders.

Results: A decreased risk of endometrial cancer was associated with users of multivitamin supplements (for 1-3 year: HR=0.33, 95%CI=0.12–0.92; and for >3 year: HR=0.41, 95%CI=0.19–0.87) and hormonal contraceptives (for 1-5 year: HR=0.43, 95%CI=0.24–0.77; and for >5 year: HR=0.17, 95%CI=0.80–0.36) compared with never users. There was no evidence of associations with intake of calcium or folic acid supplements, aspirin or ibuprofen, alcohol consumption, cigarette smoking, use of hormone replacement therapy, and increased adult body mass index.

Conclusion: Intake of multivitamin supplements and oral contraceptives might reduce risk of endometrial cancer for women with MMR gene mutations.
Many institutions and policy groups are considering whether to implement systematic testing for Lynch syndrome among endometrial cancer patients. Our analysis of the ANECS population-based endometrial cancer study indicated that identification of patients with mismatch repair (MMR) mutation-positive endometrial cancer is optimized by systematic testing for tumour MMR immunohistochemical (IHC) loss in patients younger than 60 years, tumour MLH1 methylation in individuals with MLH1 IHC loss, and germline mutations in patients exhibiting loss of MSH6, MSH2 or PMS2 or loss of MLH/PMS2 with absence of MLH1 methylation. Further, a detailed comparison of these findings to published data from 4 other studies provides support for age 60 as a suitable cut-off to minimise use of resources (tumour and genetic testing, patient counselling). Alternative strategies proposed for implementation are: universal vs age-restricted testing; 2-stain vs 4-stain MMR IHC testing; use of clinical indicators in combination with tumour IHC testing as substitute triage criteria when MLH1 methylation testing is not available.

We will now provide an update of ANECS findings, which incorporates updates to the sample set (new IHC results, re-assessment of patient eligibility), estimation of sensitivity and specificity of additional strategies that might be considered as alternative to MLH1 methylation testing, and costings for the new strategies assessed. We will also provide viewpoints on possible workflow barriers to implementation in the clinical setting, and discuss issues relevant for efficient implementation of endometrial tumour testing for MMR deficiency, and also patient referral and management.
Australian Clinicians' opinions about screening endometrial cancers for Lynch Syndrome in 2014. Where are we now?
O'Connell S¹,  Shanley S ²,  Harris M ¹
¹ Familial Cancer Clinic Monash Health
² Familial Cancer Clinic Peter MacCallum Cancer Institute

Background: Immunohistochemistry (IHC) screening of bowel cancers to detect cases of Lynch Syndrome (LS) is routine in most Australian states although the subgroup screened varies (50 years or less, 60 years or less). Endometrial cancer (EC) is the second most common cancer in LS. Consideration of screening endometrial cancers for LS is desirable. Two percent of women with EC have LS but up to 20 percent of cases have MLH1/PMS2 IHC loss due to non-inherited silencing by MLH1 promoter methylation. As BRAF V600E testing is not useful in EC, MLH1 methylation tumour testing is essential to differentiate LS from cases with somatic MLH1 loss due to promoter methylation. A recent Australian study (Buchanan et al JCO 2014) suggests screening EC cases diagnosed aged 60 and below with IHC for MMR proteins and genetic testing of cases without MLH1 promoter methylation. In this setting we sought to obtain clinicians' current opinions about screening EC cases for LS and related issues.

Methods: 20 medical specialists working in familial cancer in Australia were invited to complete a web-based survey. Clinicians answered 2 questions and gave their opinions on management of 5 cases. Participants were asked:
1. Which EC cases, if any, should be screened by IHC for LS in Australia in June 2014 according to published evidence?
2. Whether they would have confidence in using uterine tumour methylation testing results to determine whether germline genetic testing (GT) is indicated or not.
3. Whether they would have confidence in using uterine tumour methylation testing results (together with GT results) to determine if an individual has LS or not with implications for the individual's surveillance.

Results: 8/20 clinicians have responded to date with more anticipated to reply. At least one response came from each of VIC, SA, QLD, WA and NSW. Preliminary results suggest a majority support routine IHC screening of EC cases diagnosed before age 60. All were comfortable using uterine tumour methylation results combined with germline gene test results to alter surveillance for solitary EC cases irrespective of age, but some were not comfortable if the individual was a member of an Amsterdam positive family.

Conclusions: Most responding Australian FCC clinicians support the use of IHC to screen EC cases diagnosed at or before age 60 for LS. However a number of practical issues need to be resolved before such testing can become routine in Australia.
Programme

Thursday 14th

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

"Familial Cancer 2014: Research and Practice"

Session 6:

Plantation Room

Chairperson: David Thomas

"Familial Cancer 2014: Research and Practice"
Characterising cancer risks for carriers of mutations in *BRCA1*, *BRCA2*, *PALB2* and *RAD51C* genes.

Antonis C. Antoniou, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge.

The presentation will provide an overview of the latest developments and challenges in understanding the penetrance of mutations in the *BRCA1*, *BRCA2*, *PALB2* and *RAD51C* genes. Genetic counselling currently relies on average cancer risk estimates obtained from retrospective penetrance studies involving large numbers of families segregating mutations in these genes. We will present penetrance estimates from ongoing prospective analyses, based on data from the International *BRCA1/2* Carrier Cohort Study, the largest cohort of *BRCA1/2* mutation carriers worldwide that includes >3000 mutation carriers at baseline with prospective follow-up information. Several common alleles and other risk factors have now been shown to modify breast cancer risk for *BRCA1* and *BRCA2* mutation carriers. The talk will review the latest efforts and results from the Consortium of Investigators of Modifiers of *BRCA1/2* to identify genetic modifiers of risk and provide individualised cancer risks for *BRCA1* and *BRCA2* mutation carriers on the basis of polygenic risk scores. We will also present penetrance estimates based on analyses of combined data from families segregating mutations in *PALB2* and *RAD51C*, the largest efforts of their kind.
Mutations in BRIP1 and breast cancer risk: implications for gene panel testing

Georgia Chenevix-Trench, Fabienne Lesueur, Jun Jun Li, Kyriaki Michailidou, Brennan Decker, Jamie Allen, Craig Luccarini, Igor Makunin, Ian Campbell, Melissa Southey, kConFab Investigators, Irene Andrulis, Esther John, John Hopper, Paul DP Pharoah, Alison M Dunning, Florence Le Calvez-Kelm, David Goldgar, Sean Tavtigian, Douglas F. Easton and the Breast Cancer Association Consortium

BRCA1 interacting protein C-terminal helicase 1 (BRIP1) is one of the FANC family of DNA repair proteins. Biallelic mutations in BRIP1 are responsible for Fanconi Anaemia complementation group J, and previous studies have also suggested that rare protein truncating variants in BRIP1 are associated with an increased risk of breast cancer. Seal et al (Nature Genetics 2006) screened the coding sequence of BRIP1 in 1,212 women with familial breast cancer and 2,012 controls. They identified nine protein truncating mutations in cases versus two in controls, leading to an estimated relative risk of breast cancer 2.0 (1.2–3.2; P=.012). The most common mutation was R798X. This, and other studies, have led to inclusion of BRIP1 on targeted sequencing panels for breast cancer risk prediction.

We evaluated R798X (rs137852986), in 48,143 cases and 43,608 controls of European origin, from 41 studies in the Breast Cancer Association Consortium (BCAC) using a large custom array (iCOGS). The variant allele was observed in 24 cases and 18 controls (OR 1.14, 95% 0.61–2.11; P = 0.68). There was some suggestion of an increased risk of ER-negative breast cancer among carriers (OR 2.27, 0.94–5.50; P = 0.07), but no evidence of an association for ER-positive disease (OR 0.48, 0.17–1.30; P = 0.15).

There was substantial variation in BCAC in the frequency of the 798X allele by country (P<.0001) and haplotype analysis suggested that the variant has arisen multiple times. We additionally sequenced the coding sequence of BRIP1 in 1,313 cases and 1,123 controls from three population-based studies as part of the Breast Cancer Family Registry (BCFR), and in 15,264 cases and 5,962 controls from the SEARCH and RAPPER studies in the UK. In the BCFR we identified four truncating variants in cases (including two with pR798X) and three (one with pR798X) in controls. In SEARCH/RAPPER we identified 47 truncating variants in cases and 26 in controls (OR 0.71, 95% CI 0.43–1.19, P=0.15).

Finally, we sequenced the coding region of BRIP1 in 684 non-BRCA1/2 index cases from kConFab and found three truncating (all pR798X) and 13 rare, putatively deleterious, missense mutations, which we then genotyped in all available family members. We used modified segregation analysis to estimate the relative risk of breast cancer by conditioning the likelihood of the pedigree phenotypes and genotypes on pedigree phenotypes and proband genotypes, assuming Australian age-specific incidence rates in non-carriers. Based on this analysis we estimated the Relative Risk to be 0.48 (95% CI 0.13, 1.23). Any value of RR >= 1.8 is 20x less likely than RR=1.

These results suggest that truncating variants in BRIP1, in particular R798X, are not associated with a substantial breast cancer risk, and that rare missense mutations do not contribute significantly breast cancer risk either. Such observations have important implications for the reporting of results from breast cancer screening panels.
Penetrance of BRCA1 and 2 Specific Gene Mutations for Breast and Ovarian Cancers in Asian population
Boyoung Park 1, Choonghyun Ahn 2, Sung Won Kim 3, Jong Won Lee 4, Min Hyuk Lee 5, James G. Dowty 6, Aung K. Win 6, John L. Hopper 6, Sue K. Park 2
1 National Cancer Control Institute, National Cancer Center, Korea
2 Department of Preventive Medicine, Seoul National University College of Medicine, Department of Biomedical Science, Seoul National University Graduate School, Cancer Research Institute, Seoul National University, Korea
3 Department of Surgery, Seoul National University Bundang Hospital, Korea
4 Department of Surgery, Asan Medical Center, Korea
5 Department of Surgery, Suncheonhyang Medical Center, Korea
6 Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, The University of Melbourne

Background: BRCA1 or BRCA2 mutations increase risks of breast and ovarian cancer, but the risks from previous studies have been various across studies and populations. Therefore, we estimated breast and ovarian cancer penetrance in BRCA1/2 mutation families in the Republic of Korea.

Methods: The Korean Hereditary Breast Cancer (KOHBRA) Study is an ongoing project composed of affected breast cancer patients and familial members of breast cancer cases with BRCA1/2 mutations since 2007. A total 3,203 subjects were enrolled in the KOHBRA study across the country. We investigated 13,196 members of 151 BRCA1 and 225 BRCA2 mutation carrying families. Average cumulative risks of breast cancer and ovarian cancer in BRCA1/2 mutation carriers were estimated using a modified segregation analysis.

Results: The estimated average cumulative risk of breast cancer by age 70 years was estimated to be 51.1% [95% confidence interval (95% CI), 6.6-99.9%] for BRCA1 mutation carriers and 33.8% (95% CI, 12.8-85.7%) for BRCA2 mutation carriers. The corresponding ovarian cancer cumulative risks were 36.3% (95% CI, 0.6-99.9%) for BRCA1 mutation carriers and 6.8% (95% CI, 0.2-9.29%) for BRCA2 mutation carriers.

Conclusions: BRCA1/2 mutation carriers showed lower overall breast cancer risks than reported so far, while the estimates of ovarian cancer risks were similar or slightly lower as point estimates. However, the 95% CIs were wide due to insufficient statistical power to accurately estimate penetrance. Our estimates of breast cancer and ovarian cancer cumulative risks for BRCA1/2 mutation carriers are the first results in Asian population. Further cooperative study in Asian population is needed to estimate penetrance more precise with enough statistical power.
Identification of new familial breast cancer susceptibility genes: are we there yet?
Ian G. Campbell1,2, Simone M. Rowley1, Maria A. Doyle1, Jason Ellul1, Alison Trainer1,2, Paul James1,2, LifePool1, Michelle Wong3,4, Gillian Mitchell1,2, Rodney J. Scott3,4, Ella M. Thompson1
1Peter MacCallum Cancer Centre, Victoria; 2The University of Melbourne, Victoria; 3Hunter Area Pathology Service, New South Wales; 4The University of Newcastle, New South Wales.

The genetic cause of the majority of multiple-case breast cancer families remains unresolved. Next generation sequencing has emerged as an efficient strategy for identifying predisposing mutations in individuals with inherited cancer. We are conducting whole exome sequence analysis of germline DNA from multiple affected relatives from breast cancer families, with the aim of identifying rare protein truncating and non-synonymous variants that are likely to include novel cancer predisposing mutations. Data from more than 200 exomes show that on average each individual carries 30-50 protein truncating mutations and 300-400 rare non-synonymous variants. Heterogeneity among our exome data strongly suggests that numerous moderate penetrance genes remain to be discovered, with each gene individually accounting for only a small fraction of families (~0.5%). This scenario marks validation of candidate breast cancer predisposing genes in large case-control studies as the rate-limiting step in resolving the missing heritability of breast cancer. The aim of this study is to screen genes that are recurrently mutated among our exome data in a larger cohort of cases and controls to assess the prevalence of inactivating mutations that may be associated with breast cancer risk.

We are using the Agilent HaloPlex Target Enrichment System to screen the coding regions of 168 genes in 1,000 BRCA1/2 mutation-negative familial breast cancer cases and 1,000 cancer-naive controls. To date, our interim analysis has identified 21 genes that carry an excess of truncating mutations in multiple breast cancer families versus controls. Established breast cancer susceptibility gene PALB2 is the most frequently mutated gene (13/998 cases versus 0/1009 controls), but other interesting candidates include NPSR1, GSN, POLD2 and TOX3. These and other genes are being validated in a second cohort of 1,000 cases and controls.

As an alternative to a monogenic inheritance model we assessed the risk of breast cancer according to the collective burden of rare coding variants in an individual. Preliminary analysis of 500 cases and 500 controls identified a group of 5% of the cases with a non-synonymous/synonymous variant ratio (for deleterious missense variants) of >0.2 where the risk of breast cancer was equivalent to an individual moderate/high risk gene (OR 5.8 (95%CI 2.2-14.9)).

Our experience demonstrates that beyond PALB2, the prevalence of mutations in the remaining breast cancer predisposition genes is likely to be very low making definitive validation exceptionally challenging.
BRCA1 and BRCA2 mutation prediction algorithms: Argument for the inclusion of ductal carcinoma in situ and other histopathological criteria
Claire Michel¹², Elly Lynch¹, Megan Cotter¹, Matthew Burgess¹, Anna Leaver¹, Martin Delatycki¹, Thomas John¹³

(1) Department of Clinical Genetics, Austin Health; (2) The University of Melbourne, Melbourne Medical School; (3) Ludwig Institute for Cancer Research

Background:
The identification of individuals harbouring BRCA1/2 mutations is important as it informs immediate and long-term management decisions of the patient and family alike. At present, BRCA-mutation prediction algorithms rely heavily on family history and tumour histopathology as prediction inputs. Unlike in sporadic breast cancer, where the step-wise progression of tumourigenesis is well documented, it remains unclear whether ductal carcinoma in situ (DCIS) is a feature of BRCA-driven tumourigenesis; consequently non-high grade DCIS is excluded in current BRCA risk-prediction models. We therefore sought to determine whether DCIS and other histopathological criteria could improve mutation-carrier identification, thus arguing for their inclusion in prediction algorithms.

Methods:
We conducted a retrospective clinical audit of patients referred to Clinical Genetics at Austin Health between 2005 and 2013; selecting for patients having undergone germ line BRCA mutation testing. This yielded a total study population of 329 patients including 35 individuals with BRCA1, 56 with BRCA2 mutations and 238 who were mutation negative. Three-generational family history, tumour histopathology and receptor status were reviewed. Predictors of mutation-status for both BRCA1 and BRCA2 (vs mutation-negative) were identified using multiple logistic regression and subsequently grouped into prediction models from which areas under receiver operator characteristic (ROC) curves were generated.

Results:
Several features were found to increase the probability of BRCA1 mutation-carriage compared to those without a BRCA mutation including: histological grade of primary tumour (OR 10.57 (2.58–43.2) P<0.001); absence of DCIS in the primary tumour (OR 2.98 (1.46–6.09) P=0.003); and higher grade of DCIS (adjacent or intermixed with primary tumour). For BRCA2 features that increased the likelihood of a mutation being identified were: other family history of cancer (≥2 cancers including: prostate, peritoneal, and pancreatic on the same side of the pedigree (OR 2.08 (1.16 – 3.73) P=0.02)); and high grade DCIS (OR 2.84 (1.00 - 8.00) P=0.05). The area under the ROC curve for the best BRCA1 prediction model was 0.90 (0.81-0.98), and 0.77 (0.68-0.85) for the best BRCA2 model.

Conclusions:
DCIS and its histopathological features in primary invasive breast cancers act as strong predictors of BRCA1 and, to a lesser extent BRCA2, mutation-carrier status in high-risk populations. Given this, the inclusion and differential weighting of DCIS and its correlates in BRCA mutation-prediction algorithms is warranted.
Programme

Thursday 14th

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"Familial Cancer 2014: Research and Practice"

Session 7a:

Plantation Room

Chairperson: Gillian Mitchell
Randomized controlled trial of a telephone-based peer support program for female carriers of a BRCA1 or BRCA2 mutation: Impact on psychological distress

B. Meiser1, V. White2, M. Young3, A. Farrelly2, M. Jefford4,5, S. Ieropoli2, J. Duffy6, I. Winship7; 1Prince of Wales Clinical School, UNSW, Sydney, 2The Centre for Behavioural Research in Cancer, Cancer Council Victoria, Carlton, 3Familial Cancer Centre, Peter MacCallum Cancer Centre, East Melbourne, 4Strategy and Support Division, Cancer Council Victoria, Carlton, 5Sir Peter MacCallum Department of Oncology and Faculty of Medicine, Melbourne, 6Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, 7Genetic Medicine, Royal Melbourne Hospital, University of Melbourne, Parkville.

Objective: To assess the effectiveness of a telephone-based peer-delivered intervention, in reducing distress among female BRCA1 or BRCA2 mutation carriers. The intervention consisted of trained peer volunteers contacting women multiple times over a four month period to provide informational, emotional and practical support.

Methods: 337 participants completed the baseline questionnaire and those reporting interest in talking to other mutation carriers were randomized to either usual care group (UCG) (n = 102) or intervention group (IG) (n = 105). Two follow-up questionnaires were completed: i) four months after randomization (Time 2, intervention end for IG) and ii) two months later (Time 3). Outcomes included breast cancer anxiety (primary outcome), unmet information needs, and cognitive appraisals about mutation testing.

Results: Over the study period, there was a greater decrease in breast cancer anxiety in the IG than UCG (p<0.01) and at Time 2, the IG’s mean breast cancer anxiety scores were significantly lower than the UCG’s. There was a greater reduction in unmet information needs in the IG than UCG (p<0.01), with unmet needs lower in the IG than UCG at Time 2 (p<0.01). There was a greater reduction in cognitive appraisals-stress in the IG than UCG (p<.01) with significantly lower scores found at Time 2 for the IG compared to UCG (p<.01). However cross-sectional differences were not found at Time 3 for any outcome measure.

Conclusion: The intervention is effective in reducing breast cancer related anxiety and unmet information needs in the short-term. Identifying strategies for prolonging intervention effects is warranted.
Understanding and Improving Dissemination in BRCA1 and BRCA2 families with a Family Communication Tool

Emma Healey\textsuperscript{a}, Rachel Williams\textsuperscript{a}, Sian Greening\textsuperscript{b}, Linda Warwick\textsuperscript{c}, Claire Wakefield\textsuperscript{d} and Kathy Tucker\textsuperscript{a}

\textsuperscript{a}Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, New South Wales, 2031, Australia
\textsuperscript{b}Illawarra Cancer Care Centre, Wollongong Hospital, Wollongong, New South Wales, 2500, Australia
\textsuperscript{c}ACT Genetic Service, The Canberra Hospital, Woden, Australian Capital Territory, 2606, Australia
\textsuperscript{d}Behavioral Sciences Unit, Kids Cancer Centre, Sydney Children’s Hospital, Randwick, New South Wales, 2031, Australia

**Background:** BRCA1/BRCA2 predictive testing in at-risk relatives provides many benefits. Targeted screening, medical prevention, and risk-reducing surgery can improve survival outcomes for mutation-carriers, and avoid unnecessary costs for non-carriers. Realisation of these benefits relies on communication between carriers and their at-risk relatives, however disseminating this information poses significant challenges. Understanding these challenges can help genetic health professionals improve their counselling practice and follow-up procedures, and ultimately enhance the public health benefit of predictive testing. To assist, we have developed a Family Communication Tool (FCT), a table which records informed status of at-risk relatives.

**Aim:** To 1) assess the effectiveness of the FCT in increasing dissemination and uptake of predictive testing by at-risk family members; 2) determine what personal and family characteristics are associated with lower levels of dissemination; 3) determine the major dissemination challenges within BRCA1/2 families.

**Methods:** BRCA1/BRCA2-carriers identified from four hospitals were invited to participate in the study. A telephone interview of consenting patients assessed the informed status of at-risk relatives, uptake of predictive testing in relatives, geographical location of relatives. This information was recorded within the FCT. Individuals were also asked about any potential barriers and challenges faced in the disseminating process. Patients yet to inform all relatives were provided advice, offered a standard dissemination letter to provide to relatives, and advised of online resources to assist with dissemination. Patients were followed-up 2-4 months after their initial phone call to determine whether the FCT and associated counselling had facilitated dissemination. The genetic database was also audited to count the number of associated predictive testing appointments made in the study period.

**Results:** Data from 120 families revealed 54% had not informed ≥1 relative, with an average of 5.6 uninformed. In the 65 families with incomplete dissemination, the FCT significantly increased informing rates from 66.1% to 71.9% within a 2-4 month follow-up period ($p<0.001$). Regression analysis will reveal whether personal and family cancer history, family size, relatives’ geographical location, and Jewish ancestry predict dissemination rates. Individuals spontaneously described a number of difficulties associated with dissemination, which emerged as three distinct themes: 1) barriers to informing relatives 2) challenges experienced after informing, and 3) relatives’ reluctance to follow-up with predictive testing.

**Conclusion:** This study suggests the FCT phone intervention can assist with improving dissemination rates in BRCA1/2 carriers. Understanding the barriers, challenges and demographic factors associated with lower dissemination rates will help guide future initiatives for communication, follow-up and support.
Barriers and motivators for the communication of genetic information by BRCA carriers to relatives in multiracial Malaysia
SY Yoon¹, T Hassan¹, MK Thong², B Meiser⁴, NA Mohd Taib², CH Yip³, Soo H Teo¹, ²

¹Cancer Research Initiatives Foundation, Malaysia,
²University of Malaya Cancer Research Institute, Faculty of Medicine, University Malaya,
³Sime Darby Medical Centre, Malaysia
⁴University of New South Wales, Australia

Background: Although 2014 marks the 20th anniversary since the sequencing of BRCA1, there remain gaps in the availability of genetic testing in many parts of Asia, including Malaysia. In particular, there remain significant challenges in reaching the relatives in families with known BRCA mutations. Since August 2007, we have been providing genetic testing and counselling in a research setting. In this study, we address the barriers and motivators which influence the uptake of BRCA genetic testing in Malaysia.

Methods: We report the observations of the disclosure pattern to relatives and the uptake of genetic counselling among relatives of BRCA1 and BRCA2 carriers who were identified in the Malaysian Breast Cancer (MyBrCa) study. During counselling, the carriers were provided with information about the inheritance of BRCA mutations and the risk for breast and ovarian cancers and all carriers are followed up at 6 monthly intervals either by telephone or at a risk management clinic. All carriers were encouraged to inform their relatives of their status. A survey was carried out to gather information about whom the carriers disclosed to and reasons for disclosing or not disclosing the BRCA information.

Results: From August 2007 to May 2014, 67 BRCA carriers, of whom 56 were affected with breast cancer, 8 with ovarian cancer and 3 with both were provided with genetic counselling and result disclosure. The carriers comprised 14 Malays, 19 Indians, and 34 Chinese. The median age of the index BRCA carriers at genetic counselling was 51 years (range 25 to 72) and the mean duration from cancer diagnosis to results disclosure was 64 months (range 2 to 132). We report that of the 67 BRCA carriers who were followed up for a median follow up of 50 months (range 1 to 80), 57 (85%) informed their relatives about their carrier status with a median time from results disclosure to sharing results of 9 months (range 1 to 23). Of these 57 carriers, 36 (63%) responded to a counsellor-administered survey to determine the disclosure of genetic testing results to family members. We report that the majority of first degree relatives [145 of 181, 80%] were informed and by contrast to the minority of second and third degree relatives [268 of 886, 30%]. Of the 145 first degree relatives informed, 80 (55%) came forward for genetic counselling and 78 (96%) proceeded with testing. Of the 268 second or third degree relatives who were informed, only 37 (14%) came forward for counselling and 33 (90%) proceeded with testing.

