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PROFFERED PAPERS

S1-PP1

An International Interlaboratory Study of Complex Pathogenic Variants in Hereditary Breast/Ovarian Cancer

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The comprehensive assessment of inherited mutations in cancer susceptibility genes helps to optimize clinical decision-making. Conventional laboratory methods based on NGS focus on the detection of single nucleotide variants, small insertions/deletions, and certain copy-number changes in accessible regions of a patient's DNA. Other clinically significant alterations are invisible to these approaches, and for this reason their clinical impact is less well studied.

We investigated the prevalence of technically challenging mutations in a large (n = 80,000) patient population focusing on 19 genes (including *BRCA1* and *BRCA2*) associated with breast and/or ovarian cancer. Technical methods beyond conventional next-generation sequencing (NGS) were used to detect and confirm the presence of DNA alterations in these patients. We found that 8.6% of patients with a potentially actionable result harbored a mutation not easily detected by conventional NGS sequencing or copy number methods. No single class of mutation was responsible for this—rather, a diversity of challenges was present. Most of these mutations were individually extremely rare, although some were recurrent. Many would have clinical relevance in either a germline or somatic context.

Laboratory studies generally include few, if any, of these technically challenging variants. To help evaluate and improve methodologies across laboratories, we constructed a synthetic specimen containing 22 challenging variants in 7 cancer genes. This specimen was provided to collaborating laboratories who sequenced it using a total of 10 different NGS tests. Only 10 of the 22 challenging variants were detected by all tests, and just 3 tests detected all 22. Some but not all of these limitations were previously known.

In summary, technically challenging pathogenic variants are collectively prevalent in patients, although methods to detect these variants are not yet uniformly implemented. The clinical data and specimen described here are now available and mght help improve the assessment of cancer risk internationally.

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S1-PP2

Pheno Analysis Is a Highly Accurate and Robust Variant Classification Algorithm With High Tolerance for Reported Clinical History Errors

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Background Pheno analysis is a computerized statistical tool that provides very strong classification evidence used to classify variants identified in cancer-associated genes. Pheno utilizes personal and family cancer histories recorded on the test requisition form (TRF) as inputs to determine whether a variant is or is not associated with strong personal and family history of cancer, and is thus likely to be pathogenic or benign. As TRF information is self-reported by patients, it is expected that errors exist.

Methods Gene-specific analyses were performed for *BRCA1* and *BRCA2*. Pheno cases and controls are ascertained using the same TRFs. Thus, TRF errors are assumed to be uniform, and simulated errors were uniformly applied to cases and controls. For each trial, certain types and proportions of erroneous cancer histories were randomly introduced into TRF case–control data. Pheno prevalence tables were constructed targeting ≥99.5% positive (PPVs) and negative predictive values (NPVs), and 25,000 pathogenic and 50,000 benign composite variants were analyzed through two-fold cross-validations. The PPVs, NPVs, and average number of probands required for Pheno to make a classification call were calculated.

Results For all passing trials, PPVs. and NPVs. were >99.5%. As TRF error rates increased, the number of probands required to make a Pheno call also increased. TRF errors limited to 2nd-degree relatives had smaller effects than errors including 1st-degree relatives; and errors including probands in addition to family members had the greatest impact.

Conclusions Pheno is a highly accurate and robust variant classification algorithm with high tolerance for TRF errors. As TRF errors increase, Pheno utility decreases, because of larger proband numbers being required to make a Pheno call. While high TRF error rates result in Pheno failure (that is, Pheno does not make a classification call), if Pheno makes a classification call, that call is accurate, regardless of the number of TRF errors present.

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S1-PP3

Functional Assays Identify Clinically Actionable Variants in Hereditary Breast and Ovarian Cancer Predisposition Genes

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Introduction Genomic testing for hereditary breast and ovarian cancer (HBOC) is becoming widespread; however, the interpretation of variants of unknown significance (VUS) in HBOC genes remains a challenge to geneticists and patients. Here, we demonstrate an integrated DNA, RNA, and protein functional approach for the assessment of VUS that improves the identification of clinically actionable alterations in HBOC genes.
Methods We analyzed sequence data obtained from a cohort of ~23,000 individuals who underwent a HBOC DNA multigene panel test in a clinical laboratory. We then used a combination of clinical data, protein structure, and *in silico* analyses to select VUS for specific functional analysis, depending on the type of alteration. For *BRCA1* and *BRCA2* missense VUS, protein function was determined by measuring homology-directed recombination (HDR) efficiency and quantitative infrared Western blot analysis. For splicing variants, we performed targeted RNA studies. Finally, for gross duplications, a novel DNA breakpoint assay (DBA) was used to detect tandem duplications in *BRCA1, BRCA2, ATM, CDH1, PALB2,* and *CHEK2.*
Results Most of the VUS in HBOC genes were missense (91.6%), splicing (3.2%), or gross duplications (1%). To date, 22% of the missense alterations tested using the combination of structure and functional assays (HDR assay and quantitative infrared Western blot) were reclassified from VUS to likely pathogenic. For splicing alterations, targeted RNA studies resulted in ~78% reclassifications. Finally, DBA allowed us to ascertain breakpoints for 44 unique gross duplications from 156 consenting probands. We determined that the duplications occurred in-tandem in 123 individuals from this cohort (79%). Among the in-tandem gross duplications that were eligible for reclassification, 95% were upgraded to pathogenic mutations.
Conclusions The use of DNA, RNA, and protein functional assays significantly improved the overall assessment of germline variants in HBOC genes, resulting in a reduction in VUS classifications.

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S2-PP1

BRCA2 Haploinsufficiency for Replication Stress Suppression in Primary *BRCA2* Heterozygous Mammary Epithelial Cells

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BRCA2 is a breast and ovarian tumour suppressor that maintains genome integrity by engaging in multiple cellular processes, including repair of DNA damage. *BRCA2* is an important player in both DNA double-strand break repair [DSBR (via homologous recombination)] and repair of stalled replication forks. Here, we report that primary *BRCA2* heterozygous (*BRCA2*mut/+) mammary epithelial cells (MECs), though efficient in DSBR, are defective in repair of stalled forks. Stalled forks are frequent source of DNA damage in replicating cells, and their inefficient repair leads to increased replication stress, a prime contributor to epithelial cancer.

Furthermore, we show that *BRCA1* and *BRCA2* play different roles in the repair of stalled forks—leading to differences in repair pathway choices made by *BRCA1* and/or *BRCA2* mutant cells. In keeping with this, we find that primary *BRCA2*mut/+ MECs (n = 8), and not *BRCA1*mut/+ cells (n = 10), are haploinsufficient for nucleotide excision repair. This would imply higher predisposition for skin lesions, including melanoma, in *BRCA2* mutation carriers. Risk for melanoma is indeed higher in *BRCA2* mutation carriers. We also show that there exists a difference in mutational signature in whole-genome sequences derived from *BRCA1* and *BRCA2* mutant tumours, in line with the differences expected if there is an increased nucleotide excision repair defect in *BRCA2* compared with *BRCA1* mutant cells.

Together, our findings provide the first evidence for innate haploinsufficiency for replication stress suppression in primary *BRCA2*mut/+ MECs and evidence for differences between how *BRCA1* and *BRCA2* defective cells process stalled forks. This mechanistic difference between *BRCA1*- and *BRCA2*-dependent response at stalled forks, and the crosstalk with nucleotide excision repair, potentially contributes toward differences in *BRCA1* and *BRCA2* mutant breast and ovarian cancer, and could also explain the differences observed between *BRCA1* and *BRCA2* mutant tumours' response to different chemotherapeutics.

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S2-PP2

Aneuploidy and Altered Cell Fate Define the Early Pathogenesis of *BRCA2*-Associated Breast Cancer

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Germline mutations in *BRCA1* and *BRCA2* confer risks for distinct breast cancer subtypes, because most *BRCA1*-associated cancers are estrogen receptor (ER)–negative and "basal-like," whereas those arising in *BRCA2* genetic carriers are predominately ER-positive (ER+) and "luminal-like." The early events that give rise to these divergent cancer phenotypes remain unknown. We thus sought to reveal the earliest steps in *BRCA1/2*–associated breast cancer pathogenesis through detailed cellular, molecular, and functional analysis of fluorescence-activated cell sorted populations from freshly isolated, histologically normal breast tissues of *BRCA1* carriers (n = 18), *BRCA2* carriers (n = 28), and matched controls (n = 28).

We observe an age-associated increase in the luminal progenitor (LP) population and increased luminal/basal cell ratio selectively in *BRCA2* carriers. Correspondingly, RNAseq analysis demonstrates a prominent signature of G2/M stress and Aurora kinase activation selectively in LP cells of *BRCA2* carriers compared with *BRCA1* carriers and controls, associated with downregulation of genes signifying basal and bipotent cell fate. This phenotype is linked to DNA damage as evidenced by increased γ-H2AX staining in the corresponding tissues. We then used a validated next-generation sequencing (NGS)–based methodology for single-cell ploidy analysis, which demonstrates polyclonal aneuploidy in >20% of *BRCA2* LP cells. These aneuploid events are predominantly losses and include large (>10 MB) deletions never observed in normal cells.

We conclude that the early pathogenesis of *BRCA2*-associated breast cancer involves selective cell-cycle deregulation and the resulting expansion of a luminal fate-shifted progenitor population that is subject to mitotic stress, triggering aneuploidy that ultimately drives malignant progression. Notably, these findings support recent data pointing to distinct patterns of genomic damage in *BRCA1* compared with *BRCA2*-associated breast cancers and the enrichment of chromosomal losses with *BRCA2.* These findings have implications for breast cancer pathogenesis and prevention in *BRCA1/2* genetic carriers.

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S2-PP3

Functional Analysis of the *PALB2* Tumour Suppressor

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One typical mechanism to promote genomic instability, a hallmark of cancer, is to inactivate tumour suppressors such as *PALB2.* Inherited mutations in *PALB2* are associated with a predisposition to ovarian, breast, and pancreatic cancers. In particular, it has been reported that mutations in *PALB2* increase breast cancer risk up to 8- to 9-fold. *PALB2* was identified as a *BRCA2* interacting protein, essential for *BRCA2* anchorage to nuclear structures and for its function in double-strand break repair. The basis of the tumorigenic potential of *PALB2* is thought to be related to functions in homologous recombination. Our group focuses on both the regulation and activities of *PALB2* during the DNA damage response and the effect of cancer-causing mutations.

First, we will present our work in deciphering the functions of *PALB2* in DNA double-strand break repair and homologous recombination. Second, predicting the functional consequences of *PALB2* mutations or variants has been challenging because they can lead to different biologic effects. Using a novel CRISPR/Cas–based homologous recombination assay and biochemical and cellular assays, we performed a structure–function analysis of *PALB2* using *PALB2* truncated mutants (R170fs, L531fs, Q775X, and W1038X). These studies allowed us to uncover a *PALB2* regulation mechanism by which cancer cells could drive genomic instability leading to cytoplasmic accumulation of *PALB2*. We have undertaken a systematic functional analysis of *PALB2* variants of unknown significance (VUS). We now present evidence that the cytoplasmic localization of *PALB2* can be triggered by specific VUS in patients. The assays presented here will be valuable tools for the functional assessment of *PALB2* variants, or other homologous recombination genes, in cancer causation.

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S3-PP1

Modulation of Base Excision Repair Influences DNA Damage Repair for *BRCA2* Mutant Cancer: Implications for Chemotherapeutics

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BRCA2 mutation carriers have a dramatically elevated risk of developing breast and ovarian cancer during their lifetime. Women who develop *BRCA2*-mutant ovarian cancer initially respond very favourably to cisplatin or carboplatin, the first-line treatment for ovarian cancer. However, despite the high initial response rate, 70% of women with *BRCA2*-mutant ovarian cancer will develop resistance to platinum agents within 5 years.

Through a screen to identify genes and/or pathways that can modulate sensitivity of *BRCA2*-mutant cancer to cisplatin, we identified abasic site endonuclease (APE1), a central base excision repair (BER) protein, as regulating platinum resistance in *BRCA2*-deficient cells. We find that loss of APE1 confers a 2- to 5-fold increase in cisplatin resistance to *BRCA2*-deficient cells. Moreover, loss of APE1 rescues multiple cisplatin-induced DNA damage hallmarks in *BRCA2*-deficient cell. These include increase in nuclear aberrations and accumulation of replication-associated DNA double-strand breaks. We find that APE1 influences the choice of repair pathway upon cisplatin treatment, and that cells depleted of APE1 are biased away from *BRCA2*-dependent repair towards alternative repair pathways that that do not necessarily require *BRCA2* for repair. In line with these results, we find that patients with *BRCA2*-mutant ovarian cancer that expresses low levels of APE1 have a significantly worse prognosis than patients whose tumours express high levels of APE1, suggesting that APE1 regulates *BRCA2*-mutant cancer survival.

We expand on these findings to find that inhibition of certain other members of the BER pathway produce phenotypes similar to those with loss of APE1, suggesting that our findings are applicable to other proteins active in the BER pathway. Finally, we demonstrate that while loss of APE1 promotes resistance to cisplatin *in vitro*, cells deficient in both APE1 and *BRCA2* remain sensitive to multiple other DNA damaging agents, suggesting alternative treatment strategies for *BRCA2* mutation carriers with defective BER.

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S3-PP2

Impact of DNA Repair Defects on the Outcomes of Metastatic Resistant Prostate Cancer

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Background Germline DNA repair defects have been identified in up to 12% of patients with metastatic resistant prostate cancer (mCRPC) and retrospective studies have associated some of these variants with poor prostate cancer outcomes and progression to metastatic disease. However, no conclusive data are available regarding survival from mCRPC and response to currently approved therapies.
Methods REPAIR-B (NCT03075735) is a prospective observational cohort study. Patients diagnosed with mCRPC of unknown mutational status who were about to start a first-line treatment for mCRPC were eligible. Patients were screened for germline mutations in 107 DNA damage and repair genes (DDR) and treated at physician's choice with either abiraterone, enzalutamide, docetaxel, cabazitaxel, or Ra-223. Primary endpoints were to describe the prevalence of DDR germline mutations in our mCRPC population and to assess their impact in cause-specific survival (CSS) from diagnosis of mCRPC. Secondary endpoints included the impact of other DDR genes in CSS and the association between DDR defects and the response to therapies for mCRPC.
Results The study included 419 mCRPC patients. *BRCA2* (3.3%), *ATM* (1.9%) and *BRCA1* (0.9%) were the genes more commonly mutated. Pathogenic variants in any of the 107 genes analyzed were identified in 15% of patients. Carriers and noncarriers presented similar characteristics at baseline, but carriers progressed earlier to mCRPC (18.6 vs. 28.2 months), particularly *BRCA2* carriers (13.2, $p = 0.039$). The mCRPC CSS was shorter in carriers (23.3 vs. 33.2 months, $p = 0.260$), but the difference was significant only for *BRCA2* (median 17.4 months, $p = 0.025$). Carriers responded (prostate-specific antigen and radiographically) to abiraterone/enzalutamide and taxane-based chemotherapy, but the duration of the responses was significantly shorter in carriers, particularly in *BRCA2* carriers.
Conclusions Not all DDR defects have the same impact on mCRPC outcomes. *BRCA2* mutation carriers tend to shorter responses to currently approved therapies, which may contribute to the shorter survival observed.

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S5-PP1

Oral Contraceptive Use and Breast Cancer Risk: Retrospective and Prospective Analyses from a *BRCA1* and *BRCA2* Mutation Carrier Cohort Study

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Background For *BRCA1* and *BRCA2* mutation carriers, the association between use of oral contraceptive preparation (OCP) and breast cancer (BCa) risk is still unclear.
Methods BCa risk associations were estimated from OCP data on 6030 *BRCA1* and 3809 *BRCA2* mutation carriers using age-dependent Cox regression, stratified by study and birth cohort. Prospective, left-truncated retrospective and full-cohort retrospective analyses were performed.
Results For *BRCA1* mutation carriers, OCP use was not associated with BCa risk from prospective analyses [hazard ratio (HR): 1.08; 95% confidence interval (CI): 0.75 to 1.56], but from the left-truncated and full-cohort retrospective analyses, risks were increased by 26% (95% CI: 6% to 51%) and 39% (95% CI: 23% to -58%) respectively. For *BRCA2* mutation carriers, OCP use was associated with BCa risk from prospective analyses (HR: 1.75; 95% CI: 1.03 to 2.97), but retrospective analyses were inconsistent (left-truncated HR: 1.06; 95% CI: 0.85 to 1.33; full-cohort HR: 1.52; 95% CI: 1.28 to 1.81). There was evidence of increasing risk with duration of use, especially before first full-term pregnancy; for *BRCA1* mutation carriers from both retrospective analyses ($p < 0.001$ and $p = 0.001$ respectively); and for *BRCA2* mutation carriers from full-retrospective analysis ($p = 0.002$).
Conclusions Prospective analyses did not show that past use of OCP causes an increased BCa risk for *BRCA1* mutation carriers in young middle-aged women (40–50 years). For *BRCA2* mutation carriers, a causal association is also not likely at those ages. Findings between retrospective and prospective analyses were inconsistent and could be attributable to survival bias or a true association for younger women who were underrepresented in the prospective cohort. Use of OCP for indications other than contraception should therefore be avoided by *BRCA1/2* mutation carriers.

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S5-PP2

Population Genetic Testing for Breast and Ovarian Cancer Susceptibility—the Australian Experience

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To date, population-based testing of hereditary breast and ovarian (HBOC) genes has been restricted to specific *BRCA* founder mutations in high-risk populations, such as the Ashkenazi Jewish population, in whom the prevalence of such mutations ranges between 1.1% and 4.5%. In this context, a population-based testing approach saved more life-years and quality-adjusted life-years, and had potential to lower the incidence of breast and ovarian cancer compared with a family history-based testing approach.

Since 2014, population-based genetic testing of 11 HBOC genes has been offered to 5910 cancer-free unselected women recruited into the LifePool cohort study through their attendance at a government-funded population breast surveillance program. The aim of this study is to determine the prevalence of pathogenic mutations in an unselected cancer-free Western population and to assess the rate of uptake of genetic counselling, risk-reduction surgery and cascade testing after notification of a potential clinically relevant finding. This study will also provide primary data for a health economic model of HBOC genetic screening, specific to the Australian population.

To date, 38 of 5910 women (0.64%) carried a clinically actionable mutation [*BRCA1*, $n = 6$; *BRCA2*, $n = 15$; *PALB2*, $n = 14$; *ATM* (c.7271T>G), $n = 3$]. The 38 women ranged in age from 24 to 77 years, with an average age of 57 years. Of the mutation carriers, 42% did not have a 1st-degree relative with breast or ovarian cancer, and 91% accepted referral to a familial cancer clinic. Uptake of cascade testing and risk-reduction surgery was similar to that in families identified through standard clinical practice.

Within our cohort of healthy women attending population mammographic surveillance, HBOC genetic testing was well accepted. It identified families with mutations who would not otherwise have presented to a familial cancer clinic. The findings indicate that the clinical utility of identifying a mutation in this setting is in keeping with the utility reported with the current model of clinical practice.

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S5-PP3

The Screen Project: Population-Based Genetic Testing for *BRCA1/2* Genes in Canada

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The current model for delivering genetic testing for *BRCA* genes in North America was developed in the mid-1990s, at a time when genetic testing was expensive and the clinical benefits were largely unproven. In this model, women are referred by their physicians to a specialized cancer genetics clinic where a formal assessment is conducted. If women are qualified for genetic testing based on some restricted criteria, then the test for the *BRCA* genes ensues.

We believe the current model is outdated, and we propose an alternative model based on guided direct-to-consumer population-based testing. This approach uses genetic testing as a screening tool to identify high-risk patients, followed by genetic counselling in preventive options for those identified as high-risk. With these goals in mind, we launched the Screen Project in March 2017 for evaluating population-based genetic testing for *BRCA* mutations in Canada. We now offer testing to all Canadian women and men who are 18 years of age or older. We use a guided direct-to-consumer approach for enrolling individuals through the study Web site (http://www.thescreenproject.ca). We are testing for *BRCA1* and *BRCA2* only. All individuals with a pathogenic mutation in either gene will be contacted by our team of genetic counsellors in person or by telephone to discuss their options for cancer prevention. Our team will also facilitate referral to a local genetics clinic for long-term follow-up.

Among the first 330 individuals tested across the country, we have identified 8 carriers of pathogenic *BRCA* mutations. Of those 8 individuals, 4 did not meet the criteria for a provincially covered test. The other 4 carriers met the criteria, but they did not have access to a cancer genetics clinic or had not been referred by their physicians for genetic testing. We will have 1000 reported tests by May 2018.

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S6-PP2

Clinical Characteristics and Outcomes in Elderly Women with *BRCA1* and *BRCA2* Mutations

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This is a retrospective study of elderly women in a community-based health system with *BRCA* mutations identified from 1995 to 2015. There were a total of 69 women with *BRCA* mutations who lived to age 75 or greater. The median age of the cohort at time of genetic testing was 73.5 years (range: 57–92 years). Most women were white (81%), and 14% were Ashkenazi Jewish.

At the time of genetic testing, 47 (68%) had a personal history of breast cancer, and 27 (39%) had a personal history of ovarian cancer. Twenty-three (33%) were tested because a *BRCA* mutation had been identified in another family member. Of 19 women with no prior history of breast cancer, 3 (15.8%) elected risk-reducing mastectomies (RRMs) after learning their *BRCA*-positive status (at ages 58, 66, and 68). Of the 3 women who elected a RRM, 2 had a prior personal history of ovarian cancer. Among 30 women who had ovaries in place at the time of genetic testing, 14 (47%) elected to have a risk-reducing salpingo-oophorectomy (RRSO); 6 of these women were age 70 or older at time of RRSO. After genetic testing, 3 women developed cancer: 1 woman developed breast cancer at age 67, and 2 women developed pancreatic cancer at age 76. Six women (8.7%) had no personal diagnosis of a *BRCA*-related cancer.

In conclusion, most women with *BRCA* mutations who survived beyond age 75 received their genetic test result at an older age, and most had a personal history of *BRCA*-related cancer. Almost half the women with ovaries in place underwent RRSO after identification of their *BRCA* mutation. Older women are making medical decisions based on information from the *BRCA* genetic testing, and it is important that the health care needs of this cohort be acknowledged.

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S6-PP3

Outcomes Associated with Rapid Genetic Testing for *BRCA1* and *BRCA2* at Time of Breast Cancer Diagnosis

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Objective Most women are unaware of their *BRCA* status at the time of cancer diagnosis. However, there are survival advantages associated with both bilateral mastectomy and bilateral salpingo-oophorectomy (BSO) in women with a *BRCA* mutation. Rapid genetic testing (RGT) allows for genetic test results before cancer surgery, but whether RGT has an impact on surgical decision-making or psychosocial functioning is unclear. The objective of the present study was to assess the impact of RGT at the time of breast cancer (BCa) diagnosis on surgery choices and psychosocial functioning.

Methods Eligible women were referred from surgeons at time of 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 after genetic testing. Medical charts were reviewed to abstract data about pathology and treatments.

Results 894 women consented to participate, and 53 (6.0%) were identified with a *BRCA* mutation. 17.0% 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 no differences between those with and without a *BRCA* mutation were observed. 77.0% of *BRCA* carriers had a bilateral mastectomy, compared with 20.4% of noncarriers ($p < 0.001$), and 42.9% of *BRCA* carriers had a BSO by 1 year. 80.4% of the participants were satisfied or very satisfied with RGT.

Conclusions With the provision of RGT for *BRCA1* and *BRCA2* at the time of BCa diagnosis, women identified with a *BRCA* mutation are significantly more likely than noncarriers to have a bilateral mastectomy and BSO. Satisfaction with RGT is high, and there are no negative psychosocial consequences associated with RGT.

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S7-PP1

Gen Y and Hereditary Breast/Ovarian Cancer: Understanding the Experiences and Information Gaps of Young Adults

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A striking feature of hereditary breast cancer is the younger age of onset, occurring frequently in the 30s and 40s and even in the 20s. Despite growing up in an era prevalent with breast cancer awareness, the hereditary cancer information and resource needs of the young adult population (18–40 year old) with a known *BRCA1/2* gene change in the family is largely unknown. The current findings are drawn from two large data sets: young adults and their families with a known *BRCA1/2* gene change (21 families), and health professionals (for example, geneticists, genetic counsellors) working with the families recruited from familial clinics from five states of Australia ($n = 75$).

The unique information preferences of young adults (18–25 years old) were also explored. Discrepancies between the views of health professionals and those of young adults reveal possible reasons for unmet needs. Familial communication patterns, parental anxiety, and attitudes toward the health care system are poignant areas that have to be targeted to meet the information needs of young adults. Recommendations for health service delivery of information and novel interventions will also be presented.

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S7-PP2

Modified Panel-Based Genetic Counselling for Ovarian Cancer Susceptibility: A Randomized Noninferiority Trial

Jeanna McCuaig,* Alicia Tone,* Tina Romagnuolo,* Nicole Ricker,* Jennifer Shuldiner,† Gary Rodin,* Manjula Maganti,* Marcus Bernardini*

Objective An estimated 20%–30% of ovarian cancers are hereditary; however, despite available recommendations, fewer than 25% of these women are referred for genetic testing. Widespread use of poly-ADP ribose polymerase inhibitors (PARPis) has led to increased demands and urgency for genetic testing, which is not sustainable using traditional genetic counselling (GC) models. The objective of this study is to evaluate a new model to improve the efficiency of pre-test GC.

Methods A parallel, two-arm, randomized noninferiority/equivalency study compared modified and traditional pre-test GC models (2:1) before gene panel testing. Participants were adult women, whose 1st-degree relative died of serous ovarian cancer. Participants were excluded if they, or their affected relative, had received comprehensive *BRCA1/2* testing. In the modified group, participants were e-mailed a 20-minute presentation before a scheduled pre-test GC phone call. All results were disclosed during a scheduled phone appointment with the study genetic counsellor. Psychosocial and knowledge questionnaires were provided before (P1) and 1 week after (P2) pre-test GC.

Results To date, 365 women have completed pre-test GC (243 modified, 122 traditional). Women randomized to modified compared with traditional pre-test GC had no differences in marital status, education level, or household income. Pre-test GC time was shorter for the modified compared with the traditional method (average 19 vs. 46 minutes, $p < 0.0001$), with no difference in post-test GC time (average 16 minutes each, $p = 0.6$). Based on 357 and 324 responses for P1 and P2 respectively, we observed no statistically significant differences in the following variables for modified compared with traditional GC: cancer-specific distress, depression, anxiety, decisional conflict, ovarian cancer knowledge, or satisfaction.
Conclusions The use of a 20-minute presentation before pre-test phone counselling was found to be noninferior to traditional in-person GC in a low-risk population of women. This modified model improved GC efficiency without negatively affecting psychosocial outcomes.

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S7-PP3

BRCA1/*BRCA2* Population Screening in Ashkenazi Jews: Long-Term Impact and Health Behaviours

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Background In Ashkenazi Jews, population screening for common (2.5%) *BRCA1*/*BRCA2* mutations could identify all carriers, including many (about half) lacking suggestive family history. Toward implementation, we examined the psychosocial and health behaviour long-term impacts of *BRCA* screening.
Methods Unaffected Ashkenazi Jews, age ≥ 25 years were either self-referred (SR) or recruiter-enrolled (RE) irrespective of family history (FH). The pre-test process was streamlined, including written information and self-reported FH. After testing, noncarriers with significant FH and carriers received in-person genetic counselling. Psychosocial outcomes and health behaviours were assessed using questionnaires at 1 week, 6 months, and 2 years after testing
Results We report the 2-year follow-up of 1771 participants, including 32 carriers (25 women, 7 men). Psychosocial outcomes: SR and RE participants had similar rates of satisfaction (94%) and endorsement of population screening (91%), and similarly low stress [Impact of Event (IES) score: 4/75]. Knowledge scores were higher in SR that in RE participants (7.4/10 vs. 6.9/10, $p < 0.001$). Among carriers, 92% expressed satisfaction, and 92% endorsed population screening. Stress was higher in carriers, but declined over time (IES score: 13.19 at 2 years vs. 19.9 at 6 months; nonsignificant). Knowledge was greater in carriers than in noncarriers (8.7/10 vs. 7.2/10, $p < 0.001$).
Health Behavior All 25 women carriers had breast surveillance, 3 of 25 (12%) underwent risk-reducing bilateral mastectomy (similar to published rates in Israeli carriers). Of 16 carriers more than 40 years of age, 15 (94%) underwent risk-reducing salpingo-oophorectomy (RRSO). Among noncarriers, mammography screening rates did not decline compared with pre-test rates; rates even increased in participants more than 50 years of age with nonsuggestive FH ($p = 0.001$) and in participants less than 50 years with significant FH ($p = 0.009$).
Conclusions Long-term, *BRCA* screening with a nongenetic counselling pre-test process is highly acceptable, through both self-referral and recruitment. Noncarriers do not demonstrate false reassurance, and carriers universally adopted increased surveillance, with almost all undergoing age-appropriate RRSO.

Acknowledgment: Funded by the Breast Cancer Research Foundation.

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S9-PP1

Breast Cancer Prevalence and Clinical Characteristics in Carriers of *ATM* Missense Versus Loss-of-Function Variants

Katherine Skora, Jessica Mester, Hubert Kuete, Kevin Arvai, Sheila Solomon, Lauren Yackowski, Patricia Murphy, Rachel Klein, Kathleen Hruska

Background Studies suggest that rare *ATM* missense variants within important functional domains increase the risk of breast cancer (BCA), possibly above that conferred by loss-of-function (LOF) variants. However, there is limited evidence supporting this assertion, except in the case of *ATM* Val2424Gly. Here, we compare the prevalence of BCA and other clinical factors among carriers of *ATM* missense and LOF variants.
Methods We retrospectively reviewed personal and family cancer histories for female heterozygous *ATM* variant carriers identified through multigene inherited cancer panel testing. Women had testing for at least *ATM, BRCA1/2, CHEK2*, and *PALB2*, and carried a LOF or single rare missense variant. Individuals were excluded if they were < 18 years or carried a pathogenic or likely pathogenic variant in another BCA-associated gene. Variants were categorized as LOF, missense in the FAT, FATC, or kinase domains (MID), or missense outside these domains (MOD). Benign/likely benign variants were excluded. Chi-square, unpaired t-tests, and ANOVA were used in the analysis.
Results We identified 4098 women, including 484 LOF, 1335 MID, and 2259 MOD carriers, 59% of whom (2405/4098) had a personal history of BCA. There was a significant difference in the prevalence of BCA among LOF, MID, and MOD carriers (68% vs. 59% vs. 56% respectively, $p < 0.01$). Carriers of LOF or MID variants were each more likely than MOD carriers to report a family history of BCA ($p < 0.01$), but less likely to have triple-negative BCA ($p < 0.01$). No difference in bilateral compared with unilateral BCA prevalence ($p = 0.69$) or age at diagnosis ($p = 0.09$) was identified between groups. Excluding *ATM* Val2424Gly (MID) did not change these results.
Conclusions *ATM* MID variants, compared with MOD, but not LOF variants, were associated with higher prevalences of personal history and family history of BCA. Studies including evolutionary conservation and segregation data might elucidate differences in BCA risk between LOF and rare missense variants, within and outside crucial domains.

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S9-PP2

Multigene Panel Testing in *BRCA1/2* Mutation-Negative Male Breast Cancer Patients: Results from a Multicenter Study in Italy

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Background Male breast cancer (MBC) is rare, representing less than 1% of all breast cancers (BCA). Inherited mutations in *BRCA1/2* predispose to MBC and account for about 10% of all cases. To gain more insight into genetic susceptibility in MBC, we performed an extensive genomic screening of a large series of *BRCA1/2* mutation-negative MBCs.
Methods A well-characterized series of 502 Italian men with *BRCA1/2* mutation–negative MBC was analyzed by a custom multigene panel of 50 cancer-related genes, using the MiniSeq platform (Illumina, San Diego, CA, U.S.A.). We also compared the main clinicopathologic characteristics of MBCs in mutation carriers and noncarriers.
Results About 5% of *BRCA1/2* mutation–negative MBCs were found to carry a pathogenic variant in the genes analyzed. *PALB2* and *ATM* were the most frequently altered genes (1.1% and 0.6%, respectively). Mutations in known or proposed BCA genes, such as *BARD1, BLM, CASP8, CHEK2, FANCM, NF1, RAD50, RAD51C*, and *RAD51D,* as well as in genes not closely related to BCA predisposition, such as *EPCAM* and *MUTYH,* were also identified. Compared with noncarriers, mutation carriers were more likely to have a personal history of cancer ($p = 0.0045$) and a family history of cancer other than breast/ovarian cancer ($p = 0.0004$).
Conclusions Our results support a central role of *PALB2* in MBC susceptibility, point to a relevant role of *ATM* and confirm a low impact of *CHEK2* in the Italian population. Our data also suggest that the multigene testing approach might benefit appropriately selected patients, especially those with personal or family history of cancer other than breast/ovarian cancer, and indicate that the selection of appropriate genes for the genomic screening of MBC cases might be essential to develop a comprehensive cancer susceptibility panel with implications for clinical management and counselling of patients and their families.

Acknowledgment: Study supported by AIRC (IG 16933) to LO.

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S9-PP3

Utilization of Pathogenic Mutations Beyond *BRCA1/2* in Breast Cancer Patients Up to 36 Months Post-Testing

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Background Management recommendations for pathogenic/likely pathogenic (P/LP) variants in genes beyond *BRCA1/2* have only recently been included in clinical guidelines. Clinician recommendations for findings in these genes are not well studied. We report interim results from a multisite study of clinical actions taken in patients with P/LP variants in cancer risk genes beyond *BRCA1/2*.

Methods We retrospectively examined 2184 patients referred for hereditary cancer multigene testing. Clinicians of patients with P/LP findings in a non-*BRCA1/2* cancer risk gene were asked to complete a case report form describing genetic-test-result-based clinical actions. Some patients were lost to follow-up and answers of "unknown" were permitted. For this analysis, de-identified case report forms were available for 80 patients.

Results In 85% of cases, clinicians reported that counselling and/or clinical management recommendations were changed for the patient and/or patient's family members in response to the genetic test findings, with 61% of patients (49/80) receiving result-based recommendations. Pathogenic variants were identified most often in *ATM, CHEK2,* and *PALB2* and changes in management were recommended for 55%, 63%, and 69% of patients respectively. Overall, 80% of patients (8/10) with variants causing known high-risk cancer syndromes (*APC, CDH1,* Lynch syndrome, and *PTEN)* received changes to clinical management, and 63% with variants in moderate-risk breast cancer genes (27/43) received changes to clinical management. Family member testing or screening was changed for 66% of cases.

Conclusions This study provides evidence that P/LP variants in cancer genes beyond *BRCA1/2* changed clinical management for most patients. Moderate cancer-risk genes, which might not be ordered or covered by insurance, are having a significant impact on patient care. More research is needed to understand the obstacles to clinician implementation of genetic testing based management recommendations.

