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PROFFERED PAPERS

S1-PP1

Massively Parallel Experimental Analysis of Missense Mutations in *BRCA1* for Interpreting Variants of Uncertain Significance

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A substantial proportion of women who undergo *BRCA1/2* testing learn that they carry a variant of uncertain significance (VUS), whose consequences for *BRCA1/2* activity and therefore cancer risk are unknown. A path towards addressing this failure in cancer-risk assessment and prevention is to experimentally measure the functional consequences of all possible mutations in *BRCA1/2*, and to make these measurements publicly available as a resource for guiding variant interpretation. To this end, we are applying a method in which the effects of thousands of mutations in a single gene can be simultaneously measured to *BRCA1*.

For example, we comprehensively evaluated the effects of >1300 amino acid substitutions on the biochemical functions of the RING domain of *BRCA1*, as well as the effects of nucleotide substitutions in exon 18 of *BRCA1* on mRNA splicing. However, these studies were limited because they incompletely assessed the function of *BRCA1* that is most relevant to its role in tumour suppression, homology-directed repair (HDR) of dsDNA breaks. To this end, we adapted a cellular assay to test the HDR function of the full-length *BRCA1* protein for massively parallel experimental analysis.

Preliminary results show that we can distinguish HDR-functional from nonfunctional *BRCA1* variants a multiplexed format. We have now integrated 6000 *BRCA1* missense variants into a HDR reporter cell line and are presently performing an experiment that will quantify the impact of each of these mutations on HDR activity.

The sum of our results to date show that predictions based on massively parallel experimental analysis markedly outperform commonly used computational tools in predicting the effects of mutation on *BRCA1* function. As such, we anticipate that these measurements will facilitate the prospective interpretation of *BRCA1* mutations when they are observed for the first time in a clinical setting.

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S1-PP2

Studying the Functionality of the Homologous Repair Pathway in Zebrafish Embryos: Heading for an *In Vivo* Functional Test to Evaluate the Pathogenicity of *BRCA2* Variants

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Objectives Since the introduction of next-generation sequencing, the challenge for genetic testing moved from development of mutation detection methodologies towards adequate interpretation of (rare) variants. Here, we propose a novel *in vivo* approach to study the functionality of *BRCA2* missense variants in zebrafish. We aim to develop an *in vivo* functional assay to measure in zebrafish embryos the capacity of homologous recombination (HR) for human *BRCA2* mRNA containing variants of unknown clinical significance (VUS).

Methods To evaluate the efficiency of HR repair, we induce DNA double strand breaks (DSB) in zebrafish embryos by irradiation. We use γ-*H2AX* and *RAD51* foci assays as markers for DSB and HR repair respectively. We generated zebrafish *brca2* knockdown models by morpholino injection and Crispr-Cas9 mutagenesis. After synthesis of human *BRCA2* mRNA, rescue experiments will be performed with wild-type mRNA and mRNA containing the VUS of interest.

Results We developed a protocol for visualizing and quantifying *RAD51* foci in tissues of wild-type zebrafish embryos. Knockdown of *brca2* by a morpholino results in an almost complete absence of *RAD51* foci in irradiated embryos. Similar results are currently being generated in the Crispr-Cas9 *brca2* knockout model. In a next step, we will rescue the phenotype by microinjection of wild-type human *BRCA2* mRNA and mRNA containing VUS to study the effect of these VUS on the HR capacity.

Conclusions The zebrafish genome contains nearly all the genes involved in various DNA repair pathways in eukaryotes, including homologous recombination, in which *BRCA2* plays a major role. Therefore, zebrafish provides an ideal *in vivo* model for studying variants in genes involved in DNA damage and repair.

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S1-PP3

Sharing *BRCA1* and *BRCA2* Data Across Canada: A Case Study from the Canadian Open Genetics Repository

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The Canadian Open Genetics Repository (COGR) presents a large, cross-laboratory case study in sharing clinical variant interpretations across Canada. The COGR is a collaborative effort for the collection, storage, sharing, and analysis of variants reported by medical diagnostics

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laboratories across Canada. The inherent collaborative structure of the COGR promotes real-time sharing between geographically distant laboratories and enhances the exchange of information about DNA variants within the expert community. To date, there are more than 17,000 variants being shared in the system.

The COGR is currently working to create consensus on variants identified in the *BRCA1* and *BRCA2* genes. Variant data was curated from a total of 11 participating laboratories across Canada that perform *BRCA1* and *BRCA2* genetic testing. In total, 5554 *BRCA1* and *BRCA2* variants were included.

Here, we present a process for arriving at variant interpretation consensus and a system for resolving differences in variant interpretation. We report on all variants that were identified in more than one laboratory, describing the number of variant interpretations that were discordant between laboratories. As a continuing effort, the COGR endeavors to increase genetic knowledge and standardization through data sharing and consensus building, ultimately improving our ability to diagnose and treat genetic diseases.

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S2-PP1

Prostate-Specific Antigen Velocity As a Predictive Biomarker in a Prospective Prostate Cancer Screening Study of Men with Genetic Predisposition

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Objectives Prostate specific antigen velocity (PSA-V) is a biomarker aimed at optimizing screening protocols for early diagnosis and effective treatment of prostate cancer (PCa). The IMPACT study [Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted Screening in Men at Higher Genetic Risk and Controls (http://www.impact-study.co.uk)] is a PCa screening study for men with a known genetic predisposition to PCa, using annual PSA readings with diagnostic prostate biopsies triggered by a PSA above 3 ng/mL. The objective of this study was to evaluate the utility of PSA-V measurements versus a fixed PSA threshold in detecting men with PCa who have a normal PSA level in a high-risk population.

Methods We retrospectively calculated PSA-V linear regression for men in the IMPACT study. t-Tests and Pearson chi-square tests were used to compare PSA-V between groups as a continuous variable and with defined cut-offs respectively.

Results Three or more PSA readings over 18 months were available for 1654 participants within the IMPACT study, of whom 174 underwent prostate biopsy (PB), with a total of 49 PCas being diagnosed. The mean and median age of PCa diagnosis was 62.5 and 63 years respectively. A PSA-V > 0.35 ng/mL/yr was associated with a positive PB as well as with a Gleason Score (GS) ≥ 7 cancer diagnosis in the *BRCA2* carrier group; however, this was not seen in the other genetic groups (*BRCA1* carriers and controls). In the group who underwent PB, *BRCA2* carriers were 4.6 (95% CI: 1.4 to 14.5; $p = 0.017$) times and 6.5 (95% CI: 2.0 to 21.0; $p = 0.003$) times more likely to be diagnosed with cancer with a PSA-V over 0.75 ng/mL/yr and 0.35 ng/mL/yr respectively. Similarly, they were 8.4 (95% CI: 2.3 to 31.1; $p = 0.001$) and 20.2 (95% CI: 2.4 to 166.2; $p = 0.001$) times more likely to be diagnosed with a GS ≥ 7 cancer using these PSA-V thresholds.

Conclusions The PSA-V can contribute to PB decision-making for men with a *BRCA2* mutation to identify those who are most at risk of aggressive tumours.

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S2-PP2

DNA Repair–Independent Mechanisms Mediating Drug Response in BRCA2 Cancer

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Hereditary breast and ovarian cancer derive from underlying gene defects that compromise DNA repair. Thus, *BRCA*-associated tumours are sensitive to DNA interstrand crosslinking agents such as cisplatin. Remarkably, these cells have the ability to overcome cisplatin sensitivity through restoration of DNA repair by homologous recombination (HR). Evidence also indicates that *BRCA* cells have the ability to overcome cisplatin sensitivity through mechanisms distinct from restoration of HR.

To better understand how cisplatin resistance develops in HR-deficient cells, we previously performed loss of function RNAi screens. These led to the identification of several genes whose depletion enhanced cisplatin resistance in a *BRCA2*-mutant cells. One of the identified genes was the chromatin-remodelling factor, *CHD4*. Mechanistically, *CHD4* loss did not restore DNA repair by HR, but rather enhanced error-prone bypass.

Here, we present new insights as to how *CHD4* loss uniquely rescues *BRCA2* mutant cells through protection of stalled replication forks. Moreover, we show this rescue requires a chromatin-associated function of the N-terminal *BRCA2*-mutant species that is found in the majority of *BRCA2* mutant cancers. Collectively, these findings help explain why low *CHD4* expression correlates significantly with poor response and overall survival in *BRCA2*-mutant ovarian and breast cancer patients.

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S3-PP1

Systematic *BRCA1*/*BRCA2* Genetic Testing in Unselected Epithelial Ovarian Cancer—Results from the GTE OC Study

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Objectives The advent of targeted therapies for *BRCA1*/*BRCA2* mutation carriers necessitates more inclusive service delivery models for genetic testing. The Genetic Testing in Epithelial Ovarian Cancer (GTEOC) study explored the feasibility and acceptability of offering genetic testing to all women recently diagnosed with epithelial ovarian cancer (EOC).

Methods From 1 July 2013 to 30 June 2015, women newly diagnosed with EOC were recruited though 6 sites in East Anglia, U.K., which has an outbred population of 2.5 M with no *BRCA1*/*BRCA2* founder mutations. Eligibility was irrespective of patient age and family history of cancer. Consent for genetic testing was obtained by the research team after participants reviewed the study information sheet. The psychosocial arm of the study utilised quantitative questionnaires (Depression Anxiety and Stress Scale, DASS-21; Impact of Event Scale, IES).

Results In the 232 women recruited and tested, 17 mutations were detected (11 in *BRCA1*, 6 in *BRCA2*), giving a yield of 7.3%. The mutation yield is 10.9% in unselected women <70 (15/137) and 2.1% in unselected women >70 (2/95). Testing only those with a positive family history (1° or 2°) increases the mutation yield to 16.4% in women <70 (12/73), but 20% of mutations in this age group will be missed. In the 173 questionnaires returned (75%), IES and DASS-21 scores in response to genetic testing were significantly lower than equivalent IES and DASS-21 scores in response to cancer diagnosis ($p < 0.001$).

Conclusions The mutation yield in an unselected cohort of women diagnosed with EOC from a heterogeneous population with no founder mutations was 7.2% in all ages and 10.9% in women <70. Population-based genetic testing appears to be acceptable to patients and is less resource-intensive than standard practice in which all patients have a full assessment by the genetics team prior to testing.

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S3-PP2

Hormone Replacement Therapy After Risk-Reducing Salpingo-oophorectomy: Significantly Decreased Postmenopausal Symptoms in a Prospective Study

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Introduction Approximately 5%–15% of all ovarian cancers are due to inherited predisposition. Although risk-reducing salpingo-oophorectomy (RRSO) is recommended and is often performed before natural menopause,

it leads to a direct onset of menopause and may be accompanied by significant menopausal symptoms and sexual dysfunction. In this observational study, we investigated the efficacy of hormone replacement therapy (HRT) after RRSO in reducing menopausal symptoms and improving sexual functioning.

Aim To obtain insight into the efficacy of HRT in reducing menopausal symptoms and sexual dysfunction after RRSO.

Methods We recruited 178 premenopausal, high-risk women who had undergone RRSO or opted for gynecologic screening. Women completed questionnaires before surgery (T0), and at 6 (T1) and 12 (T2) months after surgery, or at equivalent time points for those who opted for screening.

Results Of the 57 women who underwent RRSO, 27 were using HRT after surgery (HRT+) and 30 were not (HRT–). The 121 women who opted for gynecologic screening were used as a control group. The groups were similar at baseline on the primary outcome variables. At T1, the HRT+ group (compared with the HRT– group) reported not only a significantly lower symptom burden from hot flushes ($p = 0.01$), cold sweats ($p = 0.04$), and night sweats ($p = 0.02$), but also less sexual discomfort ($p = 0.01$). Results were similar at T2. Compared with the screening group, the HRT+ group had significantly less vaginal irritation at T1 ($p = 0.03$), fewer headaches ($p = 0.03$), and greater weight gain ($p = 0.04$) at T2.

Conclusions Our results suggest that HRT after RRSO has beneficial effects in terms of alleviating vasomotor symptoms and sexual dysfunction in high-risk premenopausal women.

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S3-PP3

Missense c.680C>T *RAD51D* Variant Confers Predisposition to High-Grade Serous Ovarian Cancer but Not to Breast Cancer in the French Canadian Population

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Objectives Inactivating mutations in *RAD51D*, a key player in homologous recombination repair, have been implicated in the etiology of ovarian cancer (OC). However, their role in breast cancer (BCA) susceptibility remains unclear, as does the role of rare, non-truncating *RAD51D* variants in cancer predisposition. We sought to fully characterize the previously described missense *RAD51D* variant c.680C>T;p.S227L in order to elucidate its role in OC and BCA.

Methods Whole-exome sequencing was performed on germline and tumour DNA in two French Canadian kindred affected with familial high grade serous cancer (HGSC) of the ovary or endometrium. High-resolution melting, Taq-man genotyping, and Sanger sequencing were used to genotype the p.S227L variant in French Canadian HGSC of the ovary and endometrium, BCA, colorectal cancer, and healthy controls. Sensitivity to PARP inhibitors was evaluated by treatment of *RAD51D*-mutant cell lines with olaparib and BMN 673 in a cell survival assay.

Results RAD51D c.680C>T;p.S227L was identified in the germline of two French Canadian families affected with HGSC of the ovary. The presence of secondary somatic mutations in *RAD51D* was excluded. Subsequently, we used ExomeAI to confirm the presence of allelic imbalance for the entire *RAD51D* locus in tumour compared with normal-tissue DNA. A French Canadian case–control study revealed a highly significant frequency of the p.S227L variant in HGSC of the ovary (4%) compared with controls (0.3%), $p = 0.00004$), while its frequency in breast, endometrium, or pancreas cancers did not differ significantly from that in controls. Importantly, *RAD51D* p.S227L stable cells were observed to have increased sensitivity to olaparib and BMN 673.

Conclusions *RAD51D* c.680C>T;p.S227L is a susceptibility allele for HGSC, but is not involved in breast cancer susceptibility. Our functional observations show that this mutation confers PARP-inhibitor sensitivity in OC and support the value of a targeted molecular therapeutic avenue for affected mutation carriers.

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S5-PP1

BRCA Population Screening in Unaffected Ashkenazi Jewish Women: A Randomized Controlled Trial of Different Pre-test Strategies

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Approximately half of *BRCA1*/*BRCA2* carriers lack significant family history and would only be identified through general testing. The Ashkenazi Jewish (AJ) population is a model for such screening, given high prevalence (1/40) and testing sensitivity (>95%) of 3 common mutations. Towards implementation, we aim to examine the impact of excluding pre-test face-to-face genetic counselling (GC) in the population screening setting.

Healthy AJ women age > 25 years are randomized to two pre-test arms: written information only (WI) vs. GC. Post-testing, GC is provided to non-carriers indicating significant family history and to all carriers. Psychosocial outcomes [satisfaction with health decision, stress, anxiety, personal perceived control (PPC), knowledge] are assessed 1 week (Q1) and 6 months (Q2) post-testing.

Among the first 680 participants (mean age: 46 years), we identified 10 carriers (1.5%). Only 2 of the 10 carriers had significant family history. Post-testing, 95% of GC and 94% of WI participants (nonsignificant) report being satisfied/very satisfied with testing. Overall, >85% would recommend population screening. Stress (Impact of Events) scores were similar in both groups. At Q1, PPC scores and knowledge were higher in GC ($p = 0.005$; $p = 0.0001$), but absolute differences were small (PPC: 0.11 of 2 points; knowledge: 1.11 of 10 points). At Q2, only PPC scores remained higher in GC: 1.39 vs. 1.25 in WI ($p = 0.02$). Carriers had higher PPC and knowledge than non-carriers. At Q1, carriers' stress level was higher (14.9 vs. 5.3, $p = 0.0006$), as expected.

Screening using streamlined testing would identify substantially more carriers (regardless of family history) while addressing logistic and cost limitations. These ongoing results suggest that compared with WI, pre-test GC provides a mild temporary increase in knowledge, accompanied by a greater sense of control. Forgoing pre-test GC may therefore be a legitimate alternative in large-scale screening, particularly if alternative methods for imparting knowledge are explored.

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S5-PP2

Racial Disparities in *BRCA* Testing and Surgical Risk Management Uptake Among Young Breast Cancer Survivors

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Background Genomic advances have potential to further increase breast cancer (BCA) health disparities. In a population-based sample of young BCA survivors, we sought to 1) explore factors associated with *BRCA* testing; and 2) evaluate uptake of preventive surgery in the subset with a *BRCA* mutation.

Methods In 2009–2012, a population-based sample of black and non-Hispanic white (NHW) women diagnosed with invasive BCA, age < 50, were recruited through the Florida State Cancer Registry. All participants were asked to complete a questionnaire and medical records release to verify *BRCA* test results. Using multiple logistic regression, we assessed demographic and clinical variables associated with clinical *BRCA* testing and compared uptake of surgical risk reduction options among black and NHW *BRCA* carriers.

Results Of the 1186 participants, 36.1% (161/444) of black women versus 64.8% (481/742) of NHW women had *BRCA* testing. After controlling for education, income, tumour receptor status, age at diagnosis, and insurance, NHW women were 6 times more likely to have had *BRCA* testing. The most common reasons for no testing by self-report were 1) cost and insurance concerns, 2) lack of provider recommendation, and 3) belief that genetic testing would not be helpful because they already had BCA. In the subset of *BRCA* carriers, uptake of risk-reducing salpingo-oophorectomy (RRSO) and bilateral mastectomy among the 28 black women was substantially lower at 28% and 67% respectively, compared with 74% and 93% respectively, among NHW women. These differences remained statistically significant ($p < 0.05$) even after controlling for age at enrolment and time since diagnosis.

Conclusions Our results demonstrate substantial racial disparities in *BRCA* testing and uptake of RRSO and bilateral mastectomy among young black compared with young NHW BCA survivors. The rapid diffusion of *BRCA* testing into clinical practice to improve patient outcomes underscores the need to systematically address racial disparities so that all populations benefit from these scientific advances.

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S5-PP3

Quality of Risk-Reducing Salpingo-oophorectomy in Australasian Women at High Risk of Pelvic Serous Cancer

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Objectives The quality of risk-reducing salpingo-oophorectomy (RRSO) performed in Australasian women was previously reported to be suboptimal. Here, we describe the quality of contemporary RRSO in women enrolled in the same cohort, the Kathleen Cunningham Consortium for Research into Familial Breast Cancer (kConFab), and determine if it has improved.
Methods Eligible women had a high risk of pelvic serous cancer (PSC), had RRSO between 2008 and 2014, and had no personal history of gynecologic or metastatic cancer. The RRSO surgical and pathology reports were reviewed; "adequate" surgery and pathology were respectively defined as complete removal of all ovarian and extrauterine fallopian tube tissue, and paraffin embedding of all removed ovarian and tubal tissue. Associations between clinical factors and "adequate" pathology were assessed using logistic regression. Chi-square test was used to compare the data on adequacy of RRSO with published data on RRSOs prior to 2008.
Results Of 164 eligible women followed for a median of 40 months, 80 and 48 were *BRCA1* and *BRCA2* mutation carriers respectively. The RRSOs were performed in 120 centres within Australia and New Zealand, and most were done laparoscopically (74%) by gynecologic oncologists (58%). Hysterectomy was performed concurrently in 73/164 (45%). Surgery was "adequate" in 158/159 (99%), and pathology was "adequate" in 108/164 (66%). Independent predictors of "adequate" pathology included surgery by a gynecologic oncologist rather than a general gynecologist ($p \leq 0.001$), more recent year of surgery ($p = 0.022$), and clinical notes on the pathology request form that indicated high risk ($p = 0.008$). Compared with the RRSO performed prior to 2008 in the kConFab cohort, surgery and pathology were both significantly more likely to be "adequate" ($p \leq 0.001$).
Conclusions The quality of RRSO performed in Australasian women has improved dramatically since our last report. Surgery by a gynecologic oncologist who informs the pathologist that the woman is at high risk for PSC is associated with optimal RRSO.

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S6-PP2

Rapid Genetic Testing for *BRCA1* and *BRCA2* at the Time of Breast Cancer Diagnosis: The Effects on Treatment Choices and Psychosocial Functioning

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Objectives For women with *BRCA*-associated breast cancer (BCA), treatment with bilateral mastectomy improves survival, but most women do not know their *BRCA* status at the time of cancer diagnosis. Rapid genetic testing (RGT) allows for genetic test results prior to cancer surgery, but it is unclear if RGT has an impact on surgical decision-making or psychosocial functioning. The objective of the current study was to assess the impact of RGT at the time of BCA diagnosis on surgical decision-making and psychosocial functioning.
Methods Eligible women were referred from participating surgeons at BCA diagnosis. Women completed baseline questionnaires assessing treatment preferences, cancer related distress, anxiety, and depression. All participants received in-person pre-test genetic counselling. Genetic test results were given within 10 days. Participants completed surveys at 1 week and 1 year post–genetic testing.
Results 464 Women consented to participate, and 32 (6.9%) were identified with a *BRCA* mutation. Of these women, 5 (15.6%) were not eligible for genetic testing based on provincial criteria. Mean levels of cancer-related distress, anxiety, and depression declined significantly from baseline to 1 year for all women (all $p < 0.05$), and there were no differences at any time point between those with and without a *BRCA* mutation. Of those identified with a *BRCA* mutation, 64.3% reported that their surgery choice changed; 75.9% of *BRCA* carriers had a bilateral mastectomy, and 10.3% were planning for a bilateral mastectomy after chemotherapy.
Conclusions Rapid genetic testing for *BRCA1* and *BRCA2* at the time of BCA diagnosis results in a change in surgical choice for many women identified with a *BRCA* mutation, with the majority electing for bilateral mastectomy. Women identified with a *BRCA* mutation at the time of BCA diagnosis do not experience greater levels of cancer-related distress, anxiety, or depression compared with women with a negative genetic test result.

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S6-PP3

Salpingectomy with Delayed Oophorectomy in *BRCA1/2* Mutation Carriers: Estimating Ovarian Cancer Risk

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Objectives To estimate *BRCA1/2* mutation carriers' cumulative ovarian cancer (OC) risks for risk-reducing salpingectomy (RRS) with delayed risk-reducing oophorectomy (RRO) at various ages, and to compare these risks to those of risk-reducing salpingo-oophorectomy (RRSO).
Methods Cox proportional hazard models were used to estimate cumulative OC risks for various scenarios of RRS with delayed RRO and RRSO. Assumptions about efficacy of risk-reducing surgeries were based on literature.
Results Estimated cumulative OC risks for RRS with delayed RRO are highest for *BRCA1* mutation carriers, especially for those undergoing surgeries at higher age. Point estimates of a *BRCA1* mutation carrier's OC risk maximally increase with 2.3 percentage points when RRO is performed at age 45 after nonprotective RRS, compared with RRSO at age 40. In the best-case scenario, assuming 65% risk reduction by RRS, increase in point estimates of OC risk ranges from –0.4 to 0.8 percentage points depending on age at the time of surgeries. For a *BRCA2* mutation carrier, point estimates of OC risk in the worst-case scenario maximally increase with 1.2 percentage points when RRO is performed at age 50, compared to RRSO at age 45. In the best-case scenario, increase in point estimates of OC risk ranges from –0.3 to 0.2 percentage points.
Conclusions Differences in estimated OC risks between RRSO and RRS with delayed RRO are small, even in the worst-case scenario that RRS does not reduce OC risk at all. Presented estimated OC risks can be used in counseling *BRCA1/2* carriers on risk-reducing strategies, facilitating a personalized and well-informed choice for either RRS with delayed RRO or RRSO within the protection of a clinical trial (NCT02321228).

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S7-PP1

Panel Testing with a Diverse Low-Income, Limited-English-Proficient Population in the United States

Galen Joseph, Robin Lee

Objectives Advances in genomics, such as panel testing, can exacerbate cancer disparities if access and quality of care are unequal. Gaps in effective communication are widely recognized as a major contributor to health disparities. The purpose of this study was to assess the communication in HBOC genetic counselling with low-income, ethnically diverse, and limited-English-proficient patients in the U.S. public hospital setting, and to develop an intervention to improve genetic counselling.
Methods We conducted an inductive ethnographic study of HBOC counselling and testing at two public safety net hospitals providing cancer risk services to their diverse underserved patients during the time panel testing became routine practice. Research included observations and audio recording of more than 150 genetic counselling sessions conducted in English, Spanish, and Cantonese, and follow-up interviews with patients ($n = 50$), counsellors ($n = 10$), and medical interpreters ($n = 11$).
Results We identified several barriers to effective communication including a mismatch between patients' information needs and the information provided by genetic counsellors (the amount of information, level of complexity); visual aids not consistently used in an effective manner; limited dialogue, question-asking, and shared decision-making; frequent misinterpretations due to interpreters' misunderstanding of the purpose and content of genetic counselling and the inherent difficulty translating technical terminology, hypotheticals, and analogies. The complexity of explaining panel testing exacerbated some of these communication barriers, including the higher rate of VUS results and associated uncertainties.
Conclusions Tailored strategies are needed to ensure effective communication about multiplex genetic testing by genetic counsellors and the medical interpreters who work with them. Based on our findings, we are developing separate interventions for genetic counsellors and medical interpreters to ensure effective genetic counselling dialogue. The counsellor intervention will be piloted to assess feasibility of

implementation, and our cancer genetics curriculum for medical interpreters is currently being disseminated throughout California.

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S7-PP2

Incorporating Truncating Variants in *PALB2, CHEK2,* and *ATM* into the BOADICEA Breast Cancer Risk Model

Antonis C. Antoniou,* Andrew J. Lee,* Alex P. Cunningham,* Marc Tischkowitz,* Jacques Simard,† Paul D. Pharoah,* Douglas F. Easton*

Background Cost-effective sequencing technologies have brought multigene panel testing into mainstream clinical care. Although several established breast cancer susceptibility genes are included in these panels, their clinical utility is limited by the lack of risk prediction models that consider the effects of mutations in these genes and other risk factors for breast cancer, in particular family history. The BOADICEA risk prediction model incorporates the explicit effects of *BRCA1* and *BRCA2* mutations. In this work, we describe an extension to the BOADICEA model to incorporate the effects of truncating variants in the breast cancer susceptibility genes *PALB2, CHEK2,* and *ATM.*
Methods and Results We developed a model for the breast cancer incidence that depends on the explicit effects of truncating variants in *BRCA1, BRCA2, PALB2, CHEK2,* and *ATM* and a residual polygenic component representing other unobserved genetic effects. We used a synthetic model approach based on results from segregation analyses of families in the United Kingdom together with risk estimates derived from large studies of European populations. Under this model, the predicted average breast cancer risk for an unaffected 20-year-old by age 80 for a *CHEK2* mutation carrier is 30%, 28% for *ATM,* 50% for *PALB2,* 74% for *BRCA1* and *BRCA2.* However, the breast cancer risks for mutation carriers are predicted to increase with increasing family history burden. In families in which mutations are identified, the predicted risks for mutation-negative family members depend on both the family history and the specific mutation identified in the family. The reduction in breast cancer risk after negative predictive testing is greatest when a *BRCA1* mutation is identified in the family, but for women whose relatives carry a *CHEK2* or an *ATM* mutation, the risks decrease only slightly.
Conclusions The model will be a valuable tool in the counselling process of women who have undergone gene-panel testing for providing consistent breast cancer risks and thus harmonizing the clinical management of at-risk individuals. The model has been implemented in a user-friendly web application that can be used in clinical practice (http://ccge.medschl.cam.ac.uk/boadicea/).

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S7-PP3

Use of Multiple SNP Testing to Predict Breast Cancer Risk in a Familial Screening Clinic

D. Gareth Evans,*† Adam Brentnall,‡ Helen Byers,† Elaine Harkness,*§ Paula Stavrinos,* Anthony Howell,*‖ William Newman,† Jack Cuzick‡

Introduction Genetic testing for *BRCA1/2* provides important risk information for a minority of women. Use of common genetic variants associated with variation in breast cancer risk has not yet been implemented, but may have relevance to a much larger number of women.
Methods A case–control study was designed to assess the effects of the first 18 single nucleotide polymorphisms identified through genome-wide association studies on breast cancer incidence. Pre-defined polygenic risk scores for the general population (SNP18), *BRCA1* (SNP3) and *BRCA2* carriers (SNP13) were obtained by multiplying normalized risk estimates for each allele to provide an overall score. The observed/expected odds of breast cancer was estimated by logistic regression, and discrimination was measured by the area under the receiver operating characteristic (AUC). A prospective subsample was used to assess women without breast cancer at entry to the clinic.
Results SNP18 genotyping was performed in 2055 samples, including 451 women with breast cancer (364 prospective). SNP18 was a predictor in the non-*BRCA1/2* group [interquartile range odds ratio: 1.55 (95% CI: 1.29 to 1.86); AUC: 0.59 (0.55 to 0.63); O/E: 96%)]. Findings were similar for women in the prospective subsample, where SNP18 was improved using a projected absolute risk based on age at entry [IQR OR: 3.01 (95% CI: 2.16 to 4.20); AUC: 0.63 (95% CI: 0.60 to 0.67)]. There was some evidence to support the use of SNP3 [*BRCA1* carriers, AUC: 0.61 (95% CI: 0.54 to 0.69)] and SNP12 (*BRCA2* carriers, AUC: 0.55 (95% CI: 0.48 to 0.62), but the general population weights in SNP18 performed worse for these groups: *BRCA1* AUC: 0.47 (95% CI: 0.39 to 0.54); *BRCA2* AUC: 0.53 (95% CI: 0.45 to 0.60).
Conclusions SNP18 may be used to assess risks in women already at increased risk from their family history, without *BRCA1/2* mutations. Different weightings are required for families with *BRCA1/2* mutations.

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S9-PP1

Variant Testing Post Mortem: Clinical Experience with HBOC Gene Panel Variant Testing on More Than 300 Archival FFPE Non-Tumour Tissue Samples from Deceased Relatives

Anders Bojesen, Mads M. Aagaard, Annabeth H. Petersen

Objectives In many families with a cancer history indicating HBOC, the most relevant to test for genetic variants is often deceased. In such families, we rely on testing a less relevant person or indirect testing on healthy living relatives. We developed a Haloplex-based NGS gene panel for use with archival FFPE non-tumour tissue samples, which is now in use for clinical testing.
Methods DNA was extracted from 326 FFPE samples from non-tumour tissue from deceased persons with a high probability of harboring a germline variant. The DNA was subjected to NGS sequencing using a Haloplex-based multigene panel, including *BRCA1, BRCA2, CDH1, TP53, PALB2, STK11, BRIP1, RAD51C,* and *PTEN.* Variant calling and filtering was done using an in-house developed pipeline. Deletion analysis was performed using MLPA. Tissue samples were up to 43 years old.
Results 296 Samples were successfully sequenced; 30 failed quality assessment and was not sequenced. 36 Pathogenic variants (IARC class 5: 16 *BRCA1,* 11 *BRCA2,* 8 *CDH1,* and 1 *PALB2*), 2 likely pathogenic variants (IARC class 4: 1 *BRCA1* and 1 *BRCA2*), and 23 VUS (IARC class 3: 1 *TP53,* 11 *BRCA1,* and 11 *BRCA2*) were found. The MLPA analysis was informative in 141 of 247 samples, but did not uncover any significant deletions in *BRCA1/2.*
Conclusions FFPE variant testing is a promising tool in genetic investigation and counselling. In many cases, it is possible to identify pathogenic germline variants in archival FFPE tissue from deceased family members, in families in whom genetic testing would otherwise be impossible or at least with a risk of testing a less-relevant person. Finding a variant in FFPE tissue should always be followed by confirmation of the variant from another tissue sample from the same person or from a living relative.

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S9-PP2

Analysis of Cases and Controls Raises Questions About the Clinical Utility of Extended-Panel Testing for Familial Breast Cancer

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Gene-panel sequencing appears set to become the new standard investigation in hereditary breast cancer. Already, panel test results are reported as definitive explanations for an individual's family history despite scant evidence supporting an association with breast cancer risk for many of the genes included. We assessed the performance of genes commonly included in hereditary breast cancer panels in a large cohort of index cases from breast cancer families as well as in matched healthy population controls.

2000 Breast cancer–affected women, with features of heritable risk, assessed by a familial cancer centre (*BRCA1/2* wild-type) and 1997 cancer-free women from the LifePool study were sequenced for 18 common panel genes (from a custom capture array), and the data were filtered for known pathogenic or novel loss of function variants.

Excluding mutations identified in *BRCA1* and *BRCA2* (0.6% of controls), a total of 79 cases (3.9%) and 33 controls (1.6%) were found to carry potentially "actionable mutations." *PALB2* was frequently implicated (26 cases, 4 controls), and 5 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 in cases could not be individually clinically interpreted. The combined population attributable risk for breast cancer of all genes on the panel was 2.4%, nearly half of which was attributable to *PALB2* mutations. Clinical features, including 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 HBOC is low and, in many cases, similar to or lower than that observed in cancer-free population controls. Although multigene panels can significantly aid in cancer risk management, they equally have the potential to provide clinical misinformation if the data are not interpreted cautiously.