The 36 responders ranked the following in order of importance as motivators to share their genetic information 1) They felt that information was important for their relatives to make medical decisions. 2) There was a sense of obligation 3) They were encouraged by a health professional. They also ranked the barriers from approaching their relatives 1) They do not want to share bad news. 2) They wanted to protect some relatives who will be scared and 3) They do not have a close relationship with some of their relatives.

Conclusion: Our experience in a multiracial Malaysian cohort indicates high disclosure rate and uptake of counselling amongst first degree relatives but much lower disclosure and uptake of counselling amongst second or third degree relatives. More research is necessary to aid the communication of genetic information to relatives and to overcome the stigma against the families as perceived by the probands to increase uptake of genetic counselling and genetic testing.
Health literacy in the Hereditary Cancer Clinic; what do our patients understand?
Rachel Williams, Clinical Lead Genetic Counsellor (Cancer), Hereditary Cancer Clinic, South Eastern Sydney Local Heath District, and Sian Greening, Senior Genetic Counsellor Hereditary Cancer Clinic, Illawarra and Shoalhaven Local Health District.

“Health literacy” refers to the ability to obtain, process and understand health related information in order to make appropriate health decisions. About 60% of Australians have low levels of health literacy, and are not able to effectively read and use health-related information, such as appointment letters, fact sheets, and prescription information. Following a review in 2013 by the Clinical Excellence Commission, the Australian Commission on Safety and Quality in Health Care published guidelines which strongly directed Local Health Districts in NSW to develop patient resources using multiple points of consumer input, and which are written in plain English (with a readability index consistent with a 12 year old).

Our experience of undertaking health literacy training is presented, with an overview of the processes by which we developed and trialled three resources for the Hereditary Cancer Clinic; a Family Notification Letter, a brochure on Genetic Testing for Breast Cancer, and a fact sheet on Having a Family History of Cancer developed specifically for a Macedonian population. Consumer feedback on existing resources will be presented, along with consumer-led input which led to the development of final resources approved by the LHD Patient Information Portal.


Health professional views on the use of common genomic variant breast cancer risks in the assessment and management of high-risk women
Sarah D Sawyer¹, Gillian Mitchell¹,² and Paul A James¹,²,³
¹Familial Cancer Centre, Peter MacCallum Cancer Institute ²Sir Peter MacCallum department of oncology, The University of Melbourne and ³Royal Melbourne Hospital

Background: Large genome wide association studies have identified over 80 common genomic variants (SNPs) associated with increased breast cancer risk. Investigators examined the distribution of 22 SNPs in a Victorian-based cohort of women ascertained from Familial Cancer Centres after a BRCA gene test, and found women with a family history of breast cancer and no detectable BRCA1/2 mutation had a significantly higher number of risk variants than those with a BRCA1/2 mutation. Women in the highest quartile of polygenic risk were more likely to have an early-onset breast cancer and had a higher rate of second primary breast cancers (Sawyer et al 30(35)4330 JCO 2012).

These findings have implications for clinical practice, with the potential to define and characterise a group of individuals where the polygenic risk is the principal explanation for their familial breast cancer. In this study, we conducted a national online survey to explore the potential for clinical application and utility of SNPs as viewed by health professionals (HPs).

Methods: This study recruited HPs (oncologists, clinical geneticists & genetic counsellors) who worked with women or families at high-risk of breast cancer via an email invite that was distributed through membership lists of the Familial Cancer Group of COSA and Cancer Institute NSW EviQ cancer treatments online. Participants assessed 5 clinical scenarios using conventional clinical information, and then reviewed their assessment after disclosure of the relative risk of contralateral breast cancer derived from additional SNP data.

Results: A total of 31 HPs viewed the survey; 58% (18) completed the survey. The majority (70%) of HPs considered that the relative risk of contralateral breast cancer as derived from the 22 SNP profile could provide them with the ability to ‘individualise’ cancer risk assessment and management recommendations for women and families where no BRCA1/2 gene fault has been identified. HPs expressed the need for more research in this area and shared the view that SNP data is not ready for use in routine clinical practice; 23% discussed how it would be useful to have education programs and clinical guidelines for risk management recommendations if this new genetic information was to be implemented.

Conclusions: This study highlights the need to conduct further research to generate the data required to guide the integration of SNP information into familial breast cancer assessment and risk management.
Development and implementation of a molecular multi-disciplinary review process for return of individual research results
S. Simpson¹, A. Johns¹, J. Humphris¹, S. Mead¹, C. Watson¹, L. Chantrill¹, K. Tucker², L. Andrews², Australian Pancreatic Cancer Genome Initiative³, S. Grimmond⁴, A. Biankin¹⁵

¹Cancer Research Program, Garvan Institute of Medical Research, The Kinghorn Cancer Centre, Darlinghurst, NSW, Australia
²Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, NSW, Australia
³Australian Pancreatic Cancer Genome Initiative (APGI) http://www.pancreaticcancer.net.au/apgi/collaborators
⁴Queensland Centre for Medical Genomics, Institute for Molecular Bioscience, St Lucia, QLD, Australia
⁵Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland United Kingdom.

Background: Many stakeholders are now in support of returning individual ‘clinically significant’ findings. However, only a small percentage of research groups are actually putting this into practice. Two limiting factors are a lack of understanding of what constitutes a ‘clinically significant’ finding and uncertainty regarding how these findings should be disseminated. To help consider these issues, the APGI has developed a monthly molecular multidisciplinary team (MDT) to discuss individual genetic results. To help assess the practicality of this process, collaborating clinicians were asked to provide their feedback.

Methods: An internal APGI core group has been assembled to combine key skill sets of genetic pathology, oncology, bioinformatics and genetic counselling. Collaborating clinicians and clinical genetics services are also included when additional expertise is necessary. Prior to the MDT, sufficient background research on a variant is required. This includes the sequencing approach, germline or somatic, in silico predictions and locus specific database searches and primary references. To aid considerations of personal utility and meaning, participant status and their clinical situation is noted. NATA accredited laboratories and biospecimen availability for confirmatory testing is also important. In the MDT, the variant is assessed as clinically valid, clinically actionable and/or returnable whilst factoring in the complexities of participant circumstances. The background information, final decision and rationale are documented on an APGI Molecular Findings Case Report.

Results: Since the formal molecular MDT structure was implemented in January 2014, 13 cases have been discussed and actioned. 10 of these have been deemed clinically valid or actionable and have progressed further down the APGI return of results pipeline. 3 collaborating clinicians provided feedback. All were willing to be involved in the molecular MDT, either by providing professional opinion or attending and found the information provided on the APGI Molecular Findings Case Report to be adequate. All were open to be contacted with both interim results and variants with less established clinical utility. Although the process of returning results was found to be time consuming, it was also viewed as beneficial and, as one clinician noted, “highly valued by patients”.

Conclusion: The APGI has found the development of a molecular MDT to be beneficial to their return of results processes, as it allows formal documentation of the rationale behind variant classification and result dissemination. It is also reassuring to receive feedback from collaborating clinicians who support and appreciate the efforts the APGI is going to, in order to meet ethical obligations to their research participants.

References:
¹ Haga SB and Zhao JQ. Stakeholder views on returning research results. Advances in Genetics 2013;84:41-81
Programme

Friday 14th

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

"Familial Cancer 2014: Research and Practice"

Session 7b:

Plantation Room

Chairperson: Rodney Scott
Multiple variants in regulatory regions of the 6q25.1 (ESR1) breast cancer risk locus target ESR1, RMND1/c6orf211 and CCDC170.

Stacey L. Edwards¹, Alison M. Dunning², Juliet D. French¹, Catherine S. Gregory², Kyriaki Michailidou³, Karoline Kuchenbaeker², Jonathan Beesley¹, Kristine M. Hillman¹, Susanne Kaufmann¹, Deborah Thompson², Antonis Antoniou², Georgia Chenevix-Trench¹ and Douglas F. Easton² on behalf of CIMBA, BCAC and MODE

1. Department of Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Queensland 4029, Australia
2. Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, CB1 8RN, UK

The ESR1 (encoding estrogen receptor–alpha) locus at 6q25.1 was first identified as a breast cancer susceptibility locus in 2009 through a candidate gene study, and later confirmed in genome-wide association studies in women of Asian and European ancestry. Subsequent analyses in the Breast Cancer Association Consortium found that although the strongest association is with risk of estrogen-receptor positive breast cancer, there is an independent association between SNP rs2046210 and risk of estrogen-receptor negative breast cancer in Europeans but not in Asians. Furthermore, SNPs in the same region are known to be associated with breast density. To date, however, attempts to identify the single causal variant(s) underlying the associations have been inconclusive. For this reason the locus was fine mapped on the iCOGS genotyping chip. Analysis of 3872 variants in 118,816 subjects from the Breast Cancer Association Consortium (BCAC), the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) and (MODE) identified multiple SNPs associated with breast cancer risk ($P<10^{-5}$). Regression analyses identified at least five independent sets of correlated, associated variants (iCHAVs) associated with estrogen receptor-negative breast cancer, estrogen receptor-positive breast cancer and/or with breast density. The strongest candidate causal variants lie in cis-regulatory elements. Chromatin conformation capture assays indicate that the causal variants appear to cooperatively affect ESR1, RMND1/c6orf211 and CCDC170 expression.
DEPTH: A Novel Algorithm for Feature Ranking with Application to Genome-Wide Association Studies Identifies that Variation in the *ESR1* Gene Region is Associated with Risk of Estrogen Receptor Negative Breast Cancer from a Small Study
Makalic E, Schmidt S, Kapuscinski M and Hopper JL

School of Population and Global Health, University of Melbourne, Victoria, Australia
A conventional Genome-Wide Association Study (GWAS) involves selecting single nucleotide polymorphisms (SNPs), from among a very large set of correlated SNPs, that discriminate between two groups. The ultimate aim is to identify susceptibility genes, or gene regions; the dominant paradigm to date has been to identify SNPs associated with risk of disease. We propose a new algorithm, called DEPendency of association on the number of Top Hits (DEPTH), that achieves the aim more efficiently by using bootstrap statistics and stability selection and considering contiguous SNPs as a group. DEPTH is applicable to ordinary, logistic, and Cox regression and can be run on a commodity computer but is implemented to run much faster on the IBM BlueGene/Q supercomputer. In the context of a GWAS, the algorithm passes a sliding window across the whole genome, and can be applied to subsets of SNPs (e.g. in a region or pathway, or of a particular ‘type’). We have found, using simulated data, that the algorithm shows good statistical performance when compared to several established procedures.

We applied DEPTH to data from the hypothesis-generating Phase I of a GWAS that included Australian women with breast cancer diagnosed before age 40 years (72 estrogen receptor (ER) –ve; 88 ER+ve) and 287 women 40 years and older without breast cancer, genotyped using the Illumina 610KQUAD platform with standard QC. DEPTH identified that germline variation in the region of the *ESR1* gene was implicated in risk of ER–ve disease, and more so than ER+ve disease, a finding not evident from applying the conventional ‘genome-wide significant’ threshold to these data. Subsequent analysis of iCOGS data for ~9,500 ER-ve and ~32,000 ER+ve cases and ~51,000 controls found evidence consistent with these hypotheses. Our insights from a small GWAS validates the utility of our approach in terms of the novel design - using cases (controls) enriched (depleted) for putative genetic risk - and analysis using DEPTH.
Functional characterisation of the 19p13 breast and ovarian cancer risk locus identifies ABHD8 as a novel candidate breast-ovarian cancer susceptibility gene.


Multiple independent genome-wide association studies (GWASs) have identified variation at the 19p13 locus that predisposes to estrogen receptor-negative breast cancer and high-grade serous ovarian cancer (HGSOC). Fine-mapping of the region using the iCOGS customised Illumina Infinium genotyping array, followed by imputation, limited the risk associated region to a 20kb window encompassing two protein coding genes – ANKLE1, which may be involved in DNA repair, and ABHD8 of unknown function – and just distal to the BRCA1 interacting gene BABAM1. The strongest association signal is represented by 13 highly correlated single nucleotide polymorphisms ($P < 10^{-22}$). By integrating genotyping data with epigenetic data generated from normal ovarian and breast epithelial cells we identified risk SNPs intersecting known or putative enhancers, and ELF1, ELK4, GABP and GATA3 transcription factor binding sites. Expression quantitative trait locus (eQTL) analyses identified significant genotype-gene expression associations for ANKLE1 in normal ovarian epithelial cells ($P = 0.02$), and for ABHD8 in both HGSOCs ($P = 3.0 \times 10^{-5}$) and normal breast tissues ($P = 2.8 \times 10^{-3}$), but not for BABAM1. Risk associated SNPs were also significantly associated with allele specific expression of ABHD8 in breast cancer ($P < 2.5 \times 10^{-5}$). Genes in the 19p13 region are frequently overexpressed in both breast cancers and HGSOCs; however, stable overexpression of neither BABAM1 nor ANKLE1 had a significant impact on the neoplastic phenotype of normal breast and ovarian epithelial cells. Using chromosome-conformation-capture (3C) assays in these same cell types, we identified interactions between a putative regulatory region and the promoter of ABHD8, as well as in breast and ovarian cancer cell lines, but interactions with the ANKLE1 promoter could not be ruled out. We are currently testing the four risk SNPs in the putative enhancer located in the interacting region in luciferase constructs with the ABHD8 promoter, as well as the effect of two risk SNPs in the ANKLE1 promoter to determine if either, or both, of these genes are likely to be the target of the risk SNPs that underlie breast and ovarian cancer development.
Returning genetic research results to participants: How are we doing in Australia and where to in the future?
Mary-Anne Young 1, Laura Forrest 1,2
1. The Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia
2. Sir Peter MacCallum Department of Oncology, University of Melbourne, VIC, Australia

The Australian Breast Cancer Family Study was one of the first population based studies to notify research participants by letter of the availability of clinically significant genetic information. Since then a number of both population-based and clinic-based cohorts have notified research participants by letter with estimates between 8% and 44% of participants attending a familial cancer clinic to receive their results. In a multinational study, Colon CFR, Australians had the lowest uptake (56%) compared to the other participating centres in the USA and Canada, where uptake was from 72 – 86%.

Evidence indicates that most research participants are enthusiastic and willingly consent to being notified about the availability of clinically significant research results. However, the incongruence between Australian research participants’ positive attitudes to receiving genetic results and subsequent low uptake of genetic counselling and testing, has been the subject of a number of qualitative psychosocial studies examining participants’ experiences of receiving a notification letter and why they choose to accept or decline genetic counselling and testing.

The authors’ involvement in the compilation of the evidence apropos research participants’ attitudes towards returning research results, experience of receiving a notification letter and decision-making regarding clarification of genetic carrier status, has resulted in the conceptualisation and development of the INSPIRE model of telephone genetic counselling of returning research results. In order for research results to be translated to clinical outcomes such as the reduction in cancer diagnoses and improved prognosis, the results need to be communicated to research participants in a manner that is supportive and facilitates informed decision-making. Therefore, the INSPIRE model aims to provide participants with appropriate information and support in order to facilitate informed decision making about clarifying their genetic risk.

This presentation will examine participants’ experiences of receiving a notification letter and why they choose to accept or decline genetic counselling and testing. Furthermore it will present a novel form of notification that includes a telephone genetic counselling intervention providing information and support to research participants.
Prospective Family Study Cohort (ProF-SC) for Breast Cancer: Rationale and design, and conduct and analysis of the Australian and New Zealand components

John L. Hopper\textsuperscript{1}, Kelly-Anne Phillips\textsuperscript{1,2}, Carmel Apicella\textsuperscript{1}, Gillian Dite\textsuperscript{1}, Robert MacInnis\textsuperscript{1,3}, James Dowty\textsuperscript{1}, Adrian Bickerstaffe\textsuperscript{1}, Kelly Aujard\textsuperscript{1}, Sue Anne McLachlan\textsuperscript{4}, Michael Friedlander\textsuperscript{5}, Prue Weideman\textsuperscript{2}, Sandra Picken\textsuperscript{2}, Charmaine Smith\textsuperscript{2}, Roger Milne\textsuperscript{3}, Melissa C. Southey\textsuperscript{6}, Graham G. Giles\textsuperscript{3}, Mary-Beth Terry\textsuperscript{7}

\textsuperscript{1}School of Population and Global Health, The University of Melbourne; \textsuperscript{2}Division of Cancer Medicine, Peter MacCallum Cancer; \textsuperscript{3}Cancer Epidemiology Centre, Cancer Council Victoria; \textsuperscript{4}Department of Medical Oncology, St Vincent's Hospital, Melbourne; \textsuperscript{5}Department of Medical Oncology, Prince of Wales Hospital, Sydney; \textsuperscript{6}Department of Pathology, The University of Melbourne; \textsuperscript{7}Mailman School of Public Health, Columbia University, New York.

Given the familial risk ratio for breast cancer is on average \(~1.5\), and higher for early-onset disease, there must be a very strong risk gradient across the underlying genetic and/or environmental risk factors shared by relatives (familial risk profile; FRP). There is evidence that the distribution of FRP is highly skewed to the right, with a long tail. Therefore, the vast majority of women are well below population average risk (e.g. lifetime risk 2-4\% cf. 11\% for Australian women) so that traditional case-control studies using population controls have, in effect, made inference about the risk factors for low-risk women only. Whether the findings apply to women at increased if not high familial/genetic risk is not known. For genomic discoveries to impact on breast cancer control through appropriate prevention, screening and treatment for such women, it is imperative to study the wide range of ‘at risk’ women. The prospective family study cohort (ProF-SC) design involves long term follow-up of families involving women from across the full spectrum of FRP and can address the question: do risk factor associations depend on FRP, as well as many other questions; see Hopper, Epidemiol Perspect & Innov 2011:8:2. The risk gradient across the FRP can be predicted from personal and family cancer history (using e.g. BOADICEA) and measured familial risk factors, and interactions between predicted FRP and risk factors estimated. Funded by NIH, the Breast Cancer Family Registry and the kConFab Clinical Follow-Up Study have established a cohort of 18,877 adult women unaffected with breast cancer and 12,763 women affected with breast cancer at recruitment of whom 2,741 are BRCA1 or BRCA2 mutation carriers. More than 50\% of these women are from Australia and New Zealand and the remainder from the USA and Canada. All participants completed the same baseline questionnaire at recruitment. Average age at recruitment was 50 years (sd 15 years), and the average length of follow-up to date is 10 years (range 5-22). There has been 20\% loss-to-follow-up, but outcome and cancer information on some of these has been obtained from participating relatives. To date, there have been 2,127 reported incident breast cancers (including 1,048 first primaries), of which 70\% have been confirmed by pathology and blood samples have been collected from 90\%. We will report in more detail on the conduct of the Australian and New Zealand components. We will also present analyses using those components on: (a) the associations between self-reported body mass index (BMI) at age 18-21 years, and at baseline, on risk of subsequent breast cancer for women unaffected at baseline, as a function of predicted FRP; and (b) the outcomes for population-sampled women (unselected for family history) diagnosed with breast cancer at baseline as a function of predicted FRP.
Programme

Friday 15th

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

“Familial Cancer 2014: Research and Practice”

Session 8:

Plantation Room

Chairperson: Judy Kirk
Title to be announced
Judy Garber, Director, Center for Cancer Genetics and Prevention, Dana Farber Cancer Institute, Professor of Medicine, Harvard Medical School
A surveillance study in TP53 mutation carriers utilizing whole body MRI: the experience to date
Mandy L Ballinger¹, Kate A McBride², Mary-Anne Young³, Nicholas Ferris⁴, Kate Moodie⁵, Clair Shadbolt⁵, Sue Shanley⁵, Marion Harris⁶, Eveline Niedermayr⁴, Paul A James³, David M Thomas¹,⁷ & Gillian Mitchell³
¹Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia; ²The Chris O’Brien Lifehouse, Sydney Medical School, Sydney, Australia; ³Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, Australia; ⁴Monash Imaging, Monash Health, Melbourne, Australia; ⁵Department of Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Australia; ⁶Familial Cancer Centre, Monash Health, Melbourne, Australia; ⁷The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, Australia.

TP53 mutation carriers have a high lifetime cancer risk. New genetic technology utilized in both the research and clinical settings has resulted in an increasing number of TP53 mutation carriers being detected. Cancer risk management in this population is becoming a pressing clinical issue and recent reports indicate a surveillance benefit. We have initiated a pilot surveillance study in TP53 mutation carriers to estimate the prevalence and incidence of investigable lesions and the acceptability, safety, psychosocial impact and cost effectiveness of a comprehensive surveillance protocol. The protocol uses annual whole body MRI (WB-MRI), physical examination, full blood evaluation, breast MRI (females), fecal occult blood test and 2-5 yearly colonoscopy/endoscopy. Patients also complete psychosocial evaluations and a cost diary. Ten mutation carriers (6F, 4M; age 23-64yrs) have been recruited, with 6 having had a previous cancer diagnosis. Initial clinical history and physical examinations (10) resulted in 5 findings in 3 participants requiring follow up (2 dermatology referrals, 2 USS and 1 PSA). All 10 blood evaluations were normal. Nine WB-MRIs detected 36 areas of note, with 3 participants requiring further investigation (abdominal US, urology referral, dedicated liver scan). One malignancy has been detected (recurrent leiomyosarcoma). Other surveillance procedures include 3 breast MRIs, 2 colonoscopies and 2 gastrosopies with no malignancy detected. Protocol adherence and safety have been acceptable with all surveillance and follow up appointments attended (37). There have been no adverse events. 43/45 (96%) questionnaires have been completed and 11 in-depth interviews undertaken. Preliminary results indicate there are no adverse psychosocial effects for participants. Whilst the study is in early phase the acceptability, safety and lack of adverse psychosocial impact support continuation to allow longer term evaluation.
Mammographic density is associated with breast cancer risk in BRCA mutation carriers
Gillian Mitchell¹, Kate Moodie¹, Clair Shadbolt¹,², Rebecca Driessen¹, Joanne McKinley¹, Antonis Antoniou³, Geoffrey Lindeman⁴, Marion Harris⁵, Martin Delatycki⁶, Jennifer Stone⁷
¹ Peter MacCallum Cancer Centre; ² Royal Women’s Hospital; ³ Cambridge University, UK; ⁴ Royal Melbourne Hospital, ⁵ Monash Medical Centre, ⁶ Austin Hospital, ⁷ University of Western Australia

Introduction: We have shown previously that increasing mammographic density (MD) is associated with an increased risk of breast cancer (Ptrend = 0.024) in BRCA mutation carriers based on 206 female carriers. We sought to replicate these findings in a larger, independent, group of carriers as part of a wider study into personalising breast cancer risk prediction in BRCA mutation carriers.

Methods: Women with pathogenic BRCA mutations were recruited from the four Victorian Familial Cancer Centres. Women completed an epidemiological questionnaire by telephone and gave permission for access to their mammograms; the most recent mammogram for women unaffected by cancer and the mammogram prior to their diagnosis of breast cancer if affected by breast cancer. MD was determined using a visual 5-point scoring system (<10%, 10-25%, 26-50%, 50-75%, >75% dense) by two independent radiologists (KM, CS) and by a computerised scoring system (Cumulus) by an experienced MD researcher (JS). We studied the concordance of measured density scores uncorrected for confounders (eg BMI and exogenous hormone use) between radiologists and between visual and computerised density scoring methods. We additionally studied the association between mammographic density score and the diagnosis of breast cancer.

Results: 402 mutation carriers with accessible mammograms were recruited; 402 were scored using the visual scoring method and 318 of these were also suitable for scoring using Cumulus. There was good concordance between radiologists (kappa statistic 0.75; p=<0.05) and the visual scoring method was highly correlated with the continuous Cumulus measurement of percent dense area (Spearman’s r=0.79 and 0.81; p<0.001). Using the Cumulus scoring alone, preliminary analysis indicates that affected carriers were more likely to have higher percent dense area (p~0.03).

