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ABSTRACTS

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SELECTED ABSTRACTS

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PROFFERED PAPERS

S1-PP3: Variants of low allele fraction in panel testing, where are they coming from?

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The advent of massively parallel sequencing/next-generation sequencing technologies has facilitated multi-gene panel testing in hereditary cancer patients. A subset of individuals undergoing blood-based multi-gene panel testing will have variants in cancer predisposition genes at an allele fraction below the threshold of germline heterozygous variants. It is currently unclear how to effectively interpret these findings, the subsequent investigations required and management recommendations.

Low variant allele frequencies identified in the blood-based germline genetic testing may be variants exclusive to hematopoietic cells due to clonal hematopoiesis of indeterminate potential (CHIP) or a hematologic malignancy. Additionally, these findings may be indicative of a true mosaic hereditary cancer syndrome necessitating confirmation in a second tissue.

We developed a clinical workflow for these cases and identified 24 individuals harboring likely pathogenic or pathogenic variants in peripheral blood lymphocyte (PBL) analysis. We observed low allele fractions in 5 different hereditary cancer genes (APC, ATM, BRCA1, CHEK2, and TP53), the most common being TP53. For variants initially detected in peripheral blood lymphocytes, we delineated the etiology by ancillary next-generation sequencing on alternative tissues such as tumour, skin biopsy or cultured fibroblasts. Among these, we identified 3 patients with the PBL variant also present in a second tissue, suggesting a true mosaicism. The PBL variant was not identified in a second tissue in 7 cases suggesting these variants were isolated to the PBL.

Here, we describe the case-by-case management of these unique scenarios to differentiate mosaicism from CHIP and leukemia. The identification and distinction of hereditary cancer syndromes in full and mosaic states, from genetic variants isolated in peripheral blood lymphocytes has an impact on the clinical management of patients undergoing germline genetic testing. These findings represent a shift in the diagnostic utility of blood-based germline testing for oncology and genetic providers.

S2-PP2: Transcriptome-based profiles of immune cell infiltration in BRCA1/2-positive and BRCA1/2-negative male breast cancers

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Breast cancer in men is a rare disease. Inherited mutations in BRCA1/2 predispose to male breast cancer (MBC) and may characterize a subgroup of tumors with a peculiar phenotype. Here, we aimed to perform a transcriptome-based profiling of immune cell infiltration in MBC, in relation to BRCA1/2 status and pathological features.

A total of 59 invasive male breast tumors, including 21 with BRCA1/2 mutations and 38 without BRCA1/2 mutations, were analyzed. Most tumors were ER positive (94.7%) and had intermediate/high tumor grade (G2/G3, 89.5%). Whole transcriptome data were obtained by RNA-sequencing using Illumina technology. Tumor immunophenotype was evaluated using CIBERSORT, which estimates the fraction of 22 immune cell types and an absolute immune score. Statistical analyses were performed using non-parametric tests.

Overall, CD4 memory resting T cells, M2 macrophages and M0 macrophages represented the top three highest infiltrating fractions in MBC (25.9%, 21.4% and 10.7%, respectively).

BRCA1/2-associated MBCs had a higher fraction of CD4 memory activated T cells ($p = 0.04$) and a lower fraction of activated mast cells ($p = 0.03$), compared with non-BRCA1/2 MBCs. A lower proportion of regulatory T cells ($p = 0.0025$) and gamma-delta T cells ($p = 0.004$) was found in ER positive compared with ER negative tumors. In G2/G3 tumors, the fractions of CD4 memory resting T cells was higher ($p = 0.02$), whereas the fraction of eosinophils and activated mast cells was lower ($p = 0.035$ and $p = 0.04$, respectively), compared with low-grade tumors. Absolute immune score was higher in tumors with higher PD1 ($p = 0.006$) and PDL1 ($p = 0.0009$) expression.

These results provided the first evidence that MBCs, particularly those characterized by pathological features suggestive of greater biological aggressiveness, may be enriched in pro-tumorigenic immune cells. Transcriptome-based evaluation of tumor-infiltrating immune cells seem to be a valuable approach for the identification of biologically and clinically relevant immuno-subtypes of MBC.

Study supported by AIRC (IG21389) to LO.

S2-PP3: Molecular and genetic characterisation of contralateral breast cancer (CBC): the importance of CBC risk stratification and management

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The risk of contralateral breast cancer (CBC), following unilateral breast cancer (UBC) is 0.4–0.7% per year. Despite this relatively low risk, the use of contralateral prophylactic mastectomy (CPM) to treat UBC is increasing, despite no survival benefit. Known risk factors for CBC include young age at primary diagnosis and a significant family history of breast cancer. Nonetheless, there is no reliable method for identifying women at increased CBC risk who may benefit from CPM. Furthermore, prognosis following CBC is unclear, and it is uncertain what proportion of CBCs represent new primary cancers, as opposed to metastatic deposits.

To determine the impact of CBC on outcome, and to assess the contribution of known hereditary breast and ovarian cancer (HBOC) gene mutations to CBC risk, we characterised primary and CBCs in 403 women with CBC in Northern Ireland from 1993 to 2016.

Median time between primary and CBC diagnosis was 7.6 ($\pm$ 4.7) years. An excess breast cancer specific mortality hazard of 6.45 (95% C.I. 4.27–9.77, $p < 0.001$) was observed in CBC patients, compared with a matched control cohort of women with UBC.

We sequenced germline DNA (gDNA), primary and CBC in 134 women, using a custom panel, including known risk predisposition genes. 16 (11.9%) of cases shared at least one somatic variant between tumours, suggesting metastatic clonality. Additionally, gDNA analysis identified 15 (11.2%) cases with pathogenic variants in risk predisposition genes, including six in BRCA1/2, and further variants in PALB2, ATM, CHEK2, PMS2, SDHB, FANCA, BRIP1 and BARD1.

These findings indicate that CBC diagnosis has a significant impact on breast cancer survival, reflecting the fact that a proportion of CBCs represent metastatic disease. Furthermore, the prevalence of pathogenic HBOC gene mutations in CBC cases may suggest that testing women with UBC and/or those requesting CPM may represent an opportunity for CBC risk stratification.

S3-PP1: Variation in the functional effects of different protein truncating mutations in BRCA1 and BRCA2 in breast and fallopian tube epithelial cells

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Germline BRCA1 and BRCA2 mutations confer high penetrance susceptibility to ovarian and breast cancer. Most pathogenic mutations are predicted to be protein truncating and occur throughout the coding region of each gene. Genetic studies show that in both genes mutation location is significantly associated with variations in breast or ovarian cancer risks, but the underlying functional rationale for these observations in breast verses ovarian cancer precursor cells remains unknown. We used CRISPR/Cas9 tools to create protein truncating mutations in different regions of BRCA1 and BRCA2 associated either with greater risks of breast (BCR) or ovarian cancer (OCR) in mammary (MCF10) and fallopian tube (FT282) epithelial cells engineered to constitutively express the P53 hotspot mutation R175H. We clonally derived and tested the molecular and phenotypic characteristics of confirmed truncating BRCA1/2 mutations in each cell type.

For BRCA1, we could only derive heterozygous BCR and OCR mutations in MCF10A cells (i.e. homozygous mutations were not viable); but in FT282 cells homozygous OCR mutations were tolerated, while neither hetero nor homozygous BCR mutations were viable.

In BRCA2, heterozygous BCR mutations were tolerated in MCF10A cells but neither hetero- nor homozygous OCR mutation were viable, while both heterozygous BCR and OCR mutations were viable in FT282 cells. BRCA1/BRCA2 mutations led to significantly decreased proliferation and defective DNA repair capacity in both cell types. RNA sequencing of different BRCA1 and BRCA2 mutation clones showed distinct transcriptomic profiles based on the mutation location in both MCF10A and FT282 cells, indicating that BCR and OCR mutations in the same gene, and similar mutations in breast verses fallopian tube cells have different impacts on downstream transcription.

In summary, this study shows that the mutation location in BRCA1 and BRCA2 imparts differential functional effects in breast and ovarian cancer precursor cells consistent with reports from genetic studies.

S6-PP1: A gynecologic oncologist-led mainstreaming approach of germline genetic testing for patients with ovarian cancer; experiences of healthcare professionals

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Background All patients with Epithelial Ovarian Cancer (EOC) are eligible for BRCA1/2 genetic testing. Currently, referral rates are low and genetic testing is not always offered early in the diagnostic process.

Aim We evaluated acceptability and feasibility for non-genetic healthcare professionals (HCPs) to incorporate mainstream genetic testing for EOC patients into daily work.

Methods We developed a pathway for mainstream genetic testing, including an online training module for gynecologic oncologists and nurse specialists. After completing the module, they started counseling and ordering genetic tests. Experiences of HCPs were assessed before and 6 months after completing the training module, including HCPs' attitudes, perceived knowledge, and self-efficacy to discuss and order genetic testing, and their evaluation of the training module.

Results The majority of invited HCPs (90%, N = 19/21) HCPs from four hospitals completed our training module. They requested a germline genetic test for 129 patients. HCPs had a positive attitude, high perceived knowledge, and high self-efficacy toward discussing and ordering genetic testing, both at baseline and after 6 months. Their knowledge regarding genetic testing had increased significantly after 6 months. Time investment for the majority (9/15) of HCPs was between 5 and 10 min to discuss a genetic test. The training module was rated with an average of 8.1 out of 10 and was considered useful.

Discussion and conclusion Counseling and ordering a germline genetic test by trained gynecologic oncologists and nurse specialists seems feasible and acceptable for healthcare professionals; they feel competent and motivated to dicuss and order genetic testing for patients with EOC after completion of a training module.

S6-PP2: Large scale group genetic counselling: a novel service delivery model in British Columbia

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Introduction Increasing demand for genetic services has led to the introduction of novel service delivery models. The initiative presented here developed and piloted large scale group genetic counselling (GC), whereby pre-test group GC (up to 50 patients per group) was compared to traditional one-on-one GC.

Materials and Methods All patients were recruited from the Hereditary Cancer Program in British Columbia (BC) and were eligible to participate if they were unaffected, had a family history meeting provincial testing criteria, had no prior genetic testing performed in the family, and had no living testable relative in BC. Patient reported outcome measures included the Genetic Counselling Outcome Scale-24 (GCOS) (T1: immediately prior to pre-test GC and T2: 4 weeks after post-test GC), a satisfaction survey (immediately after pre-test GC) and the Multidimensional Impact of Cancer Risk Assessment (MICRA) for those undergoing testing (4 weeks after post-test GC).

Results To date, 398 patients have been seen (189 in the group arm and 209 in the traditional one-on-one arm). Nine group sessions have been held (median group size: 23 patients). A small portion of patients (7%) declined participation in the group session because they preferred one-on-one GC. Patients in both arms showed high satisfaction as the majority of patients reported that the appointment was helpful (98% group arm, 99% traditional arm) and that they understood the information presented (99% group arm, 99% traditional arm). Across the three MICRA subscales, the patients within the group arm did not score statistically differently than the one-on-one patients ($p = 0.326$, $p = 0.857$, $p = 0.512$). Additionally, there was no significant difference between the patients within the group arm and the one-on-one arm with respect to their GCOS scores ($p = 0.417$).

Conclusion Data presented here indicate that large scale group GC is feasible and acceptable to patients, representing a new streamlined model of cancer GC.

S7-PP3: A positive oestrogen receptor status and breast cancer survival in nordic BRCA2 mutation carriers

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Background The natural history of breast cancer among BRCA2 carriers has not been clearly established. In an earlier study from Iceland, a positive oestrogen receptor (ER) status and low proliferative activity were negative prognostic factors. We studied survival after invasive breast cancer in *BRCA2* carriers and sought factors which predicted survival, including ER status.

Materials & methods The study population included 608 female carriers with invasive breast cancer from four Nordic countries. Their 118 pathogenic BRCA2 mutations were classified according to location within or outside the Ovarian- or Breast Cancer Cluster Regions (OCCRs or BCCRs). Information on prognostic factors and treatment was retrieved from health records and by analysis of archived tissue specimens. Hazard ratios (HR) for various factors were estimated for breast cancer-specific survival using Cox regression.

Results 77% of cancers were ER-positive, the highest proportion (83%) was in patients under 40 years. ER-positive breast cancers were more likely to be node-positive (59%) than ER-negative cancers (34%) ($p < 0.001$). Women with high grade cancers (grade 2, 3) were less likely to die than women with grade 1 cancers (univariate HR = 0.65 (95% CI 0.40–1.05, p = 0.08)). Positive ER status was protective in the first five years from diagnosis, thereafter the effect was adverse (HR = 1.91; 95% CI 1.07–3.39, p = 0.03). The adverse effect was limited to women who did not undergo endocrine treatment (multivariate HR = 2.36; 95% CI 1.26–4.44, p = 0.01), had intact ovaries (HR = 1.99; 95% CI 1.11–3.59, p = 0.02) or had BRCA2 mutations located within OCCRs or BCCRs (HR = 2.23; 95% CI 1.21–4.10; p = 0.01).

Conclusion The adverse effect of a positive ER status in *BRCA2* carriers with breast cancer may be contingent on exposure to ovarian hormones. The results suggest novel biological qualities of breast tumours in *BRCA2* carriers.

S8-PP1: Determining women preferences for population genetic testing to inform implementation of risk-stratified breast screening

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Our increasing ability to model women's risk of developing breast cancer has potential to form the basis of individual risk-stratified screening programs. This would require women to undertake a Genomic Breast Cancer Risk Assessment (GBCRA) and accept their personal risk-stratified surveillance recommendations. The acceptability of this screening model is unknown.

Here we aim to identify what aspects of a GBCRA and its implementation women would value by determining and quantifying the impact of test-specific and test-delivery attributes on a woman's decision to participate. This information will ensure that implementation of this program will be person-centred and reflects women's values.

Methods A multi-criteria decision analysis with swing weighting framework was adopted. Test and implementation criteria were elicited through a systematic literature review, and local focus groups. An on-line MCDA swing weighting survey was sent to 2000 women at either population risk or through the Parkville familial cancer centre.

Results The eight most important attributes which impacted most on the decision to participate were Mode of Invitation, Mode of providing DNA sample, Heritability of results, Probability of underestimating risk, Probability of overestimating risk, Mode of returning results, Scope of results, and Storage of genomic information. These attributes were operationalised in an MCDA survey.

367 women completed the survey. The criteria most often ranked first were Mode of invitation (27%), Mode of providing DNA sample (20%), and Heritability of results (19%): this was reflected in the normalised weightings of 0.21, 0.16, 0.14 respectively.

77% of women wished the information and offer to participate by email compared to explained by their GP, 77% wish to take a mouth swab at home rather than blood test, and 96% wished the test to have potential to identify a high-risk within the family rather than provide only individual risk.

Preference Cluster analysis is ongoing and will be presented.

S9-PP1: Breast cancer risk genes: association analysis of rare coding variants in 34 genes in 60,466 cases and 53,461 controls from the BRIDGES project

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Despite their widespread use, the evidence for association with cancer for coding variants in many genes on genetic testing panels is often weak, and many of the underlying risk estimates are very imprecise. To provide more reliable risk estimates, we performed gene panel sequencing for 35 suspected breast cancer susceptibility genes on samples from 60,466 cases and 53,461 controls from 44 studies in the Breast Cancer Association Consortium, as part of the BRIDGES project. Protein truncating variants, in aggregate, were associated with overall breast cancer risk (Bayesian False Discovery Probability < 5%) for nine genes: ATM, BARD1, BRCA1, BRCA2, CHEK2, PALB2, RAD51C, RAD51D, and TP53. The upper 95% confidence limit excluded a twofold risk for overall breast cancer for 22 genes. ORs were larger for ER-positive disease for CHEK2 and ATM, but higher for ER-negative disease for BARD1, BRCA1, PALB2, RAD51C, RAD51D and TP53.