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S9-PP3

Breast and Ovarian Cancer Risks Beyond *BRCA1/2* from a Cohort of 15,000 Women Undergoing Multigene Panel Testing

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Multigene panel testing (MGPT) for hereditary cancer is increasing in popularity in the United States. Many panels include genes identified as hereditary breast and/or ovarian cancer (HBOC) genes despite limited data regarding the precise cancer risks associated with mutations in these genes. This study examined clinical histories, ethnicity, and test results from a cohort of 15,083 individuals who underwent MGPT of up to 20 genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MLH1, MRE11A, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, TP53*) using the BreastNext and OvaNext panels.

Most individuals were from high-risk breast and/or ovarian (Br/Ov) cancer families, with 92.4% of all probands meeting National Comprehensive Cancer Network HBOC testing criteria. Pathogenic mutations were identified in 9.4% of the overall cohort. No ethnicity-specific enrichment of mutations was observed. To further quantify gene-specific Br/Ov risks, a series of case–control analyses were performed comparing the frequencies of inactivating mutations and previously classified pathogenic or likely pathogenic missense alterations between cases from Br/Ov MGPT and controls from the Exome Aggregation Consortium (EXAC) database. Estimated risk ratios (RRS) for Br/Ov cancer in well-studied genes were consistent with previous reports, including an increased breast cancer risk, but no increased ovarian cancer risk associated with *CDH1, ATM,* and *CHEK2* mutations. Ovarian cancer risk was significantly ($p < 0.001$) increased for mutations in *RAD51D* (RR > 9), *RAD51C* (RR > 8), and *BRIP1* (RR > 7). Additional results of interest included a significantly increased risk of breast cancer at age > 50 for *NF1* carriers, breast cancer for *MSH6,* breast cancer < 50 for *RAD51D,* and ovarian cancer for *PALB2.*

This large breast and ovarian cancer case–control analysis provides useful data for many HBOC genes previously lacking risk estimates, and should prove useful for clinical risk management of patients after MGPT.

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S10-PP1

Heritable Epimutations Associated with Breast Cancer Risk

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Objectives Although 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 that 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 on 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. Of these sites, 3 are clustered within 200 base pairs of a noncoding RNA that 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 that incorporates family structure, but not affected status. We then identified 11 methylation sites that might contain heritable epimutations associated with breast cancer.

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S10-PP2

Candidate Ovarian Cancer Susceptibility Genes Identified from Whole-Exome Sequencing of Two Affected Individuals per Family from 28 Ovarian Cancer Families

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Objectives Whole-exome sequencing can be used to identify novel ovarian cancer susceptibility genes. By sequencing two affected individuals from each family, we can analyze only the shared variants from the large number of protein-truncating variants.
Methods We performed whole-exome sequencing in germline DNA from 2 affected individuals per family, from 28 *BRCA1/2*-negative families with at least 2 cases of ovarian cancer, from the Gilda Radner and U.K. familial ovarian cancer registries and the Poland family history study. The sequenced pairs were 5 first cousins, 3 aunt–niece, 10 mother–daughter, and 10 sisters. Genes with shared predicted deleterious protein-truncating variants were assessed in whole-exome sequencing data from 775 ovarian cancer cases (279 with a family history of ovarian cancer) and control data from the NHLBI Exome Sequencing Project and the Exome Aggregation Consortium (EXAC) databases.
Results From the analysis of the first 10 families, 2 families had previously unidentified *BRCA1* mutations. In one family, the mutation was present in both individuals, and in the other, only in 1 individual. The average number of protein-truncating variants per individual was 16, and the number of shared variants per family ranged from 2 to 17. Many of the shared variants were not detected by standard analysis because of coverage differences and required examination of the BAM files for all detected variants. We selected 4 genes (*GANC, KNTC1, PSG6,* and *UPK2*) for targeted gene sequencing in 5500 high-grade serous cases and 5500 unaffected controls of European origin.
Conclusions We identified a panel of genes with shared protein-truncating variants in families and performed targeted sequencing validation of 4 of the genes in large numbers of cases and controls. Risk prediction based on identifying germline mutations in ovarian cancer susceptibility genes could have a significant impact on reducing disease mortality.

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S10-PP3

The Base Excision Repair Pathway Contributes to Breast Cancer Susceptibility

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Objectives Identifying the missing hereditary factors of familial breast cancer could have a major and immediate impact on reducing breast cancer risk in these family members.
Methods Up to 1400 candidate breast cancer predisposition genes, identified through exome sequencing of 69 *BRCAx* families, were sequenced in index cases of up to 3000 *BRCAx* families and 3000 cancer-free Victoria women from the LifePool study.
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 loss of function (LOF) mutations in this dataset. Conversely, some other recently proposed breast cancer genes (*BRIP1, RINT1*) did not show a significantly higher LOF mutation frequency in cases than in controls. A top hit based on LOF mutations only was *NTHL1* (9 in cases, 1 in controls, $p = 0.01$), which is an important member of the base excision repair (BER) pathway. We examined the BER pathway further and observed a significant enrichment of potentially deleterious mutations 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*): Among the 1000 cases and 1000 controls analyzed to date, 32 LOF and 180 missense variants were detected in these genes 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 Our data implicate rare mutations in BER pathway genes as moderate penetrance breast cancer susceptibility alleles.

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POSTERS

BIOLOGY OF HEREDITARY CANCERS

Poster P001

BRCA1 and *BRCA2* Gene Expression in Tumoural Tissues of Moroccan Breast Cancer Patients

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Breast cancer is one of the most important causes of death worldwide. The *BRCA1* and *BRCA2* predisposition genes are associated with 5%–10% of familial cases of this disease.
Objective As breast cancer susceptibility genes, *BRCA1* and *BRCA2* are expressed in a varied range of human tissues and respectively encode 1863 and 3418 amino-acid proteins involved in DNA repair. For better molecular characterization, we quantified *BRCA1* and *BRCA2* mRNA using the QRT-PCR approach in large series of tumour and normal breast tissues.
Methods We analyzed the expression of *BRCA1* and *BRCA2* genes by the QRT-PCR method for 2 types of tissue: tumoural and normal in 41 patients with breast cancer.
Results We found a significant correlation between the expression of *BRCA1* in normal and its presence in tumoural tissue, $p = 0.0053$. The results also showed a negative correlation in the expression of *BRCA2* between the normal and tumoural tissue ($p = 0.0122$). Furthermore, a positive correlation was found concerning the expression of *BRCA1* and *BRCA2* ($p < 0.0001$).
Conclusions This study suggests that the *BRCA1* and *BRCA2* genes are both involved in the development of sporadic breast cancer. However, further studies are still necessary to elucidate the genetic (or epigenetic) mechanisms responsible for the observed dysregulation of *BRCA2* mRNA expression.

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Poster P002

Reduced *BRCA1* Transcript Levels in Freshly Isolated Blood Leucocytes from *BRCA1* Mutation Carriers Is Mutation-Specific

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Objectives *BRCA1* mutation carriers face a high lifetime risk of developing both breast and ovarian cancer. Haploinsufficiency is thought to predispose these women to cancer by reducing the pool of available *BRCA1* transcripts and protein, thereby compromising *BRCA1* function. Whether cancer-free *BRCA1* mutation carriers have lower levels of mRNA transcripts in peripheral blood leucocytes has not been evaluated. The primary aim of this study was to characterize an association between *BRCA1* mutation status and *BRCA1* mRNA leucocyte expression levels among healthy women with a *BRCA1* mutation.
Methods RNA was extracted from freshly isolated peripheral blood leucocytes of 58 cancer-free female participants (22 *BRCA1* mutation carriers, 36 noncarriers). The expression levels of 236 cancer-associated genes, including *BRCA1*, were quantified using the Human Cancer Reference gene panel from Nanostring Technologies' nCounter Analysis System.
Results *BRCA1* mRNA levels were significantly lower in *BRCA1* mutation carriers than in noncarriers (146.7 counts vs. 175.1 counts, $p = 0.002$). Samples with *BRCA1* mutations within exon 11 had lower *BRCA1* mRNA levels than samples with mutations within the 5′ and 3′ regions of the *BRCA1* gene (122.1 counts vs. 138.9 and 168.6 counts respectively, $p = 0.003$). Unsupervised hierarchical clustering of gene expression profiles from freshly isolated blood leucocytes revealed that *BRCA1* mutation carriers cluster with other *BRCA1* mutation carriers rather than with *BRCA1* wild-type samples. Moreover, a set of 17 genes (including *BRCA1*) previously shown to be involved in carcinogenesis were differentially expressed between *BRCA1* mutation carriers and noncarriers.
Conclusions Overall, these findings support the concept of *BRCA1* haploinsufficiency wherein a specific mutation results in dosage-dependent alteration of *BRCA1* at the transcriptional level. This study is the first to show a decrease in *BRCA1* mRNA expression in freshly isolated blood leucocytes from healthy, unaffected *BRCA1* mutation carriers.

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Poster P003

Chemoprevention in *BRCA1* Mutation Carriers—A Proof-of-Concept Study

Aideen Campbell, Kienan Savage, Stuart McIntosh, Paul Harkin

Background Women with germline *BRCA1* mutations have a high lifetime risk of breast cancer, with the only available risk-reduction strategies being risk-reducing surgery or chemoprevention. These women predominantly develop triple-negative breast cancers; hence, it is unlikely that selective estrogen receptor modulators (SERMs) will reduce the risk of developing cancer, as these have not been shown to reduce the incidence of estrogen receptor–negative breast cancers. Preclinical data from our laboratory suggest that exposure to estrogen and its metabolites is capable of causing DNA double-strand breaks (DSBs) and thus driving genomic instability, an early hallmark of *BRCA1*-related breast cancer. Therefore, an approach that lowers circulating estrogen levels and reduces estrogen metabolite exposure may prove a successful chemopreventive strategy.
Aims To provide proof of concept of the hypothesis that the combination of luteinizing-hormone releasing-hormone agonists (LHRHa) and aromatase inhibitors (AIs) can suppress circulating levels of estrogen and its metabolites in *BRCA1* mutation carriers, thus reducing estrogen metabolite levels in breast cells, reducing DNA DSBs, and potentially reducing the incidence of breast cancer.
Methods 12 Premenopausal *BRCA1* mutation carriers will undergo baseline ultrasound-guided breast core biopsy and plasma and urine sampling. Half the women will be treated for 3 months with combination goserelin (LHRHa) plus anastrazole (AI), and the remainder with tamoxifen (SERM) before repeat tissue, plasma, and urine sampling. After a 1-month washout period, groups will cross over for a further 3 months treatment before final biologic sample collection. Tissue, plasma, and urine samples will be examined using a combination of immunohistochemistry, comet assays, and ultrahigh performance liquid chromatography tandem mass spectrometry to assess the impact of LHRHa plus AI compared with SERM on levels of DNA damage, estrogens, and genotoxic estrogen metabolites. Quality of life will also be assessed during the study.
Results This trial is currently ongoing.

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Poster P004

Modeling Müllerian High-Grade Serous Carcinogenesis Using *BRCA1* Patient–Derived Induced Pluripotent Stem Cells

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Background Serous tubal intraepithelial carcinoma (STIC) lesions in the fallopian tube fimbriae of *BRCA* mutation carriers support a fallopian tube epithelium (FTE) as the origin of Müllerian high-grade serous carcinomas (HGSC). Germline mutations in *BRCA* genes are the greatest risk determinant for developing HGSC; however, little is known about the transformation of normal FTE to STICs and HGSC. Recently, patient-specific iPSC technology and 3D tissue engineering have provided an opportunity to model human disease *in vitro.* Several iPSC-derived inherited disease models have been used to reproduce associated high-risk cancers, and

these studies have revealed disease pathogenesis and carcinogenesis-initiating events in relevant human cell types.

Hypothesis *BRCA1* mutation in FTE render the cells more susceptible to neoplastic transformation as a result of hormonal and mechanical stress signals, including ovulation, oxidative stress, and inflammation.

Methods Established control iPSC cell lines were differentiated into intermediate mesoderm (IM), and IM 2D cultures were exposed to developmental growth factors of the Müllerian duct. 3D Spheroid buds from the monolayer epithelial cultures were collected and further cultured in matrigel together with pro-Müllerian growth factors until they gave rise to FTE. Intermediates were validated during the course of differentiation using qPCR and immunofluorescence analyses. We also generated and characterized 3 different *BRCA1*-mutant iPSC lines from young ovarian cancer patients and applied our differentiation protocol.

Results For control iPSCs, expression of mesoderm markers (Brachyury and Mixl1) and IM markers (Osr1, Pax2, and Wt1) were validated during the course of differentiation using qPCR analysis. Notably, a minimal amount of endoderm and ectoderm was also derived, demonstrated by low qPCR expression of AFP and Sox17 (endoderm) and NCAM (ectoderm) markers. The FTE differentiation was monitored throughout with expression of Pax8, Wt1, Ovgp1 (secretory cell marker), Tubb4a (ciliated cell marker), and E-cadherin (Cdh1, an epithelial marker) using immunohistochemistry analysis. Proper luminal structures are visualized with H–E staining. Creation of müllerian epithelium also confirmed the lack of expression for gut, lung/thyroid, and renal cellular markers Cdx2, TTF-1 (Nkx2.1), and Six2 respectively.

Conclusions We developed a rapid and efficient method to create an iPSC-derived 3D model of human FTE with the desired cell types and 3D luminal architecture. Studies are ongoing using this iPSC-derived *BRCA1*-mutant FTE model as a platform to investigate the hormonal, mechanical, and genomic mechanisms that contribute to neoplastic transformation of FTE.

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Poster P005

Genetic and Epigenetic Characterization of the *BRCA1* Gene in Brazilian Women At Risk for Hereditary Breast Cancer

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Objectives The main objective is to characterize women at risk for hereditary breast cancer (BCA) with respect to the presence of mutation and methylation in the *BRCA1* gene and correlate the gene expression levels with histopathologic characteristics and family history.

Methods Quantitative PCR was used for methylation and gene expression analysis in normal and tumour samples of patients with and without *BRCA1* germline mutations as well as in women with VUS in *BRCA1*.

Results The study included 72 women, 19 with a *BRCA1* deleterious mutation, 16 with a VUS on *BRCA1*, and 37 *BRCA1* WT. Most patients had invasive ductal carcinoma. Most tumours in women with mutated *BRCA1* were triple-negative (65.0%) and histologic grade 3 (57.9%), unlike the VUS and WT patients, in whom histologic grade 2 and the luminal B subtype predominated. Analysis of family history showed that the women with mutated *BRCA1* had more cases of BCA in the family as well as a higher percentage of cases younger than 50 years. Regarding the molecular characteristics, no patient with a pathogenic mutation in *BRCA1* showed hypermethylation. The hypermethylation was observed in only 2 patients (*BRCA1* VUS and *BRCA1* WT groups). Moreover, most of the patients in all 3 groups had lower levels of *BRCA1* mRNA in tumour tissue, indicating the loss/decrease of gene function in methylated/mutated cases, and also in cases with absence of these events suggesting that other mechanisms could be working on the silencing of the gene.

Conclusions Our findings suggest that methylation in *BRCA1* is not the "second event" for the development of BCA in patients with germline mutation in *BRCA1*. Furthermore, because a reduction in *BRCA1* mRNA levels was observed, it is suggested that other mechanisms may be involved or still that methylation analysis the whole promoter region of the *BRCA1* should be considered.

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Poster P006

The HeritX Global Initiative for Preventing Inherited Cancer

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Millions of patients benefit from improved cancer treatments. But what each of them is really dreaming about is not getting cancer at all. To achieve cancer prevention, we need to know the first step in the development of cancer before it starts. But we don't know who will get cancer, and thus whom to study or what to look for.

This does not apply to inherited *BRCA* cancer. Unlike other cancers, we already know the first step in the development of this cancer: the inherited mutation. We therefore know where to focus research. Advances developed in *BRCA* will eliminate a cancer affecting millions worldwide and translate into advances for cancer at large.

The nonprofit HeritX is the only organization solely focused on preventing inherited cancer. In November 2015, it convened the first-ever conference on preventing inherited *BRCA* cancer to kick-off a global initiative to achieve this goal.

This international Banbury Conference at the Cold Spring Harbor Laboratory convened 30 world-class researchers and drug developers. It created a roadmap with milestone goals from research to an approved prevention. Guided by this, HeritX is leading a dedicated effort by universities, government, industry, physicians, patients, and philanthropies to direct resources, coordinate across silos, and focus the brightest minds and best solutions on this goal.

We apply best practices in drug development to ensure that projects are not designed in isolation but build on each other to bring us to our goal. We encourage bold, out-of-the-box ideas. We advance understanding of what leads to cancer in healthy people, and facilitate such research through a noninvasive methodology. We help the community to have access to studies, and scientists to have needed tissue samples. And we ensure that patients remain in focus so that they and their families are true partners, and we deliver what matters most.

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BRCA1/2 MUTATIONS, VARIANTS OF UNKNOWN CLINICAL SIGNIFICANCE, AND DATABASES

Poster P007

Establishment of the HBOC Registration System in Japan

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We are establishing a national registration system for individuals who have undergone *BRCA1/2* genetic testing to clarify the clinicopathologic and genetic characteristics of hereditary breast and ovarian cancer (HBOC) in Japan, as a part of clinical research projects of The Japanese HBOC Consortium. A registration committee has been launched, and we have discussed registration contents and registration procedures. We created an original template for inputs, taking the contents of the CIMBA (Consortium of Investigators of Modifiers of *BRCA1/2*) database into account. A data centre has been established and input data will be updated once annually.

Preliminary registration of subjects from the past 3 years was performed this year as a trial in 4 institutions to which our committee members belong. As a result, we enrolled 986 subjects who had undergone *BRCA* genetic testing, including 135 carriers of the *BRCA1* mutation and 119 carriers of *BRCA2*. Of index cases in whom *BRCA1/2* genetic testing was performed, 20% were mutation-positive, and variants of uncertain significance were found in 6.6% of *BRCA1/2* genetic tests. Of patients with triple-negative breast cancer, 33% show a mutation in *BRCA1/2*. This mutation rate increases to 77.8% in patients with both early onset of breast cancer under 40 years old and a positive family history of ovarian cancers in addition to triple-negative breast cancer.

Among breast cancer patients who received preoperative genetic testing to help decide surgical procedures, 11.8% of *BRCA1/2* mutation-positive patients chose breast-sparing surgery. Risk-reducing salpingo-oophorectomy (RRSO) and risk-reducing mastectomy (RRM) were performed in 62 and 28 cases respectively. Latent cancers were found in 3.2% of RRSO cases and 7.1% of RRM cases.

We aim to develop a national registration project for general medical institutes from next year and would like to contribute to the construction of an international database.

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Poster P008

Development of a Chinese-Specific *BRCA1/2* Recurrent Mutation Genotyping Panel in Breast Cancer Patients

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Objectives Pathogenic mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2* are associated with the hereditary breast and ovarian cancer (HBOC) syndrome. From our previous genetic testing of 1358 Chinese HBOC patients with next-generation sequencing (NGS), 50.3% of the identified *BRCA1/2* mutations were recurrent mutations that had been repeatedly detected. Targeted screening of these recurrent mutation loci provides a cost-wise diagnostic measure for identifying mutation carriers. In this study, we aimed to develop a genotyping panel targeting *BRCA1/2* recurrent mutations in Chinese populations, and thus a valuable genetic testing tool for Chinese HBOC patients.
Methods Chinese high-risk HBOC patients were recruited for mutation screening in Hong Kong and the United States. A Chinese-specific genotyping panel was incorporated into our NGS pipeline, covering 25 *BRCA1/2* recurrent mutations identified in Hong Kong or overseas Chinese. Mutation loci were PCR amplified from patient genomic DNA extracted from peripheral blood. By single-base extensions of predesigned oligonucleotide probes, the loci amplicons were genotyped. Positive mutations were verified with Sanger sequencing, and those that were negative were subjected to NGS.
Results Based on the *BRCA1/2* mutation spectrum previously identified, we adopted a genetic testing strategy of screening recurrent mutations before full-gene sequencing. Among the 468 HBOC patients recruited in Hong Kong, 14 mutation probands (5 *BRCA1* and 9 *BRCA2*) were identified by the genotyping panel, and 23 non-recurrent mutations by NGS, with an overall mutation prevalence of 7.91%. The recurrent mutations pick-up rate was 37.8% of all identified mutations. In addition, 3 *BRCA1/2* mutations were identified with our panel from an overseas cohort of 60 Chinese Americans, representing 3.3% of tested cases.
Conclusions Our application of a targeted genotyping panel for *BRCA1/2* recurrent mutations demonstrated a cost-effective and timely strategy for mutation screening for Chinese HBOC patients in clinical laboratories where NGS is not available.

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Poster P009

Quality Assessment and Gene Panel Design—Important Considerations Regarding FFPE Sample Sequencing

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Objectives FFPE samples contain a valuable source of information, especially for the physician involved in genetic counselling. However, FFPE DNA is highly degraded, and DNA quality has an impact on the final NGS result when screening HBOC-related genes. At present, we have analyzed 326 FFPE samples (0–43 years of age) and developed a FFPE DNA quality assessment (QA) including fragmentation profiles, degradation level, and DNA concentration. Based on QA, requirements regarding DNA quality and variable input for targeted library preparation (HaloPlex) and NGS (Illumina) were implemented. Furthermore, optimization of DNA purification and HaloPlex design/protocol has also improved this analysis.
Methods DNA was extracted from 9×15 μm FFPE sections/sample. To verify FFPE DNA quality, DNA concentrations (PicoGreen), fragmentation profiles (TapeStation), and the level of fragmentation (PCR-based assay using HapMap DNA as a non-degraded control) were determined. According to the results, the amount of input DNA varied to compensate for the level of fragmentation.
Results 30 FFPE samples did not pass QA. The remaining 296 samples were sequenced and resulted in an average 30× coverage of 74.27%/73.07% (*BRCA1/2*) 1st HaloPlex design (191 samples), 84.44%/83.86% (*BRCA1/2*) 2nd HaloPlex design (48 samples), and 81.85%/81.97% (*BRCA1/2*), HaloPlexHS design (57 samples). Today, we use HaloPlexHS only requiring 60–350 ng of DNA depending on QA result, compared with previously 2 HaloPlex designs, where 225–1000 ng of DNA was used.
Conclusions Continuous development is the key to success when screening genes in FFPE samples. QA of FFPE samples is an important tool for omitting samples not suitable for NGS. The change of HaloPlex design/protocol shows promising improvements, and the fact that more samples will pass QA based on a lower DNA input requirement of the HaloPlexHS design allows us to help more families in genetic counselling.

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Poster P011

Enhancement of History Weighting Analysis to Accurately Classify Variants in High- and Moderate-Risk Cancer Panel Genes

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Objectives Historically, sequencing analysis to detect HBOC-associated pathogenic mutations was performed for *BRCA1* and *BRCA2* alone. These genes are now incorporated into larger gene panels. Previously, we developed a statistical family history weighting algorithm (HWA), which accurately reclassifies VUS as pathogenic or benign based on the severities of personal and family cancer histories. This algorithm was specific to testing for *BRCA1/BRCA2* gene mutations. We have enhanced this algorithm to include analysis of high and moderate cancer risk genes.
Methods The HWA was updated to combine clinical and genetic data obtained from >1 million probands clinically tested for *BRCA1/BRCA2* alone or a pan-cancer panel. Additional modifications allow for the analysis of moderate-risk genes. Gene-specific two-fold cross-validations performed on simulated variants and testing with true variants assessed final combined HWA performance for *BRCA1/BRCA2*.
Results Analysis of data comparing HWA scores obtained from *BRCA1/BRCA2* testing versus pan-cancer panel testing indicates that ascertainment biases affecting the two cohorts are relatively similar, allowing for the cohorts to be combined into an enhanced HWA. Conditional probability tables were updated based on this combined cohort. Two-fold cross validations and testing with true variants generated positive and negative predictive values of >0.998 for *BRCA1/BRCA2*.
Conclusions The ability to accurately classify variants identified in panel testing is critical for patient management. We have modified the HWA for combined use of data obtained from both *BRCA1/BRCA2* testing alone and pan-cancer panel testing. The enhanced HWA is accurate for both upgrading and downgrading VUS in *BRCA1/BRCA2*. Additional HWA modifications demonstrate that this technique can be used to accurately reclassify variants in moderate-risk genes, such as *ATM, CHEK2,* and *PALB2,* for which use of other reclassification techniques is severely limited.

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Poster P012

Outcomes of Chromosome Breakage Analysis As a Tool for *BRCA2* Variant Reclassification

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Objectives Classification of rare variants identified during genetic testing can be challenging, and appropriate individuals may undergo additional testing to provide supporting information. This is the case for variants of uncertain significance (VUS) identified in trans with a known pathogenic variant (PV) in *BRCA2*. The incidence of two PVs in *BRCA2* is typically limited to individuals with Fanconi anemia, which can be ruled out using chromosome breakage analysis (CBA). To reclassify appropriate variants in *BRCA2* from VUS to benign, the testing laboratory has developed a program to include CBA as an adjunct to genetic testing at no cost to all qualifying patients.
Methods Individuals who underwent *BRCA1/BRCA2* testing are eligible for CBA if found to have a VUS in trans with a known PV in *BRCA2* and to have a clinical presentation not consistent with Fanconi anemia. For eligible patients, CBA is discussed with the ordering health care provider and blood samples from participating patients are sent to Oregon Health and Sciences University for analysis. Negative CBA allows reclassification of a VUS to benign. Here, we assessed the impact of this program on variant reclassification by evaluating the number of CBA offers made, CBAS completed, and resulting reclassifications.
Results CBA testing was offered to 31 eligible patients. Of the 11 participating individuals (including 2 siblings), 9 had negative CBA results, and 2 had inconclusive results. As a result, 7 variants were reclassified from VUS to benign. This includes E187K, which was observed in 3 tested individuals. The reclassification of these variants affected a total of 89 individuals who underwent hereditary cancer testing.
Conclusions Our analysis reveals that CBA is an effective and necessary tool for reclassifying rare VUSs identified in *BRCA2*. Continued education and improvements to the process for providers and patients will likely lead to greater uptake.

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Poster P013

Structural Biology in Variant Classification

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Objectives Structural biology is the study of the 3-dimensional structure of proteins and nucleic acids. Given that the structure of these molecules is

intimately associated with their function, mutations that impart structural changes may lead to the production of abnormal/malfunctioning proteins that cause disease. Consequently, the 2015 ACMG guidelines state that mutations located within a "critical and well-established functional domain" may be considered moderate evidence of pathogenicity. This provides a platform for the use of structural biology in variant classification. In particular, this method is advantageous for missense variants in which the current data, in isolation, are insufficient to lead to a definitive classification. Although the methods underlying macromolecular structure determination are well established, the specialized training and required expertise have prevented structural analysis from being widely incorporated in the genetic testing field. Here, we show the benefits of incorporating structural biology, with other evidence, in variant classification in hereditary cancer testing.

Methods Two variants of uncertain significance (VUSs) were evaluated for potential reclassification: *BRCA1* c.5153G>C (p.Trp1718Ser) and *BRCA2* c.91T>A (p.Trp31Arg). Publicly available protein structures were downloaded from the Protein Data Bank (PDB) and validated using Molprobity and PDB_REDO (PDB IDs 1T15 and 3EU7). Additional functional data in the published literature were gathered and analyzed.

Results Structural analysis and functional evidence revealed that c.5153G>C (p.Trp1718Ser) severely affects multiple functions of *BRCA1*, likely because of the introduction of a severe protein-folding defect. This analysis also revealed that c.91T>A (p.Trp31Arg) abolishes a key interaction between *BRCA2* and *PALB2*. Based on this evidence, both mutations were reclassified from VUS to suspected deleterious (likely pathogenic).

Conclusions Structural biology is a powerful tool in the reclassification of rare missense variants. This is demonstrated here, with two variants that that we upgraded to suspected deleterious on the basis of structural biology and functional data.

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Poster P014

RNA Research Program to Aid in the Reclassification of Genetic Variants That Alter Splicing

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Objectives RNA splicing is the process by which noncoding intronic regions of a gene are removed. Germline variants can impair splicing and give rise to a nonfunctional protein. Specific splice junctions may tolerate wide variation and still splice correctly, while other junctions may become impaired by only minor changes. We recently established an IRB-approved research program to enrol selected patients, after clinical testing, that carry variants that may alter splicing. An additional sample is collected from these patients to generate functional RNA splicing data, to aid in the potential reclassification of the variant.

Methods RNA is first extracted from blood samples; cDNA is then synthesized, and PCR is performed, amplifying portions of the gene of interest. Splicing patterns are visualized on an agarose gel and splice products identified by sequencing. The wild-type splicing pattern is confirmed in age/gender–matched blood controls, and in normal tissue (breast, or ovarian, or both). Further experiments are then performed to determine if the mutant allele produces any wild-type splice product.

Results We have now analyzed many variants within genes in which pathogenic variants cause an increased risk of breast or ovarian cancer (or both), such as *BRCA1*, *BRCA2*, and *CDH1*. In some cases, a variant was observed to fully disrupt splicing and was reclassified; in other cases, a variant was observed to only partially disrupt splicing and remained classified as uncertain.

Conclusions These studies demonstrate that RNA studies are very helpful in the reclassification of variants that alter splicing. Variants that fully impair splicing can be reclassified, while variants that cause intermediate splicing defects may require additional data to determine if the variant causes an increased cancer risk.

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Poster P015

BRCA Mutations and Outcome in Epithelial Ovarian Cancer: Experience in Ethnically Diverse Groups

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Background Epithelial ovarian cancer (EOC) patients with *BRCA* mutations, especially of Ashkenazi Jewish (AJ) ancestry, have better outcomes than nonhereditary cases matched for histology, stage, and age at diagnosis, and treatments.

Methods We are updating data from about 1200 highly ethnically heterogeneous EOC patients diagnosed at stages IC-IV and evaluated for *BRCA* status between 1995 and 2014 in our U.S., Israeli, and Italian medical centres.

Results Of 349 patients (AJ, Jewish non-Ashkenazi, Caucasian, African-American, Hispanic), tested so far for *BRCA* mutations, median age 60 years (range: 20–87 years), 149 were *BRCA1/2* carriers (108 *BRCA1* and 39 *BRCA2*). Most mutations in AJ and non-AJ origins were 185delAG (74/149) and 6174delT (22/149). Non-Jewish Caucasians showed the widest variation (20 mutation subtypes). At the time of data collection, 76/149 of carriers (50%) are still alive, and 80/233 of noncarriers (34%) are still alive; 32% of noncarriers and 65% of carriers have platinum-sensitive disease; 32% of noncarriers and 25% of carriers are without disease recurrence. *BRCA* carriers have significantly prolonged median overall survival [66 months (range: 7.5–227)] compared with noncarriers [39 months (range: 3–161 months)]. 108 Carriers of common AJ *BRCA1* mutation have a median OS of 61 months (range: 8.4–227 months), and 39 *BRCA2* AJ common mutations have 72 months (11–170 months), 33 patients with uncommon mutations 72 months (7.5–172 months).

Conclusions Our data confirm that EOC *BRCA* mutation carriers have better prognosis, with longer median survival, than patients with nonhereditary disease. Confirmation of better outcomes in *BRCA* mutations from subset of this a highly ethnically diverse EOC population as well of unclassified *BRCA* variants will be sought in subsequent analyses.

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Poster P016

Prevalence of *BRCA1*/*BRCA2* Mutations in a Brazilian Population Sample At Risk for Hereditary Breast Cancer and Its Association with Genetic Ancestry

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Objectives There are very few data about the mutational profile of families at risk for hereditary breast and ovarian cancer (HBOC) from Latin America and especially from Brazil, the largest and most populated country in Latin America. The aim of this study was to characterize Brazilian families at risk for HBOC regarding *BRCA1*/*BRCA2* mutations, as well as to assess its ethnic composition (genetic ancestry) and correlated these molecular findings with the clinical and familial history of patients.

Methods The presence of germline *BRCA1/2* mutation was analyzed through next-generation sequencing (Ion Torrent PGM) followed by MLPA. To assess genetic ancestry, we used a panel of 46 ancestry-informative markers which proved useful for the estimation of ancestral proportions in highly admixed individuals or populations like the Brazilian.

Results The present work is the largest study of the prevalence of germline mutations in *BRCA1*/*BRCA2* genes in the Brazilian population. Of the 349 probands analyzed, 21.5% were *BRCA1/2* mutated, 65.3% at *BRCA1* and 34.7% at *BRCA2* gene. Additionally, 308 relatives were evaluated. The mutation c.5266dupC (formerly 5382insC) was the most frequent alteration in our series, representing 36.7% of the *BRCA1* mutations and 24.0% of all mutations identified. Interestingly, in the overall, 657 individuals were evaluated, and 6 new mutations were identified, 2 in *BRCA1* and 4 in *BRCA2*. Regarding the ancestry, the European component was the most prevalent (88.6%), followed by the African (6.7%), Asian (2.35%), and Amerindian (2.35%).