Conclusion: We have confirmed the association between MD and breast cancer risk in BRCA mutation carriers. We are performing more detailed analysis of MD, corrected for MD confounders and to test the strength of the association of MD with breast cancer risk for the visual scoring method. We are also undertaking a wider breast cancer risk prediction analysis combining MD scores with epidemiological risk factors, mutation position and genomic (SNP) profiles.
Rare germline copy number deletions of likely functional importance are implicated in endometrial cancer predisposition

Gemma L Moir-Meyer1,2, John F Pearson3, Felicity Lose2, The Australian National Endometrial Cancer Study Group2, Rodney J Scott4,5, Mark McEvoy6, John Attia6,7,8, Elizabeth G Holliday6,8, The Hunter Community Study5, Studies of Epidemiology and Risk Factors in Cancer Heredity9, Paul D Pharoah9,10, Alison M Dunning10, Deborah J Thompson9, Douglas F Easton9,10, Amanda B Spurdle2*, Logan C Walker1*

(1) Mackenzie Cancer Research Group, Department of Pathology, University of Otago, Christchurch, New Zealand; (2) Molecular Cancer Epidemiology Laboratory, Genetics and Computational Biology Division, QIMR Berghofer Institute of Medical Research, Queensland, Australia; (3) Biostatistics and Computational Biology Unit, University of Otago, Christchurch, New Zealand; (4) Centre for Information Based Medicine and the School of Biomedical Science and Pharmacy, University of Newcastle, Newcastle, Australia; (5) Hunter Medical Research Institute, Hunter Area Pathology Service, John Hunter Hospital, Newcastle, Australia; (6) Centre for Clinical Epidemiology and Biostatistics, School of Medicine and Public Health, University of Newcastle, Newcastle, Australia; (7) Department of General Medicine, Hunter Medical Research Institute, John Hunter Hospital, University of Newcastle, Newcastle, Australia; (8) Clinical Research Design, IT and Statistical Support Unit, Hunter Medical Research Institute, Newcastle, Australia; (9) Department of Public Health and Primary Care, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge, UK; (10) Department of Oncology, Centre for Cancer Genetic Epidemiology, University of Cambridge, Cambridge, UK.

*authors contributed equally.

Endometrial cancer is the most common invasive gynaecological cancer in women, and relatively little is known about inherited risk factors for this disease. We conducted the first genome-wide study to explore the role of common and rare germline copy number variants (CNVs) in predisposition to endometrial cancer. CNVs were called from germline DNA of 1209 endometrioid endometrial cancer cases and 604 cancer-unaffected female controls. Overall CNV load of deletions or DNA gains did not differ significantly between cases and controls (P>0.05), but cases presented with an excess of germline deletions overlapping likely functional genomic regions. This trend was especially striking for rare deletions overlapping genes (P=8x10^-10), CpG islands (P=1x10^-7) and sno/miRNAs regions (P=3x10^-9). On average, at least one additional gene and two additional CpG islands were disrupted by rare deletions in cases compared to controls. The most pronounced difference was that over 30 sno/miRNAs were disrupted by rare deletions in cases for every single disruption event in controls. A total of 13 DNA repair genes were disrupted by rare deletions in 19/1209 cases (1.6%) compared to one gene in 1/528 controls (0.2%; P=0.007), and this increased DNA repair gene loss in cases persisted after excluding five individuals carrying CNVs disrupting mismatch repair genes MLH1, MSH2 and MSH6 (P=0.03). There were 34 miRNA regions deleted in at least one case but not in controls, the most frequent of which encompassed hsa-mir-661 and hsa-mir-203. Thus rare germline deletions predicted to disrupt genes and/or gene regulation are strongly associated with endometrial cancer predisposition.
Functional evaluation of breast cancer case-associated non-coding variants in BRCA1/2
Jan Sevcik1, Philip Whiley1, Lesley Burke1, Paolo Peterlongo2, Paolo Radice2, Etienne Rouleau3, Amanda B Spurdle4, and Melissa A Brown1*
1 School of Chemistry and Molecular Biosciences (SCMB), University of Queensland, Brisbane, Australia
2 IFOM, Fondazione Istituto FIRC di Oncologia Molecolare, Milan, Italy
3 Oncogenetic laboratory, Institut Curie-Hospital René Huguenin, Saint Cloud, France
4 Queensland Institute of Medical Research, Brisbane, Australia
*correspondence to Prof. Melissa A. Brown, SCMB, University of Queensland, St. Lucia, 4067, QLD; Melissa.brown@uq.edu.au

Breast cancer (BC) is the most frequent malignancy in the female population worldwide. The high penetrant Mendelian pattern of familial BC indicates the presence of inherited genetic events that predispose to the disease. This possibility has been supported by the identification of two BC predisposition genes, BRCA1 and BRCA2. Following their discovery, the prevalence and penetrance of mutations in these genes has been studied extensively. Whilst the absolute majority of described disease-causing mutations have been found in the coding regions of these genes, it is becoming apparent that these only account for a relatively small proportion of mutations underlying BC risk. Despite the relatively subtle impact of mutations in regulatory regions to the gene and its product, such regulatory variants in many genes have been shown to contribute to cancer risk.

The aim of this work was to functionally evaluate the consequences of BRCA1/2 non-coding variants, in order to help predict their contribution to BC risk.

The promoter and 5'UTR of both BRCA1 and BRCA2 were sequenced in a cohort of 600 BC cases, with no known coding region mutations, and 600 healthy controls. A subset of detected variants was prioritized for experimental analysis, based on the results of bioinformatics analysis, including the presence of transcription binding sites, histone modifications and the position of the active promoter. To determine the influence of particular sequence variant on the BRCA1/2 promoter activity, we conducted a luciferase-based reporter assay, using a set of human BC-derived cell lines. The effect of particular variants on transcription factor/protein binding capacity was also determined, using electrophoretic mobility shift assay (EMSA) with whole nuclear extract.

Our results show that some disease-associated variants cause a significant decrease of BRCA1/2 promoter activity compared to the BRCA1/2 wild type promoter. Interestingly, this decrease in activity is associated with qualitatively and/or quantitatively altered binding capacity of proteins to the affected promoter region. These results suggest that analyzed variants may alter the occupation of BRCA1/2 promoters by proteins/transcription factors, which in turn could result in altered expression of gene products. We conclude that analyzed BRCA1/2 non-coding variants could negatively affect the levels of BRCA1/2 tumor suppressors and thus contribute the BC risk.
Programme

Friday 15th

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

“Familial Cancer 2014: Research and Practice”

Session 9:

Plantation Room

Chairperson: Melissa Southey
Epigenetic mechanisms of breast cancer risk
James M. Flanagan, Breast Cancer Campaign Fellow, Epigenetics Unit, Department of Surgery and Cancer, Imperial College London

There is accumulating evidence that the environment and various exposures can alter the epigenome and may mediate the increased risk of disease associated with those exposures. We and others, have used Epigenome-Wide Association Studies (EWAS) using the Illumina 450k methylation array to identify a strong association between white blood cell (WBC) DNA and smoking status, with consistently replicated associations in the arylhydrocarbon receptor repressor (AHRR) and an intergenic CpG island at 2q37.1. We have also shown that these methylation markers affect methylation and expression in human lung tissue and in a mouse model of smoking exposure. Combining data across 8 different studies, we have performed a meta-analysis using a random effects model to validate the strongest association in 72 CpG sites in current versus never smokers, and 18 CpG sites in former versus never smokers. Combining four of these CpG sites into a single methylation index provided a high positive predictive and sensitivity values for predicting former smoking status (AUC=0.83 (0.70-0.96)) suggesting that DNA methylation in blood may provide a direct molecular measure of prior exposure to tobacco. While smoking is only a modest risk factor for breast cancer we identified one smoking related CpG site (2q37.1) that was independently associated with breast cancer risk. Using principle components analysis we have also identified a genome-wide signature of breast cancer risk, replicating findings from other studies that support a genome-wide hypomethylation in breast cancer cases compared to matched controls. Lastly, we have estimated the intraclass correlation coefficient (ICC) for each probe on the Illumina 450K methylation array in paired samples collected approximately six years apart from healthy subjects in the Breakthrough Generations Study. This identified approximately 16% of probes on the 450K array that are variable between individuals and stable over a six year gap (ICC>0.50). Overall, we have shown that epigenetic variation may be a driver of cancer risk whether by inherent constitutional variation or as a mediator of a lifetime accumulation of cancer risk factors and may prove useful in models for predicting individual breast cancer risk.
Constitutional BRCA1 methylation is a major predisposition factor for high-grade serous ovarian cancer

A. Dobrovic1,2,3, K. Alsop2, T. Mikeska2,3, G.V. Zapparoli1, I.L. Candiloro2,3, J. George2, G. Mitchell2, D. Bowtell2,3, Australian Ovarian Cancer Study

1Translational Genomics & Epigenomics Lab, Ludwig Institute for Cancer Research, Olivia Newton-John Cancer and Wellness Centre, Heidelberg (Melbourne), Victoria, Australia; 2Research Division, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia; 3Department of Pathology, University of Melbourne, Parkville, Victoria, Australia

Constitutional methylation refers to specific promoter methylation present in the normal tissues of some individuals. This study aimed to determine whether constitutional methylation of the BRCA1 promoter region was a predisposition factor for high-grade serous ovarian cancer. We had previously shown in a case-control study of early-onset breast cancer patients that the presence of BRCA1 methylation in the blood was associated with tumors that phenocopied pathogenic germline BRCA1 mutations. This indicated that BRCA1 methylation predisposed to and drove the development of these tumors. Germline BRCA1 mutations also predispose to ovarian cancer, in particular, high-grade serous ovarian cancer. In collaboration with the Australian Ovarian Cancer Study, we determined the presence of mutations and detectable BRCA1 methylation in 154 high-grade serous cancers. Fifteen women had germline BRCA1 mutations and 11 had germline BRCA2 mutations. The germline BRCA1 mutation carriers were predominantly younger at diagnosis and 11/15 pathogenic BRCA1 mutations were seen in patients under 55 at diagnosis. Similarly, patients with BRCA1 methylated tumors were predominantly (15/25) under 55 at diagnosis. BRCA1 methylation was mutually exclusive with BRCA1 and BRCA2 mutation. Nineteen patients showed detectable levels of BRCA1 methylation in DNA extracted from their peripheral blood. Remarkably, when the corresponding tumor samples were assessed for methylation, 13 of these 19 patients had high level BRCA1 methylation in their tumor (p<.0001 for the association of blood and tumour methylation). When the 50 tumors occurring before the age of 55 were considered, 9 of the 10 patients with detectable peripheral blood mutation had a corresponding BRCA1 methylated tumor (p<.0001). This data indicates that constitutional BRCA1 methylation can drive high-grade serous ovarian cancer, in particular early onset cancer, and moreover is as important a predisposition factor as BRCA1 mutation.
**BRCA2 carrier male breast cancers show elevated methylation.**

Siddhartha Deb¹,², Jia-Min Pang¹, Elena Takano¹, kConFab Investigators³, Alexander Dobrovic¹,⁴, Stephen B Fox¹,².

1. Molecular Pathology Research and Development Laboratory, Department of Pathology, Peter MacCallum Cancer Centre, East Melbourne, Victoria 3002, Australia
2. Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Vic. 3010, AUSTRALIA
3. Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer, Peter MacCallum Cancer Centre, East Melbourne 3002, AUSTRALIA
4. Translational Genomics and Epigenomics Laboratory, Ludwig Institute for Cancer Research, Olivia Newton-John Cancer and Wellness Centre, Heidelberg, Victoria, 3084, AUSTRALIA.

**Introduction:**

Male breast cancer represents a poorly characterised group of tumours, the management of which is largely based on practices established for female breast cancer. However, recent studies have demonstrated biological and molecular differences such as methylation that are likely to impact on tumour behaviour and therefore patient outcome mirroring this practice. The aim of this study was to investigate methylation of a panel of commonly methylated breast cancer genes in familial MBCs.

**Method:** 60 tumours from 3 BRCA1, 25 BRCA2 male mutation carriers and 32 males from BRCAX families were obtained from kConFab. Methylation-sensitive high resolution melting was used to assess promoter methylation in a panel of 10 genes commonly observed to be methylated in female breast cancers (RASSF1A, TWIST1, APC, WIFI, MAL, RARβ, CDH1, RUNX3, FOXC1 and GSTP1). A cumulative methylation index (CMI) was calculated for each case as the average of the 10 genes as an indicator of overall methylation within the tumour. Methylation was correlated with BRCA carrier mutation status and clinicopathological parameters including TNM stage, grade, histological subtype and disease specific survival (DSS).

**Results:** Tumours arising in BRCA2 mutation carriers showed significantly higher methylation than other familial MBCs (average CMI 23.6 vs 16.6, p=0.01). RARβ methylation and CMI high status was significantly associated with tumour size (p=0.01 and p=0.02 respectively), RUNX3 methylation with invasive carcinomas of no special type (94% vs 69%, p=0.048), RASSF1A methylation with coexistence of high grade DCIS (33% vs 6%, p=0.04), Cluster analysis showed MBCs arising in BRCA2 mutation carriers were characterised by RASSF1A, WIFI, RARβ and GSTP1 methylation (p=0.02) whereas methylation in BRCAX tumours was more heterogeneous. TWIST1 methylation (p=0.001) and high overall methylation (CMI) (p=0.01) were also significantly prognostic for disease specific survival.

**Conclusion:** This study suggests that increased methylation can define a subset of familial MBC and that CMI may be useful as a prognostic and predictive marker. Furthermore, as methylation is characteristic of particular male breast cancer subsets, there is potential for screening for early detection and establishing trials of several of the novel methylation therapeutics that are currently under investigation in other cancer types.
Psychosocial stress remodels the tumor microenvironment: Novel points of leverage to halt cancer.

Caroline P. Le¹, Corina Kim-Fuchs¹, Sarah Creed¹, Cindy Pon¹, Cameron J. Nowell¹, and Erica K. Sloan¹,²,⁴

¹Monash Institute of Pharmaceutical Sciences, Monash University, Australia
²Dept of Cancer Anaesthesia and Pain Medicine, Peter MacCallum Cancer Centre, Australia
⁴Cousins Center for PNI, UCLA Semel Institute, and Jonsson Comprehensive Cancer Center, University of California Los Angeles.

While the psychosocial burden of cancer on patients’ wellbeing has been described, the effect of chronic stress on disease progression is still unclear. Recent clinical studies demonstrated that stress response pathways accelerated cancer progression and our preclinical studies found that breast cancer metastasis was particularly sensitive to stress signalling. To investigate the cellular and molecular mechanism of these effects, my laboratory has used advanced in vivo imaging technologies to investigate relationships between the peripheral neural system that transmits stress signals from the brain to the body, tumor cells and the cancer microenvironment. Our studies find that stress communicates through a neural-inflammation axis in the breast tumor microenvironment to remodel physical pathways of tumor cell escape. Chronic stress signal also act directly on tumor cells to make them more invasive and on immune cells to impair their function. Our recent preclinical studies in models of pancreatic cancer and leukemia found that activation of neural stress-response pathways similarly accelerated progression, suggesting that adrenergic signaling may be a general physiological regulator of cancer progression. These findings raise the possibility that beta-blockade of neural stress response pathways or blockade of stress-induced inflammation may be novel therapeutic strategies to slow or prevent metastasis in stressed patients.
Does stress increase breast cancer risk? Initial results from the kConFab psychosocial study

Phyllis N Butow,1,2,3 Kelly Phillips,4 Kathy Tucker,5 Joseph Coll,2,3 Louise Heiniger,1,2,3 Judy Wilson,1,2,3 Brandi Baylock,1,2,3 Tracey Bullen,1,2,3 Chris Tennant,6 Bettina Meiser,7,8 Prue Weideman,4 John L. Hopper,9 Sue-Anne McLachlan,10 Roger Milne,9 Michael Friedlander,11 Heather Thorne,12 kConFab Psychosocial Group on behalf of the kConFab Investigators, Melanie A Price1,2,3

1Centre for Medical Psychology and Evidence-based Decision-making, School of Psychology, University of Sydney NSW 2006; 2Psycho-oncology Cooperative Research Group, University of Sydney; 3School of Psychology, University of Sydney; 4Division of Cancer Medicine, Peter McCallum Cancer Centre, Melbourne; 5Hereditary Cancer Clinic, Dept of Medical Oncology, Prince of Wales Hospital; 6Dept of Psychiatry, University of Sydney 7Psychosocial Research Group, Dept of Medical Oncology, Prince of Wales Hospital Randwick, NSW; 8Prince of Wales Clinical School, University of New South Wales, Sydney, NSW 2052. 9Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health The University of Melbourne; 10Dept of Oncology St Vincents Hospital Melbourne; 11Dept of Medical Oncology, Prince of Wales Hospital Randwick NSW. 12Research Department, , Peter McCallum Cancer Centre, Melbourne.

Introduction It has long been thought that stress can increase breast cancer risk, and this could be particularly important for women at high absolute risk due to familial and/or genetic factors. Research has identified changes in immune and hormonal function in response to stress that could predispose to malignant growth. Furthermore, a recent animal study reported down-regulation of the BRCA1 gene after exposure to chronic cortisol excess (mimicking chronic, unremitting stress). Most epidemiological studies have used a retrospective case-control design that is open to recall bias. Retrospective studies that utilise data linkage (linking breast cancer events to recorded stressful life events, such as deaths and marriage) do not rely on patient report, but include very limited stressful life events. The kConFab Psychosocial study is the first prospective study to use gold standard life event stress measurement and adequately control for confounders. It aimed to find out if the number and severity of recent stressful life events predict future diagnosis of primary breast cancer (BC), and whether anxiety and/or depression, low social support and poor coping (low optimism, high emotional control) modify any associations.

Methods Unaffected women, aged 18-75 years, who could read/write English and were recruited into the kConFab study, were invited to participate in the psychosocial study. They completed questionnaires and a structured phone interview every 3 years for up to 12 years or diagnosis of breast cancer. Life event stressors were measured using the gold-standard Life Events and Difficulties Schedule phone interview. Anxiety and depression, social support, optimism, emotional repression and anger control were measured using validated questionnaires. Analyses are utilizing logistic regression and time to event analysis, controlling for measured potential confounders assessed by the baseline and clinical follow-up questionnaires.

Results Of 3595 eligible women invited, 3039 (84%) agreed to participate in the study, with most (85%) completing both questionnaire and interview at baseline. 2553 and 1756 women completed the 2nd and 3rd assessments respectively. During the follow-up period, 146 (5%) were diagnosed with BC. Women with and without BC were demographically similar; the majority were aged between 30 and 50, partnered and employed, and 23% had a university education. Women with BC had on average a stronger family history at baseline and were more likely to be a mutation carrier. Women with BC did not have more severe, or total, acute stressors or chronic difficulties, and on average had fewer such life events, though the differences were not nominally statistically significant. There is some evidence that very high stress could decrease risk of BC by causing amenorrhoea and thus lowering oestrogen, while stressful life events could increase resilience, prompt healthier living (such as increased exercise), and generate social support. Results of analyses adjusting for all measured confounders will be presented.

Conclusions Our analyses to date do not support the hypothesis that stress increases risk of BC for women at increased familial/genetic risk.
Programme

Wednesday 13th

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

“Familial Cancer 2014: Research and Practice”

Poster Session

6.00 – 8.00pm

In the main Foyer of Mantra
Audit of Upper GI Unit Referrals to the Familial Cancer Centre

T Schenberg,1,2 M Michael1
1Department of Medical Oncology, PMCC, East Melbourne, Victoria
2Familial Cancer Centre, PMCC, East Melbourne, Victoria

Background/Aims
Upper GI Neuroendocrine tumours (NETs) are rare, with a heterogeneous biological course and can have a familial basis. Families with underlying genetic predisposition to NETs can access the Familial Cancer Centre (FCC). These interventions allow tumours to be found earlier and treated with curative intent as well as providing psychological support.1-4

The aim of this project is to audit the spectrum of NETs reviewed in Peter MacCallum Multidisciplinary Meetings (MDMs) to identify whether there is a need to enhance awareness of eligibility criteria for referral to genetic services.

Methods
The MDM Sheets of the Upper GI Unit from January 2012 to December 2013 were reviewed. Personal and family histories of patients discussed were examined via hospital electronic records. These were audited to see if referral had occurred for those meeting current national referral criteria (as per eviQ website).

Results
599 patients were discussed in the time period stated. Demographics of those for whom FCC referral was appropriate are documented below. Of those referred to an FCC 75% had genetic testing. 7 patients had positive results – 4 for MEN1, 2 for SDH and 1 for RET. Of these patients, 6 FCC referrals were performed at other centres prior to review at PMCC.

<table>
<thead>
<tr>
<th></th>
<th>Patients Referred N=32</th>
<th>Eligible Patients not known to be referred N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Med Onc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgeon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
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<tr>
<td><strong>Sex (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>♀</td>
<td>62.5</td>
<td>53.3</td>
</tr>
<tr>
<td>♂</td>
<td>37.5</td>
<td>46.6</td>
</tr>
<tr>
<td><strong>Place of origin (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metro</td>
<td>40.6</td>
<td>20.0</td>
</tr>
<tr>
<td>Rural/Reg</td>
<td>59.4</td>
<td>80.0</td>
</tr>
<tr>
<td><strong>Referrers (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Med Onc</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Surgeon</td>
<td>18.7</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>18.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Lead Clinician (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Med Onc</td>
<td>N/A</td>
<td>73.3</td>
</tr>
<tr>
<td>Surgeon</td>
<td></td>
<td>27.3</td>
</tr>
<tr>
<td>Nuc Med</td>
<td></td>
<td>9.1</td>
</tr>
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<td></td>
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<tr>
<td>Table 1: Demographics of patients appropriate for FCC referral</td>
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</tbody>
</table>

Conclusion
The absolute numbers of patients eligible for referral were not large but the proportion of those eligible yet not known to be referred was 15/47 (31%). Guidelines for referral to the FCC with Upper GI endocrine tumours may not be well publicised and utilisation of this service may be improved by increased liaison between the FCC and the Upper GI team.
A clinical audit of patients undergoing screening for familial paraganglioma syndromes within the Victorian population.

T Schenberg,1,2 P James2
1Department of Medical Oncology, PMCC, East Melbourne, Victoria
2Familial Cancer Centre, PMCC, East Melbourne, Victoria

Background/Aims
Paragangliomas (PGL) are uncommon extra-adrenal paraganglia tumours. A hereditary cause is only found in approximately 20-40% patients1. There are several types of genetic mutations that can lead to a hereditary PGL syndrome. Mutations in several genes encoding subunits of the enzyme complex succinate dehydrogenase (SDH) have recently been delineated. Less commonly Neurofibromatosis type 1, Von Hippel Lindau syndrome or type 2 Multiple Endocrine Neoplasia can be involved. The aim of this study is to describe the clinical features and outcomes over time of the cohort of hereditary PGL families that are managed at our centre and ensure that our screening processes are appropriate and improving outcomes in these patients.

Methods
Patients with a familial syndrome of paraganglioma or phaeochromocytoma were found by performing a keyword search of the Familial Cancer Centre (FCC) database. Their FCC notes were then perused to confirm an underlying familial cause of their tumours.

Patient demographics, median age at diagnosis of first tumour, type of underlying genetic mutation, type of clinical presentation, rates of tumours for each mutation type, location of tumours, recall rate of screening, false positives, rates of missed tests or appointments, rates of metastatic disease, rates of other malignancies and rates of surgical and/or radiation therapy treatment were reviewed via review of Verdi.

Results
A total of 66 patients were included in the audit. Characteristics of participants and frequency of tumour diagnosis per tumour stream are documented in the tables below.

Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PARTICIPANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>♀ 36 (54.5%), ♂ 30 (45.5%)</td>
</tr>
<tr>
<td>Median Age</td>
<td>39.5 years</td>
</tr>
<tr>
<td>Median Age of syndrome diagnosis</td>
<td>35 years</td>
</tr>
<tr>
<td>Median Age of first tumour diagnosis</td>
<td>29.5 years</td>
</tr>
<tr>
<td>SDHB Gene mutation</td>
<td>40 (60.6%)</td>
</tr>
<tr>
<td>SDHC Gene mutation</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>SDHD Gene mutation</td>
<td>19 (30.3%)</td>
</tr>
<tr>
<td>VHL Gene mutation</td>
<td>3 (4.5%)</td>
</tr>
<tr>
<td>Index Case</td>
<td>23 (35.4%)</td>
</tr>
<tr>
<td>Affected at diagnosis but not index case</td>
<td>9 (13.8%)</td>
</tr>
<tr>
<td>Unaffected at diagnosis</td>
<td>33 (50.8%)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>5 (7.7%)</td>
</tr>
</tbody>
</table>

* All patients with metastatic disease had a SDHB mutation
Table 2. Number of tumours diagnosed per patient by genetic mutation type

<table>
<thead>
<tr>
<th>MUTATION TYPE</th>
<th>NO TUMOURS DIAGNOSED (%)</th>
<th>AVERAGE TUMOURS PER PATIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Including Nils</td>
</tr>
<tr>
<td>ALL N=65</td>
<td>30 (46.1%)</td>
<td>1.29 (0-8)</td>
</tr>
<tr>
<td>SDHB N=40</td>
<td>21 (55%)</td>
<td>0.87 (0-8)</td>
</tr>
<tr>
<td>SDHD N=19</td>
<td>5 (26.3%)</td>
<td>1.58 (0-4)</td>
</tr>
<tr>
<td>SDHC N=3</td>
<td>2 (66.7%)</td>
<td>0.3</td>
</tr>
<tr>
<td>VHL N=3</td>
<td>0 (0%)</td>
<td>7 (6-8)</td>
</tr>
</tbody>
</table>

*The one patient with maternally imprinted SDHD mutation was excluded from this analysis.