We evaluated the combined effect on risk of truncating variants in these genes and the 313 SNP PRS using case-control and case-only analyses. Combined associations were consistent with a multiplicative model for ATM and CHEK2, but less than multiplicative for BRCA1, BRCA2 and PALB2.

Rare missense variants, in aggregate, were associated with risk for BRCA1, CHEK2, ATM and TP53 ($p < 0.001$). Missense variant risks were associated with several in-silico prediction scores, but the optimal model differ markedly among genes. For BRCA1, the risks were restricted to variants in the RING, BRCT1 and BRCA2 domains, and in particular to variants defined as loss of function by saturated genome editing. For ATM, risk appeared to be restricted to a subset of variants in the PI3K/PI4K and FAT domains with high BayesDel scores; for these variants, the risk was comparable to truncating variants. In contrast, for CHEK2, the risks associated with missense variants appeared to be largely independent of domain or in-silico score.

These results should assist the design of more rational panels, the classification of missense variants in these genes and development of more reliable breast cancer risk mode.

S9-PP4: The contribution of germline pathogenic variants beyond BRCA1/2/PALB2 to contralateral breast cancer in women with a younger onset first breast cancer—a WECARE study

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Background Women with breast cancer (BC) are at risk of developing cancer in the second breast, which exceeds BC risk in the general population. Contralateral breast cancer (CBC) is associated with young age, family history and BRCA1/2 mutations. Data on genetic factors predisposing to CBC in BRCA1/2/PALB2-negative women are scarce.

Methods We analysed germline DNA from 474 CBC and 485 unilateral breast cancer (UBC) cases from the WECARE-Consortium in two groups. The first group (233-CBC vs 245-UBC, mean age at first BC 42-years) was sequenced by WES. The second group (241-CBC vs 240-UBC) included older participants (50-years at first BC) and was sequenced by Ampliseq panel. Both groups were enriched for cases with BC family history and excluded BRCA1/2/PALB2-carriers. The aggregated burden of germline pathogenic variants (PVs) in ATM, CHEK2, TP53, NF1, NBN, CDH1, PTEN and STK11 was compared between CBC and UBC patients.

Results There was significantly higher PV-burden in CBC vs UBC ($p = 0.01$, MAC = 27, OR = 2.5 95CI: 1.1–5.7) in the younger group. The comparison with non-Finnish Europeans from 1000 genomes project (NFE) showed gradual increase of PV-burden in NFE-UBC-CBC groups (mean AF in PVs 0.0002, 0.0008 and 0.002 respectively, $p = 0.004$). The association of PV-burden with CBC was not seen in the older group ($p = 0.3$, MAC = 18, OR = 1.6 95CI: 0.6–4.1). The association in the younger group was driven mainly by variants in ATM and CHEK2.

Conclusion The aggregated burden of PVs in established BC-risk genes is associated with increased risk of CBC in young BRCA1/BRCA2/PALB2-negative breast cancer patients.

POSTERS

BIOLOGY OF HEREDITARY CANCERS

P002: A cell-based reporter to screen for modifiers of BRCA1 protein expression

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BRCA1 is a tumour suppressor protein with important functions in DNA damage repair mediated through homologous recombination. Accordingly, individuals with an inherited BRCA1 mutation face a high lifetime risk of developing different cancers. Emerging evidence suggests that BRCA1 is a haploinsufficient tumour suppressor gene since mammary epithelial cells with one germline mutated BRCA1 allele exhibit genome instability and increased replication stress. Over many years, it is expected that such DNA repair deficits lead to increased DNA damage, increased mutagenesis and ultimately tumorigenesis. Our group has demonstrated that BRCA1 expression from a wild-type allele is modifiable through lifestyle and nutritional exposures. Thus, we hypothesize that modulating BRCA1 expression may modify the latency of BRCA1-associated tumour onset.

To test this, we aim to identify chemical modulators of BRCA1 protein expression and evaluate their function on measurable outputs of BRCA1 function including DNA damage repair and replication. Therefore, we engineered HEK293T and HeLa reporter cells with endogenous HiBiT-tagged-BRCA1 protein using CRISPR-editing. HiBiT is a small 11 amino acid peptide tag capable of producing bright and quantitative luminescence by high-affinity complementation, thereby permitting highly sensitive measurement of BRCA1 protein levels. BRCA1-reporter cells were validated by genomic sequencing and Western blot. We demonstrated that BRCA1-reporter

cells are sensitive to known modulators of BRCA1 expression including siRNA knockdown, proteasome inhibition, and resveratrol (RVT) treatment, suggesting that exogenous drug dosing can detectably modulate expression of the BRCA1 fusion protein. We have utilized BRCA1-reporter cells to perform high-content screens of epigenetic-modifying drugs and small molecules, to identify compounds capable of modulating BRCA1 protein expression. Candidate compounds, including bromodomain inhibitors JQ1 and BAY299, are being validated for effects on BRCA1 expression and function in cell and in vivo models of BRCA1-associated breast cancer. Overall, these findings could provide insight into the underlying pathogenesis of BRCA1-associated breast cancer and could help uncover novel strategies for prevention and treatment.

P003: Seattle Cancer Care Alliance's prostate cancer genetics clinic: a report of 125 patients between 2017–2019

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Introduction Current NCCN Guidelines (version 1.2020) recommend genetic testing for all men with metastatic or intraductal prostate cancer, and those with high-grade prostate cancer and a family history of cancer or Ashkenazi Jewish ancestry. To address this patient population, the Seattle Cancer Care Alliance established the prostate cancer genetics clinic (PCGC) in order to (1)help identify patients who meet criteria for testing, (2)ensure appropriate care for patients with pathogenic variants, (3)support cascade testing and (4)connect patients with research and clinical trial opportunities.
Materials and Methods Between July 2017 and May 2019, 125 patients were seen in the PCGC. 71/125(56.8%) patients had germline genetic testing ordered at the time of their visit. 42/125(33.6%) patients already had prior germline genetic testing completed. 12/125(9.6%) patients did not pursue germline genetic testing for various reasons.
Results Of the PCGC patients that pursued testing, 13/71(18.3%) tested positive for a pathogenic/likely-pathogenic variant in APC(1), ATM(1), BRCA2(4), CHEK2(3), HOXB13(2), NBN(1), RAD51B(1), and TP53(1) (one patient tested positive for both APC and CHEK2). 47/71(66.2%) patients tested negative. And 11/71 (15.5%) were identified to have variants of uncertain significance. For those previously tested, 24/42 (57.1%) tested positive for a pathogenic/likely-pathogenic variant in ATM(1), BRCA1(2), BRCA2(10), CHEK2(6), MITF(1), MSH2(1), MUTYH heterozygous(1), and TP53(2). As of June 2019, three PCGC patients with germline pathogenic variants were placed on either platinum-based chemotherapy or PARP inhibitor trials.
Conclusions 18.3%(13/71) of the patients tested as part of their PCGC appointment and, overall, 29.6%(37/125) of the total patients seen in PCGC were identified to have a pathogenic/likely-pathogenic variant in a cancer predisposition gene. As genetic testing guidelines continue to expand and germline testing becomes an integral part of oncologic care for men with prostate cancer, it is essential that clinics advocate for this growing population and provide adequate resources for men and their families.

P005: Bilateral disease common in Slovenian CHEK2 positive breast cancer patients

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Introduction At present there is a lack of data on pathogenic variants in the CHEK2 gene and their impact on cancer risk. The aim of our study was to explore the characteristics of families with CHEK2 gene pathogenic variants in Slovenia.
Materials and Methods In the years 2014–2019 CHEK2 pathogenic variants/likely pathogenic variants (PV/LPV) were found in 1.9% of patients who underwent genetic counseling and testing using a multigene panel at our institution. Seventy-five individuals from 50 families, who were carriers of CHEK2 gene PV/LPV were identified. The data on CHEK2 gene mutations carriers and their families in Slovenia were collected and analyzed.
Results Five recurrent CHEK2 PV/LPV were found in 90% (45/50) of our families: c.444 + 1G > A (15/50; 30%), c.349A > G (13/50; 26%), c.1100delC (9/50; 18%), deletion of exons 9–10 (6/50; 12%) and c.85C>T (2/50; 4%). Five other PV/LPVs (c.1427C>T, deletion of exon 8, c.151C>T, c.283C>T, and c.1283C>T) were each found in one family (1/50; 2%). Breast cancer (BC) was diagnosed in 41 of 75 CHEK2 PV/LPV carriers (40 females, 1 male). The mean age at BC diagnosis was 42.8 years (range 21–63), 27/41 of females with BC (65.8%) had a positive family history. Contralateral BC (CBC) was observed in 8/41 (19.5%) patients (mean age 55.6 years). Carriers of CHEK2 PV/LPVs also had: malignant melanoma (n = 3), ovarian cancer (n = 3), colon cancer (n = 3), rectal cancer (n = 2), renal cancer (n = 1), prostate cancer (n = 1), papillary thyroid cancer (n = 1), primary peritoneal serous carcinoma (n = 1), cervical cancer (n = 1), osteosarcoma (n = 1), and acute lymphoblastic leukemia (n = 1).
Conclusion BC associated with a germline CHEK2 PV/LPV occurs in younger patients than sporadic BC. Bilateral breast cancer was diagnosed in 19.5% of Slovenian BC patients with CHEK2 PV/LPV.

P006: Germline testing following somatic genetic analysis on tumors: experience of a single center

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Background Next generation sequencing has allowed the implementation of molecular tumor boards (MTB) for all cancer types with the aim to accurately classify tumors based on their molecular status, to refine prognosis and to guide treatment. Patients with pathogenic variants in tumors with particular allele frequencies can be identified as potential carriers of germline pathogenic variants or mosaic. These patients can be referred for genetic counseling and germline testing in genetic units. Here we report the experience of the Unit of Oncogenetics in our institution.

Methods Since November 2016, a weekly and video-assisted MTB has been set up in the Geneva (HUG) and Lausanne (CHUV) university hospitals. We reviewed medical consultation files of all probands who have consulted the HUG Unit of Oncogenetics between November 2016 and December 2019. We selected cancer patients who were referred for genetic counselling based on somatic genetic results and limited our study to breast, ovarian, pancreatic and prostate cancer patients. For each proband, we collected clinical information, including family history and somatic/constitutional genetic data.
Results In the selected period, 1306 consecutive probands had genetic counseling. Among them, 27 (2.1%) probands were referred because of genetic results at the tumoral level with particular allele frequencies. Eleven patients had breast, ovarian, pancreatic, or prostate cancer. Constitutional targeted testing was performed in all of them and revealed a germline origin of 7 pathogenic variants in 6 (54.5%) patients (BRCA1: 3, BRCA2: 3, ATM: 1). In addition, one case of mosaic TP53 pathogenic variant was characterised. Five of these 7 probands displayed criteria to propose germline testing according to international guidelines.
Conclusion We observed a high rate of pathogenic variants identified at the germline level after somatic genetic analysis among cancer patients, not all of them fulfilling criteria to recommend genetic counseling and testing.

P007: Germline variant prevalence of key genes connected to breast cancer in a population-based observational study

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Germline predisposition in the form of mutation in specific key genes such as BRCA1 or BRCA2 influences breast cancer onset and progression, a trait that has been continuously considered in the form of clinical germline screening of patients. In a population-based observational study from southern Sweden with 6660 patients, 924 patients (13.9%) were referred to this type of screening at some point during diagnosis. Of these, 189 patients (20.5%) had variants such as point mutation or copy number alteration in at least one of more than 20 genes connected to breast cancer in various ways. The three genes with most variants found were BRCA2 (n = 62 patients, 6.7% of those tested), BRCA1 (n = 56, 6.1%), and CHEK2 (n = 43, 4.7%), representing a confirmed germline variant prevalence of at least 0.93%, 0.84%, and 0.65% in the cohort respectively. However, not all of these variants have the same connection to this malignancy: only 36 BRCA2 (58%), 43 BRCA1 (77%), and 34 CHEK2 (77%) variants found in this cohort are known to be or likely to be pathogenic. Variants from other genes tested were present in less than 10 patients each. When it comes to connection with clinical subgroups, variants in BRCA1 were more common in triple negative breast cancer, CHEK2 variants in ER positive patients, and BRCA2 variants did not seem to be more common in any of those subgroups, as expected from the literature.

Although knowledge has greatly increased in the past two decades since the connection between these genes and breast cancer came to be known, there is still much to be investigated in hereditary breast cancer as exemplified in our data by variants of unknown significance from the three most commonly mutated genes combined (34/162, 21%).

P008: Biallelic CHEK2 germline variants in a child with a testicular germ cell tumour

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Background CHEK2 is a moderate-risk cancer predisposition gene. Loss of function (LoF) CHEK2 mutations result in reduced DNA repair ability, conferring an ~ twofold increased risk of breast cancer. The cancer risk associated with the common CHEK2 variant, p.Ile157Thr, is less clear, though likely lower. Recently, CHEK2 has also been associated with testicular germ cell tumors (TGCT). We report on a 14yo with a testicular germ cell tumor who was identified to carry biallelic variants in CHEK2.
Methods and Results We performed integrated somatic and germline sequencing through the KiCS (Sickkids Cancer Sequencing) study using a 864 gene cancer panel on a 14yo with a testicular germ cell tumor. He was found to carry two CHEK2 variants. Segregation analysis in his parents confirmed that they were biallelic in our patient. The first variant, p.Arg117Gly is a LoF variant that results in partially defective in phosphorylation of CHEK2 and is interpreted as likely pathogenic. The second variant (p.Ile157Thr) is a known low penetrance variant that is present at 1–2% in Europeans. Interpretation and clinical follow up in women with this variant varies and is influenced by family history. It causes partially defective dimerization of CHEK2, resulting in a dominant negative effect. Tumor analysis revealed copy neutral LOH of chromosome 22 in a subset of cells, resulting in selection of the likely pathogenic (p.Arg117Gly) variant. Additional copy number alterations that are recurrent in germ cell tumors were also observed in this subset of cells.
Conclusions The presence of biallelic variants in a child with a testicular germ cell tumor, and the identification of LOH as the presumed second hit, provides a unique opportunity to understand the role of these variants in tumorigenesis, and raises the possibility of a role for CHEK2 in cancer predisposition risk in children.

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

P010: Inherited pathogenic variants are prevalent among breast cancer patients not meeting Ontario and other select international genetic testing guidelines

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Background Therapeutic and risk management options have expanded for patients harboring inherited pathogenic variants (PVs) in cancer predisposition genes. Historically, testing costs and clinical implementation challenges led to restrictive testing guidelines in many countries. Increasing evidence demonstrates that broader testing is a cost-effective way to identify patients with PVs. We assessed the

efficacy of multiple international testing guidelines in identifying breast cancer (BC) patients with clinically actionable PVs.
Methods We reanalyzed a prospective cohort of U.S.-based, primarily Northern European, BC patients, referred for multigene genetic testing (PMID: 30526229). We applied testing guidelines from Australia, U.K. and 2 Canadian provinces (Ontario, British Columbia) to this cohort and focused on their sensitivity for selecting patients with PVs in high risk ($> 4 \times$ risk compared to general population) breast/ovarian cancer genes. These populations were chosen because of similar healthcare systems and ancestral distribution.
Results 193 of 857 patients (23%) met MOHLTC criteria, of which 10 (5.2%) harbored high or moderate risk PVs, similar to the 6.5% rate (n = 43) observed in the 664 OOC patients. Findings in the OOC group included BRCA1/2 (n = 9), PALB2 (4), RAD51C/D (6), MSH6 (1), ATM (5), CHEK2 (11) and other genes. Many of these findings were considered actionable by conferring potential eligibility for precision therapies, clinical trials and/or management guidelines.
Conclusions In our cohort, select international testing criteria identified $< 30\%$ of patients with PVs and $< 40\%$ of those with high-risk PVs (MOHLTC criteria identified 22% and 17% of pts, respectively). These data suggest expanding certain international guidelines would allow better identification and improved management for BC patients across the globe.