Conclusions This is the largest report of *BRCA1*/*BRCA2* assessment in an at-risk HBOC Brazilian population. We identified 21.5% of patients harbouring *BRCA1*/*BRCA2* mutations that were not associated with their genetic ancestry. Knowledge of the mutational profile in a given population can contribute to the definition of more cost-effective strategies for the identification of HBOC families.

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Poster P017

Prevalence of Germline *BRCA1, BRCA2, PALB2,* and *ATM* Mutations in Patients with Pancreatic Cancer and French Canadian Ancestry

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Objective Approximately 10% of pancreatic ductal adenocarcinoma (PDAC) cases are accounted by genetic predisposition. A proportion of these cases are attributable to rare loss-of-function mutations in *BRCA2, BRCA1, PALB2,* and *ATM*. In the present study, we investigated the prevalence of germline mutation in these genes in 96 incident PDAC cases with French Canadian (FC) ancestry.
Methods We first screened for the 20 known FC founder mutations in *BRCA1, BRCA2,* and *PALB2* by bead-based fluorescent detection and Sanger sequencing. Full gene sequencing and multiplex ligation-dependent probe amplification (MLPA) were then used to interrogate the coding regions of these 3 genes and *ATM* in all 96 cases for non-recurrent mutations and large structural changes.
Results Our results suggest a 6.25% pathogenic mutation incidence in these genes in FC cases with founder mutations representing two thirds of the mutations identified.
Conclusions These findings suggest that the prevalence of germline mutations among FC PDAC incident cases is significant, and testing for founder mutations should be considered prior to full gene interrogation among incident FC PDAC cases.

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Poster P018

Variant Classifications for *BRCA1* and *BRCA2* Are Substantially Concordant Across Major Clinical Testing Laboratories

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Background As more laboratories offer genetic tests, the potential for inconsistent reporting increases. Variant classification differences between public databases have been raised as a particular concern, although the impact is not clear. Experienced lab directors never simply copy classifications from public databases. Instead, they critically evaluate evidence and determine classifications following rigorous guidelines[1]. Our recent study[2] demonstrated high (99.8%) concordance of 975 *BRCA1/2* tests classified this way using only public data, compared with tests that also utilized non-public information. Here, we sought to similarly measure concordance in an even larger data set.
Methods ClinVar submissions of 4791 classified variants from 5 established laboratories (Ambry, Emory, GeneDx, Invitae, and Myriad) were used. Myriad data were submitted by the Sharing Clinical Reports Project. Clinically significant differences were those between pathogenic (including likely pathogenic), versus VUS, benign, or likely benign; otherwise, results were considered concordant.
Results Counting each variant separately, concordance between pairs of labs is high: 98.1%–99.7%. However, this calculation greatly underestimates the much higher concordance observed on a per-patient basis. Most discordant classifications (>90%) are in rare variants that, by definition, are present in very few patients. Moreover, most rare variants (~98%) agree. Based on observed prevalence, 99.8% of patients receive net concordant reports, similar to our previous study's results. Even after detailed examination of all evidence underlying the remaining disagreements, the maximally correct classification under current guidelines sometimes remains unclear.
Discussion Classification concordance has to be measured carefully to avoid over-counting differences. Although differences are seen in few patients, it is important to resolve them collaboratively, not competitively[3]. Thorough peer review of classifications both supports laboratory quality control efforts and helps to improve critical guidelines.

1 Richards S, Aziz N, Bale S, *et al.* on behalf of the ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–24.
2 Lincoln SE, Kobayashi Y, Anderson MJ, *et al.* A systematic comparison of traditional and multigene panel testing for hereditary breast and ovarian cancer genes in more than 1000 patients. *J Mol Diagn* 2015;17:533–44.
3 Rehm HL, Berg JS, Brooks LD, *et al.* on behalf of ClinGen. ClinGen—the Clinical Genome Resource. *N Engl J Med* 2015;372:2235–42.

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Poster P019

Detection of *BRCA1/2* Mutations in a Group of 100 Formaldehyde-Fixed, Paraffin-Embedded Tissues of Ovarian Cancer

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Objectives The overall prevalence of germline *BRCA1/2* mutations is estimated at between 11%–15% of all ovarian cancers. Individuals with germline alterations treated with PARP1 inhibitors (iPARP1) respond better than do patients with wild-type *BRCA1/2*. In addition, somatic *BRCA1/2* mutations also induce sensitivity to iPARP1. Detection of both germline and somatic *BRCA1/2* genetic variants is therefore required for effective iPARP1 treatment. The aim of the study was to identify the frequency and spectrum of germline and somatic *BRCA1/2* mutations in a group of Polish patients with serous ovarian cancer.
Methods The study enrolled 100 FFPE serous ovarian tissues. The histologic diagnosis of ovarian serous carcinoma and the tumour tissue content of each sample were evaluated. In selected cases, tissue macrodissection was performed. *BRCA1/2* mutation screening was performed using the *BRCA* Tumor MASTR Plus assay (Multiplicom) followed by MiSeq targeted re-sequencing (Illumina). In addition, to confirm the germline or somatic status of the mutation, the non-neoplastic tissue was analyzed by bidirectional Sanger sequencing.
Results In total, 27 mutations (28% of patient samples, 20 in *BRCA1* and 7 in *BRCA2*) were identified. For 22 patients, non-neoplastic cells were available, and sequencing revealed the somatic character of 2 *BRCA1* (2/16, 12.5%) and 2 *BRCA2* (2/6, 33%) mutations. Notably, we identified 6 novel frameshift or nonsense *BRCA1/2* mutations. Three individuals were compound heterozygous for *BRCA1* and *BRCA2* genetic variants—one pathogenic, and a second classified as unknown variant.
Conclusions The heterogeneity of detected mutations confirms the necessity of simultaneous analysis of *BRCA1/2* genes in all patients diagnosed with serous ovarian cancer. Moreover, use of tumour tissue for mutational analysis allowed for the detection of both somatic and germline *BRCA1/2* mutations and increased the total number of patients who may potentially benefit from targeted therapies with PARP inhibitors.

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Poster P020

The *BRCA* Challenge: Improving Clinical Care Through Genomic and Clinical Data Sharing

Rachel G. Liao,*† Steering Committee of the *BRCA* Challenge

Genomic sequencing has fundamentally improved clinical care and outcomes for those with family histories of hereditary cancer. In particular, as technical advances have reduced the cost of sequencing, barriers to accurate genetic variant identification are being overcome, enabling informed clinical decision-making.

However, as more variants of uncertain significance are identified, the complexity of interpreting an individual variant has become more challenging. Variant databases, often organized at the laboratory or national level, have begun to aggregate variants with classifications of pathogenicity, and yet any individual database is generally not able to access data from other sources and thus classifies using only incomplete data. This can lead to erroneous classifications of pathogenicity and inappropriate clinical care.

The *BRCA* Challenge, a demonstration project of the Global Alliance for Genomics and Health, was formed to tackle this issue by developing a federated network of holders of *BRCA1* and *BRCA2* variant- and case-level data, and a Web portal to display expert variant classifications. In particular, the aggregation of evidence by the *BRCA* Challenge will enable classification of variants previously described as uncertain, thereby enabling improved clinical care for patients with an identified variant in *BRCA1* or *BRCA2*. The product of this work, the *BRCA* Exchange, is a Web portal for patients, clinicians, genetic counsellors, and researchers, where the user can input any *BRCA1* or *BRCA2* variant and see aggregated consensus data from around the world, along with classifications of pathogenicity for variants that have been evaluated by the ENIGMA consortium. The *BRCA* Exchange can be accessed at http://www.brcaexchange.org.

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Poster P022

Handling the Reclassification of a Variant of Unknown Clinical Significance in *BRCA2*

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Objectives We developed a strategy for handling the reclassification of a variant of unknown clinical significance (VUS). *BRCA2* c.68–7T>A was treated as a pathogenic mutation until new knowledge suggested that cancer risk was not significantly increased. Because of this reclassification, we had to inform families in which this variant was assumed to be the factor causing disease and where *BRCA* testing therefore had been limited. We wanted to prevent unnecessary prophylactic interventions and surveillance.
Methods In the 20 families with this VUS, 102 patients (carriers and noncarriers), were contacted. First priority was to contact patients planning

prophylactic surgery. A plan for every family, describing the managing of each patient, was then prepared. Patients were categorized into 3 different groups (1. Written information, 2. Extended testing, 3. Consultation), and a letter was composed for each group. After 4 months, the test results were summarized, and each patient received a final written conclusion.

Results We found reason to offer 32 patients a re-test of the *BRCA* genes, and 26 accepted. One new mutation was found in 1 of the 20 families. Seven called after receiving the letter. Of the 19 patients offered a new consultation, 17 attended. Most patients were thankful and thought this was good news. Some had difficulties in trusting this new information and the new test result. Those who had experienced successful prophylactic surgery were more positive than those who had experienced complications. Some women wanted to continue with surveillance or to undergo prophylactic surgery despite the new information.

Conclusions Our strategy for reclassification is efficient in handling several patients and different clinical situations within a short time interval. We could not offer all patients counselling, but all had the opportunity to contact us. Given that few did, it may indicate that the written information was sufficient.

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Poster P023

Prevalence of Mutations in *BRCA1/2* and Other High/Moderate–Risk Cancer Genes in More Than 2600 Patients Tested Via the Same NGS Cancer Panel

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Objectives Determine the prevalence of mutations in high/moderate–risk cancer genes in an ethnically diverse patient population tested via the same 20-gene cancer panel.

Methods We assembled a cohort of 2675 patients (2498 women, 177 men) from a large managed care organization, Kaiser Permanente Southern California. Our panel includes 20 high/moderate–risk cancer susceptibility genes. Approximately 90% of patients tested were referred because of a personal or family history, or both, of breast or ovarian cancer (HBOC). Of these patients, 68% had both a personal and family history of cancer, 23% had a family history only, and 8% had a personal history only. Age range: 15–91 years. Ethnicity distribution was as follows: 42% European, 24% Latino/Hispanic, 14% other/mixed, 10% Asian, 7% African American, and 2% unknown/not provided.

Results We identified 344 pathogenic/likely pathogenic variants (PV/LPV) in 330 patients (12.3%) in the following genes: *BRCA1* (75), *BRCA2* (63), *MUTYH* (51), *CHEK2* (42), *ATM* (32), *PALB2* (23), *MSH6* (10), *PMS2* (10), *TP53* (9), *APC* (8), *MSH2* (7), *MLH1* (5), *PTEN* (3), *VHL* (2); 1 mutation in each of the following genes: *BMPR1A, CDKN2A, EPCAM,* and *SMAD4*; and no mutations in *STK11.* 19 Patients had previously-negative single-gene tests (17 *BRCA*, 2 *APC*, and 1 *PALB2*). Latino/Hispanic patients accounted for 33% ($n = 46$) of *BRCA1/2* mutations, but comprised only 24% of the overall cohort. No mutations were detected in 1539 patients (58%); at least 1 variant of unknown clinical significance was detected in 797 patients (30%).

Conclusions Of the patients in our cohort, 5.4% ($n = 144$) had PV/LPV in genes other than *BRCA1/2* and *MUTYH,* providing evidence that testing via multigene cancer panels can offer clinically actionable results beyond single-gene testing. Our observation of a high proportion of *BRCA1/2* PV/LPV in Latino/Hispanic patients merits further exploration of mutation prevalence in this population.

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Poster P024

Utilization of Neoadjuvant Chemotherapy in Women with Breast Cancer Tested for *BRCA* Mutations at a NCI-Designated Comprehensive Cancer Centre

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Objectives To assess treatment patterns in women with breast cancer (BCA) tested for *BRCA* mutations (*BRCA*m).

Methods Adult women with invasive BCA diagnosed from 1995 to 2014 and tested for a *BRCA*m were identified from an institutional tumour registry and via chart review. Initial treatment pathways were assessed. Changes in treatment patterns were assessed in 5-year increments over the most recent 15-year period. A logistic regression of therapy selection was performed in those with stages I–III disease treated with adjuvant and neoadjuvant chemotherapy (NAC).

Results A total of 835 women with BCA had a recorded *BRCA* status, of whom 139 (17%) had a *BRCA*m. Similar initial treatment strategies were initiated in *BRCA*m vs *BRCA* wild-type (WT) patients, with surgical resection alone in 14 (10.1%) and 67 (9.6%) respectively, adjuvant chemotherapy in 94 (67.6%) and 470 (67.5%) respectively, NAC in 22 (15.8%) and 126 (18.1%) respectively, and metastatic treatment in 9 (6.5%) and 33 (4.7%) respectively, $p = 0.80$. There was no difference in stage at diagnosis between *BRCA*m and *BRCA*wt, $p = 0.71$. NAC was administered in 7 (9.6%) patients from 2000 to 2004, in 33 (12.9%) from 2005 to 2009, and in 108 (24.8%) from 2010 to 2014, with reduced use of adjuvant treatment, $p = 0.0001$ (Pearson chi-square). NAC was more likely during 2010–2014 than during 2000–2004, was more common in stage II and III patients, and in patients with a receptor status other than ER+/PR+/HER2. *BRCA* status did not affect NAC utilization. During the study period, significantly more patients underwent bilateral mastectomy (69.1% vs. 38.1%, $p < 0.0001$) and BSO/TAH (66.9% vs. 25.4%, $p < 0.0001$) with a *BRCA*m than with a *BRCA*wt respectively.

Conclusions Increasing use of NAC was observed during the study period. There were no differences among the 4 broad initial treatment pathways examined between *BRCA*m and *BRCA*wt. A high rate of risk-reducing surgeries in *BRCA*m carriers was observed.

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Poster P025

Increasing *BRCA* Testing in Breast Cancer Patients at a NCI-Designated Comprehensive Cancer Centre

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Objectives To assess *BRCA* testing practices in women with breast cancer (BCA).

Methods Adult women with invasive BCA were identified from an institutional tumour registry from 1995 to 2014. *BRCA* testing was identified by chart review. *BRCA* testing patterns were assessed in 5-year increments during the last 15-year period. Timing of *BRCA* testing was categorized as before diagnosis (>30 days before), peri-diagnosis (30 days before to 90 days after) and post-diagnosis (>90 days after).

Results Of 5712 women with BCA diagnosed from 1995 to 2014, a total of 835 (15%) underwent *BRCA* testing. Of those tested ($n = 835$), 139 (17%) had a germline *BRCA* mutation [*BRCA*m (*BRCA1*: $n = 61$; *BRCA2*: $n = 70$; *BRCA1* and *BRCA2*: $n = 1$; *BRCA*m not otherwise specified: $n = 7$)] and 696 (83%) were considered wild-type. An increasing number of women were tested from 2000 to 2014, with 73/1273 patients (5.7%) tested from 2000 to 2004, 256/1505 (17.1%) from 2005 to 2009, and 435/1882 (23.1%) from 2010 to 2014, $p < 0.0001$ (Pearson chi-square). Lower percentages of *BRCA*m subjects were identified in the more recent time periods, but higher numerically, with 20 (27.4%) *BRCA*m subjects identified from 2000 to 2004, 45 (17.6%) from 2005 to 2009, and 58 (13.3%) from 2010 to 2014. The proportions of BCA patients tested pre-, peri-, and post-diagnosis were as follows: from 2000 to 2004, 5 (6.9%) were tested pre-, 5 (6.9%) peri-, and 53 (72.6%) post-diagnosis; from 2005 to 2009, 7 (2.7%) were tested pre-, 75 (29.3%) peri-, and 141 (55.1%) post-diagnosis; from 2010 to 2014, 32 (7.4%) were tested pre-, 227 (52.2%) peri-, and 107 (24.6%) post-diagnosis (chi-square $p < 0.0001$).

Conclusions The rate of *BRCA* testing, and the numbers of patients tested, increased during the study period; however, the proportion of patients identified with a *BRCA*m was reduced. An increasing percentage of patients were tested for a *BRCA*m around the time of BCA diagnosis.

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Poster P026

BRCA Mutation Spectrum Within the South African Indian Population: Impact on Diagnostic Services

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Objectives South Africa (SA) is the home of various genetically unique population groups that migrated to the most southern tip of Africa centuries ago. Where familial breast cancer (BCA) is concerned, this uniqueness poses complications for the national diagnostic platform because the most common mutation panel currently performed is not applicable for most SA patients. As the public demand for diagnostic testing increased, multiple high-risk SA Indian families were investigated to determine the range of mutation types present and the role that *BRCA* mutations play within this group.

Methods *BRCA* diagnostic requests were received for 112 Indian patients representing 50 unrelated high-risk families. A comprehensive *BRCA1/2* screen was performed to screen for the presence of smaller mutations using HRMA, PTT, and Sanger sequencing, and larger rearrangements using MLPA.
Results A total of 9 different pathogenic mutations were detected for the 50 families. Of the disease-causing mutations, 5 were detected within *BRCA1* (*BRCA1* 185delAG, p.Leu22_Glu23LeuValfs; c.191G>A, p.Cys64Tyr; c.1360_1361delAG, p.Ser454Terfs; c.3593T>A, p.Leu1198Ter; c.5365_5366delGCinsA, p.Ala1789_Ile1790LeuTrpfs) with 4 in *BRCA2* (c.5279C>G, p.Ser1760Ter; c.5563C>G, p.Ser1855Ter; c.5563C>G, p.Ser1855Ter; c.8754+1G>A and c.9435_9436delGT, Val3145_Phe3146=fs). Three unrelated families were carriers of the splice-site mutation found within *BRCA2* exon 21. No large rearrangements were detected.
Conclusions All these mutations were specific to the SA Indian population, with very little correlation to those observed for mainland India, confirming the genetic uniqueness of this group. The exclusivity of these mutations resulted in the development of an Indian-specific mutation panel for the SA diagnostic platform, specifically for this population group. The study also confirmed the relative absence of large genomic rearrangements within this group. The additional data contributed to more appropriate diagnostic testing and clinical management of these patients for the future.

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Poster P027

Evaluation of *BRCA* Diagnostic Strategies for a Genetically Diverse Third World Country Such As South Africa

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Objectives Diagnostics for familial breast cancer (BCA) is complicated within a Third-World country such as South Africa (SA). These factors include a lack of financial resources, a weak currency, state-of-the-art technology, and extremely diverse population groups (Black African and SA Indian populations). The aim was to evaluate the current screening strategy with regard to cost effectiveness and efficiencies, in order to financially rationalize *BRCA* testing.
Methods The current strategy was evaluated by comparing the number of requested tests to the number of *BRCA*-positive patients for two distinct phases. Phase 1 entails testing for the 7 most common SA mutations (3 Afrikaner, 3 Ashkenazi Jewish, and 1 Coloured founder mutation) using genotyping assays. If negative, comprehensive screening is performed (Phase 2) using PTT, HRMA, and Sanger sequencing of all coding areas and splice-site boundaries—and, ultimately, MLPA for the larger rearrangements.
Results 1311 Diagnostic *BRCA* requests were received. All these patients were genotyped (Phase 1), of which 14.2% (186 patients) tested positive. Of the remaining patients, 413 requested comprehensive screening. Collectively, PTT, HRMA, and MLPA identified an additional 12.3% (51 patients) carrying pathogenic mutations. Although the clinical impact of the comprehensive screen (Phase 2) was critical to patient care, the financial expenditure was vast.
Conclusions Phase 1 was the most cost- and time-effective, with the highest percentage of pathogenic mutations identified. This phase was, however, based on population-specific research and was not appropriate for all ethnic groups. Although the comprehensive screen identified pathogenic mutations in another 51 patients, the financial expenditures were not justifiable for a Third-World country using this strategy. We propose the implementation of next-generation sequencing not only for *BRCA*, but also screening for the other high-to-moderate familial BCA genes, given that most of the genetically diverse BCA patients (87.6%) were *BRCA*-negative.

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Poster P028

Implementing a Functional Assay to Investigate Predicted Splicing Aberrations in *BRCA1* and *BRCA2*

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Objectives Increasing evidence suggests that many disease genes harbour mutations that may affect pre-mRNA splicing. Mutations affecting pre-mRNA splicing might cause skipping of entire exons, retention of introns, introduction of new splice sites, activation of cryptic splice sites, or interference with isoform balance. We have implemented an mRNA-assay in our laboratory, and *BRCA1* and *BRCA2* variants were selected based on *in silico* splicing predictions.
Methods RNA was isolated from PAXgene Blood RNA tubes, followed by cDNA synthesis and a PCR reaction. The fragments were visualized by capillary electrophoresis, followed by sequencing to characterize the splicing mutations. To establish if the wild-type transcript was produced from both alleles, additional analysis was carried out, if possible. Patient results were compared with results from control samples obtained from the blood bank, all from the same type of tissue. Our mRNA splicing assay was implemented based on the outcome from the ENIGMA (Evidence-Based Network for the Interpretation of Germline Mutant Alleles) Splicing Working Group study.
Results Results were classified as followed: no effect, partial effect, or severe effect on splicing. If no effect or a severe effect on splicing, the result was used as one of several components in the classification of the variant. Here, we present an extract of the results obtained from our assay. *BRCA2* c.68–7T>A showed enhanced exon 3 skipping (partial effect), and *BRCA1* c.4986+1G>T activated a downstream cryptic splice site in the neighbouring intron (severe impact on splicing).
Conclusions Accurate splicing assay requires many key factors, including knowledge of the expected alternative transcripts. Subtle differences in the amounts of isoforms were detected by our method. In addition, different types of splicing aberrations were identified. The results show that our method is sensitive and shows concordance with other publications, and that the method fulfils its purpose.

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Poster P029

Reclassification of *BRCA1/2* Variants of Uncertain Significance: An Ongoing Responsibility Toward Breast Cancer Families

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Objectives In the last two decades, the molecular diagnosis of hereditary breast and ovarian cancer has been based on the identification of germline inactivating mutations within the *BRCA1* and *BRCA2* genes. Unfortunately, *BRCA* variants of uncertain significance (VUS) still occur in 5%–10% of tests. The aim of this study was to reassess the pathogenicity of VUS originally identified in families counselled at our hospital.
Methods VUS were reclassified into class I, II, III, IV, and V following the International Agency for Cancer Research (IARC) recommendations. This was done by means of a thorough review of online database resources such as BIC (http://research.nhgri.nih.gov/bic/), LOVD (http://www.lovd.nl/3.0/home), and KConFab (http://www.kconfab.org/Progress/Mutations.aspx), together with a systematic literature review. The final classification was based on the use of integrated analyses, *in vitro* transcript assays and *in silico* tools (Alamut Interactive biosoftware).
Results From 1995 to 2015, 1200 families were assessed and tested for *BRCA1/2* germline mutations at Sant Pau Hospital. A total of 307 variants were identified in 253 families. Of the 307 VUS identified, 182 were unique; the remaining 125 were detected more than once. Our integrative approach allowed us to reclassify 96/182 variants (53%) originally categorized as VUS (class III). Of the 96, 80 (83%) were predicted to be non-pathogenic or class I, 7 (7%) were reclassified as class II, 5 (5%) as class IV, and 4 (4%) as class V. The other 86 variants remained as VUS (class III) even after our thorough analysis. Of these 86 class III variants, 51 have never been previously described.
Conclusions The continuous reassessment of VUS remains a challenge for clinicians and geneticists alike. The wealth of information provided by NGS studies in the last years facilitated the reclassification of more than half our original VUS, thus allowing us to improve our preventive strategy.

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Poster P031

Unexpected *BRCA2* Mutations in Low-Risk Families: Report of Two Cases

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Mutations in *BRCA1* and *BRCA2* account for approximately 5% of cases of breast cancer and 10%–15% of cases of ovarian cancer. Testing for mutations in these genes has been available in Ontario as a publicly funded health service since 2000. DNA testing is limited to individuals who are expected to have a 10% or higher chance for a mutation based on their personal or family history.

Medcan is a private health clinic with an emphasis on preventive health care, located in Toronto, Ontario. Medcan provides many specialty services, including genetics. Clients can pay for genetic counselling and cancer gene testing, performed through GeneDx Laboratories, if they are concerned but do not qualify for publicly funded testing. During pre-test

counselling, a certified genetic counsellor helps to determine the most appropriate cancer panel based on family history and client needs; many request the Comprehensive Cancer Panel of 29 genes.

We report two cases of unrelated, healthy men who were found to have different pathogenic *BRCA2* variants on the comprehensive panel. One is of Chilean and non-Jewish Italian descent, with a reported family history of gastric and colorectal cancer. The other is of Spanish Moroccan and Sephardic Jewish origin, with a reported family history of colorectal cancer. These cases broaden our understanding of the penetrance of *BRCA2* mutations. In addition, they will affect how we counsel patients regarding their hereditary cancer risks. We suggest that it is time to reconsider the value of testing individuals who do not meet criteria for funded testing, and we speculate on the value of population screening for *BRCA1/2* mutations.

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Poster P034

High Frequency of Germline *BRCA1*/*BRCA2* Mutations in Ovarian Cancer Patients Regardless of Age of Diagnosis

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Objectives Ovarian cancer is strongly associated with inherited risk—much of that risk owing to mutations in the *BRCA1* and *BRCA2* genes. A retrospective review was conducted of ovarian cancer patients referred for genetic evaluation at a single centre to compare the frequency of mutations in this population compared with published data.
Methods Patients were referred for genetic evaluation and testing from 1998 to 2015. Patients with a diagnosis of ovarian cancer (serous or endometrioid) were assessed for mutation status (n = 122), and average ages of diagnosis were calculated for mutation-positive and mutation-negative categories.
Results Overall 23/122 patients (18.9%) were mutation-positive [Ashkenazi Jewish (AJ) 10/34 (29.4%); non-Jewish 13/87 (14.9%)]. Average age of ovarian cancer diagnosis for mutation-negative compared with mutation-positive patients was 56.09 years and 52.13 years respectively (*BRCA1*, 50.67 years; *BRCA2*, 53.73 years).
Conclusions Published data suggest that the overall frequency of *BRCA1/2* mutations in women with ovarian cancer is approximately 10% (29%–41% in AJ women). Mutation frequency in our population is higher than published frequencies. Recent changes in genetic testing guidelines have led, at this centre, to a genetics referral for all ovarian cancer patients, many of whom had not been previously referred because of a later age of diagnosis or a lack of family history of breast/ovarian cancer, or both. It has been shown that women with *BRCA1/2* mutations have better response to platinum therapy; therefore, our population may be enriched with long-term survivors of ovarian cancer who are more likely to be *BRCA1/2*–positive. Our data would also suggest that age of diagnosis should not be a factor that restricts testing for *BRCA1/2* mutations, and testing should thus be offered to all women with a personal history of ovarian cancer at any age.

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CLINICAL ISSUES FOR MANAGEMENT

Poster P037

Impact of an Embedded Genetic Counsellor on Breast Cancer Treatment

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Objectives A small but significant percentage of breast cancers (5%–10%) are thought to be hereditary in nature. Identification of women who carry germline mutations conferring increased risk is increasingly important in surgical decision-making. We hypothesized that embedding a genetic counsellor within our breast practice would improve identification of high-risk individuals, timeliness, and appropriateness of care. The aim of this study is to compare cancer care between 2012 and 2014, prior to embedding a genetic counsellor in the Breast Center and following the intervention.
Methods A retrospective review of patients diagnosed with breast cancer in 2012 (n = 787) and 2014 (n = 764) was performed to assess patterns of Medical Genetics referral, compliance with referral, findings of genetic testing and impact on treatment.
Results There was a significant increase between 2012 and 2014 in the likelihood of being referred to genetics (OR: 1.49; CI: 1.15 to 1.94; $p = 0.003$), the likelihood that the patient followed through with counselling was significantly higher (OR: 1.66; CI: 1.02 to 2.71; $p = 0.042$), and the wait time was significantly less (OR: 0.26; CI: 0.18 to 0.37; $p < 0.001$). Patients were more likely to have genetic test results prior to surgery (OR: 1.69; CI: 1.12 to 2.55; $p = 0.013$). Although the number of genetic mutations identified was in the expected range over both time periods (9% of those tested in 2012 vs. 6.6% of those tested in 2014), timeliness of testing may have contributed to reduced time to treatment between breast cancer patients treated in 2014 versus 2012 (means ratio: 0.69; CI: 0.55 to 0.88; $p = 0.003$).
Conclusions Awareness of the implications of germline genetic mutations is critical in the care of breast cancer patients. Having a genetic counsellor on site in a busy surgical breast clinic allows for ease and timeliness in counselling and testing, and may have influenced time to treatment in our institution.

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Poster P038

Cross-sectional Study to Identify Japanese HBOC Kindred at the Maximum Risk Categories Suitable for Expedited Genetic Screening

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Objectives In Japan, there is no reimbursement for *BRCA1/2* gene testing by a national health care insurance program. Supported by the foundation for promotion of cancer research in Japan, we launched a program in which 37% of the total cost—that is, CA$770.00—is paid from the research grant to expedite the patients to undergo *BRCA1/2* gene testing to assess the efficacy of the tentative risk categories.
Methods The expedited criteria are similar to those available in Canada. At least 1 Japanese case of cancer: 1) invasive breast cancer < 35 years of age, 2) invasive serous ovarian cancer at any age, and 3) bilateral breast cancer with the first case < 50 years, and 4) male breast cancer. At least 2 Japanese cases of cancer on the same side of family: invasive breast cancer < 50 years, with a first-, second-degree relative or cousin having 5) ovarian cancer, 6) breast cancer < 35 years, or 7) bilateral breast cancer.
Results From Sep 2011 through Dec 2014, a total of 81 cases were accrued to the study, of which 29 cases (36%) had pathogenic mutations, comprising 16 cases (20%) for *BRCA1* and 13 cases (16%) for *BRCA2*. Prevalence for *BRCA1/2* mutations were as follows: 1) breast cancer < 35 years, 8/35 (22.9%); 2) invasive serous ovarian cancer, 6/10 (60%); 3) bilateral breast cancer, 10/23 (43%); 4) male breast cancer, 2/4 (50%); 5) breast cancer < 50 years with a family history of ovarian cancer, 8/18 (44%); 6) breast cancer < 50 years with a family history of breast cancer < 35 years, 5/10 (50%); 7) breast cancer < 50 years with a family history of bilateral breast cancer, 12/23 (52%).
Conclusions Our risk categories resulted in a considerably high prevalence of *BRCA1/2* mutations that would be applicable for expedited screening program.

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Poster P039

Elevated Bone Turnover Marker Levels After Risk-Reducing Salpingo-oophorectomy in Women at Increased Risk for Breast and Ovarian Cancer

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Objectives Risk-reducing salpingo-oophorectomy (RRSO) reduces ovarian cancer risk in *BRCA1/2* mutation carriers. Premenopausal RRSO is hypothesized to increase fracture risk more than natural menopause. Elevated levels of bone turnover marker (BTM) might predict fracture risk. We investigated BTM levels after RRSO and aimed to identify clinical characteristics associated with elevated BTM levels.
Methods Levels of osteocalcin (OC), procollagen type 1 N-terminal peptide (PINP), and serum C-telopeptide of type I collagen (SCTX) were measured in 210 women ≥ 2 years after RRSO at age ≤ 52 years. Levels of BTM were standardized by calculating Z-scores based on age-matched reference values. Clinical characteristics were assessed by questionnaire and related to BTM Z-scores with regression analyses.
Results Levels of BTM after RRSO were higher than age-matched reference values, [median Z-score OC: 0.11 (interquartile range: –0.65 to 1.34), $p = 0.003$; PINP: 0.84 (–0.25 to 2.13), $p < 0.001$; SCTX: 0.53 (–0.33 to 1.45), $p < 0.001$]. After excluding women with recent fractures or BTM-interfering medication,

Z-scores were 0.34, 1.14, and 0.88 respectively. Z-Scores for OC and PINP were inversely related to age at RRSO. No correlation was found between BTM Z-score and fracture incidence or breast cancer–related factors.

Conclusions After a median time of 5 years after RRSO at premenopausal age, BTM levels were higher than age-matched reference values. Because elevated BTM levels possibly predict higher fracture risk, prospective studies are required to evaluate the long-term clinical implications of elevated BTM levels after RRSO.

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Poster P041

Squamous Neoplasia Arising from Chronic Exposure to Doxorubicin: A Result of *BRCA* Haploinsufficiency?

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At the 2014 Montreal *BRCA* symposium, Pathania and co-workers from David Livingston's laboratory presented evidence for defects of stalled replication fork repair in *BRCA* haploinsufficient cells. Could squamous neoplasms arise from chronic exposure to doxorubicin and its metabolites? These antitumour DNA-intercalating antibiotics are known to be mutagenic in bacterial and mammalian tumour cell assays and carcinogenic in rats. Normal tissues most frequently affected by pegylated liposomal doxorubicin (PLD) include oral mucosa and skin—particularly the palmar, plantar, and intertriginous areas. Partial protection by regional cooling has been attributed to diminishing drug exposure occurring shortly after PLD administration.

