# PROGRAMME

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

"Familial Aspects of Cancer 2015 Research and Practice"

## Tuesday 25th August

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<td>Welcome: Nicholas Pachter</td>
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<td>FCC Session 1. <em>Genomic issues in genetic counselling</em></td>
<td>Chairpersons: Margaret Gleeson and Mary-Anne Young</td>
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<td>9.40 – 10.00</td>
<td>Genomes, Exomes and SNPs</td>
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<td>Variants in Practice Study (VIP): Genetic health professional's beliefs and attitudes towards about the clinical utility of SNP testing in high risk breast cancer families</td>
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<td>10.30 – 11.00</td>
<td>Genomic counseling: Is it different from &quot;traditional&quot; genetic counseling?</td>
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FCC Session 2. *“Next-Generation Sequencing” and uncertainty*

Chairperson: Nicola Poplawski

Supported by: Clinical Oncological Society of Australia
11.00 – 11.20  Developing the right test – application of next-generation sequencing to familial cancer risk prediction.  
Karin Kassahn

11.20 – 11.40  Sequence variant classification: process, traps and pitfalls in reporting  
Lesley Rawlings

11.40 – 12.10  NGS: Helping clients/patients live with uncertainty  
Jemma Gilchrist

12.10 – 12.30  Panel discussion

12.30 – 1.30  Lunch

FCC Session 3.  Chemoprevention/risk reducing medication  
Chairperson: Sue Shanley

1.30 – 1.55  Risk-reducing medication for breast cancer – what’s new?  
Kelly-Anne Phillips

1.50 – 2.20  Young Australian women’s perspectives and experiences about taking medication to reduce breast cancer risk due to a BRCA1/2 mutation  
Laura Forrest

2.20 – 2.45  A national survey of clinician attitudes to risk-reducing medication  
Gillian Mitchell and Annabel Goodwin

2.45 – 3.00  Panel discussion

3.00 – 3.30  Afternoon Tea

FCC Session 4.  Session 4: Surgical Prevention of Breast Cancer  
Chairperson: Nicholas Pachter

3.30 – 4.00  Surgical prevention of breast cancer – the suite of options available for women at high risk  
Christobel Saunders

4.00 – 4.30  The surgical approach to risk reduction mastectomy and immediate breast reconstruction in the high risk patient at POW campus.  
Garry Buckland
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| 4.30 – 4.50 | Risk-reducing mastectomy: The experience of women at a high-risk clinic and psychosocial implications  
Bettina Meiser |
| 4.50 – 5.00 | Discussion                                                             |
| 5.00   | Meeting closed                                                         |
| 5.30 – 6.30 | Plantation Room:  
ENIGMA qualitative and quantitative Variant classification criteria for evaluating the clinical significance of BRCA1/2 sequence variants: A tutorial  
Mandy Spurdle |
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<td>Breast cancer risk prediction using a polygenic risk score in the</td>
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<td>familial setting: a prospective study from the Breast Cancer Family</td>
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<td>David Goldgar</td>
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<td>Screen detected and interval cancers: genomic analysis points to</td>
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<td>different molecular etiology?</td>
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<td>Kylie Gorringe</td>
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<td>10.20 – 10.40</td>
<td>Genome-wide association studies of endometrial cancer: results to</td>
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<td>date from the Endometrial Cancer Association Consortium.</td>
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<td>Tracy O’Mara</td>
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<td>10.40 – 11.00</td>
<td>Odds PER Adjusted deviation (OPERA): putting breast cancer risk</td>
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<td>factors into perspective to inform translation and precision population</td>
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<td>11.30 – 12.10</td>
<td>The Jeremy Jass Memorial Lecture</td>
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<td>Chemoprevention of Lynch Syndrome: Lessons and Progress.</td>
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<td>Tim Bishop</td>
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<td>12.10 – 12.30</td>
<td>Whole exome and genome sequencing of individuals with serrated</td>
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<td>polyposis syndrome</td>
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<td>Dan Buchanan</td>
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12.30 – 12.50  Evidence for further colorectal cancer susceptibility genes in addition to the Mismatch repair genes and MUTYH.
Aung Ko Win

12.50 – 1.10  Bi-allelic somatic mutations as a cause of tumour mismatch repair-deficiency in a population-based colorectal and endometrial cancer with suspected Lynch syndrome.
Dan Buchanan

1.10 – 2.10  Lunch

Session 3 –  Plantation Room
Chairperson: Mandy Spurdle

2.10 – 2.40  New insights into the transcriptional networks governing mammary stem cell homeostasis and basal-like breast cancer aetiology.
Alex Swarbrick

2.40 – 3.00  DNA methylation and early-onset breast cancer.
Cameron Scott

3.00 – 3.20  Breast cancer subtypes and defined by methylome-wide analysis.
Eric Joo

3.20 – 3.40  Development of a large scale construct-based targeted mRNA sequencing analysis pipeline for in vitro transcript analysis: application to validation of bioinformatics prediction of de novo donor site creation by BRCA1/2 sequence variants.
Michael Parsons

3.40 – 4.00  The molecular landscape of advanced or recurrent endometrial cancer.
Michelle Wilson

4.00 – 4.30  Afternoon Tea

Session 4 –  Plantation Room
Chairperson: Kelly Ormond

4.30 – 4.50  Returning research results to research participants: telephone genetic counselling makes a difference.
Mary Anne Young
Patient satisfaction with delivery of genetic testing results via telephone versus delivery in person; our experience in the Illawarra and Shoalhaven Hereditary Cancer Clinic.
Sian Greening

On the road to mainstreaming
Maira Kentwell

Poster Session + Wine and Cheese in the main foyer

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

Chairperson: Mathilda Wilding
Order of abstract presentation:

#9  No bullshit therapy in the familial cancer setting.
Lindy Hodgkin

#12  Patient funded genetic testing: the who, the why, and the what now
Sharne Limb

#27  Designing comprehensive, targeted inherited colon cancer screening panels...is NGS enough?
Shannon Cowie

#28  Screening Victorian women with endometrial cancer for Lynch syndrome – early results
Shona O'Connell

#22  Attitudes towards a BRCA genetic testing program within the Jewish community.
Nicole Cousens

#33  Genome-wide methylation signature as a strategy for “classifying” rare PALB2 genetic variants.
Jenna Stewart

#34  Mutation screening of RNASEL, a candidate breast cancer susceptibility gene identified via whole-exome sequencing.
Alexis Roberge

Delegates organise their own dinner
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<td>8.45 – 9.20</td>
<td><strong>Genetic counselling of the future: the role of health behaviour theory and counselling</strong></td>
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<td><strong>Communicating personalised genomic risk information to the public: a focus group study</strong></td>
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<td>Amelia Smit</td>
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<td>9.40 – 10.00</td>
<td><strong>Young Australians women’s decision-making about managing their cancer risk arising from a \textit{BRCA1/2} mutation.</strong></td>
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<td>Laura Forrest</td>
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<td>10.00 – 10.20</td>
<td><strong>How empowered do carriers of hereditary gene mutations participating in an annual review program feel about managing their cancer risk?</strong></td>
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<td>Lucinda Hossack</td>
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<td>10.20 – 10.40</td>
<td><strong>The psychological effects of a whole body screening trial (SMOC+) in germline \textit{TP53} mutation carriers.</strong></td>
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<td>Kate McBride</td>
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<td>11.10 – 11.45</td>
<td><strong>Factors moderating survival from melanoma.</strong></td>
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<td>Julia Newton-Bishop</td>
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<td>11.45 – 12.15</td>
<td><strong>The Australian Melanoma Genome Project.</strong></td>
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<td>Nick Hayward</td>
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<td>12.15 – 12.45</td>
<td><strong>Convergent intra-patient evolution in therapy naïve melanoma.</strong></td>
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12.45 – 1.00  Panel discussion

1.00 – 2.00  Lunch

Session 7  Plantation Room
Chairperson: Melissa Southey

2.00 – 2.25  A UK perspective on familial melanoma.
Julia Newton-Bishop

2.25 – 2.45  Germline genomic screening of 1,162 sarcoma families.
David Thomas

2.45 – 3.05  Predicting pathogenicity of TP53 mutations: an integrated multifactorial model.
Paul James

3.05 – 3.25  Assessment of germline cancer predisposition genes in pancreatic cancer.
Skye McKay

3.25 – 3.45  Mutations in a promoter of APC cause a syndrome of gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) without colorectal involvement.
Georgia Chenevix-Trench

3.45 – 4.05  Heritable epimutations associated with breast cancer.
James Dowty

4.05 – 4.30  Afternoon Tea

4.10 – 6.00  Streamlining genetic testing in ovarian cancer - a workshop.
All Welcome

6.00 – 8.00  Conference Cocktail drinks pool side @ Peppers.
All delegates welcome.

Delegates organise their own dinner
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<td>Clinical implications of intratumoural heterogeneity in high-grade serous ovarian cancer (HGSOC)</td>
<td>James Brenton</td>
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<td>Fertility implications of having a BRCA1 or BRCA2 mutation.</td>
<td>Kelly-Anne Phillips</td>
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<td>9.25 – 9.45</td>
<td>Quality of risk reducing gynaecologic surgery in Australasian women at high risk of pelvic serous cancer.</td>
<td>Y. C. Lee</td>
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<td>9.45 – 10.05</td>
<td>Understanding acquired resistance in high-grade serous ovarian cancer (HGSC).</td>
<td>Kath Alsop</td>
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<td>10.05 – 10.25</td>
<td>Risk of extracolonic cancers for people with biallelic and moñoallelic mutations in MUYTH.</td>
<td>Aung Ko Win</td>
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<td>The role of common genetic variation in ovarian cancer susceptibility.</td>
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<td>Searching for new familial breast cancer predisposition genes.</td>
<td>Na Li</td>
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<td>11.55 – 12.15</td>
<td>Evidence-based massively parallel translation: Application to breast cancer susceptibility.</td>
<td>Melissa Southey</td>
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<td>12.15 – 12.35</td>
<td>Germline $MLH1$ mutation type and frequency in individuals with solitary loss of $PMS2$ expression in colorectal carcinoma.</td>
<td>Mark Clendenning</td>
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12.35 – 12.55  Panel testing for familial breast cancer: tension at the boundary of research and clinical care.
Paul James

End of Meeting:  Lunch will be served
Programme

Tuesday 25\textsuperscript{th}

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“Familial Cancer 2015: Research and Practice”

\textit{FCC Session 1:}

\textit{Plantation Room}

Chairperson: Margaret Gleeson and Mary-Anne Young
Genomes, Exomes and SNPs

Alison Trainor
Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne

The genomic landscape of cancer predisposition, progression and response to treatment is being increasingly densely populated with data obtained from large international collaborative exome, genome and re-sequencing projects as well as genome wide association studies. This information, and the technology used to derive it, has already expanded current familial cancer testing through the development of multigene panels and systemic therapies targeted to germline and somatic cancer predisposition mutations. A future genome-first approach to genetic testing will foster a further shift within the current service model from uni-variant to multi-variant risk assessment as well as expand the remit of the service by using such tests to optimise primary, secondary and tertiary cancer prevention programs within high risk clinics and more generally across the population; finely tuning preventative strategies commensurate with a defined quantifiable risk at the individual level. The current challenge lies in the development of both fit-for-purpose diagnostic tests of proven clinical validity and utility, and clinical management models which can respond to and support patients undergoing such tests within an ethically and socially acceptable framework.
Variants in Practice Study (VIP): Genetic health professional’s beliefs and attitudes towards about the clinical utility of SNP testing in high risk breast cancer families.

M.A. Young¹, P. James¹,², V.M. Rasmussen¹, Mitchell G¹,², Forrest L.E.¹,², N. Hallowell³
¹The Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia, ²Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, VIC, Australia; ³Centre for Health & Society, University of Melbourne, Parkville, Victoria;

Background:
Results from genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms (SNPs) that significantly contribute to breast cancer risk. Australian data demonstrate that testing for these genetic factors identifies a group of high-risk women who have characteristic clinical features including the risk of a second primary breast cancer but no risk of ovarian cancer.

Lay and professional understandings of information generated by SNP testing need to be investigated to identify the most effective ways to communicate this polygenic risk information to patients and the treating medical team.

Methods:
Qualitative interviews investigated patient and healthcare professionals’ understandings of breast cancer SNP data. This presentation focuses upon health professionals’ (n=20) knowledge and beliefs about the clinical utility of SNP testing in family cancer clinics (FCCs).

Results:
Analysis revealed a number of preliminary themes suggesting genetic health professionals are uncertain about the clinical utility of SNP testing in high risk breast cancer families. This uncertainty is associated with a lack of definitive penetrance data, risk estimates and risk management guidelines. Whilst health professionals described acquiring knowledge about SNP testing in a variety of ways, they felt their knowledge was limited. Organisational change was identified as one area which requires examination prior to the integration of SNP testing in FCCs. Recommendations for training and support will be made.
Genomic Counseling: Is it different from ‘traditional’ genetic counseling

Kelly Ormond
Professor, Department of Genetics and Stanford Center for Biomedical Ethics
Stanford University, Stanford, CA, USA

Over the past several years, genetic testing has expanded rapidly from single gene testing to multigene panels and both research and clinical exomes and genomes. As such, clinicians including genetic counselors have had to revisit the traditional approaches to patient education, informed consent and choices about genetic testing. In this talk, we will discuss some of the changes to educational approaches and informed consent, and available data about how this is being enacted in research and clinical settings. We will discuss return of results and different approaches that are in practice, and the role of psychosocial assessment and support. We will also discuss the role of genetic counselors within the healthcare team that provides genomic testing and interpretation. Genetic counselors have a range of future roles to consider as genomic information is increasingly integrated into medical practice.
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“Familial Cancer 2015: Research and Practice”

FCC Session 2:

*Plantation Room*

Chairperson: Nicola Poplawski
Developing the right test – application of next-generation sequencing to familial cancer risk prediction

Karin S Kassahn¹,² Amanda Tirimacco¹, Lesley Rawlings¹
¹Genetics and Molecular Pathology, SA Pathology, Adelaide SA 5000
²School of Biological Sciences, The University of Adelaide, Adelaide SA 5000

Next-generation sequencing offers exciting opportunities to screen multiple disease-associated loci at once, thus reducing time to diagnosis. On the other hand, careful selection of target loci is required to allow clinical interpretation and application of the results. Analysis of large number of gene loci at once also holds challenges in variant annotation and prioritization. As part of our ongoing service development, we have recently implemented a familial cancer next-generation sequencing targeted panel which we use to create different “virtual” gene panels depending on the request for testing. This talk will outline our testing strategy, experience with triaging patients for different “virtual panels” and touch on some of the technical issues relating to quality control and measurement uncertainty using these technologies. Finally, the talk will discuss our patient consent process and how our time to diagnosis and test costs have tracked since implementation of these technologies.
Sequence variant classification: processes, traps and pitfalls in reporting.

Lesley Rawlings¹, Karin Kassahn¹,², Adrienne Sexton³, Ingrid Winship³, Denae Henry¹, Jacqueline Rossini¹, Cassandra Vakulin¹, Amanda Tirimacco¹, Grace McKavanagh¹
¹ Genetics and Molecular Pathology, SA Pathology, Adelaide SA 5000
² School of Biological Sciences, The University of Adelaide, Adelaide SA 5000
³ Familial Cancer Centre, Royal Melbourne Hospital, 2-Centre, Grattan St, Parkville VIC 3052

Methods to analyse DNA sequence variants that may be causative of disease have been available for diagnostic testing for many years and the list of genes and suspect variants within genes has grown exponentially. With the introduction of massively parallel sequencing, the tide of potential causative variants and especially those that are suspect, but have relatively little evidence for pathogenicity, has become a torrent.

For many years, the SA Pathology Familial Cancer Laboratory has taken a systematic, investigative approach that has provided standardised outcomes for reporting sequence variant classifications. This approach has been supported by recent literature and is easily carried into Next Generation Sequencing. This presentation will review the process of variant analysis used in our lab and also present a case study of how a change in variant classification can change the outcome of kindred management.
NGS: Helping clients - patients live with uncertainty

Jemma Gilchrist
Senior Clinical Psychologist, Westmead Breast Cancer Institute, NSW.

Living with uncertainty is one of the most difficult and ongoing challenges for people who have had a personal history of cancer or an identified gene mutation which increases their chances of developing a cancer. In the clinical setting, it is common to see patients who are emotionally overwhelmed, anxious, frustrated and confused about the best options for them. Communicating about uncertain but potentially distressing outcomes is a real challenge for many clinicians, whatever their role in the multi-disciplinary team and can challenge their own values and opinions. This presentation will outline the complex features which contribute to uncertainty in patients and how particular concerns and issues impact upon their clinical presentation and decision making. Focus will be placed on the psychological strategies used to tolerate and manage uncertainty and the emotions and behaviours that accompany it such as anxiety, grief, insecurity or avoidance. It will address ways to assist patients to understand the meaning of what they are facing and to make choices that are properly informed and well-considered. Finally, the presentation will aim to assist clinicians to self-reflect on how their own opinions and beliefs can impact the way in which they approach these intricate and idiosyncratic clinical situations.
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“Familial Cancer 2015: Research and Practice”

FCC Session 3:

Plantation Room

Chairperson: Sue Shanley

“Familial Cancer 2015: Research and Practice”
Risk-reducing medication for breast cancer – what’s new?

Kelly–Anne Phillips, Peter MacCallum Cancer Centre.

Use of risk-reducing medication (RRM) for the primary prevention of breast cancer is endorsed in national and international guidelines. For post-menopausal women, options include five years of the selective estrogen receptor modulators (SERMS), tamoxifen or raloxifene, or the aromatase inhibitors exemestane or anastrozole. For pre-menopausal women, tamoxifen is the only evidence-based option. Several recent reports have added to the evidence-base for RRM.

A meta-analysis of SERMS for primary prevention has confirmed a 38% reduction in breast cancer risk with 5 years of use (Cuzick J et al Lancet 2013; 381: 1827-34) and long term results from the IBIS I study show that tamoxifen reduces breast cancer incidence for at least 20 years (Cuzick J et al. Lancet Oncol 2015; 16: 67-75). Updated results of the STAR trial continue to show that raloxifene is less effective than tamoxifen, although with a better side-effect profile (Wickerham DL, ASCO 2015). The first report of the IBIS II trial has shown that anastrozole is an efficacious primary breast cancer prevention option for post-menopausal women (Cuzick J, et al Lancet 2014; 383: 1041-48).

Despite high quality evidence of the efficacy of RRM for primary prevention of breast cancer, uptake in Australia remains low. iPrevent®, a web-based breast cancer risk assessment and risk management decision support tool, has been developed to try to address clinician and client barriers to uptake (Collins IM et al. Breast 2014; 23 : 644-50 and Phillips KA Aust J Prim Health 2015 Feb 24. doi: 10.1071/PY14156). In addition submissions for tamoxifen for primary breast cancer prevention to both the Therapeutic Goods Administration and the Pharmaceutical Benefits Advisory Committee are imminent and, if successful, tamoxifen should be reimbursed for this indication in Australia after September 2016.
Young Australian women’s perspectives and experiences about taking medication to reduce breast cancer risk due to a BRCA1/2 mutation

Laura E Forrest,1,2 Mary-Anne Young,1 Sue Shanley,1 Victoria Rasmussen,1 Gillian Mitchell1,2
1. Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, Australia
2. Sir Peter MacCallum Department of Cancer Oncology, University of Melbourne, Australia

Background
Young women aged 18 – 40 years who have a BRCA1/2 mutation have the option of taking Tamoxifen for chemoprevention to reduce their breast cancer risk. Despite offering a risk reduction of up to 50%, the uptake of Tamoxifen by women with a BRCA1/2 mutation is known to be low. Studies examining women’s intentions to take Tamoxifen were associated with heightened perceived breast cancer risk and belief of the efficacy of the medication. Less is known about Tamoxifen within the context of young adulthood, a life stage characterised by the formation of intimate relationships and childbearing. This study examines young Australian women’s perspectives and experiences of taking Tamoxifen to reduce breast cancer risk due to a BRCA1/2 mutation.

Methods
A grounded theory approach has been undertaken using qualitative, semi-structured interviews to collect data. The inclusion criteria included women who have a BRCA1/2 mutation, aged 18 – 40 years, who received their genetic test result more than 12 months prior. Data were analysed iteratively and inductively to identify themes, ideas, concepts and categories.

Results
Thirty-eight of 40 semi-structured interviews have been conducted to date with women aged 20 – 40 years with a BRCA1/2 mutation. Recall of whether a healthcare professional had provided information and counselling about taking Tamoxifen to reduce breast cancer risk was variable. For the women who could recall being counselled about Tamoxifen, only six were taking or had tried to take the medication. Most of these women experienced transient side effects, but this did not warrant the cessation of the risk reducing medication. These participants described Tamoxifen as a “safety blanket”, valued for its “non-invasive” nature. In contrast, the women who had chosen not to take Tamoxifen were concerned about potential side effects, were planning to have children in the next five years, or perceived the evidence for the efficaciousness of Tamoxifen for younger women was lacking.

Discussion
These findings provide insight into the perceptions underlying young Australian women’s decision-making about taking Tamoxifen to reduce breast cancer risk. Findings must be considered alongside these young women’s decisions and experiences of other risk reducing measures including screening and surgery.
A national survey of clinician attitudes to risk-reducing medication

Gillian Mitchell, BC Cancer Agency, Canada, Annabel Goodwin Royal Prince Alfred Hospital, Sydney.

Despite good level 1 evidence for the benefits of cancer risk-reducing medication in women at high risk of breast cancer, few women at risk use this cancer risk management strategy. Understanding why so few women at risk are using this medication is key to addressing the low uptake and realising the potential of this risk management strategy. Most research into the low uptake has focussed on the women themselves and their perceptions around the pros and cons of this medication and has returned a list of potential factors including their perception of cancer risk and risk of side-effects from the medication and their doctor’s recommendations. Early research into the views of clinical staff in genetics clinics highlighted their perceived lack of knowledge about and concern about the level of evidence in support of this approach as potential barriers to their promotion of this risk management strategy. Less data is yet available around the uptake of aspirin as a risk-reducing medication in people with Lynch Syndrome or the views of clinicians managing people with Lynch Syndrome.

People at risk seek advice about their risk management options from a range of clinical staff and are influenced by the strength of their views. Hence, we sought the current views about cancer risk-reducing medication of clinicians within and outside Familial Cancer Clinics who are involved in the care of women at high risk of breast cancer or people with Lynch Syndrome with the aim of identifying potential barriers to the promotion and delivery of cancer risk-reducing medication in high risk populations. Questions focussed on their understanding of the strength of evidence in support of risk-reducing medication, their experience in prescribing these medicines and which clinicians should be responsible for assessing risk and prescribing these medicines.

We had 99 respondents to the breast cancer prevention questionnaire; 33 medical oncologists, 23 genetic counsellors, 20 breast surgeons, 7 radiation oncologists, 4 genetic/risk management nurses, 3 clinical geneticist and 3 other health professionals. Most respondents felt that the medical oncologist (84%), Cancer Genetics/Family Cancer Clinicians (84%) and breast physicians (74%) should be responsible for discussing the benefits of tamoxifen. 84% of respondents felt that it was the responsibility of the medical oncologist to initial prescription of tamoxifen compared to 70% for breast physicians, 56% for genetic counsellors, 54% for surgeons and 27% for GPs. Of the 99 respondents most felt that it was the role of the medical oncologist 73%, breast physician 71% or GP 64% to monitor patients once they had started on tamoxifen compared to 43% feeling that this was the breast surgeon’s role or 32% the genetic counsellors role.