P014: Risk of contralateral and ipsilateral breast cancer in breast cancer patients by the affected BRCA Gene from HBOC registration in Japan

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Background Breast cancer (BC) patients with BRCA1/2 mutations have a significantly elevated risk of developing contralateral breast cancer (CBC). The risk of CBC after the first BC has been estimated to 2.4–6.5% per year in BRCA1/2-mutation carriers compared to 0.4–1% in non-carriers. On the other hand, the risk of ipsilateral breast cancer (IBC) was 1.2% per year in BRCA1/2 mutations, and there was no significant difference between carriers and non-carriers. However, most of these data have been reported in western countries.
Purpose The aim of our study is to clarify the risk of CBC and IBC in Japanese BC patients by the affected BRCA gene.
Method We analyzed 2235 women with BC who had undergone BRCA1/2 genetic testing in 2014–2018 using HBOC registries. After excluding data with prophylactic surgery and uncertain data, we assessed the cumulative risk of CBC among 2047 women, and IBC among 1019 woman with breast conserving surgery, stratified by the BRCA1/2 mutation status.
Results The median follow-up was 3.0 years (0.1–34.1 years) after the first BC. The 3-year risks of CBC in BRCA1-positive and BRCA2-positive and BRCA1/2-negative BC patients was 6.4%, 4.8%, and 2.3%, (4.0%,2.9%,1.9% per year) respectively. BRCA1-positive patients had significantly higher risk of CBC than BRCA1/2-negative patients($p = 0.001$). The 3-year risks of IBC in those three groups was 4.7%, 0.0% and 0.8% (2.7%,1.4%,1.1% per year) respectively. All of CBCs of BRCA2-positive patients occurred after 5-year follow-up. There was no significant difference in IBC among three groups ($p = 0.06$).
Conclusion Our study showed the risk of CBC and IBC in Japanese BC patients. The risk of CBC in BRCA1/2-negative BC patients was higher than several previous reports. It may be influenced that patients who were assessed as high risk for HBOC underwent BRCA1/2 genetic testing. A longer follow-up is needed.

P015: Unexpected prenatal BRCA2-related Fanconi anemia diagnosis highlights the importance of variant reclassification and partner carrier screening

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Introduction Advances in genetic testing will increasingly bring to light overlap between prenatal and hereditary cancer genetics. Prenatal whole exome sequencing (WES) may confirm a genetic syndrome in a fetus and identify hereditary cancer risks for the parents, such as with BRCA2-related Fanconi Anemia (FA). BRCA2-related FA is an autosomal recessive disorder characterized by bone marrow failure, childhood cancer risk and birth defects. BRCA2 variant interpretation and reclassification is important to identify couples at risk for FA in their offspring.
Case Description The female patient had a personal history of breast cancer at 29 years of age. She and other family members with breast cancer shared a variant of uncertain significance (VUS) in BRCA2 (c.9302 T > G). After her breast cancer diagnosis, she had two pregnancies with abnormal second trimester maternal serum screening. Similar multiple congenital anomalies (MCA) were observed on fetal anatomy ultrasound in both pregnancies. Smith-Lemli-Opitz enzyme testing, microarray and karyotype on amniocentesis were normal in both pregnancies. Both pregnancies were terminated. WES was performed on fetal cells from the second pregnancy. With WES pending, the patient's BRCA2 VUS was reclassified to likely pathogenic variant (LPV). WES ultimately revealed a paternally inherited BRCA2 pathogenic variant (PV) (c.4415_4418del), and a maternally inherited BRCA2 LPV (c.9302 T > G), providing a molecular diagnosis of Fanconi anemia (FA). The same BRCA2 PV and LPV were confirmed on targeted testing of fetal cells from the first pregnancy.
Discussion This case highlights the complexities at the intersection of prenatal and hereditary cancer genetics and expands the recognized prenatal presentation of BRCA2-related FA. To our knowledge this is the first reported case of FA diagnosed by WES following abnormal maternal serum screening. It illustrates the importance of BRCA2 variant interpretation and reclassification as well as partner BRCA2 carrier screening to assess the reproductive risk for FA.

P016: Detection of mosaicism for a pathogenic variant in BRCA1 in a diagnostic laboratory

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Background Screening of BRCA1 and BRCA2 is offered to breast cancer patients who fulfill criteria, in order to identify patients with hereditary breast and ovarian cancer. Mosaicism for pathogenic variants in the BRCA-genes has only been reported a few times in the

literature. We report a case of mosaicism for a pathogenic variant in BRCA1 detected in a breast cancer patient.

Methods Sequencing analysis of BRCA1 and BRCA2 was performed by next generation sequencing of the patient's blood sample, using a custom capture kit from Illumina. The detection of a mosaic variant was confirmed in a skin biopsy.

Results The variant BRCA1 c.3756_3759del was detected in 56/288 reads in a blood sample, giving an allele frequency of 19% and approximately 38% abnormal cells. The results of a blood sample control revealed a similar result. Analysis of DNA extracted from the skin biopsy showed an allele frequency of 18% (variant detected in 50/279 reads), giving approximately 36% abnormal cells.

The patient was a 38 years old female, presenting with triple negative breast cancer. Her father died of colon cancer age 65. There were no other cancers in her family history. The BRCA1 variant was not found in her mother or in her two tested siblings.

The variant BRCA1 c.3756_3759del is predicted to lead to a frameshift and premature stop (p.Ser1253Argfs*10). It has been reported several times and classified as pathogenic by ENIGMA. Ratajska et al. reported this as a somatic ovarian cancer variant (Oncotarget 2017).

Conclusions Next generation sequencing provides a method for mosaicism detection. The mosaicism grade detected in this case was consistent across the blood and skin sample, indicating that the mutational event took place at an early stage of embryonic development. Mosaic events in the BRCA-genes may be more common than previously recognized.

P021: Genetic testing for pancreatic cancer in ambulatory oncology clinics

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Pancreatic Cancer (PC) remains a lethal malignancy of which 10% of cases may arise from hereditary risk. A unique feature of the Quebec Pancreas Cancer Study (QPCS) is the integrated genetic counseling program that provides familial risk assessment in the ambulatory oncology clinic which has become particularly clinically relevant with the emergence of immunotherapy for patients with DNA mismatch repair deficiency and targeted therapies for patients with germline BRCA1, BRCA2 and PALB2 mutations.

We hypothesize that genetic testing of incident PC cases in the ambulatory oncology setting will accelerate the identification of patients for precision therapies, as well as identify high-risk relatives for surveillance and preventative cancer protocols. Since the start of QPCS in 2012, we have identified germline mutations in 8.02% of participants, including 31 probands and 20 family members, using genetic testing criteria based on family history, ancestral risk for founder mutations, and age of PC diagnosis. As the Invitae Multi-Cancer Panel (86 hereditary-cancer genes) is now offered at no-charge with results available within 21 days, we transitioned to offer the Invitae Panel to all incident PC cases. This expansion on our previous genetic testing practice will benefit patients by aligning with the current NCCN recommendation that all incident PC cases be tested for germline mutations.

Since offering this test in September 2019, we have thus far tested 199 PC patients, with only 3 patients having declined. We have identified germline pathogenic mutations in 25 probands, an overall pick up rate of 12.5%. The results will be correlated with impact on treatment decisions, clinical outcomes, and epidemiological correlates collected by the QPCS. In addition, the Invitae testing platform will be evaluated for turnaround time, accuracy of reported variant classifications, and follow-up of reclassification of variants. Together these results will provide framework to develop practice protocols for safe implementation of genetic testing for incident PC cases across ambulatory oncology clinics.

P022: Two double heterozygote (BRCA1 and BRCA2) families with the same non-founder pathogenic BRCA2 c.5350_5351delAA variant

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Fewer than 200 cases of double heterozygotes (DH) for BRCA1 and BRCA2 have been reported in the literature. Not surprisingly, when this occurs, a rare pathogenic variant from one gene co-segregates with a higher frequency allele, typically a founder mutation. The BRCA2 c.5350_5351delAA variant is not a described founder mutation. There are no specific characteristics of this truncating variant that indicate it would not be a fully penetrant allele, and it has been described in multiple unrelated affected families. This BRCA2 variant has been reported in trans with a BRCA1 variant in the literature (Rebbeck et al. 2019). In their study of 93 DH, these authors observed that DH are clinically more likely to resemble the phenotype of BRCA1 carriers. Interestingly, there was no clear pattern of loss of heterozygosity (LOH) for BRCA1 or BRCA2 in a smaller selection of either breast or ovarian tumors studied.

We report two further cases of BRCA2 c.5350_5351delAA pathogenic variant, identified in addition to a BRCA1 pathogenic variant in unrelated individuals. In both instances the BRCA1 and BRCA2 mutations are presumed to be segregating on the same side of the family. There have been no reported cases of ovarian cancer in either family. One of our patients also has a third autosomal dominant condition also segregating on the same side of the family as the two BRCA gene mutations.

We describe two further individuals who are double heterozygous carriers of the BRCA2 c.5350_5351delAA variant and different BRCA1 pathogenic variants with planned inclusion of LOH testing for one case. In addition to highlighting the need to consider the possibility of more than one autosomal dominant genetic predisposition syndrome in the same family, our cases suggest potential interest for further study of the BRCA2 c.5350_5351delAA pathogenic variant.

P023: Genetic and clinical characterization of BRCA-associated hereditary epithelial ovarian cancer in rural area of Japan

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Background In Japan, insurance of germline BRCA (gBRCA) genetic testing for advanced epithelial ovarian cancer (EOC) was applied in June 2019 as a companion diagnostic for poly ADP ribose polymerase inhibitor. Therefore, until recently, variant frequency and relevance information are scarce in Japanese women with EOC, and genetic testing for hereditary breast and ovarian cancer (HBOC) in patients with EOC has not been generalized. We investigated the rate of gBRCA1/2 variants in Japanese patients with EOC in rural area.
Methods Unbiased 128 EOC patients who had treated at our hospital were enrolled. After genetic counselling, we screened 125 patients with written informed consent by next-generation sequencing-based target panel sequencing.
Results Pathogenic variants were identified in 19 (15.2%) cases: 6 of BRCA1 (4.8%), and 13 of BRCA2 (10.4%). Of these 19 gBRCA mutation (gBRCAm) carriers, 11, 3, 1, and 4 pathogenic mutation were observed in high grade serous carcinoma (HGSC), endometrioid carcinoma, clear cell carcinoma, and others. Median age at diagnosis was 52 (44–71), 60 (46–72), and 54 (22–87) years for gBRCA1, gBRCA2, and gBRCA wild-type (gBRCAw) carriers, respectively. The rate of one or more familial history with HBOC-related cancers for first–second degree relatives was 57.8% and 32.4% among gBRCAm and gBRCAw carriers, respectively ($p = 0.0333$). There was no difference whether they had a personal history of other cancers or not between gBRCAm and gBRCAw. There was no significant difference in overall and progression-free survival between gBRCAm and gBRCAw carriers with stage lll tumors.
Conclusion Our data suggest that the prevalence of pathogenic BRCA1/2 variants in Japanese patients with EOC in rural area is similar to that in other ethnic groups, even in rural area. The HGSC subtype and the family history of HBOC-related cancer may be useful for predicting the risk of genetic predisposition of Japanese patients with EOC.

P025: Germline mutation spectrum in Colombian hereditary breast and ovarian cancer families

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Hereditary breast cancer (BC) syndromes correspond to 10–15% of all cases diagnosed worldwide. Most of these cases are due to deleterious germline genetic variants in BRCA1/2 genes; nevertheless, multipanel testing have contribute to the identification of other risk genes, including other homologous recombination (HR) repair genes, such as PALB2, ATM, CHEK2 and RAD51D. Here we explore the mutation spectrum of Hereditary Breast and Ovarian Cancer (HBOC) Syndrome in Colombians as part of the Hereditary Cancer Program from the National Cancer Institute from Colombia, the largest reference cancer center in the country, that seeks to identified high risk families to offer preventive measures and screening recommendations.

A total of 552 patients fulfilling criteria for HBOC have been so far analyzed with Next Generation Sequencing, NGS, using a multigene panel. Overall, 34% have negative results and in the 40% we identified VUSs. In general, 26% have a pathogenic or likely pathogenic genetic variant, but only 21% (117/552) have been diagnosed with a hereditary cancer syndrome; from those, BRCA2 (n = 39) and BRCA1 (n = 32) were the most frequently mutated genes (61% among 117cases with a cancer syndrome). Deleterious mutations in RAD51D and PALB2 (also important HR repair genes) were found in 6% and 4.3% of the cases tested. Interestingly, genotype:phenotype correlations were found for these genes, as breast cancer molecular subtypes were distributed differently depending on the gene affected. In concordance with other reports, triple negative breast cancers (TNBC) were more frequent in BRCA1 (18/32, 56%) and PALB2 (5/5, 100%) carriers, and luminal subtypes were more frequent in BRCA2 carriers (23/39, 59%). Mutations in RAD51D: c.94_95del (p.Val32Phefs*67) and PALB2: c.2288_2291del (p.Leu763Ter), were both recurrent mutations in our Colombian cases. Further haplotype analysis will help us to determine if mutation carriers shared a common ancestry.

P030: Massively parallel functional analysis of missense variants in the breast/ovarian cancer gene *RAD51C*

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A proportion of hereditary breast/ovarian cancers are caused by pathogenic variants in DNA repair genes. Multi-gene panel sequencing for genetic testing has led to an increased detection of variants of unknown clinical significance (VUS). In this sense, massively parallel functional assays allow the study of thousands of variants simultaneously, representing a valuable tool to accelerate the clinical interpretation of VUS. Here we present a large-scale functional approach to measure the impact of all possible missense substitutions in the *RAD51C* gene using PARP inhibitors.

A mutagenesis library for *RAD51C* was designed to cover all possible missense substitutions ($\sim$ 7500 variants). The library was cloned into an inducible, recombinase-site containing vector, allowing the genomic integration and controlled expression of the variants into a defined locus. In parallel, HeLa "landing pad" cells were generated to ensure the recombination of one variant per cell. A subset of the library was integrated and cells were treated with olaparib. Genomic DNA from untreated and treated cells was extracted and sequenced in a MiSeq instrument.

To date, $\sim$ 160 *RAD51C* missense variants have been screened. All variants were detected in the untreated pool at a similar abundance, confirming their optimal integration and expression. Variant read counts were reduced for the positive controls after treatment, confirming the synthetic lethal effect of olaparib when *RAD51C* is not functional. Experimental replicates and calculation of loss-of-function scores using other DNA damaging agents is ongoing.

We have developed a large-scale functional approach to measure the impact of all missense variants in the *RAD51C* gene using PARP inhibitors sensitivity as a readout. Future work will focus on validating our data with published works, clinical databases and complementary assays. The final goal is to generate a functional atlas for the *RAD51C* gene in order to improve the interpretation of missense VUS and accelerate their clinical translation.

P031: Cancer spectrum and family history of cancer in men with germline BRCA1 or BRCA2 mutations

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Background Men with germline BRCA1/2 mutations are not well studied compared to their female counterparts. The lack of data has led to poor evidence to drive recommendations regarding early cancer detection and risk reduction in this population. This study's aim was to elucidate the cancer spectrum and family history of cancer in men with BRCA1/2 mutations.

Methods This is a retrospective cohort study of 323 men with confirmed BRCA1 or BRCA2 mutations who have attended genetic counselling and testing in the Department of Obstetrics and Gynecology at the Medical University of Vienna between October 1995 and October 2019. Clinical data, pathologic characteristics and family history of cancer were collected.