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S10-PP1

Polygenic Risk from Common Genomic Variants Modifies the Effect of Many Moderate-Risk Breast Cancer Predisposition Genes and Can Improve Clinical Interpretation

Paul A. James,*†‡ Li Na,*‡ Simone McInerny,* Simone Rowley,* David Goode,* Rodney Scott,§ Lisa Devereux,* Norah Grewal,* VIP Study Investigators, LifePool Study,* Ian Campbell*‡

Many "new" breast cancer risk genes fall into the moderate-risk category (typically an increased risk between 1.5- and 4-fold). Translation of these findings has been limited by inconsistent replication, the moderate level of risk, and frequent non-segregation in high-risk families. We used data from a large familial breast cancer case–control study to examine the influence of common genomic variants [single nucleotide polymorphisms (SNPS)] on these genes to determine whether combined effects could better identify women at actionable levels of breast cancer risk.

Methods 4139 women affected by breast cancer (*BRCA1*/*BRCA2* excluded) and 4244 healthy controls were screened for variants in 160 genes with known or potential association with breast cancer, and a polygenic risk score (PRS) made up of 74 SNPS reported in genome-wide association studies. Loss of function and pathogenic missense variants in established risk genes (for example, *CHEK2, ATM)* or reported candidates, such as *MRE11A, RAD51C, BRIP1,* and so on, were analysed together with the individual's PRS.

Results Rare coding variants and the PRS showed the expected association with breast cancer; the mean odds ratio (OR) for loss-of-function variants in "panel" genes was 3.3 [95% confidence interval (CI): 2.7 to 3.9]. For a large number of genes, the measured risk from rare variants was significantly modified by the PRS, with no risk observed associated with a low PRS background and clinically significant risk for the same variants associated with high PRS. For example, for 15 common panel genes: low PRS (quartile) OR: 0.8 (0.5 to 1.3); high PRS OR: 4.0 (2.7 to 5.9). The same strong modification was found for some candidate genes—for example, *RAD51B:* mean OR: 1.0; high PRS OR: 4.7 (1.9 to 11.9).

Conclusions There is evidence of significant SNP-modifying effects for many suggested moderate-risk breast cancer genes, potentially contributing to the conflicting reports of risk for these genes. Combined interpretation of rare variants with PRS data can significantly improve the accurate identification of high-risk individuals.

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S10-PP2

Functional Analysis of the *RAD51C* Tumour Suppressor

Hermela Shimelis, Kun Lee, Fergus Couch

Inherited mutations in *RAD51C* are associated with a high risk [odds ratio (OR): >5.0] for ovarian cancer and might also confer moderate risks (OR: >2) for certain subtypes of breast cancer. Many germline nonsense, frameshift, and splice consensus site mutations have been identified in *RAD51C* through clinical multigene cancer panel testing. In addition, large numbers of missense variants in *RAD51C* have been reported in public databases such as ClinVar. However, the contribution of these variants of uncertain significance (VUS) to ovarian or breast cancer has not been established.

Rad51c is directly involved in homologous recombination-based repair of DNA double-strand breaks, and loss of this activity is thought to account for the tumorigenic potential of inherited mutations. Rad51c is recruited to Rad51 foci in response to DNA damage and forms protein independent complexes with Rad51B, Rad51D, XRCC2, and XRCC3, which mediate strand exchange reactions during the homologous recombination repair process. In addition, Rad51c inactivation is associated with sensitivity to cisplatin and PARP inhibitors.

We present results from functional characterization of the DNA damage repair activity of Rad51c. In addition, we report on the application of functional assays for Rad51c activity to systematic characterization of *RAD51C* VUS. Using 70 VUS described in ClinVar from all domains of Rad51c, we conducted Rad51 foci formation, homologous recombination repair, cisplatin response, and protein–protein interaction studies in Rad51c null cells reconstituted with full-length Rad51c-expressing lentivirus. We identified VUS in all domains of the protein that disrupt homologous recombination and also established that homologous recombination defects were fully consistent with cisplatin response. Based on these results, we propose that functional assays for Rad51c are an effective method for establishing the pathogenicity of *RAD51C* VUS and for predicting response of breast and ovarian tumours with these variants to cisplatin therapy.

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S10-PP3

A Microsimulation Model for Optimizing *BRCA* Mutation Carrier Cancer Risk Management: MiBRovaCAre

Lara Petelin,*† Lucinda Hossack,* Gillian Mitchell,* Danny Liew,†‡ Alison Trainer,*† Paul James*†

BRCA mutation carriers are currently offered screening and risk-reducing surgery to mitigate cancer risk. The optimal clinical management for these patients is uncertain because of the lack of randomized trials and the expense and duration of longitudinal observational studies. An alternative approach is required for rapid initial assessment of changes in practice to improve clinical management and optimize the use of health care resources. To this end, we developed MiBRovaCAre: a validated *BRCA*-specific microsimulation model built in Python.

This model incorporates real-world values and uncertainty for cancer incidence and pathology, mortality, risk management uptake and effectiveness, and resource use. The core module predicts the natural course of *BRCA*-related disease in the absence of screening or preventive surgery. This natural history module was externally validated and accurately predicted published outcomes for *BRCA* breast and ovarian cancer risk estimates and mortality rates (by stage and pathology).

Additional inputs were incorporated for risk management behaviour and clinical pathways, which were obtained from the experiences of 983 *BRCA* carriers managed through a familial cancer clinic (FCC) in Melbourne, Australia.

Applying the MiBRovaCAre model to 100,000 women from age 25 demonstrated that standard FCC care led to an average of 4.68 and 3.49 life-years gained (LYG) per person for *BRCA1* and *BRCA2* respectively. The addition of a dedicated risk management clinic to standard care increased the clinical benefit estimates to 4.91 and 3.58 LYG, reflecting increased adherence to scheduled breast screens. The model further shows that this benefit could be increased to 5.13 for *BRCA1* and 3.74 for *BRCA2* by encouraging an additional 10% of women to undergo bilateral prophylactic mastectomy before age 45.

MiBRovaCAre accurately models existing outcomes and can identify areas that would most benefit from interventions that optimize clinical management programs, maximizing the benefit to patients in a cost-effective manner.

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POSTERS

GROUP 1 – WEDNESDAY, 9 MAY 2018

BIOLOGY OF HEREDITARY CANCERS

Poster P001

p53 Is Required for Cisplatin-Induced Drp1 Dephosphorylation and Apoptosis in Ovarian Cancer

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Mitochondria are highly dynamic organelles, and mitochondrial fission is a crucial step of apoptosis. Although Drp1 is believed to be involve in mitochondrial fragmentation, whether and how its regulation is involved in the regulation of cisplatin (CDDP) sensitivity is not known.

Chemosensitive ovarian cancer (OVCA) cells were treated with CDDP. Apoptosis, protein contents, and phosphorylation were assessed by nuclear Hoechst staining and Western blot respectively. The requirements of p53 for CDDP-induced Drp1 processing and apoptosis were examined by siRNA or cDNA. Protein interaction was also detected by proximity ligand assay and Western co-immunoprecipitation.

We showed that

- CDDP decreased Drp1 content and induced apoptosis in a concentration-dependent manner in chemosensitive OVCA;
- chemoresponsiveness is associated with Drp1 downregulation, decreased p-Drp1 (ser637), and increased ser616/637 ratio in response to CDDP in OVCA cells;
- p53 is required for CDDP-induced Drp1 downregulation, ser637 dephosphorylation, and apoptosis;
- intact cellular gelsolin interacts with Drp1 and transport to mitochondria in response to CDDP;
- chemoresponsiveness is associated with increased p-p53 (ser15)–Drp1 and decreased gelsolin–Drp1 interactions in response to CDDP.

These findings demonstrate that CDDP induces Drp1 dephosphorylation (ser637), mitochondrial fragmentation, and CDDP-induced apoptosis in OVCA cells, and that mitochondrial dynamics might in part be involved in CDDP sensitivity in a p53-dependent manner.

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Poster P002

Epigenetic Therapies to Target Ovarian Cancer

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Small-cell carcinoma of the ovary, hypercalcemic type (SCCO-HT) is a malignant tumour with a dismal prognosis observed in young women. SCCO-HT is hereditary and invariably characterized by inactivating mutations in the *SMARCA4* gene. *SMARCA4* plays an important role in gene transcription by shifting or evicting repressive nucleosomes, generally leading to transcriptional activation. *SMARCA4* and the bromodomain protein BRD4 independently co-regulate a transcriptional network of proliferation-related genes in a redundant manner. Thus, we propose that tumours with a loss of *SMARCA4* will depend solely on BRD4 for the expression of this gene network. We hypothesize that inactivating BRD4 with BET inhibitors (BETi) is a rational therapeutic approach to target *SMARCA4*-mutant cancers because that approach should critically repress BRD4-dependent oncogene expression.

Using complementary *in vitro* techniques, we demonstrated that *SMARCA4*-deficient SCCO-HT cells are exquisitely sensitive to BETi. We further established, for the first time, an orthotopic ovarian xenograft model of SCCO-HT. These tumours showed a very significant response to BETi at doses of only 20 mg/kg daily. No response in *SMARCA4*-expressing tumours was observed at that dose. To identify target genes driving the sensitivity to BETi, we carried out RNA-seq on BETi-exposed sensitive and resistant cells. Interestingly, BETi induced changes in SCCO-HT cells in mRNA levels for many genes from the oncogenic receptor tyrosine kinase pathway. Western blotting validated that BETi repressed expression of HER3 and downstream effectors. Mechanistically, our chromatin immunoprecipitation experiment revealed that BETi directly represses the transcriptional elongation of the *ERBB3 (HER3)* gene. Importantly, we found that ectopic expression of *SMARCA4* or *HER3* lead to resistance to BETi.

Our data demonstrates a potent antitumorigenic effect of BETi *in vitro* and *in vivo* against *SMARCA4*-negative SCCO-HT having poor outcome. We suggest that the loss of *SMARCA4* might act as a biomarker for therapeutic intervention with BETi.

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Poster P003

Circulating Osteoprotegerin and Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers

Tasnim Zaman,*† Leonardo Salmena,†‡ Shana J. Kim,* Ping Sun,* Jan Lubinski,§ Steven A. Narod,*† Joanne Kotsopoulos*†

Background Experimental and epidemiologic evidence points toward aberrant signalling in the receptor activator of nuclear factor κB (RANK)/RANK ligand (RANKL) pathway in the pathogenesis of *BRCA*-associated breast cancer. Osteoprotegerin (OPG) is the endogenous decoy receptor for RANKL that antagonizes RANK/RANKL-mediated signalling. Lower circulating OPG levels among *BRCA* mutation carriers compared with noncarriers has previously been reported. Furthermore, we observed an inverse relationship between plasma OPG and *BRCA* breast cancer risk. This study aims to validate those findings in a larger group of *BRCA* mutation carriers with a longer follow-up period.
Methods This prospective study included 606 *BRCA* mutation carriers with no previous history of cancer or prophylactic mastectomy who were under active follow-up. Serum OPG concentrations (pg/mL) were quantified through enzyme-linked immunosorbent assay (ELISA). Kaplan–Meier survival analysis was used to estimate the cumulative incidence of breast cancer by median OPG level.
Results Over a mean follow-up of 2.7 years (range: 0.003–7.5 years), 20 incident breast cancer cases were diagnosed. The mean serum OPG level was 124.4 pg/mL (range: 32.1–368.6 pg/mL). We stratified women by median OPG level [<116.7 pg/mL (n = 303) vs. ≥116.7 pg/mL (n = 303)]. There were 14 incident cases among women with OPG levels below the median and 6 incident cases among women with OPG levels above or equal to the median. The cumulative incidence of breast cancer for women with an OPG level <116.71 pg/mL was 31% compared with 3% for women with an OPG level ≥116.71 pg/mL (log rank p = 0.11). Quantification of OPG and RANKL from additional women and collection of follow-up information are underway.
Conclusions These interim findings support the role of aberrant RANK-signalling in *BRCA* breast cancer development and suggest that RANKL-blockade is a likely candidate for non-surgical prevention. Pending completion of the study, circulating OPG level might improve the identification of women who are ideal candidates for RANKL-chemoprevention.

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GENOME-WIDE APPROACHES TO IDENTIFY NEW GENETIC RISK FACTORS

Poster P004

Heritable Methylation Marks Associated with Breast and Prostate Cancer Risk

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Although most epigenetic marks are reprogrammed during early embryogenesis, some studies have reported Mendelian-like inheritance of germline DNA methylation—in particular, in cancer susceptibility genes. For instance, individuals with *MLH1* silenced throughout the soma fit the clinical criteria for hereditary nonpolyposis colorectal cancer indistinguishably from the syndrome that results from germline mutations in *MLH1*. Research using multiple-case breast cancer families has shown that *LINE-1* and *SAT2* DNA methylation levels are lower in individuals with a strong family history. Family clustering of cancer could therefore be attributable to epigenetic as well as genetic and shared environmental factors.

We have identified heritable methylation marks associated with breast and/or prostate cancer susceptibility by conducting genome-wide studies involving Australian multigenerational families with multiple cases of breast and/or prostate cancer who are not known to carry genetic mutations in cancer susceptibility genes. We developed and applied a new statistical method to identify heritable methylation marks based on complex segregation analysis and identified methylation marks significantly associated with breast and/or prostate cancer risk. Several marks across *VTRNA2-1*, a gene located in a differentially methylated region that is involved in imprinting and shows allele-specific methylation, were associated with heritable risk of both cancer types. A proportion of all identified marks were found to be associated with cancer risk in

independent nested case–control studies (that is, outside the multiple-case family setting). We found evidence that some of these are likely to be methylation quantitative trait loci, and some are likely to be involved in tumorigenesis.

We are expanding these successful studies to include additional families and to estimate hazard ratios and age-specific cumulative risks of cancer associated with these marks to enable the incorporation of this information into clinical tools for risk prediction.

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Poster P005

Whole-Exome Sequencing of Brazilian Families at High Risk for Hereditary Breast/Ovarian Cancer, Negative for Mutations in *BRCA1*/*BRCA2* Genes

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Background *BRCA1* and *BRCA2* testing is uninformative in approximately 80% of families with clinical features of inherited susceptibility to breast and ovarian cancers. Early identification of high-risk individuals could lead to improvements in screening and prevention strategies and could potentially improve overall cancer survival.
Aim To identify the missing heredity associated with cancer development in high-risk families, *BRCA1/2* wild-type (*BRCAx* families) through whole-exome sequencing (WES) of constitutive DNA.
Methods We performed WES (Nextera Rapid Capture Exome and Expanded Exome Kit: Illumina, San Diego, CA, U.S.A.) in 45 *BRCA1/2* wild-type individuals with high risk for breast/ovarian cancer. The criteria for data analysis were coverage ≥10x; variants present in less than 15% (≤7 samples); and missense, in-frame, and stop-loss variants classified as pathogenic by at least 3 of 6 *in silico* prediction programs selected.
Results For each sample, an average of 122 genetic changes per sample (ranging from 5 to 196 variants) were identified. In addition, most of the identified variants were of the missense type, followed by the nonsense variants. Of the 20 most commonly altered genes, many have already been associated with hereditary predisposition syndromes to cancer, such as the *ATM, MLH1, MSH6, MUTYH* genes. Besides, pathogenic or probably pathogenic alterations in DNA repair genes such as *ATXN3, ERCC3, ERCC4, EXO1,* and *FAN1* were identified.
Conclusions Our data show that significant genetic heterogeneity exists in *BRCAx* families. Large-scale collaborative efforts will be required to attain sufficient power to understand the missing heredity associated with breast/ovarian cancer development in high-risk families.

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Poster P006

Discovery of Novel Genetic Variants Predisposing to Ovarian Cancer in a Large, Affected Population of Familial and Sporadic Cases with No Known Hereditary Cause

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Many women referred for genetic testing with epithelial ovarian cancer and a family history of ovarian and/or breast cancer do not have an identifiable deleterious mutation in any of the known hereditary breast and ovarian cancer (HBOC) genes. Progress toward the identification of novel genetic causes has been slow, partly because of the limited number of cases available for discovery studies considering the likely high genetic heterogeneity of these families. We have generated and collected germline whole-exome sequencing (WES) data for a cohort of more than 1400 patients diagnosed with epithelial ovarian cancer (including high-grade and low-grade serous, endometrioid, mucinous, and clear-cell types) who tested negative for known deleterious mutations in *BRCA1/2* and other HBOC genes. Approximately 900 of those cases are women with a family history of ovarian and/or breast cancer or with young-onset ovarian cancer. We have access to tumour blocks from our patient population to perform loss-of-heterozygosity analysis and have potential access to other affected and unaffected family members for segregation studies. The WES data were interrogated for rare deleterious germline genetic variants (population allele frequency < 0.005) that were more than 3-fold enriched compared with the frequency in the GnomAD database. Preliminary analysis of a subset of the familial cases found that < 5% are explained by mutations in currently known or suspected HBOC genes (for example, *RAD51C/D*) and, at best, no single novel gene could explain more than 2% of cases.

These data demonstrate that the remaining families are likely to be extremely genetically heterogeneous, and emphasizes the need for large discovery and validation cohorts. Our poster will describe details of our methodology for identifying and validating novel genetic variants from this population, as well as early results and future work for further validation of the most promising candidate genes.

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Poster P007

Mapping Homologous Recombination Genes Using Multi-clade Phylogenetic Profiling of 600 Species

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Mutations in homologous recombination repair (HRR) genes trigger numerous genetic disorders. In hereditary breast and ovarian cancer (HBOC), these mutations are the drivers underlying approximately 30% of cases. The genetic cause of the remaining 70% is unknown, but molecular evidence suggests the involvement of uncharacterized HRR genes.

To systematically map novel HRR genes, we introduce a computational algorithm that screens 578 eukaryote genomes on different evolutionary scales. To further prove the validity of our method, functionally characterize our predicted genes, and generate a complete cohort of genes that are functionally related to the HRR, we integrate 24 different genetic screens and databases into a database (HRRbase) that maps the interaction of every gene with the HRR pathway and yields 435 genes predicted to be highly involved in HRR. These genes mght play a significant role in HRR-related genetic disorders and HBOC, potentially yielding new targets for therapeutics.

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

Poster P008

ATM Whole-Gene Deletion in an Italian Family with Familial Pancreatic Cancer

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Background Biallelic mutations in *ATM* are a known cause of ataxia–telangiectasia, while heterozygous pathogenic mutations in the *ATM* gene are known to increase risks for development of various cancers, including breast and pancreatic cancer. *ATM* whole-gene deletions have not been reported in families with either ataxia–telangiectasia or familial cancer. We report a whole-gene deletion of *ATM* in an Italian family with a history of pancreatic cancer.
Methods Next-generation sequencing of a 16-gene cancer panel identified a heterozygous deletion of *ATM* in an individual with pancreatic cancer. The presence and size of the deletion were validated and assessed by quantitative polymerase chain reaction and CytoScan HD microarray (Thermo Fisher Scientific, Waltham, MA, U.S.A.) respectively. Family studies were performed to identify at-risk individuals.
Results A heterozygous whole-gene deletion of *ATM* was identified in a 56-year-old male with adenocarcinoma of the pancreas who presented with a strong family history of pancreatic cancer. Microarray analysis suggests that the deletion spans 960 Kb and ablates *ATM*, putative tumour suppressor genes *CUL5* and *NPAT,* and various other genes. The proband's mother was diagnosed with breast cancer at the age of 75, and brother was diagnosed with non-Hodgkin lymphoma at the age of 35. Pancreatic cancer was diagnosed in a maternal aunt, maternal uncle, and maternal first cousin. Genetic testing indicates that patient's brother and daughter are carriers of the whole-gene *ATM* deletion; the genotypes of other family members remain unknown.
Conclusions This report is the first of an inherited microdeletion that fully ablates *ATM.* Given that *ATM* haploinsufficiency is a proven cause of increased cancer risk, it is reasonable to deem this copy number loss to be a cause of hereditary susceptibility to cancer in this family. The lack of breast cancer in the family makes it particularly challenging in assessing the breast cancer risk in female *ATM* deletion carriers.

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Poster P009

Genetic and Molecular Analyses of a Rare *FANCI* Missense Variant Found in a *BRCA1* and *BRCA2* Mutation–Negative Ovarian Cancer Family

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Heterozygous carriers of pathogenic germline mutations in the Fanconi anemia (FA) complementation group genes, such as *BRCA2 (FANCD1)*, *BRIP1 (FANCJ)*, and *PALB2 (FANCN)*, have been associated with increased risk of breast and/or ovarian cancer. Recently, rare heterozygous carriers of potentially pathogenic mutations in other FA genes have been reported in *BRCA1*/*BRCA2* mutation–negative breast/ovarian cancer families, suggesting that other members of this pathway might also play a role in cancer risk.

We identified heterozygous carriers of a potentially damaging missense variant in *FANCI (FANCI* p.L605F), a FA pathway gene, using whole-exome sequencing (WES) of a *BRCA1*/*BRCA2* mutation–negative French Canadian (FC) ovarian cancer (OC) family. *FANCI* p.L605F allele frequency is unknown in FCs, but varies from 0% to 1.8% in ethnically defined populations (Exome Aggregation Consortium). Thorough WES analysis of 10 other *BRCA1*/*BRCA2* mutation–negative FC OC families found no other *FANCI* p.L605F carriers, mutation screening found heterozygous carriers in 7 of 439 (1.6%) largely FC OC cases not selected for family history of cancer. Most carriers (6 of 7) had high-grade serous OC and did not carry any of the *BRCA1*/*BRCA2* mutations found to recur in FCs. Targeted mutation screening of *FANCI* p.L605F in cancer cohorts identified heterozygous carriers in another multi-case *BRCA1*/*BRCA2* mutation–negative FC OC family.

Molecular analysis of *FANCI* p.L605F protein revealed that it is destabilized *in vitro* upon treatment with endogenous or exogenous DNA-damaging agents. Immunofluorescence shows that, compared with the wild-type protein, *FANCI* p.L605F protein, although expressed, severely impedes localization of *FANCD2* (known heterodimeric binding partner of *FANCI)* to sites of DNA damage.

FANCI is an essential member of the FA DNA repair pathway that functions upstream of the homologous recombination DNA repair pathway that involves *BRCA1*/*BRCA2* function. Taken together, our data suggest the involvement of *FANCI* p.L605F in risk or progression to OC.

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Poster P010

Development and Validation of a Combined Residual Risk Score to Predict Breast Cancer Risk in Unaffected Women Negative for Mutations on a Multigene Hereditary Cancer Panel

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Background Large-scale genotyping studies have identified common variants that individually confer modest breast cancer (BCA) risk, but together partially explain BCA genetic susceptibility in many women without monogenic mutations in BCA risk genes. Here, we describe the development and validation of a combined polygenic residual risk score (CRRS) that takes into account both genetic and nongenetic factors in a large consecutive cohort of women who tested negative for mutations in known BCA susceptibility genes.

Methods This IRB-approved study included women of European ancestry who had multigene hereditary cancer testing and were negative for mutations in 11 BCA risk genes (*BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, PALB2, CHEK2, ATM, NBN, BARD1)*. Previously published variants ($n = 94$) were genotyped using next-generation sequencing. Multivariable logistic regression models were then used to develop a residual risk score (RRS) as a predictor of personal BCA history in the training cohort ($n = 24{,}259$) and to assess the performance of the RRS in the independent validation cohort ($n = 10{,}575$). Independent variables included age, personal/family cancer history, and ancestry. The RRS was combined with the Tyrer–Cuzick model to generate a CRRS and was validated in an additional independent cohort ($n = 1617$).

Results The RRS was strongly associated with personal history of BCA in the validation cohort ($p < 10^{-31}$) with the odds ratio (OR) per unit standard deviation of the RRS being 1.41 (95% CI: 1.33 to 1.49). The remaining lifetime and 5-year risk estimates were highly significant for the CRRS (OR: 2.10; 95% CI: 1.85 to 2.38; $p = 4.1\times10^{-35}$), adding significant risk discrimination independent of that captured by Tyrer–Cuzick for both remaining lifetime risk ($p = 8.3\times10^{-13}$) and 5-year risk ($p = 1.0\times10^{-12}$).

Conclusions The validation and clinical implementation of a CRRS for women at risk for hereditary BCA might offer significant potential for the management of high-risk unaffected women who test negative for monogenic BCA mutations.

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Poster P011

Familial Breast Cancer and DNA Repair Genes: Insights into Known and Novel Susceptibility Genes from the GENESIS Study

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Pathogenic variants in *BRCA1* and *BRCA2* explain about 10% of hereditary breast and ovarian cancer families. Because of cost-effectiveness, multigene panel testing is now often performed in such families, but whether the identification of an alteration in some of the genes screened in parallel with *BRCA1* and *BRCA2* is useful for clinical management of the patient and her/his relatives remains questionable. We assessed the contribution of rare, damaging predicted variants in DNA repair genes in a case–control study involving a representative set of French familial breast cancer (BCA) cases and controls from the general population (the GENESIS study).

A total of 113 DNA repair genes were screened, 77 of which were candidates selected from exome sequencing data, in 1207 cases with no *BRCA1/2* mutation and a sister affected with BCA, and in 1199 controls. Sequencing data were filtered for rare loss-of-function (LOF) variants and likely deleterious missense variants (MVS).

LOF variants in *ATM, CHEK2,* and *PALB2* were associated with an increased BCA risk (OR_{ATM}: 17.1; 95% CI: 2.3 to 129; OR_{CHEK2}: 5.9; 95% CI: 2.0 to 17; OR_{PALB2}: 3.8; 95% CI: 1.0 to 14). Likely deleterious MVS in the 3 genes were also associated with BCA risk (OR_{ATM}: 1.6; 95% CI: 1.0 to 2.4; OR_{CHEK2}: 2.5; 95% CI: 1.4 to 4.1; OR_{PALB2}: 3.5; 95% CI: 1.4 to 8.6). In addition, likely deleterious MVS in *MAST1* were associated with an increased BCA risk (OR: 2.5; 95% CI: 1.0 to 6.0), while such variants in *POLH, RTEL1,* and *FANCI* were associated with a decreased BCA risk (OR_{POLH}: 0.3; 95% CI: 0.1 to 0.9; OR_{RETL1}: 0.4; 95% CI: 0.2 to 0.9; OR_{FANCI}: 0.4; 95% CI: 0.2 to 1.0).

Hence, our approach identified more DNA repair genes (*MAST1, POLH, RTEL1,* and *FANCI)* involved in familial BCA and showed that, depending on the gene, LOF and MV might contribute differently to the susceptibility to the disease.

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Poster P012

Cellular Gelsolin Modulates Cisplatin-Induced p53-Mediated Drp1 Dephosphorylation and Apoptosis in Ovarian Cancer

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Mitochondria are highly dynamic organelles, and mitochondrial fission is a crucial step of apoptosis. Although Drp1 is believed to be involved in mitochondrial fragmentation, whether and how its dysregulation is involved in the modulation of cisplatin (CDDP) resistance and the involvement of intact cellular gelsolin (I-CGSN) is unknown.

Chemosensitive and chemoresistant ovarian cancer (OVCA) cells were treated with CDDP. Apoptosis, protein content, and phosphorylation were assessed by nuclear Hoechst staining and Western blot respectively. The requirements of p53 for CDDP-induced Drp1 processing and apoptosis were examined by siRNA or cDNA.

Protein interaction was also detected by proximity ligand assay and Western co-immunoprecipitation.

- CDDP-induced Drp1 and p-Drp1 (ser637) downregulation, ser616/637 ratio enhancement is not observed in chemoresistant OVCA cells.
- CDDP increased p-p53 (ser15)-Drp1 and decreased GSN-Drp1 interaction in chemosensitive, but not resistant, cells—a response that depends on p53.
- I-CGSN inhibits CDDP-induced Drp1 and p-Drp1 (ser637) downregulation and apoptosis in OVCA cells

These findings demonstrate that p53 mediates Drp-1 dephosphorylation (ser637) and mitochondrial fragmentation and is involved in CDDP-induced apoptosis in OVCA cells, and that dysregulated mitochondrial dynamics by I-CGSN could in part be involved in the pathophysiology of CDDP resistance.

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Poster P013

Pathogenic Variant Detection in a 19-Gene Core Panel and Yield of Opportunistic Screening in *BRCA1/2* and Mismatch Repair Genes in a Cohort of 1121 Hereditary Cancer Patients

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Background Multigene panels provide a powerful tool for analyzing several genes simultaneously and identifying cancer susceptibility beyond the suspected clinical phenotype. We evaluated the pathogenic variant (PV) frequency in customized predefined panels according to phenotype, and we extended the analysis to our 19-gene research panel. We also investigated the yield of opportunistic screening in the *BRCA1/2* and mismatch repair (MMR) genes in all patients.
Methods Overall, from Sep 2014 to Jul 2017, 1121 unrelated probands underwent multigene testing with customized predefined panels according to their phenotype and a 19-gene research panel, in addition to the *BRCA1/2* and MMR genes.
Results Overall, 1015 women and 106 men were studied, mean age at cancer diagnosis was 47 years (14), 579 had breast cancer (BCA), 258 ovarian cancer (OC), 124 colorectal cancer, and 27 were unaffected. A BCA, OC, or BCA/OC panel was requested in 66% and a hereditary nonpolyposis colorectal cancer (HNPCC) panel, in 12%. The customized diagnostic panel found 151 (13%) probands who carried at least 1 PV. All *BRCA1/2* carriers fulfilled BCA, OC, or BCA/OC criteria. Among the MMR carriers, 50 PVs (89%) were identified with the HNPCC panel, and 6 (11%) were opportunistic, all in *MSH6*. The 19-gene research panel provided 22 additional PVs (2%) beyond the customized panel according to clinical phenotype: 5 *BARD1*, 4 *NBN*, 3 *BRIP1*, 3 *ATM*, 2 *CHEK2*, 2 *RAD51C*, 2 *RAD51D*, and 1 *CDH1*. Of these PVs, 13 were in actionable genes (*BRIP1, ATM, CHEK2, RAD51C, RAD51D, CDH1)*.
Conclusions The yield of PV detection in various actionable genes identified by multiplex testing is clinically relevant. Of MMR mutation carriers (all carrying *MSH6* PVs), 11% were identified through opportunistic screening. Identification of PVs in *BARD1* and *NBN* genes by the research panel deserve further investigation.

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Poster P014

Comprehensive Analysis of Fanconi Anemia Genes in Hereditary Cancer

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Introduction Fanconi anemia (FA) is caused by biallelic mutations in the FA pathway genes. Heterozygous mutations in 4 of those genes (*BRCA2, PALB2, BRIP1,* and *RAD51C)* increase the susceptibility to breast and/or ovarian cancer and as such are used in clinical diagnostics. There is increasing evidence suggesting that other FA genes could predispose in heterozygosity to develop other tumours, especially breast cancer. To gain insights into this field, we performed an extensive analysis of 12 FA-associated genes (*FAN1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM,* and *SLX4)* in addition to *BRCA2, PALB2, BRIP1,* and *RAD51C* in a cohort of hereditary cancer patients.
Methods The mutation analysis was performed using a next-generation sequencing custom panel (Castellanos *et al.*, 2017). In total, 1021 patients were analyzed: 632 (61.9%) with clinical suspicion of hereditary breast and/or ovarian cancer, 210 (20.6%) with clinical suspicion of hereditary nonpolyposis colorectal cancer, and 179 (17.5%) with other clinical suspicions of hereditary cancer.
Results We identified 45 pathogenic mutations in the well-established breast/ovarian cancer genes: 29 *BRCA2*, 6 *PALB2*, 5 *BRIP1*, and 5 *RAD51C*. Moreover, 40 pathogenic mutations were found in the 12 remaining genes: 11 *FANCL*, 8 *FANCA*, 7 *FANCM*, 7 *FAN1*, 2 *FANCI*, 2 *FANCE*, 2 *FANCC*, and 1 *FANCF*. In this second group, 80% of mutation-positive patients have criteria of hereditary breast/ovarian cancer suspicion. In addition, 533 variants of unknown significance were detected in the studied genes, 20 of them predicted, by several *in silico* tools, to affect normal splicing. Analysis of copy number alterations and co-segregation analysis of the pathogenic variants is currently under way.
Conclusions These results support the role of FA-associated genes in cancer susceptibility, being mainly associated with predisposition to breast or ovarian cancer.

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Poster P015

Association of Non-*BRCA* Homologous Recombination Genes with Breast and Ovarian Cancers

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Introduction The association with breast and ovarian cancer is well established for *BRCA1* and *BRCA2*, but evidence for other genes involved in homologous recombination (HR) continues to evolve. We sought to determine the association of pathogenic and likely pathogenic variants (PVs) in 9 HR-related genes in a cohort of women with breast and ovarian cancers undergoing multigene hereditary cancer panel testing.
Methods We performed a retrospective case–control study to assess breast and ovarian cancer association with *ATM, BARD1, BRIP1, CHEK2, FANCC, NBN, PALB2, RAD51C,* and *RAD51D*. Cases were women with breast ($n > 31{,}000$) and/or ovarian ($n > 4500$) cancer referred for testing of up to 62 genes. Controls included 8749 reportedly cancer-free mothers of individuals referred for whole-exome sequencing. We reviewed genetic testing results and reported history of cancer for both groups. Adjusted odds ratios (ORs) were generated by multivariate logistic regression analysis, controlling for age, with a Bonferroni-corrected significance threshold of 0.005 to determine significance.
Results In this large, independent case–control cohort, a statistically significant breast cancer association was observed for *ATM* (OR: 2.44), *BARD1* (OR: 8.00), *CHEK2* (OR: 3.01), and *PALB2* (OR: 6.69) and with ovarian cancer for *RAD51C* (OR: 10.21) and *RAD51D* (OR: 16.85). Although the associations of ovarian cancer with *PALB2* and breast cancer with *RAD51D* are not significant using the defined p value threshold, the 95% confidence intervals suggest that the most probable effect sizes lie above 1.0. No significant breast or ovarian cancer associations were observed for *BRIP1, FANCC,* and *NBN*.
Conclusions Using a large control population of phenotypically well-described women, we observed significant breast or ovarian cancer associations for *ATM, BARD1, CHEK2, PALB2, RAD51C,* and *RAD51D*. This novel approach addresses limitations of previous case–control studies performed with general population database cohorts while substantiating the results of previous reports in the literature.

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Poster P016

Characterization of the Clinical Phenotype of Homozygous/Compound Heterozygous *CHEK2* Mutation Carriers

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Pathogenic heterozygous mutations in the *CHEK2* gene are associated with an approximate 2-fold increased risk of female breast cancer, estimated to be 20%–25% lifetime risk. Given that data about the magnitude of the cancer risk attributable to *CHEK2* mutations are limited, testing negative for a familial *CHEK2* mutation does not eliminate familial risk factors, and a discussion of potentially increased screening might be appropriate based on the family history of cancer. Additionally, limited data are available about breast cancer risk in the setting of homozygous *CHEK2* mutations.