155 health professionals responded to the aspirin questionnaire; 41 genetics health professionals, 44 gastroenterologists, 52 colorectal surgeons and 18 other health professionals. Aspirin was considered to a ‘very’ or ‘somewhat’ effective RRM by 85.4% of genetics health professionals, 86.3% of gastroenterologists and 59.6% of colorectal surgeons ($p = 0.001$). 80.5% of genetics health professionals, 63.6% of gastroenterologists and 61.5% of colorectal surgeons were ‘very’ or ‘somewhat’ confident in understanding the literature on aspirin ($p=0.019$). Aspirin as a RRM would be recommended by 88.2% of genetics professionals, 92.6% of gastroenterologists, and 91.3% of colorectal surgeons ($p=0.42$). Overall genetics professionals reported greater confidence regarding their knowledge of the literature than gastroenterologist or colorectal surgeons, but all specialist groups were highly likely to discuss and recommend aspirin as a risk-reducing medication.
Programme

Tuesday 25th

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

“Familial Cancer 2015: Research and Practice”

FCC Session 4:

Plantation Room

Chairperson: Nicholas Pachter
Surgical prevention of breast cancer – the suite of options available for women at high risk

Christobel Saunders

Numbers of women requesting surgical prevention have dramatically risen over recent years – in part due to media and increasing awareness.
What data do we have in Australia for numbers of women requesting preventative surgery?
How do surgeons make the decision that a woman’s risk of breast cancer warrants surgery?
When surgery is offered what reconstructive procedures are discussed and how is this decision made?
Finally this paper will outline some exciting new advances in surgical reconstruction techniques and the outcomes of these.
The surgical approach to risk reduction mastectomy and immediate breast reconstruction in the high risk patient at POW campus.

Garry Buckland FRACS (Plast)

The Hereditary cancer clinic at Prince of Wales Hospital Randwick manages a large volume of patients with the BRCA1 and 2 gene mutations and other conditions which result in an increased risk of developing carcinoma of the breast. Whilst the majority of patients elect to be managed conservatively via regular screening, a smaller group elects to be managed by Risk reduction mastectomy and immediate reconstruction.

Over the last 10 years significant refinements in surgical technique coupled with technological advances in reconstructive devices has changed the surgical approach to prophylactic surgery in the high risk patient and resulted in significantly improved functional and cosmetic outcomes.

I will present our progression in surgical techniques and discuss the advances in reconstructive devices that has led to our current approach and illustrate these with clinical cases.
Risk-reducing mastectomy: The experience of women at a high-risk clinic and psychosocial implications

Bettina Meiser, Psychosocial Research Group, Prince of Wales Clinical School, University of New South Wales and Prince of Wales Hospital, Randwick, NSW 2031, Australia

Decisions about risk reduction options for high-risk women are difficult due to the complexity of the issues to be considered. Many women without a personal history of breast cancer from hereditary breast cancer families consider risk-reducing bilateral mastectomy (RRBM). In this presentation, uptake rates of RRBM will be reviewed as will the psychosocial predictors of uptake of RRBM. Early research in this area indicated that women intending to undergo RRBM may be motivated by high levels of breast anxiety, thus raising concerns that women may choose surgical intervention without fully anticipating its psychological and medical impact. However, subsequent studies on actual uptake and impact of RRBM show that women who declined the procedure were more prone to anxiety and that women who underwent RRBM showed significantly decreased psychological morbidity, compared to those who declined the procedure. Decisions about risk-reducing surgery and genetic testing remain difficult for high-risk women and their clinicians, and women are likely to benefit from interventions aimed at facilitating shared and informed decision-making. Decision aids are an example of interventions to assist women in making informed choices about their risk management and have been shown to be effective in the cancer genetic counselling setting. Unique management issues also arise for women with a personal history of hereditary breast cancer. Many women will consider mastectomy for the affected breast plus risk-reducing contralateral mastectomy as a means of treating both their current breast cancer and preventing potential future breast cancers. Given the highly complex and personal nature of decisions about whether to undergo therapeutic mastectomy with risk-reducing contralateral mastectomy, rapid genetic testing, also referred to as treatment-focused genetic testing, following a new diagnosis of breast cancer is being offered to an increasing number of women, who have been newly diagnosed with breast cancer to help guide their surgical treatment. The psychosocial issues around treatment-focused genetic testing will be reviewed briefly.
ENIGMA qualitative and quantitative Variant classification criteria for evaluating the clinical significance of BRCA1/2 sequence variants: A tutorial

Amanda Spurdle
QIMR Berghofer Medical Research Institute, Brisbane, Qld, Australia

Large-scale studies evaluating cancer gene variants in the BRCA1/2, and now other known or suspected breast cancer predisposition genes, are being undertaken by the international consortium ENIGMA. Data curation has identified considerable inconsistency in variant nomenclature and classification across different international clinical testing and research laboratories. ENIGMA has developed and documented detailed classification criteria for BRCA1/2, to promote standardized and normalized variant classification. These criteria are being used by to review BRCA1/2 variant classifications from clinical testing sites in Australian and internationally. Further, in collaboration with ClinVar, ClinGen, LOVD, HVP and the GA4GH BRCA Challenge project, ENIGMA is developing a single portal for display of variants reviewed and classified by members of the ENIGMA BRCA1/2 Expert Panel.
Programme

Wednesday 26th

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

Session 1:

Plantation Room

Welcome: Georgia-Chenevix-Trench

Chairperson: Georgia Chenevix-Trench
The role of rare coding variations in ovarian cancer susceptibility

Paul Pharoah, Department of Oncology, Department of Public Health and Primary Care
University of Cambridge; UK

High and moderate penetrance alleles of the known ovarian cancer susceptibility genes account for less than half of the excess familial risk of disease (or genetic variance). Complex segregation analysis suggests that much of the remainder will be due to a large number of common alleles with weak effects. However, it is also likely that multiple uncommon or rare moderate penetrance alleles exist. In this talk I will describe the work we have been doing using a targeted sequencing approach within a case-control study design to investigate the role of protein truncating variants in DNA repair genes in ovarian cancer risk. So far we have sequenced over 30 candidate genes in ~3,400 cases and 3,400 controls. I will describe the risk associated alleles we have identified and their associated risks and discuss the potential for clinical translation of these findings.
Breast cancer risk prediction using a polygenic risk score in the familial setting: a prospective study from the Breast Cancer Family Registry and kConFab resources.

Hongyan Li1, Bingjian Feng2, Alexander Miron3,4, Xiaqing Chen5, Jonathan Beesley5, Emmanuella Bineh6, Daniel Barrowdale7, Esther M John7, Mary B Daly9, Irene L. Andurils10, Saundra Buys11, Peter Kraft12, kConFab investigators7, Heather Thorne7, Georgia Chenevix-Trench5, Antonis Antoniou13, Paul James14,15, Mary Beth Terry16,17, Kelly Phillips14, John L.Hopper18, Gillian Mitchel14,15, and David E. Goldgar1,2.

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Purpose: The purpose of this study is to examine the utility of panels of SNPs in the context of non-BRCA1/2 familial breast cancer (BC), where women are already at elevated risk due to their family history and to determine if such SNP panels could be of clinical utility in stratifying women into clinically useful risk groups even when they are already at higher risk as a result of having a family member with breast cancer or members who are carriers of BRCA1/2.

Patients and Methods: We used genotype results on 27 known BC risk SNPs to derive a polygenic risk score (PRS) for 5,355 women from the BCFR and kConFab familial breast cancer cohorts. We compared this score in affected and unaffected women at baseline. 3017 women who were unaffected at enrollment were prospectively followed for an average of 7.2 years. Cox proportional hazards regression was used to analyze the association of BC risk with Polygenic Risk Score (PRS) score based on the weighted sum of risk alleles at a 27 BC . PRS was treated as both a continuous variable and comparison of the upper and lower quintiles.

Results: The mean (SD) for combined PRS by affected status at baseline was 0.125 (0.37) for the affected and 0.042 (0.37) for unaffected women (p=3x10^-14). There were 240 cases occurring in follow-up in the combined cohort. The HRs for continuous PRS and upper/lower quintiles were 2.69 (95% CI: 1.93, 3.75,) and 3.75 (95% CI: 2.30, 6.08) respectively. The ten-year risks (independent of age) 17.2% for the highest quintile of the PRS compared with 6.6% for the lowest and risks to age 70 were 52% and 19% respectively.

Conclusion: Using a subset of breast cancer associated SNPs can provide substantial outcome predictive power. The level of risk found in this study could influence recommendations for cancer screening and prevention modalities and frequencies in women.
Screen detected and interval cancers: genomic analysis points to different molecular etiology?

Kylie L Gorringe¹, Sally M Hunter¹, David Byrne², Lisa Devereux³, Simone M Rowley¹, Kenny Elder¹, Rhonda Huynh³, Kenji Fujihara¹, John Hopper⁴, Vicki Pridmore⁵, Anne Kavanagh⁴, Gillian Mitchell⁶, G Bruce Mann⁷, Stephen B Fox², Ian G Campbell¹


Breast cancers diagnosed after a negative mammogram but prior to the next screening episode are termed “interval cancers” and comprise as many as 25% of all cancers diagnosed in women attending population-based screening programs. The high interval cancer rate is a major problem affecting the effectiveness of mammographic screening. It is unclear whether interval cancers represent a distinct biological entity compared to screen-detected cancers or whether their designation is simply an arbitrary outcome of screening timing. Using an Australian prospective population-based cohort of over 53,000 women (LifePool), 554 cases of breast carcinoma (in situ and invasive breast cancer) were identified, of which 399 had known screening status at time of diagnosis. Pathology reports, mammographic density data, germline DNA and tumor tissue were available for analysis.

Interval cancers had a younger age at diagnosis (p<0.001), increased tumor size (p<0.05), lower proportion of ER positive staining (p<0.01) and higher grade (p<0.05). Screen and interval cases showed no significant differences in mammographic density or PR status but there was a trend towards a higher proportion of HER2 positive cases in interval cancers. Cancers of unknown status had overlapping clinico-pathological features with interval cancers.

Somatic copy number analysis was performed on a subset of invasive screen detected and interval cancers cases using OncoScan MIP arrays. No difference in the overall number of copy number aberrations or fraction of the genome altered were observed, however specific differences were noted between interval and screen detected cases. These included copy number changes on chromosomes 8 and 11. Analysis of germline DNA was performed using a panel sequencing approach of known breast cancer genes as well as lower-penetrance breast cancer SNPs. A preliminary analysis of the contribution of low-penetrance risk alleles did not identify differences between interval, screen detected and unknown cases, however the number of cases in the analysis was small. Pathogenic mutations in BRCA1, BRCA2, TP53 and PALB2 were identified in 1/10 interval cases (in BRCA2), 1/66 screen-detected cases and 8/77 cases with currently unknown screen/interval status. Interval cancers may thus have an increased contribution from high-penetrance predisposing variants.
Genome-wide association studies of endometrial cancer: Results to date from the Endometrial Cancer Association Consortium

Tracy A O’Mara¹, Deborah J Thompson², Jodie N Painter¹, Timothy Cheng³, Stacey Edwards¹, Dylan M Glubb¹, Alison M Dunning², Ian Tomlinson³, Douglas F Easton² and Amanda B Spurdle¹ on behalf of the Endometrial Cancer Association Consortium

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Endometrial cancer is the most common cancer of the female reproductive system in developed countries. To investigate genetics of endometrial cancer, we have established the Endometrial Cancer Association Consortium (ECAC) comprising 11 study groups from Europe, the USA and Australia. We have previously identified the HNF1B locus to be associated with endometrial cancer risk by the first genome-wide association study (GWAS) for this disease. We have since conducted a meta-analysis of three endometrial cancer GWAS and two replication phases totaling 7,737 endometrial cancer cases and 37,144 controls of European ancestry. Genome-wide imputation and meta-analysis identified seven novel risk loci at genome-wide significance ($P < 5 \times 10^{-8}$). These loci included HNF1B, previously identified by our group, and the CYP19A1 candidate locus. SNPs at the CYP19A1 locus were also found to be significantly associated with serum levels of estrogen amongst postmenopausal women, exposure of which is a well-established risk factor for endometrial cancer. Bioinformatic analysis of the five novel loci found that endometrial cancer risk SNPs lie in likely enhancers predicted to regulate genes or miRNAs with known or suspected roles in tumourigenesis. Results from the meta-analysis of GWAS of endometrial cancer, as well as bioinformatics, fine-mapping analysis and initial functional studies of risk loci will be presented.
Odds PER Adjusted standard deviation (OPERA): putting breast cancer risk factors into perspective to inform translation and precision population health

John Hopper for Australian Breast Cancer Family Registry (ABCFR), Australian Mammographic Density Twins and Sisters Study (AMDTSS) and Melbourne Collaborative Cohort Study (MCCS) University of Melbourne, School of Population and Global Health, Carlton, Vic 3053

The concept of OPERA (Odds PER Adjusted standard deviation) allows comparison of risk factors on a population, as distinct from individual, basis (Hopper, Am J Epidemiol 2015). There are two key issues: (i) using standard deviation allows application to continuous, binary and ordinal risk factors, and (ii) standard deviations need to be adjusted for all other risk factors in the design and analysis. Note that the predicted inter-quartile risk ratio (IQRR) ~ OPERA^{2.5}.

Based on the literature and our new Australian studies: (a) for epidemiological risk factors such as number of child births, OPERA = 1.1; (b) for mutations in major genes such as BRCA1, BRCA2, etc. combined, OPERA = 1.2; for family history (yes/no), OPERA = 1.3; for mammographic density for age and BMI as currently defined (Cumulus), OPERA = 1.4 (Baglietto et al., Am J Epidemiol 2014); for polygenic score based on 77 ‘known’ SNPs, OPERA = 1.5; for epigenetic effects such as global methylation which has almost no genetic variance (AMDTSS), OPERA = 1.6 (Severi et al., Br Cancer Res Treat 2014, based on MCCS); family history based on multigenerational data and BOADICEA 5 year risk adjusted for age, OPERA = 1.7 with a small correlation with the polygenic score above (Dite et al., submitted, based on ABCFR and breast cancer before age 50); new measures of mammographic density for age and BMI (Altocumulus and Cirrocumulus), which have little genetic variance, OPERA = 1.8-2.0 (Nguyen et al., submitted, based on ABCFR and AMDTSS); BOADICEA plus polygenic risk score, which are at most weakly correlated, OPERA = 2.0 (Dite et al. above). OPERAs for risk scores based on more than 77 SNPs with and without inclusion of BOADICEA, epidemiological risk factors and/or mammographic density measures will be presented. For OPERA = 2, IQRR ~ 5 to 6 so that ~20% of women in the population would be at the increased risk (over average) as those in category 3 of the Guide for Medical Practitioners on Familial Aspects of Breast Cancer.

These estimates have implications for using risk prediction to lower the impact of breast cancer. Automated mammographic density measures implemented into digital screening programs such as BreastScreen, combined with BOADICEA or similar (e.g. H score) family history measures, (and potentially global methylation (if replicated) and better polygenic risk scores) could be used to triage women according to risk for more cost-effective screening and prevention strategies. Similarly, breast cancer family genetic services could counsel and manage the large proportion of women tested for Gene Panels who are not found to have high risk mutations according to their risk if the Panels included coverage of genes or SNPs across large numbers of regions identified from GWAS, and risk modelling was based on multigenerational cancer family data using e.g. BOADICEA.
Programme

Wednesday 26th

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

“Familial Cancer 2015: Research and Practice”

Session 2:

Plantation Room

The Jeremy Jass Memorial Lecture

Introduction: John Hopper

Chairperson: Mark Jenkins
Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer) is due to germline mutations in mismatch repair genes. Deleterious germline mutations predispose to colorectal cancer and other cancers with risk for colorectal cancer being 1.5 - 2% p.a. among those aged 40 - 60 years. While regular colonoscopy is the standard management with proven benefit, alternative approaches such as chemoprevention attractive options for pharmacological approaches to reducing the incidence of cancer. In the CAPP2 study which followed up on the apparent protective effect of aspirin from epidemiological studies of the general population, we showed that while regular aspirin had no effect on adenoma incidence there was a protracted period of reduced risk of colorectal cancer among those taking 600 mg aspirin per day compared to persons taking aspirin placebo.

In fact the risk reduction applied to other of the Lynch Syndrome cancers as well as colorectal cancer so that regular aspirin reduced overall cancer risk by about 40% p.a. However regular dosing with resistant starch had no effect on cancer risk in contrast to the epidemiological evidence from comparisons across world populations. Since the publications, further epidemiological evidence supports the finding of colorectal cancer prevention and we have tried to dissect some of these observations to identify potential implications. Among the studies are: (1) attempts to identify doses at which protective activity is evident, (2) the time until the protective effect of the aspirin is lost and (3) since obesity is related to the risk of colorectal cancer in the population, does obesity also modify risk in persons with Lynch Syndrome?

Although there was no strong evidence of adverse effects of 600 mg aspirin a day, there have been concerns raised about long-term dosing and so a dose-finding study CAPP3 (www.capp3.org) has been designed and funded by Cancer Research UK to compare the use of 3 doses of aspirin: 100 mg, 300 mg and 600 mg per day. Recruitment is underway with more that 100 participants enrolled. Finally other novel approaches to prevention are being considered, notably immunological interventions.

Whole exome and genome sequencing of individuals with serrated polyposis syndrome

Mark Clendenning, Christophe Rosty, Belinda N. Nagler, Sonja Woodall, Julie Arnold, Sharelle Joseland, Kevin Sweet, Melyssa Aronson, Kara Semotiuk, Steven Gallinger, Melissa C. Southey, Ingrid M. Winship, Finlay A. Macrae, Joanne P. Young, Aung Ko Win, John L. Hopper, Mark A. Jenkins, Susan Parry, Daniel D. Buchanan

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Background: Serrated Polyposis Syndrome (SPS) is a colorectal polyposis condition associated with an increased risk of developing colorectal cancer (CRC) in both the affected individual and their relatives. Currently, the underlying genetic basis of SPS is unknown. A recent study has suggested a new set of genes as putatively associated with multiple sessile serrated adenomas (ATM, TELO2, RBL1, XAF1, PIF1, RNF43 and ULK4)[1]. The aim of this study was to perform whole genome sequencing (WGS) and whole exome sequencing (WES) of individuals with SPS, including a subset of first degree relatives with SPS, in order to identify susceptibility loci for this condition.

Methods: 73 Individuals with SPS, including 65 probands and 8 first-degree relatives, were selected based on early age at diagnosis, high numbers of serrated polyps throughout the colon and having a first degree relative with SPS or CRC out of 406 SPS cases collected as part of our International Serrated Polyposis Register from Genetics or Family Cancer Clinics within Australia, Canada, USA and from a single gastroenterology service at Middlemore Hospital, Auckland, New Zealand.

Whole exome capture was performed using Agilent XT SureSelect_V4 52Mb capture while sequencing comprised of 100bp pair-end sequencing on a HiSeq2500 to a mean depth of 100x. For Whole genome sequencing, DNA was prepared to obtain a final library of 300 ~ 400 bp average insert size and sequenced as 150bp paired-end reads using Illumina Hi-Seq X Ten sequencer to average 30x coverage. Variant filtering strategies included only variants with 1) a frequency of <1% in reference databases (1000 genomes and ESP6500), 2) were likely deleterious variants producing a non-sense/stop gain, frameshift, or splice-site or non-synonymous predicted to be damaging according to at least 4 out of 5 in silico programs and 3) were present in at least 20% of the SPS cases tested. Genes were prioritised if they were in one of the following 3 groups of genes namely 1) known hereditary CRC genes, 2) recently reported CRC- and polyposis-associated genes and 3) genes putatively associated with Serrated Neoplasia [1].

Results: The findings from whole exome sequencing (n=57) and whole genome sequencing (n=16) revealed no likely deleterious germline coding mutations in hereditary CRC genes (APC, BMPRIA, CDH1, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53). For the recently reported CRC- and polyposis-associated genes, a single case carried a heterozygote non-synonymous variant in NTHL1 (c.610A>C p.Ile204Leu). No individuals with SPS carried deleterious variants within the genes recently reported to be associated with multiple sessile serrated adenomas (ATM, TELO2, RBL1, XAF1, PIF1, RNF43 and ULK4) apart from 7 SPS cases (9.6%) that carried the recurring p.E49X variant within PIF1. Our variant filtering strategies identified a further 190 candidate genes that had the highest burden of likely deleterious variants.

Conclusions: Mutations within previously identified polyposis- and CRC-associated genes do not underlie the vast majority of individuals with SPS. The recurring truncating variant p.E49X in PIF1 as well as our candidate genes require further validation in our extended SPS cohort.

Evidence for Further Colorectal Cancer Susceptibility Genes in Addition to the Mismatch Repair Genes and MUTYH.

Aung Ko Win,1 Mark A. Jenkins,1 James G. Dowty,1 Antonis C. Antoniou,2 Andrew Lee,2 Graham G. Giles,1,3 Daniel D. Buchanan,1,4 Dennis J. Ahnen,5 Stephen N. Thibodeau,6 Graham Casey,7 Steven Gallinger,8 Loïc Le Marchand,9 Robert W. Haile,10 John D. Potter,11,12,13 Yingye Zheng,11,12 Noralane M. Lindor,14 Polly A. Newcomb,11,12 John L. Hopper,1 Robert J. MacInnis.1,3

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11 School of Public Health, University of Washington, Seattle, Washington, USA.
12 Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.
13 Centre for Public Health Research, Massey University, Wellington, New Zealand.
14 Department of Health Science Research, Mayo Clinic Arizona, Scottsdale, Arizona, USA.

Background: Familial aggregation of colorectal cancer is probably due to multiple susceptibility genes, perhaps acting in conjunction with shared lifestyle risk factors. The aim of this paper was to investigate the genetic models that can best explain familial colorectal cancer not due to the DNA mismatch repair (MMR) genes or MUTYH, and to accurately estimate the mutation carrier frequency in the population.

Methods: We studied 5,744 colorectal cancer cases (proband) who were recruited from population cancer registries from the US, Canada and Australia between 1997 and 2012. Blood samples taken from the probands were analysed for mutations in MMR genes and MUTYH. We investigated major gene models (dominant, recessive, general), polygenic models, and mixed models (both major gene and polygenic) by analysing information on cancer history in first-degree relatives and on the mutation status of the probands using the pedigree analysis software MENDEL. We estimated the simultaneous effects of MMR genes (MLH1, MSH2, MSH6, PMS2), MUTYH, a sixth hypothetical gene GENE6, and a polygenic effect. The models were assessed by likelihood comparisons and by comparison of the observed numbers of mutations and affected relatives with the predicted numbers.

Results: The best-fitting model was mixed dominant model with an age-dependent polygenic standard deviation on top of the five known genes. Under this model, the estimated mutation frequency for GENE6 was 0.10% (95% confidence interval [CI], 0.02% – 0.54%) and the relative risk for GENE6 mutation carriers was 31.1 (95% CI, 11.6 – 83.4). The standard deviation of the polygenic component was 1.81 (95% CI, 1.05 – 3.12) for age <40 years, 0.96 (95% CI, 0.51 – 1.82) for age 40-49 years, 0.68 (95% CI, 0.34 – 1.34) for age 50-59 years, 0.89 (95% CI, 0.52 – 1.51) for age 60-69 years, and 0.72 (95% CI, 0.40 – 1.28) for age ≥70 years. The estimated population allele frequency (%) was 0.026 (95% CI, 0.020 – 0.034) for MLH1, 0.018 (95% CI, 0.013 – 0.024) for MSH2, 0.066 (95% CI, 0.044 – 0.098) for MSH6, 0.070 (95% CI, 0.047 – 0.104) for PMS2, and 1.11 (95% CI, 0.95 – 1.30) for MUTYH.