Results Of the 323 men included in the study, 196 (60.6%) patients carried a BRCA1-mutation, 120 (37.2%) carried a BRCA2-mutation and the remaining 7 (2.2%) carried both mutations. A total of 45 BRCA carriers (13.9%; 11 BRCA1 and 34 BRCA2; $p < 0.001$) had a primary cancer diagnosis—breast cancer (BC) being the most common (n = 26;57.7%, 3 BRCA1 and 23 BRCA2, $p < 0.001$), followed by prostate cancer (n = 7;15.6%; 3 BRCA1 and 4 BRCA2). Other cancers include gastrointestinal, skin, pancreas, throat, lung, and testicular cancer (26.7%, n = 12). Twelve patients (3.7%) had more than one primary cancer. The average age at BC diagnosis was 58 years (52.5–66.5), with invasive ductal carcinoma and hormone receptor positive being the most common subtype. Among 26 BC-affected patients, the BRCA mutation was of maternal origin in 11 carriers (42%) versus 2 (7%) paternally; two BRCA1 (66.7%) and nine BRCA2 (39.1%) did not have any relatives with cancer ($p = 0.56$).

Conclusion Our study shows the cancer spectrum of men with BRCA1/2 mutations at our institution and that not all male mutation carriers present with BC or have a family history of cancer to warrant genetic testing. More studies are needed to identify high risk male carriers.

P032: Alternative transcripts can attenuate the pathogenicity of presumed loss-of-function variants in *BRCA1* and *BRCA2*

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Genetic testing to identify pathogenic germline variants in high-risk breast and/or ovarian cancer susceptibility genes is routine clinical practice. Current variant interpretation guidelines consider predicted loss-of-function (LoF) variants, such as nonsense variants and variants in the canonical splice site (ss) sequences of *BRCA1* and *BRCA2*, to be associated with high cancer risk. However, some variant alleles produce alternative mRNA transcripts which encode (partially) functional protein isoforms leading to possible incorrect risk estimations. For accurate classification of variants it is therefore essential that alternative transcripts are identified and functionally characterized.

To this end, we used a validated mouse embryonic stem cell (mESC) based model system. The functional assay is based on the ability of human variants to complement the loss of endogenous mouse *BRCA1* or *BRCA2* and subsequent quantification of their ability to perform homology-directed DNA break repair. We systematically evaluated a large panel of human *BRCA2* and *BRCA2* variants for the production of alternative transcripts and assessed their capacity to exert protein functionality. Evaluated variants include single-exon-deletions, multiple-exon-deletions, intronic variants in canonical ss sequences and variants that previously have been shown to affect mRNA splicing in carriers.

Multiple alternative transcripts encoding (partially) functional BRCA2 isoforms were identified (e.g. Δ(E4-E7), Δ(E6-E7), ΔE(6q39_E8), Δ(E10), Δ(E12), ΔE(12–14)). Expression of these so called rescue transcripts did attenuate the impact of predicted LoF variants such as the canonical ss variants c.631 + 2 T > G, c.517-2A > G, c.6842-2A > G, c.6937 + 1G > A, and nonsense variants c.491 T > A, c.581G > A and c.6901G > T. Similarly, we identified BRCA1 rescue transcripts (e.g. Δ(E9-E10)). Retainment of BRCA1 protein activity was observed for presumed LoF variants c.616G > T (nonsense variant) and c.594-2A > C (ss variant) which both expressed significant levels of the naturally occurring Δ(E9-E10) transcript.

These results question the validity of classifying presumed LoF variants in non-essential exons or their canonical ss as being high risk pathogenic alleles.

P033: Brain metastasis among ovarian cancer patients

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Background Brain metastasis (BM) are uncommon among ovarian cancer(OC) patients. Their frequency, risk factors and clinical repercussions are not well described. We assessed OC patients who developed BM, the role of BRCA status and survival implications.

Methods Study cohort included OC patients treated at our center, from 2002 to 2020. We retrospectively evaluated clinical parameters, risk for BM development and association with survival data.

Results Among 972 OC patients, 28(2.9%) were diagnosed with BM. Comparing the BM to non-BM group, median age of 60 across both groups, stage III-IV at diagnosis was more common among BM group (96.4% vs. 84.8%, $p = 0.0065$) while platinum sensitivity was similar (92.3% in BM vs. 80.8% in non-BM, $p = 0.2193$). Out of 658 patients tested for BRCA, 33.6%(n = 221) were BRCA mutation carriers(BRCA +). Of the patients with BM, 22 tested for BRCA, 13 were carriers. BRCA+ was significantly higher in the BM group compared to the non-BM group (59.1% vs. 32.9%, $p = 0.0123$). Among BRCA+ the rate of BM was higher than among BRCA- (5.8% vs. 2.1%, $p = 0.0123$, HR = 3.029; 95%CI: 1.4–6.5). Median time from OC diagnosis to BM and from disease recurrence to BM, was longer for BRCA+ compared to BRCA- (44.3mo vs. 32.3mo and 11.8mo vs. 0.7mo, respectively). Median survival (mOS) was not significantly different among patients with BM compared to those without BM(59.4mo vs. 71.2mo, $p = 0.36$). Following diagnosis of BM, mOS

was 20.6mo among BRCA+ and 12.3mo among BRCA-(p = 0.4266). No correlation was demonstrated with PARP inhibitors or bevacizumab treatment and subsequent development of BM.
Conclusion BM are an infrequent event among OC patients. However, the risk is three-folds higher among BRCA+. Interestingly, BM do not significantly alter survival among OC patients. Our work suggests that the higher rate of BM in BRCA+ may be related to longer survival. Another hypothesis requiring further evaluation, is possible higher brain tropism among this population.

CLINICAL ISSUES FOR MANAGEMENT

P043: Genetic test results and clinical features of 111 consecutive cases of high grade serous tubo-ovarian cancers tested via a gynecologic oncology clinic

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Ovarian cancer (OC) affects 1 in 75 Canadian women, with a five year survival of 45%. In 2017, the Society of Gynecologic Oncology of Canada introduced a pan-Canadian strategy to support universal BRCA gene testing to all women with non-mucinous epithelial OC. At the time, only 20% of eligible women with OC were being referred to genetic services. Identifying women with hereditary OC can provide opportunities for treatment and facilitate the identification of at-risk relatives who may benefit from increased cancer surveillance and/or risk-reducing surgery. In August 2017, we launched Gynecologic Oncology Initiated Genetic Testing (GOIGT), a collaborative program between Genetics and Gynecologic Oncology in which women with high grade serous tubo-ovarian carcinoma (HGSOC) are offered multi-gene panel germline genetic testing at diagnosis. Age, clinical stage, tumour histology, genetic test result, previous cancer history and family history were documented.

From August 2017 to March 2021, 111 women with incident HGSOC were tested through GOIGT. 31 women (27.9%) tested positive for a pathogenic/likely pathogenic variant (P/LPV) in an OC predisposing gene (10 BRCA1, 9 BRCA2, 3 RAD51C, 2 RAD51D, 1 BRIP1, 1 PALB2, 1 MSH6, 1 PMS2, 1 TP53, 1 CHEK2). One additional TP53 mosaic pathogenic variant was identified, suspected to be due to clonal hematopoiesis. 12 women (10.8%) had a variant of uncertain significance. 68 women (61.3%) had a negative result. Mean age at diagnosis was 64.5 years for all women, 61.2 years for women with a P/LPV in any gene, and 58.6 years, 61.1 years, and 63.7 years for women with a BRCA1, BRCA2, and non-BRCA1/2 P/LPV, respectively. Of the positive cases, seven women had previous diagnoses of breast cancer. Three had synchronous endometrial cancers.

This analysis further supports the model of universal germline genetic testing for all women with HGSOC. Additional details and case vignettes will be presented.

P045: Does risk reducing mastectomy in BRCA mutation carriers affect their quality of life?

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Healthy women who test positive for a mutation on one of the BRCA genes have high risks of developing breast and ovarian cancers. Risk-reducing mastectomy (RRM) is associated with a 90% or more decreased risk of breast cancer. A significant number of female BRCA carriers will choose to undergo RRM, which has implications for psychosocial well-being, sexuality, and overall quality of life. Women may experience negative physical and emotional changes. These changes can affect their physical appearance, which in turn can have a negative psychological effect on women and their relationships. Our previous study suggested a possibility of an adverse effect of RRM on their sensory-motor status.

The aim of this study is to investigate the effect of RRM on women's daily living activities, upper extremity sensory motor functions, sensitivity to the breast area, body image and sexuality.
Method One hundred healthy women who are BRCA mutation carriers will be recruited from our high-risk clinic. The research group consists of 50 women who underwent RRM who are a minimum of 6 months post bilateral RRM, with no history of cancer, or other major health events, between the ages of 21–60. The control group includes 50 healthy BRCA mutation carriers who elected not to undergo RRM between the ages of 21–60.
Utilizing a combination of quantitative questionnaires and self-reported qualitative measures we will evaluate participants' satisfaction, well-being, body image, discomfort and physical limitations after RRM.

Using a standard goniometer we will measure shoulder range of motion. The Jamar Dynamometer will measure gross power fist grip; Semmes Weinstein monofilament will be used to measure, assess sensory, tactile, and pain perception threshold.

The results will be reported and used to develop an occupational therapy treatment plan and interventions to address the physical and psychosocial issues related to RRM in BRCA carriers.

P046: BRCA1/2 mutation carriers with a STIC at risk-reducing salpingo-oophorectomy are at high risk to develop a primary peritoneal carcinoma

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Introduction After risk-reducing salpingo-oophorectomy (RRSO), there is a residual 3.9% and 1.9% risk of developing primary peritoneal carcinoma (PPC) for BRCA1/2-mutation carriers, respectively. The origin of PPC is yet unknown. However, as the origin of ovarian cancer probably lies in the Fallopian tube, the Serous Tubal Intraepithelial Carcinoma (STIC) may be the origin of PPC as well. In this Individual Patient Data Meta-Analysis, we determine the risk of PPC for *BRCA*-mutation carriers with and without STIC at RRSO.
Methods We performed a systematic search of MEDLINE, EMBASE and Cochrane on studies providing follow up in *BRCA*-mutation carriers after RRSO. Individual patient data was extracted and the authors of eligible studies were contacted to complete this data. Additionally, we retrospectively collected data from the Radboudumc and Kaiser Permanente of *BRCA*-mutation carriers undergoing RRSO between 1996–2018 and 2007–2019, respectively.
Results After screening, 15 out of 2945 studies were included, describing a total of 3183 women without and 92 women with STIC. The retrospective case series identified another 975 BRCA-mutation carriers, of whom 20 had STIC found at initial RRSO. Resulting in a

total of 4158 women without STIC and 112 with STIC at initial RRSO. After RRSO without STIC 0.34% of the *BRCA*-mutation carriers developed PPC while 11.61% of them with STIC developed PPC. Additional individual patient data meta-analysis will follow to determine the risk according to age, type of *BRCA*-mutation and duration of follow-up.

Discussion *BRCA*-mutation carriers with a STIC at RRSO are at increased risk to develop PPC during follow up. The question arises whether a STIC should be considered as precursor or early stage ovarian cancer. Larger prospective-multicenter studies are needed to investigate the additional value of staging surgery and/or chemotherapy in case of STIC.

P047: Engaging men in population-based BRCA testing programs: preliminary data from the BRCA Founder OutReach (BFOR) study

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Background The BFOR study evaluates the feasibility of population-based genetic testing using videos and a chat-bot for education and consent. Eligibility included insured individuals in Boston, Philadelphia, NYC, and LA, age 25, with 1 grandparent of Ashkenazi Jewish (AJ) ancestry and no prior BRCA1/2 testing. Participants had blood drawn for BRCA1/2 AJ founder mutation testing at no cost to them. Results were disclosed by primary care providers (PCP) or BFOR genetic counselors (BGC), per participant selection. We sought to examine differences in study engagement between men and women.

Methods Participants completed initial questionnaires including demographics, personal/family cancer history, and how they heard about the study. Follow-up questionnaires were collected at 12-weeks and 1-year post-enrollment. Study parameters (e.g., results disclosure method, patterns of follow-up) were compared between genders using Chi-squared or Fisher's exact tests.

Results From December 2017-October 2019, 3926 participants enrolled [77% female (3032); 23% male (894)]. Men were significantly less likely to participate ($p < 0.0001$) and were older (60% of men were 55 vs 41% of women, $p < 0.0001$). Men had a 4 × higher likelihood of testing positive (8% vs 2%, $p < 0.0001$). Men were more likely to have heard about the study from a relative (31% vs 11%, $p < 0.0001$) and to have a known familial mutation (55% vs 22%, $p < 0.0001$). There were no gender differences for completion of blood draw or follow-up surveys.

Conclusion Study engagement differed between men and women and outreach methods were not as effective in motivating men to pursue testing. Compared to women, men's study participation was more likely to be prompted by a known familial mutation or the encouragement of a relative. These results suggest that BRCA1/2 testing of men entails added challenges that may be mitigated if population-based testing was standard of care.

P048: Prospective cohort study and biobanking with Japanese BRCA1/2 pathogenic variant carriers by the Japanese Gynecologic Oncology Group (JGOG) (JGOG3024)

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The Japanese Gynecologic Oncology Group (JGOG) is the largest clinical research group, which aims to establish the optimal and latest diagnostic and therapeutic strategies for patients with gynecologic malignancies, consisting of 181 major Universities and hospitals in Japan.

The JGOG3024 trial (the "Prospective cohort study with unaffected mutation carries with BRCA1 or BRCA2") is a cohort study that recruits unaffected carriers with BRCA1/2 pathogenic variant or variants of uncertain significance (VUS).

The primary outcome of the study is to estimate the incidence of ovarian, fallopian tube and peritoneal cancers (OCs) in women carrying BRCA1/2 variants. The secondary endpoints of the study are as follows: (1) to investigate risk factors concerning the development of OCs, such as loci of BRCA1/2 genetic variants, modifier genes, genetic polymorphism, hormones, and lifestyle habits, in women carrying BRCA1/2 variants, (2) to estimate the detection rates of occult cancer based on histopathological evaluations with risk-reducing salpingo-oophorectomy (RRSO), (3) to examine the risk-reducing effect of RRSO on the development of OCs in women carrying BRCA1/2 variants, and compare with those without undergoing RRSO, (4) to identify clinicopathological features in women carrying BRCA1/2 variants who had undergone RRSO, and (5) to identify the appropriate interval or degree of surveillance.

The JGOG and Tohoku University Tohoku Medical Megabank Organization (ToMMo) launched a joint Biobank (JGOG/ToMMo biobank) in 2016. From this study, germline DNAs from BRCA1/2 pathogenic variant or VUS carriers have been collected and stored at this biobank. These studies may facilitate precision medicine for BRCA1/2 pathogenic variant carriers in Japan.

ClinicalTrials.gov Identifier: NCT03296826.
https://clinicaltrials.gov/ct2/show/NCT03296826

P049: Endometrial thickness among BRCA mutation carriers undergoing prophylactic oophorectomy

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It has been suggested that BRCA mutation are at a higher risk of developing high-grade endometrial cancer. Endometrial thickness is considered a surrogate marker for endometrial cancer risk, and women with a BRCA1 or BRCA2 mutation have been reported to have significantly higher follicular, but lower luteal, endometrial thickness compared to non-carrier controls. Medications affecting endometrial thickness are often indicated for BRCA mutation carriers, and include, chemoprevention with tamoxifen, menopausal hormone therapy after preventive oophorectomy, and oral contraceptives for ovarian cancer prevention. It is important to confirm these findings to optimize cancer management in this high-risk group.