Our case series identified 23 *CHEK2* patients carrying two *CHEK2* mutations, including 6 *CHEK2**1100delC homozygotes and 17 *CHEK2* compound heterozygotes, including truncating mutations and many low-penetrant pathogenic mutations. A subset of *CHEK2* compound heterozygotes showed a profound younger age of onset and appeared to have a greater than 2-fold increased risk of breast cancer. Given that further data are needed to extrapolate the lifetime risk of female breast cancer for *CHEK2* homozygotes or *CHEK2* compound heterozygotes, our results suggest that increased earlier breast screening might be indicated for females who are identified to have two *CHEK2* mutations.

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Poster P017

Comparing Cancer Prevalence in Individuals with Biallelic Versus Single *CHEK2* Pathogenic Variants

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Background *CHEK2* pathogenic variants increase the risk for breast and other cancers. Published reports suggest that female *CHEK2* c.1100delC homozygotes could have a breast cancer risk more than twice that of heterozygous females, and biallelic *CHEK2* carriers have been reported to present with other cancer types; however, data are limited. We aimed to describe cancer prevalence among patients with biallelic *CHEK2* pathogenic or likely pathogenic variants (PVs) and to compare it with that among *CHEK2* heterozygotes.
Methods We retrospectively reviewed results and self-reported histories of individuals with *CHEK2* PVs undergoing hereditary cancer testing, excluding those with PVs in other genes. The Fisher exact test was used to assess differences in cancer prevalence between biallelic and heterozygote carriers. A two-tailed t-test showed no significant difference in age at testing between the two groups.
Results The evaluation considered 25 individuals (22 women, 3 men) with two, presumably biallelic, *CHEK2* PVs and 2087 *CHEK2* heterozygotes (1919 women, 168 men). Female breast cancer (14/22 vs. 1039/1919, p = 0.4), male breast cancer (2/3 vs. 12/168, p = 0.018), colorectal cancer (4/25 vs. 64/2087, p = 0.007), and stomach cancer (2/25 vs. 5/2087, p = 0.003) were more prevalent in our biallelic cohort; however, the results were underpowered (0.05–0.06) to detect a significant effect. Although underpowered, no difference was observed for breast cancer prevalence in women with two truncating PVs (5/7) versus those with two missense PVs (6/8, p = 1.0).
Conclusions Although we did not observe significantly increased odds (p = 0.4) for female breast cancer in women with biallelic versus single *CHEK2* PVs, colorectal cancer, male breast cancer, and stomach cancer occurred significantly more often in biallelic carriers. Those findings cannot be attributed to age differences between the two groups. However, our sample sizes might not have been large enough to detect significance. Further studies with larger cohorts are needed to assess cancer risks for individuals harbouring biallelic *CHEK2* PVs.

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Poster P018

A Likely Pathogenic Founder Mutation in *RAD51C* Causing Ovarian Cancer in Newfoundland

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Background *RAD51C* is involved in the homologous recombination and repair of DNA. If dysfunctional, the result is defective homologous recombination and increased ovarian cancer risk. Variants of uncertain significance (VUS) remain a significant challenge in the study of high risk breast/ovarian families. High-risk large pedigrees from a founder population, such as that in Newfoundland and Labrador (NL), can assist with effective characterization of those variants. Multigene panels performed on 5 women from 4 families identified the *RAD51C* c.571+4A>G (rs587780257) variant reported as a VUS.
Objective To determine if the *RAD51C* c.571+4A>G variant represents a pathogenic founder variant in NL.
Methods The 4 families, plus a series of unselected ovarian cancer cases and unaffected NL controls, were evaluated to determine if the VUS segregated with cancer diagnosis and to evaluate the variant frequency in affected and unaffected populations. The evaluation used a combination of mined existing whole-exome sequencing data and targeted Taqman analysis. Additional analyses were performed to determine if the variant affects splicing and structure.
Results *RAD51C* c.571+4A>G was detected in 5 women with breast or ovarian cancer in 4 large families from NL. The variant causes aberrant splicing and skipping of exon 3 and/or 4 and a frameshift and/or early-stop codon predicted to result in a truncated Rad51c protein (Phyre and JSmol). Of 7 additional relatives with available DNA, 2 of 3 unaffected males carried the variant. There were no unaffected carrier females (0/4). In 30 unselected NL ovarian cancer cases, no additional women with *RAD51C*+4A>G were identified. In a series of NL controls, the allele frequency in NL (0/358) was similar to that reported in the Single Nucleotide Polymorphism Database (~1/33,333).
Conclusions The *RAD51C* c.571+4A>G variant causes exon skipping and represents a rare likely pathogenic variant in the NL founder population. Additional work including haplotype analysis and further functional investigation (gene/protein expression) is ongoing.

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Poster P019

BRA-STRAP: Personalized Medicine to Precision Public Health

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In 30,000 Australian women of all ages across the cancer risk spectrum, affected and unaffected with breast cancer, and their families, BRA-STRAP is performing targeted sequencing of 24 genes commonly included on panel tests for breast cancer predisposition. Contributing to BRA-STRAP are large research cohorts (of aging populations and of women above population risk) and the clinical genetics community and women found negative for *BRCA1* and *BRCA2* mutations after testing in a Familial Cancer Centre over the last 2 decades. BRA-STRAP is also engaged with the broader translational research community and other similarly designed studies set outside of Australia (for example, BRIDGES and CARRIERS).

Data on this scale represent the spectrum of genetic variation observed in these genes and exemplify the opportunities and challenges for realizing precision medicine and precision public health for breast cancer. All women identified to carry genetic variants supported by Australian best practice guidelines have the opportunity to receive this information free of charge (should they wish to receive it) to inform risk management and treatment options and to enable predictive testing in family members.

A large number of genetic variants will require further study to determine their clinical utility, including variants of uncertain clinical significance in known breast cancer susceptibility genes, variants in genes that are not well characterized outside a specific cancer syndrome, and variants in genes for which the evidence is currently insufficient for them to be called bona fide breast cancer susceptibility genes.

We discuss these challenges, as well as those arising for precision medicine when trying to estimate breast cancer risk for women who carry a number of different rare genetic variants in these genes or when actionable mutations are identified in the healthy aging population (or both). Addressing those challenges is allowing for the shift from personalized medicine to precision public health for breast cancer.

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Poster P020

Prognosis of *BRCA1/2*–Negative Breast Cancer Patients with Hereditary Breast and/or Ovarian Cancer (HBOC) Risk Factors Compared with Sporadic Breast Cancer Patients Without HBOC Risk Factors

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Background Demands for genetic counselling with *BRCA1/2* examination have markedly increased. Accordingly, the incidence of uninformative results on *BRCA1/2* mutation status has also increased. We compared oncologic outcomes between *BRCA1/2*–negative breast cancer with high risk of HBOC and sporadic breast cancer without risk of HBOC.
Methods The criteria for high risk for HBOC were defined as family history of breast and/or ovarian cancer in 1st- or 2nd-degree relative, early-onset breast cancer at less than 35 years of age, and bilateral breast cancer. Patients were matched maximally 1:3 into those who identified as negative for *BRCA1/2* mutation with risk of HBOC (study group) and those who were not examined for *BRCA1/2* mutation without risk for HBOC (control group). Matched variables were pathologic stage and receptor status (estrogen, progesterone, and human epidermal growth factor receptor 2).
Results All matching variables were successfully matched. Median follow-up was 57.8 months. There was no significant difference between the groups in disease-free survival (DFS, log-rank $p = 0.197$); however, the study group showed significantly better overall survival (OS) and breast cancer–specific survival (BCSS) (both $p < 0.0001$). We conducted a subgroup analysis in the middle-aged group (36–54 years) and showed no significant difference for DFS ($p = 0.072$), but significantly better OS and BCSS in the study group ($p = 0.002$ and $p < 0.0001$).
Conclusions Compared with patients having sporadic breast cancer without HBOC risk factors, those having *BRCA1/2*–negative breast cancer with HBOC risk factors showed a similar DFS and better OS and BCSS.

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Poster P021

Spectrum of Benign Tumours in Families with a Germline *TP53* Gene Mutation: Clinical Experience at the Children's Hospital of Eastern Ontario

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Introduction Li–Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome causing a range of cancers across the lifespan. Germline mutations in the *TP53* gene are typically associated with LFS, but the phenotype continues to emerge. Classical cancers seen in LFS include soft-tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumours, adrenocortical carcinoma, and leukemias. Cancers often occur in childhood or young adulthood. Survivors have an increased risk for multiple primary cancers. Benign tumours are not typically described, but could be an uncommon manifestation.
Methods We performed a retrospective chart review of families with a germline *TP53* mutation at the Children's Hospital of Eastern Ontario covering a 5-year period (Jan 2013–Dec 2017). We recorded types of benign tumours, cancer history, and ages at onset. We also documented whether the mutation was *de novo*, ancestry, ascertainment because of premenopausal breast cancer, and whether the family met the classical LFS criteria.
Results We identified 12 families (23 patients) with a germline *TP53* pathogenic or likely pathogenic mutation. Among the 12 probands, 33% had benign tumours, including dermatofibromas, bilateral ovarian teratomas, schwannoma, ovarian serous tubal intraepithelial carcinoma lesion, clear-cell hidradenoma, cutaneous fibroxanthoma, ovarian atypical follicular cell proliferation, subungual glomus tumour, and cutaneous fibrous histiocytoma. None occurred in areas of previous radiation. Mean age of benign tumour onset was 18 years (range: 6–29 years). Mean age of malignant tumour onset was 25 years. Analysis revealed that 8% of probands had a confirmed *de novo TP53* gene mutation, 67% of families were of Caucasian ancestry, 67% of families were ascertained because the proband had a diagnosis of premenopausal breast cancer, and 25% of families met the classical LFS criteria.
Conclusions Benign tumours and ovarian lesions could be an uncommon manifestation in LFS. Additional studies are required to fully describe the range of benign lesions.

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Poster P022

Biallelic *CHEK2* Pathogenic Variants Identified in Two Generations of an Ashkenazi Jewish Family

Megan Priston, Wendy Meschino

Introduction Variants in the checkpoint kinase 2 (*CHEK2)* gene have been shown to confer a moderate breast cancer risk in the heterozygous state. Women with biallelic *CHEK2* variants have an increased breast cancer risk above those with heterozygous variants, based on studies of the *CHEK2* founder mutation 1100delC. Additionally, the *CHEK2* variant I157T, which is associated with a more modest breast cancer risk than some other *CHEK2* variants, is suspected to increase breast cancer risk when found in biallelic form with another *CHEK2* variant. Current data are insufficient to well-define breast and other cancer risks in such cases of biallelic inheritance, and screening recommendations rely heavily on family and personal history.
Case Description We present a 42-year-old woman of Ashkenazi Jewish ancestry diagnosed with an invasive mucinous carcinoma of the left breast. Family history includes papillary serous ovarian cancer in her mother at age 71 and breast cancer in her maternal grandmother and in two of the maternal grandmother's sisters. Our patient was offered an 18-gene breast/ovarian cancer panel which revealed the following two variants in *CHEK2:* c.1283C>T (pSer428Phe) and c.470T>C (I157T). Testing for her parents was recommended to determine zygosity. Subsequent parental testing showed that her father was heterozygous for the I157T variant, and her mother was homozygous for the S428P variant. Before genetic testing, the patient had a left lumpectomy and chemotherapy. Given her strong family history and the finding of biallelic *CHEK2* variants, the patient chose bilateral prophylactic mastectomy after chemotherapy.
Conclusions The finding of biallelic variants in *CHEK2* presents a challenge for genetic counselling. Further study into the frequency of such cases and the relative cancer risks will be essential in elucidating management recommendations for such individuals.

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Poster P023

Re-contacting 20 Years of *BRCA1/2*-Negative Cancer Genetics Patients: A Pilot Study

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In recent years, the landscape of testing for hereditary cancer predisposition has drastically changed from single-syndrome analysis to much larger multigene panels. As management guidelines evolve with advancing technology, we begin to explore the need for offering updated analysis using these expanded panels to patients who previously tested negative for single-gene syndromes. Genetics professionals have the unique opportunity to directly improve patient care by taking the initiative to proactively contact patients to educate them about the availability of additional genetic analysis and updated medical recommendations.

The Cancer Genetics department at Carolinas Healthcare System Levine Cancer Institute reviewed more than 20 years of patients tested for *BRCA1* and/or *BRCA2*. In our pilot initiative, we used a mailed letter to contact patients with a negative *BRCA1*/*BRCA2* analysis seen between 1996 and 2005, stating that they might be eligible for additional cancer predisposition testing. Since the 250 letters were sent, 37 patients (14.8%) have so far contacted our department and scheduled a follow-up visit with a genetic counsellor. Of the 28 patients who elected to proceed with panel testing, 7 (25.0%) were found to carry a pathogenic variant in a cancer predisposition gene that altered medical management recommendations. Outside of patients re-contacted by letter, 19 individuals returned for update testing either through physician or self-referral, and 2 (10.5%) were identified as having a clinically actionable variant. As knowledge about hereditary cancer predisposition expands, patients previously tested should not be overlooked, because medical management for both the patients and the family members could be affected.

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Poster P025

Hereditary Cancer Testing in Hispanic Population

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Background The clinical utility of hereditary cancer multigene panel testing is well-established. However, most testing has been performed in the Caucasian population, with a relative shortage of data in other ethnic

groups. Evaluation of hereditary cancer variants within ethnic populations is important to drive accurate variant interpretation. This study aims to describe the outcomes of hereditary cancer testing in a Hispanic population in the United States.

Methods We conducted a retrospective review of patients evaluated with the 31-gene Riscover hereditary cancer panel (Progenity, San Diego, CA, U.S.A.) from Oct 2016 to Nov 2017. We evaluated results in the Hispanic population and compared that population with the total tested population.

Results Of 219 tested individuals who self-identified as Hispanic only, 114 (52%) were negative, 13 (6%) were positive, and 92 (42%) had a variant of uncertain significance (VUS). In contrast, in the entire patient population, 58% were negative, 8% were positive, and 35% had a VUS. The difference is nominally statistically significant with p value of 0.03 based on a multinomial 2 goodness-of-fit test with 2 degrees of freedom. Within the positive and VUS results, there were certain variants whose prevalence was higher in the Hispanic population than in the general population.

Discussion Our results suggest that the VUS rate might be higher, and that certain variants might occur more frequently, in the Hispanic population than in the general population. The VUS rate might be attributable in part to a relative underrepresentation of well-characterized variant classifications in this ethnic group in the medical literature and available databases. Data-sharing practices support an increased understanding of ethnic variation in hereditary cancer and help to eliminate heath disparities.

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Poster P026

Novel Pathways Underlying the Role of *RAD51* Paralogs in the Maintenance of Genome Stability and Tumorigenesis

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DNA double-strand breaks (DSBs) are the most cytotoxic DNA lesions. They can lead to major genomic rearrangements, promoting the development of cancer if left unrepaired. Variants in genes that play a major role in DSB repair by homologous recombination (HR) are currently good predictors for the development of both hereditary and sporadic breast and/or ovarian cancers. The relevant genes include *BRCA1, BRCA2,* and *RAD51* paralogs. The latter group—which includes *RAD51B, RAD51C, RAD51D, XRCC2,* and *XRCC3*—has been described to cooperate with the recombinase *RAD51* in promoting strand invasion and sister-chromatid exchange. Still, it remains largely unclear how these paralogs promote HR and whether they might have additional function(s) in the maintenance of genome integrity. We therefore sought to provide more insight into their contribution to DNA repair.

Using a variety of DNA repair reporter assays, including the DR-GFP and SA-GFP assays, we confirmed the role of these paralogs for DSB repair by HR. To decipher their full interactome, we performed a proximity biotin-based labelling approach, called BIOID, which allows for the identification of both proximal/interacting partners of these factors. Using this approach, we identified previously uncharacterized interactors of the *RAD51* paralogs that we are currently investigating for their contribution to DNA repair. Our study confirms the central role of *RAD51* paralogs in DNA repair by HR and suggests novel signalling partners that participate in their function.

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Poster P027

Truncating and Deleterious Missense Hereditary *CHEK2* Mutations Confer a Risk for Development of Luminal Breast Cancer Subtypes

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Hereditary *CHEK2* mutations predispose to various cancer types, including breast cancer (BCA), but most studies have considered only recurrent *CHEK2* variants. Those studies revealed that the BCA risk is considerably greater for c.1100delC carriers than for p.I157T carriers. Recent inclusion of *CHEK2* into cancer predisposition gene testing panels has increased the spectrum of identified variants. Although variants truncating the *CHK2* kinase domain are considered to be deleterious, the significance of rare missense variants is largely unknown and hampers the estimation of cancer risk attributed to hereditary *CHEK2* variants.

We analyzed the entire *CHEK2* coding sequence in 1928 high-risk BCA and/or ovarian cancer (OC) patients (previously tested for mutations in BCA/OC susceptibility genes using gene-by-gene analysis or simultaneously by multigene panel testing) and in 2184 geographically-matched controls. The analysis in BCA/OC patients revealed 39 carriers of 8 deleterious truncating mutations and 92 carriers of 22 in-frame deletions or missense variants. The functional assessment of 22 non-frame-shift variants in a CRISPR/Cas9 *CHEK2* knockout cell line model identified 12 of those variants as deleterious. Compared with controls, the carriers of deleterious variants were strongly enriched in the female BCA subgroup [51/1526 (3.34%) vs. 8/2184 (0.37%), $p = 5.25^{-13}$] and in 48 male BCA patients [4/48 (8.3%), $p = 8.22^{-5}$). The prevalence of deleterious *CHEK2* variants was lower in OC-only patients [6/354 (1.69%), $p = 0.008$] and statistically nonsignificant when compared with European non-Finish controls (Exome Aggregation Consortium). The analysis of histopathologic data showed that, compared with noncarriers, female carriers of deleterious *CHEK2* variants more frequently develop the luminal A BCA subtype [19/37 (51%) vs. 269/898 (30%), $p = 0.006$] and low-grade tumours; G3 was detected in 8/40 *CHEK2* carriers (20%) compared with 366/927 noncarriers (39.5%, $p = 0.008$).

Our analysis demonstrates that deleterious *CHEK2* variants also include rare missense mutations and collectively increase female BCA risk (OR: 3.87; 95% CI: 2.80 to 5.25).

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Poster P028

NTHL1 Mutation Carriers Found in *BRCA1* and *BRCA2* Mutation-Negative Ovarian Cancer Families

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It has been proposed that germline mutations in other homologous recombination (HR) and Fanconi anemia (FA) DNA repair genes *RAD51C, RAD51D,* and *BRIP1,* together with *BRCA1* and *BRCA2,* confer increased risk for ovarian cancer (OC). Our group has shown that, because of common ancestors, recurrent *BRCA1, BRCA2,* and most recently, *RAD51D* germline mutations account for a significant proportion of hereditary OC cases in the French Canadian (FC) population of Quebec. However, we observed that 20%–30% of FC multi-case OC families are *BRCA1* and *BRCA2* mutation–negative, which prompted our investigation for new candidate OC-predisposing genes. Whole-exome sequencing (WES) analysis was performed on germline DNA extracted from 11 such families.

A candidate gene approach was applied, focusing on potentially damaging rare alleles found in 200 DNA repair pathway genes. Using various public databases, a total of 44 variants were identified in 38 DNA repair genes with minor allele frequency less than 0.1% in the general population. Heterozygous germline *NTHL1*p.Q90* reported as pathogenic in ClinVar was identified in 2 OC cases from the same family. By targeted mutation screening of *NTHL1*p.Q90* in 439 OC cases not selected for family history of cancer (~80% of FC descent), 2 *NTHL1*p.Q90* heterozygous carriers with OC were identified (0.46%). Although no significant difference between familial and sporadic OC cohorts was observed (because of the small sample size), no other potential pathogenic mutation was found by global WES analysis of all *NTHL1*p.Q90* heterozygous carriers. The Cancer Genome Atlas cohort of OC cases showed a significant association of low *NTHL1* MRNA expression with poor clinical outcome and reported significant deletion of the 16p arm where *NTHL1* is located.

Our preliminary results suggest that *NTHL1* is a potential candidate OC-predisposing gene warranting further investigation of its inactivation mechanism and overall role in ovarian carcinogenesis.

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Poster P029

Large Case–Control Study and Functional Analyses Indicate That *FANCM* Truncating Mutations Are Moderate or Low-Risk Factors for Breast Cancer Depending on Their Location

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Breast cancer is the most common female oncologic disease, and up to 15%–20% of all cases are familial. About 50% of familial cases are explained by rare mutations in *BRCA1* and *BRCA2* and other high-risk genes; by mutations in moderate-risk genes, including *PALB2, ATM,* and *CHEK2;* and by several dozens of common low-risk alleles. Truncating mutations in *FANCM* recently emerged as novel breast cancer predisposition factors. In a large case–control study, we showed that the p.Arg1931* mutation is associated with breast cancer risk. In Finland, another C-terminal

mutation, p.Gln1701*, was associated specifically with estrogen receptor (ER)–negative breast cancer. This particular association was confirmed in a mutational burden analyses in cases and controls from Germany.

In the present study, the 3 most common *FANCM* truncating mutations p.Arg658*, p.Gln1701*, and p.Arg1931* were genotyped in 67,112 breast cancer cases and 53,766 controls, collected within the Breast Cancer Association Consortium and representing the largest sample size tested to date. Logistic regression analyses in populations with mutation carriers suggested that the p.Arg658* is a moderate risk factor for ER-negative and for triple-negative breast cancer (TNBC)—odds ratios (ORs) 2.44 (1.12 to 5.34) and 3.79 (1.56 to 9.18) respectively. Similar analyses showed that p.Gln1701* and p.Arg1931* could be low-risk factors for TNBC [OR: 2.15 (1.05 to 4.38)] and for ER-negative breast cancer [OR: 1.98 (1.26 to 3.13)].

These genetic data, together with our published clinical observations on individuals homozygous for *FANCM* mutations, suggest that upstream *FANCM* protein truncation is associated with a higher breast cancer risk and more severe clinical phenotypes. We are testing this hypothesis by performing functional analyses in immortalized *FANCM*-deficient fibroblasts. Cells are transduced with vectors carrying 5 patient-derived truncating mutations to test DNA repair activity and hypomorphism of the mutant forms in an isogenic background. Our results will provide information allowing for better breast cancer risk estimation in *FANCM* mutation carriers.

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Poster P030

Emerging Genes: What Clinical Implications?

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Introduction Since next-generation sequencing (NGS) technologies have become more clinically accessible, the genetic counselling in high-aggregation families of breast (WBC) and ovarian cancers (OVC) tested negative for *BRCA1* and *BRCA2* has recently changed significantly. We present the clinical and molecular profile of 55 women extracted from our families negative for *BRCA1/2*, but positive for *PALB2, CHEK2, RAD51C, RAD51D, RAD50,* and *BRIP1*.
Results Of 55 families, 43 WBC and 12 OVC are predominantly French Canadian. Of 43 WBC, 24 had *PALB2* mutation, with 21 being French Canadian, 12 having c.2323C>T (p.Gln775*), and 7 having exon 11 deletion, and 14 having bilateral and/or triple-negative BCA. A new mutation was identified in 14 women on a clinical basis on *RAD51D* c.620C>T (p.Ser207Leu), with 8 having high-grade serous OVC and 5 having breast cancer (middle age: 52 years), of which 3 were triple-negative or multifocal tumours. *CHEK2* mutation was found in 10 WBC and 2 OVC. Only 4 of those 12 had c.1100delC mutation. On the other hand, 4 had deletion or duplication in the *CHEK2* gene or other types of mutations. Strangely, in the other cases (*BRIP1, RAD50, RAD51C)*, breast cancer predominates (5 of 6).
Commentary We observed a significant augmentation in the identification of hereditary predispositions to cancer through a nonselective multigene approach. Full sequencing and deletion/duplication research has identified non-targeted mutations in older approaches and recognition of frequent and recurrent mutation in the French Canadian population. In addition, recommendations were more complete and more appropriate to the reality of the context of family predisposition. The identification of mutations in *RAD51D, RAD51C,* and *RAD50* as well as in *CHEK2,* in proportions that seem less related to mere chance, show a greater increase in the risk of breast and ovarian cancer than we can imagine. The phenotype/genotype correlation leads us to redefine our thinking about the criteria of testing.
Conclusions This approach is essential and constitutes an important advance for personalized medicine. Screening could have an efficient impact. The expansion of genetic investigations is fundamental and must also be based on good observation of the family tumour spectrum and reassessment of the certainty of the past.

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RISK ASSESSMENT AND GENETIC COUNSELLING ISSUES

Poster P032

The Use of Software Can Address Workforce Shortage and Access Barriers to Genetic Counselling

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Since the discovery of *BRCA1* in 1994, the prevalence and uptake of germline genetic testing for hereditary cancer has increased dramatically. As a result, clinical genetics providers have struggled to keep up with the increase in demand. Previous analyses of time-based effort have determined that clinical genetic services are time-consuming and labour-intensive, with as little as 25%-41% of a genetic counsellor's time spent on direct client care and up to 3.5–7 total hours spent per client. As demand for germline testing continues to increase, the traditional delivery model for clinical genetics services has proven to be a bottleneck and a barrier to testing.

Here, we present a novel service model that uses software and technology to deliver genetic services in a more streamlined and efficient way. Using this model, genetic counsellors spend much less time than industry averages conducting non-direct client care activities, thus increasing the proportion of time spent on direct care and availability for more clients. To achieve those results, we implemented custom software tools, including online health history collection, automated pedigree creation and risk-model calculation, online scheduling and rescheduling, and templated summary notes.

Genetic counsellors tracked time spent conducting direct and non-direct care activities to provide more than 1800 post-test telephone genetic counselling sessions for clients who received a multigene panel for hereditary cancer risk. The average total time spent per client was 37 minutes, and more than 50% of the time spent on a client invovled providing direct care. Post-counselling surveys revealed high levels of comprehension and client satisfaction with their genetic counselling. Broader implementation of similar software tools for all genetic counselors providing clinical care might improve access to and efficiency of genetic counselling services to help meet rising demand.

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Poster P033

Should We Reform Our Practice in Oncogenetics?

Zaki El Haffaf,*† Pavel Hamet*†

Numerous challenges are on the horizon in oncogenetics. They are set in a context of extraordinary technological development that makes diagnostic investigations linked to hereditary predispositions to cancer more accessible. The personalization of care is more and more necessary. In fact, it depends on the speed of the teams to respond effectively to requests for investigations from oncologists, surgeons, gynecologist–oncologists, radio-oncologists, and patients themselves.

In Quebec, there is a mismatch between high demand for genetic evaluation on the one hand and the natural ability of ontogenetic teams to meet that demand on the other hand. To achieve that objective at the CHUM, we have proceeded to two levels of intervention. The first intervention was the complete overhaul of the form-based application prioritization system and a triage that takes into account the patient's therapeutic planning. The second intervention, which is much more ambitious, is the realization of an integrated evaluation activity in the cancer centre CICC (integrated oncology centre).

The response rate to "urgent" requests was very good: 98% of responses were given within the therapeutic times; but nonetheless, dissatisfaction persists. We found several factors of dysfunction.

Integration of therapeutic planning by an expert team of geneticists and genetic counsellors is a possibility. It seems that this solution is ideal for overhauling the dysfunctional elements and providing patients and their physicians with the appropriate guidelines and recommendations in a time-useful clinic. The realization of good oncogenetic evaluative integration will provide a pedagogic dimension as well as efficiency in the transversal exchange of skills. It will also contribute to the exchange of knowledge between the teams.

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Poster P034

Is It Really *BRCA1* or *BRCA2?* The Importance of Confirming the Familial Mutation in a "*BRCA*"-Focused World

Sara V. Brown, Samantha S. Wiley

As genetic testing becomes more prevalent, performing laboratories could experience a higher rate of order errors. At ARUP Laboratories, complex genetic test orders undergo pre-test review by ARUP's genetic counsellors to ensure that the most appropriate test is ordered based on the clinical information provided. This pre-test review identified a recurring scenario in which testing is ordered for a family history of "*BRCA* mutation," but the familial variant is actually not in the *BRCA1* or *BRCA2* genes.

We present three cases encountered by ARUP in which *BRCA1/2* full gene analysis was ordered on unrelated individuals with reported "*BRCA* positive" family history. Further investigation, including obtaining genetic lab reports from affected relatives, determined that there was no family history of a *BRCA1/2* mutation. Rather, patient 1 had a family history of a *CHEK2* mutation, patient 2 had a family history of an *ATM* variant

of uncertain significance, and patient 3 had a family history of Lynch syndrome caused by a *PMS2* mutation. For those 3 patients, documentation of the familial variants allowed for the inappropriate *BRCA1/2* tests to be cancelled, and targeted testing for the appropriate gene was offered. Without the correction in test orders, the *BRCA1/2* test results would likely have been clinically irrelevant and falsely reassuring, because the true familial variant would not have been analyzed.

These cases demonstrate the need for clinicians to confirm reported family history whenever possible by obtaining documentation of familial genetic variants, thereby ensuring that a clinically relevant result is issued for the patient. As genetic testing for hereditary cancer predisposition and *BRCA1/2* continues to receive attention in the media, it is crucial to raise awareness of the growing list of clinically actionable hereditary cancer genes so that patients, health care providers, and laboratories understand that a family history of a "breast cancer mutation" doesn't always mean *BRCA1/2*.

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Poster P035

Learning About Breast Cancer Risks, Stratification, and Prevention: An Innovative Web Site

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Canadian women are more likely to develop breast cancer (BCa) than any other cancer, with 1 in 8 women expected to be diagnosed in her lifetime[1]. Breast cancer accounts for 13% of female cancer deaths, making it the second leading cause of cancer deaths in women[1]. Accordingly, strategic and timely activities in early detection and actionable domains are crucial. Currently, screening practices are based mainly on age rather than on personalized risk assessment, resulting in some women not being appropriately screened according to their actual BCa risk.

A bilingual website called PERSPECTIVE was recently developed in Quebec to inform women about a novel stratification approach for BCa, including risk assessment, risk factors (for example, lifestyle, genetic), and prevention. This resource is part of a broader initiative that aims to develop this approach, specifically by providing women with the tools they need to plan, act, and follow up on their personalized risk results. The PERSPECTIVE Web site was piloted, modified, and then tested for knowledge improvement in a community sample of 156 women 30–60 years of age with no previous cancer history. Paired-sample t-tests showed significant changes in general knowledge of BCa risk factors, prevention, and genetics pre–post Web site exposure, with improvements ranging from 14% to 58% ($p < 0.001$). Knowledge improvement examples include a 48% knowledge increase for the influence of alcohol consumption on BCa risk, 31% on the nature of *BRCA1/2*, and 49% on breast density as a risk factor.

These initial findings indicate that PERSPECTIVE is a promising means to disseminate information on BCa risk factors, screening, and follow-up. Ongoing PERSPECTIVE work will provide further evidence about the extent to which e-health solutions such as this one can be used to support cancer-related decisions pertaining to personalized risk assessments. Future work will also test interactive features embedded into a PERSPECTIVE platform.

1 Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2017. Toronto, ON: Canadian Cancer Society; 2017.

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Poster P036

Impact of Genetic Counselling and Genetic Testing on High-Risk Hereditary Breast and Ovarian Cancer

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The aim of this study from the Oncogenetics Department of Barretos Cancer Hospital (Brazil) is to evaluate the effects of genetic counselling (GC) and genetic testing (GC) in families at risk for hereditary breast and ovarian cancer. The study uses four time points: M1, before GC; M2, after a GC session and blood draw for GC; M3, after the GC result; and M4, 12 months after the GC result. At points M1 and M4, questionnaires about cancer worry, risk perception, strategies for coping with problems, anxiety, and depression were administered, and the pedigree, genogram, and ecomap were constructed. In addition, at points M2 and M3, questionnaires about cancer worry, risk perception, anxiety, and depression were administered.

Qualitative analysis was performed based on content thematic analysis. Currently, 83 women have been enrolled, with 14 having pathogenic mutations, 47 being wild-type, and 3 having a variant of unknown significance (64 completed M3, and 20, M4). Mean age of the participants was 41 ± 9.77 years, and 73 participants (88%) had a diagnosis of breast cancer. The perception for risk of cancer development is lower in participants than the general population, but there is a greater concern about developing cancer at all time points. Anxiety and depression at all times were not significantly different. The coping strategy for problems is religiosity. The main topics raised by genograms and ecomaps analysis were positive or negative relationship with relatives, religiosity as a social support network, and concern about future generations. In conclusion, most patients, even in the presence of mutation, have a cancer risk perception lower than that in the general population. Few changes in family dynamics (changes of relationship) were observed. It is important to understand GC and GC processes so that the individual can adequately follow prevention and control strategies.

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Poster P037

What Do Women Want? Genetic Information Preferences Among Women Undergoing Panel-Based Genetic Testing

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Background Panel-based genetic testing (PBGT) is becoming increasingly prevalent in clinical practice, but little is understood about information preferences. In PBGT, similar genes are grouped, and results of varying significance are produced, including only a small proportion of medically actionable results. A greater understanding is essential to the development of genetic testing guidelines specific to PBGT, together with educational materials and decision-support tools for patients and providers.
Methods This mixed-methods study explored the PBGT preferences of participants with a 1st-degree relative who has died from ovarian cancer. We conducted a cross-sectional survey of self-referred unaffected women in Ontario who are undergoing PBGT through a clinical research study. Participants had the option to receive results from 4 different panels. Quantitative data were collected using a Web-based survey platform. Using logistic regression, we determined the relationship of sociodemographic and psychological factors (anxiety, depression, decisional conflict) with genetic information preferences. We also conducted semistructured telephone interviews with 20 participants who were purposively sampled based on their diverse panel selection. Transcripts were analyzed using conventional content analysis.
Results 350 women participated in pre-genetic counselling and consented to the results that they would like to receive. Most women chose to receive information from all panels (84%). Those with more decisional conflict did not want to receive genetic information from all panels. Interviews revealed that participants appreciated all forms of genetic "knowledge" and expected to use this information to reduce their cancer risk. Many contemplated participation in the program, but once committed did not truly consider which information they preferred to receive.
Conclusions In our sample, most women opted to select all panels for PBGT, including panels without actionable results. This preference was associated with a lower level of decisional conflict. Our findings have important implications for the advancement of PBGT in screening for breast and ovarian cancer.

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Poster P038

Performance of Current Hereditary Breast and Ovarian Cancer Testing Criteria for the Detection of Carriers of Pathogenic Variants in Clinically Significant Breast Cancer Risk Genes Other Than *BRCA1/2*

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Background Although genetic testing for hereditary breast cancer risk is no longer limited to *BRCA1* and *BRCA2*, it is not clear that current testing criteria adequately target individuals with pathogenic variants (PVs) in other clinically important genes. We evaluated the performance of testing criteria designed for *BRCA1* and *BRCA2* for the detection of PVs in 3 moderate-penetrance breast cancer genes: *ATM*, *CHEK2*, and *PALB2*.
Methods We analyzed multigene panel test results (Myriad Genetic

Laboratories) for 294,234 women ascertained for suspicion of hereditary breast and ovarian cancer (HBOC) to evaluate how various personal and family history factors affect the likelihood of detecting a PV in *BRCA1, BRCA2, ATM, CHEK2,* or *PALB2*. All clinical data were collected from provider-completed test request forms.