Growing evidence, mostly from the gynecologic literature, suggests that prolonged treatment with PLD leads to squamous neoplasia (high grade dysplasia and carcinoma) of oral cavity, esophagus, and skin (other than sun-exposed areas). These observations were mostly based on women being treated with PLD for ovarian cancer recurrence and lacking exposure to the usual factors associated with squamous neoplasia—most of them being carriers of deleterious *BRCA* mutations. These have not been reported during breast cancer treatment, perhaps reflecting the shorter exposure to doxorubicin or contributions to enhanced susceptibility by other drugs.

Clinical implications of these findings remain to be defined, other than raising awareness and pursuing symptomatic leads before and after treatment. In ovarian cancer patients, PLD has contributed to prolongation of progression-free survival (PFS) and overall survival, with a suggestion that maintenance therapy further prolongs PFS in women with recurrent disease. Clinical and laboratory studies by our group are underway to quantify and characterize DNA damage in the oral mucosal cells of women receiving PLD therapy, using control groups consisting of *BRCA*-mutated and non-mutated women with/without exposure to prior non-doxorubicin therapy. We are concurrently studying the DNA damage and repair response to doxorubicin in oral mucosal cells depleted of *BRCA in vitro*.

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Poster P042

The Ontario Breast Screening High-Risk Program: Which "High-Risk" Women Benefit?

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The Ontario Breast Screening Program–High Risk (OBSP-HR) is a province-wide organized screening program managed by Cancer Care Ontario, providing high-quality breast cancer (BCA) screening (annual MRI and mammogram) for women aged 30–70 years. Genetic centres from 14 local health integration networks (LHINS) play a critical role in the OBSP-HR by providing genetic counselling, genetic risk assessment (GRA), and genetic testing to women who may be at high risk for BCA. The GRA determines eligibility for breast screening through OBSP-HR.

The Eastern Ontario Regional Genetics Program at CHEO is part of Champlain LHIN. Since the OBSP-HR began in July 2011, 1946 screens have been performed; 979 were first-time MRIS, and 967 were subsequent MRIS. In the first 50 months of the OBSP-HR, 25 women were diagnosed with BCA: 11 had ductal carcinoma *in situ* (DCIS), 12 had invasive ductal carcinoma, 1 had invasive lobular carcinoma, and 1 had both DCIS and invasive cancer. Of these cancers, MRI alone detected 72% (n = 18). Only 8% (n = 2) were detected by mammogram alone. The final 20% (n = 5) were detected on both screening modalities.

Of these women, 36% (n = 9) qualified for the OBSP-HR because they are mutation carriers (*BRCA1*, *BRCA2*, or *PALB2*) or a first-degree relative of a mutation carrier (group A); 52% (n = 13) had a ≥ 25% lifetime risk of BCA as assessed by a genetics clinic using either the IBIS or BOADICEA risk model (group B); and 12% (n = 3) had received chest radiation before age 30 (group C).

Conclusions The initial 4-year data of the Champlain LHIN demonstrate that the benefit of MRI screening in "high-risk" women is clearly not limited to gene mutation carriers alone.

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Poster P043

Breast Cancer Outcomes Following Predictive *BRCA* Testing in Northern Ireland

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Objectives Since 1995, *BRCA* testing has identified 445 women in Northern Ireland who carry a pathogenic *BRCA1/2* mutation, without breast cancer (BCA) at testing. This study examined outcomes with reference to management, BCA risk, and incidence following positive predictive testing.

Methods Patients were identified from the regional genetics database. Electronic clinical records were used to obtain management and outcome details. Median follow-up was to BCA diagnosis, risk-reducing mastectomy (RRM), death, or last follow-up.

Results 169 women had a *BRCA1* mutation, and 276 *BRCA2*.

- *BRCA1* cohort: Median follow-up post-testing was 3 years. 56 Women (33%) had RRM, and 12 are awaiting RRM (total 68, 40%) at a median age of 36 years. 12 Women (7%) developed BCA, at a median of 2 years following testing. 4 Women were diagnosed with BCAs incidentally at RRM. 7 Patients had bilateral mastectomies following a cancer diagnosis. 1 Woman developed BCA following RRM (1.7%). Three deaths were reported: 1 breast cancer (1.7%), 1 ovarian cancer (1.7%), and 1 with no recorded breast/ovarian cancer diagnosis.
- *BRCA2* cohort: Median follow-up post-testing was 6 years. RRM was carried out in 75 women (27%), with 20 awaiting RRM (total 95, 35%); median age: 39 years. 16 Women developed BCA (5.8%), at a median of 5 years from testing. 6 Women were diagnosed with cancer incidentally at RRM; 9 women had bilateral mastectomy following diagnosis, and 1 developed BCA following RRM (1.3%). Five deaths were reported: 1 BCA, 1 ovarian cancer, and 3 with no recorded breast/ovarian cancer diagnosis.

Conclusions The uptake of RRM following predictive *BRCA* testing in Northern Ireland is comparable with that reported elsewhere. The incidence of BCA following RRM is low (<2%) in our cohort, with low breast and ovarian cancer–specific mortality following positive predictive testing.

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Poster P044

The First Experience of RRM for an Unaffected *BRCA* Mutation Carrier in Japan and Its Background of HBOC Management in Our Hospital

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Women with *BRCA1/2* mutations have a high risk of breast and ovarian cancer and may opt for a risk-reducing mastectomy (RRM) and a risk-reducing salpingo-oophorectomy (RRSO). In Japan, risk-reducing surgery as well as genetic counselling or genetic test is outside the health insurance, and so we perform risk-reducing surgery for *BRCA* mutation carriers in the limited hospital facilities after the Ethics Committee granted permission. The safety and feasibility of nipple-sparing mastectomy (NSM) or skin-sparing mastectomy (SSM) in *BRCA* mutation carriers is debatable, and a consensus of which procedure should be performed has not yet been reached.

Since January 2013, we started genetic counselling for patients suspected of HBOC and have achieved 128 cases of counselling and 67 cases of genetic test for 3 years. Among them, 21 cases are *BRCA* mutation–positive (*BRCA1*: 10; *BRCA2*: 9; VUS: 2). We ordered quick test for 10 cases and single-site test for 3 cases. We have performed 3 cases of RRSO and 5 cases of RRM. We now report a 38-year-old Japanese woman who was diagnosed as a *BRCA2* mutation carrier. She underwent prophylactic bilateral SSM with excision of the nipple and preservation of the areola skin. It is unclear whether a bilateral RRM leads to better survival compared with intensive surveillance. The oncologic risk associated with the presence of remnant breast glandular tissue after SSM or NSM has been obscure.

We report the first case of RRM for a Japanese *BRCA* mutation carrier and provide a literature review on risk management for *BRCA* mutation carriers, with a focus on the concepts and procedures of RRM.

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Poster P045

Social and Economic Impact of Risk-Reducing Bilateral Salpingo-oophorectomy in *BRCA* Carriers

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Objective To compare quality-of-life indexes before and after risk-reducing bilateral salpingo-oophorectomy (RRSO) for *BRCA* mutation carriers in a longitudinal cohort study.
Methods An IRB-approved prospective longitudinal cohort study was conducted of *BRCA* mutation carriers. Study participants completed questionnaires at study entry and then yearly thereafter. Data were collected on demographics, surgeries, personal cancer diagnoses, family cancer history, and quality of life (QOL) indexes. Patients who underwent RRSO between the entry questionnaire and the follow-up questionnaire were assessed for QOL using the Ferrans and Powers Quality of Life index assessing health and functioning, psychological/spiritual, social and economic, and family domains.
Results In 33 individuals who met the inclusion criteria, overall QOL did not significantly differ after BSO for the entire cohort. However, there were significant differences in the social and economic index suggesting improved QOL in this domain in those patients with a prior history of breast cancer or melanoma ($p = 0.0360$) and in those who completed their post-assessment within 1 year of their RRSO ($p = 0.0499$).
Conclusions A RRSO was not associated with a change in the overall QOL index in this prospectively collected sample. These data may be used to further guide providers as they counsel patients facing decisions regarding RRBSO. Areas of improvement were noted in social and economic QOL, suggesting that there may be areas for further study to continue to improve patient outcomes.

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Poster P046

Population-based Screening of At-Risk Women for Hereditary Breast and Colorectal Cancer in Brazil Using a Three-Question Questionnaire

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Objectives This study aims to identify and characterize individuals at risk for hereditary cancer predisposition syndromes (HCPSS) through a 3-question questionnaire about personal/familial cancer history (QRP).
Methods For the application of QRP was used prevention network in Barretos Cancer Hospital (fixed and mobile units). The QRP was applied to a population-based sample of 20,000 women.
Results Among those 20,000 women, 3121 (15.6%) had at least 1 affirmative answer on the QRP. 17.7% Women answered "yes" to the question of personal history of cancer before the age of 50; 46%, 21%, and 14.6% answered at least 1 "yes" for family history of breast, bowel, and ovarian cancers respectively, when considering an age at diagnosis less than 50 years. The third question of the questionnaire (Q3) dealt with the presence of 3 or more relatives with cancer before the age of 50, and 25.6% answered affirmatively. All women who responded affirmatively to at least 1 of the 3 questions QRP were invited to answer a secondary screening questionnaire (QRS), which contains epidemiologic data, and pedigree draw. For their application of QRS, we used three different approaches: in-person, by telephone, or by letter. 220 Women completed the QRS personally; 1408 by telephone; and 310 by letter, giving a total of 1938 individuals included in this phase. An analysis of these cases showed that 465 pedigrees (24%) had at least 1 clinical criteria for HCPSS. So, with a sensitivity and specificity of 94.4% and 74.3%, respectively, the PSQ was efficient at identifying individuals/families at risk for hereditary cancer.
Conclusions We created and validated an easy, simple, and efficient tool for population-based identification of families who are at risk for HCPS, which allows a better knowledge of these at-risk population as well as include them in cancer prevention/screening programs.

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Poster P047

Factors That May Influence Decisions on Prophylactic Breast Surgery Following Ovarian Cancer in a Multiethnic Cohort

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Objectives 1) To assess the competing risk of *BRCA1*/*BRCA2*–related ovarian cancer recurrence with or without a history of unilateral breast cancer versus development of subsequent breast cancer or other cancers, and 2) to describe factors determining the use of prophylactic breast surgery (PBS) among ethnically and geographically diverse patient population from New York's Bellevue and NYU Tisch Hospital and Tel Aviv.
Methods NYU IRB-approved waiver was obtained for retrospective analysis of subjects attending the Lynne Cohen Foundation–supported clinic included in a high-risk breast/ovarian cancer registry or within NYU medical/gynecologic oncology practices from 1998 to present (median follow-up in excess of 4 years). A parallel retrospective review was carried out at Tel Aviv Sourasky Medical Center. Data from women with confirmed *BRCA* mutations included pathology diagnosis and stage of ovarian cancer, prior or concurrent breast pathology (or both), *BRCA1* or *BRCA2* mutation, first-line chemotherapy treatment, and subsequent events [recurrence, survival status (alive, alive with recurrence, death from ovarian or other cancers), and PBS; objective 1]. For objective 2, the focus is to describe factors leading to PBS vis-à-vis surveillance by geography and ethnicity, along with details on type of breast surgery and pathology (if any). Risks for breast cancer and death calculated as Kaplan–Meier survival at 2, 5, and 10 years versus controls (*BRCA* mutation carrier without prior cancer or only a prior unilateral breast cancer) will be assessed.
Results Under review are 60 women with ovarian cancer diagnosis within the NY cohort and 93 in the Tel Aviv. Surveillance but not PBS is the standard follow-up in Tel Aviv; in NY, PBS has been applied in selected subjects.
Conclusions Our study complements published results from the Rotterdam Family Cancer Clinic[1] that found that *BRCA*-associated ovarian cancer had lower risks of breast cancer, while initial mortality rates from ovarian cancer were higher than risks of subsequent breast cancer. Additional data and counselling on PBS after ovarian cancer are needed.

1 Vencken PM, Kriege M, Hooning M, *et al.* The risk of primary and contralateral breast cancer after ovarian cancer in *BRCA1*/*BRCA2* mutation carriers: implications for counseling. *Cancer* 2013;119:955–62.

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Poster P048

A Novel Multidisciplinary Model of Care for Families with *BRCA1* and *BRCA2* Mutations: A Ten-Year Experience

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Objectives The Guy's BRCA Family Service (BRCAFS) was established to develop a streamlined model of multidisciplinary care and management of families with mutations in *BRCA1* and *BRCA2*. The primary aims were: 1) Offer every *BRCA1/2* carrier in our catchment a clinical review. 2) Devise an individually tailored counselling and risk-management strategy. 3) Address any concerns or worries individuals and their families might have. 4) Update *BRCA1/2* carriers on the newest clinical developments by discussing appropriate surveillance and risk-reducing options. 5) Ensure that the chosen surveillance and risk-reducing options were implemented. 6) Offer *BRCA1/2* carriers participation in research trials. 7) Offer clinical and peer-led psychosocial support.
Methods A successful pilot led to the establishment of 5 core elements of the BRCAFS: 1) A multidisciplinary *BRCA* clinic, 2) patient register, 3) patient update days, 4) newsletter, and 5) facilitated peer-support groups for patients.

All patients with a pathogenic *BRCA1* and *BRCA2* mutation identified through our service are referred to the BRCAFS. In one clinic visit, patients will see appropriate clinicians, including clinical geneticists, genetic counsellors, oncologist, breast surgeon, plastic surgeon, gynecologic oncology surgeon, research nurse, clinical psychologist, and breast care nurse. A multidisciplinary meeting during the clinic ensures patients are given individually tailored advice.
Results The BRCAFS has now been running successfully for 10 years, with more than 1500 carriers on the register. Patient satisfaction surveys reflect the utility and success of this model, as do the uptake rates of risk-reducing surgery.
Conclusions This model allows timely, evidence-based clinical care and decision-making for families with *BRCA* mutations. It promotes risk management adherence and psychosocial adjustment. It is also cost-effective and a good use of clinical time.

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Poster P049

Demographic, Tumour, and Recurrence-Risk Variation Comparison of *BRCA1*- and *BRCA2*-Positive Women with Breast Cancer

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Objectives We examined patient characteristics, tumour factors, and risk of recurrences in women with breast cancer by *BRCA1/2* status.
Methods We assembled a retrospective cohort of 307 women with a pathogenic/likely pathogenic *BRCA* variant (PV/LPV) that had been diagnosed with breast cancer from 1990 to 2012, and followed them through December 2013. Subjects were identified from Kaiser Permanente Southern California, a large managed-care organization.
Results Of the 307 women, 163 (53%) had a PV/LPV in *BRCA1,* 142 (46%) in *BRCA2*, and 2 (0.7%) in both. A greater fraction of women with mutations in *BRCA1* than in *BRCA2* were diagnosed with stage II–IV disease, invasive ductal carcinoma, grade 3, and triple-negative breast cancer. Patients with *BRCA1* mutations were also significantly more likely than those with *BRCA2* to be Hispanic (33.1% vs. 26.1% respectively) and black (8.9% vs. 6.0%). *BRCA1* carriers were also more likely than *BRCA2* carriers to be smokers (34.4% vs. 21.4%), obese (38.7% vs. 26.4%), and to have maternal (55% vs. 46%) and paternal family history (34% vs. 27%) of breast cancer ($p < 0.05$). Despite the long study period (24 years maximum), the median length of follow-up was roughly 5 years in both groups. Of the 163 women with *BRCA1* mutations, 27 (17%) developed a second primary cancer (mainly breast cancer) versus 23 (18%) of the 142 women with *BRCA2*. Recurrence was higher in those with *BRCA1* (21%) than with *BRCA2* mutations (17%); however, distant metastases were more common in those with *BRCA2* (63%) than with *BRCA1* mutations (42%).
Conclusions It is unclear why women with *BRCA2* mutations had more distant recurrences. Our next steps are to estimate person-year rates of contralateral breast cancer and recurrences, and to conduct multivariable Cox models, to determine if women with *BRCA2* mutations truly have an increased risk of distant metastases.

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Poster P050

Study of French Canadian *BRCA1/2*–Mutated Ovarian Cancer Patients with Primary Cytoreduction for Epithelial Ovarian Cancer

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Background and Objectives Although controversial, the combination of platinum-based chemotherapy in a neoadjuvant or in an adjuvant setting in women with optimally resected (<1 cm) stage III–IV epithelial ovarian cancer (EOC) demonstrated similar survival[1]. The aim of this study was to compare whether French Canadian women with *BRCA1/2*–mutated ovarian cancer (FC-BMOC) undergoing neoadjuvant chemotherapy followed by optimal surgical resection derived the same benefit as with primary surgical resection and adjuvant chemotherapy.
Methods This retrospective study was approved by the ethics board of Centre Hospitalier de l'Université de Montréal. A total of 111 FC-BMOC patients (*BRCA1,* $n = 57$; *BRCA2,* $n = 54$) were enrolled and underwent primary versus interval optimal debulking surgery (<1 cm). Genotype, histology, surgical outcome, overall survival (OS), progression-free survival, time to second progression, treatment-free interval, platinum-free interval, response to platinum rechallenge, timing for development of resistance to platinum, prior or late second cancer, and distant metastasis pattern were evaluated in both settings.
Results The characteristics of the patients and their disease, treatment modalities, and disease outcome were analyzed using uni- and multivariate Cox regression models. After adjusting for stage, completeness of cytoreduction (HR: 2.802; 95% CI: 1.508 to 4.969; $p < 0.001$) and resistance to platinum were both observed to significantly alter the prognosis, as did the choice of initial treatment modality (HR: 0.290; 95% CI: 0.156 to 0.541; $p < 0.001$). Lymphadenectomy (HR: 1.003; 95% CI: 0.587 to 1.17; $p = 0.991$), positive nodes (HR: 1.624; 95% CI: 0.799 to 3.399; $p = 0.181$), and prior hysterectomy had no impact on OS.
Conclusions We hope to promote universal genetic screening to optimize preventive and therapeutic clinical strategies for FC-BMOC. Timing, route, and sequence of treatments are likely to differ in the case of FC-BMOC.

1 Vergote I, Tropé CG, Amant F, *et al.* Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010;363:943–53.

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Poster P051

Relationship between Genotype and Clinical Phenotype in French Canadian *BRCA1/2*–Mutated Women with Ovarian Cancer

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Background and Objectives The precise relationship between *BRCA1/2* mutation genotype and clinical phenotype will be crucial to delineate optimal therapeutic choices in the future for patients with *BRCA1/2*–mutated ovarian cancer (BMOC). Often, we refer to the "*BRCA*ness" features as a high rate of response to platinum, long treatment-free intervals, and improved overall survival (OS)[1]. The aim of this study was to describe characteristics of FC-BMOC women.
Methods This Centre de recherche du Centre Hospitalier de l'Université de Montréal ethics board–approved study delineated the clinicopathologic features of FC-BMOC. With a sample size of 111 women with 1 of 19 French-Canadian common founders mutations and other specific mutations, we correlated the demographics, timing and sequence of therapy, OS, progression-free survival, and toxicities such as allergy or thromboembolic events to the genotype of FC-BMOC women.
Results The relationship between genotype and demographics, disease characteristics, past or concurrent gynecologic and oncologic influences, disease outcome analyses, and toxicities will be presented. We observed more advanced stage in *BRCA2* patients, very close to significance ($p = 0.062$). However, OS for stages I, II, III, and IV seems to favour *BRCA2* patients. Age ($p = 0.047$), the presence of ascites (HR: 0.461; 95% CI: 0.234 to 0.908; $p = 0.025$), and stage ($p = 0.000$) seemed to influence OS; lymph node status (HR: 1.624; 95% CI: 0.799 to 3.399; $p = 0.181$) did not. The stage I 10-year survival for both *BRCA1* and *BRCA2* was 50%, highlighting the preference toward prophylactic surgery.
Conclusions We hope that these phenotypes–genotype relations will promote hereditary cancer awareness and genetic screening to offer adequate preventive and therapeutic strategies for FC-BMOC individuals and their extended family.

1 Tan DS, Kaye SB. Chemotherapy for patients with *BRCA1* and *BRCA2*-mutated ovarian cancer: same or different? *Am Soc Clin Oncol Educ Book* 2015:114–21.

Affiliations: *Centre de recherche du CHUM, †Institut du cancer de Montréal, ‡Université de Montréal, §Centre hospitalier de l'Université de Montréal (CHUM), and ‖McGill University, Montreal, QC.

Poster P052

The Utility of a Patient Register to Provide Long-Term Follow-Up for HBOC Patients

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Background The Cancer Genetics Unit at the Royal Marsden NHS Foundation Trust (RM) London, U.K., recently established a patient register to provide long-term follow-up for *BRCA1/2* positive patients: Hereditary Breast and Ovarian Cancer (HBOC). The main aim of the Register is to monitor cancer surveillance, arrange timely referrals for screening and risk-reducing surgery, update the pedigree with new cancer diagnoses, monitor cascade testing, and offer follow-up appointments on an as-needed basis. Currently, 1233 HBOC patients are on the Register. Patients are automatically entered on the Register at the point of genetic diagnosis and are sent a leaflet explaining the purpose of the Register and the possibility to opt out of follow-up. The HBOC patient notes are reviewed at age 30, 40, and 50 to offer intervention and follow-up.
Purpose To review the use of the Register in previous 12 months and to assess impact on long-term follow-up for HBOC patients
Methods Departmental projects and monthly register activity was reviewed for 2015. Patient notes and attendance at clinic appointments were retrospectively reviewed from Register lists.
Results In 2015, 293 patient records were reviewed, and contact letters were sent regarding genetic follow-up and cancer surveillance. 346 Patients received an audit questionnaire regarding the national higher-risk breast screening program; all patients diagnosed within the previous 24 months were invited to a RM HBOC patient conference, the Register was used to audit uptake of risk-reducing breast and ovarian surgery. The register data were also used to check eligibility of breast and ovarian cancer patients for *BRCA*-related treatment trials.
Conclusions The Register provides a cost-effective mechanism for following HBOC patients in the long term, ensuring that they have opportunities to review risk-management options, and following up with cascade testing within families. Patients on the Register also benefit from regular updates regarding changes to management guidelines and opportunities to take part in relevant research.

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Poster P053

Coordinated Care Spanning Multiple Tumour Types

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The Center for *BRCA* Research at the University of California–San Francisco is a newly established program with comprehensive mutation-specific activities in 3 primary areas: education and outreach, basic science, and integrated clinical care delivered through the new Hereditary Cancer Clinic (HCC). This program will increase access to mutation screening, genetic counselling, integrated care spanning multiple tumour disciplines, and increase awareness in unaffected family members with known or unknown mutation status. Patients and unaffected mutation carriers will receive care from a group of centralized providers in a multidisciplinary clinic that will help patients to navigate the many concerns associated with a *BRCA* mutation, including *BRCA*-focused tumour surveillance and evaluations for risk-reducing surgeries.

Patients, unaffected mutation carriers, and family members will be invited to participate in a prospective large-scale cohort study at the HCC. Upon consent, data will be collected using questionnaires and medical record review, and will include family history, reproductive history, lifestyle factors, history of cancer, and history of risk-reducing surgeries. Blood, saliva, and tumour specimens will be collected where appropriate. Research findings will aid our interdisciplinary steering committee in further developing clinical guidelines for prevention and management, as well as identifying genetic and other factors that modify risk for *BRCA*-related cancers in families.

The Center will provide education and community outreach programs for clinicians, patients, and their families to allow real-time communications for rapidly changing screening and treatment recommendations. The Center has initiated a dedicated effort to engage the larger community to increase acceptance of familial testing and acceptance of clinical recommendations for care and surveillance for families.

The Center will unite UCSF's well-established platform of basic science and population-based research with clinical practices aimed at improving screening methods, preventive therapies, patient outcomes, and overall awareness and active participation in *BRCA*-related management.

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Poster P054

Instrumentation dédiée à l'imagerie peropératoire des trompes de Fallope

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Le retrait chirurgical des ovaires et des trompes de Fallope fait partie de la prise en charge de patientes présentant un risque héréditaire de cancer de l'ovaire et/ou présentant des masses suspectes. Dans les deux cas, une analyse pathologique approfondie des organes doit être réalisée.

Objectifs Un instrument peropératoire est développé afin de guider l'analyse pathologique de la face interne des trompes de Fallope.

Méthodes employées Nous avons développé un appareil de tomographie par cohérence optique (OCT) dédié à l'imagerie des trompes de Fallope. L'OCT est une technique d'imagerie laser non invasive qui permet d'acquérir une information morphologique dans les tissus avec une résolution d'environ 12 µm. Afin d'en évaluer le potentiel, des spécimens d'ovaires humains pathologiques en paraffine sont imagées à l'OCT et comparées avec l'histologie. De plus, une sonde miniaturisée est construite et assemblée pour imager l'intérieur des trompes préalablement retirées chirurgicalement. Les images acquises permettent une reconstruction virtuelle de la trompe de Fallope et l'identification des zones d'intérêt. Les résultats sont validés avec l'histopathologie.

Résultats Nous présentons d'abord les résultats de l'analyse des spécimens en paraffine. Une série de 52 blocs de la banque de tissus (Centre hospitalier de l'université de Montréal–CHUM) comprenant 5 catégories de pathologies sont analysées qualitativement et quantitativement à l'OCT et à l'histologie. La nouvelle sonde dédiée à l'imagerie interne des trompes est détaillée. Nous présenterons par la suite les résultats préliminaires de l'étude clinique en cours (CHUM Notre-Dame, protocole 14.159).

Conclusions L'imagerie OCT permet de générer des volumes de données correspondant à la morphologie de la surface interne de la trompe de Fallope. Elle permet une analyse rapide de l'ensemble de l'organe. L'OCT, éventuellement couplée à une analyse spectroscopique ou en fluorescence, est une technique prometteuse pour cibler les zones suspectes dans les trompes de Fallope.

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Poster P055

Risk of *BRCA*/HBOC Mutations via Family History Assessment Among Women Who Are Screened in Trinidad and Tobago

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Background/Objectives According to the PAHO 2012 Breast Cancer Statistics, Caribbean country Trinidad and Tobago (TT) leads, with the 2nd highest mortality rate in the Caribbean. Also, many cases in TT appear to occur at a young age; during 1998–2007, 36% of breast cancer diagnoses were under the age of 50. Therefore, our objective was to estimate the percentage of the population who would meet criteria for further *BRCA*/HBOC (hereditary breast and ovarian cancer syndrome) screening.

Methods We conducted chart reviews from all women at the National Cancer Society of TT from 2010 to 2013, looking for the presence or absence of the U.S. National Institutes of Health/National Cancer Institute (NIH/NCI) 2013 criteria for increased *BRCA* mutation risk.

Results Total sample: 1807 women. The distributions of NIH/NCI criteria follow (sample stratified for past diagnosis of breast cancer). 1) No previous breast cancer diagnosis (n = 367): 0, 262 (71%); 1, 87 (24%); >2, 18 (5%). 2) Previous breast cancer diagnosis (n = 27): 0, 9 (33%); 1, 10 (37%); >2, 8 (30%). 3) Highest criteria met: For both categories, family history–breast cancer diagnosed < 50 years.

Conclusions Based on these preliminary results, a high portion of women show genealogy patterns that suggest an increased risk of having *BRCA*/HBOC mutations. According to the U.S. Preventive Services Task Force, these women should consider further HBOC testing and counselling. Should this sample reflect the risk of the general female population over 15 years in TT, more than 23,482 women could currently be at risk. Therefore, it is important to assess whether policies should be in place to provide genetic testing and counselling for HBOC at the population level. Current ongoing studies in this population include genetic testing among women with breast cancer to investigate the prevalence and spectrum of the main genes associated with HBOC.

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Poster P056

Cardiovascular Risk After Risk-Reducing Salpingo-oophorectomy in *BRCA1*/2 Mutation Carriers: CARSOBRA Study

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Rationale Early menopause leads to an increased cardiovascular risk that might be more pronounced in women with artificial menopause than with natural menopause. Cardiovascular risk assessment based on traditional risk factors often underestimates the actual risk in middle-aged women. Measures of subclinical atherosclerosis such as increased common carotid artery intima media thickness (CCA-IMT) and pulse wave velocity (PWV) predict future cardiovascular events in this group. *BRCA1*/2 mutation carriers are generally exposed to an earlier surgical menopause, because they are strongly recommended to undergo risk-reducing salpingo-oophorectomy (RRSO) around the age of 40 to reduce their elevated risk of ovarian cancer. Until now, cardiovascular risk in *BRCA1*/2 mutation carriers after RRSO has not been studied.

Objective Is RRSO at age ≤ 45 years in *BRCA1*/2 mutation carriers a risk factor for the development of subclinical atherosclerosis, independent of traditional cardiovascular risk factors?

Methods At Radboud University Medical Center in Nijmegen, Netherlands, 268 *BRCA1*/2 mutation carriers who were known to be at least 5 years post-RRSO and who had RRSO at age ≤ 45 were invited to participate. Main study endpoints are CCA-IMT and PWV. All women filled out a questionnaire on demographics, medical and obstetrical history, family history, lifestyle, menopausal symptoms, and general well-being. They also underwent a single cardiovascular screening program consisting of measures of length, height, and waist and hip circumferences; blood pressure and fasting blood sampling (lipids, insulin, glucose); and assessment of CCA-IMT and PWV.

Results Data collection for the included 171 *BRCA1*/2 mutation carriers was performed between June and November 2015. We will present the mature data that will be available for May 2016.

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Poster P057

How Empowered Do Carriers of Hereditary Cancer Gene Mutations Participating in an Annual Review Program Feel About Managing Their Cancer Risk?

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

Background Two Australian Familial Cancer Centres (FCCS), Peter MacCallum Cancer Centre (PMCC) and Monash Health (MH), offer a long-term annual review program (ARP) for carriers of hereditary gene mutations. This program can identity patients with unmet information or support needs related to managing their cancer risk and with communicating genetic risk information to at-risk relatives. The Genetic Counselling Outcome Scale (GCOS) is a validated patient-reported outcome measure. It captures the construct of empowerment, which aligns with the ARP aims to facilitate patient adjustment and enhance confidence in the self-management of cancer risk. Using the GCOS, our aim was to assess mutation carriers' levels of empowerment during different stages of participation in the ARP.
Methods 1304 Patients from the PMCC and MH FCCS have been invited to complete 3 GCOS questionnaires in addition to their clinical ARP questionnaire over a period of 5 years (June 2013–June 2018).
Data Analysis Preliminary quantitative analysis using multiple linear regression was undertaken on data collected from June 2013 to July 2014 to predict GCOS total scores.
Results Data from the first 599 patients (45%), who completed an initial GCOS (at a median interval of 7 years post testing), have been analyzed to date. Lower age ($p < 0.001$) and higher education level ($p > 0.001$) were both significantly associated with higher GCOS score (that is, greater empowerment). We plan to have updated data by May 2016.
Conclusions The initial results provide preliminary evidence describing levels of patient empowerment when living with an increased cancer risk and providing a basis for measuring the impact of providing long-term care via an ARP. The final data will determine whether ARPS can influence the patient's level of empowerment and, with the analysis of additional data regarding the use of cancer risk management strategies, can help to determine if an ARP has an influence on uptake of effective cancer risk management strategies.

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EDUCATION

Poster P058

Experience with Opportunistic Salpingectomy in a Large Community-Based Health System in the United States

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Objectives Evaluate the trend in uptake of salpingectomy at the time of hysterectomy and assess physician attitudes toward the practice.
Methods Retrospective cohort study using the electronic medical record identified women ≥ 18 years undergoing hysterectomy from June 2011 to May 2014 in a large integrated health care delivery system. All Ob/Gyn physicians were sent an electronic survey assessing attitudes toward opportunistic salpingectomy after a practice recommendation issued May 2013.
Results Of the 12,143 hysterectomies performed over the 3-year study period, 7498 were performed without oophorectomy. There was a statistically significant rise in rate of salpingectomy over time from 14.7% for June 2011–May 2012, to 44.6% for June 2012–May 2013, and to 72.7% for June 2013–May 2014 ($p < 0.001$). Median estimated blood loss was lower in the salpingectomy group, 100 mL versus 150 mL ($p < 0.01$). Median operating time was significantly shorter (147 minutes vs. 154 minutes, $p = 0.002$) for laparoscopic hysterectomy alone vs. laparoscopic hysterectomy with bilateral salpingectomy. The survey was completed by 46% (249/543) of physicians; 89% were generalist Ob/Gyns, 76% were female, and 86% reported performing salpingectomy. Although most physicians felt that there were no barriers to performing salpingectomy (54%), the most common barriers identified were difficulty accessing the tube (36%) and increased complications (3%).
Conclusions Rates of salpingectomy increased significantly over time, consistent with the high acceptance rate reported by providers and highlighting the importance of physician education to improve compliance with risk-reducing clinical strategies.