The objective of this study is to evaluate endometrial thickness among women with a BRCA1 or BRCA2 mutation compared to published values for non-carriers. Eligible women were those with a deleterious mutation in BRCA1 or BRCA2, that were referred to Familial Ovarian Cancer Clinic at Women's College Hospital between 2007 and 2016 and who had an intact uterus. Retrospective chart review was conducted to collect information on clinical and reproductive factors, and transvaginal ultrasound reports with endometrial dating were reviewed to determine endometrial thickness (millimetres; mm).

In total, 161 women were identified, 101 of whom were premenopausal and 60 who were postmenopausal. Among premenopausal women, the median follicular endometrial thickness found was 7.18 mm (n = 37, range 3–13) compared to 6.8 mm (2.4–14) in non-carriers and the median luteal endometrial thickness was 10.85 mm (n = 30, range 5–18), compared to 9.6 mm (3.3–18.2) in non-carriers. Among postmenopausal women, the median menopausal endometrial thickness was 4.0 mm (n = 43, range 1–18) compared to 4.0 mm (1–25) in non-carrier controls. Although based on small numbers, there was no significant difference between BRCA mutation carriers and non-carrier controls. Additional studies are on-going to elucidate the impact of hormonal factors on endometrial thickness.

P051: Clinical guidelines in Japan possibly fail to identify all patients with hereditary breast and ovarian cancer

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Background Studies on hereditary breast and ovarian cancer (HBOC), conducted in the United States (US), recently showed that clinical screening, using the National Comprehensive Cancer Network (NCCN) guidelines, possibly fails to identify all patients with HBOC. As of 2018, health insurance in Japan covers genetic testing as a companion diagnostic for patients with breast cancer. As a result, many patients who had not met the high-risk guideline criteria for genetic testing, have undergone genetic testing. Using information from these tests, we evaluated the ability of the clinical guidelines to identify all patients at high risk for cancer in Japanese breast cancer patients.

Patients and Methods We reviewed the medical records of 91 breast cancer patients who underwent BRCA1/2 genetic testing at Kanagawa cancer center from October 2018 to December 2019. The patients were divided into two groups; group 1 comprised patients who met the high-risk guideline criteria for genetic testing, and group 2 comprised those who did not meet the criteria. We used the BRCA1/2 testing criteria of the NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 3.2019 as clinical guidelines.

Results Of the 50 patients who met the testing criteria of the NCCN guidelines, 6 (12%, 95% confidence interval [CI] 4.5–24.3%) were carriers of pathogenic or likely pathogenic variants. Of the 41 who did not meet the testing criteria, 2 (4.9%, 95% CI 0.6–16.5%) were carriers of pathogenic or likely pathogenic variants. No statistically significant relationship was found between meeting the criteria and the test results (odds ratio 2.6, p = 0.28.)

Conclusion This study indicated that the conventionally used clinical guidelines may exclude some of the patients with HBOC in Japan. The widespread use of companion diagnostic testing can be helpful in identifying this previously excluded patient group with HBOC.

P052: Common inquiries related to real-world use of talazoparib post launch in the United States

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Background Talazoparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, was approved by the United States (US) Food and Drug Administration (FDA) in October 2018 for adult patients with deleterious or suspected deleterious germline *breast cancer susceptibility gene* (BRCA)-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. To facilitate safe and effective use of talazoparib in real world clinical practice, inquiry reports submitted by health care providers (HCPs), patients, and caregivers were documented and addressed. An in-depth analysis of these reports allows further understanding of where additional talazoparib medical education may be warranted and assists in identifying gaps in data dissemination.

Methods Inquiry databases were accessed by Pfizer US Medical Information to capture inquiries submitted during the 28 months post-FDA's initial approval of talazoparib. Inquiry reports were evaluated to determine commonly addressed questions among HCPs, payers, patients, and caregivers. Responses to all inquires were generated from all data sources.

Results Between October 2018 and February 2021, 547 inquiries regarding talazoparib were received. Physicians (46.6%), pharmacists (29.1%), and patients (14.3%) submitted the most inquiries. The most common safety inquires received were related to hematologic concerns (31.4%). Central nervous system (CNS) penetration and use in patients with brain metastases made up 66.7% and 21.7% of Pharmacology and Special Patient Population inquires, respectively. The topics of drug-drug interactions (36.4%) and use in patients unable to swallow (51.9%) were commonly requested by pharmacists.

Responses to these frequent inquiries will be provided in the presentation.

Conclusion Most talazoparib medical inquires received post-US launch were submitted by physicians and pharmacists. These inquiries were most commonly related to safety and administration concerns and use in special populations. Providing HCPs and patients with responses to these important questions has helped to ensure the continued safe and effective use of talazoparib 28 months post-approval.

Funding Pfizer.

P053: The mainstreaming pilot process: oncologist-mediated genetic testing for hereditary cancer

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Background In 2016, the GO-BRCA pilot launched in Calgary. This collaboration between the Hereditary Cancer Clinic (HCC) and the gynecology-oncology clinic streamlined hereditary ovarian cancer genetic testing for their patients, while preserving informed decision-making and genetic counselling support. Mainstreaming aimed to build on the success of GO-BRCA, expanding and standardizing this model province-wide and including other tumour groups.

Methods Oncology teams offer multigene panel testing, supported by a centralized "HCC Hub", comprised of genetic counsellors and a clerk. Duties include education, test request validation, troubleshooting logistics, and follow-up genetic counselling: in-person for positive/variant results, or via templated letter for negative results. The HCC Hub designed multimedia pre- and post-test clinician and patient educational materials.

Mainstreaming for ovarian cancer began in February 2019, and for breast cancer in August 2019. Outcome measures include time to access testing and results compared to baseline, patient satisfaction (via survey post-results disclosure), clinician satisfaction (qualitative feedback and survey), and improved HCC capacity.

Results From February 2019 to December 2020, 855 patients were tested via Mainstreaming, with 779 results complete (46% breast, 54% ovarian). About 15% of results were positive, 17% were VUS and 67% were non-informative. The time from oncologists' discussion of genetic testing to results disclosure was at least 3 × faster for mainstreaming patients, versus baseline. Eliminating pre-test, and post-test non-informative result appointments increased HCCs capacity by 1307 h.

Of returned patient surveys, at least 85% of patients felt they made an informed decision, their expectations were met, and that oncology teams should offer genetic testing. However, under half reported using Mainstreaming educational materials. All clinicians who completed surveys reported they were comfortable with Mainstreaming and recommend it for other tumour groups.

Conclusion Mainstreaming decreased time to genetic test results for patients similar to GO-BRCA, and was acceptable to stakeholders. In 2021, Mainstreaming will expand to other tumour groups, and work continues to increase awareness and accessibility to Mainstreaming support materials.

P054: Lapses in screening for highly penetrant gene positive patients due to pregnancy and lactation

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Introduction Screening with MRI at age 25 and mammogram at age 30 coincides with the time that many women choose to child bear. This study aims to determine lapses in screening in high risk-mutation carriers due to pregnancy or lactation.

Methods We performed a retrospective chart review of patients with documented pathogenic germline genetic variants seen in the Hereditary High Risk Breast Clinic at Cleveland Clinic from April 1, 2008 to the present. Patient demographics, genetic mutation, date of imaging, date of delivery, breastfeeding status, biopsies performed, and pathology results were recorded.

Results Of 685 patients with documented mutations (85.3% with BRCA1/2), 40 had pregnancies after genetic testing (average age of 31.4 years old) with 1–2 evaluable pregnancies (51 total). 68.6% of these patients breastfed (average 7 months). Prior to pregnancy, 52.9% of patients were screened with mammography, 43.1% with MRI, and in 80.4%, clinical exam was documented. Patients had 2.8 exams (average) during pregnancy and lactation. 21.5% had whole breast ultrasound beginning in their second trimester. 9.8% patients had diagnostic imaging during lactation. After completion of pregnancy and lactation, 60.8% of patients first resumed screening with mammography and 45.1% with MRI with an average lapse without screening of 23.6 months. We identified 3 cases of pregnancy associated breast cancer (PABC) in this cohort per pregnancy episode (5.9%; Stages IIA, IIB, and IIA respectively).

Conclusions Average screening lapse due to pregnancy and lactation was 23.6 months. We observed PABC in 5.9% of pregnancies. In the absence of formal guidelines for screening during this period, clinical breast exam remains paramount every 6 months, perhaps resumption of screening mammography after delivery and resumption of screening MRI after one menstrual period. OB/GYNs must be aware of breast cancer risk in gene positive patients, with regular clinical exams at minimum.

P055: Questionnaire-based psychological and quality of life assessment after contralateral risk-reducing mastectomy for breast cancer patients with BRCA 1/2 pathogenic variants

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Background Contralateral risk-reducing mastectomy (CRRM) for breast cancer (BC) patients with BRCA1/2 pathogenic variants has been reported to reduce BC incidence and improve survival. Recently, CRRM was begun to be performed at a few institutions in Japan.

Purpose We conducted a feasibility study to confirm the safely of CRRM with reconstruction and to investigate psychosocial aspects using questionnaire-based assessments.

Methods We assessed CRRM-related adverse event, and psychological and quality of life (QOL) status before and after CRRM by original questionnaires which were distributed to those patients after surgery. To compare the status when they determined to undergo

CRRM and after CRRM, paired analysis was performed in some questionnaires. Clinicopathological data were obtained from clinical records. This study was approved by the Clinical Research Ethical Review Board of Aichi Cancer Center.

Results From 2014 to 2016, 10 patients (5 BRCA1- and 5 BRCA2-positive patients) consented to participate in this study. Median age at receiving CRRM was 37.5 (range 32–52) years. With a median follow-up of 44.9 (range 31.7–58.8) months, no grade 2 or more severe adverse events were observed. Neither recurrence nor incidence of post-CRRM BC occurred. Questionnaires were returned at a median of 27 months after CRRM. RRM did not adversely influence QOL in all patients. Significantly more patients enjoyed conversation with their friends and dressing up in daily life. Effects of CRRM on femininity and on sexual functioning differ substantially between individuals. All of the patients were more or less satisfied with CRRM with cosmetic results. However, nine patients were anxious about the recurrence of BC and issues related to the hereditary condition.

Conclusion CRRM could be performed safely and may be beneficial to BRCA1/2 variants carriers in psychosocial and QOL aspects. However, concerns for recurrence or cancer risk of inheritance need to be supported carefully after CRRM.

P058: Liquid biopsy for cancer precision medicine revealed HBOC pedigree and led to management of relatives—a case report

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A 48-year-old woman was referred for genetic counselling for cancer precision medicine. The patient was diagnosed with stage IV ovarian cancer at age 45 and received chemotherapy, but her condition progressed. She had a family history of liver cancer with HBV, but no history of HBOC related tumors. The patient and her husband requested to perform cancer precision medicine and also wanted to know germline findings. Since analysis was difficult using DNA extracted from formalin-fixed paraffin-embedded (FFPE) specimens, screening using cell-free DNA (cfDNA) from plasma was performed. The result strongly suggested that she had germline pathogenic variant of BRCA1. Our team proposed her to be treated with PARP inhibitor and provided information on the possibility of HBOC. The patient received olaparib therapy. After the genetic counselling, the patient performed a single-site genetic test for BRCA1 with her germline DNA. The results also showed a BRCA1 germline pathological variant. Her three children received single-site genetic test, and one of them had the same pathogenic variant as the mother. She led to medical management for her cancer prevention.

In this case, a HBOC pedigree was found from cancer precision medicine by liquid biopsy, and led to genetic counseling and personal management for relatives. BRCA1/2 can be found the most frequently in advanced ovarian cancer patients through cancer precision medicine. Continuous genetic counseling for proband and unaffected relatives are important, which requires further coordination between medical departments because the chances of being diagnosed as HBOC should be increase.

P059: Real-world study of patient demographics, clinical characteristics and BRCA1/2 testing in HER2-negative (HER2-) advanced breast cancer (ABC) in the US and Europe

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Background Recently, poly ADP-ribose polymerases inhibitors (PARPi) in HER2- ABC have become available and international guidelines have broadened eligibility criteria for BRCA1/2 testing. This analysis assessed demographics/clinical characteristics and BRCA1/2 testing (germline ± somatic (g ± s), s only and unknown) in HER2- ABC adults in the US, and Germany, France, Italy and Spain (EU4).

Methods Oncologists extracted data from medical charts for the next 8–10 presenting patients with HER2- ABC in 2019/2020. Differences in demographics/clinical characteristics among BRCA1/2 tested/untested patients and BRCA1/2 testing rates were analyzed via t-tests and Fisher's exact tests. Analysis of BRCA1/2 testing were stratified by region, gender and hormone receptor (HR) status [HR+/HER2− or triple negative breast cancer (TNBC)].

Results 2418 records [US 17.4% (n = 421), (EU4 82.6% (n = 1997)] were provided by 266 oncologists. The mean age was 63.1 years. Clinical characteristics were: 83.9% HR+/HER2−, 12.6% TNBC, 3.5% unknown HR status. Significantly lower BRCA1/2 testing rates were observed in EU4 vs. US; 42.2% (g ± s *BRCA*mut 26.6%, *sBRCA*mut only 10.7%, unknown 4.8%) vs. US 73.4% (g ± s *BRCA*mut 46.3%, *sBRCA*mut only 18.1%, unknown 9.0%) ($p < 0.001$). Across all countries, significantly lower BRCA1/2 testing was seen among HR+/HER2− vs. TNBC patients (42.1% vs. 82.0% ($p < 0.0001$)). BRCA1/2 tested vs. BRCA1/2 untested patients were younger (mean age 59.08 years vs. 66.8 years ($p < 0.0001$)) and more likely to have a known family history of BRCA-related cancer 26.6% vs. 10.8% ($p < 0.0001$). Males (n = 19) were more likely to have received a BRCA1/2 test than females (n = 2399) 63.2% vs. 47.5% ($p = 0.248$).

Conclusions In adult patients with HER2- ABC, differences in demographics/clinical characteristics were observed among BRCA1/2 tested vs. untested patients. Across all countries, gBRCA1/2 testing rates were low. With the advent of targeted therapies and broadening of testing guidelines, opportunities should be developed to increase gBRCA1/2 testing, particularly among HR+/HER2− patients.

Funding Pfizer.

P060: Uptake of phrophylactic mastectomy in BRCA1/2 in South Eastern Norway

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Background At Department of Medical Genetics, Oslo University Hospital, all female carriers of pathogenic variants in the BRCA1 and BRCA2 genes are informed about the possibility to undergo prophylactic mastectomy to reduce their cancer risk. Previous international studies have demonstrated that less than 30% chose this option, but rates of surgery vary between countries and will likely change over time. During the last years an increasing number of carriers in our clinic have chosen prophylactic surgery, and most newly detected mutation carriers are referred for surgery. However, we have no systematic knowledge of the actual numbers.
Methods All female BRCA1/2 carriers without previous breast cancer were identified in the quality register for inherited cancer at the department. Information was registered on year of positive test result, whether or not they had undergone mastectomy, and if yes, age at surgery.
Results In total, 1850 carriers with no history of breast cancer were identified, 1199 BRCA1 carriers and 651 BRCA2 carriers. Eight hundred and twenty of all carriers (44%), 613/1199 (51.1%) BRCA1 carriers and 207/651 (31.8%) BRCA2 carriers had undergone prophylactic mastectomy. Mean and median age at surgery was 43.2 and 42 years for all, 42.4 and 41 years for BRCA1 carriers and 45.5 and 45 years for BRCA2 carriers. Analyses are ongoing regarding uptake of surgery according to age group and year of positive test result.
Conclusion Contrary to what we expected, less than 45% of all carriers with no history of breast cancer had chosen prophylactic mastectomy. Uptake of surgery was higher in BRCA1 than in BRCA2 carriers. Further results will be presented.