Results The likelihood of finding a *BRCA1* PV was strongly affected by age of breast cancer diagnosis, with a striking inflection point between ages 41 and 45 years. In contrast, the likelihood of finding a *BRCA2* PV declined gradually from age 21 to 80 years. The likelihood of finding a PV in *ATM, CHEK2,* or *PALB2* declined slightly after age 30, and then remained almost constant from age 31 to 70 years. As expected, a personal or family history of ovarian cancer was strongly predictive of a PV in *BRCA1* or *BRCA2*, but was not consistently associated with PVs in *ATM, CHEK2,* or *PALB2*. For all probands, a family history of breast cancer increased the probability of finding a PV in all 5 genes, but that finding was largely independent of the reported age at which relatives were diagnosed.

Conclusions Current testing criteria based on the clinical features of *BRCA1* and *BRCA2* might perform poorly in distinguishing women at risk for mutations in other clinically significant breast cancer risk genes. Revision of the criteria might be appropriate if these genes are routinely included in hereditary breast cancer risk assessment.

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Poster P039

Families with a Known Mutation in a Cancer Predisposition Gene: Is Single-Site Testing Always the Best Option for Relatives?

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Background The current paradigm prescribes site-specific testing for family members when there is a known familial mutation (KFM) in a cancer-risk gene, with tested individuals typically managed as true positives or negatives. However, panel testing has revealed that some families carry more than one mutation in cancer-risk genes. Our aim was therefore to assess whether panel testing could be appropriate even in the setting of a KFM.

Methods We assessed patients who had clinical genetic testing with a multigene panel (Myriad Genetic Laboratories) after testing negative for a KFM between March 2005 and August 2017 ($n = 902$).

Results Overall, 37 individuals who tested negative for a KFM (4.1%) were found to carry ≥1 pathogenic variant (PV) upon panel testing. That group included 16 individuals whose panel test was performed ≥1 year after KFM testing, 2 of whom developed interim cancers. One woman with bilateral breast cancer tested negative for a KFM in *BRCA2* and was found to carry PVs in both *CHEK2* and *CDH1*. Several additional cases were also observed in which individuals tested positive for PVs in genes with cancer risks different from those for the KFM. Included was an unaffected woman who tested negative for a KFM in *BRCA2* and later developed colon cancer. Panel testing revealed a PV in *APC*.

Conclusions In this cohort, approximately 4% of individuals who tested negative for a KFM were found to carry a different PV in a cancer-risk gene. That finding suggests that an "informative negative" test result for a KFM might give a false sense of security when more than one mutation could be contributing to the family history of cancer. Collectively, our results suggest that there might be added value to panel testing for individuals with a KFM.

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Poster P040

Painting a Portrait: Analysis of National Health Survey Data for Cancer Genetic Counselling

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Data about the geographic and sociodemographic distribution of cancer genetic counselling (GC) at the national level are limited. However, prior studies focused on cancer genetic testing have suggested disparities in awareness and access by race, sex, education, and insurance (Wideroff *et al., Public Health Genomics,* 2003).

Using the 2015 National Health Interview Survey—a cross-sectional in-person interview survey collecting self-reported health data for the U.S. population—geographic and sociodemographic factors were compared between individuals receiving GC and the national sample. Bivariate analysis and subsequent multivariable logistic regression were performed with stratification by cancer status (affected or unaffected). The reason for GC was also assessed. To generate nationally representative estimates, all analyses were adjusted for survey weights.

An estimated 5 million individuals in the United States had undergonecancer GC by 2015. On bivariate analysis, there were significant differences in the proportions undergoing GC by sex, race or ethnicity, insurance, citizenship, education, age, and cancer status ($p < 0.001$). After adjustment, however, only female sex [odds ratio (OR): 1.78 (1.18 to 2.67)] remained a significant predictor of GC among the affected. Among the unaffected, female sex [OR: 1.70 (1.30 to 2.21)], non-Hispanic black race [OR: 1.44 (1.02 to 2.05)], and graduate education [OR: 1.76 (1.03 to 2.98)] predicted higher rates of GC. Rates of GC for those with a history of cancer were 17.8% breast, 18.7% ovarian, 10.2% uterine, 8.1% colon, and 4.4% prostate. Most individuals receiving GC reported that they did so because their doctor recommended it (65%), with smaller proportions describing self (12%), family (10%), or media (5%) influences.

This study is the first to provide a national portrait of cancer GC. Despite perceived disparities in access, with the exception of male sex, genetic counselling appears to reach across most geographic, social, and educational contexts, as well as cancer types or status. With physician recommendation as the predominant driver for counselling, targeting physician education or awareness is crucial to utilization.

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Poster P043

The Gynecology–Oncology *BRCA* Pilot Project: Oncologist-Mediated Genetic Testing of the *BRCA1/2* Genes for Women with Ovarian Cancer

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Objective Ensure that ovarian cancer patients in Southern Alberta have timely, seamless access to *BRCA1/2* testing, while preserving informed choice and genetic counselling support. Timely results disclosure is vital, because results might direct treatments. Gynecology–Oncology *BRCA* (GO-BRCA) was driven by a need to challenge existing models because of increased referrals to the Hereditary Cancer Clinic (HCC).

Methods *BRCA1/2* testing was historically offered after pre-test genetic counselling in the HCC. During GO-BRCA, pre-test genetic counselling was facilitated by the Gynecology–Oncology (GO) team, in parallel with referral to the HCC. The HCC provided results and post-test genetic counselling. GO-BRCA was a proof-of-concept pilot, modelled after the U.K. Mainstreaming Cancer Genetics program.

The GO team was oriented to pre-test genetic counselling by the HCC's geneticist and was provided with information support materials. To facilitate informed consent, the GO team provided patients with a brochure and video. To evaluate GO-BRCA, qualitative surveys were issued to the GO team at the outset and close of the pilot, and to patients when offered testing and after results disclosure.

Results 121 women opted for *BRCA1/2* testing; 109 results were disclosed. Elimination of pre-test meetings with the HCC resulted in results disclosure 1.9 times faster than before GO-BRCA (159 days vs. 306 days). Capacity of the HCC was increased by 121 hours. From the surveys returned, 97% of women felt that they had made an informed decision, 100% reported that expectations were met, and 100% were happy that testing was offered by the GO team compared with a separate HCC appointment. Clinicians felt that the model was feasible.

Conclusions GO-BRCA provided *BRCA1/2* genetic test results to ovarian cancer patients 1.9 times faster than previously, and the model is acceptable to patients and clinicians. Elimination of pre-test meetings for this cohort increased the HCC's capacity by 121 hours. This is now a provincial model, and expansion to other tumour groups is anticipated.

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Poster P044

Genetic Risk Assessment Guides Young Women Opting for Contralateral Prophylactic Mastectomy

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Purpose Genetic counselling has been introduced in the primary diagnostic workup for young women with breast cancer in Denmark. We investigated the influence of genetic risk assessment on the uptake of contralateral prophylactic mastectomy (CPM) in a prospective study.

Methods The cohort consists of 154 women with breast cancer diagnosed at a median age of 36 years (range: 21–44 years). The women were seen at the Genetics department (2013–). Risk evaluation was made using family history and the results of *BRCA1/2* screening. Women were counselled according to four categories: carriers of a pathogenic variant in *BRCA1/2,* high risk of breast cancer, moderate risk, and non-increased risk. Using electronic medical records, we examined the cumulative uptake of CPM after a maximal follow-up period of 4.2 years.

Results A pathogenic variant in *BRCA1/2* was identified in 17 of 154 women (11%). Uptake of CPM in the entire group was 38% (95% CI: 29% to 49%). Carriers of a pathogenic variant in *BRCA1/2* had the highest uptake at 80% (95% CI: 46% to 99%), followed by high-risk women at 72% (95% CI: 42% to 95%) and moderate-risk women at 28% (95% CI: 19% to 41%). The uptake increased with decreasing age up to 59% (95% CI: 36% to 83%) in those less than 30 years of age.
Conclusions The genetic risk assessment guided young women with breast cancer opting for CPM; however, a re-evaluation of the risk assessment scheme suggested that the breast cancer risk was sometimes overestimated. We are in a process of optimizing national guidelines and now attempting to implement the BOADICEA model as support for individualized risk assessment in clinical practice, because both molecular screening and family history have a major effect on the CPM rate.

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Poster P045

Predictors of Next-Generation Sequencing Panel Selection Using a Shared Decision-Making Approach: Data from Singapore

Joanne Ngeow*

Purpose Next-generation sequencing (NGS) has transformed the way clinical cancer genetics services approach testing, particularly for cancers. The Cancer Genetics Service at the National Cancer Centre Singapore was established in 2014 using a shared decision-making approach in which patients play an active role in NGS panel selection.
Methods Demographic and clinical data were gathered for female breast or ovarian cancer patients 21 years of age and older who underwent NGS panel testing. Panel type was classified as "breast cancer panel" (BCP) or "multi-cancer panel" (MCP). Univariate, multiple, and stepwise multiple logistic regression analyses were used to identify clinical factors predictive of NGS panel selection.
Results Overall, 265 subjects were included in the study: 49 (18.5%) selected a BCP and 216 (81.5%) selected MCPs. Subjects who chose MCPs were significantly more likely to be 50 years of age or older (49% vs. 31%, $p < 0.05$), to be Chinese (76% vs. 47%, $p < 0.001$), and to have have a personal history of ovarian cancer (41% vs. 8%, $p < 0.001$); the latter two characteristics were identified as being the best predictors of NGS panel selection. Family history of cancer was not significantly associated with NGS panel selection. There were no statistically significant differences in clinical outcome between the BCP and MCP groups.
Conclusions Our results indicate that personal factors, rather than family history, are more likely to predict NGS panel selection. Further research is needed to evaluate patient outcomes, empowerment, and perception in assessing the success of this approach for NGS panel selection. We will also present our 3-year experience establishing the Cancer Genetics Service and share data abot the mutation spectrum seen in Singapore HBOC cases and how subsidies affect genetic testing uptake in Singapore.

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Poster P046

DNA-Direct: Increasing Efficiency for Pre-test Genetic Counselling in Multigene Panel Testing

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Introduction With demand for cancer genetics services increasing, alternative modes of service delivery are being considered. One alternative is termed DNA-Direct, which was studied and successfully implemented with *BRCA1* and *BRCA2* testing in the Netherlands. DNA-Direct delivers an abbreviated pre-test telephone appointment to expedite the testing process. In April 2017, the Hereditary Cancer Program of BC Cancer began trialling DNA-Direct for patients undergoing multigene panel testing.
Methods The process included

- triage of eligible patients (geographic location, fluency in English, eligibility for index testing);
- brief telephone appointment to review the reason for referral, an abbreviated psychosocial assessment, and review of the testing process; and
- mailing a package containing test forms and written educational materials.

Once results were received, patients were scheduled for a typical results disclosure appointment. Patients consenting to further contact were sent the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire, assessing for coping and adaptation to genetic test results, and scores were compared with patients seen with a traditional pre-test appointment.
Results Over a 7-month period, 112 patients had a DNA-Direct appointment. A greater than 95% acceptance rate for the appointment type was observed. The average time spent for the pre-test telephone appointment was 15 minutes. Most patients were referred for query hereditary breast and ovarian cancer syndrome (82%). Among the 62 results returned to date, 8 pathogenic mutations were detected. The results of the MICRA have shown no statistically significant differences between patients who had a DNA-Direct or a longer traditional pre-test appointment ($n = 117$).
Conclusions The DNA-Direct approach demonstrates significant efficiencies in pre-test genetic testing appointments. Patient satisfaction and distress levels are comparable to those seen with longer pre-test appointments. DNA-Direct is efficacious in the setting of multigene panel testing and helps to address increasing demands for service.

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Poster P047

Oral Contraceptive Use and Ovarian Cancer Risk: A Pooled Cohort Study of *BRCA1/2* Mutation Carriers

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Background Use of oral contraceptive preparations (OCPs) might reduce ovarian cancer risk. Only a few previous studies stratified analyses for *BRCA* mutation, and possible survival bias was not well examined.
Methods Using age-dependent Cox regression, ovarian cancer risk associations were estimated from data for 4767 *BRCA1* and 3038 *BRCA2* mutation carriers, stratified by study and birth cohort. To minimize survival bias, analyses were left-truncated at 5 years before the baseline questionnaire.
Results An inverse association with ever OCP use was comparable for both *BRCA1* and *BRCA2* mutation carriers, but was significant only for *BRCA1* mutation carriers (*BRCA1* HR: 0.58; 95% CI: 0.43 to 0.78; *BRCA2* HR: 0.71; 95% CI: 0.42 to 1.19). From multivariate *BRCA1*-analyses, including various OCP characteristics, only duration of use was associated with a reduced ovarian cancer risk ($p = 0.005$). Stratified analyses of duration of use by recency showed an attenuation of the risk over time (duration of 10 years: <15 years since last use HR: 0.27; 95% CI: 0.15 to 0.49; 15+ years since last use HR: 0.61; 95% CI: 0.37 to 0.98). Multivariate and stratified *BRCA2*-analyses were underpowered; however, univariate analyses suggested an inverse association with longer duration of use (<5 years HR: 1.01; 95% CI: 0.49 to 2.10; 5–9.9 years HR: 0.46; 95% CI: 0.22 to 0.96; 10+ years HR: 0.61; 95% CI: 0.29 to 1.27).
Conclusions For *BRCA1* mutation carriers, OCP use is inversely associated with ovarian cancer risk, which is stronger with a longer duration. This reduced risk is attenuated over time, but still significantly reduced 15 years after use. For *BRCA2* mutation carriers, findings are consistent, but lack power.

In clinical management, associations of OCP use with both breast and ovarian cancer have to be considered. We will calculate the sum of the absolute excess incidence and mortality of breast cancer and the absolute reduced incidence and mortality of ovarian cancer, varying relative risks, OCP duration, and the uptake of prophylactic surgeries. Results of those calculations will be presented at BRCA 2018.

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Poster P048

Nurses' Roles and Contribution in Breast Cancer Genetic Services in Hong Kong

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Background The Hong Kong Hereditary Breast Cancer Registry has established a program to support Hong Kong patients and families in need of genetic counselling and testing services at Tung Wah Hospital since 2007. Advances in DNA sequencing technology, reduction in cost, and increasing availability have resulted in increasing demands for genetic counselling. In Asia, there is a lack of genetic counsellors and hence a pragmatic need to increase the roles of nurses in cancer genetic services to meet the demand.
Methods Since 2013, the team has adopted a new model that involves trained specialty nurses to assist in the multidisciplinary cancer genetic services under supervision. Nurse roles include initial screening of referrals, taking family history, pedigree drawing, and consolidating medical records for eligible cases. Clinical decisions will be made by the supervisory genetics team, and individuals with a true negative genetic test result will be assigned to see trained nurses to receive their results and be discharged.
Results During 2013–2016, 1030 patients attended our nurse-led genetics counselling service to receive their genetic reports. Average genetic counselling

time was approximately 30 minutes. The nurses-led genetics counselling service achieved a 30% reduction in patient waiting time to obtain results.

Conclusions Nurses can be trained to contribute more in cancer genetics services to enhance the efficiency of running a high-risk clinic and shorten patient waiting time, particularly in Asia where genetic counsellors are a rarity. With multigene panel testing and the concept of population-based genetic testing being introduced, different methods of genetic counselling rather than the traditional method will likely have to be designed based on the resources available in various countries. In our locality, the assistance of nurse-led genetic services is likely to aid in the expansion of genetic services in Hong Kong.

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Poster P049

Acting on *BRCA:* Breaking Down Barriers to Save Lives. Recommendations to the U.K. Government on *BRCA* Testing and Patient Management from Ovarian Cancer Action

Marie-Claire Platt, Joanne Stanford, Georgina Tharp

BRCA testing could prevent up to 1000 cases of ovarian cancer in the United Kingdom each year. Ovarian Cancer Action is committed to maximizing and fulfilling the potential of *BRCA* testing as an effective cancer prevention tool.

To assess current rates of testing in the United Kingdom, the charity carried out research that included commissioning surveys, interviews with case studies, Freedom of Information Requests, and literature reviews.

Quantitative data from the survey revealed that, despite current guidelines, 29% of women diagnosed with ovarian cancer after 2015 were not offered testing, and 68% of women diagnosed before 2015 had not been offered testing. Of individuals found to have a mutation, 42% received no counselling after their test results. Only 34% were given support about choosing the right risk-reducing method for them.

Qualitative data yielded insight into patient experiences and the challenges faced, particularly in terms of psychological counselling after testing and lack of support concerning risk-reducing surgery, family planning, and hormone replacement therapy.

Combining the collected data, the charity makes detailed recommendations for the U.K. Government. Those recommendations include to embed *BRCA* testing in National Institute for Health and Care Excellence guidelines, specifically at the point of an ovarian cancer diagnosis; to contact women diagnosed with ovarian cancer before 2015 to inform them of their eligibility for *BRCA* testing; to lower the testing eligibility threshold from 10% to 5% carrier probability; and to ensure that patients have access to high-quality standardized information.

With 24 recommendations in total, Ovarian Cancer Action is calling on the government to improve genetic testing services in the United Kingdom to save lives.

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Poster P050

Diagnostic Yield and Genetic Counselling Challenges of a 19-Gene Hereditary Breast and Ovarian Cancer Panel: The Trillium Health Partners Experience

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The rapid adoption of next-generation sequencing (NGS) and identification of additional non-*BRCA1/2* genetic factors in hereditary breast and ovarian cancer (HBOC) has led to a paradigm shift in genetic testing. However, multigene panels pose several challenges: interpretation of sequence variants in less-well-characterized genes, balancing diagnostic yield with the identification of more variants of unknown significance (VUS), and genetic counselling dilemmas in complex cases.

As an academic community hospital providing a regional Genetics program, Trillium Health Partners has been offering a 19-gene HBOC NGS panel since April 2017 based on Ontario's testing criteria. To compare the diagnostic yield and VUS rate of the NGS panel compared with Sanger sequencing for *BRCA1/2* only, HBOC cases tested through the panel (n = 334) were compared with cases tested by Sanger-only from the preceding 2 years (n = 723). Based on this retrospective analysis, the diagnostic yield was 14.1% (n = 47/334) for pathogenic and likely pathogenic variants in the group tested by the panel compared with 11.2% (n = 81/723) in the group tested for *BRCA1/2* alone. The corresponding VUS rates were 19.5% (n = 65/334) and 6.9% (n = 50/723).

Genetic counselling challenges specific to panel test interpretation included relaying the clinical relevance of variants in medium- and low-penetrance genes, particularly if the associated cancer risks did not match the reported family history. With panel testing, the diagnostic yield has increased and is comparable to that described in recent literature, while the clinical complexity of results interpretation highlights several challenges. We propose some strategies for pre- and post-test genetic counselling in this context.

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Poster P051

Is It Really Worth It? An Experience with Contacting Past Patients for Updated Testing

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Purpose With constant advances in genetics knowledge and testing technology, genetic counsellors are often tasked with determining whether they have a duty to inform previous patients of such updates. Many factors have to be considered, including the motivation of patients, contact methods, response rates, and overall clinical utility; however, the process is not well documented in the literature.

Methods Here, we present our experience at Virtua, a community-based hospital in New Jersey, in which we contacted patients seen through our Cancer Genetics program from 2003 to July 2015 who had previously undergone *BRCA1/2* analysis and were offered additional genetic testing. In June 2016, 1764 patients were contacted by e-mailed newsletter, which included a leading article about the option of additional genetic testing. Afterward, from August 2016 through July 2017, 1898 personal letters were mailed.

Results After distribution of the newsletter, 13 patients (0.74%) contacted us, and after receiving the mailed letter, an additional 107 patients contacted us (120 patients total, 6.3% response rate). Of those 120 patients, 87 (72.5%) were seen by 1 of 3 genetic counsellors, and 82 (94.2%) elected to pursue additional testing. Only 1 patient (1.2%) received a result that altered clinical management (pathogenic *CHEK2* alteration). In 16 patients (19.5%), at least 1 variant of uncertain significance (VUS) was found; the remaining patients were negative.

Conclusions Our experience indicates that mail contact is a more effective method than e-mail contact and suggests that we may have to consider the feasibility, design, and benefits of such a project in the future, given the low overall response rates and clinical utility.

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Poster P052

Next-Generation Counselling: A Model for Hereditary Cancer Genetic Test Results Disclosure and Counselling

Kristin Price, Rotem Ben-Shachar, Beth Denne, Kaylene Ready, Gabriel Lazarin

Objective Because of changing guidelines and increased patient demand, hereditary cancer screening (HCS), including testing and counselling, is increasingly being performed by non-genetics specialists in the United States. Genetic counselling is an important aspect of HCS, but many patients cannot access counselling services. Our laboratory provides genetic testing, as well as a proprietary service called Counsyl Complete that includes automated results delivery, Web-based education, and telegenetic counselling. We report how this service is used for patients undergoing HCS.

Methods The results delivery service is an opt-in program for ordering providers and allows patients to receive results through a secure patient portal in tandem with provider receipt of results. Negative results and variants of uncertain significance (VUS) results can be viewed immediately, accompanied by written and video resources. Additionally, patients have the option to speak with a genetic counsellor on-demand or schedule an appointment. Patients with positive results can be informed only during a genetic counselling appointment or by the ordering provider. All patient interactions are tracked and consult notes are sent to the ordering provider.

Results Between April 2015 and December 2017, 21,247 HCS results were issued through the system. Genetic consults were conducted for 4109 results. 57% of positive results, 14% of negative results, and 30% of VUS results were accompanied by telegenetic counselling. 53% of consults were completed on-demand. Median consultation time was 15 minutes (IQR: 10–22) for positive, 11 minutes (IQR: 8–16) for negative, and 15 minutes (IQR: 10–20) for VUS results. The mean patient satisfaction rating for consultations was 4.9/5.

Conclusions Using Web education, automated notifications, and telegenetic counselling, we implemented a service that manages HCS results disclosure as a companion to results discussion and management by a health care provider. This method could help overcome barriers to access to HCS for a broader population.

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Poster P053

Addressing Barriers for Rapid Cancer Genetic Counselling: Triage System for Treatment-Focused Genetic Testing

Amanda Morgan,* Nora Wong†

Objective The objective of this study is to determine the effectiveness of the new hereditary breast and ovarian cancer (HBOC) referral triage system implemented since December 2014 at the Jewish General Hospital in Montreal, Quebec. The new system aims to prioritize affected patients by decreasing the turnaround time from referral to result-giving, so that genetic results can be used to inform treatment options and management of affected patients. Analysis of the mutation yield is expected to provide insights for improvement of the triage process and resource allocation.
Methods A retrospective chart review is in progress to assess the performance of the new HBOC referral triage system at the Jewish General Hospital. Eligibility for the study included all referrals sent for a breast and ovarian cancer assessment between January 2015 and August 2017. Patient demographics, referral information, wait times, clinical characteristics, and results of genetic testing will be extracted and summarized. Yield of genetic testing will be analyzed by referral criteria using the chi-square and Fisher exact tests.
Expected Results We focused on determining whether the current HBOC referral criteria used by the triage team are performing at the expected 10% detection rate. Initial analysis shows that most of the referral criteria are performing as expected and target wait-times are being met. In the group that did not fulfill the established criteria, but were granted special consideration by the triage group, initial findings suggest a lower mutation yield.
Conclusions As the demand for treatment-focused genetic testing becomes more prevalent, so does the need for genetics departments to prioritize patients by both utility of genetic testing and by the likelihood of identifying a mutation. This study provides the first evidence of the effectiveness of the new triage system at the Jewish General Hospital for meeting wait-time targets and highlights points for future improvement.

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Poster P054

BRCA1/2 Genetic Testing Ordering Practices: A Snapshot from a Large Commercial Laboratory

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BRCA1/2 genetic testing orders received at LabCorp for a period of 4 weeks in 2017 were analyzed for their clinical appropriateness and tracked through reporting to ascertain trends in the hereditary breast and ovarian cancer ordering practices of providers. All test orders are reviewed by genetic counsellors and, during this period, 94 (approximately 15% of total orders) were identified that required a discussion of alternative testing with the ordering provider.

Of the tests that were able to be updated, more than half (61.73%) were updated to *BRCA1/2* sequencing and deletion/duplication testing (*BRCA1/2* comprehensive) from either an order of *BRCA1* or *BRCA2* targeted testing or a deletion/duplication–only order. Without genetic counsellor clarification of those test orders, only 3 (6%) total would have had *BRCA1/2* comprehensive testing performed, and only 1 of 5 medically actionable results would have been reported. Orders that were not updated to *BRCA1/2* comprehensive testing were either cancelled because of a lack of response from the ordering physician (13.83%) or were updated to a more comprehensive cancer genetic testing panel (38.27%). More comprehensive genetic testing panels include expanded breast cancer panels (9.68%), breast and gynecologic cancer panels (41.94%), general cancer panels (35.48%), or other testing. Of these samples, 18 (58.06%) received results, with 1 being a medically actionable result in a gene other than *BRCA1/2*. Most of the test orders were received from primary care physicians and general internists (59.57%) and from obstetricians and gynecologists (29.79%). Other specialists placed test orders, but none involved a clinical genetic counsellor.

These data represent the larger testing trends of *BRCA1/2* ordering at LabCorp. It suggests that laboratory genetic counsellor review of complicated testing improves the clinical appropriateness of genetic testing ordered by non-genetic specialists.

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Poster P055

Portrait de l'oncogénétique au Québec en 2017

Jocelyne Chiquette

Objectifs Évaluer les différents aspects de la pratique en oncogénétique au Québec.
Méthodes Un sondage effectué auprès des 7 cliniques de génétique du Québec, de 2 CH membres du Réseau ROSE et de 5 centres privés effectuant des consultations et des tests en oncogénétique.

Un courriel envoyé à la présidente de l'Association des conseillères et conseillers en génétique du Québec qui a répondu. Consultation du site Web de l'Association des médecins généticiens du Québec.
Résultats 9 des 9 centres publics sondés ont répondu : 7 des 7 cliniques de génétique et les 2 CH du Réseau ROSE. 1 seul des 5 centres privés a répondu pour un total de 10 réponses.

Les effectifs sont peu nombreux : 10 généticiens, 4 omnipraticiens, 4 médecins spécialistes, 2 infirmières, 16 conseillères en génétique répartis comme suit : 29 personnes pour le conseil génétique et 7 pour le suivi des porteuses.

Les consultations en oncogénétique se répartissent ainsi dans les centres : 30 %–100 % seins-ovaires; 0 %–40 % côlon; 0 %–40 % autres tumeurs.

Parmi les 10 centres répondants : 7 ont un registre des tests effectués; 9 effectuent des panels multigènes; 3 ont eu des patients ayant fait des tests en ligne; 8 font des tests en urgence; 7 font le suivi de porteuses; 8 offrent du soutien psychologique; 7 utilisent le Réseau ROSE.

Les liste d'attente varient de 0 à 1453 personnes et le délai d'attente varie selon la priorité de 2 semaines (ou moins) à plus de 1 an.
Conclusions Face à l'augmentation prévue des demandes a-t-on des effectifs suffisants au Québec avec les 30 généticiens et les 50 conseillères dont un faible pourcentage seulement fait de l'oncogénétique. Un réseau clinique multidisciplinaire est une solution possible.

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Poster P056

Prevalence and Oncologic Outcomes of *BRCA1* and *BRCA2* Germline Mutations in Unselected Patients with Triple-Negative Breast Cancer

Jai Min Ryu, Seok Won Kim, Seok Jin Nam, Jonghan Yu, Se Kyung Lee, Jeong Eon Lee

Introduction Triple-negative breast cancer (TNBC) accounts for 15%–20% of all breast cancers, and TNBC is enriched for germline mutation of *BRCA*. U.S. National Comprehensive Cancer Network guidelines suggest that a *BRCA1/2* test is needed for patients less than 60 years of age with TNBC, but many Asian countries do not suggest testing because of a lack of evidence in Asian ethnic populations. We examined *BRCA1/2* mutation in patients with unselected TNBC and analyzed prognosis.
Methods For 1051 women with TNBC operated on at Samsung Medical Center (SMC) between 2008 to 2016, 999 samples were available from the SMC biobank for testing germline *BRCA1/2* mutation by next-generation sequencing. All patients were Korean.
Results The mean follow-up duration was 60.0 months. Overall, 125 patients (12.5%) had *BRCA* mutations: 92 (9.2%) in *BRCA1*, and 33 (3.3%) in *BRCA2*. Median age was 49.7 years. Mean age of diagnosis was significantly younger in *BRCA1/2* mutation carriers than in noncarriers (45.4 years vs. 50.3 years, $p < 0.0001$). In patients less than 50 years of age with TNBC, the prevalence of *BRCA* mutation was 16.0%. No significant difference in OS and DFS was observed between patients with *BRCA1/2* and sporadic breast cancers (log-rank $p = 0.138$ and 0.993 respectively). Significantly more contralateral breast cancer is observed in patient with *BRCA1/2* mutation ($p = 0.000$).
Conclusions We found a 12.5% incidence of *BRCA* mutations in unselected TNBC. Patients less than 50 years of age with TNBC should be added as criteria to genetic screening guidelines in Korea.

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Poster P058

Group Counselling for Breast Cancer Genetics: Perspectives of Women at Risk for HBOC

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Background Genetic counselling is a standard of care before *BRCA* mutation testing. Access to timely counselling and testing is limited by time constraints and a shortage of trained health care professionals. The purpose of this quality improvement initiative was to explore whether pre-test group counselling for breast cancer genetics, followed by a "mini" individual session, would be acceptable to women at risk for *BRCA* in Newfoundland and Labrador.
Methods 60 women on the wait list for *BRCA* genetic testing through the Provincial Medical Genetics Program in St. John's, NL, were included. Between July 2016 and October 2017, women were called and offered the

option of a group counselling session, followed by a mini (~20 minutes) individual session of genetic counselling, versus waiting for their individual appointments. All women agreed to the group and mini session. A 12-item Likert survey was distributed after the conclusion of the mini session; it measured the women's perceptions of the group clinic and satisfaction with the counselling model.

Results Responses to all 12 items were overwhelmingly positive. Large proportions strongly agreed that they were comfortable with the group session: the explanation of cancer genetics was clear, they understood their cancer risks, and they would recommend such a session to others. Women strongly disagreed they would prefer to wait for an individual appointment. Genetic counsellors were also very satisfied with the new model, and the waitlist for *BRCA* counselling and testing was reduced by a year.

Conclusions Results of this quality improvement initiative revealed very positive evaluations from all participants and counsellors. Data suggest that group counselling combined with an immediate individual "mini" session is strongly supported by women on the wait list for *BRCA* mutation counselling. Further, a reduction in wait time was observed. Additional investigation of this approach in larger numbers of patients is warranted.

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Poster P059

Assessing Cascade Carrier Testing for Hereditary Cancer Across a Publicly-Funded Provincial Program

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Introduction Cascade carrier testing for hereditary cancer enables the identification of at-risk individuals most likely to benefit from increased screening and preventive measures. Despite predicted positive health outcomes, there is a paucity of recent literature on the uptake and health impact of program-wide carrier testing for hereditary cancer.

Methods We assessed carrier testing uptake and demographic factors between 1 January 1997 and 31 December 2016 for families in which the index patient received testing through the Hereditary Cancer Program (HCP) in British Columbia. We began with *BRCA1* and *BRCA2*, and will be conducting additional analyses on other high- and moderate-penetrance genes tested by the HCP. Future analyses will elucidate the health effects of carrier testing for hereditary breast and ovarian cancer syndromes.

Results A total of 424 and 398 positive *BRCA1* and *BRCA2* index cases have, respectively, been identified through our provincial program; carrier testing for at-risk family members has been performed for 723 and 664 individuals for *BRCA1* and *BRCA2* respectively. 45% (323/723) tested positive for a *BRCA1* mutation, and 45% tested positive for a mutation in *BRCA2* (298/664). The average age of individuals receiving carrier testing for *BRCA1* was 46.0 ± 15.9 years; it was 47.7 ± 16.3 years for *BRCA2*. A significantly higher number of women ($n = 1051$) than men ($n = 336$) received carrier testing for *BRCA1* and *BRCA2* ($p < 0.01$). In families with pathogenic or likely pathogenic mutations in *BRCA1* and *BRCA2*, 1.7 carrier tests (mean) per index test were performed. Carrier testing uptake corresponded with the geographic population distribution of the province.

Conclusions This analysis highlights the carrier testing uptake for *BRCA1* and *BRCA2* mutations in the population served by the HCP. Future analyses could inform decisions about how resources might be allocated to better serve this high-risk population.

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Poster P060

Polygenic Risk Score Refines Clinical Risk Model Estimates in a Population-Based Trial

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Background Genetic variants known as single nucleotide polymorphisms (SNPs) are promising markers of breast cancer risk. WISDOM (Women Informed to Screen Depending on Measures of Risk) is the first prospective trial comparing personalized with annual breast cancer screening. Personalized screening recommendations are based on sequencing of hereditary breast cancer genes and a 5-year risk estimate from the Breast Cancer Surveillance Consortium (BCSC) risk model modified by a polygenic risk score (PRS) comprised of 75 SNPs. WISDOM allows risk model performance to be compared in a population setting.

Methods The WISDOM study (NCT02620852) opened in 2016 and is enrolling women 40–74 years of age. Self-reported demographic and risk factor information was collected through an online portal. SNP genotyping was done using a panel from Color Genomics. Here we used paired statistical tests (McNemar) to compare the distributions of BCSC and BCSC-PRS risk estimates around a low-risk threshold (<1%), a moderately high-risk threshold (=3%, corresponding to a 5-year risk above which some guidelines suggest chemoprevention), and a very high-risk threshold (>6%, corresponding to the 5-year risk of a *BRCA* mutation carrier).

Results We analyzed 2060 participants in the personalized arm of WISDOM who have completed risk assessment. The median age was 56 years, with 83% being Caucasian, 1% African American, and 7% Asian. 10% self-reported as Hispanic. The median 5-year risk was 1.5% (IQR: 1.0%–2.1%) using the BCSC model and 1.4% (IQR: 0.8%–2.5%) using the BCSC-PRS model. Compared with the BCSC model, the BCSC-PRS model classified more women into the low-risk (<1%) and the moderately high-risk or very high-risk (=3% or >6%) risk categories ($p < 0.001$).

Conclusions Our findings suggest that incorporating genetic variants into a validated clinical model is feasible and could enhance risk prediction.