Conclusions: These findings suggest that it is more likely that the remaining familial aggregation of colorectal cancer is due to a major gene on top of many low-risk variants than due to many low-risk variants alone. We have also provided accurate estimates of the carrier frequency of a MMR gene and MUTYH in the population.
Bi-allelic somatic mutations as a cause of tumour mismatch repair-deficiency in population-based colorectal and endometrial cancer with suspected Lynch syndrome

Mark Clendenning, Christophe Rosty, Michael D. Walsh, Stine V. Eriksen, Susan Preston, Melissa C. Southey, Ingrid M. Winship, Finlay A. Macrae, Aung Ko Win, John L. Hopper, Graham G. Giles, Dallas R. English, Amanda B Spurdle, Mark A. Jenkins, Daniel D. Buchanan1, 2 on behalf of the Melbourne Collaborative Cohort Study, the Australian National Endometrial Cancer Study and the Colon Cancer Family Registry Cohort

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Background: Tumour mismatch repair (MMR) deficiency, determined by immunohistochemical (IHC) loss of MMR protein expression, is used diagnostically to identify individuals with Lynch syndrome. A high proportion of colorectal cancers (CRCs) and endometrial cancers (ECs) that demonstrate tumour MMR-deficiency are categorised as having “suspected Lynch syndrome” due to the absence of tumour MLH1 methylation or germline MMR gene mutations after standard screening approaches. The aim of this study was to determine the frequency and phenotype associated with tumour MMR-deficiency caused by bi-allelic somatic mutations within multiple population-based cohorts of CRC and EC cases.

Methods: Population-based incident CRC-affected cases from Australasian Colorectal Cancer Family Registry were tested for MMR protein expression by IHC (n=813). MMR-deficient CRCs (n=90) were screened for germline MMR gene mutations using Sanger sequencing and MLPA of the MLH1, MSH2, MSH6, and PMS2 genes. CRC FFPE tumour tissue DNA was also screened for MMR gene somatic mutations using AmpliSeq custom capture and sequencing on the Ion Proton and for Loss of Heterozygosity (LOH). MMR-deficient CRCs were also screened for MLH1 and MSH2 gene promoter methylation assessed by MethyLight and BRAF V600E somatic mutation. Finally, germline whole genome sequencing was performed on individuals with unexplained tumour MMR-deficiency to identify putative intronic, promoter and structural variation mutations within the MMR genes or mutations in genes other than the four main MMR genes. Family history of CRC and extra-colonic cancers, including fulfilment of Amsterdam criteria and Bethesda guidelines, along with tumour pathology features were determined for each case.

Results: The mean age at CRC diagnosis for the 813 CRCs tested for MMR-deficiency was 46.3 ± 8.0 years (range=18-59 years). Ninety (90/813; 11.1%) MMR-deficient CRCs cases were identified with 42 (42/90; 46.7%) shown to carry a germline MMR gene mutation, 13 (14.4%) were positive for MLH1 methylation with the remaining 35 (38.9%) considered to be “suspected Lynch syndrome” cases. Of these, bi-allelic somatic mutations in the MMR gene indicated by the pattern of IHC loss were identified in 14 CRCs (14/35; 40%) and were comprised of either two point mutations or a single point mutation and loss of heterozygosity. A single somatic point mutation or LOH event was identified in a further 14 (40%) of CRC-suspected Lynch syndrome cases suggesting that a germline “first hit” is still to be found. Whole genome sequencing is currently being performed to interrogate extended intronic and promoter sequences. Testing of the Melbourne Collaborative Cohort Study (MCCS) CRC and Australian National Endometrial Cancer Study (ANECS) and MCCS EC cases for bi-allelic somatic mutations is currently nearing completion with the findings to be presented.

Conclusions: Bi-allelic somatic mutations were present at a frequency equivalent to that of CRCs with MLH1 methylation and, therefore, represent a significant cause of tumour MMR-deficiency in population-based CRC cases. This approach is currently being applied to additional CRC and EC cohorts to replicate these findings for CRC and determine the significance of bi-allelic somatic mutations in EC. A revision of the current triaging and diagnostic testing strategies used to identify individuals and their relatives with Lynch syndrome may be warranted.
Programme

Wednesday 26th

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

"Familial Cancer 2015: Research and Practice"

Session 3:

Plantation Room

Chairperson: Amanda Spurdle
New insights into the transcriptional networks governing mammary stem cell homeostasis and basal-like breast cancer aetiology

Laura Baker1,2, Holly Holliday1,2, Simon Junankar1,2, Daniel L. Roden1,2, Sunil R. Lakhani3,4,5,6, Peter T. Simpson3,5,6, Warren Kaplan1, Christopher Ormandy1,2, Ewan K.A. Millar1,7,8, Sandra O’Toole1,9, Kyuson Yun10, Alexander Swarbrick1,2*

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Basal-like breast cancer (BLBC) is a heterogeneous disease with poor prognosis however its cellular origins and etiology are poorly understood. I will present evidence that the HLH transcriptional regulator Inhibitor of Differentiation 4 (ID4) is a key regulator of mammary stem/progenitor cell homeostasis and a proto-oncogene in a subset of BLBC.

Using an Id4-GFP knock-in reporter mouse and single cell transcriptomics, we show that Id4 marks a stem cell-enriched subset of the mammary basal cell population. Id4 is required for mammary stem and progenitor proliferation and ductal elaboration. Id4 maintains the mammary stem cell pool by suppressing the expression of key factors required for luminal differentiation, including BRCA1, Elf5 and Notch signaling.

Furthermore, ID4 is specifically expressed by, and genomically amplified in, a subset of human BLBC that possess a particularly poor prognosis and a transcriptional signature similar to a mammary stem cell. ID4 is also amplified in ~10% of high grade serous ovarian cancer (HGSOC), a disease with many features in common with BLBC. ID4 expression is required for the proliferation and growth of xenografts generated from cell line models of BLBC and HGSOC.

Biochemical analysis of ID4 complexes in BLBC and HGSOC identifies components of the homologous recombination DNA repair apparatus. Furthermore, early evidence from the literature suggests a high frequency of ID4 amplification in BRCA1-mutant BLBC. Together these data provide evidence for a genetic and biochemical interaction of ID4 with BRCA1. We hypothesise that ID4 is a tissue-specific modifier of BRCA1 in BLBC and HGSOC.
DNA Methylation and Early-Onset Breast Cancer

Cameron Scott¹, Ee Ming Wong¹, JiHoon Eric Joo¹, ABCFS², Graham Giles³, ⁴, John Hopper³, Melissa C Southey⁴

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Breast cancer is the most common cancer in women. Breast cancers arising in women who carry a germline mutation in BRCA1 are commonly high grade and often early-onset with poor prognosis and limited treatment options. These BRCA1 mutation-associated tumours have highly distinct morphological characteristics. Prior research conducted within the Australian Breast Cancer Family Study (ABCFS), defined “BRCA1-like” breast cancers as having five or more of the histological features commonly associated with carrying a BRCA1 mutation. These features include: a high mitotic index, high nuclear grade, little or no tubule formation, pushing margins, necrosis, lymphocytic infiltrate and trabecular, circumscribed and syncytial growth patterns. However, only 25% of women diagnosed with early-onset “BRCA1-like” breast cancer actually carry an identifiable BRCA1 germline mutation suggesting that there might be other underlying predisposition mechanisms. Indeed, our previous work has shown that a proportion of these “BRCA1-like” breast cancers that do not carry germline BRCA1 mutations are associated with elevated methylation at the BRCA1 promoter that is measurable in DNA extracted from peripheral blood and the corresponding breast cancers (Wong et al., 2011).

We hypothesise that aberrant DNA methylation marks are associated with risk of non-BRCA1 mutation carrying early-onset “BRCA1-like” breast cancers. To test this, we measured genome-wide methylation using the Infinium HumanMethylation450 beadchip assay (HM450K) in blood-derived DNA from 30 women with “BRCA1-like” breast cancers, 30 women with “non BRCA1-like” breast cancers, and 30 unaffected women (controls). Blood-derived DNA from a subset of the women with “BRCA1-like” breast cancer showed increased promoter methylation levels p≤0.05 in the promoter region of a number of key tumour suppressor genes including BRCA1 and ATM when compared to the control groups.

We are also measuring genome-wide methylation in DNA extracted from the corresponding “BRCA1-like” (n=22) and “non BRCA1-like” (n=24) breast tumours. We will describe the methylation profiles of these tumours with particular focus on the promoter regions that have been identified to be associated with breast cancer risk in the germline analysis.

These methylation marks and signatures could be important biomarkers of predisposition to “BRCA1-like” breast cancer and in the future could assist with targeted treatment options.

References:
Breast cancer subtypes as defined by methylome-wide analysis

Eric Joo1, Ming Wong1, Catriona McLean2, Roger L Milne3,4, Gianluca Severi3, Dallas English3,4, John L Hopper4, Laura Baglietto3, Graham G Giles3,4, Melissa C Southey1

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Subtyping of breast cancer via immunohistochemical (IHC) staining in two hormone receptors ER (oestrogen receptor) and PR (progesterone receptor), as well as the HER2 (human epidermal growth factor receptor 2) is now standard practice due to its utility in directing treatment and providing information about prognosis [1]. The molecular subtypes of breast cancers identifiable from IHC staining of these receptors are shown to be associated with distinct gene expression signatures involving large numbers of genes [2]. However, the mechanistic driver for these gene expression differences remains unexplained. In addition, further heterogeneity of breast cancers within these subgroups is also apparent.

DNA methylation is one of the most studied epigenetic mechanisms. It can mimic genetic mutations and directly induce gene expression changes. Aberrant DNA methylation patterns are featured in virtually all cancers. Genomic instability induced from global hypomethylation and inactivation of key tumour suppressors through promoter hypermethylation are the hallmarks of most cancers [3].

We hypothesised that there are DNA methylation signatures associated with specific IHC signals (ER, PR, HER2, Cytokeratin 5/6, EFGR) and that these methylation signatures can be used for further characterising molecular subtypes of breast tumours (Luminal A, Lumina B, Her2 and triple-negative). In order to test this, we have applied the Infinium HumanMethylation 450K assay to tumour enriched DNA extracted from macrodissected FFPE breast cancer specimens from women participating in the Melbourne Collaborative Cohort Study (n=427) whose breast tumours had previously been subtyped by immunohistochemistry.

After data processing and removing poorly performing samples and probes, β (% methylation) and M (logit transformed β) values were successfully obtained for 469,554 probes from 417 tumour samples. Hierarchical clustering analysis revealed distinct methylation characteristics shared within each of triple-negative and HER2+ tumours. The methylation marks in Luminal A and B groups were generally heterogeneous. By performing linear regression analyses, we identified extensive sets of Differentially Methylated Probes (DMPs) as well as Regions (clusters of DMPs) associated with molecular subtypes, and individual hormone receptors IHC. Our study demonstrates the capacity to further subgroup breast cancers based on methylation signatures. This approach may offer additional molecular markers that could aid the clinical management of breast cancer, most notably in the targeted use of emerging epigenetic therapies.

References
Development of a large-scale construct-based targeted mRNA sequencing analysis pipeline for in vitro transcript analysis: application to validation of bioinformatic prediction of de novo donor site creation by BRCA1/2 sequence variants.

Michael Parsons¹, Gemma Moir-Meyer¹, Darren Korbie², Andrea Hoffman¹, Melissa Brown², Maxime Vallee³, Sean Tavtigian⁴, Amanda Spurdle¹
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2. University of Queensland, Brisbane, Australia.
3. CHUQ Research Center, Quebec City, Canada.
4. Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, USA.

Clinical management of breast cancer families is complicated by identification of BRCA1 and BRCA2 sequence alterations of unknown significance. Molecular assays evaluating the effect of variants on splicing can help determine their clinical relevance. In particular, bioinformatic and mRNA analysis are used commonly to predict the disruption of native splice sites by largely intronic sequence variants. However, there has been little research done to assess the functional or clinical importance of exonic variants that may create de novo splice sites.

We have used MaxEntScan scores in a Z-score model to predict the creation of de novo donors for all possible exonic single nucleotide substitutions in BRCA1 and BRCA2. Variants were categorised based on their scores into four groups: Increased, Moderate, Low, Weak/Null. We then assessed the accuracy of these predictions by in vitro mRNA analysis of 314 splicing constructs designed to capture wildtype or variant sequences with bioinformatic predictions across the four different groups. Each construct contained one BRCA exon with flanking intronic region, and was transiently transfected into two breast cancer cell lines (HS578T and MDA-MB-231). Extracted mRNA was converted to cDNA, amplified with construct-specific primers, barcoded and pooled for next-generation sequencing using a MiSeq. Shorter exons (<120bp) were selected for construct design to reduce costs and allow the transcript to be covered by a paired-end read (single forward and single reverse). A custom analysis pipeline was established to optimise mapping, considering known vector exon sequences and the short nature of the transcripts.

We used qPCR to show that the ratio between transcripts does not differ by the amount of cDNA template after serial dilution 1:16 of input amount, thus obviating need to standardise template concentration for quantitative assessment of mRNA transcript profile. The barcode sequence was trimmed from read ends, and reads with low mapping score were removed. After applying these quality control measures, absolute read numbers were used to calculate a percentage of total transcripts for each variant, and for the wild-type construct of the relevant exon. A minimum threshold of 2,000 was based on observed sequencing artefacts in the negative controls, and maximum read coverage was 200,000. Results to date indicate that our high throughput pipeline is able to identify and separate two transcripts with 3bp difference in length, and importantly, provides a quantitative assay for measuring the effect of variant substitutions on mRNA transcripts. Strongly predicted de novo donor sites have been observed to lead to mRNA aberrations detectable in vitro, supporting the value of these methods for validation and improvement of bioinformatic tools used in variant classification.
The molecular landscape of advanced or recurrent endometrial cancer

Michelle K Wilson; Philippe L Bedard; Helen Mackay; Anthony M Joshua; Marcus O Butler; Neesha Dhani; Stephanie Lheureux; Victor Rodriguez-Freixinos; Blaise Clarke; Patricia Shaw; Anca Milea; Lisa Wang; Suzanne Kamel-Reid; Tracy Stockley; Jeff Bruce; Trevor J Pugh; Amit M Oza.

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Background: Endometrial cancer (EC) is classically categorised into two pathogenetic sub-types: type I endometrioid and type II non-endometrioid. Recently, it has been further classified into four sub-types based on mutation spectra, copy-number aberrations and microsatellite instability status. We explored the pattern of mutations in advanced EC patients enrolled in an ongoing institutional molecular profiling program.

Methods: DNA from blood and tumour (archival FFPE tissue) from EC patients (ECOG ≤1) was genotyped with a recurrent mutation(s) assay (Sequenom MassArray, 23 genes, 279 mutations) or a NGS assay (Illumina TruSeq Amplicon Cancer Panel, 48 genes) in a CAP/CLIA certified laboratory. Whole exome DNA sequencing (germline and tumour) was performed in patients with exceptional responses.

Results: From March 2011 to August 2014, 77 patients were enrolled: 33 (43%) with type I endometrioid and 44 (57%) with type II non-endometrioid EC. The median BMI was 29 with 11 (14%) patients having documented diabetes. Sixty (78%) had ≥1 line of chemotherapy. Samples analysed were from the primary site in 61 (79%) cases and a metastatic site in 16 (21%) cases.

Somatic mutations were found in 64 patients (83%) with 40 patients (52%) having ≥2 mutations. PIK3CA (42%), TP53 (32%), KRAS (20%), PTEN (16%), and CTNNB1 (16%) were the most common mutations seen. PIK3CA mutations were seen in 39% of type I and 43% of type II EC (p=0.78). PTEN mutations were more common in type I EC (p=0.02); TP53 mutations more common in type II (p<0.01). A case with paired samples pre and post-therapy demonstrated 9 mutations pre- and 12 mutations post-radiation, with 8 mutations common to both samples.

An exceptional responder with recurrent serous EC (3 mutations: PIK3CA, KRAS, APC) and a complete response on sunitinib for 7.2 years was identified. Exome sequencing found >2400 somatic coding mutations (43 point mutations/coding Mb) and few copy-number alterations (possible MSI-hypermutated subtype). Preliminary somatic mutations of interest include: 5 in genes significantly mutated in EC; 4 in genes encoding known targets of sunitinib; and 13 in kinase domains of other proteins.

Conclusions: Genotype-matched therapy in EC is complicated by genomic heterogeneity. The mutational landscape and particularly the large percentage with multiple mutations, identifies an important barrier to effective matched therapy. Future EC trials should develop algorithms for multiple mutations and additionally account for patient comorbidities in design.
Programme

Wednesday 26th

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

“Familial Cancer 2015 Research and Practice”

Session 4:

Plantation Room

Chairperson: Kelly Ormond
Returning research results to research participants: telephone genetic counselling makes a difference.

Mary-Anne Young¹, Victoria Rasmussen¹, Laura Forrest¹, Lisa Devereux¹², Paul James¹², Ian Campbell¹².
¹Peter MacCallum Cancer Centre, East Melbourne ²Sir Peter MacCallum Department of Oncology, The University of Melbourne

Background:
Australian research studies conducting genomic screening where clinically significant genetic information is identified, e.g. pathogenic BRCA1/2 mutations, have previously returned these findings to participants via a notification letter. Evidence indicates that most research participants are enthusiastic and willingly consent to be notified about the availability of clinically significant research results. However, fewer than 50% of Australian participants enrolled in studies including AOCS, kConFab, ABCFS and Colon CFR followed up the notification letter and contacted an FCC for genetic counselling and testing. Research participants experience a number of barriers to contacting an FCC after receiving a notification letter, where the lack of information and support was the most significant factor. A new evidence-based model of returning research results grounded in the experiences of research participants has been developed and rolled out through the lifepool study. This model incorporates telephone genetic counselling into the notification process, where the participant is provided with the genetic counsellor’s name and telephone number in the notification letter.

Aims and methods:
This exploratory qualitative study investigates research participants’ experiences of receiving a notification letter from lifepool and telephone genetic counselling. This presentation focusses on qualitative data from semi-structured interviews with the first 10 unaffected women who are lifepool participants and, as part of a research study, were identified as carrying a pathogenic BRCA1 or BRCA2 mutation.

Results:
All participants utilised telephone genetic counselling within 48 hours of receiving the notification letter. Telephone genetic counselling was viewed as important, as participants had an appropriately skilled health professional to contact immediately who provided information and support. The inclusion of telephone genetic counselling facilitated participants’ understanding of their family specific genetic information, provided emotional support and enabled them to be connected in a streamlined fashion with clinical genetic services. These findings suggest the inclusion of telephone genetic counselling addresses the gap in the notification process by providing information and support, enabling participants to make an informed decision about the research-generated, clinically significant genetic information. The successful inclusion of this clinical service in a research process creates implications for researchers conducting genomic screening, specifically regarding the funding required to return genetic results in a participant-centred manner.
Patient satisfaction with delivery of genetic testing results via telephone versus delivery in person; our experience in the Illawarra and Shoalhaven Hereditary Cancer Clinic

Sian Greening and Emma Healey, Senior Genetic Counsellors, Illawarra and Shoalhaven Hereditary Cancer Clinic

Emma Healey, Associate Genetic Counsellor, Illawarra and Shoalhaven Hereditary Cancer Clinic

Dr Lesley Andrews, Head of Department, Prince of Wales Hereditary Cancer Clinic, South Eastern Sydney Local Health District.

Genetic counselling for breast cancer genetics, and in particular provision of genetic testing results over the phone, rather than in person, has been the subject of previous research (Helmes, et al 2006, Jenkins et al 2007, Schwartz et al 2014). This research has shown that telephone genetic counselling is a non-inferior alternative to face to face results disclosure. Patients have expressed higher levels of satisfaction with the service when this alternative was offered, regardless of which method of delivery they chose. From 2013, patients attending the Illawarra and Shoalhaven Hereditary Cancer Clinic for both mutation analysis and predictive testing have been offered a choice in delivery of genetic testing results (telephone or face to face). Patients have since been offered participation in a patient satisfaction survey of whether their chosen method was satisfactory and whether they would have chosen to receive results differently. Patients were also questioned about why they chose the method they did. Results from this survey will be presented and implications for practice discussed.

References:


On the road to mainstreaming: An update on a specialised ovarian Familial Cancer Clinic

Kentwell M1, 2, Wrede D2, Antill Y1, McNally OM2, Hamilton A2, Ananda S2, Hallo J2, Thomas P2, Lindeman GJ1, Scott C1,2

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2. Gynaecological Oncology and Dysplasia, The Royal Women’s Hospital, Melbourne

In June 2014, The Royal Women’s Hospital Gynaecology team, and The Royal Melbourne Hospital Familial Cancer Centre began work towards mainstreaming BRCA1/2 germline testing within the gynaecology outpatients setting. This involved a Genetic Counsellor from the FCC carrying out genetic counselling on patients with recently diagnosed ovarian cancer who were attending outpatients or the chemotherapy day centre as part of their acute care.

A detailed tool was developed for the Genetic Counsellor to use as a guide for each patient from intake to discharge. From June 2014 to June 2015, the Genetic Counsellor saw 40 newly diagnosed patients with ovarian cancer in outpatients, and facilitated results before the completion of first-line chemotherapy using this tool.

This presentation will outline the experience of this model, in particular, the Genetic Counsellor’s role, and how this has developed into a streamlined genetic testing process embedded within gynaecology. Data on the patient and tumour profile of the 40 patients will also be presented.

This experience has enabled for infrastructure and necessary protocols to be put in place within the acute oncology setting for Genetic Counsellor engagement with patients, complemented by the standard back-up and expertise of the FCC. Over the past 12 months, the referral rate of patients with newly diagnosed high grade serous ovarian cancer diagnosed under age 70 has increased to 85%, demonstrating that BRCA1/2 germline testing is increasingly being considered routinely by the gynaecology team. Our findings provide an opportunity for this model of care to serve as template for further mainstreaming of genetic counselling and genetic testing for other relevant tumour streams.
Programme

Thursday 27th

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

“Familial Cancer 2015  Research and Practice”

Session 5:

Plantation Room

Chairperson: Rachel Williams
Genetic counseling of the future: the role of health behavior theory and counselling

Kelly Ormond
Professor, Dept of Genetics and Stanford Center for Biomedical Ethics
Stanford University, Stanford, CA, USA

In this era of personalized and precision medicine, genomic predictions are portrayed as playing a major role in preventative healthcare. This is especially true when returning medically actionable pathogenic variants, such as cancer predisposition variants. Genetic counselors are positioned to play a key role in empowering patients to change their health behaviors towards healthier lifestyles. In this talk I will review limited literature available around health behavior change after genomic results, and discuss various ways that genetic counselors might help patients consider moving towards beneficial screening and lifestyle changes. The talk will be grounded in health behavior theory and will provide educational resources for clinical genetic counselors to incorporate into practice.
Communicating personalised genomic risk information to the public: a focus group study
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⁶ Centre for Genetics Education, Royal North Shore Hospital Community Health Centre

Background
Personalised genomic risk information has the potential to motivate behaviour change and promote health among the general public, but the success of this will depend upon effective risk communication strategies.

Aim: To explore the potential emotional and behavioural impact of providing information on personalised genomic risk to the wider public and to determine preferences for the delivery and communication of genomic risk information.

Methods: We conducted four focus groups with 34 participants from the general population. Participants were given a hypothetical scenario that displayed an individual’s personalised genomic risk of melanoma in several graphical formats. We asked about understanding of genetic risk, potential emotional and behavioural impacts, and other concerns or potential benefits. Preferences for the graphical formats were discussed as well as who would choose to receive this risk information, how they would prefer to receive it and the role of health professionals such as GPs and genetic counsellors.