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Poster P059

Poor Genetics Referral Rate for High-Grade Serous Ovarian Cancer Patients Prompts a New Opt-Out Referral System

Karen Panabaker, Peter Ainsworth, Heather Shaddick, Jacob McGee

Background *BRCA1/2* gene mutations account for 20%–30% of all high-grade serous ovarian cancers (HGSC). In 2001, Ontario expanded the eligibility criteria for *BRCA1/2* testing to include all women with HGSC, regardless of age at diagnosis, and yet referral rates to genetics continue to be suboptimal throughout the province. Reasons for lack of appropriate referrals may be provider- or patient-driven.
Objectives The purpose of this study was to improve the genetics referral rate for HGSC patients by automatically processing a referral of all newly diagnosed patients at LHSC, creating an opt-out vs. opt-in referral process.
Methods Each month, a list of all new HGSC patients is sent directly to the Genetics clinic. Two months after a patient's surgery date, the Genetics clinic sends each HGSC patient a letter, acknowledging their referral by their surgeon, including an appointment for a genetic consultation. Patients are given an information sheet regarding the association between *BRCA1/2* mutations and HGSC, including that they have a choice in pursuing a genetics consultation. Within the 2-month lag post-surgery, it is the surgeon's responsibility to inform the Genetics clinic if a referral is not appropriate for their patient.
Results In 2015, 40 women had surgery and received a new diagnosis of HGSC at LHSC. The automatic referral letter went to 13 patients via the Genetics clinic, and 7 patient referrals are pending at the discretion of 1 surgeon. Only 1 patient (1/33) declined an appointment, and thus far, 3/13 (23%) tested *BRCA*-positive.
Conclusions An automatic genetics referral for HGSC is a reasonable approach to ensure that all eligible women are provided the opportunity to receive genetic counselling and genetic testing.

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Poster P061

Sunnybrook Familial Prostate Cancer Clinic and Male Oncology and Research Program

Justin Lorentz,* Gabriella Ghanem,* Stanley Liu,*† Danny Vesprini*†

Problem Prostate cancer (PCa) screening in the general population remains controversial. Decreased emphasis on prostate-specific antigen (PSA) screening may increase the incidence of high-risk/aggressive PCa, particularly in at-risk populations such as men with a hereditary predisposition (for example, *BRCA* mutation carriers), men of Caribbean/West African ancestry, and men with a family history of PCa. Men at risk for PCa are poorly represented in the literature. There is need to further our understanding of the causes, screening, and prevention of PCa in these populations.
Program The Familial Prostate Cancer Clinic (FPCC) is a PCa screening clinic for at-risk populations. Men are followed annually for PSA screening and digital rectal examination. Men with a *BRCA* gene mutation have clinical breast exams with or without mammograms. The Male Oncology Research and Education Program (MORE) is a monitoring research initiative that collects clinical data and biologic samples from consenting participants. The MORE program acts as a platform to recruit men for future research studies.
Progress A total of 163 men have been seen in the FPCC, with 130 enrolling in the MORE program. Of these men, 106 are known *BRCA* carriers, 48 have a *BRCA1* gene mutation, and 58 have a *BRCA2* gene mutation. 58 Men have a family history of PCa and/or are of West African/Caribbean ancestry.
Research 1) *BRCA* gene mutation carriers over the age of 50 eligible for an ongoing PCa screening study on utility of prostate MRI. 2) Qualitative research exploring whether men's bodies and sense of self are affected by the knowledge that they carry a *BRCA* gene mutation. 3) Diet and exercise-related studies with the goal of understanding novel modifiable risk factors for PCa. 4) Investigate novel hereditary PCa genes in families that display Y-linked or mitochondrial patterns of disease. 5) Molecular characterization of benign and diseased prostate tissue in *BRCA* carriers.

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Poster P062

Attitude Toward and Knowledge About Genetic Counselling and Testing for Hereditary Breast and Ovarian Cancer Predisposition Syndrome: A Survey of Physicians in Switzerland

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Objectives Despite a tremendous expansion of genetic information and testing options in predictive oncology, little is known about the capacity of non-geneticist medical doctors to correctly recognize and manage hereditary cancer cases. Becaise most of the *BRCA1*/*BRCA2* mutations carriers are currently managed in the private sector of health care in Switzerland, we decided to explore the attitude of private practitioners toward genetic counselling and to evaluate their knowledge regarding some issues in HBOC syndrome.
Methods Between November 2014 and January 2015, a survey including several case scenarios was mailed to primary care physicians/internists

($n = 317$), medical oncologists ($n = 15$), and gynecologists ($n = 154$) working in Geneva and Valais cantons, Switzerland.

Results The overall response rate was 36.4% (177/486). Gynecologists answered more frequently (43.5%) than did primary care physicians/internists (30.3%) and oncologists (28.6%). Criteria to recommend genetic counselling/testing were not regularly recognized: early-onset breast cancer patients would be referred by 91.7% of responders, but only 31.4% of physicians identified ovarian cancer as a criterion. Less than a third (31.5%) of physicians correctly calculated the probability of carrying a *BRCA1* mutation in a family with a known mutation. A minority of responders precisely estimated breast (45.2%) and ovarian (48.2%) cumulative cancer risk for female *BRCA1* carriers, with a better performance for gynecologists/oncologists vs. primary care physicians/internists (63.4% vs. 31.6% for breast cancer and 64.8% vs. 35.8% for ovarian cancer, $p < 0.001$). Regarding clinical guidelines, 45.4% of general practitioners/internists did not know the surveillance/preventive measures recommended for managing ovarian cancer risk in *BRCA2* mutation carriers.

Conclusions Important knowledge gaps in appropriate referral, counselling, and optimal management recommendations were identified among non-geneticist physicians. These findings highlight the need for improving knowledge of medical genetics for physicians in private practice and stress the importance of a closer collaboration with medical geneticists to adequately manage women with HBOC syndrome.

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Poster P063

Genetic Testing of Individuals Diagnosed with Breast or Ovarian Cancer Who Meet Testing Guidelines: Trends in Utah, 2008–2012

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Objectives Many women who meet guidelines for *BRCA1/2* testing do not pursue testing. This can be due to multiple factors, including patient preference, lack of awareness, financial limitations, or other barriers. The Utah Department of Health, with support from the CDC, is establishing a statewide cancer genomics program focusing on education, surveillance, and policy surrounding *BRCA1/2* and Lynch syndrome. To begin assessing the utilization of *BRCA1/2* testing in Utah, data from the Utah Cancer Registry and Myriad Genetics was used to compare the number of individuals diagnosed with breast or ovarian cancer who meet National Comprehensive Cancer Network (NCCN) guidelines to the number who were tested within a year of their diagnosis.

Methods All women diagnosed with ovarian cancer, women diagnosed with breast cancer at age 45 or younger, and all men diagnosed with breast cancer were identified from the Utah Cancer Registry, 2008–2012. The number of BRCAAnalysis tests (comprehensive, multi-site, and single site) ordered in Utah for individuals with the same diagnoses was obtained from Myriad Genetics for the corresponding years.

Results In Utah, the proportion of women diagnosed with ovarian cancer who underwent testing within a year of diagnosis was 13.9% in 2008 and increased to 32.9% by 2012. Among women diagnosed with breast cancer ≤ 45, 44% underwent testing in 2008 compared with 78% in 2012. Of men diagnosed with breast cancer, 8.3% underwent testing within a year of their diagnosis in 2008 compared with 61.5% in 2012.

Conclusions The appropriate utilization of *BRCA1/2* testing for individuals with a breast or ovarian cancer diagnosis meeting NCCN guidelines increased dramatically during the time period studied. However, these data indicate that barriers to testing persist, particularly among patients with ovarian cancer. Further education and outreach efforts are warranted, and research should further explore the barriers to testing within the Utah population.

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ETHICO-LEGAL ISSUES

Poster P064

Use of Open, Curated Variant Databases: Liability?

Bartha Maria Knoppers, Adrian Thorogood, Mark Phillips

Translation of genomics into medicine and drug development requires comprehensive high-quality genomic variant databases. To support translation, there is a movement toward sharing clinical annotations of variants (for example, benign, unknown, pathogenic) internationally via open access. Despite the growing popularity of variant databases, the associated liability risks have received scant attention. These may include medical liability based on potential harm to patients; liability based on third-party intellectual property or privacy rights in the data; and regulatory risks as variant data is integrated into genetic tests or devices. Can these risks be managed through appropriate governance structures, including access processes, contributor agreements, and disclaimers, while facilitating sharing and clinical use?

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Poster P065

Pre-feasibility Study of a Personalized Risk-Stratification Approach for Breast Cancer Screening in Quebec: What Is at Stake at the Organizational Level?

Julie Hagan, Emmanuelle Lévesque, Bartha M. Knoppers

While *BRCA1/2* dramatically increases the risk for breast cancer (BCa), a number of other genetic factors can influence an individual's predisposition to developing this type of cancer. Recent innovations in genomics may facilitate early detection of women who are not *BRCA1/2* carriers, but are nonetheless at high risk of developing BCa. Our study is a pre-feasibility study within the larger project "Personalized Risk Stratification for Prevention and Early Detection of Breast Cancer (PERSPECTIVE)," which aims to develop a risk-stratification approach for BCa screening in Quebec. This approach would identify high-risk individuals through an algorithm based on genetic tests as well as personal risk factors.

The main objectives of our substudy are to identify the organizational factors hindering or facilitating the implementation of a risk-stratification approach and to anticipate mitigation strategies. Following a systematic review of the grey literature (policies, guidelines, reports, etc.) on BCa screening in Quebec, we interviewed 16 managers in the Quebec health care system. Each 1-hour interview addressed the organizational issues surrounding the eventual implementation of a risk-stratification approach in Quebec. Thematic analysis of interview data allowed us to acknowledge the following priorities. Decision-makers raised structural issues such as resource allocation, time constraints, and measures of success, and concerns regarding infrastructures and expertise. Many also raised other socio-ethical concerns, including equitable participation of women regardless of their literacy level and access (or not) to a family physician; respect for the psychosocial needs of women; the additional complexity of informed decisions; and interregional equity in access to services (for example, genetic counselling).

Results from our pre-feasibility study show that implementation strategies will need to provide adapted communications tools as well as strategies promoting inclusion and mitigating inequalities in access to services.

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GENOME-WIDE APPROACHES AIMED AT IDENTIFYING NEW GENETIC RISK FACTORS

Poster P067

RNA Sequencing in High-Risk French Canadian Breast Cancer Families

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Approximately 25% of hereditary breast cancer cases associated with a strong familial history can be explained by mutations in *BRCA1*, *BRCA2*, and other lower-penetrance genes. However, most high-risk breast cancer is not yet explained by a mutation. Alternative splicing is a mechanism known to be involved in cancer development, and the analysis of transcriptome in high-risk breast cancer individuals could reveal transcripts implicated in breast cancer susceptibility and development. These specific transcripts could then be used as biomarkers for cancer detection and personalized treatment.

The RNA-seq methodology was used to characterize the transcriptome in French Canadian families with high risk of breast and ovarian cancer. The analysis used RNA extracted from immortalized lymphoblastoid cell lines of 115 women (affected and unaffected) from *BRCA1*, *BRCA2*, and non-*BRCA1/2* (*BRCAx*) families. The ANOVA and Bonferroni tests were used to detect significantly and differentially expressed transcript.

A total of 3179 transcripts corresponding to 1866 different genes were differentially expressed ($p < 0.01$) between these groups. Hierarchical clustering based on transcriptional data allowed distinctive subgrouping of *BRCA1/2* subgroups from *BRCAx* individuals, without regard for cancer status. Considering significant genes exclusively, we found enrichment for pathways in inflammation and signalling cascades such as p53-related pathways. Analyses show that these genes were also found to be related to cancer. Regarding the *BRCAx* subgroup, 190 transcripts were significantly and differentially expressed between affected and unaffected *BRCAx* individuals. These transcripts demonstrated a relation to inflammation and immunity. We are now confirming further these results, and we are pursuing the investigation of such enriched pathways in cells and tissue.

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Poster P068

Challenges in Recruiting African American Women to Participate in a Breast Cancer Genetic Testing Study

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Objective To analyze the challenges encountered in recruiting African American women with a family or personal history of breast cancer from a pre-established Spit for the Cure (SFTC) cohort to participate in a breast cancer genetic testing study.
Methods We attempted to contact a total of 994 African American women with a personal or family history of breast cancer who participated in SFTC between 2007 and 2012 and provided consent to be re-contacted. Through telephone calls and e-mails, we invited them to participate in a genetic testing study. The women were provided with genetic counselling while explaining the purpose of the study and the benefits and risks of genetic testing. Enrolment required completion of a telephone interview to obtain a detailed family and medical history and return of a signed consent form.
Results Of the 994 SFTC participants who were eligible to participate in the genetic testing study, only 174 (17.5%) completed a telephone interview and returned a signed consent form. Most SFTC participants, 594 of 994 (59.8%), were unable to be contacted using the telephone numbers and e-mail addresses they provided to SFTC. Other eligible SFTC participants did not follow through with telephone interview appointments ($n = 82$), declined to participate ($n = 57$), were deceased or too ill to participate ($n = 15$), or completed the telephone interview but never returned a signed consent form ($n = 54$).
Conclusions Enrolment of underrepresented populations in clinical trials can be challenging. Given their prior participation in a research study, we anticipated that this population would be highly motivated. Indeed, when we were able to contact prior SFTC participants about participating in our study, relatively few (15.5%) declined to participate. Improving methods of communication and keeping up-to-date contact information might have drastically improved our ability to include more of this group in our study.

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Poster P069

Characterization of Genomic Landscapes of *BRCA1*- and *BRCA2*-Implicated Ovarian Cancers from French Canadian Women

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Although molecular genetic profiling of ovarian cancers (OCs) harbouring germline *BRCA1*/*BRCA2* mutations suggest that pathways in common with sporadic cases are involved in the pathogenesis of the disease, overall survival differs in women between *BRCA1*/*BRCA2*–implicated and sporadic disease. To further dissect the molecular pathways involved, which could account for differences in pathogenesis of the disease, we have investigated the genomic landscapes of OCs from carriers of *BRCA1* and *BRCA2* mutations. Chromosomal anomalies were investigated in 28 specimens using high-density Illumina SNP array technology. The majority were serous adenocarcinomas; the remaining samples were either endometrioid or mixed-cell adenocarcinomas. The cases harbour one of several recurrent *BRCA1* or *BRCA2* mutations (or both) described for the French Canadian (FC) population, which exhibit strong founder effects.

Allelic imbalance, copy number differences, intra-chromosomal breaks, and homozygous deletions were inferred visually using the BeadStudio software followed by ASCAT analysis. A statistical analysis was also performed to directly compare the overall landscapes from the *BRCA1*- and *BRCA2*-mutated groups. The results were compared with independently derived genomic data from OC cases generated previously from our group, which was largely composed of sporadic cases from the FC population and from The Cancer Genome Atlas (TCGA) project.

The overall genomic landscapes of *BRCA1*- and *BRCA2*-mutated cancers overlap those reported in our previous studies and from the TCGA. However, there were significant differences in the overall genomic landscapes involving several chromosomal regions between our *BRCA1* and *BRCA2* mutation–positive FC cancers. The differences involving the chromosome 15q regions was also observed in an independent analysis of *BRCA1*/*BRCA2*–mutated OCs from TCGA data. This genomic distinction between *BRCA1* and *BRCA2* OC samples may point to a region containing genes important in the causation or progression of hereditary cancer.

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Poster P070

Is There More to Discover in Genome-Wide Association Studies?

Laurent Briollais

Genome-wide association studies (GWAS) have been very successful at identifying new genetic variants implicated in various human diseases and complex traits. For breast cancer (BCA), more than 90 associated loci have been discovered, explaining about 16% of the familial risk of the disease. Despite the relative merits, the SNPs selected through standard agnostic approaches usually provide limited biologic insights. Alternative approaches have tried to integrate prior biologic knowledge at the gene, gene set, or gene network level and to enrich GWAS signals by testing a group of SNPs that could be functionally related. Those analyses are hypothesis-based but rely strongly on prior information and thus limit the value of new discoveries, in particular of those SNPs located in intergenic and intronic regions (approximately 88%) that lack functional characterization. Ideally, we need an approach that could retain most of the new variant discoveries while gathering additional information on how the variants function together from both statistical and biologic perspectives.

Here, we propose a novel approach that includes two major steps: 1) Identify new GWAS loci through multivariate analyses in an agnostic way that favours new variant discoveries. 2) Search exhaustively the "neighbourhood" of these new loci and find additional variants that can have synergistic effects and suggest common functionality. This second step uses the concept of "influential priors" that strongly favour the statistical evidence for SNP-SNP interactions, where those interactions can ultimately be matched against known gene networks for biologic validation. We illustrate this new approach through an analysis of the CGEM breast cancer data that has accrued about 1200 cases and 1200 controls and more than 500K SNPs, and we introduce our R package, genMOSS, to perform the analysis.

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Poster P071

Investigation of Selected DNA Repair Genes in French Canadian Women with Ovarian Cancer Carrying *BRCA1* or *BRCA2* Mutations

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It has been proposed that germline mutations in other members of the homologous DNA repair pathways implicating *BRCA1*/*BRCA2* and Fanconi anemia genes confer increased risk to ovarian cancer (OC). Our group has shown that recurrent *BRCA1*/*BRCA2* mutations account for a significant proportion of hereditary OC in French Canadian (FC) individuals because of common founders. This has facilitated genetic testing for establishing carrier status in hereditary cancer clinics in Quebec. Our recent observations that FC *BRCA1*/*BRCA2* mutation-carrier women with breast cancer could harbour potentially pathogenic alleles in other DNA repair genes prompted our investigation of *BRCA1*/*BRCA2* mutation-carrier FC women with OC.

Whole-exome sequencing analysis was performed on 15 *BRCA1*/*BRCA2* mutation-carrier OC women from FC families with at least 2 cases of OC. Data was investigated for potentially damaging alleles occurring in 178 genes involved in multiple DNA repair pathways, including *BRCA1* and *BRCA2*. In addition to confirming the *BRCA1*/*BRCA2* mutations, a total of 105 rare variants (MAF < 2%) were identified in 68 of the 178 investigated DNA repair genes. A range of 1–6 variants per gene, and 6–15 variants per OC case was found. The vast majority of these variants were missense, but 4 were nonsense, 9 were frameshift, and 11 were splice variants. Interestingly, mutations in 2 genes involved in base excision repair were predicted to be pathogenic (ClinVar). Moreover, 10 variants of uncertain pathogenicity (ClinVar) were found in genes involved in various DNA repair pathways.

Although the sample size was limited, there appeared to be no enrichment of variants from any DNA repair pathway in *BRCA1* versus *BRCA2* mutation-carrier cases. Our results suggest that OC cases with *BRCA1*/*BRCA2* mutations also may carry potentially damaging mutations in other DNA repair genes, warranting further research to investigate their biologic implications.

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Poster P072

A Targeted Analysis of Known and Emerging Cancer Susceptibility Genes in French Canadian Women with Breast Cancer Carrying *BRCA1*/*BRCA2* Mutations

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Recurrent mutations in *BRCA1* and *BRCA2* have been found in French Canadian (FC) breast cancer (BCa) and/or ovarian cancer families because of common founders, which has facilitated genetic testing in hereditary cancer clinics in Quebec. Recently, new BCa-predisposing genes have been described, and some, such as *PALB2*, also recur in FC hereditary BCa (HBC) families. A review of our FC HBC families identified carriers harbouring mutations in more than one of these cancer-predisposing genes.

To further investigate the possibility of carrying mutations in more than one BCa susceptibility gene, we applied whole-exome sequencing (WES) to 58 *BRCA1* and/or *BRCA2* mutation-carrier BCa probands from FC HBC families. Our analysis of 26 known or emerging BCa predisposing genes identified 19 rare variants in 17 of 58 probands (29.3%). Three probands were triple heterozygotes. There was no difference in the mean ages of diagnosis, nor in the occurrence of bilateral BCa, for the double heterozygote carriers compared with the rest of the cohort ($n = 40$). All variants were missense except for 2 frameshift mutations in *ATM* and *CHEK2*. Not all variants co-segregated with cancer cases in mutation-carrier families. The *ATM* and *CHEK2* frameshift mutations have not been found among an additional 80 *BRCA1*/*BRCA2* mutation-carrier BCa cases from 35 FC HBC families, of which 29 were also investigated by WES, nor among the 44 *BRCA1*/*BRCA2* mutation-negative BCa probands from FC HBC or hereditary breast and ovarian cancer families.

Our findings suggest that carriers of a *BRCA1*/*BRCA2* mutation and another potentially pathogenic BCa predisposing allele are possible but rare in FCs. Although the biologic implications of double heterozygotes is unknown, the similarities in cancer phenotypes observed in HBC families harbouring mutations in any of these genes may be attributed to their roles in common DNA repair pathways.

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MOLECULAR PATHOLOGY AND GENETIC ANALYSES OF *BRCA1/2*–ASSOCIATED CANCERS

Poster P073

Profiling of Epithelial Ovarian Cancer as *BRCA*ness Status with MLPA Method

Akira Hirasawa, Tomoko Akahane, Kenta Masuda, Tomomi Ninomiya, Wataru Yamagami, Hiroyuki Nomura, Fumio Kataoka, Kouji Banno, Nobuyuki Susumu, Daisuke Aoki

Objective "*BRCA*ness" tumours are defined as sporadic cancers that share characteristics with *BRCA1* or *BRCA2* (*BRCA1/2*) mutant tumours. Because *BRCA*ness cancers proven to be sensitive for poly-ADP ribose polymerase (PARP) inhibitors, profiling of ovarian cancer (OC) cells with *BRCA*ness status will be essential.
Methods Using the Keio Women's Health Biobank, DNA was extracted from frozen tissues of 248 OCs (76 serous, 31 mucinous, 53 endometrioid, and 88 clear-cell). Multiplex ligation-dependent probe amplification (MLPA) was applied to detect large genomic rearrangement that classified to *BRCA*ness, and non-*BRCA*ness. This study was conducted with approval from the institutional ethics committee, and we obtained written informed consent before taking samples.
Results Of 248 cases, 70 (28.2%) were identified as tumours. *BRCA*ness tumours were significantly more frequently found in serous OC (41/76, 53.9%) than in non-serous OC (29/172, 16.9%, $p < 0.001$).
Conclusions Our result revealed the frequency of *BRCA*ness OC with large genomic rearrangement that had theoretical benefit from PARP inhibitors.

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Poster P074

Therapeutic Sensitivity of Pancreatic Ductal Adenocarcinoma Associated with *BRCA1* or *BRCA2* Germline Mutations

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Pancreatic ductal adenocarcinoma (PDAC) associated with germline homologous recombination DNA repair (HDR) mutations may have selective sensitivity to agents that exploit HDR defects. Our previous investigations suggest that this PDAC subtype has increased sensitivity to cisplatin, a DNA crosslinker, and BMN673, a PARP inhibitor.

Objectives To validate our previous findings using subcutaneous patient-derived xenograft models (PDXs), and to further characterize the therapeutic spectrum of this PDAC subtype.
Methods and Results We evaluated the efficacy of cisplatin and BMN673 monotherapies in PDXs from PDAC cases with ($n = 3$) and without ($n = 2$) germline *BRCA1* or *BRCA2* mutations. Consistent with our previous findings, we observed greater tumour growth inhibition with cisplatin and BMN673 monotherapies in the tumours with *BRCA1* or *BRCA2* defects than in tumours without mutations in these genes (95%–97% vs. 63%–64% growth inhibition, $p < 0.01$). Subsequently, we performed a multi-arm preclinical trial using paired PDXs (primary tumour, liver metastasis recurrence) generated from a *BRCA2*-associated PDAC case. We compared monotherapies of cisplatin, BMN673, and gemcitabine as well as combination therapies of gemcitabine with cisplatin, gemcitabine with BMN673, and cisplatin with BMN673. Interestingly, we observed parallel responses in the PDXs harbouring the primary tumour and liver metastasis recurrence, with 71%, 88%, and 101% compared with 69%, 89%, and 106% growth inhibition with cisplatin, BMN673, and gemcitabine monotherapies in the primary tumour and liver metastasis recurrence respectively. The efficacy of gemcitabine compared with cisplatin and BMN673 monotherapies was unexpected, because, compared with gemcitabine, the latter agents are predicted to have greater efficacy in tumours with HDR defects. In addition, our data suggest that gemcitabine with BMN673 is more efficacious than BMN673 monotherapy.
Conclusions PDAC associated with germline HDR mutations may have enhanced sensitivity to a broad spectrum of therapeutic agents, including agents predicted to exploit HDR defects, as well as gemcitabine.

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Poster P075

Efficient Detection of Both Germline and Somatic *BRCA1* and *BRCA2* Mutations in Formalin-Fixed Paraffin-Embedded Ovarian Tumours Enabling Selection of Patients for PARP Inhibitor Treatment

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Objectives Recently, PARP inhbitors were approved for treatment of metastasized *BRCA1* and *BRCA2* mutation–positive high-grade serous ovarian carcinoma. Approximately 15% of patients with ovarian carcinoma have an inactivating germline *BRCA* mutation. Additionally, according to the literature, 4%–8% of ovarian carcinoma patients have a tumour-specific somatic mutation in *BRCA1* or *BRCA2*, making them also eligible for treatment with PARP inhibitors. The detection of somatic mutations is hampered by the complexity of the genes, the low quality of DNA isolated from formalin-fixed paraffin-embedded (FFPE) tumour blocks, and the low percentage of neoplastic cells in undissected tumour material. The aim of this study was to develop a test that can detect both somatic and germline mutations in the *BRCA1* and *BRCA2* genes to identify patients eligible for PARP inhibitor treatment.
Methods DNA was isolated from dissected FFPE sections, and our newly developed SMMIP-based *BRCA1* and *BRCA2* NGS method was used on 49 tumour samples from 42 patients with a known *BRCA1* ($n = 27$) or *BRCA2* ($n = 15$) germline mutation and 57 tumour samples from 50 patients without such mutation. Molecular barcoding ensured the detection of unique reads only.
Results All expected germline mutations were detected. Moreover, in 5 germline mutation–negative patients (10%), a somatic truncating mutation in *BRCA1* ($n = 2$) or *BRCA2* ($n = 3$) was detected.
Conclusions These data show that analysis of *BRCA1* and *BRCA2* on FFPE-derived DNA for the detection of both germline and somatic mutations is both sensitive and feasible. This opens new possibilities for an efficient identification of women eligible for PARP inhibition treatment.

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Poster P076

Thorough Second-Hit Analysis in *BRCA1/2*–Associated Breast Cancer

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Objective The literature states that in *BRCA1/2*–associated breast tumours, somatic loss of the wild-type allele is the most prevalent mechanism leading to the absence of a functional *BRCA* tumour suppressor

gene product. The functional allele is lost by either incorrect mitosis or a deleterious chromosomal event. However, little is known about the prevalence of other somatic events (including point mutations). This study's objective was to paint a detailed picture of the somatic alterations in *BRCA1/2* from breast cancer patients with germline mutations in these genes.

Methods We optimized a targeted enrichment and next-generation sequencing approach to perform mutation analysis of the complete coding region of *BRCA1/2* in 99 formalin-fixed and paraffin-embedded (FFPE) breast tumours. We collected FFPE breast tumours from germline *BRCA1/2* mutation carriers diagnosed between 1989 and 2014. To enhance tumour cell percentages in each sample, we optimized a laser-guided macrodissection approach. We performed sequencing in DNA extracted from tumour and blood in parallel.

Results Results confirm loss of the wild-type allele in about half the tumours. The loss-of-heterozygosity (LOH) region spans variable proportions of the gene. Interestingly, in several tumours, loss of the mutant allele was observed, suggestive for mechanisms beyond LOH. In addition, we also see several somatic inactivating point mutations.

Conclusions We observed both loss of the wild-type and mutant allele in the tumours. In addition, a large number of somatic *BRCA1/2* variations were detected. The results of this study point out that determining the *BRCA* functionality within tumours is challenging. This implicates that LOH analyses in tumours with variants of unknown significance is not appropriate to determine the role of such variants.

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Poster P078

Induced Pluripotent Stem Cell Modelling of Cardiotoxicity in Response to Cancer Therapy of *BRCA1* Mutant Patient

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Background Germline mutations in *BRCA1* are associated with a high risk of developing breast and ovarian cancer (up to 85% and 45% respectively). While the tumour suppressor function of *BRCA1* is well established, new studies have found a novel role for *BRCA1* as a "caretaker" of cardiac function and survival, particularly in response to genotoxic stress.

Hypothesis Carriers of mutant *BRCA1* have an elevated risk of cardiac failure in the response to myocardial ischemia and genotoxic agents such as doxorubicin.

Methods Three different *BRCA1* mutant IPSC lines from patients with early-onset ovarian cancer were generated and then IPSC-derived cardiomyocytes were established. The IPSC-derived cardiomyocytes were characterized for expression of troponin, beating behaviour by image analysis (ImageJ), and Ca2+ signalling using the fluorescent indicator fluo-4 acetoxymethyl.

Results Compared with control cardiomyocytes, *BRCA1*-mutant IPSC-derived cardiomyocyte cells exhibited remarkably different morphology, electrophysiologic characteristics, and beat rhythmicity. Currently, electrophysiologic properties of IPSC-derived cardiomyocytes are being recorded with patch clamp technique. To establish the baseline cardiac activity in a patient carrying the *BRCA1* mutation, cardiac tissue morphology and function, tissue viability, and myocardial perfusion are being analyzed using MRI imaging.

Conclusions Treatment-associated cardiotoxicity can affect patient survival and quality of life. Furthermore, *BRCA1* cancer survivors may be at increased risk of ischemia-related heart failure. This *BRCA1* mutant IPSC-derived cardiomyocyte model provides an ideal platform to investigate cardiotoxicity of cancer therapies for carriers of mutant *BRCA1* and may help improve survivorship.

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Poster P079

BRCA1/*BRCA2* Testing in Patients with Breast or Ovarian Cancer without Family History: 20 Years' Experience in a Single Institution.

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Objectives Besides family cancer history, some individual clinical presentations or tumoural histopathologic characteristics are formally recognized as criteria to discuss *BRCA1*/*BRCA2* testing. In this study, we assessed a consecutive series of patients with breast/ovarian cancer without family history who underwent *BRCA1*/*BRCA2* testing. Genetic results were correlated with cancer type, age at diagnosis, and histopathologic characteristics of the tumour.

Methods Between 1996 and 2015, 828 consecutive patients (807 women, 21 men) had genetic counselling in our institution, followed by a complete *BRCA1*/*BRCA2* testing. All the pedigrees were reviewed. Inclusion criteria were female sex, breast or ovarian cancer diagnosis, and no family history of breast/ovarian cancer in first- and second-degree relatives, as well as in cousins. Cancer type, age at diagnosis, tumour characteristics, and history of other cancer were collected for each index case.

Results Overall, 184 index cases (22.8%) fulfilled the inclusion criteria: 145 (78.8%) developed only breast cancer, 29 (15.8%) presented only ovarian cancer, and 10 (5.4%) had breast and ovarian cancer. Pathogenic *BRCA1*/*BRCA2* variants were identified in 14/184 index cases (7.6%). Among breast cancer patients, 108/155 (69.7%) were diagnosed under the age of 40, and 7 (6.5%) were identified as mutation carriers; 47 (30.3%) presented a triple-negative or a high-grade hormonal receptor–negative breast cancer, and 5 (10.6%) had positive genetic results. Of 39 patients, 2 with ovarian cancer (5.1%) were identified as mutation carriers; both presented a serous-papillary high-grade tumour.

Conclusions In this cohort, 7.6% of patients with isolated breast or ovarian cancer were identified as carriers of *BRCA1*/*BRCA2* germline pathogenic variants. No clinical or histopathologic characteristic was associated with a positive testing result in this selected series of patients.

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Poster P080

An Evaluation of Tumour *BRCA* Testing Methodologies in Clinical Practice

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Ovarian cancer patients with both germline and somatic pathogenic variants benefit from treatment with PARP inhibitors. By testing a patient's tumour sample, germline and somatic mutations can both be detected. However, a tumour *BRCA* test is considerably more challenging than a germline test. Most tumour samples are formalin-fixed and paraffin-embedded (FFPE), the tumour genome is complex, and the allele fraction of somatic mutations can be low in a sample.

We collaborated with 10 labs testing *BRCA* in tumour using different approaches (amplicon-based and hybrid capture) and analysis pipelines to compare their ability to identify *BRCA* mutations in DNA extracted from FFPE tumours. The laboratories received 12 FFPE DNA samples of known genotype and were asked to use their own method to perform the analysis. Two of these samples were low-level admixtures to evaluate method limit of detection.