The average length of follow up was 47.8 months. 21 related tumours were found in patients after their initial diagnosis of a genetic mutation. Of these 16 (76.2%) were screen detected. 12 patients reviewed did not undergoing screening. In the 55 patients undergoing screening at PMCC there were 18 false positives episodes. 2 led to invasive tests.

**Conclusion**

As compared with previously published data on SDH mutations we had similar findings in regards to clinical outcomes. SDHD carriers had a highly penetrant syndrome mostly made up of head and neck tumours and no metastatic disease. SDHB carriers demonstrated less penetrance but an increased rate of other tumours such as RCC and GIST as well as metastatic disease.

**References**


REVIEW OF FAMILIES WITH VON HIPPEL-LINDAU SYNDROME AT THE FAMILIAL CANCER CENTRE, FOCUSING ON SURVEILLANCE AND CANCER DIAGNOSES.

Bich-Thu Duong¹*, Emily Higgs¹*, Adrienne Sexton¹*, Ingrid Winship¹, ²

*Joint first authors

¹Familial Cancer Centre, Royal Melbourne Hospital
²Office for Research, Royal Melbourne Hospital

Background:
Von Hippel-Lindau syndrome (VHL) is an autosomal dominant condition caused by mutations in the VHL gene and is characterised by an increased risk of benign and malignant tumours, such as haemangioma, phaeochromocytoma and renal cancer. Management includes early detection of tumours to decrease morbidity and mortality, and national surveillance guidelines are continually updated. This project investigates whether surveillance advice provided by the Royal Melbourne Hospital Familial Cancer Centre (RMH FCC) is up-to-date, and evaluates patient compliance with recommendations. This project also assesses the phenotypic features of VHL in this cohort.

Method:
The RMH FCC database was used to identify patients with germline VHL mutations, whose genetics files were reviewed by investigators. Correspondence, reports and file notes relating to risk management and phenotypic features were recorded for each individual. Data was discussed collaboratively by the investigative team.

Results:
18 patients with a germline VHL mutation were identified from 8 families. The most common phenotypic features of VHL were brain/spine haemangioblastoma (5/18) and renal/pancreatic cysts (5/18). Only two individuals had phaeochromocytoma and only two had renal cancer. Surveillance brain/spine MRI, renal ultrasound, ophthalmology and catecholamine assessment were recommended to 78%, 78%, 89% and 50% of patients respectively. Only 39% were advised abdominal MRI surveillance.

Conclusions and outcomes:
There were deviations from the current Australian guidelines in regard to both advice given by RMH FCC and recorded patient compliance. This may reflect changes to the Australian guidelines since the time of diagnosis, as patients in this cohort received diagnoses from 2005 onwards. Also, the FCC likely has not been informed of all ongoing investigations. The low proportion of patients having abdominal MRI may be secondary to the out-of-pocket costs as it is not Medicare subsidised.

Interestingly, the low rate of renal cancer in this small cohort (2/18) is in contrast to the risk estimates for renal carcinoma of up to 80% with an average onset of 40 years.

This audit has demonstrated that not all VHL patients of the RMH FCC are having up-to-date surveillance. This situation may be similar at other Australian FCCs and lack of surveillance, ultimately, has clinical implications. This audit has prompted follow-up phone calls to patients, updating the periodical ‘gene carrier review’ questionnaire, and sending letters to patients’ GPs with current recommendations. The findings of this audit highlight the challenges in follow-up of these patients and warrant development of a VHL-specific clinic at RMH.
Development of an intervention for communicating personal genetic risk of melanoma to the general public
Reanu Gopal\(^1\), Gabrielle Williams\(^2\), Louise A Keogh\(^3\), Ainsley Newson\(^4\), Phyllis Butow\(^5\), Anne E. Cust\(^1\)

1. Cancer Epidemiology and Services Research, Sydney School of Public Health, University of Sydney, NSW
2. Sydney School of Public Health, University of Sydney, and the Centre for Genetics Education, NSW
3. Gender and Women's Health / Academic Centre for Health Equity, Melbourne School of Population and Global Health, The University of Melbourne
4. Centre for Values, Ethics and the Law in Medicine, Sydney School of Public Health, University of Sydney, NSW
5. Centre for Medical Psychology & Evidence-based Decision-making (CeMPED), University of Sydney, NSW

Background: Melanoma is the most serious type of skin cancer. There are approximately 12,500 new diagnoses and 1,500 deaths in Australia each year. To date, prevention remains the most promising strategy for reducing its incidence and mortality. Advances in genetic technologies now make it feasible to use genomic information for risk stratification and cancer prevention interventions in the general population. Accordingly, it is important to identify the most effective methods of genetic risk communication in a general public setting. This study aims to develop an intervention that provides information on personal genetic risk of melanoma to participants from the general public, including risk presentation and communication materials and a telephone-base genetic counselling manual.

Methods: We will conduct a qualitative study using focus groups. Participants will be recruited through the Cancer Council NSW 'Join a research study' initiative for people ages 18-74 years, of European ancestry, who have never had melanoma. Four focus group sessions will be conducted around Sydney, with a maximum of 10-12 individuals recruited in each group. Each session will be split into 2 parts: the first part will explore current understanding of melanoma genetic risk and preferences for different risk presentation formats. We will also discuss the potential impact of receiving genetic risk information and the associated ethical, social and psychological issues. The second part of the session will explore how a genetic counsellor could aid with the communication process. This part of the session will be used to directly feed into the development of a genetic counselling manual, which could potentially be used in clinical practice. In addition to these focus groups, the intervention will be guided by a review of the literature regarding risk communication strategies and relevant ethical, social and psychological issues, as well as discussion and feedback from health professionals working in clinical genetics and genetic counselling.

Discussion: This qualitative study is part of a planned randomised controlled trial that is looking to evaluate whether or not giving personalized information on genetic risk of melanoma to members of the general public will influence skin cancer prevention behaviours. We are conducting a pilot over the next year, funded by Sydney Catalyst Translational Cancer Research Centre.
AN AUDIT OF THE IMPACT OF THE "JOLIE EFFECT" ON REFERRALS TO THE FAMILIAL CANCER PROGRAM AT GENETIC SERVICES OF WA

Rebecca Freedman ¹, Lyn Schofield ¹, Dian Karina ¹ and Helen Mountain¹

¹ Familial Cancer Program, Genetic Services of Western Australia, King Edward Memorial Hospital, Bagot Rd, Subiaco WA 6008

Influential celebritites and global media can have an unprecedented effect on the number of referrals to a publicly funded clinical service, particularly when the focus is a common condition such as breast or ovarian cancer. Details of Angelina Jolie's family history of breast cancer and genetic test results were published in the New York Times on May 14th 2013. Following this well-intended yet emotive publication and the subsequent media coverage it sparked, referrals and phone enquiries to the Familial Cancer Program (FCP) at Genetic Services of Western Australia (GSWA) were three times more than in the same period the previous year. While many enquiries were from the "worried well" or from those seeking testing where it was not warranted, some were appropriate contacts or referrals. Many clients who had previously contacted the FCP but declined family history assessment or genetic testing contacted our service again to re-activate these processes. This sudden spike in referrals resulted in staff resources being exceedingly stretched.

This paper aims to demonstrate how the impact of celebrity influenced the number of referrals and the number individuals seeking advice on breast cancer and genetic testing, and how this in turn influenced workload and practices at GSWA. A clinical audit was set up to determine the number of referrals received by the FCP in the period and the months that followed Angelina Jolie’s announcement. These numbers were compared with the number of referrals received during the same time in the previous year. New strategies were quickly devised to cope with the influx of enquiries without the benefit of additional resources. We describe the measures taken to cope with a work-load that tripled within a short period of time.

While an increased awareness of risk assessment and genetic testing for familial breast cancer may be a positive outcome of the Jolie phenomenon, it is clear that some pre-referral risk assessment by referring doctors is needed to enhance appropriateness of the referral. In addition, continued education of the public and health care professionals regarding familial cancer risk, the criteria used to determine eligibility for genetic testing, and availability and costs associated with private genetic testing would be beneficial.
Familial aspects of cancer: Research and practice, 12-15 August 2014, Kingscliff, NSW

Recommendations for the management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation

Authors: Judy Kirk¹, Anne Nelson², Tamar Dalton², Fleur Webster², Helen Zorbas²
¹Familial Cancer Service, Westmead Hospital, Westmead, NSW
²Cancer Australia, Surry Hills, Sydney, NSW

Objectives
Ensuring currency of cancer clinical practice guidelines is essential for making timely, evidence-based information available to health professionals. With input from key stakeholders across Australia, the management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation was identified as a priority area requiring clinical guidance.

Methods
A multidisciplinary working group was formed to develop the evidence-based clinical practice guideline. The guideline was based on a systematic review of the evidence covering research questions on surgical management, adjuvant and neoadjuvant systemic therapies and surgical risk reducing strategies. The systematic search was limited to women with a germline BRCA1 or BRCA2 mutation and a diagnosis of non-metastatic early breast cancer.

Results
A systematic review informed the development of recommendations and practice points to guide clinical management. Most of the included studies were observational studies, including prospective and retrospective cohort studies and case-control studies.

The guideline recommends that women diagnosed with breast cancer with a BRCA 1/2 mutation are offered a choice of either breast conserving treatment or mastectomy as both are effective in terms of survival. Clinicians should discuss contralateral risk-reducing mastectomy with these women to substantially decrease the risk of contralateral breast cancer. Clinicians should also discuss risk-reducing salpingo-oophorectomy with these women to improve overall survival and substantially decrease the risk of ovarian/fallopian tube cancer. The use and type of neoadjuvant/adjuvant chemotherapy should be based on similar considerations for women with breast cancer and no BRCA1/2 mutation.

Conclusions
Cancer genetics is a rapidly emerging area and the guideline provides updated clinical guidance to assist health professionals with treatment recommendations for this unique group of women.
Risk management of breast and ovarian cancers in Malaysian BRCA carriers attending Risk Management Clinic at University Malaya Medical Centre.

S Hamizah¹, SY Yoon², YL Woo³, Tan GH¹, R Kartini⁴, MK Thong⁵, SH Teo², NA Taib¹
¹Department of Surgery, University Malaya Medical Centre, Malaysia, ²Cancer Research Initiatives Foundation, Malaysia, ³Department of Obstetrics and Gynaecology, University Malaya Medical Centre, Malaysia, ⁴Department of Biomedical Imaging, University Malaya Medical Centre, Malaysia, ⁵Department of Pediatrics, University Malaya Medical Centre, Malaysia. Email: naisha@um.edu.my

Objective
This study aims to describe the uptake of risk reducing strategies (RRS) in Malaysian BRCA carriers who attending Risk Management Clinic (RMC) at University Malaya Medical Centre (UMMMC).

Methods
Between Jan 2003 and Sept 2013, a total number of 693 breast cancer patients were tested for a deleterious mutation in BRCA1 and BRCA2 as part of the Malaysian Breast Cancer Genetic Study [MyBrCa]. All carriers are followed up and data documenting status of genetic test result disclosure, acceptance of genetics counseling and follow up with RMC and the uptake of RRS were collected prospectively.

Results
91 patients were found to be BRCA carriers. 24 had passed away, and 67 were then followed up. Of these patients, 26 (38.8%) refused result disclosure while 41 (61.2%) chose to know their test results, one of them was a male carrier. 33 (80.5%) who knew their carrier status had agreed to attend RMC to discuss on cancer risk management. Five of them had bilateral breast cancer and underwent either bilateral mastectomy or breast conserving surgery. Hence, 28 with unilateral breast cancer history are eligible to opt for RRS for breast cancer. 6 (21.4%) chose to have risk reducing mastectomy (RRM). Two had RRM based on family history before known BRCA status. The other four had the procedure at a median of 8 months (range 3 to 32 months) after the first result disclosure. They were at a median age of 49 (range 33 to 63) when they underwent RRM. The rest (75%) opted for breast surveillance via MRI, mammogram and breast ultrasound at regular intervals. Two opted for chemoprevention using tamoxifen. Only one not had any RRS for breast cancer as she defaulted follow-up. 27 carriers did not have an ovarian cancer history. Only 22 carriers did not have previous ovarian surgery, of these 12 (54.5%) chose to have risk reducing bilateral salpingo-oophorectomy (RRBSO). Those who chose RRBSO had the procedure at a median of 11 months (range 1 to 41 months) after result disclosure. They were at a median age of 48 (range 34 to 67) when they underwent RRBSO. The 7 (31.8%) that did not undergo RRBSO opted to continue ovarian screening via annual monitoring of CA125 and trans-vaginal scan (TVS). 3 (13.6%) were not recommended for RRS for ovarian cancer as two had recurrent breast cancer and one had defaulted follow-up.

Conclusions
Different trends were seen on the uptake RRS for breast and ovarian cancers. There was a low pick up rate of contralateral RRM as compared to RRBSO. These finding should direct future research on the exploration on preference of RRS uptake in BRCA carriers.
A Review of Treatment-Focused Genetic Assessment at the time of breast cancer diagnosis by the Familial Cancer Clinic of the Peter Mac Callum Cancer Centre

Blake, M, Shanley S, Forrest L, Young, MA, James P and Mitchell, G.
Jack Brockhoff Familial Cancer Clinic, Peter MacCallum Cancer Centre, Melbourne

Introduction  Approximately 15,000 Australian women are diagnosed with breast cancer each year. Knowledge of future cancer risk including BRCA1/2 mutation status can influence a women’s cancer treatment decision.

Aims  To describe the characteristics of a cohort of women with breast cancer who were referred to the Peter Mac Callum Familial Cancer Clinic (FCC), for the purposes of a treatment-focused genetic assessment (TFGA), and to identify predictors of choice of bilateral mastectomy versus other surgical options.

Methods  Women referred between January 2011 – December 2013 < 1 year after their breast cancer diagnosis were eligible. Exclusion criteria included those who had had prior bilateral mastectomy. Paper and electronic medical records were reviewed for age at presentation, tumour pathology, type of operation and genetic test results. Parameters were compared in the two groups (those choosing bilateral mastectomy versus those choosing other procedures) using t-tests and Chi squared tests.

Results  38/144 (26%) of women underwent bilateral mastectomies (BM). They were significantly younger and more likely to be BRCA mutation carriers than those who chose other procedures (p=0.02 in each comparison). Three of 12 BRCA mutation carriers (aged 27-46) did not choose bilateral mastectomy. 22% of women, in whom no BRCA mutation was found, chose to have BM.

Discussion  Our findings are consistent with existing literature. The fact that only 26% overall chose BM is reassuring, given concerns expressed in the literature about rising rates of bilateral mastectomy in the early breast cancer population. In addition to genetic status, other factors impact on choices as some mutation carriers chose not to have BM and some women without mutations chose to have this surgery.

Conclusion  Other motivators for BM need to be studied to inform future TFGA practice. We are continuing the analysis of potential influences (using postal questionnaires) and family history factors (using measures of strength of family history).

Post Gasterectomy Follow-up Program for CDHI Mutation Carriers

Mary Shanahan, Lucinda Hossack, Gillian Mitchell, Alex Boussioutas
Peter MacCallum Cancer Centre, Melbourne, Australia

Background
Individuals carrying an E-Cadherin (CDH1) gene mutation have almost 100% risk of developing diffuse gastric cancer over the course of their lifetime. As there is no reliably effective screening test prophylactic total gastrectomy is recommended as the most effective means of managing the gastric cancer risk in these individuals. However, while gastrectomy is an effective life-saving option for individuals at risk it is not without significant morbidity which can last a lifetime. Due to workload, when patients have recovered from the effects of surgery they tend to be discharged from routine follow up by the surgical unit with a future management plan to be implemented through their family doctor.

Aim
There are few publications investigating the outcome of prophylactic gastrectomy in a systematic, prospective, manner that can guide the long term follow-up of individuals who have had a total gastrectomy. In 2012 the GI risk management clinic at the Familial Cancer Centre of the Peter Mac commenced a long term follow-up program for individuals who had undergone a total gastrectomy. The aim of the program was to monitor for evidence of anaemia, vitamin and other micronutrient deficiencies, dumping syndrome as well as more general effects of gastrectomy on life experiences and fertility and child-bearing.

Methods
A retrospective review was undertaken of the case-notes of all patients who attended the follow-up program with particular focus on blood test results (anaemia and micronutrients), dumping syndrome, weight and general wellbeing and life events. Female patients were asked about return of menstruation and fertility/childbearing.

Results
11 patients are participating in the follow-up program. The most common problems relate to ongoing dumping syndrome and iron and B12 deficiency. Two children have been born to women post-gastrectomy. Detailed results will be presented.

Conclusion
The results indicate that there are ongoing health effects after gastrectomy despite patients being given clear education regarding prevention/minimisation of these effects both before and after the surgery to the patient and their family doctor. Our experience indicates an essential need to provide patients and their family doctors with ongoing support to life post gastrectomy. The early results from our follow-up program can be used to inform the form and content future follow-up for this group of patients.
CASE STUDY OF A LONG STANDING SUPPORT GROUP FOR JEWISH BRCA MUTATION CARRIERS

L Andrews¹, S Bawden², R Williams¹, K Barlow-Stewart², J Fleming².

¹Hereditary Cancer Clinic, Prince of Wales Hospital, Sydney; ²Sydney Medical School, University of Sydney, Sydney NSW, Australia

Peer support groups for individuals at high genetic risk have had limited success in comparison with support groups for other conditions. A recent Cochrane review of familial breast cancer highlighted the need for examination of services available for such women. As members of the Ashkenazi Jewish population are at an increased risk of carrying such mutations; Jewish women identified as carrying a breast cancer gene (BRCA) mutation were invited to participate in an education and support program in 2006. Seven participants have maintained the support group and continue to communicate electronically and meet regularly. This project explores the experience of peer support with the group members and their views and attitudes. Important concepts under consideration will be why the group has lasted for such a long time, the impact of shared ethnicity, what role the members felt the support group has played in their dealing with their mutation status and how it has influenced their decision making. From this we aim to identify factors that have contributed to the longevity and perceived success of this particular group, as well as the disadvantages, in order to guide the establishment of future support groups.

From the preliminary data, the themes identified include the importance of anonymity within the wider Jewish community, the organic nature of the group, from its initiation through to its informal format, and the bonding that has occurred within the group, developed through the shared journey of the participants and their non-judgmental approach to each other.

It is proposed that hypotheses will be developed as to why this group has been successful and how this success can be replicated in other support groups. The results will be used as a basis for further care and research, specifically in the development and evaluation of a future support group, to be formed in 2015.
Predictive TP53 testing in Adolescence and Young Adults

Alexandra Lewis¹, Kate Thompson², Lucy Holland², Mary-Anne Young ¹
¹Peter MacCallum Familial Cancer Centre, Melbourne, Australia
²ONTrac at Peter Mac, Victorian Adolescent and Young Adult Cancer Service, Melbourne, Australia

The growing awareness of the contribution of genetics in cancer and genetic testing has resulted in increasing numbers of young people (16-27) at risk of Li Fraumeni syndrome (LFS) presenting to the Peter MacCallum Familial Cancer Centre for predictive testing.

The unique needs of young people in combination with the complex and unpredictable nature of cancers associated with LFS has led to a considered method of genetic counselling practice being employed when supporting these young people and their parents through predictive testing.

The methodology adopted by genetic counsellors at the Peter MacCallum Familial Cancer Centre incorporates many of the recommendations made in a locally developed model for the provision of genetic counselling to young people. This yet to be published model, was developed by a group of Melbourne based genetic health experts and adolescent health experts in response to the growing number of young people seeking advice from Familial Cancer Centres. It aims to counter the apprehension had by many genetic health professionals in working with young people by providing practical evidence based strategies.¹

The strategies employed aimed to engage and empower the young person throughout the process and included mandating direct contact with the consultand prior to the consultation. Ensuring one on one time was had for a period of the consultation to allow for unrestricted discussion and overt discussion with the young person about the level of involvement of their parents.

Ten consultations with young people requesting LFS predictive testing utilising this methodology were reviewed and will be discussed.

¹Duncan RE, Young MA. Tricky teens: are they really tricky or do genetic health professionals simply require more training in adolescent health? J.Pers.Med. 2013.10(6),589-600
Comparison of Renal Cell Carcinoma histopathology in Study Respondents and Non-respondents.

Walsh J1, Bruinsma FJ1, Tucker K2, Dudding T3, Jenkins M4, Winship I5, Jordan S6, Severi G7

Affiliations: 1Cancer Council Victoria, 2Prince of Wales Hospital, 3Hunter Genetics, 4Royal Melbourne Hospital, 5The University of Melbourne, 6QIMR Berghofer Medical Research Institute, 7Human Genetics Foundation

The CONFIRM Study (CONsortium For the Investigation of Renal Malignancies) requires participants to consent to the Victorian Cancer Registry providing their contact details to the research team. The objective of this analysis is to compare the demographic and histopathological characteristics of participants who went on to complete participation (n=582) to those who refused participation (n=128) or did not respond to correspondence from the study team or ‘passive refusals’ (n=90).

The VCR identified eligible individuals based on the study inclusion criteria:

- Histologically confirmed renal cell carcinoma diagnosis within last 12 months
- Aged between 18 and 75 years at diagnosis
- Tumour size ≥ 2 cm
- Ability to complete questionnaires in English

The VCR informed individuals of their eligibility for the CONFIRM Study and provided a name-release consent form permitting the VCR to forward their contact details to the CONFIRM team. The study team then provided more detailed information regarding study participation (which included completion of four questionnaires, supplying a 27ml blood sample and undertaking skin measurements).

Of those who agreed to participate, 64% (n=370) were male and 36% (n=212) female. The average age at diagnosis was 59 years. Of the RCC subtypes, 75% (n=436) were clear cell, 12% (n=67) were papillary and 8.9% (n=52) were chromophobe. The sample comprised of 98% (n=570) singular and 2% (n=12) multifocal tumours.

Of the refusals 67% were male (n=86) and 33% were female (n=42). The average age at diagnosis was 51 years. Amongst the subtypes, 78% (n=100) were clear cell, 12% (n=16) were papillary, 5.4% (n=7) were chromophobe RCCs. The sample comprised of 95% (n=122) singular and 5% (n=6) multifocal tumours.

Of the non-respondents, 66% (n=59) were male and 34% (n=31) were female. The average age at diagnosis was 54 years. Of the subtypes, 83% (n=75) were clear cell, 6% (n=5) papillary and 6% (n=5) chromophobe. There were 98% (n=88) singular and 2% (n=2) multifocal tumours in this sample.

Examining the characteristics of individuals who refuse research participation can help us understand why otherwise eligible people choose not to participate. We found the histopathological characteristics of respondents and non-respondents were similar. The main difference between the groups is the age of diagnosis. The lower age at diagnosis among non-participants could be a reflection of their employment status and a lack of time to commit to study participation. There did not appear to be differences between individuals who ‘actively’ or ‘passively’ refused.
Comparison of Renal Cell Carcinoma histopathology in a population and clinic-based sample.

Walsh J¹, Bruinsma FJ¹, Tucker K², Dudding T³, Jenkins M⁴, Winship I⁵, Jordan S⁶, Severi G⁷

Affiliations: ¹Cancer Council Victoria, ²Prince of Wales Hospital, ³Hunter Genetics, ⁴Royal Melbourne Hospital, ⁵The University of Melbourne, ⁶QIMR Berghofer Medical Research Institute, ⁷Human Genetics Foundation

The CONFIRM Study (CONsortium For the Investigation of Renal Malignancies) aims to investigate the genetic basis of Renal Cell Carcinoma (RCC) and identify new environmental, lifestyle and occupational risk factors. The aim of this analysis was to compare the histopathology and demographic characteristics of participants recruited through Australian familial cancer centres (FCC) to the population-based sample recruited through Cancer Registries.

Individuals diagnosed with RCC are recruited via the Victorian and Queensland Cancer Registries. Participants diagnosed with RCC or that have a confirmed or suspected inherited syndrome associated with an increased risk of RCC are recruited from FCCs. Their demographic characteristics and diagnostic histopathology reports are collected and coded.