Results: Thematic data analysis indicated that participants thought this risk information could potentially motivate preventive behaviours and related it to screening for other diseases such as breast and bowel cancer. Factors identified as influencing the decision to receive genetic risk information included education level, children, age and gender. Participants identified potential negative impacts on the recipient such as anxiety and worry, and proposed that this could be mitigated by providing additional explanatory and prevention information. They also felt that it was important that a health professional (either a genetic counsellor or ‘informed’ general practitioner) be available for discussion at the time of receiving the risk information, in order to minimise potential negative emotional responses and misunderstanding. Participants thought that email, web-based or postal mail were viable options, however face-to-face or telephone delivery was preferred for communication of high-risk results. Participants preferred risk formats that were familiar and easy to understand, such as a ‘double pie chart’ and ‘100 person diagram’ (pictograph).

Conclusions: Understanding public preferences for communication strategies of genomic risk information and potential emotional and psychological impacts as well as broader ethical and social issues that might arise from receiving personalised genomic risk information is essential for the translation of DNA-based behaviour-change interventions into routine public health policy and clinical practice.
Young Australian women’s decision-making about managing their cancer risk arising from a BRCA1/2 mutation

Laura E Forrest,1,2 Mary-Anne Young,1 Sue Shanley,1 Victoria Rasmussen,1 Gillian Mitchell1,2
1. Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, Australia
2. Sir Peter MacCallum Department of Cancer Oncology, University of Melbourne, Australia

Background
Young women aged 18 – 40 years with a BRCA1/2 mutation may experience their young adulthood, a formative developmental life stage, interwoven with an awareness of a significantly increased cancer risk. Psychosocial support needs may arise due to the tension between choosing which cancer risk management strategies to engage and when, and fundamental life events such as forming intimate relationships and childbearing. This study explores how young Australian women with a BRCA1/2 mutation balance engagement with risk management strategies and young adulthood.

Methods
A grounded theory approach has been undertaken using qualitative, semi-structured interviews to collect data. The inclusion criteria included women who have a BRCA1/2 mutation, aged 18 – 40 years, who received their genetic test result more than 12 months prior. Data were analysed iteratively and inductively to identify themes, ideas, concepts and categories.

Results
Thirty-six of 40 semi-structured interviews have been conducted to date with women aged 20 – 40 years with a BRCA1/2 mutation. Most participants have engaged in breast screening or planned to engage in screening once they reached the recommended age. Participants’ attitudes towards and perceptions of bilateral prophylactic mastectomy (BPM) were variable. Decision-making about having BPM or planning when to have BPM was greatly informed by the presence of children or childbearing plans and the desire to breastfeed. Other factors that influenced participants’ decision-making about having BPM included experiencing screening fatigue and a heightened perception of breast cancer risk. Some participants were ambivalent or had negative attitudes towards BPM. Participants felt negatively about BPM described feeling a ‘physical revulsion’ to the removal of their breast tissue. In contrast, participants were uniform in their acceptance of having a bilateral salpingo-oophorectomy once childbearing is complete.

Discussion
These findings contribute towards understanding how Australian women who have a significantly increased risk of breast and ovarian cancer make a decision about BPM. Furthermore, this illustrates the psychosocial challenges young women with a BRCA1/2 mutation experience managing their cancer risk and balancing risk management strategies with childbearing and breastfeeding.
How empowered do carriers of hereditary gene mutations participating in an Annual Review Program feel about managing their cancer risk?

Lucinda Hossack, Victoria Rasmussen, Mary-Anne Young, Dr Laura Forrest, Mary Shanahan, Clare Hunt, Lyon Mascarenhas, Chris Michael-Lovatt, Dr Susan Shanley, Dr Marion Harris, Dr Gillian Mitchell.

1Peter MacCallum Cancer Centre, East Melbourne, 2Sir Peter MacCallum Department of Oncology, The University of Melbourne, 3Monash Health, Clayton

Background
In 2009, the Familial Cancer Centre (FCC) at Peter MacCallum Cancer Centre began offering a long term follow up program for mutation carriers known as the Annual Review Program (ARP). The Monash Health FCC adopted this program in 2013. Through the ARP we can identify patients’ unmet information or support needs related to managing their cancer risk and communicating genetic risk information.

The Genetic Counselling Outcome Scale (GCOS) is a validated Patient Reported Outcome Measure specifically designed for assessing patient benefits derived from clinical genetic services. It captures the construct of Empowerment, which underlies individuals’ responses to learning about their genetic cancer risk. This outcome aligns with the aims of the ARP to facilitate patient adjustment and enhance confidence in the self-management of cancer risk.

Using the GCOS we assessed mutation carriers’ levels of Empowerment during different stages of participation in the ARP.

Method
905 patients from Peter MacCallum Cancer Centre FCC and 400 patients from Monash Health FCC have been invited by mail to complete three GCOS questionnaires in addition to their clinical ARP questionnaire over a period of five years (June 2013-June 2018).

Data analysis
Preliminary quantitative analysis was undertaken on data collected from June 2013 to July 2014. Patient demographic data such as age, gender, time since receipt of genetic testing results and survey group (e.g., baseline or review) were included in a multiple linear regression analysis predicting GCOS total scores.

Results
Results from the data from 439 (48%) Peter Mac FCC patients, who completed an initial GCOS questionnaire (at a median interval of 6 years post testing) have been analysed. Lower age and longer duration in the ARP were both significantly associated with higher GCOS scores (i.e., greater Empowerment) (p<0.05). Further analysis including patient data from Monash Health is planned and results will be presented.

Conclusion
Our preliminary results show significantly lower levels of Empowerment detected in the baseline group, compared with the review group providing initial support for the positive impact of the ARP on patients’ sense of control over their increased cancer risk.
The psychological effects of a whole body screening trial (SMOC+) in germline TP53 mutation carriers

Kate A McBride¹, ²; Mary-Anne Young³; Timothy E. Schlub¹; Judy Kirk²; Martin H.N. Tattersall⁴; Mandy L Ballinger⁵; David M Thomas⁶; Gillian Mitchell³,⁵
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Introduction: Germline TP53 mutation carriers have a high risk of cancer-related morbidity and mortality. Effective management of individuals at risk is important. A whole-body (WB) surveillance trial in adults with TP53 mutations has been established (SMOC+). The psychosocial impact of WB screening in these individuals is unknown.

Methods: Participants (n = 18) completed psychological questionnaires including the Hospital Anxiety and Depression Scale (HADS), Cancer Worry Scale (CWS) and Impact of Events Scale (IES) at baseline and several time-points post WB-MRI. Linear mixed-modelling assessed short-term and long-term effects of WB-MRI. Two semi-structured interviews were also conducted with participants. Transcripts were analysed by thematic analysis.

Results: At baseline, 17/18 participants were below the clinical cut off for anxiety and depression, had only mild intrusive thoughts of cancer and had less than frequent cancer worry. Mean reduction in participants’ anxiety (HADS) from baseline to two weeks post WB-MRI was 0.93 (95% CI 0.01 to 1.85, p = 0.048) and cancer worry (CWS) from baseline to 12 weeks was –0.36 (95% CI -2.25 to 0.55, p = 0.68). HADS and IES scores remained stable over time. Post WB-MRI scores showed cancer worry significantly reduced over time (p = 0.04). Emerging themes from interviews show that participants are somewhat emotionally contained by screening and believe that ‘knowledge is power’, despite the lack of evidence currently around efficacy. Participants feel lucky to be taking part in the trial, and are motivated by their immediate concern of staying alive and being there for the next generation. However, possible abandonment from research is a concern for participants. For some screening is a burden, and heightens the constant awareness of cancer susceptibility experienced by carriers of mutations in TP53.

Conclusion: WB-MRI may help emotionally contain individuals with TP53 mutations despite the burden of screening and the absence to date of proven efficacy.
Programme

Thursday 27th

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

“Familial Cancer 2015 Research and Practice”

Session 6:

Plantation Room

Chairperson: Stephen Fox
Factors moderating survival from melanoma

Julia Newton-Bishop on behalf of the Section of Epidemiology and Biostatistics, University of Leeds, UK

Melanoma is unusually clinically and pathologically heterogeneous. Moreover it is probably the most immunogenic form of cancer (putatively related to the number of UV induced mutations it carries). We postulate that melanoma survival is determined by an interaction between inherited variation in tumour directed immune responses, angiogenesis and factors yet unknown, but also by environmental exposures and crucially by genetic variation in the tumours. We have therefore created large sample/data sets to allow us to model this interaction and developed use of emerging platforms to generate high quality data from formalin fixed paraffin embedded (FFPE) tumours.

In terms of evidence that inherited genetic variation moderates survival expectation, we have reported evidence for 3 genes: PARP-1 $^1$, the red hair gene MC1R $^2$, and the gene coding for the vitamin D binding protein $^3$. The identification of such genes (especially those identified using agnostic genome wide association studies) may tell us something very important about the biology of the interaction between the host and the tumour.

We have identified gene expression patterns in primary tumours of prognostic value $^4,5$ and more recently identified immune pathways as being modified in relation to ulceration We have identified low vitamin D levels at diagnosis $^6$ and smoking as adverse risk factors for survival, which I will explore in the talk.

References:
Australia has the highest incidence of cutaneous melanoma worldwide, where it is the fourth most common cancer and a leading cause of cancer death in young adults. Late stage metastatic melanoma was until very recently usually rapidly fatal. However, inhibitors of the MAP kinase pathway and of immune checkpoint mechanisms have dramatically extended patient survival, highlighting the importance of identifying therapeutic targets in cancer through comprehensive molecular characterization. Melanomas typically have very large numbers of somatic mutations, including some which affect key driver genes, both within and outside of coding regions. To comprehensively extend the molecular characterization of melanoma, the Australian Melanoma Genome Project (AMGP) was launched in August 2012 with the support of Melanoma Institute Australia (MIA), the Australian Government, via Bioplatforms Australia, NSW Health, and the Cancer Council NSW. The AMGP aims to analyse whole genomes from 500 primary and metastatic melanomas. The majority of samples were sourced from the MIA Biospecimen Bank and have comprehensive, prospectively collected clinical annotation. To date, whole genome sequencing (WGS) has been completed and analysed on samples from 183 patients: including 48 primary melanomas, 120 metastases and 15 cell lines derived from metastases. WGS is being performed on the Illumina HiSeq 2000 and Xten platforms at Australian and Korean sequencing centres. Tumours are analysed at ≥60X coverage, germline DNA at 40X, and cell lines at 40X. Mapping, alignment, variant calling and structural variant determination are assessed with ICGC-compatible pipelines. Complementary RNAseq and methylome data are being obtained on a subset of cases, facilitating an integrated ‘omics’ approach to analysis. All data will be released into the public domain.
Convergent intra-patient evolution in therapy naïve melanoma

Clare G. Fedele, Vincent Corbin, Damien Kee, Robert Ware, Samantha E. Boyle, Rod Hicks, Tony Papenfuss and Mark Shackleton.
The Peter MacCallum Cancer Centre, Melbourne, Australia.

Regardless of whether neoplastic transformation is facilitated by germ line or somatic genetic mutations in cells, at least some cancers continue to acquire new genetic changes after they have developed. Although many of these new changes may be passenger mutations that do not alter disease biology, the demonstration of clonal evolution indicates that some genotypes are favourably selected during tumor progression because they confer advantageous cell phenotypes. Identifying genotype-phenotype changes that drive evolutionary change to more aggressive malignant states is predicated to improve disease prognostication and to reveal new opportunities for treatment.

We have observed that most tumorigenic cells in most melanomas harbour the potential to acquire new mutations during disease progression, indicating pervasive genomic instability. Although this predicts that melanomas may follow a multitude of evolutionary paths, particularly in the absence of treatment, this has not been tested.

To identify evolutionary paths in melanoma, we evaluated biopsies removed serially from patients. In fractional sampling of metastatic disease, >20% of pigmented primary melanomas seeded metastases that were amelanotic, indicating that melanoma progression is linked to melanocytic de-differentiation in some patients. Consistent with this, positron emission tomography (PET) revealed 7/10 melanoma patients with FDG-PET positive metastatic disease that did not bind the melanin-binding tracer MEL050.

Heritable de-differentiation phenotypes were also evident sub-clonally during early passaging of 13/17 patient-derived xenografted (PDX) melanomas. Evolved non-pigmented sub-clones were less necrotic, more vascular and more proliferative than pigmented sub-clones in the same tumor, in line with selection of more aggressive disease. Genetic differences between pigmented and non-pigmented sibling sub-clones indicated clonal evolution of more aggressive, de-differentiated disease.

These data indicate that melanoma progression can be driven by acquisition of new genetic changes that drive heritable loss of melanin-production and increased tumorigenicity. Despite the vast potential of melanoma cells to generate genetic diversity, evolution during therapy-naïve disease progression in many patients converges on shared mechanisms linked to melanocytic de-differentiation.
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"Familial Cancer 2015  Research and Practice"

Session 7

Plantation Room

Chairperson: Melissa Southey
A UK perspective on familial melanoma

Julia Newton-Bishop on behalf of the Section of Epidemiology and Biostatistics, University of Leeds, UK

The incidence of melanoma is rising in all birth cohorts in the UK, but the rise in the younger cohorts is very small: the greatest increase is in men over the age of 60. Given the evidence that it is vacational sun exposure that is causal for melanoma, this increase is supposed to reflect the changed behaviours of pale skinned UK citizens who have holidayed increasingly in hotter European countries in the last 40 years.

Clustering in families of this cancer occurs and in the Leeds Melanoma Cohort, comprised of 2184 melanoma cases, small numbers of cases with germline mutations in CDKN2A (2%), BAP1 (<1%) and POT1 (<1%) have been identified.

We have collected data from melanoma families in the Leeds Familial Melanoma Study for many years. In these families, ascertained for multiple cases of melanoma from the whole of England and Wales, the prevalence of germline CDKN2A mutations increases with numbers of melanomas in the family, consistent with the view that CDKN2A is the commonest high penetrance susceptibility gene in the UK. In the UK we don't see much pancreatic cancer but we do see some and we also see occasional additional cancers in CDKN2A mutation carriers such as the smoking related cancers described by other groups (1, 2). We don't offer pancreatic screening routinely but for families with pancreatic cancer in the family we would recommend considering taking part in the EUROPAC study. Smoking cessation is strongly encouraged in cases and especially in younger members of the family.

Screening, for most families, is carried out by dermatologists, and the recommendation is lifelong review. It is my experience that this is variably adhered to nationally. To some extent that is reasonable in alert well-trained family members with few or no naevi but surveillance is preferable. For the families with newly recognized germline mutations in BAP1 etc, the screening recommendations remain unclear but are necessary e.g. screening for renal call cancers, mesotheliomas etc.

The usual advice given to family members is to reduce vacational sun exposure and never to burn in the sun, as these are the exposures associated with risk. However in the UK, vitamin D levels tend to be low, and people commonly “top up” their vitamin D levels on holiday. Therefore testing vitamin D levels and supplementing where necessary is important.

References:
Germline genomic screening of 1,162 sarcoma families

Mandy L. Ballinger,1 David Goode,1 Isabelle Ray-Coquard,2 Ajay Puri,3 Rajiv Sarin,3 Joshua D. Schiffman,4 Ian Judson,5 Paul James,1 Gillian Mitchell,1 Sue Shanley,1 Victoria Beshay,1 Mary-Anne Young,1 Iain Ward,6 Ian Campbell,1 Sung-Min Ahn,7 David M. Thomas,1,8 for the International Sarcoma Kindred Study.

1Peter MacCallum Cancer Centre, Australia; 2Centre Leon Berard, France; 3Tata Memorial Hospital, India; 4University of Utah, USA; 5The Royal Marsden NHS Foundation Trust, UK; 6Christchurch Hospital, New Zealand; 7Asan Medical Centre, Korea; 8The Kinghorn Cancer Centre and Cancer Division, Garvan Institute of Medical Research, Australia.

Background
Sarcomas are strongly driven by genetic risk, whose clinical significance is largely unknown. We have undertaken a comprehensive clinical and genetic screen of adult-onset sarcoma families with the goal of defining the biological and clinical implications for health outcomes.

Methods
Clinical, pathologic and pedigree information were collected on 1,162 ISKS families recruited from sarcoma clinics in Australia, New Zealand, France, the United States, Korea and India. A 74-gene cancer panel screen was undertaken. Controls included 2245 unaffected individuals sequenced using the gene panel, and 4,300 samples from the NHLBI whole exome dataset. Both within-and between-cohort analyses were performed for age of cancer onset (ACO), sarcoma subtype, and cancer susceptibility in first-degree relatives (FDR), as well as overall and gene-specific enrichment in the ISKS.

Results
ISKS participants demonstrated early age of cancer onset (average 46y), multiple primary cancers (16% of cases), and excess family cancer burden (25%). 192 (17%) individuals carry known or expected pathogenic (KEP) variants with a younger ACO (median 44y vs 50y for those without pathogenic variants, \( P=0.004 \)), as well as 398 individuals (34%) carrying variants of uncertain significance (median ACO 45 years, \( P<0.007 \)). In addition, 140 (12%) individuals carrying multiple VUS developed early-onset cancer (median ACO for 3+ variants=37y; Log Rank \( P=0.0007 \)). There was a lower cancer rate and higher age of cancer onset in FDR of multiple variant cases, consistent with polygenic transmission. Using a test and replication set approach, across all genes we noted modest excess pathogenic variation in ISKS cases compared to controls (Odds Ratio (OR): 1.1-1.3, combined \( P<0.00001 \)), mostly attributable to 10 expected (eg. TP53, \( P<0.00001 \)) and also unexpected genes (eg. BRCA2, ATM, ERCC2). 76 individuals (7%) carry KEP mutations in ACMG reportable hereditary cancer genes, including 34 in BRCA1, BRCA2 or PALB2, and 17 in APC or mismatch repair genes. Many genes are implicated in radiation sensitivity, which may impact treatment choices, while 23% of the ISKS cohort carries variants with potential therapeutic significance, including PTCH1 (hedgehog inhibitors), BRCA1/2 or other HR pathway genes (PARP inhibitors).

Conclusion
These data establish a major and previously unrecognised role of germline genetic variation in clinic-ascertained sarcoma probands, with major implications for cancer screening, treatment and prevention.
Predicting pathogenicity of TP53 mutations: an integrated multi-factorial model

Arcadi Cipponi,1 Mandy L. Ballinger,2,3 Gillian Mitchell,4 Sean V. Tavtigian,5 Magali Olivier,6 Vatsal Ruparel,2,3 Ygal Haupt2,3, Sue Haupt2,3, International Sarcoma Kindred Study,2,3 Kathy Tucker,7 Amanda B. Spurdle,8 David M. Thomas1 & Paul A. James3,9

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Germline TP53 mutations are the underlying cause of Li Fraumeni Syndrome, an autosomal dominant condition that predisposes individuals to a wide range of malignancies, including sarcomas. Accurate interpretation of the pathogenicity of germline TP53 variants may improve clinical management and outcomes for individuals and families. We have developed an evidence-based tool to systematically assign a numerical estimate of the pathogenicity of germ line TP53 variants by employing a multi-factorial model that integrates independent clinical, in vitro and in silico data. Twenty-one TP53 variants were selected from the International Sarcoma Kindred Study and functionally characterized in p53-null human H1299 cells using clonogenic cell survival assays. TP53 variant data from the IARC TP53 database (682 neutral and pathogenic deleterious variants) were used as a calibration set for an independent in silico tool that generated a likelihood ratio of the probability of TP53 function. A linear regression model was also used to demonstrate the correlation between variant classification and the germline:somatic ratio in the complete set of variants in the IARC TP53 database. Combining the in silico analyses with the functional assay outputs allowed classification of two thirds of the ISKS missense TP53 variants into a clinically interpretable class. In addition, using the in silico tools developed here an analysis of all the TP53 missense variants found in the IARC database was performed. The quantitative outputs provide the basis for personalized assessment of TP53 associated cancer risk which may be useful for clinical cancer genetics services.
Assessment of Germline Cancer Predisposition Genes in Pancreatic Cancer

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Background: It is estimated that up to 10% of pancreatic cancer (PC) cases are familial. 15-20% of cases can be attributed to known inherited tumour syndromes, with the remaining genetic predisposition mostly unexplained1. The underlying genetic contribution to sporadic disease is even less well defined. Further characterisation of germline genetics in PC has the potential to identify individuals at an increased risk of PC, along with other cancers.

Methods: Whole-genome (n = 184) and exome (n = 208) sequencing was performed on matched tumour-normal DNA pairs from 392 PC patients. The cohort was predominantly sporadic, with 28 (7.1%) reporting at least one other affected family member and fitting the definition of familial PC. Pathogenic mutations were assessed in 13 cancer predisposition genes associated with PC risk (APC, ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, PRSS1, STK11, TP53). The somatic genomic data was analysed for evidence of biallelic inactivation.

Results: A total of 377 unique high confidence variants were called in the 13 PC predisposition genes. 23 pathogenic germline variants were identified in 23/392 (5.9%) mostly sporadic (91.3%) PC patients. The mutations were observed in BRCA2 (n=9), ATM (n=4), BRCA1 (n=3), PALB2 (n=3), CDKN2A (n=2) and one each in PMS2 and STK11. Truncating BRCA2 and PALB2 mutations were seen in the 2 familial PC cases. The second-hit mechanism could be assessed in tumours with >30% cellularity (n=16), with 75% (7 BRCA2, 4 ATM, 1 BRCA1) showing evidence of biallelic inactivation. There was no difference in average age at diagnosis (67.5 vs 66.6, P = 0.7100) between those with and without a pathogenic germline PC risk mutation. Patients identified to harbour BRCA1, BRCA2 or PALB2 mutations were not associated with a significant personal (6.7% vs 2.7%, P = 0.3623), or family history (13.3% vs 6.3%, P = 0.2866) of breast or ovarian cancer than those without a pathogenic germline mutation.

Conclusion: In this cohort, 5.9% of patients with predominantly sporadic disease have a pathogenic germline mutation in cancer predisposition genes associated with PC risk. Second hit mechanisms were identified in 12 (52.2%) cases, supporting a potential role in pancreatic tumourgenesis. An expanded analysis of the germline data is required to further understand the genetic basis of both sporadic and familial pancreatic cancer.

References:

Mutations in a promoter of *APC* cause a syndrome of gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) without colorectal involvement

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_Gastric_ adenocarcinoma and _proximal polyposis of the stomach_ is a rare cancer syndrome with a significant risk of gastric adenocarcinoma that we previously described. It is characterised by autosomal dominant transmission of fundic gland polyposis, including areas of dysplasia or intestinal-type gastric adenocarcinoma, restricted to the proximal stomach, with no evidence of colorectal or duodenal polyposis, or other heritable cancer syndromes. Using a large Australian pedigree with over 30 affected individuals, we mapped the gene to an interval of 18Mb at 5q22 containing 51 genes, including *APC*. In total, we have identified five families with GAPPS, in all of which coding and large rearrangements of *APC* have been excluded by extensive sequencing and multiplex ligation-dependent probe amplification analysis. Extensive targeted (mean coverage = 27X), whole exome (59X) and whole genome sequencing (WGS; 24X using HiSeq) in the largest family failed to identify any novel or rare coding mutations, or obvious regulatory mutations. Whole genome copy number analysis showed loss of heterozygosity (LOH) only on 5q in 7/14 fundic gland polyps from four affected individuals, with loss of the wildtype allele. The minimal common region of loss overlapped the linkage region by 12 Mb, centered around *APC*. We used Sanger sequencing of the promoters to find informative polymorphisms for allelic imbalance analysis at *APC*. This revealed a novel mutation in promoter 1B in the large pedigree (missed by previous WGS because of low coverage, but subsequently found by WGS using XTen). X Ten WGS also identified somatic mutations in *APC* in 4/7 polyps without LOH, providing the ‘second hit’. The other four small GAPPS families from North America all had the same novel mutation four base pairs away, which cosegregated with disease. Sanger sequencing of a 3’ UTR polymorphism in cDNA showed reduced expression of the mutant allele in blood from affected individuals. Electrophoretic mobility shift assays showed that both mutations reduced transcription factor YY1 binding, as predicted. Furthermore, luciferase assays showed that both mutations abrogated activity of the *APC* 1B promoter in gastric and colorectal cancer cell lines, suggesting that YY1 normally acts as an activator of this promoter. In summary, we have shown that GAPPS is caused by point mutations in the 1B promoter of *APC*, with LOH or somatic mutations involving *APC* common in the fundic gland polyps from affected individuals.
Hertiable Epimutations Associated with Breast Cancer

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Aim
While most epigenetic marks are reprogrammed during early embryogenesis, some studies have reported Mendelian-like inheritance of germline DNA methylation in particular cancer-susceptibility genes. In this study, we attempted to identify such heritable epimutations for breast cancer using epigenome-wide methylation data and multiple-case families.