No false positives calls were made in this small data set; however, a number of significant variants were missed because of either the bioinformatics analysis pipelines or failure to correctly classify variants. When the raw sequences were examined, our analysts detected these variants. Hybrid capture methods requiring a higher DNA input tended to generate poor-quality results on low concentration samples. Most labs detected the low-level variants if the data passed acceptance criteria.

A range of methods are suitable for tumour *BRCA* FFPE DNA testing. Different bioinformatics pipelines can fail to detect all variants and must be validated on a range of mutations types and optimized for analysis of FFPE samples. Furthermore, experience with *BRCA* classification is important to identify all significant variants.

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Poster P081

Small RNA Sequencing Reveals a Comprehensive miRNA Signature of *BRCA1*-Associated High-Grade Serous Ovarian Cancer

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Objectives *BRCA1* mutation carriers are at increased risk of developing high-grade serous ovarian cancer (HGSOC), a malignancy that develops in most (if not all) cases from fallopian tube epithelium. Micro RNAs play a key role in cancer, but their expression patterns have not been completely described in HGSOC. We therefore aimed to use small RNA sequencing with tubal tissue as normal control to identify differentially expressed miRNAs in *BRCA1*-associated HGSOC.

Methods Small RNA sequencing was performed on 8 normal tubal and 5 HGSOC samples from *BRCA1* carriers. Differential expression of a subset of known and novel miRNAs was validated by qRT-PCR on the samples used for small RNA sequencing and a second sample cohort comprising tissue

of matched *BRCA1* carriers (8 normal tubal and 11 HGSOC) and non-*BRCA* (8 normal tubal and 12 HGSOC). Data from the Cancer Genome Atlas were used to determine the clinical relevance of the validated differentially expressed miRNAs.
Results A >4-fold difference in expression between normal tubal tissue and HGSOC was observed for 59 known and 20 novel miRNAs. Validation by qRT-PCR confirmed a significant difference in expression levels for 10 of 11 known miRNAs in *BRCA1* and non-*BRCA* HGSOC. Upregulation of 2 novel miRNAs could not be confirmed. Expression levels of MIR-145-5p significantly increased with FIGO stage, while the expression levels of the other 9 miRNAs were not associated with clinical characteristics.
Conclusions We report a comprehensive expression signature including both known and novel miRNAs of *BRCA1*-associated HGSOC compared with normal tubal tissue. Among the independently validated miRNAs, MIR-145-5p levels increased with disease severity. This study is a reliable source for selecting deregulated miRNAs in HGSOC for identifying their downstream mechanisms.

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NON-*BRCA1/2* GENETIC FACTORS ASSOCIATED WITH CANCER RISK

Poster P084

Yield of Pathogenic/Likely Pathogenic Variants in Individuals with Triple-Negative Breast Cancer Undergoing Inherited-Cancer Panel Testing

Megan L. Marshall,* Lisa R. Susswein,* Laura M. Andolina,* Kathleen S. Hruska,* Rachel T. Klein†

Objectives Studies investigating an inherited predisposition to triple-negative breast cancer (TNBC) have focused on *BRCA1/2* and more recently *PALB2*[1,2]; however, data regarding the diagnostic yield of multigene panels are limited. The focus of this analysis was to determine the yield of pathogenic/likely pathogenic variants (P/LPV) in dominant hereditary cancer genes in women with TNBC.
Methods We reviewed the results of multigene panel testing comprised of combinations of 29 genes in 1053 women with TNBC. Individuals with previous *BRCA1/2* testing were excluded. Genes analyzed were broadly grouped into 3 risk categories based on penetrance and published management guidelines: high-risk, moderate-risk, and newer genes.
Results In total, 150 P/LPVs were identified in 147 individuals with TNBC (14%, 147/1053). P/LPVs were identified in *BRCA1* (71), *BRCA2* (40), *PALB2* (7), *BARD1* (5), *BRIP1* (4), *ATM* (4), *CHEK2* (3), *FANCC* (3), *RAD51C* (3), *PMS2* (2), *XRCC2* (2), *APC* (1), *MLH1* (1), *MSH6* (1), *NBN* (1), *PTEN* (1), *RAD51D* (1), *TP53* (1). Of all P/LPVs, 118 (78.7%) were detected in high-risk, 14 (9.3%) in moderate-risk, and 18 (12.0%) in newer genes. Genes other than *BRCA1/2* together accounted for 26% (39/150) of all positive findings. Only 4 P/LPVs (2.6%) were detected in genes not historically thought to be associated with breast cancer risk (*APC, MSH6, PMS2*); however, 2 of these individuals also reported a personal history of adenomatous colonic polyps.
Conclusions Although most P/LPVs were identified in the *BRCA1/2* genes, many were identified in non-*BRCA1/2* genes and would not have been detected by testing *BRCA1/2* only. Of the P/LPVs, 88% were detected in high- or moderate-risk genes with published management guidelines. Thus, multigene cancer panels should be considered as an initial test for individuals with TNBC who are being evaluated for hereditary cancer risk. [Updated data to be presented]

1 Heikkinen T, Kärkkäinen H, Aaltonen K, *et al.* The breast cancer susceptibility mutation *PALB2* 1592delT is associated with an aggressive tumor phenotype. *Clin Cancer Res* 2009;15:3214–22.
2 Couch FJ, Hart SN, Sharma P, *et al.* Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol* 2015;33:304–11.

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Poster P085

Yield of Pathogenic/Likely Pathogenic Variants in Women with Lobular Breast Cancer Undergoing Hereditary-Cancer Panel Testing

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Objectives Lobular breast cancer (LBC) accounts for 5%–10% of all breast cancers. Studies of the genetics of LBC are limited and have focused on a small number of genes, including *BRCA1, BRCA2,* and *CDH1,* a gene associated with hereditary diffuse gastric cancer syndrome, of which LBC is a feature. Pathogenic variants/likely pathogenic variants (PV/LPVs) in *CDH1* are uncommon in women with LBC without a personal or family history of gastric cancer. In women with *BRCA1, BRCA2,* and *TP53* PV/LPVs, LBC is underrepresented. We sought to determine the frequency of PV/LPVs in women with LBC undergoing multigene hereditary-cancer panel testing. Panel offerings in our laboratory include high-risk, moderate-risk, and newer genes. High-risk genes are clinically well-characterized, confer a significantly increased risk for cancer, and have published management guidelines. Moderate-risk genes are generally associated with a 2- to 3-fold increased risk of cancer, and have published management guidelines. Newer genes have been identified in familial cancer cases, but lifetime cancer risks have not been robustly determined.
Methods We reviewed the cancer panel results for up to 29 genes associated with hereditary cancer risk in 474 women with LBC.
Results In total, 40 PV/LPVs were identified in the following genes: *CHEK2* (12), *BRCA2* (7), *PALB2* (5), *MSH6* (4), *ATM* (4), *BRCA1* (2), *CDH1* (2), *PTEN* (1), *PMS2* (1), *FANCC* (1), and *NBN* (1).
Conclusions Overall, PV/LPVs were identified in 39/474 women with LBC (8.2%); 1 woman had 2 PV/LPVs. Two *CDH1* PV/LPVs were identified; the remaining PV/LPVs were in other genes. Most PV/LPVs (38/40; 95%) were detected in high- or moderate-risk genes with published management guidelines. Hereditary-cancer panel testing should be considered for women with LBC, because our data demonstrate that panel tests identified PV/LPVs with published clinical guidelines in 37 of 474 women (7.8%) in our clinical series.

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Poster P086

Genetic Testing for Hereditary Cancer: Is Exome Sequencing Ready or Is There Still Room for *Ad Hoc* Designed Panels?

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Purpose Next-generation sequencing (NGS) has changed genetic testing. In the field of hereditary cancer, several NGS panels have been developed. There is a debate about its cost-effectiveness compared with exome sequencing. The performance of 2 gene panels compared with exome sequencing for diagnosing hereditary cancer is presented.
Methods Of 24 selected patients, 10 were a control set with pathogenic mutations; the remaining 14 were suspected for hereditary cancer, but without any identified mutation ("discovery set"). Two hereditary cancer panels, the TruSight-Cancer (94 genes) and a custom panel (122 genes), plus exome sequencing were assessed.
Results The analysis of the coverage of the common genes (n = 83) evidenced that ≥99% of the bases had read depth over 30× (C30) in the panels; exome sequencing covered 95% of these positions at C30. Variant calling with the 3 approaches identified the 10 control pathogenic mutations, except for *MSH6* mutation c.255dupC in TruSight-Cancer. Approximately 200 different non-silent coding variants in the common set of genes were identified in the remaining 14 samples, 7 being putative pathogenic (nonsense, frameshift, and canonical splice-site mutations) in *ATM, BARD1, CHEK2, ERCC3, FANCL, FANCM,* and *MSH2.* Applying the 3 systems, the number of variants in common genes was very similar, although coverage depth was low in intron–exon boundaries and did not reach diagnostics quality parameters in exome sequencing. In terms of cost, exomes were, on average, 3 times as expensive as panels.
Conclusions Our results indicate that there is still room to use *ad hoc* designed panels when considering the sequencing quality parameters required for genetic diagnostics and its constrains in terms of cost and turnaround time.

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Poster P087

Germline *SMARCA4* Mutations Account for Almost Half of All Cases of Small-Cell Carcinoma of the Ovary, Hypercalcemic Type

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Background Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), is the most common undifferentiated ovarian tumour in women below age 40. It is an extremely aggressive tumour, with long-term survival rates at ~50% in early-stage disease. Thirteen families have

been reported with more than 1 member having SCCOHT. In 2014, we discovered that SCCOHT is monogenic, characterized by germline and somatic deleterious mutations in the chromatin remodelling gene, *SMARCA4*. Subsequent reports have demonstrated the specificity and sensitivity of *SMARCA4* molecular testing in the diagnosis of SCCOHT, but the clinical effect of *SMARCA4* mutations, germline or somatic, has not been analyzed.

Methods To determine the effect of these mutations clinically, we compiled data on age and stage at diagnosis, overall survival, and mutation on 89 SCCOHT patients who have been tested for *SMARCA4* mutations. We also collected inheritance patterns when possible.

Results Of 60 patients in which constitutional and tumour DNA was tested, 27 (45%) carried germline *SMARCA4* mutations, 21 of whom had no family history of SCCOHT. In 11 germline mutation carriers, the parents' genotype was known: 1 mutation arose *de novo*, and 10 were inherited (4 from unaffected fathers, 5 from affected mothers, 1 unknown). Overall, germline mutation carriers were diagnosed at a younger age than those with somatic mutations only ($p = 0.02$), but carrying a germline mutation had no significant effect on overall survival ($p = 0.63$), nor on the stage at diagnosis.

Conclusions A large fraction of SCCOHT patients have germline *SMARCA4* mutations, warranting genetic testing for all patients diagnosed with SCCOHT. Patients with germline mutations are diagnosed earlier than patients with somatic mutations only. More complete genotype information is needed to fully estimate penetrance of these mutations.

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Poster P088

Identification of Potentially Pathogenic Variants in Candidate Breast and Ovarian Cancer Susceptibility Genes in *BRCAx* Patients

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Mutations within the *BRCA1* and *BRCA2* genes account for approximately 20% of hereditary breast cancers, with a further 10%–15% being attributable to rare mutations in moderate-risk genes and common variants in low-risk genes. The genes harbouring mutations in the remaining ~65% of hereditary breast cancers are unknown. The identification of mutation carriers in hereditary breast and ovarian cancer (HBOC) families is critical for determining who is most at risk of developing the disease and therefore who should be offered risk-reducing procedures or more intensive screening, or both.

Many of the high- and moderate-risk genes for hereditary breast cancers encode proteins that work in concert to maintain genomic stability and in DNA damage signalling and repair. A novel *BRCA1* protein complex identified within the research group whose target genes are involved in DNA repair provided novel candidates for HBOC susceptibility genes. These 12 candidate genes were sequenced in a cohort of 675 affected individuals from the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) with hereditary breast or ovarian cancer, but with no mutations in known susceptibility genes (*BRCAx* patients). This analysis identified 20 individuals (each from a different *BRCAx* family) with different potentially pathogenic variants across 6 of the candidate HBOC susceptibility genes. The family members of each *BRCAx* index case were tested for the presence of the specific mutation identified in the proband to examine segregation with disease. To further expand on the potential role of the novel candidate HBOC susceptibility genes identified in this study, the genetic variation of a second cohort of 520 Northern Irish *BRCAx* patients is being characterized using a 61-gene panel.

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Poster P089

Yield of Pathogenic and Likely Pathogenic *BRIP1* Variants on Next-Generation Hereditary-Cancer Panels

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Objectives *BRIP1* has only recently been described in association with cancer predisposition, and the risks are not well understood. Data suggest that a *BRIP1* pathogenic variant may confer an increased risk for female breast and ovarian—and possibly pancreatic—cancer[1–3]. *BRIP1* is now included on several clinical hereditary next-generation sequencing (NGS) cancer panels, providing more information regarding the frequency of *BRIP1* pathogenic and likely pathogenic variants (P/LPV) in families with breast or ovarian cancer.

Methods Since the launch of the NGS cancer panels at GeneDx, 14,137 individuals have been tested with gene panels that include *BRIP1*. We retrospectively queried genetic testing results and clinical histories of *BRIP1* carriers. Individuals reporting prior genetic testing were excluded.

Results Among 70 individuals (68 women, 2 men), 30 unique *BRIP1* P/LPVs were identified, representing an overall yield of 0.5% (70/14,137) in those undergoing testing. Among women with breast cancer, the yield was 0.4% (31/7181), and among those with ovarian cancer, it was 0.8% (10/1323). Of women with *BRIP1* P/LPVs, 45.6% (31/68) had a personal history of breast cancer, and 14.7% (10/68) had been diagnosed with ovarian cancer. None of the 89 individuals with pancreatic cancer was found to carry a *BRIP1* P/LPV. Two likely pathogenic missense variants at the same position, Pro47Ala and Pro47Thr, accounted for more than half of all P/LPVs, while the rest of the P/LPVs were truncating. One family showed segregation with breast and ovarian cancer; a *BRIP1* truncating variant was present in a mother with serous fallopian tube cancer at age 62 and a daughter with breast cancer at age 40.

Conclusions *BRIP1* is emerging as an important gene in hereditary breast and ovarian cancer. Identifying more families with P/LPVs in *BRIP1* will allow us to better assess the risks associated with the gene.

1 Rafnar T, Gudbjartsson DF, Sulem P, *et al.* Mutations in *BRIP1* confer high risk of ovarian cancer. *Nat Genet* 2011;43:1104–7.
2 Pennington KP, Walsh T, Harrell MI, *et al.* Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res* 2014;20:764–75.
3 Ramus SJ, Song H, Dicks E, *et al.* Germline mutations in the *BRIP1, BARD1, PALB2,* and *NBN* genes in women with ovarian cancer. *J Natl Cancer Inst* 2015;107:pii:djv214.

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Poster P090

Clinical Actionability of Multigene NGS-Based Tests for Hereditary Cancers in a Large Multicentre Study

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Background Genetic testing for hereditary breast and ovarian cancer is evolving with the introduction of multigene panels, and yet questions remain about these new tests. Most importantly, do these tests affect clinical management despite the increased uncertainty that naturally follows from testing more genes in more patients?

Methods In recently published work[1], we tested 25–29 cancer-risk genes in a prospective cohort of more than 1000 patients, all of whom met criteria for *BRCA1/2* testing and were *BRCA1/2*–negative. After panel testing, we evaluated management actions that would be recommended considering gene-specific consensus management guidelines, gene-associated cancer risks, and personal and family history, and compared those to recommendations based on personal and family history alone. In ongoing work, we continue to monitor the potential actionability of mutations found in more than 10,000 patients studied retrospectively in both laboratory-based and clinic-based populations.

Results In the prospective cohort, 63 patients harboured mutations in genes other than *BRCA1/2*. In a great proportion (>90%), the presentation in the patient or their family was consistent with the known effects of the gene they carry. However, many of these patients would not have met testing guidelines for that gene. A change in management would be considered for more than half these patients, and a change would be considered for an even larger fraction (72%) of their first-degree relatives, if also found to be mutation-positive. Ongoing analyses of prospective and retrospective populations suggests a roughly similar degree of clinical actionability.

Discussion In appropriately referred patients, multigene testing yields clinically relevant findings with potential management effects for substantially more patients than does *BRCA1/2* testing alone. (De-identified data from patients in this study has been contributed to the ClinVar database.)

1 Desmond A, Kurian AW, *et al.* Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol* 2015;1:943–51.

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Poster P091

Prospective Evaluation of Plasma Folate, B6 and B12, and Breast Cancer Risk in *BRCA1/2* Mutation Carriers

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Objectives Folate and other B vitamins play an important role in DNA synthesis, repair, stability, and methylation, aberrancies of which have been implicated in cancer development. In the general population, high blood folate concentrations and folic acid (synthetic folate) supplement use has been associated with an increased breast cancer risk. Given that high folate status is prevalent in North America, it is of interest to clarify the role of the B vitamins in breast cancer development among women with a *BRCA1/2* mutation. Thus, we prospectively evaluated the relationship between plasma folate, pyridoxal 5′-phosphate (PLP, the biologically active form of vitamin B6) and B12, and breast cancer risk among women with a *BRCA1/2* mutation.
Methods Baseline blood samples and questionnaire data were available from 173 eligible women with no previous history of breast or ovarian cancer. Plasma B vitamins were categorized dichotomously as high or low based on the upper and lower 75th percentile of each B vitamin distribution in the final cohort. Cox proportional hazards were used to estimate relative risk (RR) and 95% confidence intervals (CIs) for the association between plasma biomarkers of each B vitamin and incident breast cancer.
Results Over a mean follow-up of 6.1 ± 4.6 years, 21 incident cases of primary breast cancer were observed. Women with high plasma folate concentrations (>24.5 ng/mL) were associated with a significantly increased breast cancer risk (RR: 3.60; 95% CI: 1.28 to 10.14; p trend = 0.03) compared with those with low plasma folate (≤24.5 ng/mL). Plasma PLP and B12 were not associated with breast cancer risk. There was no evidence of effect modification by alcohol, menopausal status, or *BRCA* mutation type.
Conclusions Findings from this study suggest that elevated plasma folate concentration may be associated with an increased risk of breast cancer among women with a *BRCA1/2* mutation. Further studies are warranted to clarify this relationship.

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Poster P092

Are Cancer Risks for the *CHEK2* Founder Mutation c.1100del Applicable to Other Pathogenic Variants in *CHEK2*?

Amanda Gammon,* John Abernethy,† Eric Rosenthal,† Heidi Gorringe,† Krystal Brown,‡ John Kidd,‡ Susan Manley†

Objectives Current cancer risk estimates for pathogenic variants (PVs) in *CHEK2* are based largely on studies of the c.1100del founder mutation common in individuals of European ancestry. We compared the clinical histories of individuals with c.1100del to those with other PVs in *CHEK2* to determine if these risk estimates are applicable to other *CHEK2* PVs. This is an important issue in the era of panel testing, because risk estimates for newer genes are often based on data heavily weighted toward founder mutations studied in limited populations.
Methods Individuals ascertained for suspected hereditary cancer risk were tested with a clinical 25-gene hereditary-cancer panel between 20 September 2013 and 14 August 2015. Clinical information was obtained via health care provider report on the test request forms. Variants with a laboratory classification of "deleterious" or "suspected deleterious" were regarded as pathogenic. The cohort excluded 48 individuals with PVs in *CHEK2* and another gene.
Results Of 1001 individuals identified with a PV in *CHEK2*, 644 (64.3%) had c.1100del. One of 104 different PVs in *CHEK2* were identified in 357 (35.7%). Pathogenic variants other than c.1100del were found in individuals of all ancestries. Comparing histories of breast and other cancers, early-onset breast cancer (diagnosed before age 50), triple-negative breast cancer, and median age of diagnosis, we found no evidence for any significant differences in the cancer risks associated with c.1100del or with other PVs in *CHEK2*.
Conclusions Based on this analysis, risk estimates for *CHEK2* carriers based on c.1100del appear to be applicable to individuals with any PV in *CHEK2*.

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Poster P093

Implementing a Customized Multiplex Panel Testing Pathway for Hereditary Cancer

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Introduction Massive sequencing is being implemented in clinical practice of hereditary cancer. Because of the large amount of data generated and their complexity, its optimal clinical implementation requires evidence from gene prevalence, clinical utility, and analytical validity of techniques. Two main national health system centres (Institut Català d'Oncologia, ICO, and Hospital Vall d'Hebron, HVH) offering genetic diagnosis of hereditary cancer in Catalonia (Spain) have established an alliance with the aim of generating a common approach on these procedures.
Methods A consensus strategy was proposed for genetic testing algorithms of several panels according to patient phenotype, as well as for consent forms, bioinformatic analysis, and storage of genetic information. Evidence from the literature and from research studies in our setting were considered. Preliminary research data were obtained from ICO testing 122 genes in 24 samples with known mutations and validation in 40 prospective cases, and HVH testing 98 genes in 200 breast/ovarian *BRCA*-negative individuals.
Methods SureSelect XT Agilent, Miseq Illumina, confirmation by Sanger.
Results A 2-step algorithm for a clinical panel comprising 3 (level 1) and 11 (level 2) genes for breast–ovary patients, and 5 (level 1) and 9 genes (level 2) for colon–endometrial patients was agreed. Other genes will continue under investigation in an extended panel and might be incorporated. The research panels provided unexpected findings in high- and moderate-penetrance genes (*PMS2, BRIP1, RAD51D, SMAD4, CHEK2, KLLN,* and *POLD1*), mutations in genes that would have traditionally been tested sequentially (*TP53, PALB2, PTEN, RAD51D*), and variants of unknown significance in several genes.
Conclusions In a dynamic setting, we opted for a panel of genes based on prevalence and clinical indication with the possibility of increasing knowledge through a research wider panel. Multiplex panel testing from the research projects improved the genetic diagnosis of hereditary cancer through identification of mutations in genes with clinical utility.

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Poster P094

Exploring New Regulators of DNA Repair Pathways As Predictors of Response to Chemotherapy and Overall Prognosis in Ovarian Cancer

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Background Approximately 50% of ovarian cancers exhibit some form of homologous recombination defect. We analyzed the association between DNA repair pathway gene expressions and clinical outcome in a cohort of women with ovarian cancer.
Methods Evaluation of hotspot mutations for 170 DNA repair genes by customized next-generation sequencing (NGS) panel using Roche MiSeq sequencer platform, followed by NanoString customized ncounter panel expression analysis. We further developed a functional assay for HR to evaluate the prevalence of functional defects. We then confirmed the differential expression by immunohistochemistry with further validation by Western blotting.
Results Data indicated a correlation between *ATM, RAD51, RAD52, CHEK2, BRCA1/2,* and *FANCF* repair genes, and clinical outcome. Differences in *RAD51, H2AX, BRCA1/2,* and *FANCD2* foci formation further indicated an association between these DNA repair genes with clinical outcome. Univariate and multivariate analyses are currently ongoing.
Conclusions Differences in DNA repair pathways identified by some combination of NGS, Nanostring, and functional assays correlate with response to treatment in patients with ovarian cancer.

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Poster P095

Tumour Subtype and Age-Specific Breast Cancer Risk Estimates for *CHEK2**1100delC Carriers

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Objectives *CHEK2**1100delC is a well-established breast cancer risk variant, mostly prevalent in European populations. However, there are

limited data on risk of breast cancer by age and subtype, limiting its usefulness in breast cancer risk prediction. We aimed to generate tumour subtype and age-specific risk estimates using data from the Breast Cancer Association Consortium, including 44,777 breast cancer cases and 42,997 controls from 33 studies genotyped for *CHEK2**1100delC.

Methods Data were extracted from the Breast Cancer Association Consortium database. *CHEK2**1100delC genotyping had been done mostly by a custom TaqMan assay. Breast cancer relative risks [odds ratios (ORs)] for *CHEK2**1100delC carriers versus noncarriers were estimated using logistic regression. Analyses were adjusted for study (categorical) and age; the main analyses presented here only included invasive breast tumours from population- and hospital-based studies.

Results The proportions of *CHEK2**1100delC carriership in controls, breast cancer patients from population- and hospital-based studies, and breast cancer patients from familial or clinical genetics centre–based studies were 0.5%, 1.3%, and 3.0% respectively. The estimated OR for invasive breast cancer was 2.26 (95% CI: 1.90 to 2.69; $p = 0.23*10^{-19}$). The OR was higher for estrogen receptor (ER)–positive tumours (2.55; 2.10 to 3.10; $p = 0.49*10^{-20}$) than for ER-negative tumours (1.32; 0.93 to 1.88; $p = 0.12$) (p interaction: $0.01*10^{-3}$).

The OR declined with age for ER-positive tumours, from 3.26 (1.05 to 10.18, $p = 0.04$) for women aged < 35 years, to 3.12 (2.13 to 4.58, $p = 0.05*10^{-7}$) for 35–50 years, 2.73 (2.02 to 3.70, $p = 0.07*10^{-9}$) for 50–65 years, and 1.58 (1.01 to 2.49, $p = 0.05$) for women aged 65 and older. This interaction with age was to a lesser extent, and not statistically significantly, seen for ER-negative tumours. Using these relative risk estimates, lifetime (up to 80 years) cumulative absolute risks for women with a *CHEK2**1100delC mutation to develop an ER-positive or ER-negative breast cancer are 3% and 19.5% respectively.

Conclusions These *CHEK2**1100delC breast cancer risk estimates provide a basis for incorporating *CHEK2**1100delC into breast cancer risk-prediction models. Our findings will be discussed in the light of the recent introduction of routine *CHEK2**1100delC diagnostic screening in the Netherlands.

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Poster P096

RNASEL, A Modifier of Breast Cancer Risk in *BRCA1* and *BRCA2* Carriers?

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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 both to manage sequencing artefacts and to annotate variant sharing between relatives. Findings from WES were prioritized by shortlisting candidate genes, based on plausible biology and observation of multiple, rare, predicted deleterious variants, in more than one family. Using these criteria, we identified *RNASEL* as a candidate breast cancer susceptibility gene.

Validation studies have been performed by targeted, massively parallel sequencing of women from the Australian population at high risk of carrying a genetic predisposition to breast cancer (population-based cohort, $n = 600$; women selected by family history, $n = 700$).

We identified 6 carriers (1%) of the truncating variant *RNASEL*:p.E265* in our population-based cohort, 4 of which (67%) also carry a "high-risk" mutation in *BRCA1, BRCA2, ATM,* or *PALB2*. We observed 5 carriers (0.7%) of p.E265* in the women selected by family history, 2 of whom (40%) also carried a "high-risk" mutation. In addition, we identified 1 carrier of a frameshift mutation, *RNASEL*:p.157_158del, who also carries a "high-risk" mutation in *BRCA1*.

Our data indicate that a high frequency of *RNASEL* variant carriers also carry high-risk mutations in known breast cancer susceptibility genes. The variant p.E265* has been included on an OncoArray and genotyped within the BCAC and CIMBA resources.

We will present findings from the sequencing and the OncoArray. We will also present family pedigrees that carry high-risk mutations and rare *RNASEL* variants. We will discuss how this genetic information might affect risk assessment and the clinical management of family members.

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Poster P097

COMPLEXO: Identifying the Missing Heritability of Breast Cancer Via Next-Generation Collaboration

COMPLEXO

Objectives A proportion of the remaining unexplained genetic susceptibility to breast cancer is likely to be explained by many rare mutations in a large number of genes. Coordinated international collaboration offers great potential to advance the discovery of additional breast cancer susceptibility genes by increasing the likelihood of identifying functionally relevant genetic variants in the same genes in multiple families.

Methods COMPLEXO (a name chosen to reflect the complexity of the exome), has been formed to facilitate collaborations between researchers actively applying massively parallel sequencing to understand the genetics of breast and ovarian cancers. The aim of COMPLEXO is to bring to massively parallel sequencing the same power of large sample sets that has proven so successful in examining the role of common variants in cancer populations via the consortium model used by the Breast Cancer Association Consortium, the Ovarian Cancer Association Consortium, and the Collaborative Oncology Gene-Environment Study.

Results Membership of COMPLEXO has grown to 30 institutions. Currently, COMPLEXO has combined the data from 1000 exomes representing women at high risk of breast cancer. Combining data from multiple massively parallel sequencing studies is not straightforward because of differences in sequencing, targeted capture, and bioinformatics platforms. In the first instance, the members combined a standardized file of variant calls and identified a number of candidate genes that are being followed up in targeted sequencing activities by members. To improve the quality of integrated data, COMPLEXO members have contributed FASTQ files to a central point and will process this data via a common analysis and filtering pipeline.

Conclusions We will describe our working and governance structures, our early experiences, and ongoing activities aimed at identifying more of the missing heritability of breast cancer.

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Poster P098

Early Results from Panel Testing Using High-Risk Family Analysis in a Large Canadian Cancer Genetics Clinic: 10% Prevalence of Non-*BRCA* Pathogenic Variants

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Objectives To evaluate comprehensive cancer gene panel–positive families and panel–negative families 1) to determine differences in family histories, 2) to determine prevalence of pathogenic variants and unclassified variants (UCVs), and 3) to establish preliminary cancer panel testing criteria.

Methods A clinical database from a large academic cancer genetics program was used to identify probands who had negative *BRCA* testing in the family. Of these probands, those who underwent comprehensive cancer gene panel testing based on clinical judgment were selected. Personal and family history of cancer in first-, second-, and third-degree relatives of each proband were catalogued.

Results A total of 86 probands underwent comprehensive cancer gene panel testing from 5 different companies. Non-*BRCA* pathogenic variants were identified in 10/86 probands (11.6%), and UCVs were identified in 42/86 probands (48.8%). Ten pathogenic variants occurred in the following 5 "moderate-risk" genes: *ATM, CHEK2, PALB2, FANCC,* and *BRIP1*. Preliminary cancer panel testing criteria, when retrospectively applied, would have identified pathogenic variants in 6/10 probands (60%), and UCVs in 19/86 probands (22.1%). Cancer history in panel-positive and panel-negative families were similar, with the exception of panel-positive families consistently having more breast and ovarian cancer cases.

Conclusions Comprehensive cancer gene panel testing using clinical judgment identifies pathogenic variants as often as *BRCA* testing using Ontario Ministry of Health criteria. Criteria for comprehensive cancer gene panel testing are needed, but are difficult to establish because the characteristics of high-risk cancer gene panel positive–, negative–, and UCV families are all very similar. The role of genetic counselling in comprehensive cancer gene panel testing is fundamental, given that all pathogenic variants occurred in moderate-risk genes where cancer risks and screening recommendations are unclear, and that 48.8% of probands had 1 or more UCVs where pathogenicity is uncertain.

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Poster P099

Rare Pathogenic Mutations Causing Hereditary Breast and Ovarian Cancer Beyond Diagnostic Genes

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Hereditary breast and ovarian cancer (HBOC) is caused mainly by pathogenic mutations in *BRCA1* and *BRCA2*. Although several additional genes were linked to HBOC, only a few are part of current diagnostic genetic testing. Here, we present data from 575 patients with family history suspicious for HBOC that underwent genetic testing at our institute between May 2013 and May 2015. Next generation sequencing combined with a panel of 68 genes was applied and analyzed for each patient. Pathogenic mutations were validated using Sanger sequencing. The present study shows the results of all but the diagnostic genes (*TP53, ATM, NBN, PALB2, CDH1, CHEK2, RAD51C, RAD51D, BRCA1*, and *BRCA2*). In total, 2190 variants were detected. All variants were filtered according to frequency (MAF < 1% in common databases), mutation effect (coding), and in-house database.

The remaining 987 variants were classified according the 5-class system published by Plon *et al.*[1]. In 4.5% of patients, pathogenic and likely pathogenic mutations (class 4/5) were found in genes other than the diagnostic genes, including *FANCA* (5 mutations), *FAM175A* (2 mutations), *BARD1* (3 mutations), *MRE11A* (2 mutations), *RAD51B* (1 mutation), *BRIP1* (1 mutation), and *MUTYH* (12 mutations). Co-segregation of these variants with cancer within families was analyzed, and cDNA analysis for splice-site variants was performed to provide evidence for pathogenicity of the variants. Our data suggest that pathogenic mutations can be found in genes other than standard diagnostic genes and that these mutations variations may be of relevance to the families.

1 Plon SE, Eccles DM, Easton D, *et al.* Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Hum Mutat* 2008;29:1282–91.

Affiliation: Institute of Medical Genetics and Applied Genomics, Tubingen, Germany.