P064: The British Columbia Hereditary Cancer Follow-up Initiative (HCFI): a provincial approach to providing support to people living with hereditary cancer syndromes

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Background The BC Cancer Hereditary Cancer Program (HCP) is a consultative service providing hereditary cancer genetic counselling and testing across BC and Yukon. Risk management is available for a subset of patients through the HCP High-Risk Clinic; however, the majority of individuals with hereditary cancer risk are followed by their primary care providers. To better understand barriers and gaps in accessing follow-up care, the HCP launched a clinical pilot, the Hereditary Cancer Follow-up Initiative (HCFI).
Methods Between July 2020 to March 2021, 3826 eligible individuals (19 and over) were contacted by email or mail and invited to complete an online questionnaire. Information was obtained on access and frequency of cancer surveillance/screening, risk reducing surgeries, family communication about genetic risk and additional support needs. Completed surveys were reviewed by a genetic counsellor (GC) who provided phone appointments to those who reported screening discordant with current recommendations or who requested follow-up for additional support.
Results To date, 885 (23%) surveys have been completed. Response rates were higher for patients contacted by email as compared to mail (51% vs 18%). Of the completed surveys, 60% (528) of respondents required additional GC follow-up. 228 individuals (26%) reported screening inconsistent with current recommendations. Reasons for delayed or missed screening included lack of access to a health care provider to organize screening, lack of clarity or knowledge regarding screening recommendations, difficulty traveling to appointments and delays due to the COVID-19 pandemic.
Conclusions Preliminary results show a positive impact of the HCFI and highlight the need for improved continuity of care. Data gathered by this initiative will be used to advocate for resources to improve access to early detection and preventive measures, facilitate cascade carrier testing and provide additional psychosocial supports for high-risk patients and families, ultimately reducing risk and improving quality of life for these individuals.

P065: Variant reclassification and its impact on clinical care in an Asian country

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Background Genetic testing has demonstrated clinical utility in the identification and subsequent surveillance of patients with cancer predisposition syndromes. However, the increased likelihood of encountering a variant of uncertain significance (VUS) in individuals of non-European descent such as Asians may be challenging to both clinicians and patients in interpretation and management. VUS can be reclassified as more data becomes available. VUS reclassification is important, as it may have implications for surveillance and treatment. This study aims to evaluate the prevalence and patterns of variant reclassification in an Asian country and its impact on patient management.
Methods A prospective cohort of patients seen at the Cancer Genetics Service at the National Cancer Centre Singapore between February 2014 to March 2020 was evaluated. The frequency, direction and time to variant reclassification was assessed by comparing the reclassified report against the original report.
Results A total of 1412 VUS were reported in 49.9% (845/1695) of patients. Over six years, 6.7% (94/1412) of variants were reclassified. Most VUS (94.1%; 80/85) were downgraded to benign/likely benign variant, with a smaller proportion of VUS (5.9%; 5/85) upgraded to pathogenic/likely pathogenic variant. Actionable VUS upgrades and pathogenic/likely pathogenic variant downgrades, that resulted in management changes, happened in 31.0% (39/126) of patients. The median and mean time taken for reclassification were 1 and 1.62 year(s) respectively.
Conclusions Clinicians need to put in place a system for review of variants, as variant reclassification can lead to changes in management in nearly 1/3 of patients. Management should be based on the patient's personal history, family history and variant interpretation. We propose a clinical guideline to standardize management of patients with VUS. For clinically relevant or suspicious VUS, follow-up is recommended every two years, as actionable reclassifications may happen during this period.

P066: The patient perspective: experiences of Canadian women undergoing genetic testing and risk-reducing surgery for ovarian cancer prevention

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Purpose To understand the experience of previvors who have undergone genetic testing (GT) and/or gynecologic risk-reducing surgery (RRS) in Canada, to identify gaps and opportunities for advocacy.
Methods A 10-question anonymous online survey was open from October–November 2019, followed by 1-on-1 semi-structured interviews between June–September 2020.
Results Responses were received from 61 previvors (N = 42 surveys and 19 interviews) from 7 provinces. Interviewees included women with mutations in BRCA1, BRCA2 and BRIP1. Most (79%) interviewees had undergone GT within the past 5 years and 74% had completed RRS. Interviewees had a family history of ovarian (74%) and/or breast (84%) cancer, and 16% noted a personal history of breast cancer. Among all respondents, 51% and 31% considered GT based on recommendation from a relative or healthcare provider. Only 28% had spoken with their family doctor about their family history prior to GT. During pre/post-test counselling, previvors were generally satisfied with explanations provided on estimated lifetime cancer risk for themselves or relatives (72–87%) and strategies for risk reduction (78%). Fewer previvors had a satisfying discussion on the psychosocial impact of GT (52%) and how to communicate GT results to relatives (38%). During pre-surgical consultations, many were satisfied with explanations provided on the best time to have surgery (72%), what to expect during recovery (64%) and potential risks/side effects of surgery (62%), but not post-surgical options for hormonal treatments (38%), reducing impact on bone and/or cardiovascular health (33%) and fertility/reproductive options (7%). Most RRS procedures were performed by gynecologist/obstetricians (76%) and 82% had ovaries and fallopian tubes removed. While 71% had RRS prior to 50, only 42% of interviewees had RRS by the recommended age based on their mutated gene.
Conclusion Feedback from Canadian women at risk for ovarian cancer has identified gaps in communication with family doctors, during pre/post-test counselling and pre-surgical consultation.

P067: Quality of life: a challenge for the multidisciplinary management of hereditary breast and ovarian cancer patients

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Quality of life assessment has become a challenge for clinical care Hereditary Breast and Ovarian Cancer (HBOC) patients, due to medical, psychological and economic implications, particularly linked to Risk Reduction Surgeries (RRS). The aim of the present study was to evaluate the quality of life in two groups of oncological patients with BRCA1/2 germinal mutations, divided by the decision of RRS measures versus Surveillance (S).
Methods We carried out a cross-sectional study of a population of 60 patients with BRCA1/BRCA2 mutations, from the Hereditary Cancer Clinic, of the National Cancer Institute (Mexico). Close S and RSS were performed, according to medical and personal election. The Spanish version of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) instrument was used to evaluate quality of life. Also, a semi-structured interview for sociodemographic aspects and comorbidities was conducted.
Results The most prevalent diagnosis found was breast cancer in 72% of the sample. 68% of the patients carried BRCA1 mutations; 22% carried BRCA2 mutations. For the RRS subgroup, the mean age at the time of application of the instrument was 43 years. Bilateral salpingo-oophorectomy was the most prevalent surgery in the RSS group, representing the 63% of the procedures. It is expected that a comparison of the level of quality of life in both groups will reveal factors that may be conditioning the type of intervention chosen.
Conclusions Quality of life assessment remains a main challenge for the clinical care and multidisciplinary management of HBOC patients. However, there are factors contemplated in the social and economic context that can be considered as determinants in our population, for optimizing medical management and patient's decision-making.

P068: The current and future problems of genetic tests in our institution

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Background Genetic testing has progressed. Diagnoses and treatment for BRCA-positive breast cancer have been remarkably developed, however we are still worried about who and when we need to perform the genetic test. There are a wide range of issues including the interpretation of the results and subsequent counseling involving the family.
Objectives We retrospectively examined the clinical characteristics, test results, and subsequent treatment of patients who underwent BRCAnalysis in our department.
Results We analysed 15 patients with advanced and recurrent breast cancer. Median age of patients was 50 years (35–65). Six (40%) had a family history of breast cancer and one had a father with a history of prostate cancer. Biological characteristics were 10 in Luminal type and 6 in triple negative type, and one of them was HER2 positive in primary tumor but HER2 negative in metastatic lesion. ER high expression was observed in 6 patients (40%).

The test was performed during the period from no previous treatment to the second treatment in four patients, and the rest were performed during the third treatment to the sixth treatment. It is probable that the test was conducted in the late phase because of the timing of the insurance application. The results showed variants in three of them, two of which had pathological significance. The mutation of one person is BRCA1 comprehensive rearrangement/del exons 5–7/deleterious, and to date there have been similar reports

from Asia and Turkey. At the age of 64 at the time breast cancer was diagnosed, the biology of the primary tumor in Stage III was triple negative, and her sister had bilateral breast cancer. Olaparib was used for third line therapy, after first-line EC and second-line PTX. However, Grade 3 anemia was observed after 1 month of administration of Olaparib. The peritoneal dissemination progressed and ileus occurred, making it difficult to continue. Another variant is BRCA2 c.475 + 1G > A, and one similar report was done in Japanese data. The disease was found at the age of 46 as StageIV. At the time of the examination, she was 47 years old. The primary tumor was triple negative, and her younger sister had breast cancer. She was examined during the fifth treatment and found to have a mutation, but she has not taken oralarib at present.

Consideration In this experience, there was one case in which HER2 in the metastatic focus was reversed and BRCAnalysis was performed. In many cases, the primary tumor was tested, but if possible, it would be necessary to conduct a biopsy of the metastatic focus in advance to confirm the biological characteristics. In addition, at the time of testing and the time of prescribing Olaparib, there was a case in which ileus occurred and it was impossible to continue taking the oral dose. In the case of an example, it is necessary to consider that an inspection is performed early.

ETHICS AND LEGAL ISSUES

P085: Pre-Mayo & post-Myriad: Effect(s) of Supreme Court case decisions Mayo Collaborative Services v Prometheus Laboratories (2012) and Association for Molecular Pathology v. Myriad Genetics (2013) on hereditary cancer genetic testing practices & access

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Genomic variants associated with inherited cancer risk are a battleground between open science and proprietary data practices. As an integral part of the "Sulston Project Making the Knowledge Commons for Interpreting Cancer Genomic Variants More Effective," we examine the Supreme Court case decisions Mayo Collaborative Services v. Prometheus Laboratories (2012) and Association for Molecular Pathology v. Myriad Genetics (2013), identifying any resultant effect(s) on hereditary cancer genetic testing practices, data-sharing, and access.

We identified relevant genomics policy researchers, molecular diagnostics laboratories, freely available databases (e.g., ClinVar, gnomAD, and LOVD), and subscription-based databases (e.g., Human Gene Mutation Database and Universal Mutation Database). A significant focus was placed on suspected high-volume hereditary cancer molecular diagnostics laboratories, with subsequent, and primarily qualitative, interviews conducted through encrypted video conferencing and stored on a secure cloud database.

While this case study is currently in progress, I anticipate having interviewed: Mayo Clinic, Invitae, Color, GeneDx, ARUP, Ambry, Quest, Veritas, LabCorp, University of Chicago, and Myriad (amongst others). Our scoping interviews are primarily focused on questions relating to: offering of BRCA1/2 testing (and date first offered), inclusion of any major rearrangements, offering of cancer gene panel testing (and date first offered), gene selection (and associated criteria), data-sharing, and patent effects on hereitary cancer testing practices.

Together, this data offers a snapshot of the battleground between open science and proprietary data practices relating to both BRCA1/2 and other genes associated with inherited cancer risk.

P086: Is there any legal framework regarding genetic discrimination in Mexico? A review of the legal system

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Genetic discrimination (GD) refers to discrimination against an individual or his family based on genetic variation; GD could impair access to healthcare and employment. To our knowledge, no recent reviews exist in the Mexican context. Herein, we performed a review of GD in the literature and Legal System of Mexico. Google Scholar was searched using the key words: "GD" "Mexico" "genetic employment" "genetic insurance". We also searched in the levels of hierarchy of the Mexican legal system. Finally, we consulted the General Insurance and Mutual Companies Law (GIMCL), and 2 insurance representatives, who agreed to participate anonymously. 1 paper published in 2006 described a legal framework.

Our findings according to the hierarchy of the legal system was: 1. Constitution: no mention of GD. 2. International Treaties are not signed by the Mexican state. 3. Article 103 of General Health Law was added in 2011, discrimination is prohibited on the grounds of genetic features, and fines are stipulated for its offenders. General Labor Law: no mention of GD. 4. Article 9 of Federal Law to Prevent and Eliminate Discrimination (includes genetic features) prohibits denying or conditioning medical care and the imposition of limitations for the contracting of medical insurance. GIMCL does not contemplate the use of genetic information.

Representatives don't estimate premiums according to family history; disclosure or previous genetic testing is not required. No specific act against GD in Mexico exists. Nonetheless, it is contemplated in 2 laws in the legal system, which offers a protection framework. GD is a topic to be addressed during genetic counseling sessions for patients to make informed decisions. 1/263 Mexicans would be carriers of BRCA1&2 mutations, it would be a priority to identify those carriers, but also to ensure that they will not be victims of GD and they will receive adequate healthcare services.

P087: Sponsored genetic testing in Canada: current perspectives and practices

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Background Sponsored genetic testing (SGT) programs offer reduced or no-cost testing to patients who meet broad eligibility criteria. In exchange for accessible clinical testing with short turnaround times, genetic data and clinical information is shared with program sponsors. Despite increased prevalence and marketing to cancer patients and clinicians, little is known about Canadian SGT practices and limited guidance exists on the use of SGT.

Methods This online survey explored perspectives and practices of SGT among members of the CCMG Canadian Cancer Genetics and Genomics (C2G2) Community of Practice. All participants were provided with an option to submit their responses anonymously.

Trends and common themes were identified. Preliminary findings were presented and discussed with C2G2 members at a virtual meeting, alongside SGT experiences at three Canadian centres.

Results Of the 354 C2G2 members, 54 responded to the survey. Almost half (48%) submitted their responses anonymously. While the majority (59%) were genetic counsellors or clinical/medical geneticists, respondents included a variety of non-genetics clinicians, laboratory geneticists, scientists, and patient advocates. 74% indicated that SGT should be offered to all or select patient populations, while 15% were unsure. Suggested conditions for offering SGT included non-partisan pre-test genetic counselling and discussion of alternative testing options to facilitate informed decision making. Perspectives regarding the impact of SGT were also elicited. Participants identified potential challenges, risks, and improvements concerning patient privacy and data sharing, ordering clinicians, and Canada's single-payer health insurance systems. A broad range of clinician practices surrounding SGT were reported.

Conclusions Findings from our survey have initiated a nation-wide multidisciplinary discussion regarding SGT and have revealed variation in Canadian practices and perspectives on this novel testing option. More comprehensive research will contribute to the development of guidelines and resources for patients and clinicians considering SGT.

P088 Rapid Fire Presentation: Polygenic risk scores and the return of breast cancer risk results: Canada—United States experience

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Large scale research projects using Polygenic Risk Scores (PRS) and non-genetic risk factors to estimate breast cancer risk raise specific ethical and social issues with regard to the return of results to participants and their healthcare providers. These issues arise due to: the novelty of the information returned; the uncertainties regarding interpretation and clinical utility, in particular those from non-European ancestry; the genetic markers included or excluded; the diversity of possible screening and follow-up measures that may be proposed; the need to align with healthcare systems; and, the adoption of risk-adapted screening recommendations by individuals and their healthcare providers. Under a comparative approach, we describe how two large-scale similar projects – combining PRS and non-genetic risk factors to individualize breast cancer screening practices – are addressing these challenges.

The first project (PERSPECTIVE I&I) is recruiting 8000 Canadian women in a publicly funded healthcare system that includes various governmental breast cancer screening programs. The second project (WISDOM) is recruiting 100,000 US women into a pragmatic randomized controlled trial in a publicly and privately funded healthcare system with various and often conflicting screening guidelines. In these two projects, the absence of face-to-face interaction with participants (for consent and the collection of saliva samples), and the use of online tools (for recruitment, data collection and return of results) elicit specific inclusion and communication issues. Moreover, in the US context, insurance coverage for screening using PRS and the regulation of PRS remain unclear. We focus on practical solutions for a future clinical implementation of a scaled-up multifactorial risk-based screening approach. We will also demonstrate the importance of having a transdisciplinary approach with researchers specialized in ethical and social issues embedded in the projects in order to bring innovative, adaptable and evolving solutions that adequately address these emerging challenges.