Methods
We studied 25 families that were recruited through Australian family cancer clinics and that each had multiple cases of breast cancer but no mutations in any known breast cancer-associated gene. Methylation was measured at approximately 480,000 genetic loci in 210 of the 2141 family members using the Infinium HumanMethylation450 BeadChip array. We hypothesized that some heritable epimutations are caused by rare genetic variants which predispose carriers to aberrant patterns of methylation at particular loci. We developed a novel statistical method to identify methylation sites whose measured values are most consistent with a Mendelian inheritance pattern, based on segregation analysis and the expectation-maximization algorithm. Carrier probabilities for the hypothesized rare, autosomal, dominant DNA variants inducing these inheritance patterns were calculated for the 1000 most-Mendelian methylation sites, based on family structure but not affected status. Cox proportional hazards survival analysis was then used to assess associations between these carrier probabilities and breast cancer. Probes located on the X-chromosome or within 10 base pairs of known SNPs were excluded.

Results
After correcting for multiple testing, we identified 11 methylation sites whose corresponding carrier probabilities are associated with breast cancer. Three of these sites are clustered within 200 base pairs of a noncoding RNA which is known to have a tumour suppressor role and is suspected to be regulated by DNA methylation.

Conclusions
We screened almost half a million methylation sites for those with Mendelian inheritance patterns, using a novel statistical method which incorporates family structure but not affected status. We then identified 11 methylation sites which might contain heritable epimutations associated with breast cancer.
Programme

Friday 28th

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“Familial Cancer 2015 Research and Practice”

Session 8:

Plantation Room

Chairperson: Clare Scott
Clinical implications of intratumoural heterogeneity in high-grade serous ovarian cancer (HGSOC)

James D. Brenton, MB BS PhD FRCP, Senior Group Leader and Honorary Consultant in Medical Oncology, Cancer Research UK Cambridge Institute, University of Cambridge

The major challenge for the development of personalized treatment for HGSOC is the extreme genomic heterogeneity observed between cases, lack of strong genomic classifiers and the common finding of intratumoural heterogeneity (ITH). We have previously shown that HGSOC is characterised by ubiquitous TP53 mutation and have proposed that early loss of TP53 may be permissive for the development of diverse mutator phenotypes, which could contribute to the development of ITH and platinum resistance.

I will discuss our recent findings that show that ITH is common in HGSOC and that methods of quantifying clonal divergence may have prognostic associations. Large scale patient studies of the relationship between copy number and heterogeneity are now needed and we have developed new methods to use shallow WGS to estimate copy number profiles from small biopsies of relapsed disease in the BRITROC trial. I will also discuss show how ctDNA may be used as a patient-specific specific biomarker for measuring response to treatment and will outline how the Genomics England 100K project may provide critical data to develop trials of personalized treatment strategies for women with HGSOC.
Fertility Implications of Having A BRCA1 or BRCA2 Mutation

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Background: It is uncertain whether mutations in the DNA repair genes, BRCA1 or BRCA2, result in reduced ovarian reserve. Anti-müllerian hormone (AMH) is a surrogate marker of fertility; higher levels are associated with greater ovarian reserve. This study examined AMH levels of BRCA1 and BRCA2 mutation carriers and their non-carrier blood relatives. This study examined AMH levels of BRCA1 and BRCA2 mutation carriers and their non-carrier blood relatives.

Methods: Eligible women were from families segregating BRCA1 or BRCA2 mutations. Women had been tested for the family mutation and had completed an epidemiological questionnaire and provided a blood sample at cohort entry. Women were aged 25-45 years, had no personal history of invasive cancer, had two intact ovaries and were not pregnant or breastfeeding at the time of blood draw. AMH was tested on stored plasma samples using an electrochemiluminescence immunoassay platform. Associations between AMH level and carrier status were tested by linear regression, using the natural logarithm of AMH as the outcome variable, carrier status as the explanatory variable, and adjusting for age at blood draw, oral contraceptive use, body mass index and cigarette smoking. Robust standard errors were estimated to account for the inclusion of multiple members from the same family.

Results: AMH level was measured for 172 carriers and 216 non-carriers from families carrying BRCA1 mutations, and 147 carriers and 158 non-carriers from families carrying BRCA2 mutations. Within both groups, mutation carriers were younger at blood draw than non-carriers (p≤0.031). Age was negatively associated with AMH level for carriers and non-carriers of BRCA1 and BRCA2 mutations (p<0.001). BRCA1 mutation carriers had, on average, 25% lower AMH levels than non-carriers (p=0.022). There was no evidence of an association for BRCA2 mutation carriers (p=0.94).

Conclusions: Women with a germline mutation in BRCA1 may have reduced ovarian reserve. This could have important implications for their fertility, family planning and age at natural menopause. Avoiding unnecessary delays in childbearing might be prudent for BRCA1 mutation carriers.
Quality of Risk-reducing Gynaecologic Surgery in Australasian Women at High Risk of Pelvic Serous Cancer

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Introduction: Bilateral salpingo-oophorectomy (BSO) is recommended for women at high risk of pelvic serous cancer (PSC). Occult carcinoma or precursor lesions are detected in a subset of preventive BSO specimens, highlighting the importance of comprehensive histopathologic assessment. Previously, we reported that for risk-reducing gynaecologic surgery (RRGS) performed in high risk Australasian women prior to the year 2008, 91% had adequate surgery and only 23% had adequate pathology [1]. Here, we report the quality of surgery and pathological evaluation for RRGS performed from the year 2008.

Methods: Eligible women were identified from the kConFab Follow-Up Study database with high risk of PSC (i.e. carried a mutation in BRCA1 or BRCA2, or had a 1st or 2nd degree relative with a history of PSC), and had RRGS between 2008 and 2015. Women who did not carry the documented family BRCA1 or BRCA2 mutation (non-carriers) and those with metastatic cancer or prior personal history of invasive gynaecological cancer were excluded. Surgical and pathology reports were reviewed; “adequate” surgery was defined as complete removal of all ovarian and extra-uterine fallopian tube tissue, whilst “adequate” pathology was defined as paraffin embedding of all removed ovarian and tubal tissue. Predictors of “adequate” pathology, including clinical notes indicating high risk, surgeon type, year and type of surgery, were assessed using logistic regression.

Results: The study sample comprised 164 women, including 130 mutation carriers (80 BRCA1, 48 BRCA2, 2 BRCA1&2). Median age of RRGS was 48 years for both BRCA1 and BRCA2 mutation carriers, and 54 years for other women. Most RRGS were performed by gynaecologic oncologists (58%) with the remainder by general gynaecologists (40%) and general surgeons (2%). 73/164 (45%) had hysterectomy performed with RRGS. 158/159 (99%) had adequate surgery and 108/164 (66%) had adequate pathology. Independent predictors of adequate pathology in a multivariable model included having surgery performed by a gynaecologic oncologist rather than a general gynaecologist (p=0.001), more recent year of surgery (p=0.038), and clinical notes on the pathology request form that indicated high risk (p=0.018). 3/164 (1.8%) women had occult cancers and a further 2 (1.2%) had a precursor lesion identified.

Conclusion: The quality of RRGS performed in Australasian women, in particular the pathological evaluation, appears to have improved dramatically since our last report. Women are more likely to receive optimal RRGS if they are operated on by a gynaecologic oncologist who informs the pathologist that the woman is at high risk for PSC.

References:

Understanding acquired resistance in high-grade serous ovarian cancer (HGSC).

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The molecular and genomic features of primary high-grade serous ovarian cancer (HGSC) have been well characterized, and recent studies have documented extensive intra-tumoural heterogeneity within these, and other, solid tumours. Less understood are the effects of the selective pressure of chemotherapy on cancer cell populations and genomic evolution leading to acquired treatment resistance. Genomic studies undertaken in recurrent disease have been limited, primarily due to challenges in tissue acquisition. We recently completed a whole-genome sequencing analysis of germline and tumour DNA samples from a large series of HGSC patients (n = 92) to better understand the drivers of refractory, resistant and acquired resistant phenotypes. As part of this investigation, we utilised a rapid autopsy program to sample multiple intra-patient metastatic tumour deposits. Several different molecular events associated with treatment resistance were observed, including the identification of multiple independent \textit{BRCA1/2} germline mutation reversions occurring within individual patients. Discrete intra-patient tumour deposits were found to contain more than one reverted clone, and similarly specific reverted clones could be found in more than one metastatic deposit. Our findings highlight the complexity of the recurrent, treatment-resistant HGSC genome.
Risk of extracolonic cancers for people with biallelic and monoallelic mutations in MUTYH

Aung Ko Win,1 Jeanette C. Reece,1 James G. Dowty,1 Daniel D. Buchanan,1,2 Mark Clendenning,2 Christophe Rosty,2,3 Melissa C. Southey,4 Joanne P. Young,5,6,7 Sean P. Cleary,8 Hyeja Kim,8 Michelle Cotterchio,9 Finlay A. Macrae,10,11,12 Katherine M. Tucker,13 John A. Baron,14 Terrielle Burnett,15 Loïc Le Marchand,15 Graham Casey,16 Robert W. Haile,17 Polly A. Newcomb,18,19 Stephen N. Thibodeau,20 John L. Hopper,1,21 Steven Gallinger,6 Ingrid M. Winship,10,11 Noralane M. Lindor,22 Mark A. Jenkins.1

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9 Prevention and Cancer Control, Cancer Care Ontario, Toronto, Ontario, Canada.
10 Genetic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Australia.
11 Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia.
12 Colorectal Medicine and Genetics, Royal Melbourne Hospital, Parkville, Victoria, Australia.
13 Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, New South Wales, Australia
14 Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA.
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16 Department of Preventive Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA.
17 Department of Medicine, Division of Oncology, Stanford University, California, USA.
18 School of Public Health, University of Washington, Seattle, Washington, USA.
19 Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.
20 Molecular Genetics Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA.
21 Department of Epidemiology and Institute of Health and Environment, School of Public Health, Seoul National University, Seoul, Korea.
22 Department of Health Science Research, Mayo Clinic Arizona, Scottsdale, Arizona, USA.

Background: Germline mutations of the DNA base excision repair gene MUTYH are known to be associated with an increased risk of colorectal cancer. The estimated cumulative risks (95% confidence interval [CI]) to age 70 years were 75% (41%–100%) for male and 72% (45%–92%) for female carriers of biallelic mutation, and 7% (5%–11%) for male and 6% (4%–9%) for female carriers of a monoallelic mutation. Because these mutations are rare, risk of cancers other than colorectal cancer (extracolonic cancers) for MUTYH mutation carriers are uncertain.

We identified 41 biallelic and 225 monoallelic MUTYH mutation carrier probands from the Colon Cancer Family Registry. Mutation status, sex, age, and histories of cancer were obtained from 5,846 of their first- and second-degree relatives. Hazard ratios (HRs) and age-specific cumulative risks of extracolonic cancers were estimated using modified segregation analysis conditioned on the ascertainment criteria.

Results: Compared with incidences for the general population, HRs (95% confidence intervals [CIs]) for biallelic MUTYH mutation carriers were: urinary bladder cancer, 19 (3.7–97); and ovarian cancer, 17 (2.4–115). The HRs for monoallelic MUTYH mutation carriers were: gastric cancer, 9.3 (6.7–13); hepatobiliary cancer, 4.5 (2.7–7.5); endometrial cancer, 2.1 (1.1–3.9); and breast cancer, 1.4 (1.0–2.0). We did not find evidence for an increased risk of cancers at the other sites examined (brain, pancreas, kidney or prostate). The estimated cumulative risks (95% CI) to age 70 years for biallelic mutation carriers were: bladder cancer, 25% (5%–77%) for males and 8% (2%–33%) for females; and ovarian cancer, 14% (2%–65%). The cumulative risks for monoallelic mutation carriers were: gastric cancer, 5% (4%–7%) for males and 2.3% (1.7%–3.3%) for females; hepatobiliary cancer, 3% (2%–5%) for males and 1.4% (0.8%–2.3%) for females; endometrial cancer, 3% (2%–6%); and breast cancer 11% (8%–16%).

Conclusion: These unbiased estimates of both relative and absolute risks of extracolonic cancers for MUTYH mutation carriers will be important for the clinical management of carriers.

Bibliographical References
Programme

Friday 28th

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

"Familial Cancer 2015: Research and Practice"

Session 9:

Plantation Room

Chairperson: John Hopper
The role of common genetic variation in ovarian cancer susceptibility

Paul Pharoah, Department of Oncology, Department of Public Health and Primary Care, University of Cambridge, UK

High and moderate penetrance alleles of the known ovarian cancer susceptibility genes account for less than half of the excess familial risk of disease (or genetic variance). Complex segregation analysis suggests that much of the remainder will be due to a large number of common alleles with weak effects. In this talk I will describe progress over the last ten years in the search for such common alleles: Genome-wide association studies and large-scale replication carried out by the Ovarian Cancer Association Consortium have now identified 18 common susceptibility alleles. I will discuss the contribution of these alleles to risk in the population and the implications for the management of risk.
Searching for new familial breast cancer predisposition genes

Na Li, Ella Thompson, Simone Rowley, Paul James, Alison trainer, Gillian Mitchell, Lisa Devereux, Ian Campbell
Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia.

Introduction: About 20-40% of breast cancer patients are diagnosed less than 50 years old and/or have a family history of breast/ovarian cancer suggesting a considerable proportion of cases are caused by inherited factors (1). BRCA1 and BRCA2 mutations account for about 20 to 25 percent of hereditary breast cancers and other high to moderate penetrance genes such as PALB2 and ATM account for a further 5 to 10 percent (2). However, in approximately half of high risk families the causative genetic factor remains unknown (BRCAx families). Identifying the full repertoire of breast cancer predisposition genes could have a major and immediate impact on reducing breast cancer risk in these family members.

Methods: Up to 1,400 candidate breast cancer predisposition genes, identified through exome sequencing of ~70 BRCAx families, were sequenced in index cases of up to 2,000 BRCAx families and 2,000 cancer free Victoria women from the LifePool study. The data was filtered to identify genes with an excess of loss of function (LoF) mutations in cases versus controls.

Results: Interrogation of the data to refine the highest priority candidates is ongoing, but it is noteworthy that known (PALB2) or suspected (MRE11A) moderately penetrant breast cancer genes showed enrichment of LoF mutations in this dataset, although some other recently proposed breast cancer genes (BRIP1, RINT1) did not show a significantly elevated LoF mutation frequency in cases compared to controls. The strong enrichment for PALB2 mutations in cases compared to controls reflects recent reports that establish PALB2 as the next major breast cancer gene after BRCA1 and BRCA2. One of the top hits based on the number of LoF mutations only, was the gene NTHL1 (9 in cases, 1 in controls, \( p=0.01 \)). Interestingly this gene is a member of a family of genes encoding DNA glycosylases that recognise the products of oxidative damage to the nucleotides of DNA which is an essential first step in the base excision repair (BER) pathway. Based on this result we examined the BER pathway further, considering the variants detected in each of the genes that recognize DNA-base lesions and the DNA polymerases, endonucleases or ligases associated with the BER pathway. A strong pattern was found in the group of DNA glycosylases, represented by 12 genes in the capture design (NTHL1, OGG1, APEX1, APEX2, NEIL1, NEIL2, NEIL3, MUTYH, MPG, ALKBH1, ALKBH2, ALKBH3): 32 LoF and 180 missense variants in these genes were detected in the cases versus 10 LoF and 139 missense changes in controls (\( p=0.0008 \) for LoF, \( p=0.0003 \) for all variants). Based on the overall distribution of variants between cases and controls the probability of selecting 12 genes with such enrichment from the 1325 genes screened was less than 1 in 200.

Conclusions: Massive Panel sequencing among familial breast cancer cases and cancer free controls is an efficient way to identify and validate suspected breast cancer predisposing genes. This study not only provided up to date validation result of known breast cancer predisposition genes as well as the evidence for new candidate genes, but also addressed the population frequency of hereditary breast cancer pathogenic mutations in Australia woman.

Evidence-based massively parallel translation: Application to breast cancer susceptibility.

Melissa C. Southey1, Paul A James3,4, Katherine Tucker5, Judy Kirk6, Alison Trainer3,4, Ingrid Winship2,4 and Nicholas Pachter7.

1Department of Pathology, 2The University of Melbourne, 3Peter Mac Callum Cancer Centre, 4Royal Melbourne Hospital, 5Prince of Wales Hospital, Centre for Cancer Research, 6Westmead Millennium Institute, University of Sydney, Sydney, Australia; Westmead Hospital, Sydney, Australia, and 7King Edward Memorial Hospital for Women.

A new, NBCF supported, 5 year research program, has recently commenced that aims to provide new data that will support the translation of new genetic information and testing model (including gene panel testing) into clinical genetic services throughout Australia.

Overview:
Since 1997, genetic testing of the BRCA1 and BRCA2 genes has been offered to selected women attending clinical genetics services throughout Australia. For the vast majority of women (~80%) these tests are uninformative. Continued research has identified additional breast cancer susceptibility genes and today commercial and direct-to-the-public diagnostic testing facilities are including a larger number of breast cancer susceptibility genes, in a single test, at considerably reduced costs. These tests pose considerable challenge to clinical genetic services, as very little is known about the cancer risks associated with any of the observed genetic variation. Recently, we have demonstrated evidence-based clinical translation (via eviQ) of genetic information about the third breast cancer gene, PALB2. The community now needs similar information about the larger number of genes that are being tested routinely by commercial facilities so that this data can be used to inform clinical management and counseling of women attending clinics around Australia. We will provide this data via the conduct of a large nation-wide study of women at high-risk of breast cancer who have tested negative for mutations in BRCA1 and BRCA2. We will apply a “gene panel” test including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, STK11 and TP53 to 10,000 women. As demonstrated by our PALB2 work, this data will 1) enable Australian population-specific estimates of mutation penetrance and prevalence, 2) be combined with similar data from international efforts* that will provide additional capacity for these analyses and 3) facilitate the translation of this new testing model and new genetic information into clinical genetics services. This work will realize an environment where a heritable cause of breast cancer susceptibility is identified in the majority women seeking advice about their personal and/or family history of breast and/or ovarian cancer.

* We will present our study aims in the context of other international efforts in this area including;

2015-2020 European Commission Horizon 2020
Breast Cancer Risk after Diagnostic Gene Sequencing (BRIDGES)
Devilee, Easton, Benitez, Borg, Engel, Stoppa-Lyonnet, Schmutzler, Hall, Bojesen, Blavier, Southey, Goldgar, Spurdie, Couch, Simard.

2015-2020 NHMRC European Union Collaborative Research Grant GNT1101400
BRIDGES: Breast Cancer Risk after Diagnostic Gene Sequencing
Southey MC and Spurde A
Germline MLH1 Mutation Type and Frequency in Individuals with Solitary Loss of PMS2 Expression in Colorectal Carcinomas

Mark Clendenning1, Christophe Rosty, Michael D. Walsh, Stine V. Eriksen, Melissa C. Southey, Ingrid M. Winship, Finlay A. Macrae, Alex Boussioutas, Judy Kirk, Nicola K Poplawski, Susan Parry, Julie Arnold, Joanne P. Young, Graham Casey, Robert W. Haile, Steven Gallinger, Loïc Le Marchand, Polly A. Newcomb, John D. Potter, Melissa DeRycke, Noralane M. Lindor, Stephen N. Thibodeau, John A. Baron, Aung Ko Win, John L. Hopper, Mark A. Jenkins, Daniel D. Buchanan on behalf of the Colon Cancer Family Registry Cohort

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

Background: Immunohistochemistry for DNA mismatch repair proteins is used to screen for Lynch syndrome in individuals with colorectal carcinoma (CRC). Although solitary loss of PMS2 expression is indicative of carrying a germline mutation in PMS2, a mutation cannot always be identified. Therefore, we hypothesized that germline mutations in MLH1 may underlie a proportion of CRCs demonstrating solitary loss of PMS2 expression.

Methods: We included 88 individuals affected with a PMS2-deficient CRC from the Colon Cancer Family Registry Cohort. Germline PMS2 mutation analysis (long-range PCR and Multiplex Ligation Dependent Probe Amplification (MLPA)) was followed by MLH1 mutation testing (Sanger sequencing and MLPA).

Results: Of the 66 individuals with complete mutation screening, we identified a pathogenic PMS2 mutation in 49 (74%), a pathogenic MLH1 mutation in 8 (12%) individuals and a MLH1 variant of uncertain clinical significance predicted to be damaging by in silico analysis in 3 (4%) individuals with the remaining 6 (9%) individuals had no clinically significant variation. Missense point mutations accounted for most alterations (83%; 9/11) in MLH1. The MLH1 c.113A>G p.Asn38Ser mutation was found in 2 related individuals. One individual who carried the MLH1 intronic mutation c.677+3A>G p.Gln197Argfs*8 leading to the skipping of exon 8, developed 2 CRCs, both of which retained MLH1 expression.

Conclusion: In summary, we report that a substantial proportion of CRCs with solitary loss of PMS2 expression are associated with a pathogenic MLH1 germline mutation supporting the screening for MLH1 in individuals with CRC of this immunophenotype, when no PMS2 mutation has been identified.
Panel testing for familial breast cancer: tension at the boundary of research and clinical care

Paul A James, Ella R Thompson, Simone M Rowley, Na Li, Simone McInerny, Lisa Devereux, Michelle W Wong-Brown, Alison H Trainer, Gillian Mitchell, Rodney J Scott, and Ian G Campbell.

Cancer Genetics Laboratory, Peter MacCallum Cancer Centre, East Melbourne, Victoria, (ERT, SMR, NL, LD, AT, IGC); Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, (ERT, AT, GM, PAJ, IGC); Cancer Biology Research Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China (NL); Familial Cancer Centre, Peter MacCallum Cancer Centre, East Melbourne, Victoria, (SM, AT, GM, PAJ); Discipline of Medical Genetics and Centre for Information-Based Medicine, The University of Newcastle and Hunter Medical Research Institute, Newcastle, NSW (MWWB, RJS); Division of Genetics, Hunter Area Pathology Service, Newcastle, NSW (RJS); Department of Pathology, University of Melbourne, Melbourne, Victoria, (AT, PAJ, IGC); Hereditary Cancer Program, BC Cancer Agency, Vancouver, Canada (GM).

Gene panel sequencing is predicted to become the new standard of practice for hereditary breast cancer. Already results from commercial panels are reported as providing the definitive explanation for an individual’s family history, despite scant evidence supporting an association with breast cancer risk for many of the genes involved. We assessed the frequency of mutations in genes commonly included in hereditary breast cancer panels in a large cohort of index cases from breast cancer families and matched population controls.