The histopathology of 1036 population-based participants were examined. Of the 114 clinic participants, 47 had a confirmed cancer diagnosis with 18 awaiting confirmation.

The population-based sample consists of 64.4% males (n=667) and 35.6% females (n=369) with an average diagnosis age of 59.6 years. Of their cancers, 76.7% were clear cell (n=794), 10.9% papillary (n=113), 8.8% (n=91) chromophobe and 0.10% (n=1) of the collecting duct. There were 996 singular (97.6%), 23 multifocal (2.3%) and 3 bilateral tumours (0.1%). Of the sample, 63.2% (n=636) were in the TNM Stage 1, 8.2% (n=83) in Stage 2, 27% (n=272) in Stage 3 and 1.6% (n=16) in Stage 4.

The clinic-based sample to date consists of 55.3% (n=26) males and 44.7% (n=21) females with an average diagnosis age of 51.1 years. There were 68.1% (n=32), clear cell, 14.9% (n=7) papillary and 14.9% (n=7) chromophobe subtypes. There were 40 (85.1%) singular and 7 (14.9%) multifocal tumours. Of the sample, 69% (n=31) were in the TNM Stage 1, 20% (n=9) in Stage 2 and 11% (n=5) in Stage 3.

The incidence of RCC in men is reported as double that of women, which is consistent with our population-based findings. However, in the clinic-based sample the proportion of males to females decreases. The distribution of histopathological subtypes reported in the literature is consistent with our population-based sample, although the proportion of chromophobe RCCs in this study is slightly higher. Papillary and chromophobe RCC’s are associated with inherited cancer syndromes, possibly explaining their higher representation in the clinic-based sample. The proportion of multi-focal tumours is also higher in the clinic-based sample, however it is still lower than those reported in the literature.
Five Case Studies of Atypical Teratoid Rhabdoid Tumours and Investigations of SMARCB1 Germline Mutations

Meera Warby*, Jessica Duffy*, Dr Kathy Tucker*

*Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, New South Wales, 2031, Australia

**Introduction:** Germline mutations of the tumour suppressor gene, SMARCB1, predispose to atypical teratoid rhabdoid tumour (ATRT) and schwannomatosis. Rhabdoid tumours are rare and aggressive paediatric cancers characterized by loss of function in SMARCB1. Despite the rarity of rhabdoid tumours, five cases were seen within a year period and investigated by the Prince of Wales Hospital Hereditary Cancer Clinic. The following case examples provide insight into the difficulty of assessing children with often-fatal tumours and the various counselling issues that have arisen.

**Case descriptions**

**Case1:** AM, 2yo girl diagnosed with ATRT with no family history. AM’s mother was currently 16 weeks pregnant and was interested in SMARCB1 germline testing for postnatal testing. A germline SMARCB1 mutation was identified in AM. Although testing in the parents was discussed, it was decided jointly to be inappropriate at present. A management plan for a positive result was formulated, however fortunately, AM’s second child was negative.

**Case 2:** OE, 5 month old girl with an ATRT and was the first child to otherwise healthy parents. Parents had conflicting views towards genetic testing and predictive testing if OE was positive. Germline testing of OE did not reveal a mutation in SMARCB1.

**Case3:** RO, 16-month-old girl, diagnosed with ATRT seen in the ward with her parents. RO was the first child born to otherwise healthy parents. Limited tumour sample was available for testing due to position and size of tumour. No germline mutation identified in RO.

**Case 4:** HL, diagnosed with a CNS rhabdoid tumour age 2 years seen at follow up 12 months later. SMARCB1 testing discussed with the parents and consent obtained. Subsequently, no germline mutation was identified.

**Case 5:** AB, while doing predictive testing for APC testing it was noted that AB’s sibling had died of bilateral renal rhabdoid tumours at 6 months indicating a likely germline SMARCB1 mutation1. Tumour testing showed mutations in both alleles of SMARCB1. Discussed with parents the possibility of testing other sibling. All bilateral disease to date has been due to a germline mutation.

**Discussion**

These cases outline and discuss:

- The challenges met when counselling parents in a palliative care setting
- Ideal protocol when testing for SMARCB1 gene faults and the difficulties in achieving this
- Exploring parents often differing attitudes towards genetic testing in an acute setting
- Implications for future pregnancies and other siblings
- Counselling families when penetrance data ambiguous

Study on the penetrance of FLCN mutations in the Birt-Hogg-Dube’ (BHD) syndrome

Winship I\(^1\), Bondavalli D\(^2\), Walsh J\(^2\), Bruisma F\(^2\), Maher E\(^3\), Severi G\(^4\) and members of I-CONFIRM

Affiliation: \(^1\)Royal Melbourne Hospital, \(^2\)Cancer Council Victoria, \(^3\)University of Cambridge, \(^4\)Human Genetics Foundation

I-CONFIRM (International CONsortium For the Investigation of Renal Malignancies) is a consortium of researchers and clinicians interested in inherited renal malignancies. The aim is to investigate questions that are only possible through the pooling of resources and data.

The aim of this retrospective study is to collect additional information and verify information of patients (published in the medical literature and/or from medical records of patients seen by researchers involved in the I-CONFIRM project) with a molecularly detected mutation in the \(FLCN\) gene (known to cause the BHD syndrome). Data about the incidence of typical (cutaneous, pulmonary and renal) BHD lesions and the age when they occurred will allow better definition of the true penetrance of \(FLCN\) mutations (as a whole) and to estimate lifetime penetrance of each typical BHD lesion. Information on atypical signs (i.e. colonic polyps), will be collected in order to investigate if they co-occurred or are potential syndromic features of BHD.

A comprehensive literature search was undertaken for papers reporting BHD case reports/series. Papers published in languages other than English, French, Italian or Spanish or without germline pathogenic \(FLCN\) mutations or \(FLCN\) deletion/duplication were excluded.

Data on 1198 individuals from 361 different families, from 98 papers, were collected and analyzed. Authors of these 98 articles have been invited to verify the data abstracted from the published paper, to provide missing or additional data and to share previously unpublished families.

Preliminary analysis of the abstracted data found that 18% of individuals with a pathogenic mutation in \(FLCN\) developed RCC (usually chromophobe but also clear cell and hybrid RCC), while none of the individuals without the known \(FLCN\) familial mutation did.

About 64% of individuals with a pathogenic mutation in \(FLCN\) developed lung disease. Lung cysts, pneumothorax and lung cysts combined with pneumothorax were almost equally represented. Only one individual without the known \(FLCN\) familial mutation developed a pneumothorax.

Skin lesions were reported in 43% of individuals with a pathogenic mutation in \(FLCN\) while all individuals without the known \(FLCN\) familial mutation were skin disease free.

Data on the incidence of colonic polyps in the general population is not available; instead the prevalence of colorectal cancer in patients with a \(FLCN\) mutation was examined. Based on a small number of cases, the findings suggest an increased risk of colorectal cancer. This requires further investigation and replication when the verified data is available and segregation analysis conducted.
Population-based screening for Lynch Syndrome in Western Australia 2012-2013

Lyn Schofield\textsuperscript{1} and Cathy Kiraly-Borri\textsuperscript{1}

\textsuperscript{1} Genetic Services of Western Australia, King Edward Memorial Hospital, WA Australia

We showed earlier that routine screening for microsatellite instability (MSI) and loss of mismatch repair (MMR) protein expression in colorectal cancer (CRC) led to the identification of previously unrecognized cases of Lynch syndrome (LS). This led in 2008 to the implementation of routine laboratory-based screening for all younger (<60 years) CRC patients, regardless of a family history of cancer.

Four years of experience with routine screening (Jan 2009 to December 2012) has demonstrated that new cases of LS are being identified, confirming that the strategy of screening all young CRC cases aged <60 years is effective in identifying Lynch-related cases. However we currently only identify two-thirds of the expected annual LS cases. A number of factors account for this. Older patients would not be detected using an age threshold of < 60 years for screening. Secondly we cannot be certain that all pathology service providers have carried out IHC testing on all appropriate cases. Third, there are currently no local quality control procedures in place to ensure the accuracy of IHC testing. Fourth, a small number of red flag cases are not referred by their clinician to GSWA, some were referred but did not attend, some died prior to attending and other attended but did not give consent for germline testing.

We report on our experience in following up Western Australian patients screened for MSI or IHC abnormalities in 2012 and 2013 and, based on our experience so far, make further recommendations to ensure that screening of all Lynch-like tumours, including those identified pre-surgery becomes a routine part of management.
Immunohistochemistry for Lynch syndrome – is it being done?


* Joint First Authors
1. Clinical Genetics, Austin Health 2. Familial Cancer Centre, The Royal Melbourne Hospital 3. Department of Pathology, Austin Health 4. Department of Pathology, The Royal Melbourne Hospital 5. Department of Colorectal Medicine & Genetics, The Royal Melbourne Hospital

Introduction
In May 2007, the Victorian Cancer Oncology Hereditary Bowel Cancer Group (VCOG HBCG) released a position statement in regards to the identification of Lynch syndrome by immunohistochemistry (IHC) testing. The VCOG HBCG recommendation was to test all colorectal cancers in patients under 50 years of age by IHC for mismatch repair (MMR) proteins MLH1, MSH2, MSH6, and PMS2 as part of the routine pathological assessment of cancers presenting in these patients, without direct consent. This recommendation was widely circulated to the clinical community from 2007.

In 2011, an audit to ascertain the frequency of IHC being performed for consecutive patients diagnosed with colorectal cancer (CRC) under 50 years of age, by the Pathology Departments of Austin Health and Melbourne Health, was performed. The audit was conducted for the period since the introduction of the position statement in 2007 up to February 2011. This audit demonstrated that the frequency of IHC being performed in individuals diagnosed with CRC under the age of 50 had increased over time at both sites but was not 100%. All patients at The Royal Melbourne Hospital with absent staining for any of the four proteins were referred to the Family Cancer Centre, however this was not the case for all patients with abnormal staining at Austin Health.

Audit aims
This audit aims to identify whether there has been an increase in the frequency of IHC being performed for patients diagnosed with colorectal cancer diagnosed under the age of 50 at Austin Health and Melbourne Health. The audit also aims to identify whether the number of patients demonstrating absent staining being referred to a Familial Cancer Clinic has increased.

Methods
Lists of patients with colorectal cancer diagnosed under 50 years of age from February 2011 until June 2014 will be extracted from each hospital database. Pathology reports for all patients will be checked to assess whether IHC was performed. For those patients with absent staining, the records of the Victorian Familial Cancer Centres will be checked to ascertain whether the patient was referred.

Conclusion:
Identifying colorectal cancer caused by germline mutations in the MMR genes facilitates evidence based surveillance programmes. Similarities and differences between hospitals in the uptake of the recommendation to implement routine IHC for this subset of patients will be analysed, and barriers and enablers identified for initiating routine IHC testing at the hospitals will be explored.
Germline whole exome sequencing (WES) in patients with a suspected genetic predisposition to colorectal cancer (CRC) or colonic polyposis

Mei Sim Lung¹, Lara Lipton⁴, Robyn Ward², Nicholas Pachter³, Marion Harris⁵, Finlay Macrae⁶, Sally Hunter¹, Maria Doyle¹, Paul James¹, Martin Delatycki⁷, Ian Campbell¹, Alison Trainer¹,⁶

¹Peter MacCallum Cancer Centre ²Royal North Shore Hospital ³King Edward Memorial Hospital ⁴Cabrini Hospital ⁵Monash Medical Centre ⁶Royal Melbourne Hospital ⁷Austin Health

Introduction: Australia and New Zealand have the highest rate of colorectal cancer (CRC) incidence in the world. Colorectal cancer that occurs in multiple individuals in a family, or that occurs at a young age (<40 years old), may be due to an inherited predisposing genetic mutation. While some of these cases are due to mutations in known CRC-predisposing genes, a significant proportion of cases do not have mutations in these genes.

Methods: Patients with CRC or colonic polyps were recruited from collaborating Familial Cancer Centres across Australia. Recruitment criteria focused on 2 groups of patients: 1) patients who develop CRC or colonic polyps before 40 years of age, regardless of family history, and 2) affected patients with a family history of CRC or colonic polyps, prioritising those in which the proband had CRC or polyps before 50 years of age. Whole exome sequencing (WES) was performed on DNA from peripheral blood leucocytes. In the first instance, potential pathogenic mutations are looked for in genes known to be associated with an increased CRC risk (APC, MLH1, MSH2, MSH6, PMS2, MUTYH, SMAD4, BMPR1A, STK11, POLE, POLD1, EPCAM, GREM1, TP53, PTEN, CDH1, BUB, BUB1b, CHEK2). In families where no mutations in known CRC predisposition genes are identified, other genes with protein-truncating variants are investigated as potential candidates.

Results: To date 21 patients have had WES of germline DNA performed. A truncating APC mutation c.4545delT, was found in a 44 year old individual with colonic polyps. The patient’s mother died of CRC at age 44. This patient had previously had protein truncation testing (PTT) of the APC gene which did not detect a mutation. None of the remaining 20 patients had any evidence of pathogenic mutations in known CRC predisposition genes. Analysis of novel variants in novel genes is ongoing. The median number of protein-truncating variants per individual was 57. 566 genes had at least one protein-truncating variant. 215 genes had a protein-truncating variant in more than one individual. The updated results of the analysis will be presented at the meeting.

Discussion: Whole exome sequencing of germline DNA can identify causative mutations in known or novel CRC-predisposing genes that have been missed on clinical testing. Patients with a suggestive clinical phenotype for a particular gene mutation, who were tested using older diagnostic methods, may benefit from re-testing with more comprehensive methods such as Sanger sequencing. Identifying such patients from existing clinical databases is important.
Defective MMR is rare in multiple case breast cancer families.

Peter Simpson¹, Mike Walsh², Mark Clendenning³,⁴, Rhiannon Walters³,⁴, Sunil Lakhani¹,⁵,⁶, Margaret Cummings¹,⁶, Dan Buchanan³,⁴ & kConFab Investigators.

¹ The University of Queensland, UQ Centre for Clinical Research, QLD, Australia.
² Sullivan & Nicholaides Pathology, Brisbane, Australia
³ Oncogenomics Group, Genetic Epidemiology Laboratory, Department of Pathology, and ⁴ Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne.
⁵ The University of Queensland School of Medicine, QLD, Australia
⁶ Pathology Queensland, The Royal Brisbane & Women’s Hospital, QLD, Australia

Defective DNA mismatch repair (MMR) is rare in sporadic breast cancer¹, however breast cancers arising in a background of Lynch Syndrome (MMR germline mutation carriers) have defective MMR as evidenced by loss of immunohistochemical detectable expression of MSH2, MSH6, MLH1 and PMS2². The morphological and immunophenotypic characteristics of these breast cancers overlap with those of BRCA1-associated breast cancers, being poorly differentiated, high mitotic count, lymphocytic infiltrate and ER/PgR negative². Based on these observations, the aim of this study was to investigate the frequency of MMR deficiency in multiple case breast cancer families from kConFab.

Immunohistochemistry was performed for MLH1, MSH2, MSH6 and PMS2 on the kConFab tissue microarrays (TMAs) comprising 76 BRCA1, 99 BRCA2 and 298 non-BRCA1/2-associated breast tumours. All cases, except one non-BRCA1/2 breast tumours exhibited normal expression of these proteins inferring the vast majority of tumours are MMR pathway proficient. The one non-BRCA1/2 tumour of interest demonstrated deficiency in MLH1 and PMS2 expression, which was verified by staining whole sections of the relevant tumour block. This tumour was an invasive carcinoma-no special type that was negative for ER, PgR, HER2, CK5/6, CK14 and EGFR (i.e. triple negative and basal marker negative). No evidence for somatic methylation of the MLH1 gene was found in tumour DNA from this case. According to our knowledge of MMR in colorectal and endometrial cancer³, MLH1/PMS2 deficiency and lack of promoter methylation is suggestive of a germline variant affecting the MLH1 gene and so we are currently undertaking germline testing by sequencing and MLPA for large deletions and duplications. Although incomplete, no mutation has yet been identified. If this remains to be the case we will then undertake somatic mutation testing to determine whether MLH1/PMS2 loss is driven by somatic alteration. Exome sequencing data from the TCGA resource for sporadic breast cancers demonstrates that 25/962 (3%) breast tumours harbor one or more somatic mutations (not including copy number alterations) in any of these four MMR genes. Generally mutations were mutually exclusive, although one tumour had a mutation of both MLH1 and MSH6 and one tumour had a mutation in MSH2, MSH6 and PMS2. Tumours with a mutation in any of these four genes have significantly more somatic non-synonymous mutations (median = 138, range 19-4185) than tumours with a BRCA1 or BRCA2 mutation (median = 73, range 6-4185; P=0.0373); a TP53 mutation (median = 43, range 7-4185; P <0.0001) or a PI3KCA mutation (median = 27, range 4-4185; P<0.0001); suggesting that although MMR gene mutations are rare they probably make an important contribution to the mutation landscape of breast cancer.

In summary MMR deficiency is extremely rare in multiple case breast cancer families. We will soon be able to report back regarding whether our index case has a germline or somatic variant in MLH1 or PMS2 that is responsible for the MMR deficiency in this case.

Two families with Lynch syndrome and unusual cancers with absent mismatch repair protein staining

Burgess MJ¹, Cotter MN¹, Williams D², John T¹, Delatycki MB¹

1. Clinical Genetics Service, Austin Health, Victoria
2. Department of Pathology, Austin Health, Victoria

Lynch syndrome (LS) or hereditary non-polyposis colorectal cancer, predisposes to a number of cancers with colorectal and endometrial cancer being the most common. It remains somewhat controversial which other cancers are part of the LS spectrum. We report a family with LS with a MSH2 mutation in which absent MSH2 staining was identified in several sebaceous adenocarcinomas, adrenal cortical and prostate carcinomas. We report another family with a MSH6 mutation where the proband had loss of MSH6 staining in a medullary thyroid carcinoma. These families add further evidence for adrenal cortical and prostate carcinomas being part of the LS spectrum and for the first time, reports medullary thyroid carcinoma with absent mismatch repair protein staining in an individual with LS.
THE AUSTRALIAN FAMILIAL PANCREATIC CANCER COHORT (AFPaCC): AN UPDATE

S. Simpson1, A. Johns1, J. Humphris1, S. Mead1, A. Spigelman2, D. Williams3, A. Stoita3, K. Tucker4, L. Andrews4, J. Kirk5, M. Nikfarjam6, A. Collins7, M. Delatycki8, S. Grimmond9, A. Biankin1,10

1Cancer Research Program, Garvan Institute of Medical Research, The Kinghorn Cancer Centre, Darlinghurst, NSW, Australia
2Familial Cancer Clinic, St Vincent’s Hospital, The Kinghorn Cancer, Darlinghurst, NSW, Australia
3Gastroenterology, St Vincent’s Hospital, Darlinghurst, NSW, Australia
4Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, NSW, Australia
5Familial Cancer Service, Westmead Hospital, Westmead, NSW, Australia
6Department of Surgery, Austin Health, Heidelberg, VIC, Australia
7Bowen Centre, Austin Health, Heidelberg, VIC, Australia
8Clinical Genetics Service, Austin Health, Heidelberg, VIC, Australia
9Queensland Centre for Medical Genomics, Institute for Molecular Biosciences, St Lucia, QLD, Australia
10Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland United Kingdom.

Background: The majority of pancreatic cancer cases are termed sporadic, although it is estimated that 10% are familial. Known genetic conditions account for less than 20% of this familial aggregation. The predisposing genetic basis for most families with familial pancreatic cancer (FPC) is unspecified, and the predicted risks to unaffected family member can be ambiguous1. The Australian Familial Pancreatic Cancer Cohort (AFPaCC) was established in 2011 to help further characterise risks and underlying genetic susceptibility in an Australian population, as well as to identify high-risk individuals eligible for a pancreatic cancer screening trial.

Methods: AFPaCC recruits families with multiple relatives affected or known FPC associated genes, such as BRCA2. Recruitment mainly occurs via online participant enquiries and collaborating family cancer clinics. Eligible individuals provide personal and family history information, which is collated in a central database. Attempts are made to consent other affected and unaffected relatives, confirm pancreatic cancer diagnoses in the family and obtain peripheral blood and archival samples. Unaffected relatives considered to be at a higher risk of developing pancreatic cancer (i.e. > 5% lifetime risk) are also notified of screening trials conducted at St Vincent’s Hospital in Sydney and Austin Health in Melbourne.

Results: As of July 2014, AFPaCC had consented 181 participants representing 112 Australian families. Of these families, 65 (58%) are classified as true FPC with at least one pair of first-degree relatives affected and 16 (14.3%) have inherited cancer syndromes known to be associated with an increased risk of pancreatic cancer (i.e. Hereditary Breast and Ovarian Cancer Syndrome, Peutz-Jeghers Syndrome and Familial Atypical Multiple Mole Melanoma). The pancreatic cancer diagnosis has been verified in at least one relative in 48 (42.9%) families, and biospecimens for affected relatives sourced in 32 (28.6%) families. 72 high-risk individuals registered with AFPaCC have commenced pancreatic cancer screening trials. One prospective pancreatic cancer has been confirmed in an AFPaCC family in a high-risk relative who declined participating in the registry and screening trial.

Conclusion: AFPaCC recruitment is progressing well, however confirmation of pancreatic cancer diagnoses and sample acquisition are proving to be rate-limiting steps. These issues are not unique to AFPaCC, however are perhaps exacerbated by the poor prognosis of pancreas cancer and that only 20% of patients are able to undergo surgical resection. As AFPaCC moves into the next phase, it is not only important to continue improving the quality of data and samples acquisition but also to commence follow up for families registered over 2 years.

References:
An International Survey of Awareness of Genetic Risk in the Clinical Sarcoma Community

Kate A McBride\(^1\), Tim Schlub\(^2\); Mandy L Ballinger\(^3\); David M Thomas\(^4\); Martin Tattersall\(^1\);

\(^1\)The Chris O’Brien Lifehouse, Sydney, NSW; \(^2\)School of Public Health, The University of Sydney, Sydney, NSW; \(^3\)Peter MacCallum Cancer, East Melbourne, VIC; \(^4\)The Kinghorn Cancer Centre and Garvan Institute, Darlinghurst, NSW

**Introduction & aims**
Integration of clinical genetics into oncology is variable. For some cancers, genetic literacy is high. This is not the case for most cancers. Sarcomas have a strong genetic component, with 1/30 patients carrying germline mutations in TP53. We aim to define genetic risk awareness amongst sarcoma clinicians.

**Methods**
An online survey was emailed to membership of the Connective Tissue Oncology Society and the Australian Sarcoma Study Group, comprising a diverse group of clinicians working in the field of connective tissue tumours. 159 of 1200 recipients from 21 countries responded to the survey (13%). One hundred and twenty four sarcoma clinicians participated. Other respondents include researchers (9%), pathologists (6%). The primary outcome was attitudes towards genetic testing, levels of cancer risk, and awareness of risk reduction measures.

**Results** 96% of clinicians indicated that they routinely take a family history during the initial consultation. 40% favoured routine TP53 mutation testing in children regardless of family history, increasing to 80% if a family history was present, and 87% if multiple primary cancers were present, regardless of subspecialisation. The likelihood of TP53 mutation carriers developing cancer approaches 80% by 50 years of age. 41% of clinicians estimated cancer risk accurately, while 37% thought the risk was less than 40%. Risk estimates were lower in older clinicians, surgeons, and in clinicians from the Asia-Pacific region (including Australia). 3% of clinicians were not aware that screening of at-risk individuals may identify some cancers at an earlier, more curable stage. 57% of clinicians were not aware that reproductive strategies exist to reduce the chance of passing on a mutation to offspring, although most clinicians (75%) considered these options acceptable. No significant differences were observed according to gender, subspecialisation, or age.

**Conclusions** Because clinical genetics is not yet standard of care for multidisciplinary management of sarcoma, awareness of genetic risk is critical amongst the sarcoma clinical community. Although attitudes amongst the sarcoma community were generally positive, education on the implications and opportunities for genetic risk modification may improve quality of care.
The Psychological Impact of a Pilot Whole-Body Screening Trial (SMOC) on individuals with Li–Fraumeni Syndrome

Kate A McBride¹,²; Mary-Anne Young⁴; Tim Schlub²; Mandy L Ballinger³; David M Thomas⁵; Gillian Mitchell³,⁴

¹The Chris O’Brien Lifehouse, Sydney, NSW; ²School of Public Health, The University of Sydney, Sydney, NSW; ³Research Division & Familial Cancer Centre, Peter MacCallum Cancer, East Melbourne, VIC; ⁴The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Darlinghurst, NSW

Introduction
Individuals who have a germline TP53 mutation have Li-Fraumeni Syndrome (LFS) and have a markedly increased risk of cancer-related morbidity and mortality during both childhood and adulthood. There is little evidence for clinicians to guide cancer risk management practices for these individuals therefore appropriate and effective cancer risk management is an important issue. A pilot whole-body (WB) screening trial (SMOC) in adults with TP53 mutations, or at 50% risk of carrying a mutation, has been established to estimate the prevalence and incidence of investigable lesions identified through the screening trial. The psychosocial impact of using WB MRI in individuals with LFS is unknown.