Poster P100

Whole-Exome Sequencing Revealed a Novel *PALB2* Mutation in a Male Breast Cancer Family

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Objectives Male breast cancer (MBC) is a rare disease, whose causation appears to be largely associated with genetic factors. Whole-exome sequencing (WES) is a powerful tool to explore the heritability of complex diseases, including breast cancer (BCa). Our aim was to evaluate whether rare mutations may explain a fraction of MBC not accounted for by *BRCA1/2* genes. Here, we applied WES analysis to a high-risk MBC family.
Methods A *BRCA1/2*–negative family with 2 first-degree male and 4 female BCa cases was selected for the study. Peripheral-blood DNA samples from 1 male and 2 female BCa cases were examined. Libraries were prepared and sequenced on the Illumina HiSeq instrument. A bioinformatic pipeline available at https://bioinformatics.cineca.it/wep/ was used. A validation series of 48 high-risk *BRCA1/2*–negative MBC patients from the Italian Multicenter Study on MBC was analyzed by Sanger sequencing.
Results A novel *PALB2* truncating mutation, c.419delA (p.K140fsX35), was identified by WES in a female BCa case and her paternal uncle, diagnosed with melanoma and BCa, but not in her maternal aunt, affected with BCa; her father, diagnosed with BCa, was an obligate mutation carrier. *PALB2* mutational analysis of 48 high-risk MBCs identified another truncating mutation, c.1984A>T (p.K662X), in a man diagnosed with breast, lung, and prostate cancer, and with family history of BCa. Overall, 3/50 high-risk MBCs (6%) were carriers of *PALB2* pathogenic mutations.
Conclusions This study highlights the importance of a particular selection of pedigrees including MBC to better define the fraction of BCa attributable to genetic predisposition. Our results add to the accumulating evidence that *PALB2* is strongly involved in BCa risk in both sexes. Consideration should be given to clinical testing for *PALB2* in *BRCA1/2*–negative families, including not only multiple female BCa cases, but also 1 or more members diagnosed with MBC or other cancers.

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Poster P101

Relationship Between Physical (In)activity and Levels of DNA Repair in Women With and Without a *BRCA1* Mutation

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Objective *BRCA1* maintains genomic integrity through double-stranded DNA break repair by homologous recombination. A state of haploinsufficiency is thought to predispose women with an inherited *BRCA1* mutation to breast cancer. We previously showed that sedentary behaviour was associated with lower *BRCA1* mRNA expression in *BRCA1* mutation carriers. The goal of the current study was to evaluate whether physical (in)activity was associated with levels of DNA repair among women with and without a *BRCA1* mutation.
Methods Levels of physical (in)activity from 25 *BRCA1* mutation carriers and 25 noncarriers were collected and categorized as high vs. low using the 75th percentile. The DNA repair capacity of peripheral blood lymphocytes was measured at baseline and after cell exposure to gamma irradiation (2 Gy) using 3 validated assays: 1) the single-cell alkaline gel electrophoresis (comet) assay (tail moments), 2) the micronucleus test (per 1000 binucleated cells), and 3) the enumeration of gamma-*H2AX* nuclear foci. Multivariate linear regression was used to evaluate the associations between physical (in)activity and DNA repair.
Results Among all 50 women, physical (in)activity was not associated with measures of DNA repair ($p \geq 0.06$). Findings differed when stratified by *BRCA1* mutation status. Among *BRCA1* mutation carriers, women with high sedentary time (hours/week) had significantly higher baseline mean tail moments than did women with low sedentary time (3.88 vs. 2.30, $p = 0.04$). One hour post-irradiation, mean tail moments were not significantly different ($p = 0.09$). Physical (in)activity was not associated with other measures of DNA repair ($p \geq 0.06$). Physical (in)activity was not associated with DNA repair in noncarriers ($p \geq 0.06$).
Conclusions Although preliminary, these findings suggest that decreased *BRCA1* mRNA expression associated with sedentary time may affect DNA repair capacity among *BRCA1* mutation carriers. Prospective evaluations of physical (in)activity and breast cancer risk are warranted.

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Poster P102

Breast Cancer, Macrocephaly, and *PTEN* Mutations in a Familial Cancer Clinic Population

Nicola Poplawski,*† Jacqueline Armstrong,* Gemma Correnti,* Vanessa Huntley,* Alisha McLauchlan,* Sally Russell,* Debra Trott*†

Objective It has been suggested that women with macrocephaly and breast cancer, but no other features of Cowden syndrome, should have genetic testing of the *PTEN* gene. In 2011, measurement of head circumference in women with breast cancer became a routine procedure in our clinic. We aimed to determine the prevalence of pathogenic *PTEN* variants in our clinic-referred population of women with invasive breast cancer and macrocephaly.
Methods Audit period: 1 January 2011–31 December 2015. Using the clinical activity data prospectively entered into the service's clinical patient database, we retrospectively audited the outcome of *PTEN* mutation testing in female probands with breast cancer and a measured head circumference > 97th centile for height. Head circumference was measured by the attending clinician. Height was either that reported by the patient, or as measured by the attending clinician using a wall-mounted height measuring tape. The charts published by Bushby *et al.*[1] were used to determine centiles for adult head circumference. *PTEN* was analyzed in DNA extracted from blood, using Sanger sequencing and MLPA.
Results In the audit period, 43 women with breast cancer and macrocephaly had a mutation search in the *PTEN* gene. Four had a pathogenic variant identified; all had other features of Cowden syndrome, including at least 1 mucocutaneous feature. Three had a variant of uncertain significance; none had other major or mucocutaneous features of Cowden syndrome. The remaining 36 had normal *PTEN* studies, none of whom had mucocutaneous features of Cowden syndrome.
Conclusions Pathogenic *PTEN* mutations are not a common finding in women with breast cancer and macrocephaly who do not have other features of Cowden syndrome. Testing of a larger cohort of women is needed to determine the prevalence of *PTEN* mutations in this clinical setting.

1 Bushby KM, Cole T, Matthews JN, Goodship JA. Centiles for adult head circumference. *Arch Dis Child* 1992;67:1286–7.

Affiliations: *SA Pathology at the WCH, North Adelaide, and †University of Adelaide, Adelaide, Australia.

Poster P103

Homozygosity for the *FANCM* C.1972C>T (p.Arg658X) Nonsense Mutation in a Patient with Early-Onset Breast Cancer, Endometrial Carcinoma, and Recurrences of HNSCC but Not Fanconi Anemia: A Case Report

Irene Catucci,* Giovanna De Vecchi,* Federica Zanardi,* Simone Minardi,* Mirko Riboni,* Jacopo Azzollini,† Bernard Peissel,† Lidia Pezzani,† Sara Volorio,‡ Valeria Pensotti,‡ Stefano Casola,* Paolo Radice,† Siranoush Manoukian,† Paolo Peterlongo*

Fanconi anemia (FA) is a recessive disease characterized by bone marrow failure, chromosome fragility, nonhematologic cancers and malformations. To date, 15 different FA genes have been identified (*FANCA, B, C, D1/BRCA2, D2, E, F, G/XRCC9, I, J/BRIP1, L, N/PALB2, P/SLX4, Q/ERCC4* and *T/UBE2T*). An FA-like syndrome that does not include bone marrow failure is caused by mutations in the *FANCO/RAD51C, R/RAD51* and *S/BRCA1* genes. Monoallelic mutations in some of the FA and FA-like genes are associated with breast cancer risk. Pathogenic variants of *FANCS/BRCA1, D1/BRCA2* and *N/PALB2* are recognized high-risk factors for the disease, while evidences of the effect of mutations in other genes including *FANCJ/BRIP1, O/RAD51C* and *R/RAD51* are less convincing or initial.

The role of an additional gene, *FANCM*, in FA is still controversial. However, as for other FA genes, monoallelic *FANCM* mutations have been reported to be moderate breast cancer risk factors. Here, we present the case of a woman born to first-cousin parents who developed breast cancer at 29 years, several head-and-neck squamous cell carcinomas (HNSCC) possibly because of radiosensitivity, and endometrial adenocarcinoma at age 51, but without evidence of FA. This patient was screened for mutations by next-generation sequencing in 20 known or candidate breast cancer predisposition genes, and among the 29 variants found, the homozygous nonsense mutation c.1972C>T (p.Arg658X; rs368728266) of *FANCM* was observed. To our knowledge, this is the first report of a cancer phenotype in a carrier of biallelic *FANCM* mutations.

Our data sustain the notion that biallelic mutations in *FANCM* are not causing FA. Nevertheless, additional data may clarify if lack of *FANCM* function associates with a milder FA-like syndrome characterized by breast cancer, radiosensitivity, and HNSCC recurrences. Our observations also indicate that homozygous *FANCM* truncating mutations might be high-risk factors for breast cancer.

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Poster P104

An Extended Analysis of Hereditary Ovarian Cancer in Poland

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Objectives To date, Poland was recognized as a country with a strong founder effect resulting in a limited spectrum of detected *BRCA1/2* mutations. Yet, more recent studies revealed a large variety of *BRCA1/2* alterations within our population. In addition, recently published papers indicate that a significant portion of breast and ovarian cancer occurs in individuals with germline mutations in other than *BRCA1/2* genes. Therefore, the aim of this study was to estimate the prevalence of mutations in 19 known breast and ovarian cancer genes among Polish patients with ovarian cancer.

Methods The study comprises 141 unselected ovarian cancer patients who were referred to the University Hospital in Gdansk and the Red Cross Hospital in Gdynia between 2012 and 2013. *BRCA1/2* mutation screening was performed using the *BRCA* MASTR assay (v1.2: Multiplicom, Niel, Belgium). Subsequently, all the samples were analyzed using a supplemental assay compromising additional 17 genes (*TP53, PTEN, STK11, CDH1, CDKN2A, CHEK2, PALB2, BRIP1, ATM, RAD50, RAD51, RAD51B, RAD51C, RAD51D, BARD1, NBN,* and *MRE11A*).

Results In the studied group, pathogenic *BRCA1/2* mutations were found in 23 individuals (16.3%). 19 Patients carried *BRCA1,* and 4, *BRCA2* mutations. Molecular analysis of additional 17 genes was performed in 122 patients. In total, 12 pathogenic mutations (9.8%) were found. Five mutations were located in *NBN,* three in *CHEK2,* and single alterations were found in *ATM, BARD1, PALB2,* and *RAD50.* Two patients were found to carry 2 pathogenic mutations; one *BRCA1/CHEK2,* and the other *NBN/PALB2.*

Conclusions Our findings suggest that a significant number of ovarian cancer patients may carry pathogenic mutations in other than *BRCA1/2* genes.The extended panels based on next-generation sequencing should therefore be introduced to routine clinical practice.

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Poster P107

The Comprehensive Analysis of the *CHEK2* Gene in 940 High-Risk Czech Breast/Ovarian Cancer Patients

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Breast cancer (BCA) is the most frequent oncology diagnosis in the Czech female population. Hereditary breast cancers (HBCS) account for 5%–10% of all cases. The most frequent genetic alterations in Czech HBC patients represent *BRCA1* mutations; mutations in *BRCA2* and other known BCA-susceptibility genes occur with lower frequency. Our previous analysis shown that recurrent *CHEK2* variant c.1100delC affects <1% of high-risk individuals. To assess the spectrum and frequency of all *CHEK2* mutation, we performed a mutation analysis of the entire *CHEK2* coding sequence in high-risk BCA and ovarian cancer (OC) patients.

We analyzed 940 samples of patients negatively tested for the presence of pathogenic *BRCA1/2* mutations using a combination of next-generation sequencing (NGS), high-resolution melting analysis, and multiplex ligation-dependent probe amplification. Found variants were genotyped in 990 controls. The catalytic activity of missense variants was analyzed by *CHK2 in vitro* kinase assay.

Eight truncating mutations (including 2 large genomic rearrangements) were identified in 29/940 patients (3.1%) and in 4/990 controls (0.4%, $p < 0.0001$). The highest incidence of these variants was found in the groups of early-onset female BCA patients (7/190, 3.7%) and in HBC patients with 2 BCA cases diagnosed at < 50 years (4/87, 4.6%). The most frequent missense variant was I157T, found in 3.6% patients and 2.7% controls ($p = 0.2$); however, we found also another 14 rare missense variants in 21 patients (2.2%) and 5 controls (0.5%, $p = 0.001$). The kinase assay analysis revealed that all 9 rare missense variants affecting kinase domain in 12 patients resulted in loss of *CHK2* catalytic activity.

Our results indicate that *CHEK2* analysis should be implemented for evaluation of BCA/OC predisposition in our population and should not be restricted to c.1100delC only.

Acknowledgment: This work was supported by the grants NV15-28830A and NV15-27695A.

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Poster P108

Identification of Potential Novel Candidate Genes Linked to Breast Cancer Susceptibility Through Exome Sequencing of Greek Families with Unexplained Hereditary Breast and Ovarian Cancer Syndrome

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Breast cancer (BCA) is the most common type of cancer in women worldwide. Hereditary breast and ovarian cancer (HBOC) accounts for ~10% of BCA cases, a fraction that stems from the genetic effects of rare alleles. At least 20 genes have been linked to BCA susceptibility and more genetic effects remain to be explained. The aim of this project is to identify genetic variants that confer high or medium risk to BCA development through exome sequencing in Greek patients with HBOC syndrome that were found to be negative for mutations in known candidate genes.

Exome sequencing was performed in a total of 15 HBOC syndrome patients and additional 1–3 informative relatives (50 samples in total). Exome capture was through the Ion TargetSeq Exome Capture kit and sequencing was performed on the Ion Proton platform. An analytical pipeline was compiled adapting the GATK software package to IP data.

We detected an average ~55,000 variants per exome. We filtered our data using criteria based on BCA segregation in families, minor allele frequency of variants, and *in silico* functional evaluation. This resulted in a collection of shortlisted variants amounting to 1100 in total (50–150 per family), of which 418 had never been reported before in 1kg, ESP, or EXAC. A validation experiment of the 418 unique variants with independent technology was conducted, which confirmed 88.2% of the variants.

Preliminary analysis has identified ~50 loss-of-function variants including variants in genes *PRDM2*, *KIF2C*, *TUSC3*, and *MDM1*. In addition, a large number of rare missense variants with high pathogenicity scores allocated by bioinformatic prediction tools have been detected, including variants in genes *HIPK1*, *PBRM1*, *WNT16*, and *MAFF*. Further functional validation is necessary to confirm the pathogenicity of the candidate variants.

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PSYCHO-ONCOLOGY

Poster P109

Intuition Versus Theory: Enhancing the Replicability of Patient Behaviour Change Interventions in Cancer Genetics

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Objectives Interventions to support patient behaviour change developed by health care professionals often use intuition rather than theory. Their valuable tacit knowledge can be difficult to communicate, and this creates problems that affect replicability and generalizability. This leads those attempting to solve similar problems to waste time and resources ("reinvent the wheel"). Interventions informed by theory are significantly more effective. The objective of this study is to demonstrate whether an intuitive intervention designed by health care professionals to overcome patient barriers to communicating *BRCA1/2* risk to family members aligns with a theoretical framework of behaviour change.
Methods *Phase 1*: As part of a quality improvement pilot study funded by a translational research grant, barriers to dissemination of information to family members were recorded by a genetics counsellor during 200 telephone interviews with *BRCA1/2* patients within 4 Australian hospitals. Barriers were coded and themed after consultation with the literature. Interventions to overcome barriers were designed and implemented after consultation with experienced colleagues. Pre–post rates of dissemination of information from patients to family members were compared.

Phase 2: A health psychologist worked with the genetics counsellors to code barriers according to a theoretical framework of behaviour change [the Theoretical Domains Framework (TDF)]. Next, interventions designed to address barriers were coded according to a taxonomy of published behaviour change techniques (BCTS).
Results Originally coded key barriers to dissemination ($n = 5$ main themes) aligned with the TDF and represented the following psychological domains of behaviour change: 1) emotion, 2) environmental context and resources, 3) motivation and goals, 4) skills, 5) social role, 6) beliefs about consequences, 7) knowledge. The interventions trialled aligned with theoretical BCTS.
Conclusions Coding intuitively identified barriers and interventions according to theory is possible, facilitating replicability. This supports health care professionals in identifying effective strategies for achieving patient behaviour change and translating cancer genetics evidence into practice.

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RISK ASSESSMENT AND GENETIC COUNSELLING ISSUES

Poster P111

Breast and Ovarian Cancer Prevention: Is It Time for Population Screening for *BRCA* Mutations?

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Germline mutations in *BRCA1* and *BRCA2* confer high lifetime risk of breast and ovarian cancer, but importantly, these risks are not irreversible. Identification of asymptomatic carriers could significantly reduce the incidence of these diseases. The traditional model of familial breast and ovarian cancer practice involves ascertaining high-risk individuals based on family history. In general, the family is first identified because 1 member develops cancer and, because of high-risk indicators, is referred to a familial cancer centre. However, more than 50% of women who carry a *BRCA1/2* mutation may not have a family history of cancer in a close relative. Momentum toward genetic screening of the asymptomatic population is growing, but there remain some significant unknowns. For example, it is unclear what is the true frequency of actionable mutations in the general Western population and the extent to which the public would accept such screening, particularly for those individuals identified with an actionable mutation in the absence of an overt family history.

As a first step toward population-based *BRCA* gene screening, we are sequencing the entire coding region of 18 known and proposed HBOC genes in 4000 cancer-free Australian women recruited from the LIFEPOOL study (http://www.lifepool.org.au/), which is a cohort of women attending the Australian population-based mammographic screening program. To date, data from 1997 women have identified 17 with actionable mutations in *BRCA1* (4 mutations), *BRCA2* (9 mutations), or *PALB2* (4 mutations). All 17 women subsequently accepted an invitation to attend a familial cancer centre and then proceeded to formal clinical genetic testing. In addition 4 women had pathogenic mutations in *BRIP1*.

Our unique pilot data directly demonstrates a population carrier frequency of ~1% for pathogenic mutations in these recognized high-risk breast and ovarian cancer genes and that such testing is well accepted by the screened population.

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Poster P112

Absolute Breast and Ovarian Cancer Risks in *BRCA1* or *BRCA2* Mutation Carriers

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Background Accurate absolute risk estimates are necessary for clinical decision-making in women with inherited *BRCA1* or *BRCA2* (*BRCA1/2*) mutations. No estimates of breast (BCA) and ovarian cancer (OVCA) risk for *BRCA1/2* mutation carriers are available that consider 2 well-established *BRCA1/2*–associated cancer risk modifiers: risk-reducing salpingo-oophorectomy (RRSO) and oral contraceptive (OC) use.
Methods We estimated absolute risks of BCA and OVCA according to age at RRSO and history of OC use, with baseline hazard rates of cancer, hazard ratio estimates of RRSO and OC, and hazard rates of competing mortality obtained from published data.
Results For *BRCA1*, absolute risk of BCA between ages 30 and 70 years was 39.7% (range: 33.5%–45.9%) if RRSO is used at age 40 and 49.9% (range: 41.5%–57.8%) if RRSO is not used before age 70. For OVCA, risks were 5.1% and 49.0% (range: 42.2%–55.7%) respectively. Absolute lifetime OVCA risk if RRSO is used at age 40 was 4.9% for OC ever-users and 6.3% for never-users, and becomes 8.6% (range: 7.0%–11.1%) and 13.1% (range: 10.3%–17.4%) respectively if RRSO is used at age 45 instead. For *BRCA2*, absolute BCA risk between ages 30 and 70 years was 36.1% (range: 25.4%–48.5%) if RRSO is used at age 40 and 52.6% (range: 38.7%–66.4%) if RRSO is not used before age 70. The corresponding estimates for OVCA were 2.6% and 20.7% (range: 14.8%–27.9%) respectively.
Conclusions Absolute risk estimates varied by age at RRSO and OC use. With validation, these estimates can help to optimize risk assessment and counselling of *BRCA1/2* mutation carriers.

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Poster P113

The Prevent Ovarian Cancer Program: A New Model for the Identification and Care of Women at Risk for Ovarian Cancer

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Objectives To perform comprehensive germline testing and genetic counselling in 1000 women with a first-degree relative who died from high-grade serous ovarian cancer, but who may not have received *BRCA1/2* genetic testing as per Ontario Ministry of Health criteria.
Methods Potential participants self-identify in response to an ongoing educational campaign, followed by eligibility screening, confirmation of diagnosis, and panel-based next-generation sequencing for established and emerging hereditary cancer genes. Genetic counselling is provided before sequencing using a standard or modified process, and again when results are disclosed. As part of the consent process, participants indicate whether they prefer to receive results for *BRCA1/2* only or additional genes available on the panel in a binned fashion. The psychosocial impacts of panel testing and modified counselling are determined using validated scales at multiple time points. Clinical follow-up and risk-reducing surgeries are facilitated based on test results.
Results Since launching the program Web site (http://www.preventovariancancer.ca) in May 2015, there have been 15,819 page views and 255 women from across Ontario have registered. Initial eligibility criteria were met by 218 women, of whom 126 enrolled to date after review of their deceased relative's pathology report. Of those enrolled participants who completed a family history questionnaire, 80/81 (99%) do not meet provincial testing criteria based on risk estimation models. On a baseline questionnaire, 53/81 (65%) women indicated that they would like to receive

results for all genes being tested; 30/32 (94%) expressed this wish after completion of pre-test genetic counselling. Genetic results are pending.
Conclusions The Prevent Ovarian Cancer Program is successfully identifying a population of women who may be at increased risk for ovarian cancer. The majority of participants wish to receive results for all genes on an expanded panel after preliminary genetic counselling. These findings are compatible with recent trends toward greater patient empowerment in medical decision-making.

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Poster P114

Performance of *BRCA1/2* Mutation Prediction Models in Male Breast Cancer Patients

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Objectives Female breast cancer patients are offered genetic testing based on mutation probability calculated by prediction models. However, it is not known whether these models accurately predict mutation probability in males. As a result, all male breast cancer patients are currently offered DNA screening. We compare the performance of 3 commonly used *BRCA1/2* mutation prediction models, BOADICEA, BRCAPRO, and Myriad to determine if one of these models is suitable to decide which male patients should be tested.
Methods We evaluated BOADICEA, BRCAPRO, and Myriad using family history data of 307 male breast cancer index cases who were tested for *BRCA1/2* at Dutch family cancer clinics, of whom 58 (19%) were *BRCA1/2* mutation carriers. We compared the numbers of observed versus predicted mutation carriers and assessed the area under the receiver operating characteristic curve (AUC) for each model.
Results BOADICEA quite accurately predicted the total number of *BRCA1/2* mutation carriers (observed/predicted ratio: 0.94). However, when a cut-off of 10% and 20% mutation probability was used, BRCAPRO performed better (observed/predicted ratio BOADICEA: 0.81 and 0.79; BRCAPRO: 1.02 and 0.94 respectively). Myriad underestimated the number of mutations in up to 69% of the cases. Compared with BOADICEA, BRCAPRO showed a nonsignificantly higher AUC (0.798 vs. 0.776). Myriad showed a significantly lower AUC (0.671).
Conclusions Our results support the use of BRCAPRO and BOADICEA for determining the probability of carrying a *BRCA1/2* mutation in male breast cancer patients.

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Poster P115

Population-wide Versus Risk-Based *BRCA1/2* Mutation Testing in the Washington Ashkenazi Study

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Objectives Population-wide *BRCA1/2* testing is a special case of risk-based *BRCA1/2* testing, in which the carrier-probability threshold for testing is the mutation prevalence in the population (without regard to family history). We estimate the performance of population-wide vs. risk-based *BRCA1/2* testing in the Washington Ashkenazi Study (WAS), a population-based study of Ashkenazi volunteers.
Methods We calculated the impact of *BRCA1/2* testing for detection and for prevention of breast cancer by risk-reducing salpingo-oophorectomy (RRSO). We considered 4 cohorts of age 40 probands with no personal cancer history, each with a family history that defines their carrier-probability: 10% and 5% (two currently used testing thresholds), 2.5% (all Ashkenazim), and 0.25% (general non-Ashkenazi population). We estimated the sensitivity, specificity, and area under the curve (AUC equal to the average of sensitivity and specificity) for *BRCA1/2* testing to identify breast cancer in the 4 cohorts. Because there was no follow-up in WAS, we combined available WAS data with parameters from the BRCAPRO risk model to estimate the expected reduction in breast cancer incidence from RRSO.
Results As *BRCA1/2* carrier-probability decreases (10%, 5%, 2.5%, 0.25%), the specificity of *BRCA1/2* testing to predict breast cancer incidence increases (94.3%, 97.2%, 98.6%, and 99.9% respectively). However, sensitivity collapses (41%, 25%, 14%, 1.5% respectively), driven by the decreasing fraction of total breast cancers that are *BRCA1/2*–related as carrier-probability decreases. The AUC falls with declining risk threshold (0.68, 0.61, 0.56, and 0.51 respectively), showing that *BRCA1/2* testing has a poorer ability to predict breast cancer incidence as carrier-probability decreases. If all *BRCA1/2* mutation-positive probands underwent RRSO, we estimate that the yearly incidence of breast cancer in each cohort would decrease by 83, 42, 21, and 2 cases per 100,000 respectively.
Conclusions Because the cancer-prevention benefit of *BRCA1/2* testing plummets with decreasing carrier-probability, cost-effectiveness analyses should focus on identifying a cost-effective carrier-probability threshold for *BRCA1/2* testing.

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Poster P116

The Expanding Phenotype of *PALB2*-Related Cancer: Clinical Presentations of 106 Identified Carriers

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Objectives *PALB2* is now known to be a moderate- to high-penetrance breast cancer predisposition gene, with lifetime risks for breast cancer that vary based on family history from 30% to more than 60%[1]. It has been suggested that other cancer types, including ovarian, pancreatic, and prostate cancer, may also be prevalent in *PALB2*-positive families; however, data supporting these associations are limited. In this case series, we describe the clinical presentation of 106 *PALB2* mutation carriers, to further delineate the spectrum of cancers reported in affected families.
Methods 106 Sequential clinical cases with a pathogenic or likely pathogenic variant in *PALB2* were analyzed. De-identified personal and family histories were provided by ordering clinicians.
Results Among the 106 patients assessed (100 females, 6 males), 79 had a personal history of cancer and 27 were unaffected carriers. Of the 79 cancer-affected patients, almost half were 49 years old or younger, and 5 were younger than 35; 14% presented with bilateral breast cancer, and 14% presented with breast cancer and an additional primary tumour; 8% had triple-negative breast cancer; 13% reported a personal history of pancreatic cancer (4 of whom were males); 73% of affected carriers described a significant family history of cancers.
Conclusions In these cases, we observed early-onset breast cancer and multiple primary cancers in both the patient and at-risk family members, consistent with a high-penetrance effect of *PALB2* in a subset of families, including the 17% of patients who presented with multiple primary tumours, including prostate, colorectal, thyroid, endometrial, gastric, melanoma, and other cancers. This study suggests that clinicians need to consider *PALB2* mutation status in a broadening spectrum of cancer phenotypes to inform risk assessment and management decisions, and that more research is warranted to understand the relationship between *PALB2* and other cancer risks.

1 Antoniou AC, Casadei S, Heikkinen T, *et al.* Breast-cancer risk in families with mutations in *PALB2*. *N Engl J Med* 2014;371:497–506.

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Poster P117

Baseline Characteristics and Psychosocial Profile of Hong Kong Chinese Females Eligible of Undertaking Genetic Counselling and Testing for Hereditary Breast and Ovarian Cancers

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Objectives Genetic testing for hereditary breast and ovarian cancer syndrome (HBOC) can facilitate more precise risk estimations, can guide surveillance regimes and prophylactic procedures, and has become the standard of care in most developed countries. The present study focused on studying the baseline characteristics and psychosocial profile of at-risk individuals undertaking genetic counselling and testing for HBOC among Southern Chinese females residing in Hong Kong.
Methods Hong Kong Chinese females who met the selection criterion were offered free genetic counselling and testing service sponsored by The Hong Kong Hereditary Breast Cancer Family Registry. They were surveyed in a face-to-face interview at a multidisciplinary breast clinic before they received pre-testing genetic counselling consultation. Sociodemographic information, medical history, pre-testing knowledge on HBOC, coping style, and mood were also obtained.
Results The study recruited 142 females (88.7% with cancer history). Better pre-testing baseline knowledge on HBOC was significantly associated with higher education level ($p < 0.001$) and younger age ($p < 0.001$). Cancer survivors were more resourceful in coping when facing adversities in life ($p < 0.05$). A minority of participants (9.9%) showed considerable level of

depressive mood even at the pre-testing stage (all of them with cancer history). However, cancer survivors anticipated greater positive changes and posttraumatic growth if they proved to be mutation-carriers ($p < 0.05$) and more likely to believe that a negative result will bring relief ($p < 0.05$) if to be compared with those without cancer history.

Conclusions Results showed that high-risk Hong Kong Chinese females with cancer history, higher education level, and younger age were more receptive to breast cancer risk assessment. Although enduring a relatively higher level of distress if to be compared with their non-cancer counterparts, cancer survivors appeared to be more resourceful in coping methods when facing life adversities and their self-perceived resilience was higher in terms of facing a possible positive genetic testing result.

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Poster P118

Factors Associated with Interest in Gene-Panel Testing and Risk Communication Preferences in Women from *BRCA1/2*–Negative Families

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Scientific advances have allowed the development of multiplex gene panels to assess many genes simultaneously in women who have tested negative for *BRCA1/2*. We examined correlates of interest in testing for genes that confer modest and moderate breast cancer risk and risk-communication preferences for women from *BRCA*-negative families.

Female first-degree relatives of breast cancer patients who tested negative for *BRCA1/2* mutations ($n = 149$) completed a survey assessing multiplex genetic testing interest and risk-communication preferences. Interest in testing was high (70%) and even higher if results could guide risk-reducing behaviour changes such as taking medications (79%). Participants preferred to receive genomic risk communications from a variety of sources including primary care physicians (83%), genetic counsellors (78%), printed materials (71%), and the Web (60%). Factors that were independently associated with testing interest were perceived lifetime risk of developing cancer [odds ratio (OR): 1.67; 95% confidence interval (CI): 1.06 to 2.65] and high cancer worry (OR: 3.12; CI: 1.28 to 7.60).

Findings suggest that women from *BRCA1/2*–negative families are a unique population that are especially primed for behaviour change. Findings also provide guidance for clinicians who can help develop genomic risk communications, promote informed decision-making, and customize behavioural interventions.

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Poster P119

Factors Associated with *BRCA1/2* Status in Ovarian Cancer Patients: Who to Select for Genetic Testing?

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Objectives Identifying clinical, demographic, and tumour characteristics that predict *BRCA1/2* status in patients with ovarian cancer.

Methods From October 2012 to February 2015, 100 women diagnosed with invasive ovarian carcinoma between 2009 and 2014 who were undergoing follow-up or treatment in a tertiary hospital in São Paulo (Brazil) were enrolled in this cross-sectional single-centre study. There were no restrictions for age or family history of cancer. Information regarding demographic characteristics, medical background, and personal and family history of cancer was obtained from all patients. After informed consent, a blood sample was collected from each patient for genetic testing. Deleterious *BRCA1/2* mutations were identified in 19 patients. Patients were classified in two groups according to the results of their genetic test: carriers and noncarriers of *BRCA1/2* mutations. Univariate and multivariate logistic regression analyses were performed to detect possible predictors of a patient's *BRCA1/2* status.

Results Multivariate analyses revealed that *BRCA1/2* mutations were more frequent among women who had a 10% or higher predicted probability of testing positive for a *BRCA1/2* mutation according to the Manchester scoring system, which is based on personal and family history of cancer (OR: 5.49; 95% CI: 1.74 to 17.34). Moreover, mutations were less frequent among women who reported menarche before age 12 (OR: 0.16; 95% CI: 0.04 to 0.62). If selection of patients for genetic testing was based on these two factors, 17 patients would have been tested, 8 of whom had a mutation (sensitivity: 42.1%; specificity: 88.9%); 9 mutation carriers would have been missed.

Conclusions The predictability of *BRCA1/2* status among ovarian cancer patients using risk-prediction models is limited. Although the predicted probability of testing positive according to the Manchester scoring system and age at menarche were significant predictors of mutation status, their accuracy was not sufficient for selecting patients for genetic testing in this clinical setting.

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Poster P120

Determining Genetics Referral Eligibility for Hereditary Breast/Ovarian Cancer Risk Assessment: An Electronic Solution

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Objectives To develop and validate an electronic tool to enhance referrals to the Familial Breast/Ovarian Cancer Clinic.

Methods Patients attending the Breast Diagnostic Clinic were recruited for this nonrandomized 3-phase study, in which paper questionnaires (PQS) and surgeon assessments were traditionally used to determine genetics referral eligibility. In phase 1, patients completed PQS ($n = 201$). In phase 2, an electronic tool (ET) was developed; tested for usability, readability, design, and interface. Tool accuracy assessed by comparing results for patients completing both PQ and ET ($n = 100$). In phase 3, patients completed ET only ($n = 200$). Health records reviewed to determine data accuracy. Number of study patients eligible for referral compared with referrals received across all 3 phases. Patient/provider satisfaction assessed.