Cases were 2000 breast cancer-affected women, with features of heritable risk, assessed by a familial cancer centre (BRCA1 and BRCA2 wild-type). Controls were 1,997 cancer-free women from the LifePool study (www.lifepool.org). A group of 18 genes that appear on available breast cancer sequencing panels were identified and sequencing data (from a custom capture array) were filtered for known pathogenic or novel loss of function variants.

Excluding additional mutations identified in BRCA1 and BRCA2, a total of 79 cases (3.9%) and 33 controls (1.6%) were found to carry a potentially “actionable mutation”. PALB2 was most frequently mutated (26 cases, 4 controls), and 5 described pathogenic variants were detected in TP53 (0 controls). Among the remaining genes, loss of function mutations were rare and similar in frequency between cases and controls. An excess of novel missense variants was noted in cases but could not be individually clinically interpreted. The combined population attributable risk for breast cancer of all the genes on the panel was 2.4%, nearly half of which was due to PALB2 mutations. Clinical features, including young age of diagnosis, bilateral breast cancer, ovarian cancer or tumour characteristics did not predict pathogenic variants.

The frequency of mutations in most breast cancer panel genes among individuals selected for possible hereditary breast cancer is low and, in many cases, similar or lower than observed in cancer-free population controls. While multi-gene panels can significantly aid in cancer risk management, they equally have the potential to provide clinical misinformation if the data is not interpreted cautiously.
Programme

Wednesday 26th

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

"Familial Cancer 2015: Research and Practice"

Poster Session

6.00 – 8.00pm

In the main Foyer of Mantra
Paediatric Cancer Genetics at POWH 1994-2014 what have we learnt
Katherine Tucker\textsuperscript{a} ; Meera Warby\textsuperscript{a}

\textsuperscript{a} Hereditary Cancer Clinic, Prince of Wales Hospital (POWH), Randwick, New South Wales, 2031, Australia

**Background:** Cancer Genetic services have been available at POWH Randwick since February 1994. The paediatric service has increased especially in the past 10 years. We sought to determine trends in referral and genes tested.

**Objective:** to determine the rate of increase and reasons for pediatric cancer referrals in the past 20 years in order to better plan for the next 20 years

**Method:** All new patient < 18 years at initial visit reviewed. Referrals divided into initial mutation search, predictive testing and opinion; genes tested noted.

**Results:**

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<td>Predictive</td>
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<td>Opinion</td>
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**Paediatric Referral**

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**Predictive test**

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<td>PTCH1; SMARCB1; BRCA2; KRIT1*</td>
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**Management opinion**

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\* = gene for congenital cerebral malformations
** =2 with deletion of a cancer predisposing gene found on CGH

Discussion: Paediatric referral are increasing as more genes are discovered; cost of testing decreases; parental awareness increases and management implications are identified. The POWH experience is likely to be the tip of the iceberg, and clinicians need to educate themselves about the needs of parents, children and adolescents. The 2 cases of CGH identified deletions including cancer predisposing genes hints at the coming avalanche of unclassified variants when genomic testing becomes more widespread. Workforce issues and education needs of referring clinicians and the genetic workforce need attention.

"Familial Cancer 2015: Research and Practice"
Paediatric Cancer Genetic QA project

*Meera Warby*, Katherine Tucker

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

Background:
Fortunately childhood cancer occur at only 600 new cases aged 0-14 years diagnosed per year in Australia. However parents are plagued by guilt and the constant question of ‘Why’? Answering this question requires obtaining a detailed personal cancer history, clarification of developmental history, family history and clinical examination. Each year more cases are being referred to cancer genetic services. Early and accurate identification of cancer predisposition can provide prevention and screening of other family members. Paediatric cases are increasingly impinging on POWH service workflow.

Objective:
To identify the main paediatric referral categories, counselling issues and possible strategies to improve management.

Methods:
patients referred in 2014 <18 years were reviewed. Referrals were coded into 3 groups: 1. Full mutation analysis; 2. predictive testing and 3. management opinions. The main counselling issue was recorded as distress about a) the cancer/ tumours already present; b) potential cancer predisposition; c) concern for other family members; d) other. Potential time saving ideas were sought.

Results:
59 consultations were identified:
29 full mutation analyses of gene/s;
19 predictive testing in children/ adolescence;
21 management opinions -including 2 CGH identified deletion of possible cancer predisposing gene ; KRIT1 testing in 3.
44 consultations contained distress about tumour diagnosis &/or potential predisposition. In 15 cases distress was absent (diagnostic or management of a known disorder).
Time saving ideas included: a dedicated paediatric clinic; a protocol for making paediatric appointments; better data support; and continuing education for genetic staff and paediatric clinicians.

Discussion:
With the increasing referral of paediatric cases, adult services need to identify and modify existing service delivery to the needs of already distressed parents and children. This Quality Assurance project helped identify potential time savers and clarified the different genetic counselling tasks. A review of the initiatives implemented is planned for six months time.
Case study: Identification of a mosaic VHL gene mutation following sudden death and subsequent organ donation; implications for family and transplantation recipients

Sally Russell\textsuperscript{1}, Jacqueline Armstrong\textsuperscript{1}, Nicola Poplawski\textsuperscript{1,2} and Lesley Rawlins\textsuperscript{3}

1. Adult Genetics Unit, SA Pathology (WCH Site), North Adelaide, South Australia
2. University Department of Paediatrics, University of Adelaide
3. Molecular Pathology Laboratory, SA Pathology (Frome Rd site) IMVS, Adelaide, South Australia
Email: sally.russell@sa.gov.au

A 34 year old man was declared brain dead following an acute cerebral haemorrhage. A number of his organs were used for transplantation. Subsequent investigation identified that this man had died from an acute haemorrhage from a cerebellar haemangioblastoma. He had a number of other features suggestive of von-Hippel-Lindau (VHL) disease including multiple simple cysts of the left kidney, and a neuroendocrine tumour of the small bowel (identified in the failed pancreas and small bowel transplant). The 5 year old only child of the deceased man was referred to our service to clarify his risk of developing VHL disease.

This poster describes the results from genetic testing on stored tissue and blood samples from the affected man. These results suggested that the deceased man was mosaic for VHL disease based on the blood and tumour genetic test results and his clinical phenotype.

Predictive genetic testing was performed in a blood DNA sample from his child (no VHL mutation identified).

The transplantation recipients remain at some risk of developing tissue-relevant VHL disease and their medical practitioners were advised of this risk.

This case was complex in its genetic implications for the transplantation recipients but testing was able to provide his immediate family with reassuring information.
Using Genealogy in cascade testing - the value in concatenation.

B. Patterson\textsuperscript{1}, J. Burke\textsuperscript{1} & P. James\textsuperscript{2}

1. Tasmanian Clinical Genetics Service, Royal Hobart Hospital,
2. Familial Cancer Service, PeterMacCallum Cancer Centre, Melbourne

The role of cascade testing in the setting of hereditary cancer syndromes is to provide useful genetic information and risk advice to as many relatives within a mutation positive family as possible. Therefore, the more relatives within a family who are tested, the more valuable the original mutation detection test becomes.

The Tasmanian population, with its relatively small number of founders and limited migration, provides a unique opportunity to trace the ancestors of mutation positive families. We are able to electronically access records of births from 1800 through to 1930 and deaths and marriages through to 1920, which potentially allows us to identify the ancestors for many of our mutation positive families. As the Tasmanian Clinical Genetics Service covers the whole of Tasmania we are ideally positioned to use this information to concatenate the branches of distantly related pedigrees. While we currently do not have the resources to apply this to every mutation positive family, from the genealogical explorations that we have performed, several useful outcomes have come to light.

The motivation for our initial genealogical explorations was to recognise when the pedigree of a newly referred family could be concatenated with an existing mutation positive family, enabling us to offer predictive testing rather than more expensive mutation detection. In three cases this has been successful, however as we do not have the resources to investigate the ancestors of every Tasmanian mutation positive family the strategy has not yet been universally applied.

In addition to the savings associated with offering predictive testing rather than mutation detection, concatenation of pedigrees has other benefits. It has the ability to significantly enlarge pedigrees, maximising the number of at-risk relatives to whom predictive testing can be offered, and it can also provide valuable penetrance data for a particular mutation. In one family, with attenuated FAP where the clinical phenotype is variable, this has been particularly relevant.

Another benefit to come from concatenation is identifying whether a mutation has been maternally or paternally inherited, in cases where the parents (or grandparents) are deceased, estranged, or decline testing. This information has allowed us to rapidly exclude and reassure relatives who we can see are not at risk and at the same time, focus our energies towards the mutation positive side of the family.

Examples will be presented to highlight the benefits of genealogical linking in the familial cancer clinic.
Risk-reducing surgery in a cohort of Australian BRCA1 and BRCA2 carriers

Katherine Tucker\textsuperscript{a*}, Emma Healey\textsuperscript{b}, Rachel Williams\textsuperscript{a}, Sian Greening\textsuperscript{b}, Linda Warwick\textsuperscript{c}, Claire E Wakefield\textsuperscript{d,e}

\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
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Objectives: Female BRCA1/BRCA2 carriers can consider a range of options to manage their cancer risks, outlined at www.eviq.org.au. These include high risk screening, risk-reducing medication (RRMed), risk-reducing mastectomy (RRM), and risk-reducing salpingo-oophorectomy (RRSO). Risk-reducing surgical options offer these women the greatest survival benefit, however uptake rates vary significantly worldwide. The aim of this study was to determine the uptake rate of RRM and RRSO in Australian BRCA1/BRCA2 carriers.

Methods: 514 female BRCA1/BRCA2 carriers who were contactable by mail or phone from four hospitals in New South Wales and the Australian Capital Territory were invited to participate in a mutation dissemination study. One hundred and sixty one consented to the study (30% response rate). Participants completed a telephone questionnaire evaluating current risk-management choices. Logistic regression analyses were carried out to determine factors associated with risk-reducing mastectomy uptake. As a comparison, the clinical database was checked for all unaffected and affected mutation carriers to determine whether management choice differed between study and non-study participants.

Results: RRM uptake rate was 49% across all participants (n=161). Personal breast cancer history was the strongest predictor of RRM uptake, with affected women seven times more likely to have RRM than unaffected women (p<0.001) (70% affected vs 30% unaffected). Women of Jewish ancestry (p=0.028), and those without ovarian cancer (p=0.005) were also more likely to have undergone RRM. The RRSO rate was too high to analyse associations, with uptake 90% (n=114) in women aged 40 or older who had not had ovarian cancer. The clinical data base revealed a similar pattern of management choices in non-study participants – 65% (96/147) of affected and 29% (42/145) of unaffected women had bilateral mastectomies, and 92% of women ≥40 had completed RRSO.

Discussion: Uptake of RRM in Australian unaffected carriers is similar to rates in Holland (32.7%) and USA (36.3%) in 2008 (Metcalf et al., 2008 Int J Cancer). However, recent findings suggest increasing uptake in USA - 42% amongst unaffected carriers (Singh et al., 2013 AJOG). Uptake of RRSO is much higher in Australian than in other countries (Metcalf et al., 2008 Int J Cancer) suggesting successful implementation of eviQ guidelines with high patient compliance.

Conclusions: The uptake of RRM in Australian women is similar to that of other countries, the uptake of RRSO is higher. Australian guidelines which do not support CA-125 screening, may explain this variation.
At risk and unreachable - Implementing the Family Communication Tool into the clinic to improve dissemination of information.

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Aim: The hereditary nature of Lynch syndrome makes it essential for those diagnosed to provide their relatives with information about their increased risk of carrying the gene. Our previous work demonstrated that emotional, geographical, or family dynamics and miscommunication barriers can prevent BRCA1/BRCA2 mutation carriers from sharing this information with family members, and that these can be addressed by a telephone intervention, using a family communication tool (FCT) to guide discussion. This study aims to: 1) determine the effectiveness of the FCT in the dissemination of information in Lynch syndrome families, 2) assess the effect of FCT on workload, and 3) implement the FCT into standard clinical practice.

Method: MLH1, MSH2, MSH6 PMS2 mutation carriers from four participating hospitals were identified through the genetic data-base. Training of genetic counsellors was conducted in twenty minute to one hour sessions with documents and support provided. Following training, genetic counsellors conducted follow-up with these carriers using the FCT as part of clinical care. Genetic counsellors recorded details including family members informed, resources provided, risk management changes and then recorded the time of the process.

Results: To date, 60 identified mutation carriers have been followed up using the FCT. Data analysis identified 31 Lynch syndrome families with incomplete family dissemination and incomplete testing uptake. The intervention led to provision of resources to assist in family discussion about screening recommendations or availability of testing, and identified cases requiring further clinical review. Clinical time averaged thirty minutes per individual. Time was reduced in family clusters due to the electronic FCT. Feedback regarding the FCT was positive, particularly that the FCT assisted them in streamlining discussion.

Conclusion: This follow-up study is providing evidence that the FCT is valuable in reaching “at risk” relatives in the clinical setting and in different hereditary cancer syndromes.
Pilot testing of an educational resource on genomic testing for low-risk breast cancer variants.

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Introduction
Patients who are at risk of a heritable condition are often faced with a difficult decision as to if they should uptake testing. This means that they need to be adequately informed so that they fully understand the risks and benefits of testing and acknowledge the degree of importance they attach to each option. We are undertaking a prospective, quantitative study of the psychological impact of disclosure of testing results for low-risk breast cancer variants on patient outcomes, including understanding of results and impact on screening and risk-reducing behaviours. An information resource was developed for women considering genetic testing for common variants associated with breast cancer risk. Participants of an existing study, the ‘Common Genetic Variants and Familial Cancer’, also referred to as Variants in Practice (ViP) study, which is enrolling ~4,000 women and men who have a high-risk family history of breast cancer, including index cases with cancer and their affected and unaffected relatives in Victoria, Australia.

Methods
The two-page educational pamphlet provides a brief explanation of rare high-risk and common lower-risk variants in breast cancer and the meaning and implications of low and high PRSs. It covers a range of topics relevant genomic testing for breast cancer risk. The pamphlet was pilot-tested with 28 female ViP participants.

Results
Most of the participants (23/28) said that they had gained information about genomic testing from the pamphlet. All participants understood the implications for them if they were found to have a low polygenic score. All women thought their understanding of the risks and benefits of testing had improved. The majority of participants (68%) reported that the pamphlet did not make them feel worried, with 71% actually reporting feeling reassured. There is some scope for improvement, particularly with regard to visual presentation, and participants also provided detailed suggestions for amendments, which will be incorporated before using the pamphlet as part of the prospective study.

Conclusions
We are going to incorporate changes suggested by the participants from our pilot test and will perform a randomised controlled trial to test it on ViP study cohort.
Developing a decision aid for genomic research participants notified of clinically actionable research findings.

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Background
Use of genomic screening to identify genetic cancer risk in research is rapidly expanding, with research participants routinely notified of clinically actionable findings. However, the results can be unexpected and researchers currently face the challenge of how best to notify and support research participants through subsequent decision-making. Uptake of cancer genetic counselling (GC) among both referred individuals and research participants has been historically low. This is of concern given these individuals are at potentially high risk of cancer and often have no formal decision support regarding GC attendance. We present the results of a systematic literature review regarding cancer GC uptake, and describe the development of the resulting decision aid, which aims to facilitate informed decision-making among those considering GC for clinically actionable research findings.

Methods
We conducted a systematic literature search for articles examining factors influencing GC uptake, with a focus on barriers to attendance. The results of this review and the International Patient Decision Aid Standard 2013 guidelines informed the content of a decision aid booklet, which was developed by a steering committee of clinicians, psychosocial researchers and consumers. The booklet will be pilot tested with kConFab and International Sarcoma Kindred Study research participants who have been notified of clinically actionable research findings and subsequently attended for GC (n=30), with feedback provided by mailed questionnaire.

Results
A significant proportion of at-risk individuals do not attend GC, including those notified of clinically actionable research findings. With the exception of education level, socio-economic status and actual/perceived risk, socio-demographic, clinical and psychosocial factors tend to be poor predictors of GC uptake. Cost and logistical barriers, emotional concerns, family-based concerns and perceived personal relevance were consistently reported as important considerations for those declining GC. In addition, GC is often seen as synonymous with genetic testing. Thus, the decision aid content focuses on improving knowledge of GC and increasing awareness of the range of services provided while providing practical information to facilitate attendance. The advantages and disadvantages of GC are outlined and a values clarification exercise is included to facilitate informed decision-making.

Pilot testing is soon to be underway.

Conclusion
There is consistent evidence that non-attendance may be attributable to low awareness and poor understanding of the goals of GC. We conclude there is a need for additional decision support for individuals considering GC for cancer risk. If successful in the research setting, this decision aid could be adapted for clinical use.
No bullshit therapy in the familial cancer setting: A client-centered approach to cutting the crap in genetic counselling

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In 2011, genetic counsellors at The Royal Melbourne Hospital (RMH) attended a workshop on “No Bullshit Therapy” (NBT) at The Bouverie Centre of La Trobe University.

Devised by family therapist, Jeff Young, NBT is about marrying honesty and directness with warmth and care in a working therapeutic relationship. The approach is highly relevant in genetic counselling for cancer, and consistent with existing principles and techniques used such as single session therapy, genuineness, immediacy, and challenging.

Three principles are key to effective use of NBT: a mandate with the client to be direct, identifying opportunities for ‘moments’ of honesty, and making a feature of constraints that exist in the counselling session.

Subsequent to the workshop undertaken in 2011, focused follow up sessions with Jeff Young were arranged in 2015 for genetic counsellors at RMH to focus on the use of NBT in genetic counselling. Learning points and case examples in the Familial Cancer setting will be presented.
Breast cancer genetic testing at Austin Health – an audit of clinical indications for testing and outcomes

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In Victoria, individuals are eligible for state-funded genetic testing of BRCA1 and BRCA2 when there is greater than a 10% chance of identifying a mutation, as determined by the mutation prediction algorithms BRCAPro1 or more recently BOADICEA2. Other clinical indications for testing include triple negative breast cancer <50 years3, high grade, non-mucinous ovarian cancer <70 years4, breast cancer diagnosed <35 years, and male breast cancer diagnosed at any age. Some individuals who do not meet the above criteria may be offered genetic testing on the basis of clinical judgement.

A review of all breast cancer mutation detection testing performed by Austin Health Clinical Genetics between January 2009 and June 2015 was conducted to determine the clinical utility of current testing criteria. In total, 669 individuals underwent mutation detection of the BRCA1 and BRCA2 genes. Of these, 14% (n=92) had a pathogenic mutation identified and 86% (n=574) had an inconclusive result (variant of unknown significance or no mutation). Of all individuals tested, 27.4% (n=183) did not meet any of the clinical criteria for testing, however, some of these individuals (n= 18), privately funded genetic testing. Of those identified with a BRCA mutation and a BRCAPro or BOADICEA score calculated, 75% had a score of greater than 10%. Of those that met a clinical indication for testing, >10% had a pathogenic mutation identified.

We will present further data on the clinical audit including a more detailed breakdown of the clinical indications for testing and will comment on the clinical utility of current guidelines.

Changing work patterns in the South Australian Familial Cancer Unit: the last decade

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BACKGROUND: The Familial Cancer Unit of the South Australian Clinical Genetics Service (SACGS) was established in 1998, led by a single clinical geneticist. The service employed its first associate genetic counsellors in July 1999, the first of whom achieved HGSA certification in 2004. In 2014 SACGS was organisationally restructured into the Paediatric and Reproductive Genetics Unit, the Metabolic Unit and the Adult Genetics Unit (AGU). The AGU provides both familial cancer and general genetics care for adults, with the cancer work load provided by 1.2 FTE clinical geneticist, 3.5 FTE genetic counsellor, 1.5 FTE administrative officer, 0.33 FTE data manager and 0.8 FTE data officer.

AIMS AND METHODOLOGY: Using the clinical activity data that was prospectively entered into the Service’s KinTrak database, we audited the last 11 years (2004-2014) of clinical services provided by SACGS where the primary focus was cancer.

RESULTS: During 2004-2014:
- 9553 referrals were received (median 852 per year; mean 868 per year; range 518-1439), with the number of referrals gradually increasing over the audit period.
- The number of referrals managed by letter, in lieu of an appointment, increased from a trivial number prior to 2007, to more than 250 in 2014.
- The number of face to face appointments was relatively constant for the first 9 years of the audit period (~800/year), but increased by >25% to more than 1000/year over the most recent 2 years.
- Excluding appointments for predictive testing, most appointments (64%) related to concern about the risk of breast and/or ovarian cancer.
- 1691 predictive tests were arranged (median 149 per year; mean 153 per year; range 113-240), and 31.5% of test results were “abnormal” (mutation detected).
- The annual number of predictive tests was constant during the first 9 years of the audit period (~150 per year) but increased in 2013/14, with the increase beginning shortly after Ms Angelina Jolie’s public announcement that she had had a risk reducing mastectomy.
- In the predictive testing setting, the most frequently tested genes were BRCA1/2 (63.1% of predictive tests), the MMR genes (16%), APC (6.6%), RB1 (2.8%) and SDH subunit genes (2.5%).

Limitations of the data: accuracy and completeness of data entry into KinTrak

CONCLUSION:
In South Australia there has been a recent increase in the demand for clinical genetics services that address concern about familial cancer risk. Work practices have changed to respond to this increased demand; more referrals are now managed by letter and the annual number of face-to-face appointments has increased. Most appointments address breast and/or ovarian cancer risk; families at risk of colorectal cancer are under referred. As demand for familial cancer services is expected to continue to increase, the service is proactively introducing new ways to manage this increasing work load.
Patient-funded genetic testing: the who, the why, and the what now

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To assess the impact of patient-funded testing on FCC service provision, an audit of patient-funded genetic testing at the Peter MacCallum Familial Cancer Centre between 2009 and 2015 was undertaken. In this time period approximately a 12-fold increase in the number of patient-funded BRCA1/2 tests was observed, with 5 patient-funded tests in the 2009-2010 financial year compared with over 60 tests in 2014-2015. Three individuals also specifically funded testing for TP53, RET and PALB2 respectively in the 2014-2015 period. Results showed pathogenic mutations were detected in approximately 4% of tests. Variants of unknown clinical significance were detected more frequently in around 10% of tests.

To better understand the profile of individuals choosing to self-fund genetic testing, personal and family cancer history characteristics of the 2013-2015 cohort were analysed and showed that those choosing to self-fund testing could be separated into three distinct groups:

- Individuals affected by cancer but ineligible for a publically-funded test and making treatment decisions,
- Individuals with a moderate or average risk personal and/or family history of breast/ovarian cancer (with no treatment decision),
- Unaffected individuals with a high risk family history of breast/ovarian cancer but no living/willing family member to test.

This data provides a baseline to understand the changing nature of genetic testing patterns and the impact of patient-funded testing on Familial Cancer service provision. Several cases that serve to illustrate the benefits and challenges for both patients and clinicians in this previously untested population and will also be presented. Future research which assesses the motivations for and clinical and psychological utility of patient-funded testing is planned.
Impact of \textit{BRCA1}/\textit{2} genetic testing on psychological distress and cancer worry in relatives from carrier families in Malaysia

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Background
In Asia, including Malaysia, there have been no reports on how family members in Asian \textit{BRCA} families who undergo predictive testing are affected by genetic counselling and testing. This study aims to determine whether genetic testing has an impact on the psychological distress and cancer worry in relatives of cancer patients with germline \textit{BRCA1} or \textit{BRCA2} alterations.

Methods
Eligible participants (n=64) were relatives who were informed by index patients that there is a genetic alteration in the family and who have agreed to proceed with predictive genetic testing. We administered the HADS (Hospital Anxiety and Depression Scale) and CWS (Cancer Worry Scale) questionnaires during the pre-test counselling and again within 1 month after results disclosure. For individuals that have been followed up for at least 24 months (n=27), we administered the HADS and CWS again to determine long term changes in distress levels 24 months post result disclosure. Statistical analysis (ANOVA and t-tests) were done using SPSS.