Aim to assess the psychosocial effects of participation in a WB screening program.

Methods
Ten individuals with germline TP53 mutations are currently enrolled. Participants complete validated psychological questionnaires at baseline, 12 weeks, 26 and 52 weeks post WB-MRI as well as pre and post results, As well, they are invited to take part in two in-depth semi-structured interviews (prior to screening commencement and 6 months post WB-MRI). The interviews explore factors influencing participants’ decisions to take part, evaluates their views and hopes for screening and allows participants to reflect on their screening experience.

Results
Forty-six questionnaires have so far been completed by 10 participants. Preliminary quantitative data indicates unchanged levels of anxiety and depression and cancer related worry (from baseline to 6 months). All participants have reported a high level of satisfaction with WB MRI. Emerging themes from the qualitative interviews indicate that the WB screening trial gives some TP53 carriers a sense of control over cancer risk and that ‘something is being done’. Conversely, some feel overwhelmed by the screening intensity. Other participants are still struggling to adjust to their genetic test results despite it being some time since receiving their genetic test result. It is possible the screening tests may be adding to their anxiety.

Conclusion
Preliminary data suggests that the WB-MRI screening program is not adding to the psychological burden experienced by individuals with a TP53 mutation although timing of the screening may be an issue in individuals who have suffered a recent bereavement or who have recently received their genetic test results. These individuals may benefit from additional support during the screening process.
Developing a model of support for young women at confirmed genetic risk of breast and ovarian cancer

Laura Forrest,1, 2 Mary-Anne Young,1 Sue Shanley¹ and Gillian Mitchell¹, 2

1. Familial Cancer Centre, Peter MacCallum Cancer Centre
2. Sir Peter MacCallum Department of Oncology, University of Melbourne

The psychosocial implications for young women aged 18 to 40 years living with confirmed genetic risk of breast and ovarian cancer are complex and varied. The knowledge of being ‘at risk’ and utilisation of risk management strategies poses unique challenges for young women and impacts on important aspects of this developmental stage, such as partnerships, childbearing and career development. The psychosocial issues potentially encountered by young female carriers can be unanticipated, despite the genetic counselling process which would have outlined many of these issues around the time of genetic testing. Hence, young female carriers may benefit from routine multidisciplinary, psychosocial supportive care over time, tailored to age-specific and life stage needs. However, there is limited empirical Australian evidence regarding the psychosocial experiences of these young women, which is needed to develop an appropriate and effective model of psychosocial support. Therefore, the aim is to understand the impact of living with confirmed genetic risk of breast and ovarian cancer and identify the unmet psychosocial support needs of young women, who are at confirmed genetic risk of breast and ovarian cancer.

Forty young women aged between 18 and 40 years who carry a BRCA1, BRCA2 or TP53 mutation will be invited to participate in semi-structured interviews. The interviews will examine how these young women balance their cancer risk with risk management strategies and the impact of these aspects on their career, relationships and children, and their own health and wellbeing. The interviews will be audio-recorded, transcribed verbatim and de-identified. A grounded theory approach will be used to guide the data collection and analysis, and constant comparison within and between interview transcripts using an inductive approach, will stimulate the emergence of themes that will form the basis of the research results.

This presentation will draw on evidence from existing literature and present the preliminary findings from the semi-structured interviews to illustrate some of the psychosocial challenges young women experience through living with genetic cancer risk. The findings from this study will contribute to the development of an evidence-based, accessible, life-stage appropriate and feasible model of psychosocial supportive care that meets the needs of young women at confirmed genetic risk of breast and ovarian cancer.
Polymorphisms in Cyp2r1 and disruption of the vitamin D pathway associate with the SuprMam1 breast cancer susceptibility locus in mice.

Madara Ratnadiwakara¹, Rohan Williams², Melissa Rooke¹, Stephen Ohms¹, Anneke C. Blackburn¹

¹John Curtin School of Medical Research, Australian National University, Canberra ACT 0200. ²Molecular System Biology Group, John Curtin School of Medical Research, Australian National University, Canberra ACT 0200.

High levels of vitamin D are hypothesized to reduce the risk of breast cancer. In order to be biologically active, dietary vitamin D must be converted to its biologically active form 1,25(OH)₂D₃. Cyp2r1 is a major vitamin D hydroxylase that catalyzes the first step of this activation producing 25(OH)D₃. Cyp2r1 is located within SuprMam1, a mammary tumour susceptibility locus identified in the BALB/c-Trp53+/- mouse model of spontaneous breast cancer (Blackburn et al, Am J Path, 2007). We have examined the vitamin D pathway in SM09 congenic mice, which contain the BALB/c SuprMam1 locus on a C57BL/6 background.

qPCR and western blotting for Cyp2r1 in tissues from SM09 and control mice revealed a significant 2-3-fold reduction in Cyp2r1 expression in mammary glands and liver (female but not male) of SM09 mice, however differences in plasma 25(OH)D₃, calcium or phosphate levels were not found. Instead, 3-fold higher levels of plasma parathyroid hormone (PTH), a major vitamin D / calcium regulator, were present in female (but not male) mice carrying the BALB/c allele of the SuprMam1 locus. Affymetrix expression profiling of mammary glands found differential expression of many genes of the vitamin D pathway, consistent with disruption of the pathway. Increasing dietary calcium or vitamin D returned PTH levels to normal in BALB/c and SM09 mice. We are currently characterizing several polymorphisms in the Cyp2r1 promoter which may alter promoter function.

Thus, chronically elevated PTH levels due to an interaction between low calcium / vitamin D intake and reduced Cyp2r1 expression from the BALB/c allele of Cyp2r1 may contribute to increased breast cancer susceptibility. The SM09 congenic mice may serve as a valuable model for studying the role of gene-environment interactions of the vitamin D pathway in cancer and other diseases.
Prostaglandin E\textsubscript{2} inhibits p53 in human breast adipose stromal cells: A novel mechanism for the regulation of aromatase in obesity and breast cancer.

Xuyi Wang\textsuperscript{1,2}, Maria M. Docanto\textsuperscript{1}, Hironobu Sasano\textsuperscript{5}, kConFab, Camden Lo\textsuperscript{4}, Evan R. Simpson\textsuperscript{1,3}, Kristy A. Brown\textsuperscript{1,2}

\textsuperscript{1}Metabolism & Cancer Laboratory, MIMR-PHI Institute, Clayton VIC, Australia; Departments of \textsuperscript{2}Physiology and \textsuperscript{3}Biochemistry & Molecular Biology, \textsuperscript{4}Monash Micro Imaging, Monash University, Clayton VIC, Australia; \textsuperscript{5}Department of Pathology, Tohoku University School of Medicine, Sendai, Japan

Obesity is a risk factor for postmenopausal breast cancer and the majority of postmenopausal breast cancers are dependent on locally produced estrogens for growth. Aromatase converts androgens into estrogens and its increased expression in breast adipose stromal cells (ASCs) is believed to be a major driver of estrogen receptor-positive breast cancer. In particular, obesity-associated and tumor-derived factors such as prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) have been shown to drive the expression of aromatase by stimulating the activity of the proximal promoter PII. We have identified three putative p53 response elements on aromatase PII. Despite sporadic mutations in TP53 being common in breast cancer, these are rare in the tumor-associated stroma. This study therefore aimed to determine the role of p53 in regulating aromatase expression and the effect of PGE\textsubscript{2} on p53 in ASCs. Results demonstrate that PGE\textsubscript{2} significantly decreased p53 transcript and nuclear protein expression in primary human breast ASCs. Phosphorylation of p53 at Ser15 was also decreased in response to PGE\textsubscript{2}. Stabilization of p53 with the HDM2 inhibitor RITA led to a significant decrease in the PGE\textsubscript{2}-stimulated expression of aromatase mRNA and activity, as well as a significant decrease in PII activity. Chromatin immunoprecipitation demonstrated that p53 interacts with a region of PII which encompasses the distal p53 response element and that this interaction is decreased in the presence of PGE\textsubscript{2}. Moreover, mutation of this site leads to an increase in the basal activity of the promoter supporting the hypothesis that p53 suppresses aromatase expression via interactions with this site. Immunofluorescence performed on sections of breast tissue from cancer-free women, as well as women with breast cancer demonstrates that p53 is decreased in tumor-associated ASCs compared to ASCs from normal breast tissue, and that there is a positive association between perinuclear (inactive) p53 and aromatase expression in these cells. Furthermore, aromatase expression is increased in breast ASCs from Li-Fraumeni patients (germline TP53 mutations) compared to non-Li-Fraumeni breast tissue. Overall, our results demonstrate that p53 is a negative regulator of aromatase in the breast and its inhibition by PGE\textsubscript{2} provides a novel mechanism for aromatase regulation in obesity and breast cancer.
Molecular differences between Interval and Screen Detected Breast Cancer

Jacquie Raison1,2, Sally M Hunter1, Lisa Devereux3, Rhonda Huynh3, Ravikiran Vedururu4, G Bruce Mann4, Stephen B Fox5, Kylie L Gorringe1, Ian G Campbell1

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

In Australia, population-based mammography screening starts at age 50 and is repeated at two yearly intervals. However, some breast cancers develop between screenings and are known as interval breast cancers. Interval breast cancer accounts for up to 30% of all diagnosed breast cancers and are thought to be more aggressive than screen detected cancers. A true interval breast cancer occurs after a negative mammography test and develops before the next scheduled screening examination. They are normally only detected through self-examination or visual physical changes. The aim of this study is to determine the presence of molecular differences between interval and screen detected breast cancers. Cases have been identified through Lifepool and comprise women undergoing mammographic screening through Breast Screen Victoria. Interval cancers were defined as those occurring within 12 months of a confirmed negative mammogram. Statistical analysis of age of diagnosis, ER, PR, HER2, nodal status and grade were conducted from pathology reports of interval and screen detected cases. Grade was found to be statistically significantly higher (p=0.0059) in interval breast cancer compared to screen detected cancer. This result is consistent with previous studies. FFPE blocks are being called in and DNA extracted from tumour cells following needle microdissection. Copy number variation will be detected by molecular inversion probe SNP arrays. A Fluidigm and MiSeq assay will be used to detect somatic mutations in 16 known cancer genes. This study will determine whether copy number or somatic mutations differ between interval and screen detected breast cancer.
Mutational profiling of familial male breast cancers reveals similarities with luminal A female breast cancer with rare TP53 mutations.

Siddhartha Deb\textsuperscript{1,2,3}, Stephen Q Wong\textsuperscript{1}, Jason Li\textsuperscript{4}, Hongdo Do\textsuperscript{5}, Jonathan Weiss\textsuperscript{5}, David Byrne\textsuperscript{1}, Anannya Chakrabarti\textsuperscript{6}, Trent Bosma\textsuperscript{7}, kConFab Investigators\textsuperscript{8}, Andrew Fellowes\textsuperscript{7}, Alexander Dobrovic\textsuperscript{1,5}, Stephen B Fox\textsuperscript{1,2,3}.

1. Department of Molecular Pathology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, 3002, AUSTRALIA.
2. Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Vic. 3010, AUSTRALIA.
3. Department of Pathology, University of Melbourne, Parkville, Vic. 3010, AUSTRALIA.
4. Bioinformatics, Cancer Research Division, Peter MacCallum Cancer Centre, East Melbourne, Victoria 3002, AUSTRALIA.
5. Translational Genomics and Epigenomics Laboratory, Ludwig Institute for Cancer Research, Olivia Newton-John Cancer and Wellness Centre, Heidelberg, Victoria, 3084, AUSTRALIA.
6. Metastasis Research Laboratory, Peter MacCallum Cancer Centre, East Melbourne, Victoria, 3002, AUSTRALIA.
7. Molecular Diagnostics, Department of Pathology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, 3002, AUSTRALIA.
8. Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer, Peter MacCallum Cancer Centre, East Melbourne 3002, AUSTRALIA.

Abstract

Male breast cancer (MBC) is still a poorly understood disease. A large proportion arises in breast cancer families. While most genomic studies have focused on germline determinants of MBC risk, only a handful of studies have evaluated somatic changes. Using a TruSeq amplicon cancer panel, this study evaluated 48 familial MBCs (3 BRCA1 germline mutant, 17 BRCA2 germline mutant, 28 BRCAX) for hotspot somatic mutations and copy number changes in 48 common cancer genes.

Twelve missense mutations were present with 9 PIK3CA mutations (7 in BRCAX patients), 2 TP53 mutations (both in BRCA2 patients) and 1 PTEN mutation (in a BRCA2 patient). Across the MBC cohort, common gains were seen in GNAS (34.1%) and losses seen in GNAQ (36.4%), ABL1 (47.7%) and ATM (34.1%). Gains of HRAS (37.5% vs 3%, p=0.006), STK11 (25.0% vs 0%, p=0.01) and SMARCB1 (18.8% vs 0%, p=0.04), and the loss of RB1 (43.8% vs 13%, p=0.03) were specific to BRCA2 tumours. Comparison of gene copy numbers showed different subsets correlated in BRCA2 (SMO and SMARCB1, PTPN11 and CTNNB1, CSF1R and RET, RET and CTNNB1) and BRCAX (KDR and EGFR, ERBB4 and FBXW7, PDGFRA/FIP1L1 and PTEN, RB1 and SMAD4).

This study is the first to perform high throughput somatic sequencing on familial MBC. Overall, PIK3CA mutations are most commonly seen, with fewer TP53 and PTEN mutations, similar to the profile seen in luminal A female breast cancers. Differences in mutation profiles and patterns of gene gains/losses are seen between BRCA2 (associated with TP53/PTEN mutations, loss of RB1, gain of HRAS, STK11, SMARCB1) and BRCAX (associated with PIK3CA mutations) tumours suggesting BRCA2 and BRCAX tumours may be distinct and arise from different tumour pathways which may impact on screening and therapeutic targeting depending on the BRCA status of male breast cancer patients.
Targeted high-throughput DNA sequencing of selected hormone metabolism genes for women with early-onset breast cancer

Miroslaw K. Kapuscinski¹, Khalid Mahmood², John L. Hopper¹

¹School of Population and Global Health and ²Victorian Life Sciences Computing Initiative, The University of Melbourne, Victoria

Large genetic epidemiological studies have found associations between single nucleotide polymorphisms (SNPs) in the region of hormone metabolism genes and breast cancer risk. To try to find the causal genetic variants in these regions, we have had performed a targeted high-throughput DNA sequencing of 10Mb in and around selected hormone metabolism genes for 150 women with breast cancer diagnosed before the age of 40 years from the Australian Breast Cancer Family Study. The bioinformatics analysis was performed using GATK best practices followed by variant calling using VarScan, UnifiedGenotyper and HaplotypeCaller with high concordance observed between the three algorithms. Variants were filtered based on quality measures and 1KGP variants and split into coding and non-coding categories. Coding variants were annotated using SnpEff and functional effects were predicted using PolyPhen. Approximately 99% of the variants were non-coding and ranking these was not trivial, so we used an ensemble of resources to rank these variants including ENCODE (transcription factors binding sites etc.) and sequence conservation scores (e.g. PhastCons and GERP++), as well as annotation scores from CADD and FunSeq. We have identified a few hundred coding and non-coding variants with putative deleterious effect. Work in the area of identifying causal variants is ongoing using selected UK10K whole genomes as a reference group, by taking into account the family cancer histories of case-carriers and the variant status of relatives from whom a blood sample has been obtained, and in the longer term by measuring candidate causal variants for thousands of cases and controls. Our software pipeline for variant annotation, ranking and multi-sample statistics has potential for wider use in this area and it will be made available through open source websites.
ENIGMA & The BRCA Challenge:
Working towards international standardization of \textit{BRCA1/2} variant classification

Amanda Spurdle and Michael Parsons
Genetics and Computational Biology Division, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

The clinical challenge presented by variants of uncertain significance detected during gene testing is well recognized, with complications and/or negative impacts for test reporting, genetic counselling, patient eligibility for intensive surveillance and gene-targeted therapies, and gene testing and guided management of relatives. It is difficult for most testing labs to collect enough information to robustly classify individual variants, leading to inconsistent classification between clinics. Further, high throughput deep-sequencing now covers non-coding potential regulatory regions and there are no established methods to assess novel variants in these regulatory regions. The Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) international consortium is engaged in applying, and further developing, statistical and laboratory methods to standardize clinical classification of variants in breast cancer susceptibility genes. Nomenclature has been standardized for >3,200 distinct variants submitted to ENIGMA for study. Using accepted classification criteria of variant frequency >1\% in a non-founder population, and posterior probability from existing multifactorial likelihood analysis results, 212 of the submitted “unclassified” variants were found at baseline to be class 1 NOT pathogenic (relevant to >10,000 ENIGMA families) and 34 were clearly class 5 pathogenic (relevant to 224 ENIGMA families). Current submissions also include 356 class 2 (likely not pathogenic) or class 4 (likely pathogenic) variants in 1,168 families, information relevant to clinical management. Since the information ENIGMA used to define these classifications was available in public websites or publications, the findings highlight the need to standardize BASELINE classification across clinical sites internationally.

ENIGMA has recently engaged in a major global effort, termed the BRCA Challenge project, to collate \textit{BRCA1} and \textit{BRCA2} variant information internationally, in collaboration with the Human Variome Project, the Global Alliance initiative (GA4GH), ClinVar/ClinGen, LOVD, kConFab and ENIGMA members from clinical, research and corporate groups. At recent meeting of representative from these groups, there was agreement to collate lists of \textit{BRCA1/2} variants submitted to ClinVar/ClinGen/BIC (US-centric entries) and the LOVD \textit{BRCA1/2} locus-specific variant databases (currently largely European entries, with potential to access information from HVP country nodes internationally), and formal recognition of ENIGMA as the expert panel to develop and document standardised BRCA variant classification methods and apply them to all \textit{BRCA1/2} variants submitted.

In this presentation, we will provide an update on the current status of ENIGMA classification criteria to be applied for assessment of BRCA variation collated through the BRCA Challenge project, in an effort to seek input from the Australian clinical genetics community on content and ease of application. We will also provide an overview of clinical and laboratory data deemed suitable for robust classification of variants using multifactorial likelihood analysis methods or qualitative criteria, to encourage routine collection of such data in the clinical setting and so facilitate future variant classification.
Prevalence of putative predisposition genes in Malaysian high risk familial breast cancer patients

PS Ng¹, Zaki F¹, M.Dharni¹, SY Yoon¹, NA Mohd Taib², CH Yip³ and Soo H Teo¹,²

¹Cancer Research Initiatives Foundation, Sime Darby Medical Centre, Malaysia,
²University Malaya Cancer Research Institute, Faculty of Medicine, University Malaya, Malaysia,
³Sime Darby Medical Centre, Malaysia

Background: To date, more than 10 genes have been identified to be associated with increased predisposition to breast and ovarian cancer. However, with the exception of BRCA1, BRCA2, TP53 and PALB2, few studies have been conducted to determine the prevalence of the majority of these genes in Asians. In this study, we sought to determine the prevalence of 113 selected cancer predisposition genes in a cross sectional cohort of breast cancer patients who were deemed to have high risk of inherited predisposition based on age of onset and family history of breast and ovarian cancer.

Methods: From January 2013 to January 2014, 574 breast cancer patients were recruited into the Malaysian Breast Cancer Genetic Study, of whom 45 were diagnosed ≤35 years old (regardless of cancer family history), 56 were diagnosed >35 (and had at least one first- or second-degree relatives with breast or ovarian cancer), 7 were affected with bilateral breast cancer, 2 had both breast and ovarian cancer, 2 were diagnosed <50 with triple negative breast cancer and 1 male breast cancer. The NimbleGen Sequence Capture panel for 115 cancer-related genes designed by Beijing Genome Institute was used to capture and enrich the target sequences from genomic DNA. Targeted regions were sequenced on Illumina Hiseq with 97% of targeted region achieved more than 150x coverage in all samples. Putative mutations were confirmed by direct DNA sequencing.

Results: Of the 113 high and moderate risk breast cancer patients included in this cross sectional study, 18 women were found to have germline mutations in either BRCA1 [10] or BRCA2 [8]. In addition, we identified 38 putative frameshift, nonsense or splice site mutations in 25 genes, including BARD1, MSH6 and PTEN. 51 missense mutations were shortlisted and all mutations were validated by direct DNA sequencing.

Conclusion: Our pilot cross sectional study suggests that mutations in cancer related genes are rare even amongst high and moderate risk patients and at present, it is unclear how to proceed with the risk management of patients with alterations in these genes.
**Anecdotally noted Breast Cancer in Chinese Women younger than age 35**

**Risha Zia**
1 Hereditary Cancer Clinic  
Saint George Hospital

**Dr Kathy Tucker**
2 Hereditary Cancer Clinic  
Saint George Hospital

**Background:** St George Area Health Service has a large Chinese ethnic community. Anecdotally it was noticed that a number of young <35 yr old Chinese women were presenting to the St George Hereditary Cancer Clinic (STGHCC) with breast cancer.

**Method:** Chinese ancestry was defined as first language Cantonese or Mandarin, self-identifying as Chinese, born in China, Singapore or Hong Kong with a Chinese surname. The KINTRAK Database was searched for referrals for breast cancer below the age of 35 between January 2012- June 2014. Each file was then reviewed for Chinese ancestry, use of Mandarin or Cantonese interpreters, Chinese names, age of diagnosis and histopathology.

**Results:** 15 women had Chinese ancestry. 13 / 15 women were offered BRCA1 and BRCA2 mutation analysis- 11 results available- 2 pending; 1/15 was also offered TP53 testing. 1, a student, could not pay and one refused testing because of concerns about her children’s access to insurance.

3/11 had mutations identified: 1 in BRCA1, 1 in BRCA2 and 1 in TP53. 8/11 had no mutation identified in BRCA1 and BRCA2; 2 pending

0/15 had cancers related to Hereditary Breast Ovarian Syndrome

10 /15 women had no reported family history of any cancer.

14 out of 15 women had ER/PR positive breast cancer. 3 had ER,PR and her2 positive breast cancer. In one the Her-2 was variable. Only the BRCA1 carrier had ‘ER, PR and her2 negative ie ‘Triple negative’ breast cancer.

**Discussion:** In this small review none of the 15 young Chinese breast cancer patients had a significant family history of cancer, even the 3 mutation carriers. This compares with 33% of the <=30y in a British cohort.( Laloo et al Lancet 2003). In a young Malaysian breast cancer cohort <35 years (53% of whom were Chinese) 11% BRCA1 ; 6% BRCA2 and 5% TP53. However unlike our TP53 carrier, their TP53 patients had significant Family history typical of Li Fraumeni Syndrome. It is possible that there are more cancers in the family but cultural barriers and family separation prevent discussion in family. This lack of family history in migrant Chinese families, needs confirmation in a larger prospective sample.

**Conclusion.** Young Chinese women presenting with breast cancer may have no reported family history but harbour a mutation in a high risk breast cancer gene.
Low prevalence of germline \textit{PALB2} mutations in Australian triple-negative breast cancer

1 Michelle Wong-Brown and 1,2 Rodney Scott

1 Discipline of Medical Genetics and Centre for Information-Based Medicine (CIBM), The University of Newcastle and Hunter Medical Research Institute (HMRI), Newcastle, Australia
2 Division of Genetics, Hunter Area Pathology Service (HAPS), Newcastle, Australia

\textbf{Background and Aims}

TNBC is a classification of breast cancer with ER-, PR-, and HER2-negative tumours. TNBCs share a similar gene expression profile as tumours with \textit{BRCA1} or \textit{BRCA2} mutations and a high proportion of these germline \textit{BRCA} mutation carriers display a triple-negative tumour phenotype.

Recent studies have shown that up to 20\% of tumours classified as TNBC have \textit{BRCA} mutations. This suggests a link between the \textit{BRCA}-associated DNA repair pathway and TNBC. It has also been suggested that TNBCs may harbour pathogenic mutations in genes that are involved in the \textit{BRCA}-associated DNA repair pathway, such as the FA pathway.