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Poster P061

Genetic Counselling and Testing for Hereditary Breast and Ovarian Cancer: 22 Years' Experience in a Single Swiss Institution

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Objective Genetic counselling and testing for cancer predisposition syndromes have been available in a clinical setting for many years. In this study, we assessed genetic consultation and testing, particularly for hereditary breast and ovarian cancer (HBOC) syndromes, performed for more than 20 years in a single Swiss university hospital.

Methods All pedigrees of probands managed in the Unit of Oncogenetics and Cancer Prevention in the Geneva University Hospitals between 1996 and 2017 were reviewed. Types of consultation were classified according to personal or family history. For pedigrees suggestive of HBOC syndrome or familial breast or ovarian cancer, we collected BRCAPRO scores and, if performed, genetic testing results. Over time, we evaluated the medical history of probands referred to counselling, the clinical criteria and BRCAPRO scores used to propose genetic testing, and the rate of pathogenic variants identified.

Results Between 1996 and 2017, 3489 consecutive probands from distinct families had genetic counselling. New families managed per year increased over time, and thus half the families have been seen since May 2013. Altogether, 66% of all consultations concerned familial or hereditary breast or ovarian cancer; 12%, familial or hereditary colorectal cancer; and 22%, other situations. Overall, 1253 genetic analyses for HBOC were performed, with a spectacular increase over time. 149 (11.9%) pathogenic variants (81 *BRCA1*, 67 *BRCA2*, 1 *ATM)* were identified. The mutation detection rate was 15% during 1996–2002, 18.5% during 2003–2009, and 10% during 2010–2017. Mean BRCAPRO scores decreased to about 1% in 2017 from 10% before 2010. The number of asymptomatic index cases increased to 15% after 2010 from 9% before 2010.

Conclusions Genetic counselling and testing for HBOC drastically increased over time. The rate of pathogenic variants detection decreased, concurrently with a decrease in BRCAPRO scores and the proportion of index cases affected by cancer. Swiss guidelines for counselling and testing for genetic predisposition to HBOC were set up in 2017.

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Poster P062

Age-Specific Ovarian Cancer Risks Among Young Women with a *BRCA1* or *BRCA2* Mutation

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For women at high risk of developing ovarian cancer, it is important to provide an accurate recommendation for the optimal age for preventive surgery to maximize cancer prevention while delaying symptoms associated with early surgical menopause. The goal of the current study was to estimate age-specific incidence rates of ovarian cancer among young women with a *BRCA1* or *BRCA2* mutation.

From our international registry, we identified 5689 women with no previous diagnosis of ovarian or fallopian tube cancer or preventive oophorectomy. Women were followed from the date of completion of the baseline questionnaire until either a diagnosis of ovarian or fallopian tube cancer, prophylactic oophorectomy, death, or last follow-up. The annual and cumulative incidence rates of ovarian cancer were estimated. Over a mean follow-up period of 4.7 years (range: 0–22.6 years), 195 incident ovarian or fallopian tube cancers were diagnosed [169 ovarian cancers (86%), 22 fallopian tube cancers (11%), and 4 cancers that involved both the ovaries and fallopian tubes (2%)]. Of those cancers, 45 (23%) were diagnosed at preventive surgery (occult cancers). The cumulative risk of ovarian cancer to age 80 was 49% for *BRCA1* and 21% for *BRCA2* mutation carriers. Mean age at diagnosis was 51.3 years (range: 33–84 years) among women with a *BRCA1* mutation and 61.4 years (range: 44–80 years) among women with a *BRCA2* mutation. Based on a cumulative risk of 0.55% to age 35 for *BRCA1* mutation carriers and 0.56% to age 45 for *BRCA2* mutation carriers, we recommend bilateral salpingo-oophorectomy at age 35 for women with a *BRCA1* mutation and age 45 for those with a *BRCA2* mutation to maximize prevention.

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Poster P063

Cascade Genetic Testing of Relatives for Hereditary Cancer Risk: First Year of a Low-Cost, Accessible Family Testing Program

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To achieve the goal of genetically-targeted primary disease prevention, testing for an identified familial mutation must extend to unaffected relatives in a process known as "cascade testing." However, there are major barriers to effective cascade testing of relatives, including cost, insurance constraints, and confidentiality laws.

We report on the first year of a low-cost, accessible cascade testing initiative offered by a testing laboratory and supported by a genetics-focused foundation. The family testing program allowed 1st-degree relatives (FDRs) of individuals ("carriers") with a pathogenic variant in any of 30 cancer-associated genes, including *BRCA1* and *BRCA2*, to be invited to undergo testing at an out-of-pocket cost of US$50. The FDRs were invited by e-mails directly from the testing laboratory.

From 27 September 2016 to 26 September 2017, 1118 applicants (748 carriers, 370 FDRs) invited 2645 FDRs. Of the carriers, 44.0% had a *BRCA1* (n = 221) or *BRCA2* (n = 271) mutation. More than half (56.0%) of all invited FDRs underwent genetic testing. Uptake specifically by FDRs of *BRCA* carriers was similar to that by all carriers: 56.8% for *BRCA1* and 57.2% for *BRCA2*. Of the 1480 invited FDRs who underwent genetic testing, 46% tested positive for the known familial pathogenic variant (KFPV) only; 1.6% tested positive for the KFPV and for a pathogenic variant in a different gene; 3.4% tested positive for a pathogenic variant in a different gene only; 7.6% had a variant of uncertain significance, but no pathogenic variant; and the remaining 41% had normal results. Among all invited FDRs who tested positive, 11% continued the cascade by inviting other FDRs.

Future research should explore relatives' motivations and barriers to testing and strategies to integrate clinician expertise with low-cost, direct-contact approaches to cascade testing.

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Poster P064

Portrait of a Divorce: When Variants of Unknown Significance and Cancer History Are Not Meant to Be

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When patients come to a hereditary cancer clinic, their expectation is that genetic testing will provide a more precise estimate of their cancer risk, which may in turn affect their clinical management. The ultimate goal is to decrease the morbidity and mortality associated with a potential cancer diagnosis by methods that include increased surveillance or prophylactic surgery. The identification of mutations in the highly-penetrant hereditary breast and ovarian cancer (HBOC) susceptibility genes *BRCA1* and *BRCA2* provides a well-established example of this. With the advent of next-generation sequencing (NGS), the classification of some variants in known or proposed cancer predisposing genes as variants of unknown clinical significance (VUS) has led to the complicated issue of untangling rare but non-pathogenic variants from those that might confer an increased risk of disease.

An example from our lab to illustrate this potential conundrum follows whole-exome sequencing (WES) performed on 14 families of French Canadian descent with at least 2 cases of ovarian cancer (OC) in 1st-degree relatives, where a pathogenic *BRCA1* or *BRCA2* mutation had previously been identified by panel testing. Of those families, 6/14 (42.9%) were found to carry a rare VUS (minor allele frequency < 0.1%), including 1 in *MSH2*, which reportedly has a role in OC. In 2 families, 1 or more VUSs in other genes were detected. Interestingly, VUSs in *PALB2* and *CHEK2* were identified in women who also had a personal and family history of breast cancer. If these multi-case OC families had not harboured known *BRCA1* and *BRCA2* mutations, one could argue whether it would have been tempting to assign disease causality to the VUS, especially when identified in a gene already suggested to have a role in susceptibility to the diagnosed cancer. Cautionary interpretation of VUSs remains essential in research and clinical settings.

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Poster P065

Case Presentation: Unexpected Findings from a Hereditary Breast/Ovarian Cancer Panel

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A 68-year-old woman was referred for genetic counselling to discuss her personal history of bilateral breast cancer diagnosed at ages 50 and 68, squamous cell skin cancer, and a keratoacanthoma diagnosed at age 66. Her family history included esophageal, bladder, and colon cancer. She was given a moderate risk for a hereditary cancer syndrome and initially declined testing.

Two years later, the patient was re-referred. Immunohistochemistry on the keratoacanthoma was intact, making Lynch syndrome less likely. A breast/ovarian 18-gene next-generation sequencing (NGS) cancer panel return a result of uninterpretable because of "a mixed genetic profile." A skewed allele frequency was seen for some common sequence variants in *BRCA1*, but not *BRCA2*. Quantitative fluorescence polymerase chain reaction showed 2 female profiles, with some shared alleles on chromosomes 13, 21, and X. A bone marrow transplant was ruled out, leaving the possibility of sample mix-up or contamination. Results from a second blood sample were consistent with the original, showing skewed allele frequencies in *BRCA1* and several other genes. The normal cut-off for heterozygous state allele frequency is 0.3–0.7. For this patient, the skewed ratios were ~0.22. The variants with normal allele frequencies likely shared the same haplotype.

Two female profiles were seen consistently on both testing attempts. This patient is likely a chimera (one individual with two distinct genotypes). In follow-up, we discussed the unknown frequency of this rare event, how chimerism can occur (that is, vanishing twin), and the implications for the patient overall. Ultimately, NGS technology was unable to provide a result, and no other affected relatives are available for gene panel testing. This is the first time our lab has come across this situation in the context of NGS cancer gene panel testing, and the first time our clinical staff have counselled on this complex issue.

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Poster P066

Implementation of Oncology Clinic–Based Genetic Testing in the Population-Based Health Care System of British Columbia

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Patients of BC Cancer's Hereditary Cancer Program are experiencing extended wait times for genetic counselling appointments and genetic testing results because of increasing demand for services. To reduce patient wait times, we implemented a modified strategy that was pioneered in the United Kingdom by George *et al.* (2016), where oncologists are given a more substantial role in the genetic testing and counselling process.

After completing a brief orientation, participating oncologists were able to initiate genetic testing for selected patients, who then received genetic test results from a genetic counsellor. Over an 18-month period, patients were offered either the standard genetic counselling clinical pathway or the oncologist-initiated (GENONC) clinical pathway. Patients in both clinical pathways (n = 155) received a mailed survey package after their genetic test results disclosure appointment.

Key study findings were that patient satisfaction ($n = 155$) was similar for each clinical pathway and that the timeline to receive genetic test results ($n = 1539$) was reduced by half (to 170 from 407 days) for the GENONC group. In addition, participating oncologists and genetic counsellors confirmed the acceptability and feasibility of the GENONC process.

Next steps will focus on increasing the number of participating oncologists and expanding GENONC eligibility criteria beyond hereditary breast and ovarian cancer with the goal of significantly reducing wait times for all British Columbia patients seeking hereditary cancer risk assessment.

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Poster P067

Racial and Ethnic Differences in Hereditary Cancer Multigene Panel Testing Results Among Breast Cancer Patients

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Recently, the use of next-generation sequencing panels to aid in the diagnosis of hereditary cancer predisposition has increased. The discovery of pathogenic variants (PVs) in known susceptibility genes leads to focused screening and prevention strategies for individuals at increased risk of cancer. However, studies supporting the utility of multigene panel testing have focused on Caucasian individuals.

To understand the influence of results from panel testing on breast cancer (BCA) risk in non-Caucasian individuals, we studied BCA cases who underwent hereditary cancer panel testing at Ambry Genetics between 2012 and 2016. The frequency of PVs and variants of unknown significance (VUS) in African American, Asian, Caucasian, and Hispanic populations was assessed, and gene-specific BCA risk associations were estimated for each population by comparing PV frequencies between BCA cases and Genome Aggregation Database African/African American, East Asian, non-Finnish European, and Latino reference controls. African American, Hispanic, and Asian (non-white) BCA cases were significantly younger at testing relative to Caucasians ($p < 0.05$), suggesting population-specific differences in panel testing referral. Across 21 known and candidate BCA predisposition genes, similar overall frequencies of PVs were identified in African American, Hispanic, and Caucasian BCA cases (~11%). The PV frequency was relatively lower in Asian cases (~8%). VUS frequency was significantly higher in non-Caucasian BCA cases, with the VUS frequency being highest among Asian cases. In an exploratory analysis of population-specific BCA risk associations, PVs in *BRCA1, BRCA2,* and *PALB2* were associated with high risk of BCA across all ethnic groups. However, PVs in the *ATM, CHEK2, MSH6, BARD1,* and *RAD51D* moderate-risk genes showed population-specific associations with BCA.

These studies provide important insights into the risks of BCA associated with predisposition gene mutations in non-Caucasian populations and demonstrate the need for continued investigation of population-specific factors contributing to inherited BCA risk.

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Poster P068

Barriers and Opportunities for Genetic Testing of *BRCA* Mutations in Breast Cancer Across Europe

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Background This research aims to provide an overview of possible barriers to genetic screening, information, and support for individuals with *BRCA*+ breast cancer in Europe.
Methods A pragmatic review of the published and grey literature was conducted. Focusing on 6 countries, we looked for epidemiologic data and assessed which systems, policies, and services are in place for testing, genetic counselling, and care. We also conducted qualitative, semi-structured telephone interviews with thought leaders from across Europe to supplement secondary data findings and identify opportunities for improvement relevant to policymakers and patients.
Results Current guidelines for *BRCA* gene testing are insufficient to detect all carriers of *BRCA* mutations. Testing is restricted to high-risk patients, despite evidence that more than half of those diagnosed with *BRCA*+ breast cancer do not have a family history of breast cancer. Structural barriers to access to information and services vary greatly between countries. Such barriers include low referrals by physicians, limited knowledge of genetics in a general practitioner setting, and unequal access to genetic screening and counselling based on region, race, and age. Fear of discrimination prevents many people from undergoing screening, particularly in relation to employment or insurance coverage. Additionally, up-to-date prevalence data are rare, making it difficult to estimate the full impact of this condition in the general population.
Conclusions This research aimed to identify areas in which policy change are needed in genetic testing and care pathways for women with *BRCA*+ breast cancer. Those areas include greater public awareness, investment in professional training and capacity-building, and reduced inequalities in access to genetic testing. Protection against discrimination for diagnosed patients is also critical in all social policies. Genetic testing should be built into comprehensive care pathways that offer individuals and their families appropriate information, support, and care through every stage of their journey.

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Poster P069

Evolving Testing Strategies and Outcomes in the Ashkenazi Jewish Population

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Background 1 in 40 (2.5%) individuals of Ashkenazi Jewish (AJ) ancestry will have at least 1 of the 3 AJ *BRCA1/2* founder variants (AJFVS). Testing for the AJFVS is recommended as a first-line test for AJ individuals with histories suggestive of hereditary breast and ovarian cancer syndrome (HBOC). We aim to compare testing strategies and outcomes in the AJ population to determine if there is a benefit to more comprehensive testing.
Methods We retrospectively reviewed genetic testing strategies for individuals with self-reported AJ ancestry. We then analyzed results to calculate yield for all AJ individuals who underwent testing using a select panel of genes related to HBOC and who had no previous *BRCA1/2* testing.
Results As of November 2017, 8347 individuals reporting AJ ancestry underwent testing. The rate of AJFV testing as a proportion of all testing for AJ individuals has remained constant since 2013 (30.0% in 2013 vs. 34.0% in 2017), but the use of panel testing as a first-line approach has increased at an average rate of 27% per year (22% in 2013 to 52% in 2017).

The positive yield among AJ individuals tested with the genes of interest was 10.1% (89/885). Of the 93 PVs identified in 89 individuals, 43% (40/93) were AJFVs. The 53 non-AJFVs (57% of all PVs) were identified in *CHEK2* ($n = 31$), *FANCC* ($n = 6$), *NBN* ($n = 3$), *ATM* ($n = 3$), *BRCA1* ($n = 3$), *BRCA2* ($n = 3$), and 1 each in *MSH2, MSH6, RAD51C,* and *XRCC2*.
Conclusions Testing for AJFVs and even *BRCA1/2* alone could potentially miss more than 50.0% of PVs in breast/ovarian genes in the AJ population. A broader approach to genetic testing among AJ individuals has been observed in recent years, often because of mixed ancestry, bilineal risk, and history of non-*BRCA1/2*–associated cancers, and should continue to be considered.

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GROUP 2 – THURSDAY, 10 MAY 2018

PSYCHO-ONCOLOGY

Poster P070

Facteurs psychosociologiques et cliniques impactant la communication familiale et la réalisation des tests dans les familles porteuses d'une mutation des gènes *BRCA1/2*

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Contexte Nous avons précédemment montré que seulement un tiers des apparentés potentiellement testables réalise le test ciblé dans une famille où une prédisposition *BRCA1/2* a été identifiée (Pujol *et al.,* BCRT, 2013). Le cas-index a un rôle déterminant dans la diffusion de l'information aux apparentés.
Objectifs et méthodes Cette étude prospective multicentrique vise à identifier les facteurs psychosociologiques et médicaux du cas-index impactant l'information familiale et la réalisation de tests ciblés dans les familles prédisposées. Des questionnaires psychologiques validés ont été recueillis pour mesurer: le trait anxiété (STAI), les traits dépressifs (BDI), l'alexithymie (TAS-20), les niveaux de conscience émotionnelle (LEAS), l'optimisme dispositionnel (LOT-R), les stratégies de coping (WCC), le vécu de la tâche de messager (échelles EVA), et la qualité des relations familiales (FRI).
Résultats 103 cas-index porteurs d'une mutation des gènes *BRCA1/2* ($n = 81$) ou MMR ($n = 22$) ont été inclus. 68% des apparentés qui pouvaient bénéficier d'un test ciblé en avaient été informés. 37% des apparentés

informés avaient réalisé un test ciblé. Le taux d'information était inversement corrélé à l'éloignement générationnel ($p < 0.0001$). En analyse multivariée, les facteurs corrélés à l'information familiale étaient l'ancienneté du diagnostic génétique ($p < 0.01$) et la cohésion au sein de la famille (FRI, $p = 0.01$). La présence de traits dépressifs chez le cas index était positivement associée à la réalisation de tests ciblés ($p = 0.02$) et une tendance à un coping centré sur l'émotion était observée ($p = 0.09$). La réalisation de tests ciblés était négativement associée à une forte perception du risque de cancer chez le cas index ($p = 0.03$) et un vécu difficile de sa tâche de messager ($p = 0.07$).

Conclusions Cette étude permet de mieux comprendre les déterminants psychologiques et relationnels impactant la qualité de l'information et la réalisation des tests au sein de familles prédisposées. Une information et un accompagnement personnalisés du cas-index pourraient améliorer l'accès aux tests dans les familles.

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Poster P071

An Evaluation of Memory and Attention in *BRCA* Mutation Carriers Using an Online Cognitive Assessment Tool

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Background *BRCA* mutation carriers might be at risk for cognitive impairment given their uptake of preventive surgery, exposure to chemotherapy, and increased psychosocial distress. In this preliminary evaluation, we used an online assessment tool designed to screen for cognitive deficits (http://www.cogniciti.com) to investigate the effect of potential risk factors on memory and attention in *BRCA* mutation carriers.

Methods *BRCA* mutation carriers from a longitudinal study were invited to complete a validated online brain health assessment that evaluates 4 measures of memory and executive attention. Normative Z-scores were adjusted for age and education level for each task, and an overall cognitive score, approximately equal to a percentile, was calculated from the mean of the Z-scores. Participants reported if they had a past history of any conditions (for example, anxiety, depression, chemotherapy-treated cancer). The Student t-test was used to determine differences between various factors and the mean overall score.

Results The online cognitive assessment was completed by 302 women with a *BRCA* mutation. The average age of the participants was 57.6 ± 9.2 years, of which 50% had a history of chemotherapy treatment, 25% had memory concerns, 16% had anxiety, and 9% had depression. The mean overall test score was 56 ± 22 (range: 0–93). Scores were significantly lower for women with self-reported anxiety than for women without anxiety (50 vs. 57; $p = 0.05$). Scores were also significantly lower for current smokers than for those who had never smoked (42 vs. 59; $p = 0.02$). The overall cognitive test score was not different for women who had memory concerns, a history of depression, or chemotherapy-treated cancer.

Conclusions Preliminary findings suggest that a history of anxiety and smoking might impair memory and attention, while depression and chemotherapy treatment might not affect cognitive ability in *BRCA* mutation carriers. Participant enrolment is ongoing and additional analyses will focus on the role of prophylactic surgery and exogenous hormone use on cognitive deficits.

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Poster P072

Implications of Multigene Panel Testing on Psychosocial Outcomes: A Comparison of Pancreatic and Breast or Ovarian Patients

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Pancreatic adenocarcinoma (PAC), like breast and ovarian (BROV) cancers, is associated with many hereditary cancer syndromes, making multigene panel testing ideal for identifying high-risk families. However, unlike BROV patients, PAC patients are not, in routine clinical practice, referred to genetic counselling. Research is needed to examine similarities and differences in the responses of these patients to complex test results.

This study examined cognitive and affective responses to genetic counselling and multigene panel testing among PAC and BROV patients. Questionnaires were completed by 32 PAC and 51 BROV patients before genetic counselling and 4 weeks after return of results ($n = 13$, $n = 20$). Testing was ordered (range: 15–28 genes) through CLIA-certified labs. At baseline, PAC and BROV patients reported similar interest in learning more about the role of genetics in cancer (somewhat or very important: PAC, 90%; BROV, 96%) and a similar number thought that genetic factors explained their cancer (somewhat or very likely: PAC 72%; BROV 78%). At follow-up, patients in both groups reported low levels of worry (PAC, 15%; BROV, 10%), sadness (23%; 5%), anxiety (8%; 5%), and loss of control (15%; 5%) about their test results. Conversely, a feeling of little to no relief about genetic test results was reported more often by PAC patients than by BROV patients (PAC, 60%; BROV, 30%; $p < 0.03$). Although interest in and response to testing was similar for BROV and PAC patients, PAC patients were in poorer health, and 29% passed away after counselling.

Although multigene panel testing is not used as often for PAC patients, this study shows that interest in and reaction to testing is similar for PAC and BROV patients. Novel strategies that incorporate health status and prognosis might be needed to effectively incorporate multigene panel testing into routine care, but overall genetic results are perceived to be as valuable in PAC patient as in other populations.

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Poster P073

Building a Patient-Oriented Research Program in Inherited Cancer: Early Experiences from Newfoundland and Labrador

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Background Women with mutations in *BRCA1/2* face very elevated risks of breast and ovarian cancer. Despite clear recommendations to guide optimal cancer prevention and screening, many women in Newfoundland and Labrador (NL) do not receive care in accordance with published guidelines. A recent project evaluating compliance with breast and ovarian cancer screening and prevention showed that 30% of women chose mastectomy despite the associated 98% reduction in breast cancer risk. Of women not choosing mastectomy, 108 of 145 were eligible for breast MRI screening, and yet only 37% received that test within recommended timeframes according to guidelines.

Methods The *BRCA* research team at Memorial aims to improve the care of *BRCA*-positive women in NL through the development of an evidence-based and patient-oriented research program. Patient-oriented research aims to improve patient outcomes by focusing on patient-identified priorities and outcomes. We held two workshops with carriers of inherited cancer mutations ($n = 7$) to determine their priorities for care, ongoing management, and research.

Results Mutation-positive carriers endorsed the need for a patient-oriented research program in inherited cancer and, specifically, the value of a cancer registry. Carriers confirmed the ongoing burden of screening and difficulties in coordinating appointments and tests. Family communication and understanding of the family risk were also identified as challenges. Workshop participants contributed as partners to two patient-oriented grant applications, one of which was successful.

Conclusions Partnering with mutation carriers identified their priorities and outcomes, resulting in a successful patient-oriented grant application. This work will explore deficiencies in the current care model in NL and engage with patients to explore solutions. Ongoing work with patient partners ultimately aims to improve the care of high-risk individuals, but also to build a successful patient-oriented research program from which lessons learned can be distilled and shared.

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Poster P074

Hereditary Breast Cancer Risk: Depression, Anxiety, and Impact of Cognitive Behavioral Therapy

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Patients with hereditary risk for breast cancer (HBCR) face psychosocial challenges such as anxiety about cancer risk, decision-making about risk-reducing surgery, and coping with family issues, including cancer-related grief. Although mood and cognitive behavioral therapy (CBT) have been widely studied within the breast cancer population, there is less information about how patients with HBCR experience distress or benefit from psychological treatment. CBT might help HBCR patients by targeting cognitions associated with cancer-related anxiety, developing decision-making skills, and providing training in stress management.

Methods Retrospective chart review of 43 consecutive patients with HBCR (mean age: 43.88 years; 93% Caucasian; 32.6% breast cancer survivors) referred to a psychologist embedded into an academic medical centre breast clinic completed diagnostic evaluation, the 7-item Generalized Anxiety Disorder (GAD-7), and the 9-item Patient Health Questionnaire (PHQ-9). A subsample of 17 patients completed at least 3 CBT sessions.

Results The PHQ-9 and GAD-7 showed high reliability in the HBCR population (Cronbach alpha 0.90 and 0.93) and construct validity, with the PHQ-9 being more highly associated with depression diagnosis ($F = 3.88$, $p < 0.01$) and the GAD-7, with anxiety diagnosis ($F = 2.72$, $p < 0.05$). HBCR patients showed clinically elevated anxiety (34.9%, GAD-7) and depression (30.1%, PHQ-9). Levels of depression, but not anxiety, were significantly higher in patients with a history of breast cancer than in those with no history of breast cancer ($t = 2.31$, $p < 0.05$). Brief CBT was effective in reducing depressive symptoms ($t = 4.84$, $p < 0.001$) and anxiety symptoms ($t = 3.76$, $p < 0.01$) for HBCR patients. Preliminary results suggest that CBT was effective for HBCR patients with no history of breast cancer in reducing depressive symptoms ($t = 2.65$, $p < 0.05$, $n = 6$).
Conclusions The PHQ-9 and GAD-7 show promising reliability and validity for use with the HBCR population. This study represents a significant impact in showing brief CBT as effective for patients with HBCR.

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

Poster P075

Functional Mapping of Secondary Structures in the *BRCA1* Tandem BRCT Domains Can Improve Cancer Risk Assessment

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Approximately one third of more than 1700 *BRCA1* variants in the Breast Cancer Information Core database are missense variants of uncertain significance (VUS). They lack evidence for an association with disease risk and present a challenge in making clinical decisions. Functional assays combined with bioinformatics prediction tools can be used to aid in the clinical annotation of VUS. Importantly, higher prior probabilities of pathogenicity are assigned to variants in domains and motifs essential for *BRCA1* function than to variants outside of those regions. However, the exact borders of the domains and the functional importance of their secondary structures remain uncertain.

In this study, we interrogated three underexplored features of tandem *BRCA1* C-terminus (TBRCT) domains based on their sensitivity to missense variants: the TBRCT borders, the linker region, and both a1 helices. A total of 92 naturally occurring missense variants were subjected to transcriptional assay based on a fusion of the GAL4 DNA-binding domain to *BRCA1* C-terminus (aa 1396–1863) in 293FT cells.

Analysis of the 20 variants at the border between the disordered region and the TBRCT (residues K1648, R1649, M1650, and S1651) revealed the TBRCT border to lie between residues M1650 and S1651. Of the 65 variants within the 23-aa linker region, 43 displayed less than 80% transcriptional activity, and 6 demonstrated inconsistent activity, suggesting a severe effect on *BRCA1* function. Of 7 novel mutations in the TBRCT a1 helices, 5 also performed with impaired function, despite the lack of functional impact of 16 of the 17 variants previously analyzed.

In summary, our study provides a refined understanding of *BRCA1* regions less tolerant to changes and therefore more likely to contain pathogenic variants. That understanding will be critical for the assignment of different prior probabilities of pathogenicity given the variant location, improving risk assessment and clinical management for carriers of *BRCA1* missense alleles.

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Poster P076

Intra-laboratory *BRCA1* and *BRCA2* Variant Reclassification Over a Five-Year Period

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Background Genetic testing can identify individuals at risk for hereditary breast and ovarian cancer (HBOC) and inform risk management. Although the *BRCA1* and *BRCA2* genes are well-characterized, variants are susceptible to inter-laboratory discordance and might be reclassified over time as new evidence is generated. The Advanced Molecular Diagnostics Laboratory (AMDL) at Mount Sinai Hospital in Toronto provides *BRCA1/2* testing for patients who are eligible based on Ministry of Health and Long-Term Care guidelines. Here, we report *BRCA1/2* variant reassessment and reclassification at the AMDL between 2012 and 2017.
Methods Patients received complete sequencing of *BRCA1/2*; analysis of Ashkenazi Jewish founder mutations; or analysis for a known familial variant. Variants were assessed using a standardized variant assessment tool aligned with guidelines published by the American College of Medical Genetics and Genomics. Variant reassessment was tracked in an in-house database. Variants were shared through the Canadian Open Genetics Repository and submitted to ClinVar.
Results Between 1 January 2012 and 18 August 2017, 1213 *BRCA1/2* variants were reported. In total, 33.1% (402/1213) were reassessed, and 37.8% (152/402) of those that were reassessed were reclassified. 453 variants were originally classified as VUS and 34.0% (154/453) of them were reassessed. Of the VUS that were reassessed, 43.5% (67/154) were reclassified: 41 to benign, 23 to likely benign, 2 to likely pathogenic, and 1 to pathogenic.
Conclusions The foregoing results demonstrate that *BRCA1/2* variants, particularly VUS, can undergo reclassification over time, highlighting the importance of periodic intra-laboratory reassessment. Reclassification presents ethical and practical challenges and suggests a need for research and guidance on the ethical, legal, and social implications, especially when reclassification could affect patient management. Data sharing within and between laboratories is essential for self-improvement and for accurate variant interpretation to ensure that patients receive the most appropriate care based on their genetic results.

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Poster P078

Prevalence of Mutations in a Diverse Cohort of 3407 Subjects Tested Via the Same Multigene Cancer Panel in a Managed Care Health Plan

Mónica Alvarado, Xiaoquing Xu, George E. Tiller, Syed A. Ahmed, Joanie Chung, Reina Haque

Objective Report on the prevalence and distribution of pathogenic or likely pathogenic variants (PV/LPV) by cancer history in an ethnically diverse cohort tested using the same cancer gene panel.
Methods We conducted a cross-sectional analysis of 3407 subjects (>18 years, 3162 women, 245 men) referred for genetic counselling and tested for hereditary cancer using the same multigene cancer panel in a large nonprofit health plan in southern California. We examined the PV/LPV prevalence for all genes by clinical and demographic factors and stratified by sex and personal or family cancer history (or both). We calculated adjusted odds ratios for the association between race/ethnicity and mutation result using logistic regression.
Results Median age at testing was 51 years in women and 54 years in men, with 11.7%/20.4% PV/LPV prevalence. Among women, the most common anatomic cancer sites were breast (75.1%), ovary (8.5%), and colon/rectum (4.3%). In men, the most common cancers were colorectal (41.3%), breast (16.8%), and prostate (13.2%). In women, 5.4% had *BRCA1/2* mutations, and 6.3% had at least 1 mutation in other genes. In men, PV/LPV prevalence was higher for non-*BRCA* genes implicated with breast cancer (6.5%) and Lynch syndrome genes (6.1%) than for *BRCA1/2* (3.3%). Overall, 53.8% of the total mutations (PV/LPV results) in women were in non-*BRCA* genes. The distribution of mutations was similar in women with and without a personal history of cancer. Latina/Hispanic subjects were half as likely as those from other ethnicities to have mutations in non-*BRCA* genes implicated with breast cancer (odds ratio: 0.55; 95% confidence interval: 0.36 to 0.87).
Conclusions Given that more than half the PV/LPV results in women and 85% in men were in genes other than *BRCA1/2*, our results suggest that multigene cancer panel testing is appropriate for detecting germline mutations in a high-risk cohort in a managed care setting.

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Poster P079

Broader Testing Identifies *BRCA* Mutation Carriers Missed by Testing Guidelines

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Screening for *BRCA* mutations was initially proposed for high-risk groups (Gabai-Kapara *et al.*, 2014; Grindedal *et al.*, 2017) and has more recently expanded to a call for universal population screening (King *et al.*, 2014; Hughes 2017; Akbari *et al.*, 2017). One barrier to expanding testing from high-risk groups to universal screening has been cost. However, a recent study demonstrated that there is a price point at which universal screening

becomes cost-effective from a quality-adjusted life year perspective (Long and Ganz, 2015).

Here, we present our experiences with a more accessible genetic testing and delivery model, analyzing a cohort of 23,179 individuals who took a 30-gene panel for hereditary cancer risk. In this cohort, 846 individuals carried a pathogenic or likely pathogenic mutation in *BRCA1* or *BRCA2*, for a *BRCA* mutation carrier rate of 3.6% (846/23,197). Because the test had an affordable cash-pay option, it was taken by individuals who both met and did not meet traditional criteria for genetic testing from the U.S. National Comprehensive Cancer Network (NCCN). Only 33.6% of these *BRCA* carriers reported a personal history of breast or ovarian cancer. In the entire cohort, just under half (48.5%) the individuals would have met NCCN testing criteria, 30.1% would not have met the criteria, and 21.4% did not provide sufficient information to determine eligibility. Importantly, among *BRCA* mutation carriers, 72.8% would have met the criteria, 12.6% would not have met the criteria, and 14.5% did not provide sufficient information to determine eligibility, demonstrating that current testing guidelines can miss *BRCA* mutation carriers. Additionally, 37.2% of *BRCA* carriers in the cohort were less than 40 years of age, and 73.0% of those individuals reported no history of cancer, indicating the importance of screening in younger populations, at an age when more preventive actions can be taken.

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Poster P080

Reconsideration of Risk-Reducing Surgery for *BRCA* VUS Patients

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Background Risk-reducing surgery has come to be performed in Japan for patients with pathologic *BRCA* variants, but interventions for *BRCA* variants of uncertain significance (VUS) have some obstacles to overcome. We report a patient that was confirmed *BRCA1* VUS in a juvenile breast cancer.

Case Description The patient was 30-year-old woman with triple-negative breast cancer (T2N1M0, stage 2b). The patient received preoperative chemotherapy (epirubicin–cyclophosphamide followed by weekly paclitaxel) and surgery (mastectomy and axillary lymph node dissection). The patient wanted genetic testing because of her age at diagnosis and family history of breast cancer in her mother, although other relatives were estranged. Genetic testing revealed a *BRCA1* VUS (Y1853N(5676T>A).

The patient would like to undergo risk-reduction contralateral mastectomy, but obtaining approval from the ethics committee is difficult. Furthermore, risk-reducing surgery for VUS cases is supposed to be considered in the same condition as before genetic testing, which leads to agonize over in such a case that is not pathologic.

Discussion *BRCA*1c.5676 is in BRCT domain (*BRCA1* C-terminal). The influence of this mutation for this domain function has yet to be determined. Although the mutation has not been reported in ClinVar, it has continues in some families with high penetrance. With respect to this family, surveillance as an HBOC family and risk-reducing surgery might be required.

Conclusions It is important to make an effort to reduce VUS by examining cellular functions as well as databases. Establishing systems to determine procedures for surveillance and indications for risk-reducing surgery is now required for VUS cases, considering family history. Furthermore, it is also important to establish the standards for surveillance and indications for risk-reducing surgery for VUS according to individual VUS family.

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Poster P081

The Influence of *BRCA* Variants of Unknown Significance on Cancer Risk Decision-Making

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Objective To compare gynecologic cancer risk management between women with *BRCA* VUS to women with negative genetic testing.