Results Sex, education, number of patients with breast/ ovarian cancer, age at diagnosis, family history, proportion of patients meeting referral criteria were similar across all study phases. No statistically significant differences in either the number of patients eligible for referral or overall referral rates (phase 1: 16.9%; phase 3: 18.0%) was found. Patients preferred (67%) ET over PQ. Patients found ET questions easier to complete and understand. Physician satisfaction was higher with ET in reviewing family history, identifying eligible patients, making timely referrals.

Conclusions The ET was accurate and useful in determining referral eligibility. Similar referral rates were seen across study phases. Patients and physicians had positive experiences with the ET. It is feasible to use this tool to identify patients eligible for genetics referral. Further studies are in progress to investigate why some eligible patients were not referred.

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Poster P122

Fast-Track Genetic Counselling Determines Breast Cancer Risk in Families with a Limited Family History of Breast and/or Ovarian Cancer and Increases Patient Capacity

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Objectives Patients with a family history of cancer are traditionally referred to a clinic of medical genetics for genetic counselling and potential genetic testing. The process of evaluating family history of cancer, confirming diagnosis and getting in contact with an affected family member for genetic testing is time-consuming. When Angelina Jolie announced in public that she was a *BRCA1* mutation carrier, the referrals to our department were doubled. To handle the increasing waiting list, we had to reorganize our clinic.

Methods From June 2014 to October 2015, 1450 patients referred to us with a personal history of breast and/or ovarian cancer or with at least 1 first degree relative with breast cancer below 50 years or ovarian cancer at any age were offered 30 minutes of genetic counselling. The patient had, prior to this consultation, received written information about hereditary breast and ovarian cancer and after consultation was offered a complete *BRCA1/2* test.

Results Of the 29 (2%) patients identified with a deleterious *BRCA1/2* mutation, 23 were unaffected, 4 had breast cancer, 1 had ovarian cancer, and 1 had prostate cancer. One patient with ovarian and endometrial cancer in the family was offered extended genetic testing and was identified with a deleterious mutation in the *MSH6* gene. Variants of uncertain clinical significance in *BRCA1/2* were found in 48 (3.3%) patients. Because of less time spent evaluating family history, our clinic increased its patient capacity dramatically.

Conclusions Fast-track genetic counselling is a useful and effective way to determine cancer risk in families with breast or ovarian cancer. Offering genetic testing to healthy first-degree relatives reveals a significant number of deleterious *BRCA1/2* mutations, even though these families do not necessarily meet the standard criteria for hereditary breast cancer. Fast-track counselling is time-saving and increases patient capacity.

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Poster P123

Challenging the Cancer Genetic Counselling Unit with Treatment-Focused Genetic Testing for Ovarian Cancer Patients: The ICO Network Experience

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Since the approval of the PARP inhibitor olaparib, the treatment-focused genetic testing (TFGT) indications for ovarian cancer (OC) have increased. Furthermore, several guidelines include genetic testing for all non-mucinous OC patients regardless of age and family history. All these new indications challenged our Cancer Genetic Counselling Unit (CGCU) and Molecular Diagnosis Laboratory (MDL).

The ICO network comprises 3 CGCUs and 2 Cancer Family Units (CFUs), all being referral centres for a total of 25 hospitals that cover a population of 3.5 M inhabitants. In December 2014, the Gyne Oncologists Team (GOT), CGCU members, and MDL established a consensus protocol on indications for risk assessment (RA) and TFGT. An express track for RA at CGCU/CFU (0–10 days) and test results delivery (<35 days) was defined for patients whose germline *BRCA1/2* test results were needed to tailor their treatment.

Between 1 Jan and 30 Nov, 115 new OC patients were seen at the CGCU/CFU, with 27 (23%) following the express track. Median time from referral date to test results for standard GC was 77 days (36–98); it was 27 days (18–65) for express GC. Median age was 59 (23–80), and 63% had no family history of cancer. Serous carcinoma was the most frequent histology (96%). *BRCA1/2* results were available for 100 patients. Deleterious mutations and VUS were identified in 22% (15% in the group without family history of cancer) and 9% of patients respectively.

The development of an express GC track for OC patients with a potential olaparib indication allowed us to offer RA and *BRCA1/2* TFGT through our CGCU/CFU, thus avoiding direct testing from the GOT. Time to first appointment for RA and test results was optimal for patients with olaparib indication. The relatively high frequency of *BRCA1/2* mutations could be explained by the bias selection of patients with platinum-sensitive relapse.

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Poster P124

Ashkenazi Jewish Descent and Panel Testing: Beyond *BRCA* Founder Mutations

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Objective Most hereditary breast and ovarian cancer syndrome in individuals of Ashkenazi Jewish (AJ) ancestry is attributed to 3 founder mutations in *BRCA1* and *BRCA2*. Recently, multigene panel testing (MGPT) has allowed testing to expand beyond these genes. The purpose of this study is to determine the frequency of mutations beyond the *BRCA* founders in AJ individuals undergoing MGPT.
Methods Test results were reviewed for individuals undergoing MGPT from June 2013 to September 2015 at 1 diagnostic laboratory. Individuals underwent sequencing and deletion/duplication analysis of 5–49 genes. Ethnicity was obtained from requisitions. Statistical analyses were performed using the Fisher exact test.
Results Of 77,133 individuals undergoing MGPT, 5143 were AJ. 566 Mutations were identified in 541 AJ individuals, yielding an overall positive rate of 10.5%. Of these, 27.9% (n = 158) of mutations were in *BRCA1/2*, 18.4% (n = 29) of which were non-founders. The remaining 72.1% (n = 408) of mutations were in non-*BRCA* genes (n = 131 were moderate-risk mutations: *APC* p.I1307K and *CHEK2* p.I157T). Mutations were detected in 28 genes, with *APC, CHEK2, FH,* and *ATM* most commonly mutated non-*BRCA* genes (7.0%, 3.7%, 1.9%, and 0.9% of individuals tested for each gene respectively). Interestingly, when comparing across ethnicities, AJ individuals were less likely to test positive for *PALB2* (0.3% vs 0.8%, $p < 0.001$), but had, overall, the highest mutation-positive rate in non-*BRCA* genes (10.5% vs. 8.7%, $p < 0.001$).
Conclusions Beyond the 3 founder mutations in *BRCA1* and *BRCA2*, 437 mutations were identified, raising the question of when to offer founder mutations vs. MGPT. Prospective cohorts of AJ individuals undergoing MGPT are needed to further assess the prevalence of non-founder mutations. Our results demonstrate that AJ individuals who are candidates for *BRCA1* and *BRCA2* genetic testing are also candidates for MGPT.

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Poster P125

Assessing Hereditary Predisposition to Cancer: Multigene Panel Testing in Breast Cancer Patients

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Objective We sought to investigate our centre's experience with multigene panel testing in breast cancer patients. Our goal was to identify predictors of variants (pathogenic or uncertain significance) and assess management changes based on test results.
Methods We conducted a retrospective review of breast cancer patients who underwent panel testing between May 2011 and August 2015. A variety of commercial gene panels were used with variant classification determined by the individual laboratory. Differences in patient demographics, tumour characteristics, number of primaries, prior *BRCA1/2* testing, and family history were analyzed among pathogenic variant, negative, and VUS patient subsets with a chi-square test and one-way ANOVA. Binary logistic regression analysis was used to find potential predictors of mutation. Post-test change in management was identified by chart review.
Results We identified 139 patients who underwent panel testing: the average age of patients was 53 ± 12, with cancer onset at 46 ± 12; 54% lived in USDA rural areas; 24% had multiple primaries; 29% had prior single-gene testing; 54% had receptor-positive tumours, 7.2% had HER2+ tumours, and 19.4% had triple-negative tumours. Overall, 26% had positive test results, with 14% having VUS and 15% having pathogenic mutations (4% had both). Pathogenic variants were associated with multiple primary tumours (p = 0.03) and HER2+ tumours (p = 0.05). On bivariate analysis, decreased age at first cancer was a significant predictor for increased VUS findings. Of all patients, 16% had management changes based on the testing.
Conclusions Specific tumour patterns (that is, HER2+) and number of primary tumours may be important indicators for genetic testing in breast cancer patients. In our cohort, younger breast cancer patients were more likely to have VUS, and this may have counselling implications. Furthermore, multigene panel testing did lead to clinical management changes in a significant portion of patients.

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Poster P126

Gene Panel Testing for Hereditary Breast and/or Ovarian Cancer: Current Canadian Status and Provider Opinions 2015

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In recent years, gene panels have become an important tool in the assessment of hereditary cancer. However, clinical practice varies significantly with regard to their utilization both across Canada and within provinces. Our objective is to assess current practices of cancer genetics clinics related to the use of panels for hereditary breast and/or ovarian cancer (HBOC). In addition, we will evaluate challenges experienced with panel testing and elicit opinions of genetic counsellors (GCS) related to their current and future use.

A survey assessing current practices related to gene panels for HBOC was completed by a representative GC from 24 of the 32 Canadian sites. Subsequently, 43 attendees at a cancer education session at the 2015 Canadian Association of Genetic Counsellors Annual Education Conference participated in an in-person discussion and opinion survey.

The online survey revealed significant differences across Canada with regard to panel use, approach, and provider perspectives. Only 5 Canadian centres reported using panels routinely for HBOC families. Of these, the use of a high-penetrance gene panel upfront (rather than a comprehensive panel, moderate-penetrance panel, or commencing with *BRCA1/2* analysis) was slightly more common. Of those not using panels, "questionable utility" was cited as the most common reason.

Conference attendees were asked to vote on a series of 10 consensus statements related to panel use for HBOC. Of the respondents, 94% agreed that "the optimal integration of multigene panels in breast cancer risk stratification and clinical management remains to be established." All (100%) agreed that families would be best served by Canada-wide consistency in practice and equal access to testing.

Our assessment concludes that Canadian genetics centres may benefit from a broader discussion of the utility and impact on clinical care of the use of gene panels for HBOC, and suggests value to the development of Canadian guidelines.

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Poster P127

Male Carriers of *BRCA1/2* Mutations: Impact Analysis and Risk Perception

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Mutations in *BRCA* (mainly *BRCA2*) genes confer a risk up to 6.9% of developing male breast cancer and up to 40% for prostate cancer. Environment of a family with mutated *BRCA* is commonly focused on female members because of the higher risk of cancer. It is hypothesized that male needs cannot be completely satisfied.
Objectives The study is aimed to analyze risk perception of family males and to review genetic counselling process from men's point of view.
Methods To obtain information about risk perception and other variables related to genetic counselling process, a questionnaire was developed. We surveyed 41 men with deleterious mutation in *BRCA* genes who visited in Duran i Reynals Hospital from October 1998 to December 2014.
Results According to the reasons, 27% of males underwent a genetic counselling process to determine the cancer risk for offspring. The second most common (23%) reason is to know personal cancer risk. Regarding risk perception, 59% indicated that they are at higher risk compared with other men of the same age. None of the respondents sense a high or very high probability of breast cancer. There are 11 males with previous history of breast cancer, and 10 of them claim to be at high risk of developing another cancer. There are 31 males who have a relative (mother or sister) affected with cancer, and 21 of them (67.74%) refer a high risk perception.
Conclusions Analysis of the results reveals the importance of focusing on men regardless of the status of their offspring, of involving them in the process of their daughters, and of emphasizing their own clinical monitoring. Involvement of mothers and sisters is postulated as a factor to consider related to a higher perception of risk. All these issues should be assessed in male genetic counselling.

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Poster P128

An Online Results Delivery and Counselling System May Increase Access to Hereditary Cancer Testing and Genetic Counselling

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Objectives As hereditary cancer testing demand increases, patients are increasingly tested in primary care settings. Nonetheless, genetic counselling services remain important, though limited capacity restricts access. Counsyl addresses this limitation with a Web-based results delivery and tele-counselling platform, described here.
Methods Following test order by an enrolled provider, patients are contacted via e-mail to activate their accounts. Upon availability, results are released to the provider, and patients are notified of results via e-mail or automated telephone message, or both. Negative and VUS results can be viewed directly and are accompanied by tailored educational videos. Patients have the option of speaking to a genetics counselor immediately or may choose to schedule an appointment. All positive and unviewed results are released directly by a genetics counselor. Importantly, every patient interaction is tracked in accordance with professional society guidelines.
Results Between 1 September 2014 and 30 September 2015, 54% of patients proceeding with the Inherited Cancer Screen obtained results using the automated system. Of these, 18% elected post-test genetic counselling. The mean time duration between learning the results to genetics consult was 1.77 hours, and the satisfaction rating with experience was 4.9 out of 5. Compared with a model in which the ordering provider discusses the results with the patient and then refers to genetic counselling, this service demonstrates an efficient approach to results delivery.
Conclusions We believe that this system may make cancer genetics testing and counselling accessible to a larger number of providers and patients who may be underserved with more traditional models.

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Poster P129

Comparing Commercial (U.S.) Genetics Testing Laboratories Offering Multigene Hereditary Cancer Panels

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Objectives With dozens of multigene cancer panels of variable size and scope available from multiple commercial laboratories, it is increasingly difficult for clinicians to stay informed of technical differences and ever-changing gene additions among labs. An electronic clinical support tool curated by a neutral 3rd party was developed to allow easy, multi-lab comparisons in one location.
Methods A spreadsheet was created to compare information from commercial genetic testing labs within the United States. Data points included price, tested genes, *BRCA* variant rate, presence of staff genetic counsellors, financial and insurance assistance, variant classification and follow-up programs, analytical sensitivity, minimum reads per base pair, Sanger confirmation, deletion/duplication technology, appropriate promoter region coverage, and more. Representatives from each lab were asked to provide relevant information, which was organized to compare related tests (for example, breast, colon, or pan-focused panels), as well as lab-specific pages that offer overviews of all tests within one lab. The spreadsheet has been available to genetic counsellors and other clinicians through online professional forums since March 2014. Periodic updates have been made.
Results Although many technical aspects of DNA analysis are similar between labs, the spreadsheet illustrates several significant differences—for example, low base-pair reads, limited deletion/duplication analysis, cost. Analytics show that the spreadsheet has been accessed more than 700 times with unsolicited positive commentary from users.
Conclusions Organizing information from multiple labs into an easily referenced spreadsheet allows clinicians to more critically analyze testing options and notice shortcomings in the competitive landscape of commercial genetic testing. Such differences affect test accuracy and should be well understood by the patient and provider before ordering testing. High viewing rates and positive informal feedback show clinician interest in and appreciation of this tool. Future efforts should include more detailed and standardized technical information and broader access, such as through a public Web-based portal.

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Poster P130

Guidelines for Breast Cancer Gene (*BRCA*) Mutation Testing in Healthy Individuals and Patients Diagnosed with Breast Cancer

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Objectives To evaluate and compare current breast cancer gene (*BRCA*) mutation testing guidelines for healthy women and breast cancer (BCa) patients.
Methods *BRCA* testing guidelines were identified through evidence-review searches of Ovid and targeted professional society Web sites. Eligible guidelines were published in English, 2006–2015.
Results Nine guidelines met inclusion criteria; five were from the United States. Two guidelines were limited to BCa patients; one guideline was limited to healthy women; and the remaining six referred to both. All U.S. guidelines included healthy individuals, and four of five included BCa patients. Similar risk-factor criteria for *BRCA* testing appeared across guidelines. However, there was variability in how risk factors were defined and the level of detail provided. Young age at BCa diagnosis was identified as a risk factor in all guidelines. Only one of four ex-U.S. guidelines specifically defined young age at BCa diagnosis, while four of five U.S. guidelines included a specific definition. Seven guidelines identified Ashkenazi Jewish ancestry as a risk factor, with three combining ancestry with other risk factors such as age at diagnosis. All guidelines identified a family history of BCa or ovarian cancer, though definitions ranged from "strong family history" to specific combinations of number and closeness of relatives with age at diagnosis. Four guidelines identified triple-negative BCa as a risk factor. All guidelines recommended genetic counselling services prior to undertaking genetic testing.
Conclusions The nine guidelines originating from different institutions are not fully aligned in terms of recommendations. In general, guidelines for *BRCA* testing in healthy individuals and patients with BCa contain similar criteria for referral for *BRCA* testing. However, they vary in terms of how individual risk factors are defined, which results in variable criteria for referral to genetic counselling or testing.

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Poster P131

Ovarian Cancer in a Family with Coexistence of Germline *NF1* and *BRCA1* Mutations: Case Report

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Objectives A 37-year-old woman presented with multiple café au lait spots, axillary freckling, and cutaneous neurofibromas. At the age of 35 years, she developed ovarian cancer, a high-grade adenocarcinoma serosum. Her daughter (14 years) and a son (5 years) presented the symptoms of neurofibromatosis, including Lisch nodules. In addition, hyperintense lesions on T2-weighted brain MRI were found. Proband's younger sister presented typical-for-NF1 multiple café au lait spots and cutaneous neurofibromas. Proband's mother was also affected with NF1, and she died at the age of 29 from carcinoma of the papilla of Vater.

Methods Molecular analysis was performed using TruSight Cancer panel (MiSeq, Illumina). The mean region coverage depth was 2631.5 times. The presence of identified alterations was confirmed by independent PCR followed by bidirectional sequencing (ABI PRISM 3130, Life Technologies).
Results Mutational analysis revealed that proband was a carrier of a missense mutation at *BRCA1* (c.181T>G, p.Cys61Gly) and a frameshift mutation at *NF1* (c.2080delT, p.Leu695Cysfs*53). Analysis of family members showed that both mutations were present in proband's son, daughter, and younger sister. In the remaining individuals neither *BRCA1* nor *NF1* mutation was detected.
Conclusions We conclude that the early-onset ovarian cancer diagnosed in the proband could be explained by the presence of a germline *BRCA1* mutation. However, because the risk of developing ovarian cancer in *BRCA1* mutation carriers before 40 years is relatively low, an additional role of *NF1* alteration in the pathogenesis of this neoplasm cannot be excluded. Considering the possible cooperation in cancer development between the pathways regulated by these genes, we postulate that individuals with *BRCA1* mutation and a second independent mutation should be very carefully screened for different types of cancer, including rare tumours besides the spectrum of detected mutations.

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Poster P132

Predictors of Sexual Functioning After Risk-Reducing Salpingo-oophorectomy: Impact of Sex Hormone Levels in Serum

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Objectives Women after risk-reducing salpingo-oophorectomy (RRSO) experience postmenopausal complaints including reduced sexual functioning and less frequent sexual activity. Premenopausal RRSO results in a substantial loss of circulating estrogen and testosterone, which may influence sexual functioning. We aimed to study the impact of sex hormone levels on sexual pleasure and discomfort after RRSO.
Methods Participants were 210 sexually active women who had undergone RRSO. Sexual functioning was measured with the Sexual Activity Questionnaire. Thyroxin, thyroid-stimulating hormone (TSH), estradiol, luteinizing hormone (LH), follicle-stimulating hormone, sex hormone-binding globulin (SHBG), testosterone, and dehydroepiandrosterone sulfate (DHEA-S) were measured. Free androgen index (FAI) was calculated as testosterone × 100 / SHBG. Box–Cox transformations of the hormone values were performed to obtain normality. Correlations were reported using the Spearman rho (Sr). Predictors of sexual functioning scores were examined by multiple linear regression. In addition to hormones, the covariates were age, body image, education, paired relation, quality of life (QOL), care from partner, prior breast cancer, and systemic hormone replacement therapy (HRT).
Results Sexual pleasure score was correlated with LH (Sr: 0.142; $p = 0.049$). Sexual discomfort score was correlated with DHEA-S (Sr: –0.174; $p = 0.016$) and FAI (Sr: –0.214; $p = 0.003$). In multiple linear regression, sexual pleasure score was significantly associated with care from partner ($p < 0.001$) and current use of systemic HRT ($p = 0.008$). Significant associations with decreased discomfort score were high level of TSH ($p = 0.044$), high FAI ($p = 0.038$), better QOL ($p = 0.024$), and systemic HRT ($p = 0.035$).
Conclusions Sexual pleasure score was associated with care from partner and systemic HRT; however, we found no associations with sex hormone levels. Sexual discomfort score was significantly associated with TSH, FAI, QOL and systemic HRT use. Our results support that systemic HRT may improve sexual functioning.

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Poster P133

Impact of Tyrer–Cuzick Version 7 on Breast Cancer Risk Assessment

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Objectives The Tyrer–Cuzick (TC) model has long been a widely used clinical breast cancer risk assessment tool. In 2013, an updated version of the TC model (TC v.7) was released. It has been noted that the risk estimates projected by TC v.7 are higher than those from the previous version (TC v.6). The objectives of this study are to determine if there is a significant difference in the lifetime breast cancer risk scores between TC v.7 and TC v.6 and to determine the effect of TC v.7 scores on clinical recommendations.
Methods Individuals referred for breast cancer risk assessment who met with a genetics counsellor between January 2009 and November 2015 were eligible for chart review. Exclusion criteria were referral for family history of ovarian cancer only, personal history of cancer, and missing all necessary data points for risk modelling. Breast cancer risk was assessed by TC v.6 and v.7, as well as by the Gail and Claus models.
Results Preliminary analysis of 150 samples indicates that TC v.7 scores (mean: 21.079) are significantly greater than TC V.6 scores (mean: 20.039; $p < 0.0001$). The TC v.6 and TC v.7 scores are both significantly greater than those from the Gail model ($p < 0.0001$; $p < 0.0001$) and the Claus model ($p = 0.0002$; $p < 0.0001$). Within the TC v.7 model, calculations including competing mortality (mean: 21.024) were significantly less than calculations not including competing mortality (mean: 25.099; $p < 0.0001$).
Conclusions Compared with the TC v.6 model, the TC v.7 model for breast cancer risk assessment produces significantly higher lifetime risk estimates. This leads to an increase in the number of women eligible for breast MRI, a more expensive screening modality. This increase may also lead to an increase in the number of breast biopsies as well as an increase in diagnosis of early-stage breast cancers.

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Poster P134

Young Women Over High-Risk Women: A Possible Bias in the High-Risk Ontario Breast Screening Program

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The High Risk Ontario Breast Screening Program (HR-OBSP) provides annual breast magnetic resonance imaging and mammogram to women ages 30–69 found to be at ≥25% risk of developing breast cancer by age 80. Presumably, once a woman is enrolled, she will receive the screening until age 69. Genetics professionals use genetics testing or computer software programs, or both, to determine eligibility. We present data from a retrospective review of cases assessed for HR-OBSP from 2011 to 2015 in the Genetics Clinic at Rouge Valley Health System.

The program assessed 338 women, and 87 (26%) were eligible for breast screening. Of the 87, 1 was eligible because of radiation exposure from previous lymphoma treatment, and 13 were eligible because they carried a *BRCA1* or *BRCA2* gene mutation. The remaining 73 qualified because of family history with or without personal risk factors, and most cases were assessed using the International Breast Cancer Intervention Study model. In this last group, a predilection toward younger women was observed, with 33% of women in their 30s qualifying for the breast screening, 24% of women in their 40s, 17% of women in their 50s, and only 5% of women in their 60s. However, among the women who qualified, the average risk to develop breast cancer in the next 10 years showed the opposite trend: only 4% for women in their 30s versus 22% for women in their 60s. ANOVA analyses to determine statistical significance are pending.

These data suggest that the HR-OBSP, as well as other programs that use lifetime cancer risk to determine eligibility, may be preferentially selecting younger individuals while excluding older individuals who are actually at higher risk to develop cancer in the near future.

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Poster P135

Bénéfices cliniques et financiers des panels multigènes

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Objectif Évaluer l'impact d'un panels multigène (PMG) sur une pratique clinique évaluant des femmes et des familles à risque de cancer du sein et de l'ovaire concernant une meilleure identification des mutations génétiques et une réduction des délais et des coûts reliés à ces tests.
Méthodes employés L'utilisation d'un panel de 25 gènes MyRisk à un coût moindre que l'analyse complète *BRCA1* et *BRCA2* a été offerte à notre équipe à l'automne 2013. Jusque-là, les analyses étaient faites de façon séquentielle. L'équipe médico-administrative a accepté l'essai de ce panel afin de répondre plus rapidement aux besoins de la clientèle et diminuer les coûts. Les données recueillies entre 2014 jan 1 et 2015 déc 31 avec l'utilisation du panel MyRisk en 2014 et d'un autre PMG en 2015 ont été analysées. Les patients testés pour une mutation familiale déjà identifiée et ceux dont les résultats sont incomplets ont été exclus.
Résultats Sur 325 personnes testées, 44 ont été identifiées comme étant porteuses de mutations. 26 Mutations *BRCA* ont été trouvées (15 *BRCA1*, 11 *BRCA2*), et 6 (23%) de ces mutations ne sont pas dans le panel *BRCA* canadien-français. 18 Mutations se retrouvent au niveau des gènes autres que *BRCA*.

Bénéfices cliniques 1) Des recommandations de suivi personnalisées pour les diverses mutations non identifiées autrement. 2) Délais de divulgation 65% plus rapide avec les PMG. 3) Meilleur choix de chirurgie et d'utilisation de la radiothérapie.

Bénéfice financier 1) 14/325 PMG évités. 2) 311 panels *BRCA* canadien-français faits inutilement. 3) Autres dépenses hospitalières et des patients aussi à considérer.

Conclusions Le coût des PMG moindre que l'analyse séquentielle et que l'analyse conventionnelle *BRCA1*/*BRCA2*, et l'identification plus complète des mutations démontrent un bénéfice clinique mais aussi financier à l'utilisation des PMG d'emblée dans notre contexte clinique.

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Poster P136

Isolated Ovarian Carcinosarcoma As an Eligibility Criterion for *BRCA1/2* Testing

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Background Women with germline *BRCA1* or *BRCA2* gene mutations are at increased risk to develop breast or ovarian cancer over their lifetime. The most common type of ovarian cancer associated with pathogenic *BRCA1/2* mutations are epithelial ovarian cancers, including high-grade serous cancer, fallopian tube cancer, and primary peritoneal carcinoma. Carcinosarcomas are rare malignant tumours (1%–2% of all ovarian tumours) that consist of a mixture of carcinoma (or epithelial cancer) and sarcoma (or mesenchymal cancer), and can arise in diverse organs, including ovaries.
Objective To describe 4 cases of *BRCA*-positive women with a diagnosis of ovarian carcinosarcoma (OCS) and to compare them with similar cases reported in the literature, to determine whether an isolated case may be sufficient for *BRCA1/2* testing eligibility.
Methods The presentation includes tumour pathology, cancer treatment, gene mutation, and family history. A review of the OCS literature will also be presented.
Results A germline *BRCA1* mutation was found in 2 of the OCS cases, and a germline *BRCA2* mutation in 2. Age at diagnosis ranged from 54 to 76, and 2 are deceased. All 4 cases had a family history of other *BRCA*-associated malignancies, including breast, prostate, or pancreatic cancer.
Conclusions Given the rarity of OCS, accurate prevalence data for *BRCA* mutations in women with OCS are currently unknown. We propose that until such data become available, OCS patients be considered for *BRCA1/2* testing even in the absence of other *BRCA*-associated cancer family history.

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Poster P137

Double Heterozygosity in Hereditary Breast and Ovarian Cancer Found by Panel Testing

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Increasing use of panel testing in hereditary breast and ovarian cancer has led to the identification of families harbouring mutations in multiple genes. This raises the question of the true incidence of double heterozygosity and its impact on cancer risks and phenotype. Although several publications agree that the presence of a second pathogenic mutation does not increase the cancer risk, data are limited.

We report 2 families with individuals who are double heterozygotes for mutations discovered by panel testing. The first includes a mother and 2 daughters all positive for pathogenic mutations in both *BRCA2* and *CHEK2*. The daughters were diagnosed with breast cancer at ages 32 and 37, and their mother with bilateral disease at 58. Interestingly, the younger breast cancer diagnoses appear even earlier than would be predicted for *BRCA2* alone. The second family includes a proband positive for pathogenic mutations in both *NBN* and *RAD51D*. This individual has a history of papillary thyroid cancer only. The maternal family history includes ovarian cancers (OVS) diagnosed in the mother at 54, 2 aunts at 77 and 70, grandmother, and great aunt. Paternal lineage includes an aunt with postmenopausal breast cancer. It is unclear through which lineage these mutations were inherited or to what extent the *RAD51D* mutation is responsible for the strong maternal OV history. It is possible the *NBN* mutation, while not strongly related to OV risk, could be modifying the risk conferred by the *RAD51D* gene. Further testing in this family will help us understand the clinical implications of these mutations, thus providing a more effective cancer screening and risk management plan for this family.

With the large uptake of commercial panel testing, double heterozygotes will become more common, furthering our understanding of these families on both a molecular and clinical level.

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Pertinence d'une analyse multigène élargie dans l'évaluation génétique des cancers du sein et l'ovaire : une réalité incontournable

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Introduction Les présentations cliniques des syndromes de prédispositions aux cancers du sein et l'ovaire sont très hétérogènes et dépendent de nombreux facteurs. La disponibilité récente d'investigation multigène par séquençage de nouvelle génération offre la possibilité d'une plus complète évaluation.
Objectif Rétrospectivement nous avons revu sur dossier les 110 nouveaux cas positifs de patients référés pour cancers du sein ou ovaire/endomètre diagnostiqués entre 2014 oct et 2015 déc 31. Nous rapportons notre expérience récente.
Résultats 78/110 Patients (70 %) avec âge médian de 45 ans (extrêmes: 26–75 ans) référés pour cancer du seine; 27/110 pts (24.5 %) cancer ovaire dont l'âge médian est de 54,5 ans (extrêmes : 47–73 ans); ainsi que 5/110 pts (4.5 %) cancer de l'endomètre (extrêmes : 39–69 ans). La majorité de nos patients sont de souche canadienne-française 89/110 (81 %). Une mutation dans les gènes *BRCA1/2* a été identifiée dans 69/110 (62.7 %), dont 2/69 (2.9 %) associée avec une mutation *CHEK2*, et 2/69 (2.9 %) une délétion complète de *BRCA1* est inscrite dans un cadre de microdélétion. L'approche d'investigation multigéne a identifié une mutation dans un autre gène que *BRCA* dans 37.3 % (41/110 pts) repartie en 28/78 cancers du sein (35 %), 8/27 cancers de l'ovaire (29 %), et 5/5 cancers de l'endomètre. Il a été constaté une prédominance de mutation dans les gènes *MMR* 13/41 (31 %), ainsi que 7/41 (17 %) patients avec mutation *PALB2*. Une mutation dans *CHEK2* a été identifiée 4/28 cancers du sein (14 %) dont une fois mutation homozygote. Finalement, le spectre des mutations observé est assez large mettant à défaut les tests ciblés selon la fréquence allélique (*CHEK2*) ou ethnique.
Conclusions L'étiologie moléculaire est partagée avec grande pertinence par une proportion considérable (37.3%) de gènes en dehors de *BRCA1/2*. Les patientes relevant d'un syndrome de Lynch ne rencontraient pas les critères diagnostics classiques. L'ajustement de la prise en charge et le conseil génétique repose sur cette pertinence d'évaluation.

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Evaluating a Novel Oncologist-Led *BRCA* Genetic Testing Counselling Model for Ovarian Cancer Patients: Interim Results from the ENGAGE Study

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Objectives With the availability of *BRCA*-targeted therapies, *BRCA* testing is an important component of ovarian cancer diagnosis. An oncologist-led, streamlined *BRCA* testing and counselling model, first introduced in the United Kingdom by the Institute of Cancer Research (ICR), reported an average *BRCA* testing turnaround time (TAT) of 4 weeks. This prospective, observational study of adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, conducted in the United States, Italy, and Spain will assess overall testing TAT, counselling quality, and patient satisfaction.
Methods Participating sites were trained in pre–*BRCA* test counselling. Baseline demographic, clinical, and therapeutic data, and information on *BRCA* testing TAT (primary outcome) were collected. Satisfaction surveys were completed by patients, clinicians, and genetics counsellors to assess the *BRCA* testing model.
Results Interim analyses were conducted on 132 patients enrolled at 10 U.S. sites. Mean age was 65.3 ± 9.6 years. Mean time since diagnosis was 2.4 ± 3.5 years. Pre–*BRCA* test counselling was provided mainly by oncologists (44%) and nurse practitioners/physician assistants (21%). *BRCA* testing consisted of single-gene analysis in 74% and gene panels in 26% of patients. Mean TAT from initial counselling to *BRCA* test results was 4.4 ± 3.4 weeks. Test results were provided to patients by nurses (41%), oncologists (34%), or genetics counsellors/geneticists (25%). The patient satisfaction rate about pre-test counselling was > 95%. Mean satisfaction scores were consistently higher than 3.5 (1: completely dissatisfied; 4: completely satisfied). After the pre-*BRCA* test counselling, no patients requested additional genetic counselling; 89% were satisfied to have had genetic testing at an existing oncology appointment, rather than in a separate visit.
Conclusions Consistent with the ICR pilot study, interim results indicate that an opportunistic, oncologist-led *BRCA* testing model appears to be efficient, has acceptable TAT, high rates of patient satisfaction, and increased uptake by patients who might not have previously complied with such recommendations.

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