From our previous study, it was shown that deleterious mutations are present in \textit{PALB2}, a moderate-penetrance breast cancer gene in the FA pathway that is associated with \textit{BRCA1} and \textit{BRCA2}. Some studies suggest that \textit{PALB2}-associated breast cancers display a more aggressive phenotype and have a higher tumour grade compared with sporadic breast cancer. This raises the possibility that germline \textit{PALB2} mutations may be involved in the pathogenesis of TNBC. To date it has been shown that nearly 40\% of \textit{PALB2}-associated breast cancers display a triple-negative phenotype. However, the prevalence of germline \textit{PALB2} mutations is yet to be comprehensively investigated in patients who developed TNBC in the absence of a family history of disease. This part of the study aims to observe the prevalence of germline \textit{PALB2} mutations in TNBC.

The aim of this study was to investigate the prevalence of germline \textit{PALB2} mutations in TNBC cases unselected for family history of disease.

\textbf{Methodology}

This study involved 347 patients with TNBC and unselected for age of disease onset, family history of cancer, and \textit{BRCA} mutation status. The entire \textit{PALB2} coding sequence was amplified and sequenced by Sanger sequencing.

\textbf{Results and Discussion}

Two novel truncating mutations (c.758dup and c.2390del) and one previously-detected truncating mutation (c.3113+5G>C) were found. In addition, five variants predicted to be protein-affecting were also identified. This study shows that the prevalence of \textit{PALB2} germline mutations in individuals with TNBC is approximately 1\%, similar to the prevalence of \textit{PALB2} germline mutation of 1\% in familial non-\textit{BRCA1}/2 breast cancer cohorts.

\textbf{Acknowledgments}

This study was funded by a National Breast Cancer Foundation grant. MWB was supported by an Australian Postgraduate Award.
PIK3C2G as a candidate breast cancer susceptibility gene

Jun Li, Igor Makunin, Ella Thompson, Simone Rowley, kConFab Investigators, Ian Campbell, David Goldgar, Georgia Chenevix-Trench

Phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing gamma polypeptide, encoded by PIK3C2G gene, belongs to the phosphoinositide 3-kinase (PI3K) family. PI3-kinases play roles in signalling pathways involved in cell proliferation, oncogenic transformation, cell survival, cell migration, and intracellular protein trafficking. The biological function of this gene has not yet been determined.

Whole exome sequencing we performed previously of two familial breast cancer cases from kConFab identified two rare truncating variants in PIK3C2G. We therefore carried out targeted sequencing of the coding exons of PIK3C2G in 684 index breast cancer cases from kConFab by using 100bp paired-end reads on an Illumina HiSeq 2000 platform. We obtained high-quality sequencing data with average depth of 800-fold, and completed sequence alignment and variant calling by BWA and GATK respectively. We identified seven novel variants of interest in PIK3C2G, including three protein truncating (predicted to undergo nonsense mediate decay) and four missense variants that were predicted to be “deleterious” by at least four of the following tools: SIFT, Polyphen2, LRT, MutationTaster and CADD. In addition, in a parallel whole exome sequencing study of 69 non-BRCA1/2 kConFab families we identified another novel truncating variant in PIK3C2G. So far we have Sanger sequenced three out of four truncating variants, and three of the four predicted deleterious missense variants in all available family members’ DNA. We used modified segregation analysis to estimate the relative risk of breast cancer by conditioning the likelihood of the pedigree phenotypes and genotypes on pedigree phenotypes and proband genotypes, assuming Australian age-specific incidence rates in non-carriers. Based on this analysis we estimated that the maximum likelihood estimate of the Relative Risk associated with a PIK3C2G variant 1.2 (95% CI 0.4 - 2.8). There is therefore no evidence that PIK3C2G mutations are associated with a moderate-high breast cancer risk.

This study emphasises the challenges of finding additional breast cancer susceptibility genes through whole exome sequencing and targeted screening. Even though multiple, novel truncating variants, as well as putatively deleterious missense variants, were identified in non-BRCA1/2 families in PIK3C2G, segregation analysis demonstrated they were not likely play a role in breast cancer predisposition.
Identification of somatic copy number alterations associated with the recurrence of DCIS

Kylie L Gorringe¹,²,³, Sally Hunter¹, Simone Rowley¹, Jia-Min Pang⁴, David YH Choong¹, Ella R Thompson¹, Ken Opeskin⁵, Prue Hill⁵, G Bruce Mann*⁶, Ian G Campbell*¹,²,³

¹VBCRC Cancer Genetics Laboratory, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia. ²,³ Department of Pathology, and the Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia. ⁴Molecular Pathology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia. ⁵Department of Anatomical Pathology, St Vincent’s Hospital, Fitzroy, Victoria, Australia. ⁶The Royal Melbourne and Royal Women’s Hospitals, Parkville, Victoria, Australia.

BACKGROUND: Ductal carcinoma in situ is a non-obligate precursor of invasive breast cancer and a frequent mammographic finding requiring treatment. 10-25% of DCIS can recur and half of recurrences are invasive. There are no robust biomarkers of recurrence.

Copy number alterations are common in breast carcinomas, including DCIS. The difference in gene expression caused by such events may alter the probability of recurrence. Thus, copy number events are potential biomarkers of recurrence.

METHODS: We analysed a cohort of 48 pure, screen-detected DCIS treated only with wide local excision [1] using Affymetrix OncoScan MIP arrays to obtain genome-wide copy number and loss of heterozygosity. All cases underwent pathology review and immunohistochemistry was performed for ER and Ki67 for 38/40 cases. DNA was extracted following needle microdissection of 10-40 ten micron sections of FFPE tissue.

RESULTS: Pure DCIS had broadly similar copy number changes compared to three invasive breast cancer cohorts [2-4], with the consistent exception of a greater frequency of ERBB2 amplification in DCIS. A subset of 15 cases with recurrence between 1 and 5 years after diagnosis and 25 cases without recurrence in 7 years follow up were compared. There were no significant differences for ER status or Ki67. The fraction of the genome altered by copy number was higher in the recurrence cases than the non-recurrence cases (P=0.03). Copy number gains of 20q, losses on 15q and 10q and AI on chr10 were more frequent in recurrence cases than non-recurrence (P<0.001). ERBB2 gain was somewhat more frequent in cases with recurrence than without (P=0.02), and this effect was stronger for DCIS recurring as DCIS (6/8 amplified) rather than as invasive (3/7 amplified). Interestingly, when stratifying the cases by ERBB2 status, recurrence ERBB2+ cases more often had gain of CCND1 than non-recurrence, while recurrence ERBB2- cases had more frequent gain of EGFR than non-recurrence.

CONCLUSION: Overall copy number load and specific copy number alterations may differ between DCIS cases that recur compared to those that do not recur, and the chromosome regions may vary depending on ERBB2 amplification status. However, validation in an independent cohort is required.

Genomic profiling of kConFab men with a BRCA mutation status and prostate cancer

Ania Sliwinski\(^a\), Sally Hunter\(^b\), Ian Campbell\(^b\), kConFab\(^a\), Jason Li\(^d\), Gail P. Risbridger\(^h\), Renea A. Taylor\(^h\), David Clouston\(^l\), Gillian Mitchell\(^a\), Declan Murphy\(^e\), Mark Frydenberg\(^g\), Melissa Papagiris\(^h\), Damien M. Bolton\(^l\), Heather Thorne\(^a\)

\(^a\)kConFab, Research Department, \(^b\)Cancer Genetics Laboratory, \(^c\)Familial Cancer Centre, \(^d\)Bioinformatics and \(^e\)Division of Cancer Surgery, Peter MacCallum Cancer Centre, East Melbourne; \(^f\)Department of Urology, University of Melbourne, Austin Hospital, Heidelberg, Victoria; \(^g\)Sir Peter MacCallum Cancer Centre Department of Oncology, University of Melbourne; \(^h\)Prostate Cancer Research Group, Department of Anatomy and Developmental Biology and Department of Physiology, Monash University, Melbourne; \(^i\)Tissupath, Mt. Waverley, Victoria; \(^j\)Epworth Research Centre, Epworth Healthcare, Victoria; \(^k\)Department of Urology, Monash Medical Centre, Monash University, Melbourne.

Background: Family history is a well established risk factor for prostate cancer. Men from high-risk breast cancer families with an identified BRCA2 mutation but also from breast cancer families where no BRCA mutation has been identified (BRCAX), have an increased risk of prostate cancer and higher rate of prostate cancer-specific mortality. Standard clinical features such as tumour stage and/or outcome prediction models are less predictive of treatment outcomes or indicate the poorer outcomes in BRCA2 carriers with prostate cancer. Other histological features that are also important in determining patient prognosis may be more useful in predicting outcomes in this patient group and include the presence of intraductal carcinoma. Intraductal carcinoma of the prostate (IDCP) is regarded as an adverse pathological finding, and has recently been associated with reduced progression free and cancer-specific survival. It is still unclear whether IDCP is simply a predictive or prognostic factor or if it has a specific pathogenic role in prostate cancer itself. It has not been firmly established whether prostate cancer develops as a progression with prostatic intraepithelial neoplasia (PIN) as a non-obligate precursor and, further, if adenocarcinoma is potentially a precursor of IDCP, or vice versa. Thus to investigate the routes of tumourigenesis of these distinct prostate histotypes we undertook genome-wide copy number analysis of normal matched prostate glandular epithelium, PIN, adenocarcinoma and IDCP from BRCA2 mutation carriers, and adenocarcinomas from BRCAX carriers for comparison.

Methods: Pathologist (DC) reviewed areas of normal prostate, PIN, adenocarcinoma and IDCP were microdissected from archival FFPE blocks. Genome-wide copy number data was generated using the Affymetrix OncoScan\(^{\text{TM}}\) array and interpreted using Nexus Copy Number\(^{\text{TM}}\) software for areas of copy number gain or loss, and loss of heterozygosity. Comparison was then made across samples to ascertain which areas of aberration were common to each tissue type and the levels of genomic aberration for each sample.

Results: Normal tissue was the most genomically stable, followed by PIN tissue. PIN tissue was more stable than adenocarcinoma tissue (p=0.0497). The average fraction of the genome altered (FGA) in adenocarcinoma tissue was marginally lower than that in IDCP tissue of BRCA2 carriers (0.14 vs 0.16). Adenocarcinoma tissue from BRCA2 carriers also displayed, on average, higher levels of aberration than adenocarcinoma tissue from BRCAX patients (FGA 0.14 vs 0.09). Broadly, the copy number aberrations observed in PIN, adenocarcinoma and IDCP were similar, with some of the most common aberrations being well-known prostate cancer-associated losses on 6q, 8p, 10q (PTEN) and 13q, and \(\text{ERG-TMPRSS2}\) fusions.

Conclusions: Further work is needed in greater numbers to confirm these trends and sampling tissue from single index lesions within the prostate may lead to a greater understanding of the genetic evolution of prostate cancer.
High grade serous ovarian carcinoma is genetically defined by somatic p53 mutations and widespread copy number variation. Co-occurring genetic changes may be positively selected in cancer due to additive or synergistic effects on tumour progression. Previously, we used siRNA knockdown in a functional screen to identify genes in the most commonly amplified regions that contribute to ovarian cancer cell survival. Four genes that were found to specifically affect cell viability in amplicon-containing cell lines when knocked down, DYRK1B, PAK4, SAMD4B, and ZFP36, are located on the same chromosome amplicon 19q13. As these genes are located on the same amplicon, they are a suitable model to examine if co-amplified driver genes work synergistically to drive ovarian carcinoma. This will be achieved by knocking down combinations of the target genes to determine if a more profound loss of viability in cells containing the amplicon occurs.

The functional assays will be performed in vitro using ovarian cancer cell lines with and without the 19q13 amplicon. Gene knockdown will occur via lipid transfection with siRNA and qRT-PCR will be performed on RNA extracted at 24 hours post-transfection to determine the percent knockdown. Replicate plates will be fixed and stained with DAPI at 72 hours to determine the fold-change in cell numbers in treated compared to control wells.

Confirmation of cell line identity has been established using STR profiling and conditions for optimal siRNA transfection are currently in the process of being optimized. The next step is to perform titration curves of the siRNA in each cell line to determine the lowest concentration that produces the most significant knockdown and viability effect in cell lines containing the 19q13 amplicon. The lowest siRNA concentrations to produce a significant effect will be used in all combinations for a multi-knockdown of genes to determine if there is a significant phenotypic difference between single and multiple gene knockdowns.
IDENTIFYING THE MISSING GENETIC RISK IN OVARIAN CANCER

Na LI, Ella THOMPSON, Ian CAMPBELL

Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia

Telephone: +61 3 96561803 Email: ian.campbell@petermac.org

Introduction: Germline BRCA1/2 mutations strongly influence the response of women with ovarian cancer (OC) to therapy. Identifying genetic risk in family members is the most successful available preventive strategy in OC, through targeted surgical intervention. However, BRCA1 or BRCA2 mutations account for only ~40% of the heritable fraction. Our aim is to identify additional risk loci, with an emphasis on rare, moderate penetrance alleles in individual families. Identifying the full repertoire of ovarian cancer predisposition genes could have a major and immediate impact on reducing OC risk in these family members. Methods: We are using family-based whole exome sequencing (WES) to screen women with a personal and strong family history of ovarian cancer but who are negative for known pathogenic mutations. Results: We are generating WES data from 40 “OvCaX” families and are currently identifying candidate genes that can progress to a validation phase by firstly prioritising those with overtly deleterious mutations. We have also derived germline variant data for 387 ovarian cancer patients sequenced as part of The Cancer Genome Atlas (TCGA) and 557 non-cancer controls[1] and this will be used to further prioritise candidates based on the frequency of germline and somatic mutations in the TCGA cases. We have generated a list of possible candidate genes from our preliminary analysis including ATM, CYP3A5, PTGER3, DUOX1 and ALKBH5. Access to detailed pedigree, tumour pathology information and DNA from family members through the Variants in Practice (ViP) study and a national collaboration of Australian familial cancer centres (the ICCon Partnership) will allow us to examine co-segregation of candidate ovarian cancer predisposition genes. Conclusions: Preliminary analysis of the data suggests that the missing heritability of ovarian cancer is due to many genes, each responsible for only a small fraction of families.

**TITLE:** Lifepool: a resource enabling research into aspects of breast cancer risk, detection and outcomes

**Authors:** Ian Campbell¹, Vicki Pridmore², Stephen Fox¹, John Hopper³, Paul James¹, Carolyn Nickson⁴, Bruce Mann⁴, Gillian Mitchell¹, Anne Kavanagh³, Rhonda Huynh¹, Kelly Aujard³, Adrian Bickerstaffe³, Jaymes Charlesworth³, Lisa Devereux¹

Lifepool is a prospective cohort of women recruited primarily through a key collaboration with BreastScreen Victoria. To date, over 51,000 Victorian women have agreed to participate in Lifepool, making this one of the largest cohorts of its type in Australia. Lifepool can support a range of research projects into breast cancer and other women’s health issues and is open to access by researchers nationally and internationally.

**AVAILABLE RESOURCES:**

Lifepool participants complete the Baseline Health & Lifestyle questionnaire, providing information about general health, parity, menopause, regular medications, exercise and exposure to alcohol and tobacco, in addition to occurrence of cancer for self and first degree relatives. Participants give consent for:

- access to **mammogram data**
- collection of **cancer incidence data** through linkage with the Victorian Cancer Registry. Women are separately asked for permission to access Medicare and Pharmaceutical Benefits Scheme data (over 80% agree),
- access to **archival breast tumour tissue** and **clinical information**, if diagnosed with breast cancer
- use of the data and samples provided in future research into breast cancer and other women’s health issues. Women are also asked for consent to future contact (over 80 % agree) to facilitate request for DNA and/or other research activities.

**DNA:**

>290 women with breast cancer  >4,300 women with no cancer at time of donation. **Tissue Microarray blocks** are being constructed from pathology archive tumour blocks.

A number of research projects using Lifepool biospecimens and data are underway, including:

- validation of putative breast cancer susceptibility genes
- molecular genetics of interval cancer
- genomic profiling of breast cancers that occur in the context of high versus low mammographic density
- validation and identification of genetic determinants of breast cancer risk and mammographic density.

Work to develop a breast cancer risk assessment tool is in the planning stage. The tool will calculate a polygenic risk score combined with other risk factors including mammographic density and lifestyle data. This tool will be modelled on the Lifepool cohort to provide an estimation of potential improvements in screening performance. Such work is enabled because the majority of Lifepool participants (~98%) are active clients of BreastScreen Victoria.

**AFFILIATIONS:**

1. Peter MacCallum Cancer Centre
2. BreastScreen Victoria
3. Melbourne School of Population and Global Health, University of Melbourne
4. Royal Melbourne and Women’s Hospitals

LIFEPOOL is funded by the NATIONAL BREAST CANCER FOUNDATION CG-08-02
Examining the utility of DNA extracted from Saliva and Blood for use in genome-wide molecular platforms.

Bruinsma F¹, Joo E², Wong M², Giles GG¹, Southey M².
Affiliations: ¹Cancer Epidemiology Centre, Cancer Council Victoria. ²Genetic Epidemiology Laboratory, University of Melbourne

There is increasing interest in both clinical and epidemiological studies to investigate the genetic and epigenetic markers for diseases and in the possible interaction of these markers with environmental factors. Historically, blood samples have been commonly used as the source of DNA for high density molecular platform analysis.

More recently, many cohort studies have begun collecting saliva samples in addition to, or as an alternative to, the collection of blood. Collecting saliva for cohort studies can be cost-effective and less invasive than collecting blood. Saliva samples collected using commercial kits are stable at room temperature and readily transportable without the need for refrigeration. Kits can be sent to participant’s homes and can be returned at their convenience making this an attractive alternative to many researchers and research participants.

The aim of the study was to investigate the suitability of DNA extracted from blood and saliva provided by the same research participant for high-throughput molecular platform analysis. The study investigated whether DNA extracted from saliva samples produced data of the same quality as DNA extracted from a blood samples on the Illumina Infinium HumanMethylation 450 Beadchip array® and the Illumina Infinium HumanCore Array®.

Based on data from the Illumina HumanCore Array®, both blood and saliva samples returned high quality data with SNP call rates and reproducibility frequencies of >99%. Based on data from the Illumina 450K Array®, both saliva and blood DNA returned high quality genome-wide DNA methylation data. We observed slightly higher global DNA methylation levels in whole blood samples than saliva (average β-value 0.488 vs. 0.496), when using average β-values across all detected probes (471,899) as surrogate measurements.

Cluster analysis illustrated that samples of similar tissue type had more similar methylation patterns than different sample types from the same individual. Whole blood DNA from different individuals shared greater similarities, whilst saliva samples from different individuals were less similar to each other. Correlations between individuals for each tissue type were generally greater than correlations between two tissue types from the same individual (Spearman’s correlation, ρ = 0.9509 in 10 pairs of matched blood and saliva samples and ρ = 0.9674 between all saliva samples, and ρ = 0.9683 between all blood samples).

DNA extracted from saliva is a suitable template for high density molecular platforms relevant to current key research questions and applicable to large epidemiology studies that have, or are collecting, these biological resources.
TITLE: ICCon Familial Cancer Database

AUTHORS: L Petelin1, I Campbell1, H Dawkins3, S Fox1, J Hiller6, P James1, J Kirk7, G Lindeman10, F Macrae5, L Mascarenhas1, J McGAughran12, B Meiser4, N Pachter9, C Saunders3, C Scott8, G Suthers11, A Trainer1, R Ward2, MA Young1, ICCon Collaborators and G Mitchell1. 1Peter MacCallum Cancer Centre, 2Prince of Wales Clinical School, 3University of Western Australia, 4University of NSW, 5Royal Melbourne Hospital, 6Australian Catholic University, 7Westmead Hospital, 8Walter and Eliza Hall Institute, 9King Edward Memorial Hospital for Women, 10Royal Melbourne Hospital, 11Women’s and Children’s Hospital, SA, 12Royal Brisbane and Women’s Hospital

The ICCon Partnership was formed in 2013 through the support of a CCNSW STREP grant. A principal goal of this collaboration is to build a national database of individuals with hereditary cancer syndromes to promote a cohesive approach to drive translational research and improve the health of people with a hereditary predisposition to cancer.

The ICCon database currently in development aims to create aggregated de-identified clinical data that can be extracted for the purposes of linking families across FCCs, providing supportive data for health policy applications, responding to feasibility enquiries for clinical trials, or to identify those patients who are eligible to participate in specific trials, or who may benefit from new advances in therapeutic interventions. We propose to include all known carriers of a presumed pathogenic mutation in a cancer predisposition gene who have attended an FCC (aged over 18). The ICCon database will comprise of a series of data modules which will cover the range of hereditary cancer syndromes and include data collected as part of routine clinical care within the FCC. Data that is planned to be stored include mutation type, cancer diagnosis (if appropriate), cancer treatment (if known), family pedigree (de-identified) and cancer risk management information (if known). FCC patients will have the opportunity to provide additional consent for their treatment information to be linked to ICCon through the CART-WHEEL rare cancer registry.

In addition to enabling HREC-approved projects and providing data to inform national policy in the hereditary cancer arena, data from the ICCon database will be able to contribute to both clinical and translational research activities. In the translational research arena the ICCon database will be able to contribute data to the international initiatives aiming to amalgamate mutation data, such as BIC (the Breast Cancer Information Core http://research.nihri.nih.gov/bic/) and InSiGHT (the International Society for Gastrointestinal Hereditary Tumours http://www.insight-group.org/).
The Forgotten Cancers Project

Anderson J, Bruinsma F, Giles G.

Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne

Through extensive research, significant progress has been made in understanding, treating and preventing the most commonly diagnosed cancers; prostate, breast, bowel, lung and skin, however less common cancers remain comparatively under researched.

The Forgotten Cancers Project is an epidemiological research program into less common cancers. It aims to study the role of genes, lifestyle and early life environment in the development of these cancers. The project uses a family case-control design, with the aim to recruit 15,000 cases and an equal number of controls. Any Australian, diagnosed as an adult, with one of the less common cancer, is eligible to participate.

Cases are self-referred and registration can be completed via the website or over the phone. Participants are asked to complete 4 comprehensive questionnaires and provide a saliva sample for DNA analysis. The questionnaires collect information about family cancer history, health, lifestyle, occupation and residential history and can be completed online or through the post. Saliva collection kits are sent through the mail and can be returned via reply-paid post. Once a case has completed the family history questionnaire permission is sought to invite a sibling and/or spouse to participate as a control. Where the case indicates on the family history questionnaire that there is one or more other family members with the same, less common cancer, all first and second degree relatives are invited to participate. Controls and invited relatives complete the same 4 questionnaires and provide a saliva sample.

The information we collect will allow us a unique opportunity to study the interaction between lifestyle and genetics in identifying risk factors in the development of these diseases. It will also act as research platform, providing a resource that will be available to other researchers investigating these cancers as well as contributing to international collaborations on less common cancers.

More information about The Forgotten Cancers Project, including the full list of the cancers we are focusing on can be found at www.forgottencancers.com.au or call 1800 068 289.
The Queensland Familial Cancer Registry (QFCR)

Jan Wakeling¹, Annette Hattam¹, Julie McGaughran¹, Rachel Susman¹

The Queensland Familial Cancer Registry (QFCR) was established in 2013 following a review and restructure of the Queensland Familial Bowel Cancer Registry (QFBCR). The QFCR is a register of Queensland residents who have a familial cancer predisposition syndrome and includes patients who were previously on the Queensland Familial Bowel Cancer Registry. The QFCR is part of Genetic Health Queensland (GHQ) and is co-ordinated by a Genetic Counsellor under the supervision of a specialist in cancer genetics. The number of patients on the QFCR is growing annually, and GHQ has introduced a number of initiatives which will ensure that the best possible service is available to all of the patients on the registry. We will be outlining and expanding on some of the key changes and initiatives of the QFCR. These include employing a dedicated full-time genetic counsellor; having an easier system of recruiting people to the registry; and maintaining an annual screening reminder based on the eviQ risk management guidelines for people with inherited cancer predisposition syndromes.

1. Genetic Health Queensland, c/- Royal Brisbane and Women’s Hospital, Butterfield St, Herston QLD 4029.
The Victorian Familial Adenomatous Polyposis Register – 25 Years On
Toula McArdle¹, Marita Black¹, Helen Farrugia²
¹ Victorian Family Cancer Registry (VFCR), Cancer Council Victoria (CCV)
² Victorian Cancer Registry, CCV

Purpose: To provide a description of changes to the Victorian FAP Register over a 25 year period, from when it was established in 1988, to its amalgamation with the Victorian Family Cancer Register in 2000, to current day and the challenges that lie ahead with winding up the FAP Register.

Background
The role of the FAP Register, managed by Cancer Council Victoria since 1988, was to ensure FAP families were advised, managed and screened appropriately and, as genetic testing became available, referred to Genetic Health Services Victoria for genetic testing.