Results
From 23 \textit{BRCA} families, 47 first degree relatives (17 males and 30 females), 10 second degree relatives (5 males and 5 females) and 7 third degree relatives (3 males and 4 females) were informed about the genetic test results and came forward for genetic counselling and testing. When compared within the group of carriers (45%, 29/64) and non-carriers (55%, 35/64), there were no significant changes in anxiety, depression and cancer worry after result disclosure. However, depression levels were significantly reduced after result disclosure when compared regardless of carrier status (P=0.026). Both carriers and non-carriers showed an overall trend of reduced anxiety and depression 24 months post result disclosure.

Conclusions
This pilot report showed that genetic counselling and testing does not cause significant increase in distress and cancer worry among relatives from \textit{BRCA} carrier families in Malaysia. This suggests that genetic counselling may have provided information and increased their knowledge about testing, and relatives who come forward for genetic counselling have been psychologically prepared for the test results.
A new model of care for clients at low-moderate risk of familial breast cancer
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BACKGROUND
Familial cancer services in Victoria are funded by the Department of Health to provide services to high risk individuals/families. Currently at The Royal Melbourne Hospital Familial Cancer Centre all high risk referrals undergo standard verification of cancers and family history, with a subset of referrals then re-assessed as moderate or low risk with the additional information. These individuals, who have already engaged with the FCC, generally have an expectation of an appointment. Previously, these clients were allocated a 45-60 minute telephone appointment with a consultant. A novel model of care was developed to address the growing number of individuals at low-moderate risk of familial breast cancer.

METHOD
Clients deemed to be at low-moderate risk of familial breast cancer, based on the National Breast and Ovarian Cancer Centre guidelines, were invited to attend a 45 minute group information session. Following this, attendees were invited to a 5-10 minute individual consultation with a genetic counsellor and medical oncologist to address any specific concerns and to receive tailored advice. They were also given the option of arranging self-funded genetic testing at this point. Attendees were asked to complete a feedback questionnaire at the end of the session. All attendees received a standard summary letter following the session, with additional tailored advice if they attended the individual consultation.

RESULTS
For the pilot group information session, 19 clients were invited to the information session, with nine accepting the invitation. Two clients brought a relevant family member, comprising 11 attendees. Of these, seven elected to take up the brief individual consultation with one proceeding with self-funded BRCA testing. None of the clients’ risk assessments changed following the individual consultations. Summary family history data are presented, as well as a summary of client feedback. Feedback from clients who attended the pilot group information session suggests this model was well-received.

CONCLUSION
Genetic counselling research has highlighted the need for flexible approaches to delivery of services in response to increasing demand. Our experience, together with published evidence, supports consideration of group counselling as a potential approach for some areas of healthcare.
“But I want to know!” Challenges in providing predictive genetic testing by proxy.

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The provision of predictive genetic testing for hereditary cancer syndromes is undertaken within the framework of the fundamental medical ethics principles of autonomy, beneficence, nonmaleficence and justice. These are described in the Code of Ethics documents published by the Human Genetics Society of Australasia and the Australasian Society of Genetic Counsellors. In the context of adult-onset cancer conditions such as Lynch syndrome and Hereditary Breast and Ovarian Cancer, this includes respecting the right of individuals not to know their genetic status, the importance of individuals accessing predictive testing free from coercion and each individual making an informed decision about learning their genetic status. This process is inevitably tied to their family context. In some circumstances an individual’s decision to seek predictive genetic testing may provide their first degree relatives with information about their own risk indirectly – a test “by proxy”. These situations include monozygotic twins, where one twin declines predictive testing, and individuals at 25% risk whose intervening relative is unaffected, alive, and declines predictive testing. Does the right of the individual seeking information about their risk out-weigh the right of their family member not to know? It is clear in the literature that in the Huntington Disease context (which originally provided the basis for cancer predictive testing programs); preference is usually given to the person seeking testing. These requests may occur infrequently, but require careful management. Very little has been published on this topic in the context of hereditary cancer syndromes. We present two cases:

Case 1: 37 year old man (twin A) at 50% risk of an MSH6 mutation. He reported at telephone intake that he had an identical twin brother (twin B). Attempts were made to contact twin B to assess his understanding of the situation and his interest in participating in predictive genetic testing. These attempts were unsuccessful. Twin A was insistent on undergoing predictive genetic testing to clarify his cancer risk and screening needs. As we could not be certain the men were truly monozygotic twins, testing went ahead, and twin A received a negative result. It was emphasised that it could not be assumed that twin A’s result would be the same for twin B. Twin B may still be at risk of inheriting the mutation, and may wish to undergo screening if he does not pursue predictive genetic testing. Twin B has not presented for genetic counselling in the seven years since his brother’s test.

Case 2: 28 year old woman (ME) at 25% risk of a BRCA2 mutation. Initially, ME’s mother (CM, 50 years old) had refused to be tested but responded to the suggestion that she attend to at least hear the information about testing and possible implications. ME and CM eventually attended together and CM decided to proceed with testing to guide her own medical management. She received a positive result and was referred for risk-reducing bilateral salpingo-oophorectomy and annual mammography. ME subsequently received a negative test result. If CM had not been tested her genetic status would have been uncertain and a valuable chance to reduce cancer mortality for CM would have been missed.
An evaluation of the outcomes of patients attending the royal north shore hospital multidisciplinary familial endocrine clinic

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Background: Royal North Shore Hospital is a tertiary referral centre for the surgical and medical management of patients with endocrine tumours and a centre for molecular research into heritable endocrine neoplasia. In April 2013 the endocrinology and genetic services commenced a combined multi-disciplinary clinic to coordinate the management of families with familial endocrine syndromes. The strong research interest and capacity to perform genetic testing on site at the Kolling Institute has led to a slightly more permissive local genetic testing policy than is currently recommended in existing eviQ guidelines. We carried out a recent audit of the outcomes of the clinic to determine our mutation detection rates and the sensitivity of the current eviQ testing guidelines.

Methods: A retrospective audit of medical records was undertaken of all patients who had been referred to the clinic between April 2013 and July 2015. Patient characteristics, referral details, clinical and genetic diagnoses were assessed.

Results: Sixty-eight new patients were referred to the clinic, aged between 12 to 83 years. Twenty-five patients had a new mutation search for potential familial tumour susceptibility syndromes. Genetic mutations in patients presenting with paraganglioma and phaeochromocytoma include \( SDHA \) (n=3), \( SDHC \) (n=1), \( SDHD \) (n=2), \( NF1 \) (n=1), and pending (n=7) results. Genetic screening of four individuals with neuroendocrine tumours identified one \( MEN1 \) gene mutation. No mutations were identified in three patients with medullary thyroid and three patients with adrenocortical cancers. Seventeen patients (25%) underwent predictive genetic testing for an identified familial mutation.

Conclusion: The spectrum of genetic mutations found in our audit is comparable to other studies. To date, no further mutations have been detected in those offered testing outside of the recommended eviQ guidelines.
Multiple endocrine neoplasia type 4 (MEN4): a case study

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Multiple endocrine neoplasias (MEN) are a group of autosomal dominant disorders characterised by the presence of tumours in two or more endocrine glands within a single patient, although less commonly nonendocrine organs can be involved. Multiple endocrine neoplasia type 4 (MEN4) is a newly described member of this family and typically present with a MEN1-like phenotype including parathyroid and anterior pituitary tumours. Other possible features of MEN4 include tumours of the adrenals, kidneys and reproductive organs. The clinical description of MEN4, however, is still not clearly defined given the limited number of patients identified to date.

MEN4 is associated with the presence of heterozygous pathogenic variants in the CDKN1B gene (located on chromosome 12p13) that cause impaired function of the p27kip1 (p27) including reduced expression, mislocalisation or altered interaction networks. p27 is a cyclin-dependent kinase inhibitor that plays a role in the regulation of G1 to S phase of the cell cycle. Currently, only 9 MEN4 cases have been reported in the literature, each carrying a different heterozygous pathogenic variant in CDKN1B.

IB was referred due to a personal history of multiple primary cancers. At 49 years he was diagnosed with a pure seminoma and metastatic clear cell renal cancer. Later, at 60 years he was diagnosed with a multifocal papillary thyroid cancer and a parathyroid adenoma. He has a possible history of hypercalcaemia. IB belongs to a large Maltese family and is one of 16 siblings. He has a brother diagnosed with lymphoma at 58 years and a sister who died aged 58 years reportedly from ovarian cancer. Additionally, IB’s father was diagnosed with colorectal cancer at 68 years. There is no further family history of cancer reported, however, IB is not in contact with many of his relatives. MEN1 was initially considered as a possible explanation, however, given the presence of renal and testicular cancers in IB, germline CDKN1B testing has been initiated for this patient (sequencing results still pending).

All reported cases of MEN4 have been in female patients and most have involved hyperparathyroidism, with a variety of other features. If a germline CDKN1B pathogenic variant is identified in IB, this case will add further to the literature regarding the MEN4 phenotype. Emerging cases, such as these, help with structuring future clinical management guidelines and genetic testing criteria for MEN4.
Analysis of screening program for Von Hippel-Lindau mutation carriers.

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Background: Von Hippel-Lindau is a rare autosomal dominant cancer predisposition to renal cell carcinoma, haemangioblastoma of the cerebellum and spine, phaeochromocytoma, endolymphatic sac tumours, retinal angioma and epididymal cystadenoma. VHL is caused by a mutation in the VHL tumour suppressor gene. Mortality for individuals with VHL syndrome is related to complications from cerebellar haemangioblastoma and metastatic renal cell carcinoma. Current eVIQ risk management guidelines recommend MRI of abdomen, spine and brain 2nd yearly and yearly plasma catecholamines.

Aim: To assess the detection rate, compliance and cost-effectiveness of screening in VHL mutation carriers.


Results: Detection of 3 patients with renal cell carcinoma, 4 patients with haemangioblastoma and 1 patient with phaeochromocytoma. The compliance rates for imaging and plasma catecholamines were 85%. Cost effectiveness analysis to follow.
The 'likely pathogenic' variant: genetic counselling challenges

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With significant advances in genetic testing technology, molecular laboratories are increasingly detecting sequence variants of uncertain pathogenicity. This trend is likely to continue to escalate as we move towards diagnostic genomic testing. The American College for Clinical Genetics and Genomics and the British Society for Genetic Medicine published practice guidelines in 2015 and 2013, respectively concerning the evaluation of pathogenicity and the reporting of sequence variants. 'Likely pathogenic' variants can be challenging results for genetic health professionals to counsel patients and families due to the possibility of reclassification over time, and differences in interpretation of variant pathogenicity between laboratories and genetic health professionals. Here we present case studies that illustrate some of the genetic counselling challenges that can arise from a 'likely pathogenic' variant result. We will focus on the effect such a result may have on client confidence, and how identifying a likely pathogenic variant may impact on predictive testing and medical management. The cases will be drawn from the experience of the NSLHD familial cancer service based at Royal North Shore Hospital.
Case Study: Incidental BRCA2 pathogenic mutation identified in ‘tumour biomarker’ testing to determine a carcinoma of unknown origin

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Background: A diagnosis of a carcinoma of unknown primary makes treatment difficult. Tumour genetic testing allows cancer clinicians to test tumour tissue to look for the presence or absence genetic sequence variants to help determine the origin of a cancer. The use of molecular testing is becoming more common in clinical practice. As the panels of genes become larger, they can uncover genetic information about the patient that is unexpected.

Case Report: We describe a 66 year old woman managed through the Adult Genetic Unit at the Women’s and Children’s Hospital in Adelaide. The index case was diagnosed with a carcinoma of unknown primary. To determine the origin of the cancer a genetic ‘tumour profile’ was ordered by the oncologist. Tissue was sent overseas to CARIS Life Sciences in the USE for a MI PROFILE (NGS sequencing of 70 genes associated with cancer). The genetic profile indicated the carcinoma was most likely a hepatocellular carcinoma in origin.

In addition, two pathogenic variants were identified in the BRCA2 gene. One of the sequence variants [c.8673_8674delAA] was present at a 50% mutant load and the second variant [c.3405C>A] at 35%. These results suggest that the first variant is likely to be germline in origin. Should the suspected germline mutation be confirmed (in progress) the familial risk will need to be considered. To this date BRCA2 mutations are not strongly associated with hepatocellular carcinoma.

A detailed pedigree revealed only two women affected by breast cancer in their 50s; a situation where we would not usually offer BRCA1 or BRCA testing. As the index case was under the impression that biomarker testing would only inform treatment decisions and contact from a ‘familial cancer service’ was unexpected, therefore she was unprepared for this information.

Conclusion: The rapid expansion of molecular biomarker testing is certain to be associated with an increase in unexpected findings, including familial germline mutation associated with familial cancer syndromes. This case highlights the need for careful counselling prior to any test that may identify mutations that can have impact for the patient and their family.
Serrated Polyposis Syndrome; the development of a safe and efficient template for management by the genetic counsellor.

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The existence of Serrated Polyposis Syndrome and its link to familial factors has been recognised since 1996 (Jeevaratnam et al). The WHO criteria for the clinical diagnosis of Serrated Polyposis Syndrome were established in 2010 (Snover et al 2010), and since 2012 a significantly increased number of referrals for genetic counselling in this condition have been received at Familial Cancer Clinics.

We performed clinical audit of patients referred since 2012 to two outreach services (one metropolitan and one regional/rural). Data has been gathered about the clinical presentation of clients who were referred and comparisons made to Kalady et al’s proposed phenotypes (2011).

A template for autonomous genetic counselling in this condition was developed in 2013, and used with a sub group of clients from the South Coast regional and rural area. The findings of a client satisfaction survey indicate that this template session is found to be very useful by patients, and has led to follow-up colonoscopy in the majority of first degree family members at risk. The use of a genetic counsellor-led clinic for patients with Serrated Polyposis Syndrome was found to be a safe and efficient approach to management.


Snover DC, Ahnen DJ, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated (“hyperplastic”) polyposis. In: Bosman ST, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of tumours of the digestive system. Berlin: Springer-Verlag; 2010
Attitudes towards a BRCA genetic testing program within the Jewish community

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Over 2% of the Jewish population within Australia carry a mutation in the BRCA1/2 genes, compared with 0.2% of the general Australian population. Unlike the general population, only three specific “founder” mutations (two in BRCA1 (185delAG and 5382insC) and one mutation in BRCA2 (6174delT)) are commonly found within the Jewish population. Therefore, testing for these specific “founder” mutations, within the Jewish population, is relatively simple, unlike the general population which requires a complete sequence analysis of both genes. At present, testing is offered to anyone of Jewish ancestry with any personal or family history of breast and/or ovarian cancer through familial cancer clinics. However, the presence of a genetic predisposition is not always evident through a family history within the Jewish population, with studies showing that over half of BRCA1/2 carriers within Jewish communities do not have a family history of breast or ovarian cancer, and are therefore not identified through current practice. Offering testing to all adults of Jewish ancestry, irrespective of their personal or family history, would therefore double the number of mutation carriers identified. The current model of pre-test face-to-face counselling is financially unsustainable and inefficient within a population screening program, as only 2% of the population is likely to be a BRCA1/2 carrier. Therefore we believe that pre-test education and consent can be offered through an online session, and only post-test counselling is required for carriers identified through the screening program. Before developing a program however, it is important to explore the community’s level of interest and satisfaction towards such a screening program. Aim: To assess the attitudes of a representative sample of Sydney’s Jewish community towards a BRCA genetic screening program offered to adults within the Jewish community, and preferences for pre-test education for such a screening program. Method: An online questionnaire is currently being distributed throughout the Jewish community in Sydney. Preliminary Findings: Among 241 participants, 89% are female, with 56% under 50 years of age. 97% are supportive of a BRCA community screening program. Only 14% had previously undergone BRCA testing. Amongst those that have not been tested previously, 63% do not have a family history of breast or ovarian cancer and 78% are personally interested in undergoing the test. 41% would prefer to receive all pre-test information online, with 50% preferring to receive information in-person and 9% currently unsure. However, 65% would be satisfied to provide online consent for testing.
Women undergoing BRCA testing during breast cancer treatment regard genetics as relevant to surgical choices and have low decisional regret


Aims:
This study examined surgical choice (bilateral mastectomy versus other surgical options) and potential influences on this process, including genetic input, in women with breast cancer who had BRCA1 and BRCA2 diagnostic mutation searching during the course of their cancer treatment.

Methods:
Women were identified by a database search of records at the Familial Cancer Centre (FCC) at The Peter MacCallum Cancer Centre of those tested between January 2011 and December 2013. Exclusion criteria included bilateral mastectomy (or conservative surgery and commencement of radiotherapy) prior to referral to the FCC. Questionnaires exploring psychosocial aspects of surgical decision-making including: external influences, internal rationales, timing of decisions and decisional-regret were mailed to women in May 2014.

Results:
The questionnaire response rate was 59% (n=83). Mutations were detected in 12% of respondents. Bilateral mastectomy was undertaken in 80% of BRCA mutation carriers and in 30% of those in whom no mutations were identified. 52% of women reported that they made their surgical choices prior to referral to the FCC.

Genetic test results were a strong influence on choice of procedure for 41% of women, ranking second to the impact of surgical advice (83%). The most frequently reported decision rationales were the desire to minimise risk of death (74%), further breast cancer events (70%) and the likelihood of undergoing future chemotherapy (46%). Overall, decisional-regret was low in the sample ($M=11.15$, $SD=15.08$). A non-significant trend toward higher decisional-regret was detected in women who did not undergo bilateral mastectomy ($p > 0.05$). Logistic regression analyses revealed that young age and BRCA mutation carrier status increased the likelihood of bilateral mastectomy. Women who reported moderate to high influence from genetic test results were less likely to choose bilateral mastectomy compared to those where results had no to little effect ($p < 0.05$).

Conclusions:
Genetic information has a prominent role in patients’ surgical decision-making as part of cancer treatment in half of the population referred to the FCC. It is encouraging that regret regarding surgical choice appears low for women undergoing the current care pathway. Mainstreaming of genetic testing (in surgical and oncological consultations) will require high levels of professional genetic literacy and workforce education. Prospective analyses of decision-making in the current pathway will provide a foundation for optimising care in new (mainstreamed) paths.
Development and pilot-testing of a national audit of the use of the eviQ guidelines in Australian familial cancer clinics

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Clinical guidelines are developed to support clinician and patient decision-making, and to promote quality and consistency in healthcare. The eviQ Cancer Treatments Online guidelines (available from https://www.eviq.org.au) were developed in 2000 initially to provide point-of-care guidelines for cancer treatment, but extended in 2008 to include cancer genetics. In the familial cancer setting, eviQ uses current, evidence-based resources to provide standardised genetic testing thresholds and cancer risk management advice in an attempt to streamline clinical practice across Australia. Use of, and adherence to, the eviQ guidelines in familial cancer clinics has not yet been formally assessed. An initiative of the Inherited Cancer Connect Partnership (ICCon), this study aims to evaluate the impact of the guidelines on both clinical practice and patient uptake of risk management strategies by examining timepoints before and after guideline implementation.

There will be 11 participating familial cancer clinics across Australia (NSW=5, VIC=3, WA=1, SA=1, QLD=1). The study will consist of two stages. The first involves four different types of file audits to assess compliance with the following four eviQ cancer genetics guidelines:

1. Genetic testing for heritable mutations in the BRCA1 and BRCA2 genes
2. Risk management for unaffected female BRCA1 mutation carriers
3. Risk management for unaffected female BRCA2 mutation carriers
4. Risk management of Lynch syndrome

For each of the audits above, files from three different time periods will be selected to reflect timepoints for comparison before and after the implementation of the eviQ guidelines. For each audit type and time period, 32 files will be selected randomly from each of the involved sites. An online checklist will then be completed to assess whether the offering of genetic testing or risk management recommendations were compliant with the eviQ guidelines at that time. The second stage will involve a short, semi-structured patient interview by telephone to determine uptake of risk management strategies. Results will be analysed using descriptive statistics and chi-square analyses.

The methodology is currently being piloted at The Prince of Wales Hospital. The results of the pilot testing have not yet been analysed. If successful, we anticipate this study will identify inconsistencies in the use of, and adherence to, the eviQ guidelines across Australian familial cancer clinics. This may highlight areas of future research and the development of strategies to ensure consistency across clinics.
Fanconi anaemia in 55 year-old identical twins presenting with fatal chemotherapy induced pancytopenia

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Background
Fanconi anaemia (FA) is a rare, inherited disease characterised by physical abnormalities, progressive bone marrow failure and increased risk of haematological and solid organ malignancies. Diagnosis is usually made in childhood with the oldest reported age at diagnosis of 56 years.

Case report
A 55-year-old male presented with febrile neutropenia (FN) and severe pancytopenia 10 days after transcatheter arterial chemoembolization for hepatocellular carcinoma. The profound pancytopenia persisted over coming weeks despite G-CSF and multiple donor granulocyte infusions. A bone marrow biopsy demonstrated severe hypocellularity. Attempts to mobilise peripheral stem cells from his identical twin brother, who had mild pancytopenia, using G-CSF and plerixafor in preparation for a syngeneic stem cell transplant were unsuccessful. The patient subsequently died of severe sepsis. The patient and his brother had microcephaly, short stature, radial-ray abnormalities and a history of undescended testes. Chromosomal breakage analysis was abnormal on the brother’s peripheral blood lymphocytes. A chromosomal microarray on the brother also identified small regions of homozygosity encompassing RAD51C and BRIP1, suggesting they were possible candidate genes. The results from massively parallel sequencing studies are pending.

Conclusion
DNA repair disorders such as FA should be considered in older patients with unexplained marrow hypocellularity, malignancy and dysmorphic features.
A prospective surveillance study for genotype identified cancer risk

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Genetic cancer risk has traditionally been studied in rare cancer prone families with high penetrance genes. The advent of improved sequencing technologies at decreased cost means that many more at risk individuals are being identified by genotype. For example, in the clinic-based International Sarcoma Kindred Study (ISKS), over 75 sarcoma probands have been identified to date who carry known or expected pathogenic germline mutations in ACMG reportable genes. The limited nature of the screening panels almost certainly under-estimate the numbers of individuals who carry potentially actionable genetic variants, and other clinic-based germline sequencing studies are underway that will identify further individuals at increased cancer risk. It will be important to track these individuals over time, to explore whether and how genotype-identified cancer risk may inform personalised risk management and shape public screening strategies. To address this issue, we are undertaking a prospective surveillance study of individuals at heightened cancer risk identified by genotype. The aims are to estimate the prevalence and incidence of investigable lesions, as well as the acceptability, psychosocial impact and cost effectiveness of a surveillance schedule. For those at multi-organ risk (eg., TP53), the protocol includes annual whole-body (WB) MRI, clinical review and physical examination, full blood evaluation, fecal occult blood testing (FOBT), breast MRI (females) and 2-5 yearly colonoscopy/endoscopy. For those specifically at increased risk for breast or bowel cancers, currently recognised surveillance recommendations are utilised. All participants complete psychological questionnaires and a cost diary. Eighteen TP53 mutation carriers (9F, 9M; age 18-62yrs) have been enrolled to date. 10/18 participants had a total of 20 malignancies prior to enrolment. Clinical examinations (27 total; 19yr1, 8yr2) resulted in 12 referrals for 9 individuals (6 skin reviews, 3 US, 1 PSA, 1 CT, 1 gynaecology review). From 23 WB-MRI (16yr1, 7yr2), 8 participants have required 12 further investigations including chest CT, thallium scan, PSA, 3 US, liver US and biopsy, lumbar MRI and biopsy, jaw MRI and brain MRI. Two malignancies have been detected, a primary well differentiated liposarcoma and a recurrent gastric leiomyosarcoma. Blood evaluations (27), FOBTs (7), breast MRIs (5), colonoscopies (7) and endoscopies (6) have all been normal. No adverse psychological effects have been observed. At this early stage the acceptability and lack of negative psychological impact warrants continuation of the multi-organ risk surveillance schedule for longer term evaluation. In the near future, 41 and 18 ISKS families will be invited to participate in the breast and bowel cancer risk streams, respectively.
Designing comprehensive, targeted inherited colon cancer screening panels…is NGS enough?