Methods At a single institution, 99 patients whose *BRCA* genetic testing yielded VUS were matched with 99 control patients with definitive negative *BRCA* results. Demographics and risk management decisions were obtained through chart review. The primary outcome was the rate of risk-reducing bilateral salpingo-oophorectomy (RRBSO). Chi-square tests, t-tests, and logistic regression were performed, with significance considered at $p < 0.05$.

Results VUS patients were more likely to be non-Caucasian ($p = 0.000$) and of Ashkenazi Jewish descent ($p = 0.000$). No differences in gynecologic oncology referrals or recommendations to screen or undergo risk-reducing surgery were observed for VUS and for negative patients. Ultimately, 44 patients (22%) underwent RRBSO, with no significant difference in the surgical rate based on the presence of VUS. Ashkenazi Jewish descent was associated with a 4.5 times increased risk of RRBSO (OR: 4.489; 95% CI: 1.484 to 13.579) and family history of ovarian cancer was associated with a 2.6 times increased risk of RRBSO (OR: 2.641; 95% CI: 1.107 to 6.299).

Conclusions In our institution, patients with VUS were surgically managed similarly to those with negative *BRCA* testing. The numbers of patients with VUS are likely to increase with the implementation of multigene panel testing. Our findings underscore the importance of genetic counselling and individualized screening and prevention strategies in the management of genetic testing results.

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Poster P082

A Breast Cancer Case with *BRCA2* Variant of Uncertain Significance Suffering from the Concurrence of Pancreatic Cancer

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BRCA1- and *BRCA2*-associated hereditary breast and ovarian cancer (HBOC) is characterized by an increased risk for breast cancer, ovarian cancer, and to a lesser extent, other cancers such as pancreatic cancer. Medical management for variants of uncertain significance (VUS) is recommended based on the strength of personal and family cancer history. Most VUS are unlikely to be pathogenic, although some have been found to be.

A 49-year-old woman had an operation for left breast cancer followed by adjuvant chemotherapy and hormonal therapy. Her family history of cancer raised suspicions of HBOC. Her older sister was diagnosed with breast cancer at age 47, and her father was diagnosed with prostate cancer in his 80s. She took a genetic test, analysis for germline *BRCA* mutations, which revealed *BRCA2* VUS. At 19 months after her operation, stage IV pancreatic cancer was detected. Although chemotherapy was administered, the disease progressed. She died of her disease 10 months after the diagnosis of pancreatic cancer.

Surveillance for early detection of pancreatic cancer developing in HBOC has not been established. We are planning a clinical trial for early detection of pancreatic cancer in cooperation with the gastroenterology department in our hospital. We will also discuss the reasonableness of risk-reducing surgery for *BRCA* VUS instead of *BRCA* pathologic variants.

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Poster P083

Mutations in Unexpected Genes of Hereditary Cancer Panels: Incidental Findings or a Path for Reviewing Gene-Testing Criteria?

Damien Feret, Aude Lombard, Pascale Hilbert, Karin Dahan

The use of multigene panels in the diagnosis of hereditary cancers has become common in cancer genetics. However, with the use of these panels, we observed the emergence of variants in unexpected genes with respect to the clinical picture.

Between March 2016 and December 2017, we tested 2162 patients for hereditary predisposition to cancer using the Hereditary Cancer Solution panel (Sophia Genetics, Montpellier, France). 65 patients were found to carry a pathogenic variant in a clinically relevant gene that has, *a priori,* no link with the presenting disease (no or insufficient evidence for recommendations). Most of the variants ($n = 33$) were heterozygous mutations in the recessive *MUTYH* gene; 32 pathogenic variants were identified in autosomal dominant genes (*APC* I1307K, 6; *ATM,* 5; *BRIP1,* 4; *CHEK2,* 3; *MLH1,* 1; *MSH2,* 2; *MSH6,* 3; *NBN,* 3; *PALB2,* 1; *PMS2,* 2; *RAD51C,* 2).

Available clinical data and family histories were then analyzed with respect to the identified mutation. We found that 18 patients had at least 1 relative affected by a cancer associated with the mutated gene. However, for those patients, the criteria to undergo specific gene testing were insufficient. We also found 47 patients who had no relatives affected by the gene-related disease.

These variants were reported as incidental findings. Genetic counselling and patient management were done regarding their clinical relevance and the family histories. However, this study suggests that, in some cases, the use of restrictive criteria alone might exclude relevant patients from specific gene testing, particularly in small families or in carriers of moderate-penetrance gene variants. It also questions some established recommendations in genes for which the evidence for specific cancer-site risk is insufficient. For patients with unexpected discoveries, genetic counselling remains complex, especially with respect to the risk assessment for cancer sites not part of the diagnosed cancer syndrome spectrum.

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Poster P084

Assessment of Genetic Variation at Splicing Junctions Using an In-Cell Fluorescence Reporter System

Nikko Torres, Christina Yeh, Leo Wan

Sequencing technologies have facilitated comprehensive cataloguing of disease-associated single nucleotide polymorphisms at intron–exon junctions. However, the bottleneck of determining the effect of those variants on alternative splicing or protein function remains. Minigene assays have proven to be the "gold standard" of measuring splicing efficiency, but they are tedious to implement because of the RNA isolation steps, and they offer only a qualitative assessment of splicing.

To make the assessment of genetic variation at exon–intron junctions quantifiable and easy to implement, we developed a simple fluorescence-based reporter to quantify splicing efficiency in mammalian cells. Splicing efficiency can be measured quantitatively and on a per-cell basis by fluorescence microscopy or through cell sorting. Additionally, our fluorescence reporter affords scalability and flexibility, as well as an intrinsic fluorescence control for reporter plasmid intake efficiency. To demonstrate the clinical and biological relevance of our reporter system, we have performed proof-of-concept experiments with *BRCA1* junctions that involve pathogenic mutations known to disrupt splicing.

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Poster P086

Simultaneous Defect in *BRCA1* and *BRCA2* in a Male Subject with Late-Onset Breast Cancer and Family History of Breast and Lung Cancers

Christopher Ede,* Jeannine Oldzej,* Candice Jackel-Cram,† Kellie Davis,† Samuel Strom*

A male subject, presenting with late-onset breast cancer (64 years of age at Dx), was referred to our laboratory for molecular genetic testing. Significant family history includes a sister with breast cancer (Dx: 82 years) and a maternal aunt with ovarian cancer (Dx: 87 years). Further family history includes at least 7 cases of lung or oral cancers, and other unspecified cancers, all within the maternal family, strongly suggesting a genetic predisposition. Sequencing of 14 hereditary breast cancer–associated genes revealed 2 pathogenic frameshift variants, one in the *BRCA2* gene (c.2808_2811del) and another in the *BRCA1* gene (c.3481_3491del), consistent with a significantly increased risk for both male and female breast cancers. Although statistics about the effect of concomitant *BRCA1* and *BRCA2* mutations are not well established, available evidence suggests an earlier age of onset in individuals with 2 mutations (PubMed ID: 20924075).

Contrary to those findings, the proband, as well as his sister and maternal aunt (genotype not available), were diagnosed at an atypically late age. More interestingly, the family history provided, including several cases of lung and oral cancers, does not match the cancer spectrum commonly associated with *BRCA1/2* defects. However, this individual also harboured a variant of unknown significance in the *CHEK2* gene (c.1420C>T, p.Arg474Cys), which has previously been reported to potentially be causative in an unrelated family presenting with multiple members diagnosed with lung cancer, including 2 individuals with multiple primary lung cancers who were homozygous for the variant (PubMed ID: 27900359).

The atypical clinical presentation within the proband's family, together with the concomitant appearance of two pathogenic variants and a possibly causative *CHEK2* mutant, potentially implies a modifying effect on age of onset, severity, and cancer spectrum resulting from genetic interactions between the observed mutations, and might provide new perspectives for the evaluation of concomitantly occurring mutations in cancer susceptibility genes.

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Poster P087

Mosaic *BRCA1* Pathogenic Variant in a Male with Breast Cancer

Andrea Vaags, Cynthia Forster-Gibson, Kaitlyn Higgins, Andrea Newell, Shamini Selvarajah, Marsha Speevak, Loren Mackay-Loder

Heterozygous germline mutations in the *BRCA1* and *BRCA2* genes are routinely screened in individuals at increased risk of hereditary breast and ovarian cancer (HBOC). Detection of low-level mosaic germline mutations is very rare (Freidman *et al.*, 2015). The adoption of next-generation sequencing (NGS) at high read depth allows for a limit of detection of <20% variant allele frequency (VAF) and, as such, will likely increase the detection of additional mosaic variants in HBOC.

Here, we present a case of low-level mosaic *BRCA1* mutation in a male breast cancer patient. This case was initially detected by manual inspection of Sanger sequencing trace, later confirmed by NGS. The *BRCA1* mutation (c.685delT) was present at 14% VAF in peripheral blood. Testing of additional tissues showed low-level mosaicism in saliva and histologically normal breast tissue. However, the variant was not detected in the buccal or breast tumour tissue.

These results suggest the possibility of tissue-specific constitutional germline mosaicism or acquired somatic mosaicism. From a clinical perspective, this case highlights the unique challenges that mosaic results can present, both in providing genetic counselling and in providing the appropriate cancer screening recommendations to the proband and his family members. Although genetic counsellors face challenges in the transmission of complex genetic information in many scenarios, this case underlines the need for comprehensive pretest genetic counselling and also the difficulty, when providing results, of selecting the pertinent information to relay to the proband and the family.

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Poster P088

Expanded Panel Testing in Patients with Breast Cancer in a Rural Familial Cancer Program

Kara K. Landry, David Hermel, Melissa Cuke, Wendy C. McKinnon, Laura Colello, Marc S. Greenblatt, Marie E. Wood

Objective To assess indicators of pathogenic variants for expanded genetic testing, we examined results from multigene panel testing in patients with a history of breast cancer, DCIS or invasive, from a largely rural patient population.

Methods We conducted a retrospective review of breast cancer patients who underwent panel testing between May 2011 and August 2017. A variety of commercial gene panels were used, with variant classification determined by the individual laboratory. The chi-square test of independence or one-way ANOVA was used to analyze differences in patient demographics for the pathogenic variant–positive, –negative, and VUS patient subsets. The chi-square or Fisher exact test was used to analyzehormone and HER2 status, histology, and differentiation by pathogenic panel test result.

Results We identified 422 patients with breast cancer who underwent panel testing, and 104 (24.5%) of those patients had a reportable finding of either "pathogenic variant–positive" ($n = 38$, 9.0%) or "VUS" ($n = 66$, 15.6%). Median age at the time of genetic testing was 54 years (range: 24–89 years), and median age of first cancer onset was 47 years (range: 6–89 years). Panel test results were significantly associated with median age of first cancer diagnosis ($F_{2,416} = 5.61$, $p = 0.004$); individuals with pathogenic variants tended to be younger at the time of diagnosis. Panel test results were not associated with age at genetic testing, the number of primary cancers (single vs. multiple), or the number of genes tested. Panel test results were associated with breast tumour histology (Fisher exact test $p =< 0.001$), with most patients having invasive ductal carcinoma (73.0%), but were not associated with hormone receptor or HER2 status, or tumour differentiation.

Conclusions Expanded panel testing should be considered in breast cancer patients, because about 9% will have a pathogenic mutation. Tumour characteristics do not seem to be important in identifying who should undergo expanded panel testing.

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Poster P089

Clinicopathologic Features of Patients with *BRCA1* c.5339T>C (p.leu1780pro) Variant Based on Multicentre Data in Korea

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Purpose *BRCA1* c.5339T>C, p.Leu1780Pro mutation (L1780P) has been considered to be a variant of unknown significance. The recent evidence with respect to the function of L1780P suggests that L1780P is pathogenic or likely pathogenic. The aim of the present study is to use retrospective multicentre data to evaluate the clinicopathologic features of patients with L1780P in Korea.

Methods Data of 51 cases from 8 institutions were collected. Their clinicopathologic data and genetic variants of *BRCA1/2* other than L1780P were reviewed and analyzed. Survival curves were assessed according to onset of ovarian and breast cancer.

Results Median age of patients with L1780P was 37.6 years (range: 25–58 years). The proportions of patients with a family history of breast and ovarian cancer were 64.1% and 28.1% respectively. Bilateral breast cancer was shown in 7 of 51 cases. More than one third of germline L1780P tumours (39.7%) were grade 3 and had a high Ki-67 proliferation index. More than two thirds of patients showed estrogen and progesterone

receptor negativity. HER2 overexpression was shown in only 3.9% of all patients with L1780P (2/51). In cases with immunohistology data available, triple-negative breast cancer was the most common subtype (32/50). Risk-reducing oophorectomy was performed in 4 patients. Recurrence was observed in 13 patients with L1780P. The 5- and 10-year recurrence-free survival rates of patients with L1780P were 68.4% and 42.8% respectively.
Conclusions Most breast cancers in patients with L1780P showed aggressive clinicopathologic features, including younger age, poor histologic grade, triple-negative status, and high Ki-67 index. Patients with L1780P showed clinicopathologic features that were similar to those in patients with *BRCA1* pathogenic mutations.

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Poster P090

Qualitative and Quantitative Splicing Analysis by Targeted RNA-Seq for Hereditary Breast/Ovarian Cancer Genetic Diagnosis

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A subset of genetic variants found during genetic screening of patients with hereditary breast and ovarian cancer (HBOC) syndrome have an effect on RNA splicing. A targeted RNA-seq approach was used to analyze the naturally-occurring splicing events for a panel of tumour suppressor genes that are important for genetic screening of individuals with HBOC and hereditary nonpolyposis colorectal cancer (*BRCA1, BRCA2, RAD51C, RAD51D, PTEN, STK11, CDH1, TP53, MLH1, MSH2,* and *MSH6)*. For *BRCA1, BRCA2, RAD51C,* and *RAD51D,* the results were validated by capillary electrophoresis and were compared with a non-targeted RNA-seq approach. We also compared splicing events from our lymphoblastoid cell lines with those from breast and ovarian fimbriae tissues. The potential of targeted RNA-seq to detect pathogenic changes in RNA-splicing was validated by inclusion of samples with previously characterized *BRCA1/2* spliceogenic variants.

The first step was to validate the approach. We detected 94% and 96% of the previously described naturally-occurring splicing events in *BRCA1* and *BRCA2* respectively. Additional splicing events were also detected and further confirmed with PCR-based techniques. For *RAD51C* and *RAD51D,* we detected 44 and 34 alternative splicing events respectively. In most samples, a *RAD51D* isoform lacking exon 3 was more abundant than the full-length transcript or the isoform containing a downstream alternative exon 3. Additionally, the aberrant *BRCA1* and *BRCA2* events caused by variants were also identified, and we could distinguish between complete and partial exon-skipping events. Comprehensive lists of alternative splice events for the other tumour suppressor genes were also obtained.

Our results indicate that targeted RNA-seq provides sufficient sensitivity/specificity to be used in clinical testing. This approach is an improvement of the current RT-PCR–based RNA-splicing screening protocols. In addition, this approach has the potential to identify mutations in deep-intronic regions that affect RNA splicing, but that are missed with current DNA genetic, exon-focused, screening methods

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Poster P091

Pathogenic Mutations Other Than the *BRCA1/2* Founder Mutations in Ashkenazi Jewish Patients Undergoing Genetic Testing

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Background People of Ashkenazi Jewish (AJ) descent have a 2.5% risk of carrying 1 of the 3 *BRCA1/2* founder mutations. Because of this risk, AJ patients often undergo founder mutation evaluation as the first step in genetic assessment, and based on the results, make a decision with their physician about reflex evaluation of the complete *BRCA1/2* genes or a larger panel that includes *BRCA1/2* and other cancer-associated genes. We sought to evaluate the prevalence of pathogenic mutations other than founder *BRCA1/2* mutations in AJ patients.

Methods Genetic results for all AJ patients presenting for counselling and testing at a single institution between Jan 2013 and Dec 2016 were reviewed.
Results 730 AJ patients underwent genetic testing. Of those patients, 53% (390) had a personal cancer history, and 87% (637) had a family cancer history. In 97 patients (13%), a pathogenic mutation was detected; in 40 (6%), a VUS; and in 2 (0.2%), mutation and VUS. In 2 patients, 2 mutations were detected. Among the 101 identified mutations, 80 (79%) were in *BRCA1/2,* and 21 (21%) were in non-*BRCA1/2* genes. Among the 47 *BRCA1* mutations, 1 (2%) was a non-founder mutation, and among the 33 *BRCA2* mutations, 3 (9%) were non-founder mutations.
Conclusions Genetic testing in the AJ patients in our population identified 25 pathogenic mutations (25% of all identified mutations) that would be missed with *BRCA* founder mutation testing alone. That result emphasizes the utility of multigene panel testing in AJ patients and the need to re-evaluate our current practice of genetic testing in this population.

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CLINICAL ISSUES FOR MANAGEMENT

Poster P092

Bridging the Gap: A Priorities Assessment Tool to Support Shared Decision-Making, Maximize Limited Appointment Time, and Increase Patient Satisfaction in Women with *BRCA1/2* Mutations

Melissa Frey,* Annie Ellis,† Savannah Shyne,† Ryan Kahn,* Stephanie Blank‡

Objective Our previous qualitative and quantitative work has shown that women with ovarian cancer identify patient–physician communication as an essential element in determining treatment course and believe that a discussion about goals and values should precede all treatment decisions. We sought to develop a patient-centreed priorities assessment tool (PAT) that could be completed quickly and easily in the waiting room immediately before appointments to streamline communication, enhance treatment discussions, and increase patient satisfaction. This is especially pertinent for women with *BRCA1/2* mutations who demonstrate improved progression-free and overall survival and increased sensitivity to anticancer agents, and who, as a result, often undergo multiple lines of treatment.
Methods We designed a 1-page PAT using the validated ovarian cancer symptom index (NCCN-FACT FOSI-18) combined with an index to assess daily quality of life priorities that could be affected by treatment side effects. The PAT was distributed to women with ovarian cancer in small focus group settings and online.
Results Between September 2015 and May 2016, 36 women completed the PAT. All participants reported that the PAT was easy to understand and comprehensive in scope. Of those participants, 34 (94%) completed the PAT in under 15 minutes, with most (29, 81%) completing it in 5–10 minutes. Most participants (31, 86%) were able to stratify their priorities and identify 5 top treatment-related priorities. Participants who indicated that their goals and priorities had changed since diagnosis (26, 72%) reported that the PAT helped them to identify current goals and priorities (22 of 26, 85%) and that the PAT would help them feel more comfortable participating in shared decision-making with their medical team (21 of 26, 81%).
Conclusions A PAT that combines a current symptom index with daily quality-of-life priorities was easy to complete and viewed as comprehensive and useful in a pilot cohort of women with ovarian cancer. Use of a PAT has the potential to enhance communication, promote shared decision-making, and improve patient satisfaction, especially in women with *BRCA1/2* mutations who have a long disease course and undergo multiple treatment regimens. A pilot of this PAT in gynecologic oncologists' offices, including post-activity assessments from survivors and physicians, is ongoing.

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Poster P093

Seeking Molecular Mechanisms of Diminished Ovarian Reserve in *BRCA1/2* Mutation Carriers

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Several studies have suggested that female *BRCA1* mutation carriers have diminished ovarian reserve (loss of oocytes). This would imply that these women could have a decreased chance of a successful pregnancy (spontaneous or *in vitro* fertilization/preimplantation genetic diagnosis). Decrease in ovarian reserve is a normal phenomenon seen with increasing

age, but is associated with chemotherapy and with mutations in genes such as *FMR1* and *ATM*. Because *BRCA1* and *BRCA2* are both involved in DNA damage repair and spindle checkpoint, we hypothesize that decreased ovarian reserve in *BRCA1/2* carriers is the result of increased DNA damage in oocytes, leading to apoptosis.

Normal paraffin-embedded ovarian tissue from 16 *BRCA1* and 17 *BRCA2* mutation carriers and 11 age-matched (29–45 years) non-carrier controls who underwent preventive surgery was collected in two Dutch centres. γ-H_2AX and cleaved caspase-3 (Asp175) immunohistochemistry analysis to test for DNA damage and apoptosis respectively was performed in triplicate. Our preliminary results show significantly increased DNA damage in follicles from *BRCA2* carriers than in follicles from controls (17.6% vs. 11.2%, $p = 0.023$), but not in follicles from *BRCA1* carriers (15.5% vs. 13.2%, $p = 0.235$). Despite this, apoptosis doesn't seem to be increased ($p = 0.324$). Analysis of replicates is ongoing, but our preliminary results do not seem to support that an increased loss of oocytes is present among *BRCA1/2* carriers. Interestingly, a recent study reported that levels of anti-Müllerian hormone are not significantly different in Dutch *BRCA1/2* carriers than in controls. And yet, *BRCA1/2* carriers required 40% higher doses of follicle-stimulating hormone and had a lower number of mature oocytes collected upon *in vitro* fertilization.

Diminished ovarian reserve and oocyte/embryo quality in *BRCA1/2* carriers are important factors to take into account during counselling because of the effect they could have in the reproductive choices of *BRCA1/2* couples. An extension of our studies will help to clarify whether *BRCA1/2* mutations lead to diminished ovarian reserve and reduced oocyte/embryo quality.

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Poster P094

Comparing Surveillance Strategies Among Women with *BRCA1/2* Mutations at High Risk of Developing Ovarian Cancer

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Objective Current surveillance recommendations for ovarian cancer are limited because tests for cancer antigen 125 (CA125) are poor predictors, and biannual compliance with ultrasound and blood tests is low. The primary objective of this pilot is to test the acceptability of two surveillance strategies for ovarian cancer in women with *BRCA1/2* mutations. Here we present patient recruitment and baseline characteristics.
Methods We recruited participants with *BRCA1/2* mutations from Kaiser Permanente Northern and Southern California, the state's two largest managed care organizations, for a nonrandomized prospective study. Eligible women were offered enrolment in the standard of care (SOC) arm, which included ultrasonography and CA125 testing every 6 months, or the ROCA (risk of ovarian cancer algorithm) arm, which included CA125 testing and human epididymis protein 4 (HE4) testing performed every 4 months. Patients will be enrolled from 4 Aug 2016 to 30 Jun 2018.
Results From among 547 eligible women, we recruited 204 (38%) *BRCA* carriers. Of those carriers, 160 (78%) elected the ROCA arm, and 44 (22%), the SOC arm. The retention rate has been high (75%). Withdrawal has been similar in the two groups (25% ROCA; 23% SOC). Compared with the SOC arm participants, the ROCA-arm participants tended to be younger (13% vs. 23%, 40–49 years), less likely to be Ashkenazi Jewish (17% vs. 23%), and postmenopausal (18% vs. 9%). Most who underwent prior gynecologic surgeries or mastectomy (for breast cancer) elected the ROCA arm. To date, 355 combined HE4 and CA125 tests have been performed in the ROCA arm, and 84 ultrasound and CA125 tests in the SOC arm.
Discussion and Next Steps This pilot study demonstrates that high-risk women are interested in participating in biomarker surveillance, with a ROCA score combining longitudinal CA125 and HE4 tests 3–4 times annually. Our next steps include calculating each participant's longitudinal ROCA scores and determining if the scores affect the surveillance behaviour of the participants.

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Poster P096

A Review of Current Breast Reconstruction Options for Women with *BRCA1* and *BRCA2* Mutations Choosing Risk-Reduction or Prophylactic Mastectomy to Prevent Breast Cancer

John L. Semple, Kelly A. Metcalfe, Ali Candib, Tulin Cil

Introduction Breast reconstruction is an option for women with *BRCA1* or *BRCA2* mutations who elect to undergo risk-reduction or prophylactic mastectomy to prevent breast cancer. Here, we report on advances in reconstruction after mastectomy, specifically examining the differences and outcomes of the available options and the outcomes of immediate reconstruction in an ambulatory setting.
Methods Women with *BRCA1* and *BRCA2* mutations choosing risk-reduction or prophylactic mastectomy to prevent breast cancer who had surgery at Women's College Hospital during the period 2014–2017 in an ambulatory setting were retrospectively reviewed. Current trends and selection preferences in available reconstructive options, including the use of acellular dermal matrix, and outcomes of immediate reconstruction in an ambulatory setting will be discussed. ERAS ("enhanced recovery after surgery") in relation to international protocols will be reviewed.
Results The long-term follow-up time post-mastectomy and reconstruction was 60 months (5 years). For the entire cohort, younger women tended to choose less-invasive procedures without donor-site morbidity such alloplasty (implant and expander). Nipple-sparing and less conspicuous scars were most common in selection. Complication rates were low and reconstruction failure was minimal.
Conclusions Most women elect for breast reconstruction after risk-reduction or prophylactic mastectomy. However, younger women tend to choose less-invasive procedures (implant and expander). Current updated reconstructive options, trends in ambulatory surgery or same-day surgery, and selection preferences will be discussed.

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Poster P097

Comparison of Cancer Risks in Truncating Compared with Missense *CHEK2* Pathogenic Variants

Erin Mundt, Jean Paul De La O, Ryan Bernhisel, Irene Rainville, Susan Manley

Background Estimated *CHEK2*-associated cancer risks are based mainly on studies of the common truncating variant, c.1100del, leaving uncertainty about cancer risks associated with other types of pathogenic variants. Here, we compare personal and family cancer histories of individuals with pathogenic *CHEK2* truncating variants and missense variants.
Methods Patients who had pan-cancer panel genetic testing (Myriad Genetic Laboratories) and were found to carry 1 truncating or missense pathogenic variant in *CHEK2* were included in this analysis ($n = 3368$). Personal and family histories (1st- and 2nd-degree relatives) of breast cancer, colorectal cancer, prostate cancer, gastric cancer, and melanoma were evaluated based on variant type (truncating vs. missense). All clinical information was obtained from the provider-completed test request form.
Results In total, truncating *CHEK2* pathogenic variants were identified in 2650 individuals, and missense *CHEK2* pathogenic variants were identified in 718 individuals. No significant differences were observed in the proportions of patients reporting a personal history of breast cancer (43.8% truncating, 46.4% missense; $p = 0.23$) or colon cancer (2.5% truncating, 1.7% missense; $p = 0.20$). Comparisons of personal histories of other assessed cancers were similar, with no differences between the two variant types. Some differences were observed in reported family history of breast cancer (74.4% truncating, 69.1% missense; $p < 0.01$), gastric cancer (4.9% truncating, 7.2% missense; $p = 0.02$), and prostate cancer (16.5% truncating, 13.0% missense; $p = 0.02$). No significant difference was observed in family history of colorectal cancer (25.6% truncating, 23.4% missense; $p = 0.23$).
Conclusions In this cohort, no significant differences in personal cancer history and only slight differences in reported family history were observed between *CHEK2* pathogenic truncating and missense variants. These data demonstrate that missense and truncating variants in *CHEK2* are associated with similar cancer risks, which can inform management recommendations for individuals with missense pathogenic *CHEK2* variants.

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Poster P098

First Results of the Prospective Multicentre TUBA Study in *BRCA1/2* Mutation Carriers

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Background Risk-reducing salpingo-oophorectomy (RRSO) around the age of 40 is currently recommended to *BRCA1/2* mutation carriers, resulting in premature menopause. Approximately 70% of the epithelial ovarian cancers are high-grade serous ovarian carcinomas (HGSCS). Recent data indicate that the Fallopian tube and not the ovary is the origin of HGSC, and so more research into the role of risk-reducing salpingectomy (RRS) is

necessary. The TUBA study (NCT02321228) investigates quality of life for standard RRSO and for RRS with delayed oophorectomy (RRO).

Methods In a multicentre nonrandomized trial in 13 oncology centres in the Netherlands, premenopausal *BRCA1/2* mutation carriers choose between RRSO at age 35–40 (*BRCA1*) or 40–45 (*BRCA2*) and the innovative strategy (RRS after completion of childbearing and RRO) at age 40–45 (*BRCA1*) or 45–50 (*BRCA2*). This abstract focuses on decisive elements at the patient level.

Results Of the first 200 participants, 95 (47.5%) chose RRO at the recommended age, and 105 (52.5%) chose to delay RRO. Women choosing delayed RRO were more likely to be conjoined in a relationship and to have known their *BRCA* mutation diagnosis for longer. Most important reasons to delay RRO were the opportunity to delay premature menopause, trust in the hypothesis, and a willingness to participate in research for the next generation. Defining factors for choosing RRSO were the known safety of RRSO and fear of ovarian cancer.

Conclusions More understanding of the key factors in the process of decision-making between RRO at the recommended age and delayed RRO can enhance patient satisfaction. We invite more countries to take an initiative such as the TUBA study; pooled data will inform us not only about quality of life for and decision-making by *BRCA1/2* mutation carriers, but also about the safety of salpingectomy with delayed RRO in cancer prevention. We expect to present data from more than 300 *BRCA* mutation carriers at the symposium in Montreal.

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Poster P099

EMBRACA: Quality of Life in Patients with HER2-Negative Advanced Breast Cancer and a Germline *BRCA1/2* Mutation Receiving Talazoparib Compared with Physician's Choice Chemotherapy Treatment

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Background EMBRACA, a randomized 2:1 open-label phase 3 study (NCT01945775), showed a statistically significant improvement in progression-free survival with talazoparib (n = 287) compared with physician's choice chemotherapy [PCT (n=144)] in patients with HER2-negative advanced breast cancer and a germline *BRCA1/2* mutation (HR: 0.54; 95% CI: 0.41 to 0.71; $p < 0.0001$). This study evaluated exploratory quality-of-life (QOL) endpoints.

Methods QOL was assessed at day 1 (baseline), at the start of each treatment cycle (every 3 weeks), and at the end of treatment, using EORTC QLQ-C30 and its breast cancer module, QLQ-BR23. Higher scores indicate better functioning or global health status (GHS)/QOL or worse symptom severity. Pre-specified QOL analyses of both GHS/QOL and breast symptom scales include overall mean change from baseline (per longitudinal repeated measures mixed-effects model) and time to clinically meaningful deterioration (TTD) (per survival analysis methods). Between-arm comparisons of TTD were made using a stratified log-rank test and a Cox proportional hazards model.

Results Baseline scores were similar in the treatment arms. A statistically significant estimated overall mean improvement from baseline in GHS/QOL was seen for talazoparib compared with a statistically significant deterioration for PCT [3.0 (95% CI: 1.2 to 4.8) vs. –5.4 (–8.8 to –2.0); between-arms $p < 0.0001$]. A statistically significant greater delay in TTD in GHS/QOL favouring talazoparib was observed (HR: 0.38; 95% CI: 0.26 to 0.55; median: 24.3 months vs. 6.3 months; $p < 0.0001$). A statistically significant estimated overall mean improvement from baseline in breast symptoms with talazoparib was observed compared with a non-statistically significant improvement with PCT [–5.1 (95% CI: –6.7 to –3.5) vs. –0.1 (–2.9 to 2.6), between arms $p = 0.002$]. A statistically significant delay in TTD in breast symptoms favouring talazoparib was observed (HR: 0.39; 95% CI: 0.20 to 0.78; because of censoring, median times not reached for both arms; $p = 0.005$).

Conclusions Talazoparib resulted in significant overall improvements and delayed TTD in both GHS/QOL and breast symptoms.

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Poster P100

TRACEBACK: Finding *BRCA1* and *BRCA2* Mutations in Women with Ovarian Cancer Diagnosed Prior to Changes to Genetic Testing Guidelines

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Background Women with deleterious germline *BRCA1/2* mutations are at increased lifetime risk of breast and ovarian cancer (OC)[1]. Population-based studies indicate an incidence of pathogenic germline mutations of 14%–17%[2]. Testing provides a cost-effective and efficient mechanism to detect mutations in unaffected relatives for whom effective risk-reducing strategies are available[3].

Australian guidelines were revised in 2013 recommending *BRCA1/2* testing for patients diagnosed with non-mucinous epithelial OC. Historically fewer than 50% of eligible patients were referred for testing[4]. We estimate that, over the last 15 years, more than 11,000 OC patients in Australia were not tested. Many of those patients will since have died of their disease, and their family members could unknowingly be at risk, with no current systematic process for them to be found or tested.

TRACEBACK aims to reduce the number of *BRCA1/2*-related cancers in Australia by identifying undiagnosed germline *BRCA1/2* and other pathway-related pathogenic mutations in OC patients that have been missed, and then returning findings to family members to facilitate cascade testing.

Methods Participants are recruited by 3 methods: cancer cohort studies, self-referral, and clinic-based outreach. Living women are referred to a familial cancer centre (FCC). For deceased women, targeted sequencing is performed on DNA from blood or formalin-fixed paraffin-embedded tissue, assessing 9 genes of interest, including *BRCA1/2*. We are now piloting all aspects in conjunction with patient advocacy groups, researchers with large patient cohort collections, and FCCs.

Conclusions Although conceptually simple, the study is logistically and ethically challenging. TRACEBACK will allow unaffected carriers of germline *BRCA1/2* mutations and additional OC susceptibility genes the opportunity to adopt risk-reducing strategies. The study will establish methodology and experience returning unanticipated genetic information to individuals, which is likely to be relevant to other cancers and inherited disorders.

[1] Kuchenbaecker, 2017.

[2] Alsop, 2012.

[3] Eccleston, 2017.

[4] Cohen, 2016.

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Poster P101

BRCA2 Mosaicism As a Cause of Young-Onset Breast Cancer

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A 29-year-old, previously well, nulliparous woman was diagnosed with a 16 mm invasive ductal breast cancer, estrogen and progesterone receptor–positive and HER2-negative. She underwent wide local excision and sentinel node biopsy, and had egg harvesting and embryo freezing before chemotherapy. She is undecided about bilateral mastectomy or radiotherapy.

Both of her parents are unaffected by cancer, but her father reported 2 sisters being diagnosed with breast cancer in their 60s, one of whom has a granddaughter who was diagnosed with breast cancer at 35.

The patient underwent next-generation sequencing to a depth greater than 200× of *BRCA1*, *BRCA2* (using reference sequence NM_000059.3), *TP53*, *PALB2*, and *PTEN*. A pathogenic mutation of *BRCA2* [c.2152G>T; p.(Glu718*)] was identified at a low level of approximately 16% in 2 independent white blood cell samples and was confirmed by Sanger sequencing, using reference sequence NM_000059.3. The same mutation was identified in approximately 13% of normal breast tissue and 50% of breast tumour cells. As expected, the mutation was not identified in the white blood cells of either parent.

This case represents a rare example of *BRCA2* mosaicism resulting in young-onset breast cancer. With the increasing use of NGS, mosaicism is more frequently being identified. *BRCA1* or *BRCA2* mosaicism poses a number of management and counselling challenges. The risks of contralateral breast cancer and ovarian cancer cannot be accurately quantified without knowing the mutation level in each tissue. Additionally, the risk of an offspring carrying the mutation cannot be quantified, complicating decisions about preimplantation genetic diagnosis.