By 2000, the role of the FAP Register changed, with cancer risk assessment and genetic counselling provided by the Family Cancer Clinics (FCC) based at major public hospitals in Melbourne. The FAP Register information was transferred to the Victorian Family Cancer Register (VFCR) and further expanded to include high risk Breast/Ovarian and Lynch syndrome families. Existing FAP Register families were invited to join the VFCR.

Description:
The numbers of FAP families and individuals over the 25 year period are represented graphically. Outcomes from transferring the FAP Register to the VFCR and follow up of ‘at-risk’ group are presented.

Summary
Sixty per cent of individuals on the FAP Register re-joined the VFCR, twenty-one per cent lost to follow or are deceased and for the remaining eighteen per cent their intention to re-join is still unknown. During the transfer from the FAP Register to the VFCR there were concerns that familial relationship information for ‘at-risk’ children would be lost. To address this issue, the VFCR has ethics approval to confirm if the FAP registrants who have not re-joined the VFCR or are known to be ‘at-risk’ of FAP, are under the care of a Victorian FCC. The VFCR has confirmed that one third of this group is under the care of a Victorian FCC.

The FCCs play a major role in continuing the work of the FAP Register. CCV continues its support of FAP families by providing screening appointment reminders, by following up screening outcomes and with the provision of information resources.
SPARK – A Supercomputing Pipeline for The Ark

Ranaweera, T, Makalic, E. Hopper JL, Bickerstaffe A
School of Population and Global Health, The University of Melbourne, Victoria

Advances in genotyping technologies have paved the way for cost effective and large scale human genetic research. These advances have has an impact on the biomedical research community, particularly in the domain of translational genomic research on complex human diseases, such as cancers. To investigate the possibility of such associations, the Genome-wide Association Study (GWAS) methodology was designed, and has led to the production of very large heterogeneous GWAS datasets. The first wave of GWAS has had success by identifying a number of genetic markers associated with disease phenotypes. Research groups across the globe are now developing novel GWAS analysis techniques which often require very large amounts of computational power, far more than a standalone personal computer can provide.

Biomedical informatics plays a pivotal role in GWAS research by providing crucial data management, processing and modelling facilities. One such data management platform is The Ark, an open source web-based biomedical data management system capable of handling study, subject (participant), pedigree, phenotypic and biospecimen data, in addition to tracking and invoicing research-related work requests, and facilitating custom reporting and data extraction.

The proposed SPARK platform will extend The Ark to handle large genomic datasets and provide a seamless, user-friendly web interface to massively parallel high-performance computing (HPC) resources such as the IBM Blue Gene/Q supercomputer at The University of Melbourne. SPARK will introduce a state-of-the-art data model for large genomic datasets, and a generic programming interface to allow the system to interoperate with a range of high-performance computing architectures, e.g. clusters or grids. Ultimately, SPARK will provide the worldwide GWAS research community with an extendable, collaborative genomic knowledge discovery platform which facilitates data sharing with a fine-grained user access and security model, and novel HPC-enabled analysis techniques.
The kConFab – 17 years of biobanking

Heather Thorne, Eveline Niedermayr, Lynda Williams, Lana Djandjgava, Carla Osinski, 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 1,623 families during the past 17 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 134 research projects world-wide.

The kConFab biological repository contains blood specimens from a total of 13,327 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, 1825 unique EBV cell line transformations are available.

As of July 2014, 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 or TP53 genes. Of the 2502 female participants who harbour the germline mutation, 68% are affected with breast or ovarian cancer.

kConFab has collected a total of 1165 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.

kConFab has constructed a total of 29 tissue microarrays (TMAs) (both sporadic and familial tumours) from our tissue bio bank. Where possible, tumour is matched to normal from the same archival block.

kConFab are currently working to supplement our glass slide archive with a digital slide repository. This will provide researchers with high resolution, high quality whole slide digital images for ease of transport, storage, review and analysis. Currently we have >1000 slides scanned for more than 600 participants.

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)
# Delegates List 2014

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<tr>
<td>Lesley</td>
<td>Andrews</td>
<td><a href="mailto:lesley.andrews@sesiachs.health.nsw.gov.au">lesley.andrews@sesiachs.health.nsw.gov.au</a></td>
</tr>
<tr>
<td>Antonis</td>
<td>Antoniou</td>
<td><a href="mailto:aca20@medschl.cam.ac.uk">aca20@medschl.cam.ac.uk</a></td>
</tr>
<tr>
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<td>Arnold</td>
<td><a href="mailto:JulieA@adhb.govt.nz">JulieA@adhb.govt.nz</a></td>
</tr>
<tr>
<td>Sonya</td>
<td>Bacic</td>
<td><a href="mailto:sonya.bacic@dhhs.tas.gov.au">sonya.bacic@dhhs.tas.gov.au</a></td>
</tr>
<tr>
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<td>Ballinger</td>
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</tr>
<tr>
<td>Jonathan</td>
<td>Beesley</td>
<td><a href="mailto:Jonathan.Beesley@qimrberghofer.edu.au">Jonathan.Beesley@qimrberghofer.edu.au</a></td>
</tr>
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<td>Bolton</td>
<td><a href="mailto:damienmb@unimelb.edu.au">damienmb@unimelb.edu.au</a></td>
</tr>
<tr>
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</tr>
<tr>
<td>Michael</td>
<td>Bowman</td>
<td><a href="mailto:michael.bowman@qimrberghofer.edu.au">michael.bowman@qimrberghofer.edu.au</a></td>
</tr>
<tr>
<td>Kristy</td>
<td>Brown</td>
<td><a href="mailto:krisy.brown@mimr-phi.org">krisy.brown@mimr-phi.org</a></td>
</tr>
<tr>
<td>Fiona</td>
<td>Bruinsma</td>
<td><a href="mailto:fiona.bruinsma@cancervic.org.au">fiona.bruinsma@cancervic.org.au</a></td>
</tr>
<tr>
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<td>Bryant</td>
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<tr>
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<td>Burgess</td>
<td><a href="mailto:Matthew.Burgess@petermac.org">Matthew.Burgess@petermac.org</a></td>
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<tr>
<td>Christopher</td>
<td>Butler</td>
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</tr>
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<td><a href="mailto:lisa.devereux@petermac.org">lisa.devereux@petermac.org</a></td>
</tr>
<tr>
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<td><a href="mailto:lana.djandjgava@petermac.org">lana.djandjgava@petermac.org</a></td>
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</tr>
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<td><a href="mailto:Samantha.Eccles@petermac.org">Samantha.Eccles@petermac.org</a></td>
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</tr>
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<td><a href="mailto:laura.forrest@petermac.org">laura.forrest@petermac.org</a></td>
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<tr>
<td>Stephen</td>
<td></td>
<td><a href="mailto:Stephen.fox@petermac.org">Stephen.fox@petermac.org</a></td>
</tr>
<tr>
<td>Juliet</td>
<td></td>
<td><a href="mailto:juliet.french@qimrberghofer.edu.au">juliet.french@qimrberghofer.edu.au</a></td>
</tr>
<tr>
<td>Kimberley</td>
<td></td>
<td><a href="mailto:kimberleyg@adhb.govt.nz">kimberleyg@adhb.govt.nz</a></td>
</tr>
<tr>
<td>Judy</td>
<td></td>
<td><a href="mailto:Judy_Garber@dfci.harvard.edu">Judy_Garber@dfci.harvard.edu</a></td>
</tr>
<tr>
<td>Jane</td>
<td></td>
<td><a href="mailto:jane.garrad@cancerinstitute.org.au">jane.garrad@cancerinstitute.org.au</a></td>
</tr>
<tr>
<td>Genna</td>
<td></td>
<td><a href="mailto:Genna.Glavich@petermac.org">Genna.Glavich@petermac.org</a></td>
</tr>
<tr>
<td>Margaret</td>
<td></td>
<td><a href="mailto:margaret.gleeson@hnehealth.nsw.gov.au">margaret.gleeson@hnehealth.nsw.gov.au</a></td>
</tr>
<tr>
<td>David</td>
<td></td>
<td><a href="mailto:david.goldgar@hsc.utah.edu">david.goldgar@hsc.utah.edu</a></td>
</tr>
<tr>
<td>Annabel</td>
<td></td>
<td><a href="mailto:annabel.goodwin@sswahs.nsw.gov.au">annabel.goodwin@sswahs.nsw.gov.au</a></td>
</tr>
<tr>
<td>Reanu</td>
<td></td>
<td><a href="mailto:rgop8673@uni.sydney.edu.au">rgop8673@uni.sydney.edu.au</a></td>
</tr>
<tr>
<td>Kylie</td>
<td></td>
<td><a href="mailto:kylie.gorringe@petermac.org">kylie.gorringe@petermac.org</a></td>
</tr>
<tr>
<td>Sian</td>
<td></td>
<td><a href="mailto:sian.greening@sesihs.health.nsw.gov.au">sian.greening@sesihs.health.nsw.gov.au</a></td>
</tr>
<tr>
<td>Alexandra</td>
<td></td>
<td><a href="mailto:alexandra.groves@hnehealth.nsw.gov.au">alexandra.groves@hnehealth.nsw.gov.au</a></td>
</tr>
<tr>
<td>Marion</td>
<td></td>
<td><a href="mailto:marion.harris@monashhealth.org.au">marion.harris@monashhealth.org.au</a></td>
</tr>
<tr>
<td>Annette</td>
<td></td>
<td><a href="mailto:Annette.Hattam@health.qld.gov.au">Annette.Hattam@health.qld.gov.au</a></td>
</tr>
<tr>
<td>Emma</td>
<td></td>
<td><a href="mailto:emma.healey@sesihs.health.nsw.gov.au">emma.healey@sesihs.health.nsw.gov.au</a></td>
</tr>
<tr>
<td>Emily</td>
<td></td>
<td><a href="mailto:emily.higgs@mh.org.au">emily.higgs@mh.org.au</a></td>
</tr>
<tr>
<td>Lindy</td>
<td></td>
<td><a href="mailto:lindy.hodgkin@mh.org.au">lindy.hodgkin@mh.org.au</a></td>
</tr>
<tr>
<td>Bruce</td>
<td></td>
<td><a href="mailto:bruce.hopper@hnehealth.nsw.gov.au">bruce.hopper@hnehealth.nsw.gov.au</a></td>
</tr>
<tr>
<td>John</td>
<td></td>
<td><a href="mailto:j.hopper@unimelb.edu.au">j.hopper@unimelb.edu.au</a></td>
</tr>
<tr>
<td>Clare</td>
<td></td>
<td><a href="mailto:clare.hunt@monashhealth.org">clare.hunt@monashhealth.org</a></td>
</tr>
<tr>
<td>Rodney</td>
<td></td>
<td><a href="mailto:rodney.scott@newcastle.edu.au">rodney.scott@newcastle.edu.au</a></td>
</tr>
<tr>
<td>Sally</td>
<td></td>
<td><a href="mailto:sally.jackson@ccdhb.org.nz">sally.jackson@ccdhb.org.nz</a></td>
</tr>
<tr>
<td>Paul</td>
<td></td>
<td><a href="mailto:paul.james@petermac.org">paul.james@petermac.org</a></td>
</tr>
<tr>
<td>Mark</td>
<td></td>
<td><a href="mailto:m.jenkins@unimelb.edu.au">m.jenkins@unimelb.edu.au</a></td>
</tr>
<tr>
<td>Thomas</td>
<td></td>
<td><a href="mailto:tom.john@ludwig.edu.au">tom.john@ludwig.edu.au</a></td>
</tr>
<tr>
<td>Amber</td>
<td></td>
<td><a href="mailto:a.johns@garvan.org.au">a.johns@garvan.org.au</a></td>
</tr>
<tr>
<td>Dian</td>
<td></td>
<td><a href="mailto:Dian.Karina@health.wa.gov.au">Dian.Karina@health.wa.gov.au</a></td>
</tr>
<tr>
<td>Maira</td>
<td></td>
<td><a href="mailto:maira.kentwell@mh.org.au">maira.kentwell@mh.org.au</a></td>
</tr>
<tr>
<td>Cathy</td>
<td></td>
<td><a href="mailto:borri_kiraly@iinet.net.au">borri_kiraly@iinet.net.au</a></td>
</tr>
<tr>
<td>Judy</td>
<td></td>
<td><a href="mailto:judy.kirk@sydney.edu.au">judy.kirk@sydney.edu.au</a></td>
</tr>
<tr>
<td>Aung</td>
<td></td>
<td><a href="mailto:awin@unimelb.edu.au">awin@unimelb.edu.au</a></td>
</tr>
<tr>
<td>Anna</td>
<td></td>
<td><a href="mailto:anna.leaver@austin.org.au">anna.leaver@austin.org.au</a></td>
</tr>
<tr>
<td>Sharon</td>
<td></td>
<td><a href="mailto:Sharon.Leong@nbcf.org.au">Sharon.Leong@nbcf.org.au</a></td>
</tr>
<tr>
<td>Jun</td>
<td></td>
<td><a href="mailto:JunJun.Li@qimrberghofer.edu.au">JunJun.Li@qimrberghofer.edu.au</a></td>
</tr>
<tr>
<td>Na</td>
<td></td>
<td><a href="mailto:na.li@petermac.org">na.li@petermac.org</a></td>
</tr>
<tr>
<td>Sharne</td>
<td></td>
<td><a href="mailto:sharne.limb@petermac.org">sharne.limb@petermac.org</a></td>
</tr>
<tr>
<td>Caroline</td>
<td></td>
<td><a href="mailto:Caroline.Lintott@cdhb.health.nz">Caroline.Lintott@cdhb.health.nz</a></td>
</tr>
<tr>
<td>Elly</td>
<td></td>
<td>elly.lynch@ austin.org.au</td>
</tr>
<tr>
<td>Finlay</td>
<td></td>
<td><a href="mailto:finlay.macrae@mh.org.au">finlay.macrae@mh.org.au</a></td>
</tr>
<tr>
<td>Lyon</td>
<td></td>
<td><a href="mailto:Lyon.Mascarenhas@petermac.org">Lyon.Mascarenhas@petermac.org</a></td>
</tr>
<tr>
<td>Toula</td>
<td></td>
<td><a href="mailto:toula.mcardle@cancervic.org.au">toula.mcardle@cancervic.org.au</a></td>
</tr>
<tr>
<td>Kate</td>
<td></td>
<td><a href="mailto:kate.mcbride@sydney.edu.au">kate.mcbride@sydney.edu.au</a></td>
</tr>
<tr>
<td>Name</td>
<td>Contact Email</td>
<td></td>
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<tr>
<td>---------------</td>
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<td></td>
</tr>
<tr>
<td>Fiona McKenzie</td>
<td><a href="mailto:fiona.mckenzie@health.wa.gov.au">fiona.mckenzie@health.wa.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Bettina Meiser</td>
<td><a href="mailto:b.meiser@unsw.edu.au">b.meiser@unsw.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Roger Milne</td>
<td><a href="mailto:rlm@unimelb.edu.au">rlm@unimelb.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Gillian Mitchell</td>
<td><a href="mailto:gillian.mitchell@petermac.org">gillian.mitchell@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Gemma Moir-Meyer</td>
<td><a href="mailto:gemma.moir-meyer@qimrberghofer.edu.au">gemma.moir-meyer@qimrberghofer.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>April Morrow</td>
<td><a href="mailto:a.morrow@unsw.edu.au">a.morrow@unsw.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Anna Nash</td>
<td><a href="mailto:Anna.Nash@health.wa.gov.au">Anna.Nash@health.wa.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Annabelle Ng</td>
<td><a href="mailto:annabelle.ng@sswahs.nsw.gov.au">annabelle.ng@sswahs.nsw.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Patsy Ng Pei Sze</td>
<td><a href="mailto:patsy.ng@carif.com.my">patsy.ng@carif.com.my</a></td>
<td></td>
</tr>
<tr>
<td>Cassandra Nichols</td>
<td><a href="mailto:Cassandra.Nichols@health.wa.gov.au">Cassandra.Nichols@health.wa.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Eveline Niedermayr</td>
<td><a href="mailto:eveline.niedermayr@petermac.org">eveline.niedermayr@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Shona O’Connell</td>
<td><a href="mailto:shona.oconnell@monashhealth.org.au">shona.oconnell@monashhealth.org.au</a></td>
<td></td>
</tr>
<tr>
<td>Tracy O’Mara</td>
<td><a href="mailto:Tracy.OMara@qimrberghofer.edu.au">Tracy.OMara@qimrberghofer.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Carla Osinski</td>
<td><a href="mailto:Carla.Osinski@petermac.org">Carla.Osinski@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Margaret Ottowski</td>
<td><a href="mailto:Margaret.Ottowski@utas.edu.au">Margaret.Ottowski@utas.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Driss Ouakrim</td>
<td><a href="mailto:drissao@unimelb.edu.au">drissao@unimelb.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Boyoung Park</td>
<td><a href="mailto:hayejine@ncc.re.kr">hayejine@ncc.re.kr</a></td>
<td></td>
</tr>
<tr>
<td>Michael Parsons</td>
<td><a href="mailto:michael.parsons@qimr.edu.au">michael.parsons@qimr.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Linda Patrick-Miller</td>
<td><a href="mailto:lpatrickmiller@medicine.bsd.uchicago.edu">lpatrickmiller@medicine.bsd.uchicago.edu</a></td>
<td></td>
</tr>
<tr>
<td>Lara Petelin</td>
<td><a href="mailto:Lara.petelin@petermac.org">Lara.petelin@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Nicola Poplawski</td>
<td><a href="mailto:nicola.poplawski@health.sa.gov.au">nicola.poplawski@health.sa.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Xiao Qing Chen</td>
<td><a href="mailto:XiaoQing.Chen@qimrberghofer.edu.au">XiaoQing.Chen@qimrberghofer.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Jacqueline Raison</td>
<td><a href="mailto:Jacqui.Raison@petermac.org">Jacqui.Raison@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Jeanette Reece</td>
<td><a href="mailto:jreece@unimelb.edu.au">jreece@unimelb.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Gail Risbridger</td>
<td><a href="mailto:gail.risbridger@monash.edu">gail.risbridger@monash.edu</a></td>
<td></td>
</tr>
<tr>
<td>Nandor NandorR</td>
<td><a href="mailto:NandorR@geneworks.com.au">NandorR@geneworks.com.au</a></td>
<td></td>
</tr>
<tr>
<td>Sarah Sawyer</td>
<td><a href="mailto:sarah.sawyer@petermac.org">sarah.sawyer@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Tess Schoenberg</td>
<td><a href="mailto:tess.schenberg@petermac.org">tess.schenberg@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Lyn Schofield</td>
<td><a href="mailto:lyn.Schofield@health.wa.gov.au">lyn.Schofield@health.wa.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Hamish Scott</td>
<td>Scott, Hamish (Health) (<a href="mailto:Hamish.Scott@health.sa.gov.au">Hamish.Scott@health.sa.gov.au</a>)</td>
<td></td>
</tr>
<tr>
<td>Jan Sevcik</td>
<td><a href="mailto:j.sevcik@uq.edu.au">j.sevcik@uq.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Adrienne Sexton</td>
<td><a href="mailto:adrienne.sexton@mh.org.au">adrienne.sexton@mh.org.au</a></td>
<td></td>
</tr>
<tr>
<td>Kylie Shackleton</td>
<td><a href="mailto:kylie.shackleton@mh.org.au">kylie.shackleton@mh.org.au</a></td>
<td></td>
</tr>
<tr>
<td>Sue Shanley</td>
<td><a href="mailto:sue.shanley@petermac.org">sue.shanley@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Mei Sim Lung</td>
<td><a href="mailto:mei.lung@petermac.org">mei.lung@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Skye Simpson</td>
<td><a href="mailto:s.simpson@garvan.org.au">s.simpson@garvan.org.au</a></td>
<td></td>
</tr>
<tr>
<td>Peter Simpson</td>
<td><a href="mailto:p.simpson@uq.edu.au">p.simpson@uq.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Ania Sliwinsk</td>
<td><a href="mailto:ania.sliwinski@gmail.com">ania.sliwinski@gmail.com</a></td>
<td></td>
</tr>
<tr>
<td>Erica Sloan</td>
<td><a href="mailto:Erica.Sloan@monash.edu">Erica.Sloan@monash.edu</a></td>
<td></td>
</tr>
<tr>
<td>Courtney Smyth</td>
<td><a href="mailto:Courtney.smyth@monashhealth.org">Courtney.smyth@monashhealth.org</a></td>
<td></td>
</tr>
<tr>
<td>Melissa Southey</td>
<td><a href="mailto:msouthey@unimelb.edu.au">msouthey@unimelb.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Amanda Spurdle</td>
<td><a href="mailto:Amanda.Spurdle@qimr.edu.au">Amanda.Spurdle@qimr.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Rachel Susman</td>
<td><a href="mailto:rachel.susman@health.qld.gov.au">rachel.susman@health.qld.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Graeme Suthers</td>
<td><a href="mailto:graeme.suthers@health.sa.gov.au">graeme.suthers@health.sa.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Emma Swain</td>
<td><a href="mailto:emma.swain@health.nsw.gov.au">emma.swain@health.nsw.gov.au</a></td>
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<tr>
<td>Yen</td>
<td><a href="mailto:yen.tan@qimrberghofer.edu.au">yen.tan@qimrberghofer.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Margaret</td>
<td><a href="mailto:mctassell@bigpond.com">mctassell@bigpond.com</a></td>
<td></td>
</tr>
<tr>
<td>Jessica</td>
<td><a href="mailto:jessica.taylor@mh.org.au">jessica.taylor@mh.org.au</a></td>
<td></td>
</tr>
<tr>
<td>Renea</td>
<td><a href="mailto:renea.taylor@monash.edu">renea.taylor@monash.edu</a></td>
<td></td>
</tr>
<tr>
<td>David</td>
<td><a href="mailto:d.thomas@garvan.org.au">d.thomas@garvan.org.au</a></td>
<td></td>
</tr>
<tr>
<td>Bryony</td>
<td><a href="mailto:Bryony.Thompson@qimrberghofer.edu.au">Bryony.Thompson@qimrberghofer.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Heather</td>
<td><a href="mailto:Heather.thorne@petermac.org">Heather.thorne@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Kathy</td>
<td><a href="mailto:kathy.tucker@sesiahs.health.nsw.gov.au">kathy.tucker@sesiahs.health.nsw.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Ashok</td>
<td>Ashok Venkitaraman <a href="mailto:arv22@hutchison-mrc.cam.ac.uk">arv22@hutchison-mrc.cam.ac.uk</a></td>
<td></td>
</tr>
<tr>
<td>Jan</td>
<td><a href="mailto:jan.wakeling@health.qld.gov.au">jan.wakeling@health.qld.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Jennifer</td>
<td><a href="mailto:jennifer.walsh@cancervic.org">jennifer.walsh@cancervic.org</a></td>
<td></td>
</tr>
<tr>
<td>Meera</td>
<td><a href="mailto:meera.warby@sesiahs.health.nsw.gov.au">meera.warby@sesiahs.health.nsw.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Clare</td>
<td><a href="mailto:c.watson@garvan.org.au">c.watson@garvan.org.au</a></td>
<td></td>
</tr>
<tr>
<td>Prue</td>
<td><a href="mailto:prue.weideman@petermac.org">prue.weideman@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Sheau</td>
<td><a href="mailto:sheau.lok@mh.org.au">sheau.lok@mh.org.au</a></td>
<td></td>
</tr>
<tr>
<td>Julie</td>
<td><a href="mailto:JulieA.White@health.qld.gov.au">JulieA.White@health.qld.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Allison</td>
<td><a href="mailto:Allison.Wicht@health.qld.gov.au">Allison.Wicht@health.qld.gov.au</a></td>
<td></td>
</tr>
<tr>
<td>Rachel</td>
<td><a href="mailto:R.williams@unsw.edu.au">R.williams@unsw.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Lynda</td>
<td><a href="mailto:lynda.williams@petermac.org">lynda.williams@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Michelle</td>
<td><a href="mailto:Michelle.Wong-Brown@newcastle.edu.au">Michelle.Wong-Brown@newcastle.edu.au</a></td>
<td></td>
</tr>
<tr>
<td>Sook-Yee</td>
<td><a href="mailto:sookyee.yoon@carif.com.my">sookyee.yoon@carif.com.my</a></td>
<td></td>
</tr>
<tr>
<td>Mary-Anne</td>
<td><a href="mailto:mary-anne.young@petermac.org">mary-anne.young@petermac.org</a></td>
<td></td>
</tr>
<tr>
<td>Risha</td>
<td><a href="mailto:risha.zia@sesiahs.health.nsw.gov.au">risha.zia@sesiahs.health.nsw.gov.au</a></td>
<td></td>
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