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The landscape of hereditary colon cancer is vast and testing for germline mutations in well-established genes with clear clinical diagnostic criteria based on personal and family history is seemingly straightforward. Screening for mutations in mismatch repair genes (MMR) responsible for Lynch syndrome (MLH1/MSH2/MSH6/PMS2) have long been established with clear diagnostic criteria for testing and well referenced databases are available for variant interpretation (InSight). Additional tests like MSI and immunohistochemistry analysis of the MMR proteins enables targeted analysis of specific genes. However, genetic screening may still require testing of more than one MMR gene. In addition, there are patients who do not meet the classic criteria for some cancer predisposition syndromes and screening a larger, targeted gene panel may be required.

We have developed a targeted NGS cancer panel with over 100 genes linked to hereditary risk for cancer. The panel includes the known diagnostic genes as well as the emerging genes such as POLE, POLD1 and GREM1. Our approach is to offer diagnostic testing for specific cancer syndromes with targeted NGS panels, which target only those genes that are known to cause the disorder. If this initial diagnostic screen is negative, then an expanded hereditary cancer panel with genes reported to have a known increased risk for colorectal cancer can be analysed.

With this testing protocol, we are increasing the possibility of finding a mutation with a single analysis. We can distinguish between those results which are identified in clinically actionable, high risk, highly penetrant genes vs those emerging, research genes which are less well known. The analysis allows us to collect a body of data on lesser known genes which will help decipher what is natural variation vs a potential pathogenic change for future clinical application.

After NGS testing has been completed and no pathogenic mutations have been identified, what is next? Current pipeline analysis will not detect large exon or whole gene deletions/duplications, separate quantitative analysis is required to exclude these. In addition, investigations for gene rearrangements should also be considered particularly for genes with large regions of repetitive elements. We will present some examples of these.
Screening Victorian women with endometrial cancer for Lynch Syndrome - Early results

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Purpose: To pilot the use of Mismatch Repair Immunohistochemistry (IHC) as a screening test to detect Lynch syndrome (LS) in women with endometrial cancer (EC) at or before age 70 at 3 Victorian centres in a 12 month period. The second aim was to determine if women with absent MLH1/PMS2 IHC in their EC had LS or not via MLH1 tumour methylation testing and germline testing.

Methodology: IHC was requested by pathologists at 3 centres between 1/4/2013 and 1/4/2014. IHC results were added to the pathology report as standard. Treating centres referred abnormal IHC results to Familial Cancer Clinics (FCCs). Patients referred to FCCs with abnormal IHC audit results were asked to consent for their clinical information to be released to study follow up. In addition, women with absent MLH1 and PMS2 IHC were invited into a study for MLH1 germline testing on blood samples and MLH1 methylation testing on their EC, with results interpreted by their treating FCC doctors.

Results: Across the 3 centres, 172 women had IHC performed (median age 59y, range 37-70y). 27 were aged 49 years or under, 62 were aged 50-59y and 83 were aged between 60-70y. Of the 172 ECs tested, 50 (29%) had abnormal IHC (27 absent MLH1/PMS2, 5 absent PMS2 alone, 7 absent MSH2 and MSH6, 11 absent MSH6 alone). Of the women with abnormal IHC, 7 were under 50y, 1 died before FCC referral and 6 are yet to be referred. 43 women were referred to a FCC: 1 died before attending clinic, 8 declined service or further testing, 10 are awaiting appointments and 24 have been recruited (16 results completed, 8 results pending).

As of July 2015, 3 LS cases have been identified (one MSH2 germline mutation with MSH2/MSH6 IHC absent, one MSH6 germline mutation with MSH6 IHC absent and one MLH1 constitutional methylation with MLH1/PMS2 IHC absent) and 1 case of probable LS. Of the 14 women with absent MLH1/PMS2 IHC who entered the study, 14 had no MLH1 germline mutation detected and all 14 had EC MLH1 methylation.

Conclusion: IHC performed on EC from 172 women detected 50 cases with abnormal IHC and genetic testing to date has identified 4 LS cases (3 definite and 1 probable) (2% of the total 172 cases) but the results of 24 cases (14%) are still pending. Another 8 cases (5% of total group) declined the service or testing. These results demonstrate the feasibility of an approach to screen patients with EC for LS.
A cryptic paracentric inversion within \textit{MSH2} causes Lynch syndrome

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Lynch syndrome is an autosomal dominant disorder that predisposes heterozygous carriers of a DNA mismatch repair (MMR) gene mutation to early-onset cancer. People with a clinical suspicion of the syndrome are offered predictive germline genetic testing that can detect mutations in the exons and splice sites of the MMR genes, but this does not examine introns for genetic alterations. A significant proportion of suspected Lynch syndrome cases have no identifiable pathogenic MMR gene mutation, and this may in part relate to testing that only targets the coding regions. We identified a 38 year old male proband with a clinicopathological and family history consistent with Lynch syndrome, including a tumour with high microsatellite instability that had lost MSH2/MSH6 staining. Even though he had a negative germline genetic test, germline cDNA sequencing found he had a heterozygous deletion of exons 2-6. Direct sequencing of inverse PCR products generated from germline DNA identified breakpoints in a long terminal repeat in intron 1 and an \textit{Alu} repeat in intron 6. The 3’ end of the inverted sequence had a 1.2 kb deletion and an 8 bp insertion at the junction with intron 6. A PCR screen of 55 additional patients (recruited from 15 family cancer clinics in Australia) that were negative in a germline screen for MHS2 mutations identified another inversion-positive individual. Our study highlights the need to screen for this inversion in suspected Lynch syndrome cases that have lost MSH2 staining in the absence of coding mutations. Our study also corroborates the findings of previous research that implicates \textit{Alu}-mediated recombination as a cause of Lynch syndrome, illustrates the potential of cDNA sequencing for aiding in the identification of genomic rearrangements, and clarifies why routine diagnostic testing may fail to detect some pathogenic alterations.
**MLH1 Methylation Screening for the Triage of Patients for Lynch Syndrome Testing**

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Purpose: When immunohistochemistry of a Lynch syndrome spectrum tumour is negative for MLH1 and/or PMS2, MLH1 mutation testing is indicated. However, the MLH1 locus undergoes frequent methylation in colorectal cancer particularly in those tumours in the serrated adenoma pathway with the CpG island methylator (CIMP) phenotype. Both MLH1 methylated tumours and tumours arising from patients with a germline MLH1 mutation have the same phenotype: microsatellite instability and negative immunohistochemistry for MLH1 and PMS2. MLH1 methylation in tumours of this phenotype is associated with a very low likelihood of there being a MLH1 germline mutation. Most CIMP tumours also have BRAF V600E mutations and testing for this mutation has been extensively utilised to identify patients that will not be tested for MLH1 mutations [1]. However, it makes more sense to test directly for MLH1 methylation when immunohistochemistry is negative for MLH1. Moreover, MLH1 methylated endometrial cancers do not have BRAF mutations so MLH1 methylation is the only option in this instance. We therefore established a workflow for DNA methylation analysis of MLH1 for use in molecular diagnostics to support Familial Cancer Centres in the diagnosis of Lynch syndrome.

Methodology: Tumour rich and normal areas are identified by a pathologist on H&E stained sections of formalin-fixed, paraffin-embedded (FFPE) tumours. DNA is extracted from the macrodissected material and bisulfite-modified for DNA methylation analysis. The sample is then tested for DNA methylation in region C of the promoter region of the MLH1 gene using methylation sensitive-high resolution melting analysis (MS-HRM). The use of a biotinylated primer allows for a quantitative result using bisulfite pyrosequencing after MS-HRM if required.

Results: MS-HRM allowed the reliable semi-quantitative detection of MLH1 methylation in both colorectal and endometrial cancer studies including samples referred to us by Familial Cancer Centres. Methylation-positive samples could be verified by bisulfite pyrosequencing. The established MLH1 methylation assay allowed an easy and unambiguous interpretation of results. In addition, individuals with constitutional MLH1 methylation were identified by our workflow.

Conclusions: The workflow established for MLH1 methylation analysis meets the requirements for Lynch syndrome evaluation using standardised procedures to ensure high-quality and reproducible results as well as a fast turn-around-time.

High Risk Genes for Lobular Breast Cancer

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For many years, it has been known that one of the strongest risk factors for the development of lobular breast cancer is having a close relative with the disease. Some understanding of the specific genetic factors that underlie breast cancer susceptibility has been achieved through the discovery of some high-risk genes, some intermediate-risk genes, and most recently, common genetic variants that are associated with very modest risk. However, the known spectrum of genetic effects explains only a very small proportion of lobular breast cancer.

We are conducting a study that hypothesises that the majority of the yet unidentified lobular breast cancer susceptibility genes can be identified using whole-genome massively parallel sequencing applied to highly selected lobular breast cancer families from international resources.

Analysis of the whole genome sequencing (WGS) data from the first 38 families is underway. In keeping with previous WGS studies, we observe a vast array of genetic variation. We will report our strategies for genetic variant/gene prioritization, including data cleaning, ‘evolutionary likelihood’ and ‘enrichment’ analyses, and consideration of lobular breast tumour-specific genetic/epigenetic events.

Of note is the lack of identification of mutations in the currently recognised lobular breast cancer predisposition genes, BRCA2 (n=1) and CDH1 (n=0).
Epigenome-wide methylation signatures in matched blood, normal breast and breast tumour samples.

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DNA methylation is a reversible gene silencing mechanism which could explain the onset and progression of a non-trivial proportion of breast cancers. Many studies have measured methylation in DNA derived from the blood of affected women and from their breast tumour tissues.

In blood, we have previously shown that detectable methylation of the \textit{BRCA1} promoter is associated with a 3.5-fold increased risk for breast cancer displaying specific histological features (1). More recently, using the Infinium HumanMethylation450 (HM450K) Beadchip assay we have demonstrated that women in the highest quartile of epigenome-wide methylation were at decreased risk for breast cancer [odds ratio 0.42 (95\% CI 0.20–0.90)] compared with women in the lowest quartile (2). In breast tumours, promoter methylation of tumour suppressor genes is commonly associated with corresponding loss of gene expression. Using the HM450K Beadchip assay, epigenome-wide methylation profiling efforts have identified distinct methylation signatures associated with specific breast cancer subtypes (3, refer to abstract by Joo et al.). These signatures could reveal important biological pathways involved in breast tumourigenesis and potential molecular targets for epigenetic therapies.

Despite significant advances in this field, few studies have compared methylation on an epigenome-wide scale in DNA derived from blood and the corresponding tumour tissue, with matched normal breast tissue. We have conducted a small pilot study using resources from the Melbourne Collaborative Cohort Study. Epigenome-wide methylation was measured with the HM450K Beadchip assay using DNA derived from the following samples:

1. Breast tumours from women diagnosed with late-onset breast cancer (n=18)
2. Corresponding normal breast tissue (n=18)
3. Corresponding blood samples collected prior to diagnosis (n=10)

We will present the outcomes of our study by addressing the following questions:

1. Are the methylation marks detected in blood-derived DNA reflected in the corresponding normal breast tissue; ie, is methylation constitutional?
2. Are there breast cancer risk markers that are present in the blood prior to diagnosis?
3. Are there differential methylation marks between normal and tumour tissues?

References

Genome-wide methylation signatures as a strategy for “classifying” rare PALB2 genetic variants

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Partner and localiser of BRCA2 (PALB2) is an established breast cancer susceptibility gene with a penetrance of 14% (95% confidence interval [CI], 9-20) by 50 years old and 35% (95% CI, 26-46) by 70 years old [1]. Currently, PALB2 c.3113G>A (p.W1038*) is the only mutation in PALB2 that has been incorporated into the Australian eviQ guidelines for practice. The majority of PALB2 genetic variants is of uncertain clinical significance, highlighting the need to develop additional assays to assist with genetic variant classification. We are developing methods to assist with the “classification” of PALB2 genetic variants.

One method involves the possibility of identifying a genome-wide methylation signature associated with tumours that carry a PALB2 mutation. It has been suggested that an identifiable tumour-derived methylation signature may be associated with carrying a germline variant in BRCA1 or BRCA2 [2]. Consequently, we hypothesise that a tumour-derived methylation signature predictive of PALB2 variant carrier status might be identifiable and could be used to assist with the classification of rare PALB2 genetic variants. The Australian Breast Cancer Family Study (ABCFS), the Variants in Practice Study (VIP) and the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) research resources were used to source 14 formalin-fixed paraffin-embedded (FFPE) breast tumour samples from women carrying the germline mutation PALB2 c.3113G>A (p.W1038*). Tumour-enriched DNA samples were assessed using the Infinium HumanMethylation450 (HM450K) BeadChip Array. We will describe the analyses we have conducted to identify a possible PALB2 c.3113G>A variant-associated methylation signature, that could have utility in the assessment of unclassified rare PALB2 genetic variants.

By developing this assay we aim to determine the pathogenicity of rare, currently unclassified, PALB2 genetic variants. This will facilitate a personalised approach to clinical risk assessment and risk management for families carrying these variants.

References
Mutation screening of \textit{RNASEL}, a candidate breast cancer susceptibility gene identified via whole-exome sequencing

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Our laboratory has performed whole-exome sequencing (WES) on highly selected multiple-case breast cancer families to identify more of the as yet unidentified breast cancer susceptibility genes. This strategy offers some capacity to use the family design in data filtering pipelines to both manage sequencing artefacts and annotate variant sharing between relatives. Findings from WES were prioritised by shortlisting candidate genes, based on plausible biology and observation of multiple, rare, predicted deleterious variants, in more than one family. Using this approach, we have identified \textit{RNASEL} as a candidate breast cancer susceptibility gene.

Initial validation studies so far have been performed by targeted-massively parallel sequencing of 834 breast cancer cases. This data supports \textit{RNASEL} as strong candidate breast cancer susceptibility gene, however screening of \textit{RNASEL} on a larger scale is required to further examine the possible association of this candidate gene with breast cancer risk.

To this end, we screened the coding regions of \textit{RNASEL} in 779 women with early-onset breast cancer, recruited through the Australian Breast Cancer Family Study (ABCFS). Screening was conducted using Hi-Plex, a targeted-massively parallel sequencing approach that allows high-throughput screening in a simple, inexpensive and robust way. We will present findings from the sequencing and information on the families carrying variants of interests.

With this study, we aim to i) further document the genetic variation present in \textit{RNASEL} and ii) estimate breast cancer risk associated with variants that are predicted to be “pathogenic” in highly selected and population-based samples from the Australian population at high-risk of carrying a genetic predisposition to breast cancer. The identification of more genetic factors for susceptibility to breast cancer will improve the diagnosis, screening and monitoring of women at risk and their families, and help in the choice of treatment.
Revaluation of involvement of RINT1 in familial breast cancer

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Introduction: RINT1 (Rad50 interactor 1) plays a critical role in DNA check point regulation and telomere lengthening control. Recently RINT1 has been reported to function as a moderately penetrant breast and Lynch syndrome-spectrum cancer predisposition gene. Therefore we sequenced RINT1 in 1000 familial breast cancer cases and 1000 cancer-free Australian controls to determine the prevalence of RINT1 mutations.

Method: The case cohort consisted of index cases from 1000 familial breast cancer families who tested negative for BRCA1 and BRCA2 mutations. The controls were 1000 cancer free Victoria woman from the Lifepool cohort. Whole exon sequencing of RINT1 gene was performed by targeted next generation sequencing. All identified rare variants were validated by Sanger sequencing.

Result: There were no RINT1 protein truncating variants detected in either the cases or controls, while 14 distinct rare missense variants were identified, of which 7 were novel missense variants. There were 11 (1.10%) missense variant carriers in the cases, however, 13 (1.30%) were found in the controls. Data from The Exome Aggregation Consortium (ExAC) public database indicated 41 (0.11%) protein truncating and 484 (1.32%) missense carriers in ~36000 European individuals which was similar to the frequency in the case cohort.

Conclusion: Our result does not support RINT1 to be a breast cancer predisposition gene. Nonetheless, considering RINT1 mutations are very rare, more studies with larger power are still necessary to confirm the role of RINT1 mutations in familial breast cancer predisposition.

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Genome wide association studies in BCAC have identified over 90 loci associated with genetic susceptibility to breast cancer. One of these is the ESR1 locus which is the target of tamoxifen. We therefore predict that other breast cancer risk loci might provide novel targets for treatment and prevention. We have identified two ER+ breast cancer loci of particular interest because bioinformatic analyses predict that one of the probable target genes encodes a protein for which an approved drug is already available, but not used for breast cancer. We predict that, at 3p14.1 and 6p23 (Michailidou et al., 2013) breast cancer risk SNPs lie in enhancers which regulate druggable genes through their protein products. At 3p14.1, the predicted target is the gene encoding PSMD6, a regulatory subunit of the 26S proteasome, involved in degradation of ubiquinated proteins. Many cancers show increased levels of proteasomal proteins and inhibition is predicted to confer anti-tumour potential. Bortezomib is an FDA-approved inhibitor of the 26S proteasome and is used in the treatment of multiple myeloma. SIRT5 is the predicted target gene for 6q23. SIRT family members regulate epigenetic gene silencing. Panobinostat is a SIRT5 inhibitor that acts on histone deacetylases leading to apoptosis, and is used as a combination therapy for multiple myeloma. Another SIRT5 inhibitor, Suramin, is an antiprotozoal agent that has been effective in slowing the progression of prostate cancer. We have performed chromosome conformation capture which identified interactions in a normal breast cell line, Bre-80-TERT, between the promoters of PSMD6 and SIRT5 and putative regulatory elements containing risk-associated SNPs at 3p14.1 and 6p23, respectively. We will next seek to validate this interaction in a second breast cell line and then plan to identify the causal SNPs by a combination of fine mapping through the OncoArray, and luciferase assays. We will then test the relevant drugs in vivo using mouse models to determine whether the genes perturbed by our candidate causal SNPs are possible breast cancer drug targets. Confirmation of these target genes would accelerate the path to translation, paving the way for clinical trials of current pharmaceuticals as breast cancer risk reducing or treatment medications.
PEDIGREE

Melissa Southey and PEDIGREE investigators

A resource of 100,000 people, 20,000 families, 1,000,000 bio-specimens, Big Data, experienced researchers and community representatives who conduct cutting edge cancer research.

**Aim:** to generate the evidence so that cancer genomics can be used to prevent cancer, through:
- leading, and contributing to, the discovery of new genomic and molecular advances that help identify people at genetic risk of cancer
- using epidemiological and epigenetic data to find the environmental and lifestyle exposures relevant to people at genetic risk of cancer
- developing novel statistical and high performance computing methods
- nurturing and building the expert multi-disciplinary research team
- curating and building all aspects of the resource
- growing national and international collaborations

**Cohorts:**
- Melbourne Collaborative Cohort Study (MCCS)
- Australian Breast Cancer Family Registry (ABCFR)
- Australasian Colorectal Cancer Family Registry (ACCFR)
- Australian Prostate Cancer Family Register (APCFR)
- EMMA, LEAF, CONFIRM, Forgotten Cancers, ABC Study

**Data:**
- extensive epidemiological data and detailed family histories
- targeted sequencing of major genes
- genome-wide sequencing, SNP and epigenetic data

**Researchers:**
- led by 10 world leading senior researchers
- 28 next-generation researchers

**Past and current funding:**
- $>50$ million from NIH grants
- $>50$ million in NHMRC and other local grants

**Publications:**
- 900 using PEDIGREE resources, increasing by ~100 per year
The intron 3 16bp duplication polymorphism of p53 (rs17878362) in breast cancer is associated with a high Δ40p53:p53 ratio and outcome.

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Breast cancer is the most common cancer in women, but surprisingly it has relatively low rates of p53 mutations, suggesting other mechanisms are responsible for p53 inactivation. We have shown that the p53 isoform, Δ40p53, is highly expressed in breast cancer, where it may contribute to p53 inactivation. Δ40p53 can be produced by either alternative splicing of p53 in intron 2, or alternative initiation of translation. The alternative splicing of p53 to produce Δ40p53 is regulated by the formation of G-quadruplex (G4) structures in p53 intron 3, from which the nucleotides forming these structures overlap with a common intronic polymorphism (rs17878362).

The presence of this polymorphism alters p53 splicing to favour the production of Δ40p53 mRNA and decrease the expression of the fully spliced p53 form in vitro. Hence, the presence of this polymorphism may be an important mechanism to regulate the ratio of Δ40p53 to full-length p53 in breast cancer. This study aimed to determine if the rs17878362 polymorphism was associated with altered Δ40p53 and p53 expression and outcome in breast cancer. We sequenced p53 in breast tumours from 139 patients and compared this to the relative mRNA expression of the Δ40p53 and p53 transcripts using real-time qRT-PCR. We found that the ratio of Δ40p53:p53 was significantly higher in tumours that were homozygous for the polymorphic allele compared to those who were wild-type. Furthermore, there was a higher proportion of homozygous rs17878362 polymorphisms in breast cancers from patients who subsequently developed metastasis compared to those that did not; and this was associated with a significantly increased Δ40p53:p53 ratio in these cases.

Finally, we show that patients whose tumours were homozygous for the polymorphic allele had significantly worse disease-free survival. These results show that the rs17878362 polymorphism is associated with high Δ40p53:p53 expression in clinical breast cancer specimens and that this is associated with worse disease outcome.
kConFab – 18 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 1,658 families during the past 18 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 144 research projects worldwide.

The kConFab biological repository contains blood specimens from a total of 13,496 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, 1932 unique EBV cell line transformations are available.

As of June 2015, 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 PALB2, 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 1225 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 31 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)
The experience of a large hereditary diffuse gastric cancer family at the Royal Melbourne Hospital familial cancer centre: examining the counselling and clinical issues
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Background: Hereditary Diffuse Gastric Cancer (HDGC) is an inherited cancer syndrome caused by mutations in the CDH1 gene. National guidelines recommend prophylactic total gastrectomy for CDH1 mutation carriers based on published estimates of 80% lifetime risk of advanced gastric cancer. This case study examines genetic counselling and clinical issues arising within a large family with HDGC.

Methods: The pedigree and genetic results are presented, along with a review of clinic database notes, including information about cascade testing, risk management decisions, and cancer diagnoses. Genetic counselling issues were considered collaboratively by the investigative team.

Results: At present, 14 family members are known mutation carriers; 10 are unaffected (34-80y), 2 have died from gastric cancer (41y, 51y), one has had breast cancer (40y) and one has had cancer found on gastrectomy specimen (45y). This family’s experience encompasses the full range of severity of HDGC; early death, as well as mutation carriers unaffected in the ninth decade. Two mutation carriers presented with gastrointestinal co-morbidities.

Conclusion: This family’s experience of CDH1 penetrance does not reflect the published 80% lifetime risk. This experiential risk perception within the family coupled with the life-changing risk management options (total gastrectomy versus “wait and see”) has raised unique counselling issues. These considerations can be used in a broader context as cascade testing continues, as well as in other CDH1 families where the lived experience does not reflect published risk estimates. We suggest a possible extension of the CDH1 phenotype based on gastrointestinal co-morbidities within the family. Finally, data from larger prospective cohorts is needed to produce more robust penetrance figures for CDH1 mutation carriers.
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