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Poster P102

Molecular and Genetic Characterization of Contralateral Breast Cancer (CBC) and the Identification of Markers of CBC Risk: Opportunities for Personalized Surgery

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The incidence of contralateral breast cancer (CBC) is 0.4%–0.7% per year after initial diagnosis. Young age at primary tumour diagnosis and family history are known risk factors for CBC development, in common with hereditary breast and ovarian cancer syndromes. Although the CBC incidence is low, requests for contralateral prophylactic mastectomy (CPM) for treatment of unilateral breast cancer are rising, despite the absence of a survival advantage. This study aims to guide CPM decision-making by improving our understanding of CBC risk in individuals.

403 women with CBC in Northern Ireland were identified. Detailed clinicopathologic and survival data were curated on each patient. Archival formalin-fixed paraffin-embedded primary and contralateral tumours were obtained for each patient for targeted sequencing of a panel of genes, including those commonly mutated in breast cancers and all known breast cancer risk predisposition genes. This study had two principal aims:

- To determine the clonal relatedness of primary and contralateral tumours
- To investigate the rate of underlying predisposition gene mutations in this cohort by sequencing germline DNA from normal tissue

This study is ongoing. Preliminary data suggest limited clonal relatedness between primary and contralateral tumours, but have revealed a higher-than-expected rate of both known pathogenic mutations and variants of unknown significance (VUS) in known predisposition genes in the germline of these women. Further sequencing and analysis is currently ongoing.

Our data suggest that a significant proportion of women who develop CBC might do so because of the presence of a predisposing mutation in a known breast cancer risk gene, although the completed sequencing of this cohort will refine these data. Nonetheless, if these findings bear out, our data might suggest that the use of routine panel testing in women requesting CPM could be a strategy to help tailor surgical treatment to the individual.

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Poster P103

Do Women After Risk-Reducing Salpingo-oophorectomy Have Increased Risk of Cardiovascular Disease?

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Objective Premenopausal bilateral oophorectomy increases the risk of cardiovascular disease (CVD); however, hormone replacement therapy (HRT) might attenuate this risk. Our primary aim was to examine CVD risk in women after risk-reducing salpingo-oophorectomy (RRSO) compared with premenopausal women from the general population. Secondarily, we aimed to study the effect of HRT on CVD risk after RRSO.

Methods Participants were 138 women after RRSO and 1352 premenopausal women from the general population (control group), all 52 years of age or younger. Both groups underwent physical examination and blood sampling. The 10-year CVD risk was estimated by the NORRISK 2 score, based on age, systolic blood pressure, cholesterol, daily smoking, antihypertensive medication, high density lipoprotein, and CVD in the family. CVD risks were compared by the independent samples t-test.

Results The CVD risk was significantly higher in the RRSO group than in the control group (1.27% vs. 0.89%, $p = 0.001$), but not after age adjustment ($p = 0.37$). Further, compared with the controls and adjusted for age, the women after RRSO had higher systolic blood pressure (123 vs. 117, $p = 0.036$), total cholesterol (5.49 vs. 5.13, $p = 0.021$), and high-sensitivity C-reactive protein (2.34 vs. 1.82, $p = 0.035$), and lower body mass index (25.0 vs. 25.9, $p = 0.015$) and waist circumference (86.3 vs. 88.4, $p = 0.016$). Within the RRSO group, total cholesterol and waist circumference were significantly lower for the HRT users than for the HRT nonusers, but the NORRISK 2 scores in the HRT users and nonusers were similar.

Conclusions The 10-year CVD risk was similar in the RRSO and control groups. Major CVD risk factors were increased in the RRSO group even though the women were slimmer and had a lower body mass index. We found no effect of HRT on CVD risk. We speculate that a detrimental effect of RRSO on CVD risk is outweighed by a healthy lifestyle.

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Poster P104

Uptake of Pre-implantation Genetic Diagnosis in Female *BRCA1* and *BRCA2* Mutation Carriers

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Background Women with a germline mutation in the breast cancer genes (g*BRCA*) have an increased risk of breast and ovarian cancer. Healthy g*BRCA* carriers of childbearing age can choose to preclude mutation transmission to the next generation with preimplantation genetic diagnosis (PGD). We report on PGD practices in g*BRCA*-positive Israeli women who were offered PGD at no cost.

Methods The sample consisted of healthy g*BRCA* carriers 25–36 years of age seen in the genetics clinic from January through August 2015 who were offered PGD (at no cost) and who agreed to complete 3 questionnaires. Age, education level, occupation, years married, parity, religious affiliation, history of infertility, age at time g*BRCA* testing, prior risk-reducing mastectomy (RRM), receipt of prior information about prenatal genetic testing, decision regret scale (DRS), and satisfaction with decision (SWD) scale were obtained from participants. Univariate and multivariate analyses were performed for predictors of PGD uptake and were tested for multicollinearity. Differences in the outcomes of the DRS and SWD scales were tested using independent t-tests.

Results The final sample ($n = 70$) had a median age of 31.95 years; 84.3% had more than 1 child; and 8.6% had undergone RRM. PGD uptake was 25.7% (18/70) for the entire sample. PGD uptake differed significantly ($p < 0.001$) for the subsets with and without a history of infertility: 70% (7/10) and 18% (11/60) respectively. Prior infertility was the only significant predictor of PGD uptake ($p < 0.001$) on multivariate analyses. Uptake of PGD was not predicted by age or religious affiliation. SWD scores were significantly higher for those who had PGD ($p < 0.04$).

Conclusions Compared with g*BRCA* status, a history of infertility has a greater effect in the decision-making process for PGD in women with a g*BRCA* mutation.

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Poster P105

Impact of g*BRCA* Identification on Subsequent Breast Cancer Stage and Therapy—Implications for Routine Screening

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Background Screening healthy Ashkenazi Jews (AJS) for germline *BRCA1*/*BRCA2* mutations (g*BRCA*) is not standard policy, despite a high carrier rate (2.5%). Most carriers are identified only after breast cancer (BCa) diagnosis. We hypothesized that pre-symptomatic knowledge of carrier status would favourably affect BCa stage and management.

Methods We reviewed records of g*BRCA* carriers who did not undergo risk-reduction mastectomy and who were diagnosed with BCa between April 1996 and April 2016. Patient age, parity, family history, genotype, screening compliance, method of BCa detection, disease characteristics (grade, receptor status, stage), and treatment [breast and axillary surgery, chemotherapy (CTX)] were compared between carriers whose g*BRCA* was identified before and after BCa.

Results 165 women with g*BRCA* and BCa were identified, in whom carrier status was determined pre-BCa in 45 (27%) and post-BCa in 120 (73%); mean age at BCa diagnosis was similar in both groups (50.6 years and 50.5 years; range: 27–86 years), as was the *BRCA1*:*BRCA2* distribution (64%:36% and 65%:35%). Pre-BCa carriers were significantly ($p < 0.001$) more likely to have a suggestive family history (90% vs. 62%), prior BCa screening (78% vs. 60%), and BCa diagnosed by imaging (78% vs. 25%) rather than by clinical symptoms (19% vs. 73%). Pre-BCa carriers had a higher DCIS:invasive BCa presentation (40%:60% vs. 2%:98% in post-BCa) and lower T, N, and combined staging ($p < 0.005$). No differences in tumour grade or estrogen receptor or HER2 status were identified. Compared with post-BCa carriers, pre-BCa carriers were more likely to undergo sentinel lymph node biopsy

(91% vs. 45%), less likely to receive CTX, and more likely to elect bilateral mastectomy (62% vs. 10%, $p < 0.001$ for all comparisons). Overall, pre-BCA g*BRCA* identification and routine screening predicted for early-stage (0–I) BCA diagnosis ($p < 0.001$).

Conclusions Pre-symptomatic identification of g*BRCA* status is significantly associated with BCA screening and earlier-stage BCA diagnosis, requiring less axillary surgery and CTX. These significant health effects support routine g*BRCA* testing in all healthy AJ women.

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Poster P106

BRCA Testing in Ovarian Tumours Initiated by a Pathologist: A Pre-screen for Genetic Testing and Therapy Choice

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Background Germline *BRCA* mutation testing is advised to all ovarian cancer (OC) patients. According to the literature, approximately 20% will have *BRCA* mutations in their tumour DNA, of which about 75% are germline and 25% somatic mutations. Both may benefit from PARP inhibitor therapy. We evaluated the yield of tumour DNA *BRCA* testing initiated by the pathologist in all newly diagnosed OC patients (OPA) as pre-screen for germline DNA *BRCA* testing and therapy choice.

Methods Pathologists were invited to submit formalin-fixed paraffin-embedded samples of all newly diagnosed epithelial OCS. Tumour DNA *BRCA* testing was performed using single-molecule molecular inversion probe–based, targeted, next-generation sequencing and *BRCA1* multiplex ligation-dependent probe amplification. The gynecologist was to communicate outcomes and refer patients with tumour DNA *BRCA* mutations for genetic counselling. Patients experiences were evaluated by semi-structured interviews.

Results From October 2015 to June 2017, OPA was initiated in 312 OC patients. In 9 women (3%), OPA was not feasible. In 303 women with a median age of 66 years at OC diagnosis, OPA revealed 53 tumour DNA *BRCA* mutations (17%). Germline testing was performed in 42 women and revealed 24 *BRCA* mutations (57%). The experiences of the first patients were positive; however, waiting times for germline testing after tumour testing were considered inconvenient.

Conclusions OPA provides a feasible pre-screen for genetic testing and PARP inhibitor therapy shortly after OC diagnosis. If evaluation by patients and physicians is positive, national implementation can be considered.

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Poster P107

Pilot Study of Denosumab in *BRCA1/2* Mutation Carriers Scheduled for Risk-Reducing Salpingo-oophorectomy

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Denosumab is a monoclonal antibody that inhibits RANKL. It is approved for prevention of fractures in patients with osteoporosis or bone metastases. Adverse effects of denosumab include hypocalcemia and osteonecrosis of the jaw. The RANKL signalling pathway has been shown to be involved in *BRCA*-associated mammary tumorigenesis via a progesterone-induced paracrine effect of RANKL on luminal progenitor cells. Preclinical studies have demonstrated that RANKL inhibition results in reduced progression of mammary tumours.

Early findings from an ongoing presurgical study demonstrate that denosumab treatment results in decreased Ki-67 expression in breast tissue. Based on those data, denosumab is being pursued as a potential preventive agent for breast cancer in *BRCA1/2* mutation carriers. Although promising, the effect of RANKL inhibition on gynecologic tissues such as the ovaries and fallopian tubes, in which progesterone has a protective effect, is unknown.

We will conduct a multicentre, open-label randomized pilot of presurgical administration of denosumab compared with no treatment in premenopausal women with *BRCA1/2* mutations undergoing risk-reducing salpingo-oophorectomy. A total of 60 women will be randomized 1:1 to arm 1 (3–4 doses denosumab 120 mg subcutaneously every 4 weeks) or arm 2 (no treatment). Participants will be stratified by mutation status (*BRCA1* or *BRCA2*) and use of hormonal contraceptives within the past 3 months (yes or no). Assuming a 10% unevaluable rate, we expect to have 54 evaluable participants (27 per arm).

Our primary objective is to compare denosumab with no treatment with respect to the effect on Ki-67 expression in the fimbrial end of the fallopian tube. Secondary objectives are to assess Ki-67 in ovary and endometrium; to investigate apoptosis, RANK/RANKL, estrogen/progesterone receptor, CD44, and STAT3 expression in fallopian tube, ovary, and endometrium; to analyze gene expression profiling in the fallopian tube and ovary; to investigate serum markers and drug levels; and to evaluate toxicity.

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Poster P108

Screening Accuracy and Breast Cancer Characteristics in *BRCA* Mutation Carriers in the High-Risk Ontario Breast Screening Program

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Background The Ontario Breast Screening Program (OBSP) expanded in July 2011 to screen women 30–69 years at high risk for breast cancer with annual magnetic resonance imaging (MRI) and digital mammography (DM). This study examined the accuracy of MRI and DM in mutation carriers by *BRCA* status, age, and breast cancer characteristics.

Methods Information was collected for eligible women referred to the high-risk OBSP from July 2011 to June 2015, screened until 30 June 2016, and followed until 31 December 2016 ($n = 9003$). Among *BRCA1/2* mutation carriers, cancer detection rates (CDRs), sensitivity, and specificity were compared stratified for *BRCA* mutation status and age (30–49, 50–69). Prognostic features of cancers by *BRCA* mutation status were also examined.

Results In 1771 *BRCA1/2* mutation carriers (*BRCA1,* 870; *BRCA2,* 901) having 4499 screening episodes, 114 breast cancers were detected (*BRCA1,* 61; *BRCA2,* 53; CDR: 25.3/1000; 95% CI: 20.9 to 30.4). The CDR was nonsignificantly higher in women with *BRCA1* compared with *BRCA2* mutation [CDR: 27.9/1000 (95% CI: 21.4 to 35.6) vs. 23.0/1000 (95% CI: 17.2 to 29.9)], especially among those 50–69 years of age [CDR: 30.2/1000 (95% CI: 20.9 to 42.2) vs. 22.6/1000 (95% CI: 15.3 to 32.1)]. Among the women overall, screening sensitivity and specificity were 90.6% (95% CI: 83.0 to 96.0) and 83.5% (95% CI: 82.2 to 84.8) respectively. Among women 50–69 years of age, sensitivity was nonsignificantly higher by 14% in women with *BRCA1* compared with *BRCA2* mutation [95.8% (95% CI: 78.9 to 99.9) vs. 81.8% (95% CI: 59.7 to 94.8%)], while specificity was significantly higher in women with *BRCA2* mutation [89.5% (95% CI: 87.4 to 91.3) vs. 85.8% (95% CI: 83.2 to 88.2)]. In *BRCA2* compared with *BRCA1* mutation carriers, the risk of ductal carcinoma *in situ* was significantly higher (OR: 3.63; 95% CI: 1.04 to 12.61) and the risk of triple-negative cancers was significantly lower (OR: 0.17; 95% CI: 0.05 to 0.67).

Conclusions Screening with annual MRI combined with DM has been effectively implemented into an organized breast screening program and could be considered an important management option for known *BRCA* gene mutation carriers.

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Poster P109

Preventive Care Patterns in Utah Women with *BRCA* from 1995 to 2017

Lindsay Hunter,* Whitney Espinel,† Lisa Pappas,† Ken Smith,† Wendy Kohlmann,† Sarah Colonna*†

Background Women who have *BRCA1/2* pathogenic variants are advised to obtain intensive screening and/or risk-reducing surgeries to prevent breast and ovarian cancer. Inappropriate use of risk-reduction measures could result in unnecessary morbidity or preventable cancers. This study characterizes preventive care patterns from 1995 to 2017.

Methods Data for 3442 women 18 years of age and older with *BRCA1/2* testing were identified using clinical genetic testing records at the University of Utah Huntsman Cancer Institute. Women were included if they were *BRCA1/2*-positive with at least 1 visit after the genetic test date. Demographics, breast screening tests, risk-reducing surgeries, and hormonal medication data from 1995 to 2017 were gathered using ICD and CPT codes pulled from the Utah Population Database and the University of Utah electronic data warehouse. These variables were described using means, medians, ranges, and proportions.

Results 592 women from 1995 to 2017 who met the inclusion criteria were identified. Most women were non-Hispanic white (72%) and less than 50 years of age at genetic testing (72%). Median follow-up time was 56.4 months. 235 women had at least 1 breast MRI, 60% of whom had annual testing. 310 women had at least 1 mammogram, 42.9% of whom had annual testing. Of those without breast cancer at the time of genetic testing, only 67 individuals (14.9%) underwent risk-reducing mastectomy (RRM). For women without a diagnosis of ovarian cancer, only 71 (12%) underwent risk-reducing bilateral salpingo-oophorectomy (RRBSO).
Conclusions This is a large cohort of women with *BRCA1/2* followed over several decades. For women who had ever had breast imaging, the proportion undergoing yearly breast imaging was high at 60%; however, the number of women who underwent RRM or RRBSO was lower than expected. That observation might be attributable to incomplete data sources, or it could represent a change in women's risk management choices over time. Further analysis is needed to clarify.

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Poster P111

The Incidence of Occult Ovarian Neoplasia and Cancer in *BRCA1/2* Mutation Carriers After Bilateral Prophylactic Salpingo-oophorectomy: A Single-Centre Prospective Study

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Background Because of ineffective ovarian cancer (OC) screening programs, prophylactic bilateral salpingo-oophorectomy (PBSO) is suggested for *BRCA1/2* mutation carriers. The reported incidence of clinically occult neoplasia and OC detected during PBSO varies widely (2%–17%), reflecting differences in study designs.
Objective We aimed to prospectively evaluate the incidence of occult neoplasia in specimens collected during PBSO performed in a single tertiary centre and to determine the effectiveness of this procedure in *BRCA1/2* mutation carriers.
Methods Between January 2010 and October 2016, 564 new germline *BRCA1/2* mutation–positive women were identified, and 71 carriers underwent laparoscopic PBSO. The date and time of operation, the woman's age, complications, histologic reports of adnexa and *BRCA1/2* gene mutation types were reported.
Results Serous tubal intraepithelial carcinoma (STIC) was diagnosed in 7 women (9.85%), and OC, in 4 women [5.6%; 1 advanced (FIGO IIIC) and 3 early (FIGO IA/C)], for a total incidence of 15.5%. Mean age at the time of surgery was 46.5 years. The mean age of women diagnosed with STIC and OC was 45.9 years, the youngest women being 42 and the oldest, 64. Median time to perform PBSO was 43 minutes (range: 25–65 minutes). No surgical complications occurred during the operations. Interestingly, we found a statistically significant enrichment of STIC lesions in the *BRCA1* c.4035delA (an established Baltic founder mutation) carrier group (6 of 7 STIC patients, $p = 0.0105$).
Conclusions The incidence of pathologic findings in *BRCA1/2* mutation carriers after PBSO is sufficiently high, and our prospective data support PBSO as the most effective measure for reducing the risk of OC in *BRCA1/2* mutation carriers. A novel finding of the enrichment of STIC lesions in *BRCA1* c.4035delA carriers might show important biologic differences in OC tumorigenesis between different *BRCA1* mutations, warranting further investigation.

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Poster P112

Fertility and Risk-Reduction Surgery

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Both risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) for the patient with *BRCA* pathologic variants have come to be recommended even in guidelines in Japan in 2017. We have carried out heredity counselling for 224 HBOC high-risks individuals since January 2013, and 102 (46%) have undergone genetic testing, revealing 23 cases (23%) of *BRCA* pathologic variants. Afterward, 5 cases of RRM and 6 of RRSO were carried out by the end of 2017. Furthermore, a genetic counsellor has been consulted about the desire for childbearing and has offered information about fertility preservation before start of breast cancer treatment since 2013.

We now report the distinctive case of a 38-year-old female patient. She noticed induration on the right breast soon after nursing was finished. Needle biopsy revealed triple-negative breast cancer. Family history revealed breast cancer and cervical cancer in the mother, stomach cancer in the maternal grandmother, and prostate cancer in a maternal uncle. Genetic testing revealed a deleterious variant in *BRCA1* [L1086X (3376T>G)].

The patient required neoadjuvant chemotherapy, but she wanted to maintain her fertility. After breast surgery, she still wanted the second child, and so we could not discuss contralateral RRM and RRSO. She has received gynecologic examinations every 6 months. One year after breast surgery, she consulted our gynecology department complaining of the left lower abdominal pain. Because diagnostic imaging showed swelling of the left ovary, she underwent laparotomy, and an intraoperative pathology examination demonstrated bilateral ovarian cancer with lymph node metastases.

In conclusion, specific consideration is required to resolve a dilemma between fertility and risk-reducing surgery in juvenile HBOC patients because of associated cancer development. A consideration of the patient's marriage status and social situation is also required. RRSO/RRM should be carried out based on sufficient informed consent and the patient's wishes with respect to childbearing.

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Poster P113

Impact of Breast Cancer Hereditary High-Risk Medical Home

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Background Women carrying certain germline genetic mutations have markedly elevated risks for cancer. Surgical interventions and surveillance outlined in U.S. National Comprehensive Cancer Network guidelines reduce the risk in such patients; however, guideline adherence is required for optimal outcomes. We analyzed the effect of a central interdisciplinary "Medical Home" on guideline adherence and long-term follow-up.
Methods Patients carrying germline mutations at a single institution (2000–2017) were retrospectively reviewed. Rates of risk-reducing salpingo-oophorectomy (RRSO), risk-reducing mastectomy (RRM), and adherence to recommended breast cancer screening (mammography and MRI) were evaluated for patients with *BRCA* mutations.
Results 313 patients with mutations conferring increased cancer risk were identified and followed for an average of 10.5 years. The average age at genetic testing was 43.7 years. 298 carried mutations in highly penetrant genes, 287 in *BRCA1* and *BRCA2*. 93% (226/242) had RRSO (if >41 years of age), and 43% overall (105/242) had RRSO while less than 41 years of age (61 *BRCA1*, 44 *BRCA2*). Of 210 *BRCA* patients without a previous breast cancer diagnosis, 91 (43.3%) chose RRM at an average age of 43. Younger age at genetic testing correlated with RRM ($p = 0.003$). Of patients who were being followed, 75% (77/103) remained current with mammographic guidelines, and 77.3% (75/97) with MRI guidelines. Overall, 81 patients (28.2%) were diagnosed with breast cancer, 16 after genetic diagnosis (3 stage 0, 12 stage I, and 1 stage III). 29 (10.1%) had an ovarian malignancy, 5 after the genetic diagnosis.
Conclusions Early identification of genetic mutation carriers, coupled with adherence to national guidelines for risk management, improves early cancer detection through surveillance and provides the opportunity for chemoprevention and discussions concerning RRSO and RRM. Creation of a "Medical Home" at our institution has resulted in reasonable adherence to guidelines, but challenges remain.

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Poster P114

Synchronous Breast and Ovarian Cancers in *BRCA* Mutation Carriers: An Emerging Issue

Pooja Murthy,* Leslie Boyd,* Tamar Safra,† Franco Muggia*

Background Although the lifetime risk of both ovarian cancer (OC) and breast cancer (BCa) is a high in *BRCA* mutation carriers (61%–79% BCa risk, and 11%–53% OC risk), synchronous cancers, defined as the diagnosis of both cancers in the same patient within 6 months of each other, are rare, with only a few cases being reported in the literature. In 2008, we reported a case series of 8 *BRCA*-mutated patients who had both BCa and OC, and we highlighted the unusual features and variable management of both synchronous and metachronous cancers. We now focus on synchronous presentations.
Methods 6 patients with *BRCA* germline mutations and synchronous diagnoses of BCa and OC were identified at New York University Langone Medical Center and Tel Aviv Sourasky Medical Center. Their clinical presentations and outcomes to date were analyzed.
Results In 3 of 6 patients, the diagnoses of synchronous BCa and OC were a result of risk-reducing surgeries or initial staging imaging. The BCas were all early-stage disease (I and II); the OCs were high-grade, primarily serous, and advanced even if detected incidentally during the BCa work-up. All 6 patients received chemotherapy with platinum and a taxane initially, a

regimen that doubled as adjuvant or neoadjuvant treatment for BCa. All 6 patients had excellent local and systemic control of BCa, but the eventual progression in their OC or the occurrence of another primary cancer resulted in unfavourable outcomes.
Conclusions Synchronous BCa and OC diagnoses in *BRCA*-mutated women might become more common because of widespread genetic testing, use of staging imaging, and prophylactic surgeries. Platinum- and taxane-based chemotherapy directed at OC, coupled with local and systemic treatments, appears to adequately deal with BCa, but long-term outlook is driven primarily by risk of OC recurrence or unrelated cancers. Dual primaries might provide a further rationale for consolidation with PARP inhibitors.

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Poster P115

Mosaic or Not? Additional Investigations to Explore the Validity of Mosaic Results Identified Using NGS

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Introduction Since February 2016, patients who met eligibility criteria were offered a hereditary cancer panel at London Health Sciences Centre (LHSC). Our targeted deep-sequencing approach has enabled effective detection of mosaicism. Low-level mosaicism creates challenges in management and genetic counselling. Here, we report on our centre's experience with 4 local patients who elected to pursue additional investigations after a positive mosaic result.
Methods A positive mosaic result was identified in 4 local patients. Repeat analysis using a new blood sample, in addition to a skin biopsy or tumour analysis, was performed. Sequence variants were detected either by deep-sequencing approaches, including the LHSC custom targeted hereditary cancer next-generation sequencing (NGS) panel (PMID 27376475, 28818680), or the AmpliSeq Cancer Hotspot Panel [for *TP53* only (Thermo Fisher Scientific, Waltham, MA, U.S.A.).
Results Mutant allele frequencies ranged from 12% to 15% on initial testing. On repeat testing, the levels of mosaicism either decreased or remained unchanged in 3 of the 4 cases. Tumour testing in 1 case failed to confirm the presence of the mosaic mutation identified in peripheral blood. On repeat analysis after chemotherapy, a reduction in the mutation frequency was observed. All 4 cases were 55 years of age or older, with 3 being in their mid-60s to late 70s, suggesting the possibility of age-related clonal hematopoiesis (Jaiwal *et al.*, 2015). Germline mosaicism could not be excluded.
Conclusions This case review is one of the first to report on additional testing after detection of a low-frequency pathogenic germline mosaic result. These findings emphasize the power of custom targeted NGS sequencing to uncover mosaicism as an important, but not yet well understood, molecular mechanism of disease.

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Poster P116

Prospective Results of Breast Cancer Screening in 2049 Norwegian Women with *BRCA* Mutation

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Background The Section of Inherited Cancer at Oslo University Hospital (OUH) has referred *BRCA1/2* mutation carriers not choosing prophylactic mastectomy to annual breast screening with, first, only mammography and then, since 2002, also MRI. In this study, we describe prospective breast cancers (BCas) detected in these women, and therefore avoid the selection bias associated with retrospective studies.
Methods We identified 1385 *BRCA1* carriers and 664 *BRCA2* carriers who had been followed prospectively for 8186 and 3421 years respectively. Information was collected on all BCas detected during follow-up. Cancers detected on the first round were excluded. All first BCas occurring after the first round were included. The study was defined as a quality-of-care study by the Data Protection Officer at OUH.
Results BCa was detected in 164 of 1385 *BRCA1* carriers (11.8%) and 55 of 664 *BRCA2* carriers (8.3%). The annual incidence rate was 2.0% for *BRCA1* and 1.6% for *BRCA2*. For *BRCA1* carriers, mean age of onset was 49.5 (26–90), and 93 cancers (56.7%) occurred before 50 years of age. Of those cancers, 120 (73.2%) were node-negative, 28 (17.1%) were node-positive, and 16 (9.8%) were DCIS. HER2 was analyzed in 103 tumours. Of those tumours, 67 (65.0%) were triple-negative. For *BRCA2* carriers, mean age of onset was 54.1 (30–78), and 21 cancers (38.2%) occurred before 50 years of age. Of those tumours, 33 (60%) were node-negative, 8 (14.5%) were node-positive, and 14 (25.4%) were DCIS. HER2 was analyzed in 30 tumours. Of those tumours, 7 (23.3%) were triple-negative.
Conclusions Most prospective *BRCA1* BCas occurred before the age of 50 years and were triple-negative. However, overall, about 50% of *BRCA1/2* BCas occurred after 50 years of age, and 44% were not triple-negative. DCIS constituted 10% of *BRCA1* BCas and as many as 25% of *BRCA2* BCas. These observations could be of importance when selecting patients for *BRCA* testing.

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Poster P117

Preventive Ovarian Cancer Clinic: A Model for Care of Women at Risk for Hereditary Ovarian Cancer

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Objective Gynecologic care for women with hereditary breast and ovarian cancer syndrome is complex. These women have unique challenges throughout their reproductive lives. The Preventive Ovarian Cancer and Aftercare Clinic (POCC) was established to address those needs through expert and evidence-based care. The aim of this study was to examine the outcomes of our clinic 2 years after its inception.
Methods A retrospective chart review of women with confirmed *BRCA1/2* mutations referred to the POCC at Women's College Hospital, Toronto, was performed. Patient demographics, diagnostic codes, preoperative investigations, and intraoperative and pathology findings were recorded.
Results After referrals from genetic counsellors in Toronto, our clinic expanded in 2017 to 175 new patients visits, 75–85 outpatient procedures [that is, bilateral salpingo-oophorectomy (BSO), bilateral salpingectomy], 20 inpatient procedures (total laparoscopic hysterectomy or medically complex BSO), and 130 aftercare visits. Our cohort included 183 women, of whom 132 (72.1%) underwent risk-reducing salpingectomy (RRS) and 51 (27.9%) deferred or declined surgery. In women who underwent RRS (mean age: 46 years; range: 30–72 years), 115 (87.1%) underwent RRSO, and 17 (12.9%) chose initial risk-reducing bilateral salpingectomy with delayed oophorectomy. Three occult malignancies (2.3%) were detected (2 serous tubal intraepithelial carcinoma, 1 invasive ovarian cancer). Preoperative investigations were normal in all women with abnormal pathology. Visit codes included contraception counselling, liaison with fertility specialists, counselling in risk reduction, risk-reducing surgery, and menopause management.
Conclusions The POCC is providing comprehensive clinical care to women at risk of hereditary ovarian cancer. This unique model encourages comprehensive management and continued research collaboration and advancement. Ongoing goals include collection of patient satisfaction data and integrative care with the breast centre.

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Poster P118

Collection of Fallopian Tube Cytology with a Novel Hysteroscopic Tubal Catheter

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Objective To demonstrate the ability of a hysteroscopic tubal catheter to collect samples from the fallopian tube for identification of cytologic abnormalities and correlation with histopathology.
Methods Study subjects were recruited prospectively to an institutional review board–approved trial in 3 gynecologic oncology centres of women undergoing salpingo-oophorectomy. Eligibility criteria included women undergoing risk-reducing surgery for *BRCA* mutations or for pelvic masses suspicious for malignancy. A novel hysteroscopic catheter (nVision Medical, San Bruno, CA, U.S.A.) was used to collect cells from the fallopian tube. Cytology from the collection was compared with pathology findings.
Results 50 patients were enrolled, of whom 8 were *BRCA* mutation carriers undergoing surgery for risk reduction; the other 42 had a pelvic mass. In 42 evaluable cases, hysteroscopy was performed in 40 women with 78 fallopian tubes, of which 63 ostia were identified, with 58 catheterizations. There were 44 adequate samples (44/58, 76%), with 34 being benign; 5, reactive atypical; and 5, neoplastic. There were 11 cases of ovarian cancer. In 9 of those cases, cell collection was attempted, with adequate specimens collected in 7 cases on the side of the carcinoma. When a specimen was successfully collected and the tube was involved with carcinoma on histology, cytology was positive in all 3 tubes. In 2 stage I ovarian cancers, tubal cytology was positive on the side of the cancer. There were 3 ovarian cancers with negative tubal cytology and tubal histology: stage I cystic teratoma containing invasive squamous carcinoma, stage IC endometrioid ovarian cancer, and stage II high-grade serous ovarian cancer. The 32 benign and 5 reactive atypical cytology results corresponded with the histology.

Conclusions Malignancy can be identified in the hysteroscopic collection of cytology from the fallopian tube in cases of ovarian cancer. This device could be used for high-risk surveillance in the outpatient setting.

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Poster P119

The Incidence of Peritoneal Cancer After Oophorectomy and Among *BRCA1* and *BRCA2* Mutation Carriers

Steven A. Narod,*† Joanne Kotsopoulos,*† Ping Sun,* Jan Lubinski‡

We followed 5475 *BRCA1* and *BRCA2* carriers from date of oophorectomy to June 2017 to estimate the 20-year cumulative incidence of primary peritoneal cancer. After a mean of 7.8 years of follow-up, 40 incident peritoneal cancers were diagnosed in the cohort. The annual risk was 0.13% for *BRCA1* carriers and 0.06% for *BRCA2* carriers. The annual risk of peritoneal cancer was constant throughout the 20-year follow-up period. The risk of peritoneal cancer varied substantially by current age: among *BRCA1* carriers, the annual risk of peritoneal cancer was higher for women between 45 and 60 years of age (0.16% per year) than for women between 35 and 44 years of age (0.06% per year). The actuarial risk of peritoneal cancer to age 60 was 2.1% for those who underwent their oophorectomy before or at age 45 and 1.9% for those who had the operation after age 45. The 10-year cumulative risk of peritoneal cancer in *BRCA1* carriers was 1.4% for women who had the oophorectomy before 2000 and 1.4% for women who had the oophorectomy after 2000.

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Poster P120

Is Prophylactic Breast Surgery Essential in *BRCA* Mutation Carriers After Diagnosis of Ovarian Cancer?

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Background Prophylactic salpingo-oophorectomy significantly reduces ovarian cancer risk in *BRCA* mutation carriers diagnosed with breast cancer. Conversely, after a diagnosis of ovarian cancer, patients can be followed annually with MRI or can undergo prophylactic breast surgery (PBS) to mitigate potential breast cancer risk.
Objective To define actuarial risks of breast cancer and overall mortality in a multi-ethnic cohort of *BRCA1* and *BRCA2* mutation carriers after a diagnosis of ovarian cancer.
Methods *BRCA* mutation carriers were diagnosed with ovarian cancer from 2000 to 2017 at New York University (n = 140) and the Tel Aviv Sourasky Medical Center (n = 124). Clinical data about PBS, diagnosis of subsequent breast cancers, and type of deleterious *BRCA* mutation (1 or 2) were analyzed.
Results During this period, 6 women underwent PBS. The cumulative risk of breast cancer after OC in *BRCA* carriers was lower than projected. Of the 124 Israeli *BRCA*-carrier OC patients with annual MRI (automatically reimbursed for *BRCA* carriers in Israel), none went through PBS and only 3 (2.4%) developed sequential breast cancer. Issues to be studied further include risk according to the specific *BRCA* mutation, instances of synchronous presentations, pre-existing breast pathology, and the emerging role of PARP inhibitors.
Conclusions We presume that the observed lower-than-expected rates of breast cancer are partially attributable to mortality from ovarian cancer, which occurs before the affected patients develop any breast cancer. Our data are consistent with 4 prior series of *BRCA* mutation carriers diagnosed with ovarian cancer[1–4]; PBS or MRI breast surveillance are unlikely to affect outcomes until ovarian cancer survivors have been disease-free for 10 years.

[1] McGee *et al., Gynecol Oncol* 2017;145:346–51.

[2] Gangi *et al., JAMA Surg* 2014;149:1306–13. [Erratum in: *JAMA Surg* 2015;150:183]

[3] Vencken *et al., Cancer* 2013;119:955–62

[4] Domchek *et al,. Cancer* 2013;119:1344–8.

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Poster P121

Mortality After Ovarian Cancer by Method of Detection Among Women with a *BRCA* Mutation

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Women with a *BRCA* mutation have a 20%–40% lifetime risk of developing ovarian cancer. Most *BRCA*-associated ovarian cancers are of an aggressive subtype and are diagnosed at a late stage, resulting in a poor prognosis. We sought to determine ovarian cancer–specific survival rates by method of detection in *BRCA* mutation carriers enrolled in a longitudinal study and diagnosed with incident ovarian cancer.