P089: Introduction for "Clavis Arcus", a patient association supporting BRCA1 and BRCA2 pathogenic variant carriers and their families in Japan

Makiko Dazai

Nonprofit organization Clavis Arcus, Tokyo, Japan

Clavis Arcus is the first and only patient association supporting BRCA1 and BRCA2 pathogenic variant carriers and their families in Japan. The organization was established in 2014 and was certified as a nonprofit organization by the Tokyo Metropolitan Government in 2015. The organization aims to provide a gathering space for the members to support each other and to deepen knowledge and understanding of hereditary tumors. There are 78 members among Japan, and has a branch in Pennsylvania, US.

The organization provides consultations by phone, e-mail and in person as well as holding patient gatherings. We started the "Institute of Genetic Studies" for further understanding of hereditary cancers, education for peer support and to hold Learning about Genetics for Families seminars annually.

Recently, photo panel exhibitions are running nationwide in Japan. The photos consist of the image of the members themselves and letters from their family.

http://www.clavisarcus.com

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

P093: CHARM Consortium: early cancer detection in BRCA1 and BRCA2 carriers using cell-free DNA sequencing

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Background BRCA1/2 carriers are enrolled in surveillance programs using annual mammography and MRI. While this screening modality has high sensitivity for detection of breast cancer (93 –100%), there is no screening test for ovarian cancer or other BRCA1/2-associated malignancies such as ovarian and pancreatic cancer. We hypothesize that cfDNA analysis can detect many BRCA1/2-associated malignancies and enable earlier cancer detection.
Methods We established a national consortium termed CHARM (cfDNA in Hereditary And High-Risk Malignancies) to collect serial plasma samples from $\sim$ 1000 BRCA1/2 carriers. With 9 sites across Canada, any carrier regardless of their cancer status is eligible for the study and undergoes annual plasma, extensive medical history, and imaging collection. All active cancer patients, and their matched tumour specimen when available, will be evaluated using shallow whole genome sequencing, targeted panel sequencing (BRCA1, BRCA2, PALB2, TP53, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MSI loci, identity SNPs), and Cell-free Methylated DNA Immunoprecipitation and High-throughput Sequencing. During the course of the study, participants may phenoconvert and we will analyze their past plasma samples to determine clinical limit of detection. Alongside genomic analyses, we are performing multiple qualitative studies to assess patient and provider perspectives on the test's clinical utility and implementation.
Results Active recruitment has begun at two sites with 234 BRCA1/2 carriers enrolled (147 BRCA1, 85 BRCA2, 2 both) and 194 samples collected, with > 1 plasma sample collected on 18 participants. Funding contracts are established, and sequencing protocols have been harmonized between BCCA and UHN thereby providing capacity in eastern and western Canada. Ongoing efforts include research ethics submissions, a large consortium agreement, development of a database to house clinical data, and interviews with health care providers.
Conclusions This study will develop national infrastructure for collection, profiling, and analysis of serial blood samples for early detection of cancer.

P094: Establishing a BRCA1/2 variant screening method in ovarian tumor tissue for potential PARP inhibitor treatment

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Introduction In Norway, more than 500 women are diagnosed with ovarian cancer every year. Around 25% of the patients have a BRCA1/2 pathogenic variant, of which 10% are somatic. These patients are associated with a favorable response to poly ADP ribose polymerase (PARP) inhibitor treatment.

Historically, ovarian cancer patients were only offered germline testing. The Division for Laboratory Medicine at OUS started a project in 2019, with collabaration between gynecology, pathology and cancer genetics, aiming to offer routine diagnostic BRCA1/2 tumor testing. The project was succesful and routine testing for somatic variants using isolated DNA from tumor material has been established. The national strategy for ovarian cancer now states that PARP inhibitor treatment can be given as a first-line treatment/therapy to ovarian cancer patients with a somatic pathogenic BRCA1/2 variant.

Method Using needle biopsies or ascites fluid as sample material, estimated to contain at least 30% tumor tissue by a pathologist, we perform next-generation sequencing using a custom capture kit from Illumina. Variants are called using a tumor pipeline. The method is validated to detect variants with an allele frequency $> 5\%$ and a read depth of 250x. Only variants classified as likely pathogenic or pathogenic are reported.
Results We successfully established a method for detecting somatic BRCA1/2 variants. In the beginning the laboratory received 1–2 samples/week. The project collaboration has been satisfying and we have developed a good sample handling workflow, resulting in reports delivered within a 3 week t93rnaround time. The sample material gives high quality DNA, but is invasive and can be contaminated with DNA from non-neoplastic cells.
Future aspects As PARP inhibitors have been approved for first-line therapy, there will now be a need for extensive testing. We aim to analyze DNA isolated from FFPE, as this will give more patients the oportunity to have their tumor assesed for potensial PARP inhibitor treatment.

P095 Rapid Fire Presentation: A rapid point-of-care test for detection of pathogenic BRCA1/2 founder variants: pharmacogenetic evaluation of South African breast cancer patients selected by tumour molecular subtype

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Background Poly(ADP-ribose) polymerase (PARP) inhibitor treatment approved for patients with breast, ovarian, prostate and pancreatic cancer underpinned by pathogenic BRCA1/2 variation, becomes clinically applicable through pharmacogenetic germline and somatic DNA testing. Cascade family testing and reduction of recurrence risk are particularly important considerations in South Africa due to an increased frequency of at least eight pathogenic BRCA1/2 variants detected across ethnic groups.
Methods A novel fluorescent polymerase chain reaction (PCR) assay using HyBeacon probes was developed to enable genotyping directly from buccal swabs, blood samples or extracted DNA using the ParaDNA instrumentation (LGC, Teddington, UK). Software was also developed to automatically report genotyping results. The assay and software was validated against Sanger and next generation sequencing (NGS) results obtained for BRCA1 c.68_69delAG, c.1374delC, c.2641G $>$ T, c.5266dupC and BRCA2 c.5771_5774delTTCA, c.5946delT, c.6447_6448dupTA, c.7934delG. Subsequently, the BRCA1.0 point-of-care (POC) Research Assay was evaluated in 64 DNA samples of histopathologically confirmed breast cancer patients previously referred for NGS or microarray-based tumor molecular subtyping and CYP2D6 genotyping using real-time PCR.

Results The performance of the BRCA 1.0 Research Assay and accuracy of software calls were verified using 10 control DNA samples of known BRCA1/2 genotype as well as non-template controls. All control samples were assigned the correct software calls from 2 ng down to 62.5 pg of input template DNA. Genotyping of 64 breast cancer patients revealed that eight (12.5%) patients tested positive for variants included in the POC assay.
Conclusions We observed excellent correlation with laboratory-based methods using the newly developed method as a rapid first-tier test to determine the need for NGS. Germline DNA screening for the eight known pathogenic BRCA1/2 variants can inform clinical decision-making within 1 h assay time. Further studies are warranted to determine the cost-effectiveness of BRCA POC testing combined with CYP2D6 genotyping in comparison with NGS enabling simultaneous pharmaco-diagnostic assessment.

P096: Detection of germline and somatic BRCA mutations using a 50-gene next-generation sequencing panel

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Objectives Breast and ovarian cancer patients may benefit from treatment with PARP inhibitors, but testing for somatic and/or germline BRCA mutations may be needed to evaluate eligibility. We previously developed a next-generation sequencing (NGS) panel that simultaneously detects somatic and germline mutations in breast and ovarian FFPE tumor specimens. Here we report the prevalence of BRCA1/2 and TP53 mutations in real-world specimens submitted for testing at a national reference laboratory.
Methods We retrospectively analyzed de-identified results from 240 consecutive FFPE tissues submitted for testing with a 50-gene panel. This assay uses targeted exon capture and NGS to detect variants in BRCA1, BRCA2, TP53, and 47 other actionable genes frequently altered in solid tumors. Specimens were from patients with breast cancer (n = 124, median age 54), ovarian cancer (n = 115, median age 63), or both (n = 1, age 48).
Results In total, pathogenic BRCA mutations were identified in 4.8% (6/124) of breast cancer (4 in BRCA1 and 2 in BRCA2) and 13.9% (16/115) of ovarian cancer patients (11 in BRCA1 and 5 in BRCA2). Variants of unknown significance in BRCA1/2 were detected in 10.5% (13/124) of breast and 7.0% (8/115) of ovarian cancer patients. Notably, pathogenic TP53 mutations were detected in 93.3% (14/15) of BRCA1 mutation-positive patients, compared with 62.8% (137/218) BRCA1/2 mutation-negative patients ($p = 0.016$). The BRCA1+ /TP53− patient specimen had a TP53 Pro47Ser (rs1800371) variant, a polymorphism with unknown cancer risk. Among 3 patients who had matching blood specimens available, 1 BRCA1 mutation was confirmed to be germline, while 2 BRCA1 and 3 TP53 mutations were somatic.
Conclusions Our optimized NGS method detected actionable BRCA mutations in breast (5%) and ovarian (14%) cancer patients, in accordance with previously published data. Pathogenic TP53 mutations accompanied most (93%) BRCA1 mutations in the breast and ovarian tumors examined.

P097: Heading towards an in vivo predictive test for personalized ovarian cancer treatment: application of novel therapies in zebrafish patient derived xenografts

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Most ovarian cancer patients are diagnosed at an advanced stage, resulting in a poor prognosis. Standard therapy schemes are applied to all epithelial ovarian cancers, but specific histologic subtypes do not respond. To improve treatment, an in vivo predictive test for treatment response is warranted. Very promising are zebrafish patient derived xenograft (zPDX) platforms which are cost-effective, require limited donor material and allow to evaluate initial therapy response within 2 weeks.

The aim of this study is to optimize this zebrafish xenograft platform starting from cancer cell lines. Tumor cells are first labeled with a fluorescent dye, Vybrant CM-DiI. A few hundred of these cells are injected into the perivitelline space of 2 dpf transparent zebrafish embryos. Xenografts are kept individual for treatment and are followed for 4 executive days. Then, PDX models are euthanized and fixated for whole mount staining. PDX are either stained for cleaved-caspase 3 (apoptosis) or Ki67 (proliferation) to score tumor response. Zebrafish xenografts are visualized by a fluorescence confocal microscope.

We have successfully engrafted several ovarian cancer cell lines (A2780, OVCAR-3, M28/2). Both in vivo and post mortem we can appreciate clear and compact tumor masses. One LGSOC cell line derived from mice PDX shows a KRAS c.35G > T (p.(Gly12Val) variant and is sensitive to the MEK inhibitor, trametinib (De Thaye et al., 2020). This cell line engrafts well in zebrafish embryos and shows clear proliferation as illustrated by Ki67 staining. Upon treatment with trametinib these xenografts showed higher caspase activity, in agreement with previous in vitro experiments. To allow quantification, a higher resolution fluorescence confocal microscope will be introduced. After optimization of the xenografting with cell lines and validation of read-outs, engraftment of tumour tissue from patients will be performed. We are convinced that the information generated from the zPDX experiments will lead to improvements in personalized medicine.

NON-BRCA1/2 GENETIC FACTORS ASSOCIATED WITH CANCER RISK

P104: Pathogenic germline mutations and clonality of paired tumours in a population of synchronous breast cancers

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Synchronous breast cancer (SBC—bilateral breast cancers diagnosed within 6 months of each other) accounts for 1–3% of all breast cancer diagnoses, in contrast to the majority of breast cancers, which are unilateral. Furthermore, current clinical practice assumes that SBCs represent two independent primary tumours. Given this, we hypothesise that women with SBC may carry undetected germline mutations in breast cancer risk predisposition genes, resulting in the development of bilateral tumours. Furthermore, published data suggests that women with SBC have a significantly worse prognosis than those with unilateral disease, implying that a proportion of these cases may represent metastatic disease rather than two independent tumours.

To determine the impact of SBC on outcomes, and to assess the contribution of known hereditary breast and ovarian cancer (HBOC) gene mutations to SBC risk, we identified 221 women diagnosed with SBC in Northern Ireland between 2000 and 2015. To date, we have sequenced germline DNA (gDNA), and primary and SBC DNA in 143 women, using a custom panel, including known risk predisposition genes.

Preliminary data has identified 16 patients (11.2%) with pathogenic germline mutations in BRCA1, BRCA2(× 3), PALB2, & FANCL. Shared somatic variants were found in 13 (9.8%) tumour pairs, indicating a shared clonal origin suggestive of metastatic disease.

The high incidence of pathogenic germline mutations indicates a potentially significant influence of inherited risk for these women developing breast cancer. This suggests that women with SBCs may benefit from gene panel testing at diagnosis in order to guide treatment strategies. Furthermore, such testing may identify women at increased risk of ovarian cancer, facilitating risk reduction strategies. Additionally, the incidence of metastatic disease in this cohort (9.8%) emphasises the need to consider this scenario in women presenting with bilateral breast cancers.

P105: Phenotypic characterization of carriers of CHEK2 c.470T>C variant

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Background Functional studies have indicated that binding of p53 and BRCA1 by CHEK2 is deleteriously affected by the c.4700T>C variant (p.Ile157Thr). However it is considered a low-penetrance breast cancer (BC) susceptibility allele with a relative risk < 2. We analyzed the frequency of CHEK2 c.4700T>C among familial BC patients and the phenotype associated with this variant.
Methodology The frequency of the CHEK2 c.4700T>C variant was analyzed in 1661 familial non-BRCA1/2 BC patients who underwent next generation sequencing with a panel of BC susceptibility genes. Patients' medical records were reviewed for clinical data and family history of cancer.
Results The CHEK2 c.4700T>C variant was found in 15 (0.9%), c.1100delC in 12 (0.7%) and c.1283C>T in 9 (0.5%) patients. Two patients with both c.4700T>C and c.1100delC variants and one with both c.4700T>C and c.1283C>T were identified (cis or trans to be determined).

Among carriers of c.4700T>C, four (26%) had two or more BCs, with a total of 20 BC diagnoses. Median age of first BC was 49 (range: 21–74) years. Pathological characterization showed 14 invasive ductal carcinomas (IDC)—6 ER+/PR+, 6 HER2+ and 2 triple negative breast cancers (TNBC), 4 ductal carcinomas in-situ, 1 invasive lobular carcinoma, and 1 lobular carcinoma in-situ.

Two patients (13%) were diagnosed with BC under age 31, the first with IDC ER+/PR+/HER2+ at 21 years and the second with IDC ER+/PR+/HER2− 30 years. Both had a limited family history and were carriers of only the c.4700T>C variant.
Conclusion In our cohort, 0.9% of familial non-BRCA1/2 patients were carriers of the CHEK2105470T > C variant. We observed multiple cases of aggressive phenotype (young age at diagnosis or multiple breast cancers), more suggestive of a high-risk breast cancer gene. Further characterization in conjunction with polygenic risk assessment is warranted to better define the phenotype of this variant.

P106: Functional characterization of non-truncating SMARCA4 variants in familial SCCOHT

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Germline variants in SMARCA4 predispose women to small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). Loss of function (LoF) of the SMARCA4 gene combined with loss of SMARCA4 protein expression on immunohistochemistry (IHC) in an ovarian tumour is pathognomonic for SCCOHT. However, non-truncating variants in SMARCA4, such as missense and in-frame variants, are difficult to classify due to their unknown effect on the gene. We present two familial cases of SCCOHT where all affecteds carried non-truncating germline SMARCA4 variants. To further investigate the effect of these variants and better classify other non-truncating variants, we developed an SCCOHT-specific in vitro assay.