Women diagnosed with an incident ovarian cancer (or fallopian tube cancer) were categorized into 3 subgroups defined by method of detection: screen-detected (cancer antigen 125 test, ultrasonography), clinically detected (physician, self-report), and occult (at the time of preventive oophorectomy). A cohort of 195 incident ovarian cancer cases was followed for an average of 4.7 years from their date of diagnosis until death or end of follow-up. Kaplan–Meier survival estimates were generated to estimate 10-year ovarian cancer–specific survival by method of detection. Survival was 18% among women with clinically detected cancers, 40% among those with screen-detected cancers, and 76% among those with occult cancers. A statistically significant difference across subgroups was observed (log-rank $p < 0.0001$). Better survival for women with screen-detected cancers might merit the implementation of ovarian cancer screening programs in high-risk women. Improved survival for woment with occult cancers suggests the need for detection of ovarian cancer in the earliest stages.

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EDUCATION

Poster P122

Reducing Disparities in Referral to Breast Cancer Genetic Counselling: Development and Evaluation of a Blended Learning Program for Health Care Professionals

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Patients with less education or a non-Western migrant background have poorer access to (breast) cancer genetic counselling. Because of limited health literacy or language barriers, referral is not always adequately discussed with these vulnerable groups of patients. Erfo4all is a multicentre project designed to address the problem of disparity in referral to breast cancer genetic counselling.

In co-creation with health care professionals and patients, a blended learning program was developed for surgeons and specialized nurses involved in the referral process. Awareness, knowledge, attitude, and (perceived) skills to communicate with patients having a low education background, low health literacy skills, or migrant status will be assessed before (T0) and 6 months after the training. Effectiveness on referral will be assessed prospectively by clinical geneticists and genetic counsellors for all new counselees referred for breast cancer genetic counselling in 4 academic centres. The relative number of referred patients with a low education background and migrant status will be compared in a one-group pre-test/post-test design, taking into account differences between trained and untrained hospitals. We expect to include more than 2500 completed checklists (900 before the training and 1600 after the training). Baseline data from the 4 academic centres will be presented at the conference, as will preliminary data from the T0 questionnaire completed by participants attending the first-trained hospitals (n = 30).

First results at T0 indicate that professionals had poor knowledge about (recognizing) low health literacy and had lower perceived skills to communicate effectively with vulnerable groups of patients. Although they recognized the importance of considering the background and literacy skills of patients, it seems that they experienced problems in adapting their communication to the needs of patients.

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Poster P123

The High-Risk Ontario Breast Screening Program: Organized Screening of *BRCA* Mutation Carriers

Lauren Chun,* Ayesha Salleh,* Chamila Adhihetty,* Derek Muradali,* Joan Glazier,* Anna Chiarelli*†

Established in 2011, the High-Risk Ontario Breast Screening Program (OBSP) is an organized breast screening program for women 30 to 69

years of age identified as "high risk," including known carriers of a deleterious gene mutation (for example, *BRCA1*, *BRCA2*). Gene mutation carriers can be eligible for screening in the program through one of two pathways, depending on whether they are known or suspected carriers. Known mutation carriers referred into the High-Risk OBSP are considered immediately eligible to begin high-risk screening. Suspected mutation carriers (based on personal or family history) referred into the High-Risk OBSP are required to undergo genetic assessment. Genetic testing might be performed as part of genetic assessment, and women found to be *BRCA1/2* mutation carriers are eligible for high-risk screening. In the High-Risk OBSP, women are screened with annual mammography and breast magnetic resonance imaging (MRI)—or, if MRI is not medically appropriate, screening breast ultrasonography.

The objectives of this poster are to describe the High-Risk OBSP and clinical pathway, and the experience of the High-Risk OBSP in identifying and screening *BRCA1/2* mutation carriers. Since its inception, the High-Risk OBSP has evolved in response to operational and clinical needs. The program is continually monitored and adopts best practices to provide optimal breast screening services to high-risk women.

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Poster P124

Salpingectomy for Ovarian Cancer Prevention at the Time of Cesarean Delivery: Comparison of Outcomes of Surgical Technique

Nancy Nguyen,* Amy Alabaster,† Sarah Simmons,‡ Bethan Powell‡

Objective To evaluate the surgical outcomes of prophylactic salpingectomy during sterilization at time of cesarean delivery by surgical technique (bipolar electrocautery vs. suture ligation).

Methods This retrospective cohort study uses electronic medical records at Kaiser Permanente Northern California of women 18 years of age and older undergoing sterilization by salpingectomy at the time of cesarean delivery. The study includes all eligible women from 2011 to 2016 at time of elective surgical sterilization. The primary objective is to compare surgical outcomes by electrosurgical bipolar (LigaSure: Medtronic, Minneapolis, MN, U.S.A.) or suture ligation, including estimated blood loss, major or minor intraoperative complications, blood transfusions, operative time, length of hospital stay, and postoperative readmission and emergency department visits.

Results There were 190 patients with salpingectomies for sterilization at time of cesarean delivery identified. There were 96 salpingectomies by bipolar electrocautery device and 94 by suture ligation. The primary indication for a caesarean procedure was repeat cesarean delivery. In Cesarean deliveries with salpingectomies estimated blood loss was lower in procedures performed by bipolar electrocautery than by suture ligation (average: 600 mL vs. 762 mL, $p = 0.03$). Surgery time and operating room time were longer for suture ligation than for electrocautery (66 vs. 60 minutes, $p = 0.03$, and 104 vs. 100 minutes, $p = 0.04$, respectively) During cesarean delivery with salpingectomy, 2 major and 8 minor intraoperative complications occurred, but only 2 minor complications were specifically related to salpingectomy. There was 1 postoperative blood transfusion. No emergency room visits occurred within 7 days of discharge in either group, and no difference in the readmission rate was observed. The postoperative length of stay did not differ.

Conclusions Salpingectomy instead of tubal ligation at the time of cesarean delivery for sterilization is faster and associated with less blood loss when performed with a bipolar device than with suture ligation. However, there are no differences in postoperative care complication rates. The balance of the cost of the instrument and the time saved could vary in different health care systems.

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ETHICS AND LEGAL ISSUES

Poster P125

Ensuring Equity of Access to *BRCA* Testing

Alison Trainer,*† Helen Widdowson,‡ Helen Farrugia‡

Because *BRCA* mutations affect both cancer treatment and familial risk assessments, equitable access to testing is of increasing social importance. The association between *BRCA* mutations and the development of triple-negative (TN) breast cancer diagnosed at the age of less than 50 years, or high-grade serous ovarian (HGSO) cancer diagnosed at the age of less than 70 years defines a cohort of women who warrant *BRCA* testing based on tumour-pathology alone. Comparing the characteristics of women referred and not referred to familial cancer clinics (FCCS) can identify and quantify drivers underlying inequitable access to testing at a population level.

We performed a retrospective data cross-match of all women with *BRCA*-related cancers (defined by ICD-O and ICD-10 codes and immunohistochemistry) reported to the Victorian cancer registry from 1 Jan 2008 to 31 Dec 2014, with the subset of women referred to the Victorian FCCS. All Victorian women with an incident TN breast cancer or HGSO cancer were categorized as either "referred" or "not referred." Individual-level parameters relating to year and age of diagnosis, survival, socioeconomic indexes, geographic location, and region of birth were available.

Logistic regression analysis was undertaken using "not referred" as the outcome variable. The results indicate that, compared with 2008 (55%), TN breast cancer referrals significantly increased from 2011 to 2014 (80%); HGSO cancer referrals remained constant at 65%. Evidence of an inequitable referral process was demonstrated, because the multivariate analysis demonstrated that increased age at diagnosis, tumour grade, decreased length of survival, and increased socioeconomic disadvantage were significantly associated with decreased referral of HGSO cancers, and that increased age at diagnosis, increased grade, survival, and non-native English speaker status were associated with decreased referral for TN breast cancers.

Those findings have led to development of the EMBED study. EMBED circumvents current barriers to FCC referral by integrating the cancer registry directly into the FCC referral process. The logistic regression results and the description of EMBED will both be discussed in more detail.

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Poster P126

Counselling in the Population Genomics Context: Participant Experiences in the WISDOM Breast Cancer Screening Trial

Jennifer James, Barbara A. Koenig, Leslie Riddle, Galen Joseph

Population-based genomic screening is at the forefront of a new approach to disease prevention and raises many ELSIS (ethical, legal, and social issues). Our "embedded" ELSI study of the WISDOM trial, an innovative randomized controlled trial comparing annual mammography with risk-stratified breast cancer screening based on genetic testing (9 genes plus a polygenic risk score), uses mixed methods to assess the effect of genomic screening on a healthy population of women. In this presentation, we offer insight into several key ethical and social questions concerning population-based genetic testing for breast cancer–associated gene mutations.

First, we describe the return of results procedure in the WISDOM trial, which is preceded by an online consent process without traditional pre-test counselling. Women categorized at high or moderate breast cancer risk, including but not limited to those with a gene mutation, receive a "breast health specialist" (BHS) consultation by telephone. That session, conducted by a nurse or a genetic counsellor, involves disclosure of the genetic mutation, basic information about the mutation, and recommendations for follow-up care—often including referral to formal genetic counselling. Second, we describe the process of giving and receiving positive genetic testing results in this population screening context based on audio-recordings of sessions with BHSS. Third, we present results of qualitative interviews with women conducted after the BHS consultation, focusing specifically on issues such as how women without a personal or family history of breast cancer and who might not even remember the possibility of receiving such a result (because of the remote consent process) make sense of the news that they have a mutation and/or are at high risk.

Our examination of the implementation of the WISDOM trial will provide practical ethical and policy guidance on the translation of genomic findings into precision medicine and population health.

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Poster P127

Guidelines for Reporting Secondary Findings of Genome Sequencing in Cancer Predisposition Genes: French Society of Predictive and Personalized Medicine Recommendations

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The use of multigene panel analysis to explore familial cancer syndromes or to identify somatic mutations in tumours has led to increased discovery of inherited variants that are not directly related to the initial yield of the search. The American College of Medical Genetics and Genomics published a clear policy statement about secondary findings management for a list of genes, including 23 cancer-related genes. Europe currently has

no equivalent recommendations. The French Society of Predictive and Personalized Medicine undertook an in-depth multidisciplinary reflection on the restitution of secondary findings to the patient.

We present guidelines concerning the management of secondary findings in cancer-predisposing genes in adults. From June 2016 to May 2017, 47 experts were divided into two working subgroups: one dedicated to medical expertise (consisting of oncologists, clinical geneticists, and molecular geneticists), and the other specialized in ethical and legal expertise (psychologists, ethicists, lawyers, and representatives of patient associations). 61 genes were evaluated by a mean of 3 different experts (228 evaluation forms collected). The main criteria for the recommendations were their "actionability" (access to validate screening or prevention strategies), risk evaluation (severity, penetrance, and age of disease onset), and the level of evidence from published data. Genes were divided into 3 subgroups according to the score.

Of 28 genes in class 1 (for which return of the result is recommended), the breast cancer predisposition genes *BRCA1, BRCA2, TP53, STK11, PTEN, CDH1,* and *PALB2* were retained. Classes 2 and 3 included the genes *BAP1, ATM, CHEK2, RAD51C, RAD51D,* and *BRIP1, BARD1,* and *NBN* respectively. The ethics group provides information recommendations and information materials in various forms (written consent and video). These first European recommendations for secondary findings could help clinician to standardize and guide practices for genetic predispositions to cancer.

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

Poster P129

Distinct Molecular Pathways Expression Profiles After Neoadjuvant Chemotherapy Associated with Survival in Patients with High-Grade Serous Ovarian Cancer

David Octeau,*†‡ Roy Kessous,*† Liron Kogan,*† Ido Laskov,*† Kathleen Klein,†§ Manuela Pelmus,‖ Shannon Salvador,* Susie Lau,* Patricia Tonin,§ Walter Gotlieb,*† Amber Yasmeen*†

Background Tumour biomarkers, such as germline and somatic mutations in *BRCA1* and *BRCA2,* and aberrant expression profiles have been linked to improved response in patients with high-grade serous ovarian cancers (HGSCs) undergoing primary debulking surgery. Recently, the use of neoadjuvant chemotherapy (NACT) has become more widespread. Although large-scale genomic studies have detailed the molecular landscape of tumours from patients who underwent primary debulking surgery and correlated the identified subgroups with survival, none have done the same for patients who received NACT.
Objective Describe the underlying genomics of NACT-treated HGSC and correlate them with patient progression-free survival (PFS) and overall survival (OS).
Methods Tumour samples were collected from patients with HGSC after neoadjuvant chemotherapy (NACT cohort, n = 39). Tumour content was validated by histologic examination and by biostatistical analysis. Gene expression analysis was performed using a tailored NanoString-based assay, and next-generation sequencing was performed on the MiSeq platform. Unsupervised pathway-based clustering and the appropriate survival models were used to assess the associations between genetic alterations and survival.
Results Mutations in *BRCA1* and *BRCA2* (n = 6 and n = 7 of 39 respectively) did not correlate with better OS (log rank p = 0.24). Unsupervised pathway-based clustering of the gene-expression data revealed a better outcome in patients characterized by lower expression of DNA damage and cell-cycle genes (PFS p = 0.02; OS p < 0.05).
Conclusions A partial genomic profiling of the intratumoural molecular pathway signatures observed after NACT revealed prognostic significance that was different from that for chemonaïve tumours.

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Poster P130

lncRNA HOTAIRM1 Might Be a Novel Tumour Suppressor in the Basal-Like Subtype of Breast Cancer

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Breast cancer is a heterogeneous disease that can be classified in 4 subgroups using transcriptional profiling. The role of long non-coding RNA (lncRNA) expression in human breast cancer biology, prognosis, and molecular classification remains unknown. Using an integrative comprehensive analysis of lncRNA, mRNA, and DNA methylation in 900 breast cancer patients from the Cancer Genome Atlas project, we unraveled the molecular portraits of 1700 expressed lncRNA. Some of those lncRNA (for example, HOTAIR) are previously reported; others are novel (that is, HOTAIRM1, MAPT-AS1).

The lncRNA classification correlated well with the PAM50 classification for the basal-like, HER2-enriched, and luminal B subgroups; in contrast, the luminal A subgroup behaved differently. Importantly, estrogen receptor expression was associated with distinct lncRNA networks in lncRNA clusters III and IV. Gene-set enrichment analysis for *cis*- and *trans*-acting lncRNA showed enrichment for breast cancer signatures driven by breast cancer master regulators. Almost two thirds of those lncRNA were marked by enhancer chromatin modifications (that is, H3K27ac), suggesting that lncRNA expression might result in increased activity in neighbouring genes. Differential analysis of gene expression profiling data showed that lncRNA HOTAIRM1 was significantly downregulated in the basal-like subtype, and DNA methylation profiling data showed that lncRNA HOTAIRM1 was highly methylated in the basal-like subtype. Thus, our integrative analysis of gene expression and DNA methylation strongly suggested that lncRNA HOTAIRM1 should be a tumour suppressor in the basal-like subtype.

Our study provides the first lncRNA molecular portrait of breast cancer and shows that lncRNA HOTAIRM1 might be a novel tumour suppressor.

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Poster P131

Association Between *BRCA* Mutations and Survival in the Epithelial Ovarian Cancer COEUR Cohort

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Background The Canadian Ovarian Experimental Unified Resource (COEUR) is a Canadian repository of epithelial ovarian cancer that provides researchers with biologic material and associated clinical data to conduct biomarker validation studies. Here, we describe the presence and prognostic value of germline *BRCA* mutations in the COEUR cohort.
Methods With participation from 12 Canadian biobanks in Canada, we created a central retrospective cohort comprising more than 2000 patient tissue samples with associated clinical data. Cases tested at collection sites for germline *BRCA* mutation included 488 high-grade serous (HGSC), 35 low-grade serous, 44 endometrioid, 25 clear cell, and 6 mucinous carcinoma histotypes. A 2-step reclassification process, blinded of genomic *BRCA* sequencing, was applied to ensure contemporary histologic classification. We used Kaplan–Meier, Cox proportional hazards, and logistic regression analyses to evaluate the association between the *BRCA* mutation and disease-specific survival in HGSC platinum-treated patients only.
Results After histotype reclassification, *BRCA* mutations (n = 112) were observed only in serous cases. Compared with HGSC noncarriers patients, patients with HGSC harbouring a *BRCA* mutation (n = 108) were younger (53 years vs. 60 years) and presented more often with advanced-stage disease (n = 370). When restricting the analysis to advanced-stage disease, the *BRCA* mutation carriers (n = 45 *BRCA1,* n = 26 *BRCA2*) demonstrated increased survival (HR: 0.57; 95% CI: 0.41 to 0.80; p < 0.001). There was no statistical evidence of improved outcome in women with early-stage HGSC (p = 0.82, n = 28). Compared with their *BRCA1* counterparts, patients with *BRCA2* mutations had a slightly better prognosis (*BRCA2* HR: 0.41; 95% CI: 0.22 to 0.76; *BRCA1* HR: 0.65; 95% CI: 0.44 to 0.95) We also observed increased long-term survival (>10 years) in *BRCA* mutation carriers (21% vs. 11%; OR: 0.432; 95% CI: 0.21 to 0.90; p = 0.024).
Conclusions Our results suggest that, in ovarian cancer, germline *BRCA* mutations are largely restricted to HGSC. In the setting of platinum-based standard treatment, *BRCA* mutations (particularly *BRCA2* mutations) are associated with increased long-term survival.

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Poster P132

Sequential Therapeutic Targeting of Ovarian Cancer Harbouring Dysfunctional *BRCA1*

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Background *BRCA1* is mutated or epigenetically silenced in up to 23% of high-grade serous ovarian cancers (HGSCS). PARP inhibitors (PARPi) are the first approved personalized treatments for *BRCA1*-mutated patients and have shown promising clinical results. Recently, in collaboration with Dr. Witcher's lab, we described a significant reduction in PARP1 protein levels in patients after standard carboplatin–paclitaxel chemotherapy. PARPi are currently administered after standard chemotherapy, when PARP levels are the lowest. Changing the sequence of administration—giving PARPi first, followed by standard chemotherapy—might improve response rates. This study aims to evaluate that strategy in *in vitro* preclinical models.
Methods *BRCA1*-mutated (UWB1.287, SNU-251), epigenetically silenced (OVCAR8), and wild-type *BRCA1* (OVCAR3, SKOV3, A2780P, and A2780R) cell lines were exposed either to clinically relevant doses of PARPi followed by standard chemotherapy, or to the inverse sequence of agents. Therapeutic efficacy was assessed by colony-formation assay, cell-cycle analysis, and apoptotic assays using flow cytometry. Western blotting was used to detect the levels of relevant apoptotic and cell-cycle proteins.
Results Exposure to PARPi before standard chemotherapy sensitized *BRCA1*-mutated or epigenetically silenced *BRCA1* cell lines to lower doses of cisplatin or paclitaxel. Similarly, pre-treatment with PARPi before chemotherapy induced apoptosis more effectively in the same cell lines. Similar results were observed in *BRCA1* wild-type cell lines and cell lines in which *BRCA1* functionality was restored.
Conclusions Pre-treatment of cell lines with PARPi, followed by standard chemotherapy, is more efficient (*in vitro*) in inhibiting growth and inducing apoptosis than is the present sequence of chemotherapy followed by PARPi.

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Poster P133

One in Three Greek Patients with Early-Onset or Strong Family History of Breast Cancer Carries a Loss-of-Function Cancer-Predisposing Allele

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Introduction The evolution of DNA sequencing has revolutionized the clinical approach to genetic testing. Multiple genes can now be analyzed simultaneously at relatively low cost, providing important information for patient management. Although *BRCA1* and *BRCA2* mutations dominate the spectrum among breast cancer patients, additional genes are associated with susceptibility. We therefore sought to investigate the contribution of predisposing alleles in a highly selected cohort of Greek breast cancer patients.
Methods To identify loss-of-function (LOF) mutations, the sequences of 94 cancer genes were targeted by implementing the Trusight cancer panel (Illumina, San Diego, CA, U.S.A.) in 1382 breast cancer patients of Greek descent with diagnosis at very young age (<35 years) and/or a strong family history (at least 3 breast, ovarian, or pancreatic cancer cases).
Results Approximately one third of the patients tested (437/1382, 31.6%) carried at least 1 LOF mutation in 26 different genes, namely: *BRCA1*, *BRCA2*, *ATM*, *BLM*, *BRIP1*, *CDKN2A*, *CHEK2*, *DICER1*, *ERCC3*, *FANCC*, *FANCI*, *FANCL*, *FANCM*, *MLH1*, *MSH6*, *NBN*, *NF1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *PMS2*, *SLX4*, *TP53*, *SDHB*, and *SDHC*. Of those patients, 6.7% (93/1382) carried LOF alleles in genes involved in DNA repair (other than *BRCA1* and *BRCA2* genes), with mutations in *CHEK2*, *ATM*, and *PALB2* genes being the most frequent (4.5%). Of note are the remaining 2.2% of LOF alleles, which to date have unclear associations with breast cancer susceptibility, which can be regarded as incidental findings, cannot be excluded as having putative causality for breast or ovarian cancer.
Conclusions In a high-risk group of breast cancer patients of Greek descent, where there are strong founder effects, the mutational spectrum is heterogeneous with respect to both loci and alleles. This approach can shed light on associations with mutations in the post-*BRCA* genes and will provide connections of phenotypes with mutations in additional DNA repair genes.

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Poster P134

Implementation of Universal *BRCA* Screening for Germline and Somatic Variants in Patients with Epithelial Ovarian Cancer

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Introduction With introduction of PARP inhibitors as therapy for *BRCA*-positive high-grade serous ovarian cancer (HGSOC), *BRCA* screening has become part of standard diagnostics for HGSOC patients. Approximately 10% of HGSOC patients are expected to carry a germline pathogenic variant. The frequency of somatic variants is poorly described. Various mutation screening strategies have been used: either screening restricted to germline variants, screening of tumour tissue for somatic variants with subsequent germline screening of patients with a *BRCA*-positive tumour, or parallel screening of both types.
Methods In the North Denmark region, treatment of ovarian cancer is centralized at Aalborg University Hospital. Since March 2016, all newly diagnosed patients with HGSOC and other epithelial ovarian cancers have been offered *BRCA* screening for both germline and somatic variants. Parallel screening for germline and somatic variants is requested after multidisciplinary conference and referral to genetic counselling. Patients diagnosed before March 2016 were identified at the Department of Oncology. From March 2016 to December 2017, 153 patients were screened.
Results Pathogenic variants were identified in 40 patients (26%). Of those variants, 11 were germline variants (7%), and 24 were somatic variants (16%); 5 patients had screening conducted only on tumour tissue (3%). All germline variants were identified in the tumour. More than half of all somatic variants were whole-gene deletions (14/24). In 14 patients, variants of unknown significance were reported as the only finding (9%).
Conclusions Most variants were of somatic origin, emphasizing the importance of screening tumour tissue. In addition, the high proportion of large structural variants substantiates the need for the use of analysis methods capable of detecting this group of variants. No germline variants were missed in analyzing tumour tissue. These findings have to be confirmed in larger studies, before tumour tissue screening is used as primary screening.

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Poster P135

Evaluation of Cancer Stem Cells in Epithelial Cells from Different Regions of the Fallopian Tubes in Healthy *BRCA1* and *BRCA2* Carriers at Time of Risk-Reducing Salpingo-oophorectomy

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Introduction Evidence suggests that early serous ovarian carcinomas originate in the distal part of the fallopian tube. Protocols examining the fimbriated end of the fallopian tube in carcinoma patients revealed a noninvasive, but potentially lethal form of serous tubal intraepithelial carcinoma. At least 10% of all epithelial ovarian cancers are hereditary, with mutations in *BRCA1* and *BRCA2* accounting for most cases. Ovarian cancers associated with germline *BRCA* mutations are diagnosed at a younger age, and are high-grade and advanced-stage serous carcinomas. For affected patients, risk-reducing bilateral salpingo-oophorectomy (RRBSO) remains the mainstay for preventing malignancy. In recent years, the cancer stem cells model has suggested that a small proportion of cells are capable of initiating tumour growth.
Objective This study aimed to combine the two models by testing the fallopian tubes of unaffected *BRCA1/2* carriers for presence of the ovarian cancer stem-cell marker CD44 in various areas of the fallopian tube at the time of RRBSO.
Methods Fallopian tubes removed from 49 *BRCA1/2* carriers were tested for the presence of the CD44 cancer stem cell marker by immunohistochemical staining in 3 areas: the fimbria, the ampulla, and the isthmus. Each slide received a score based on the percentage of CD44-positive cells and the intensity of staining, ranging from 0 (no cells stained) to 8 (all cells strongly stained).
Results CD44 staining was positive from the fimbria in 98% of samples from normal-appearing fallopian tubes of healthy carriers at the time of RRBSO. The population of CD44-positive cells was most dense in the fimbria (score: 3.2), then their presence gradually decreased toward the ampulla (score: 1.9), declining to very few in the isthmus (score: 0.5).
Conclusions The distribution patterns of CD44-positive cells resembles that of serous tubal intraepithelial carcinomas, suggesting that the stem cells play a role in the formation of tumours.

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Poster P136

Exome Characterization of High-Grade Serous Epithelial Ovarian Cancer Cell Lines with Varying Sensitivity to the PARP Inhibitor Olaparib

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Olaparib (Lynparza) is an oral inhibitor of poly (ADP-ribose) polymerase (PARP), currently developed by AstraZeneca (Cambridge, U.K.). It is indicated for use as monotherapy for maintenance treatment of platinum-sensitive relapsed *BRCA*-mutated (germline or somatic) high-grade serous ovarian, fallopian tube, or primary peritoneal cancer. Olaparib induces death in *BRCA*-mutated, homologous recombination repair (HRR)–defective tumour cells by blocking PARP-mediated DNA repair. Few biomarkers of olaparib sensitivity are available to help identify suitable cases for treatment. Apart from defective HRR, additional DNA repair pathways have been implicated in olaparib sensitivity.

This study involved 18 high-grade serous ovarian carcinoma cell lines classified as sensitive (n = 5), intermediate (n = 9), and resistant (n = 4) based on their response to olaparib. Two of the cell lines are *BRCA* germline-mutated: a *BRCA1*-mutated cell line classified as intermediate, and a *BRCA2*-mutated cell line classified as sensitive. Because only about 40% of *BRCA*-mutated cases respond to olaparib, our objective is to identify additional genetic markers of olaparib response by first analyzing the exomes of these cell lines.

We found that the frequency of nonsense, frameshift, splice, and missense variants (moderate- and high-impact variants) in genes of 6 DNA repair pathways does not separate cell lines into olaparib-response groups. Similarly, hierarchical clustering of cell lines based on copy number variants does not separate them, but reveals a unique cluster of germline *BRCA*-mutated cell lines. Cell lines harbour variants potentially relevant for olaparib response. Notably, one resistant cell line has a potentially damaging missense variant in *ATM* despite the association of *ATM* loss-of-function with increased olaparib sensitivity. Interestingly, the *BRCA2*-mutated cell line is enriched in moderate- and high-impact variants in genes of the Fanconi anemia pathway, in addition to harbouring *BRCA1* missense variants. Further characterization of these exomes will inform our ongoing investigations into biomarkers of olaparib sensitivity.

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Poster P138

Characteristics and Outcomes of Individuals Referred to Genetic Counselling on the Basis of a Personal History of Breast/Ovarian Cancer Without Family History

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Objective Criteria to refer individuals to cancer genetic counselling and testing for hereditary conditions are based on personal and/or family cancer history. We aimed to retrospectively assess the proportions, characteristics, and outcomes of individuals referred to counselling on the basis of their personal medical history without family history, with a particular focus on breast and ovarian cancer.
Methods Pedigrees of probands managed in the Unit of Oncogenetics and Cancer Prevention in the Geneva University Hospitals during 1994–2016 (n = 3000) were extensively reviewed. Probands with features (cancer or benign lesions) suggesting cancer predisposition syndromes and having no 1st- or 2nd-degree relative with such a phenotype, were included in the study. Clinical characteristics, indication to perform genetic analyses, and testing results were evaluated.
Results 438/3000 probands (14.6%) were eligible for the study. The proportion increased over time, to 16.2% (391/2411) during 2006–2016 from 8.0% (47/589) during 1994–2005. Overall, 285 (65.1%) probands (272 women, 13 men) had a breast cancer diagnosis (median age: 40 years), and among those, 63 showed a triple-negative phenotype; 40 (9.1%) probands were diagnosed with ovarian cancer (median age: 51 years). Genetic testing was proposed to 336 probands (76.7%) and performed in 275/336 cases (81.8%). In 203 *BRCA1*/*BRCA2* analyses, 20 (9.8%) pathogenic variants were identified. The mutation detection rate remained stable over time and was 9.4%, 12.5%, and 13.8% in probands with breast cancer, triple-negative breast cancer, and ovarian cancer respectively.
Conclusions Despite the fact that cancer family history is key information in recognizing hereditary cancer predisposition syndromes, personal history should also be considered as a predictor of hereditary conditions, even in the absence of other familial cancer cases. Several factors such as lack of or incorrect knowledge about family history, incomplete penetrance, *de novo* pathogenic variants, or non-paternity can contribute to this observation.

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Poster P139

The Global HeritX Initiative to Prevent Inherited *BRCA* Cancer

Thomas A. Bock, Douglas F. Hager

Background An estimated 20 million people face an up to 87% risk of 5 aggressive cancers because of defective *BRCA* genes: breast, ovarian, prostate, and pancreatic cancers, and melanoma. These cancers strike at an early age, in women and in men, and their risk is passed from one generation to the next.
Goal In 2015, we launched the global HeritX Initiative through an international Banbury Conference. Academic researchers, biopharmaceutical drug developers, U.S. Food and Drug Administration experts, and affected families created an R&D roadmap to *BRCA* prevention that includes all required parts, aspects, and anticipated roadblocks to an approved preventive (non-surgical) therapy.
Methods To implement the roadmap faster than is traditional for R&D timelines, we redesigned the traditional R&D model into an Accelerated Roadmap to Prevention:

1. *Open-Source Approach* To identify the best ideas from all fields, sectors, and geographies, we pursue an open-source approach through 1:1 scientific exchange, think tanks, and global RFPs.
2. *Faster R&D Model* Rather than pursuing a traditional sequential, phase-after-phase R&D process, we work on all drug development phases simultaneously from the start. This enables us to anticipate hurdles, and provides the time to set up accelerating solutions. As of today, we have initiated 6 acceleration projects.

Results In less than 2 years, we connected with more than 200 scientific teams worldwide, selected their best ideas for HeritX support, and initiated 8 *BRCA* cancer prevention programs. Each program pursues a different scientific strategy. This portfolio includes pre-cancer vaccines to eliminate pre-cancer cells before they develop into cancer, and DNA-repair-enhancing therapies to preclude cancer development before it starts. Across the portfolio, we collaborate with more than 15 scientific teams at recognized institutions in 5 countries and with 2 biopharmaceutical companies.
Priorities Forward In 2018, we will focus on advancing current and adding new programs to maximize speed and success. We continue to seek partners to further accelerate momentum.

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Poster P140

An Unexpected *BRCA2* Mutation in a Never-Smoker Woman Diagnosed with Lung Cancer at 30—A Case Report

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Introduction Molecular tumour profiling can lead to the detection of somatic and germline mutations. Certain mutations can predict who might respond to targeted therapy and what the cancer risk is for family members. Numerous gene panels are available for testing solid tumours, and the results can yield unexpected opportunities.
Case Description A 30-year-old woman, a never-smoker, was diagnosed with a pulmonary adenocarcinoma and bone metastasis. The tumour progressed in spite of treatment. Tumour tissue was selected for molecular profiling. A somatic mutation in the *BRCA2* gene was detected and implicated a possible effect of a PARP inhibitor. The patient was also referred for genetic assessment.

The family is small, with no cancer cases in the last three generations. Germline testing confirmed a founder mutation in the *BRCA2* gene, passed down from the paternal family, most likely through several generations of male carriers.

She has recently started experimental treatment with a PARP inhibitor.
Discussion Lung cancer has been reported in Li–Fraumeni syndrome, but is not considered important in other hereditary cancer syndromes. Most cases are related to smokers. In the Western world about 15% of cases are found in nonsmokers.

In our registries, 10 *BRCA2* mutation carriers from among 1354 individuals tested, have been diagnosed with a primary lung cancer at a mean age of 63 years (30–76 years). We lack information about smoking habits in most of these patients. We have confirmed that a never-smoker male *BRCA2* mutation carrier was diagnosed with a pulmonary adenocarcinoma at 52 years of age.
Conclusions More extensive use of molecular tumour profiling will lead to increased detection of somatic and germline mutations. It will also yield important knowledge about the associations between tumour-spectrum

and mutated genes. Those advances will have implications for the patient's treatment and the family's risk.

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Poster P141

miRNA Expression Profiles in *BRCA1*-Associated Breast Cancers Reveal Upregulation of Specific miRNAs in Tumours Lacking a Clear Second Hit in a Large Proportion of the Tumour Cells

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Background miRNAs are small, non-coding regulators of gene/protein expression. Several were found to be associated with specific molecular characteristics in breast cancers. Specific miRNA signatures have been published in *BRCA1*-associated breast cancers. However, no studies have correlated miRNA expression with the presence or absence of second hits at the *BRCA1* locus. We found that a considerable proportion of *BRCA1*-associated breast cancers do not display a clear second hit in more than 50% of tumour cells (loss of heterozygosity, methylation, inactivating mutation). We hypothesize that, in these tumours, overexpression of oncogenic miRNAs might downregulate expression of the retained wild-type *BRCA1* allele.

Methods Using small RNA sequencing, we investigated the expression of 1232 miRNAs in a well-characterized cohort of 51 *BRCA1*-associated breast cancers. We evaluated the association with molecular subtype and histopathologic features, and with loss of a functional *BRCA1* wild-type allele.

Results Our study confirmed previous associations between miRNA expression and specific morphologic and molecular features of breast tumours. Differential expression analysis yielded fourteen miRNAs that were upregulated in tumours not displaying loss of the *BRCA1* wild-type allele in more than 50% of the tumour cells. According to http://www.mirdb.org/, none had any seed complementary to *BRCA1*, but for 5 miRNAs complementarity was predicted to the 3′-untranslated region of *BAP1* or *BRIP1*, both interaction partners of *BRCA1*.Those miRNAs might therefore affect *BRCA1* functionality in an indirect manner.

Conclusions Our study revealed several candidate miRNAs that could play a role in *BRCA1*-associated breast tumorigenesis. Those findings warrant further functional analyses and validation in other datasets to evaluate their potential to act as a non-coding second hit, deactivating *BRCA1* functionality in breast cancer cells retaining a wild-type *BRCA1* copy. OncomiRs could be an interesting target for future therapies.

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