Both families consisted of a mother and daughter affected with SCCOHT. In Family 1 (previously published in Witkowski et al., 20,141), the two women carried a missense variant in SMARCA4: c.3239G > A (p.Gly1080Asp). Both tumours showed loss of SMARCA4 protein expression by IHC. In Family 2, the two women carried an in-frame deletion in SMARCA4, c.2311_2316del (p.Asn731_Asn732del), and both tumours showed weak nuclear SMARCA4 staining by IHC.

In vitro studies demonstrated that these variants had a similar effect as other LoF SMARCA4 variants. We have previously shown that SCCOHT tumours have loss of cyclin D1 expression.2 Ectopic expression of wild-type SMARCA4 in SCCOHT cells resulted in strong growth suppression and elevation of cyclin D1 mRNA and protein levels, while expression of these two familial variants failed to do so. Consistent with these in vitro observations, tumours from both families were negative for cyclin D1 IHC, phenocopying other LoF SMARCA4 variants associated with SCCOHT.

Using a clinically-relevant in vitro assay, we show that non-truncating variants found in two familial cases of SCCOHT phenocopy other SMARCA4 LoF variants, leading to SCCOHT. This assay can be applied to all exonic SMARCA4 variants in affected and unaffected carriers to help classify non-truncating SMARCA4 variants.

Refs:
1. Witkowski et al. Nat Genet. 2014 May;46(5):438–43.
2. Xue et al. Nat Commun. 2019 Feb 4;10(1):558.

P107: Integrative approaches to identifying the causes of familial breast cancer

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In search of additional high-risk genetic factors of breast cancer, we analysed over 1400 genes in up to 6000 non-BRCA1/2 familial index cases and 6000 Australian population controls using targeted exome sequencing. A significant overall enrichment of rare loss-of-function (LoF) variants was found in the case cohort among the genes examined ($p = 7.42 \times 10^{-5}$). However, identification of the specific genes responsible for the increased risk has been challenging due to the rarity of variants in individual genes and their apparent low-moderate penetrance. Additional evidence is needed to support their breast cancer predisposition role.

Sequencing of breast cancers from germline variant carriers can provide strong evidence for their causative role through identification of bi-allelic inactivation and characteristic mutational signatures, as we demonstrated previously for PALB2 and RAD51C. We have extended this approach to the top candidate genes from the case–control analysis. Targeted and whole exome sequencing of 25 tumours from BARD1, BRIP1 and RAD51D LoF variant carriers showed that bi-allelic inactivation and associated mutational signature 3 occurred in over 40% of these tumours, with the majority of these being triple-negative breast cancers, indicating phenotype-specific predisposition for each of these genes. We have also sequenced 30 additional breast cancers from five novel candidate genes with an excess of LoF mutation in the cases versus control; CTH (9 cases vs 2 controls), BLM (20 vs, 8), CDK9 (5 vs 0), ERCC5 (5 vs 1), PARP2 (10 vs 2), MUTYH (15 vs 8) and WRN (34 vs 17). In addition, 36 breast cancers from carriers of potentially pathogenic missense variants in PALB2 and RAD51C have also been analysed, providing evidence for individual variants. To investigate the functional impact and ability to recapitulate breast cancer mutational signatures in candidate genes, we are establishing mono- and bi-allelic knockout models of candidate genes using CRISPR/Cas9 in MCF10A isogenic cell lines.

P108 Rapid Fire Presentation: BRA-STRAP: towards precision medicine and precision public health for breast cancer

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BRA-STRAP is an Australian nation-wide study of breast cancer predisposition that brings together genetic data on 24 genes commonly included on panel tests for breast cancer predisposition. Represented in BRA-STRAP are 30,000 Australian women of all ages across the cancer risk spectrum, affected and unaffected with breast cancer. These include women tested in an Australian Familial Cancer Centre and found negative for BRCA1 and BRCA2 mutations over the last two decades, as well as women participating in two Australian research studies: (i) the Australian Breast Cancer Family Registry (ABCFR), which includes 1400 case probands and their families, and matched population-based controls and (ii) the ASPREE study, that has contributed panel test data for over 13,000 healthy, elderly Australians. BRA-STRAP is also engaged with other similarly designed studies set outside of Australia (e.g. BRIDGES and CARRIERS).

Data on this scale represents the spectrum of genetic variation observed in these genes and exemplifies the opportunities and challenges for realizing precision medicine and precision public health for breast cancer.

Sequencing and data analysis was performed in-house for nearly 9500 women. All clinically actionable pathogenic variants in BRCA1, BRCA2, PALB2, TP53 and ATM have been validated using an orthogonal method in-house (validation rate 99.8% (488/489)), then in a NATA-accredited diagnostic laboratory before making the data available to families.

We estimated overall breast cancer risk (odds ratios), separately for loss-of-function and rare missense variants, and assessed missense variants by domain and clinical classification of pathogenicity. Using the population-based resources of the ABCFR, we estimated the age-specific cumulative risk of breast cancer (penetrance) for carriers (by gene and variant type). These results contribute to international efforts to more precisely identify the genes most clinically useful for inclusion on panels for breast cancer risk prediction and their associated risks.

P109: TUMOSPEC: a nation-wide family-based study to assess cancer risks in families with a predicted pathogenic variant identified through hereditary breast and ovary multi-gene panel testing

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Assessment of age-dependent cancer risk conferred by germline predicted pathogenic variants (PPV) in cancer susceptibility genes is often hampered by the way the data are collected. Cohort-based data sets frequently contain an overrepresentation of patients carrying a variant of interest and an underrepresentation of cancer-free variant carriers. Here we present the design and protocol of TUMOSPEC, whose purposes are to estimate the penetrance of PPV identified in a gene usually tested in parallel of *BRCA1* and *BRCA2* in a hereditary breast and ovary cancer context and to determine their associated tumour spectrum.

Index cases are enrolled consecutively among patients who are being offered a genetic test as part of their care plan. If a PPV is identified, first-, second-degree relatives and cousins are invited regardless of whether they are affected with cancer or not. Their genotype for the familial PPV is determined, and the coordinating centre collects also epidemiological questionnaire about their medical history and exposure to various risk factors, core family history data, as well as clinical data.

The feasibility study (September 2017 to December 2019) included 4502 index cases, and on average 4.3 relatives per family invited by the coordianting centre consented to participate. Inclusion processes are well adapted to the clinics and laboratories constraints and communication between the various partners (clinicians, biologists, investigators and study participants) is quite smooth. Rates of inclusions for relatives (60.6%), for index cases questionnaire completion (39.5%), and relatives biological sample collection (50%) are also very satisfactory and yet underestimated due to the recent start of relatives' inclusion.

This national effort will be pursued on a larger-scale in order to gather sufficient number of positive families for each gene. It will allow us to appropriately assess risks of cancer for PPV carriers, an essential step to optimize clinical management guidelines specific to each gene.

P110: Toward a better understanding of the experience of patients with moderate penetrance breast cancer gene mutations: a focus on ATM and CHEK2

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Multi-gene panels have changed the landscape of genetic testing for hereditary breast cancer. While the high risk population has been well studied, little is known about the experiences of patients with mutations in moderate risk breast cancer genes. The purpose of this study was to explore the experiences of patients with moderate penetrance breast cancer gene mutations by focusing on ATM and CHEK2.

139 surveys were sent to women with pathogenic or likely pathogenic variants in the ATM or CHEK2 genes who received genetic counseling Massachusetts General Hospital Center for Cancer Risk Assessment between 2014–2018. The surveys collected information about the perceived clinical significance of test results, adherence to management recommendations, disclosure of test results to relatives, and resources needs.

66 patients completed the survey. Most participants correctly identified their mutation status and understood the medical management recommendations. About 20% reported it was upsetting to share results with relatives, however nearly all participants shared with at least one relative. Over half (55%) of participants reported seeking additional resources for better understanding of results.

Our center's ATM /CHEK2 positive population appears to have a good understanding of the personal and familial implications of their results but may benefit from additional resources. It is unclear whether similar results would be found in patients who do not receive formal genetic counseling, and this should be examined. As multi-gene panel testing becomes commonplace, this study is one of the first to assess the experiences and needs of the moderate risk population.

P111: Mutational spectrum in hereditary breast cancer in a referral cancer center in Colombia

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Background Hereditary breast cancers account for 5–10% of all breast cancers and are caused by germline mutations in BRCA1, BRCA2 and other less studied genes. The Colombian population is understudied due to limitations in health care access, high costs and lack of Genetic services/counseling in certain regions of the country.
Aim This study describes the spectrum of germline mutations in breast cancer patients referred to the Instituto de Cancerologia Las Americas (IDC), a Comprehensive Cancer Center in Medellin (Colombia), in a 5-year period (2015–2020).
Methods Women with breast cancer referred to the Oncogenetics Unit of IDC, meeting NCCN testing criteria for Hereditary Breast and Ovarian Cancer syndrome, were tested using commercial BRCA1/2 comprehensive tests and multi-gene panels.
Results 485 women had genetic testing. 74 patients (15,25%) carried a germline mutation in a cancer susceptibility gene, with BRCA1 and BRCA2 accounting for 57,8% of the total of mutations (18 and 24 mutations, respectively), PALB2 12% (9 mutations) and TP53 9,5% (7 mutations). Two patients were double heterozygous (BRCA1-PMS2 and BRCA1- BARD1). Known breast cancer genes (i.e. BRCA1/2, PALB2, TP53, CHEK2, ATM, NF1), as well as genes with less evidence for breast cancer susceptibility (i.e. PMS2, MSH2, APC I1307K, RAD51D, MUTYH) were found mutated in our breast cancer patients. BRCA1 mutation carriers had a median age of diagnosis of breast cancer of 36,8 years (SD 8,7), BRCA2 of 36,9 years (SD 5,7), PALB2 of 38,7 years (SD 13,2) and TP53 of 30,6 years (SD 6,3).
Conclusions BRCA1/2 mutations account for more than 50% of our hereditary breast cancers and PALB2 is the third most frequently mutated gene. Although access to genetic services and testing is still limited in Colombia, reduction in costs and progressive access to multi-gene panel testing is revealing a new landscape of breast cancer genetic predisposition in Colombia.

P113: Missense ATM variant c.6919C>T (p.Leu2307Phe) may be associated with breast cancer risk but not ataxia telangiectasia

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Background Individuals with monoallelic pathogenic variants (PVs) in ATM have increased risks for female breast and pancreatic cancer, as well as possibly increased risks for aggressive prostate cancer and other malignancies. Individuals with biallelic PVs in ATM have Ataxia telangiectasia (AT), typically manifesting diverse and severe clinical features in childhood. Although variants in ATM are presumed to be pathogenic for both phenotypes, we find that monoallelic carriers of the variant c.6919C>T (p.Leu2307Phe) may have an increased risk for cancer, although biallelic carriers do not have clinically-apparent AT.
Methods De-identified clinical information from provider-completed test request forms was evaluated for both monoallelic and biallelic carriers of ATM c.6919C>T. The variant was assessed with a previously-described history weighting algorithm (HWA) comparing variant-associated cancer histories to histories of matched controls with known PVs in the same gene and matched controls with no PVs. A multivariate logistic regression model was used to estimate odds ratios (ORs) for breast cancer, reported with 95% confidence intervals (CIs).
Results The HWA indicates ATM c.6919C>T is associated with increased cancer risk with a high degree of confidence, based on 1760 observations. The allele frequency is 3.08% in the Ashkenazi Jewish population per gnomAD, and we have identified over 2300 monoallelic carriers of primarily AJ ancestry. No clinical features of AT have been reported for any of the 40 biallelic carriers with a median age of 55. The OR for female breast cancer in monoallelic women was calculated as 1.59 (95% CI 1.33–1.76), compared to 2.03 (95% CI 1.89–2.19) for previously-established ATM PVs.
Conclusion Monoallelic c.6919C>T ATM variants may be associated with increased cancer risk, but not recessive AT in the biallelic state. This has implications for how ATM variants are classified, as well as for assumptions influencing the classification of other hereditary cancer genes with recessive phenotypes.

P114: Breast cancer incidence in women with a first degree relative with male breast cancer who tested negative for BRCA1/2

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Background Unaffected women who have a close relative with male breast cancer (MBC) are at an elevated risk of developing breast cancer (BC) themselves. Negative genetic testing for men with MBC, can make counselling female first degree relatives (FFDR) on cancer risks, and providing screening recommendations, challenging. In this study we analyzed a cohort of FFDR of men diagnosed with MBC who tested negative for common breast cancer-associated genes.
Methodology A clinical genetics database of patients accrued between 1995 and 2019 was searched to identify men with MBC. Genetic test results and family history of cancer was collected. In this analysis, the cancer history of the mothers and sisters of these men were included.
Results Seventy men with MBC were identified. The average reported age was 76 (range 38–101). The average age of onset of MBC was 66 (range 34–88), MBC at age 50 or under occurred in 5/70 (7.14%) men. Genetic testing for BRCA1 and BRCA2 only occurred in 56/70 (80.00%) men, the rest received multi-gene panel testing.

There were 194 FFDR of men with MBC. The average reported age of FFDR was 76 (range 34–102). Breast cancer occurred in 37/194 (19.07%) FFDR. The average age of onset of BC was 59 (range 35–85). BC at age 50 or under occurred in 10/194 (5.15%) women.

The incidence of other common hereditary cancers in the FFDR cohort were as follows; colon cancer 8/194 (4.12%), ovarian cancer 4/194 (2.06%), uterine cancer 5/194 (2.58%). There were no cases of pancreatic cancer in FFDR.
Conclusion Almost 1 in 5 women with a first degree relative with MBC who tested negative for BRCA1 or BRCA2 developed BC. Further studies with larger cohorts of FFDRs of men with MBC could help increase confidence in counselling these women, and help provide more clear screening recommendations.

P116: Characteristics of 339 CHEK2 mutation carriers in a large academic health center

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Background Germline CHEK2 mutations predispose to breast, colon, and other cancers. Research regarding the clinical characteristics, cancer risks, and outcomes are under investigation.
Methods Patients with a germline CHEK2 mutation tested between September 2013 and December 2019 were identified. Genetics results, demographics, tumor characteristics and outcomes were analyzed.
Results 339 CHEK2 mutation carriers were identified. Most individuals were female (84%) and Caucasian (99%). Forty-two (12%) were Ashkenazi Jewish. The cohort included 36 families with at least two positive individuals tested through our program (86 individuals). The most common variants were I157T (36%), c.1100delC (24%), and p.S428F (12%). Four individuals had biallelic CHEK2 mutations. Twenty-seven patients (8%) had a mutation in at least one additional cancer gene. The mean age at cancer diagnosis was 63. Breast cancer was the most common malignancy in females (78%), with a mean age of diagnosis of 54. The majority had grade I/II breast tumors (74%), T1 (63%), node negative (64%), and estrogen/progesterone receptor positive, HER2neu negative (74%).

Of the 133 female mutation carriers with breast cancer, 28% underwent bilateral mastectomy. The 1- and 5-year survival was 100%. Sixteen females (12%) developed a contralateral breast cancer. Five developed in-breast tumor recurrence at 2, 5, 11, 12, and 21 years, respectively. Four males had breast cancer. Thirty-eight individuals (12%) had multiple primary malignancies. One patient developed angiosarcoma of the chest wall two years after radiation. Other cancers observed were thyroid, colon, prostate, and ovarian cancer.
Conclusion Our study describes the unique clinical characteristics of a large cohort of CHEK2 mutation carriers. The majority of breast cancers were early stage, ER/PR positive, with excellent outcomes. A significant proportion of patients carried mutations in other cancer genes, underscoring the importance of comprehensive panel testing.

Future studies are needed to continue to define the unique characteristics of CHEK2 mutation carriers.

P118: Frequency of pathogenic and likely pathogenic variants in breast and ovarian cancer genes identified in a 34-gene hereditary multi-cancer panel at a diagnostic reference laboratory

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Introduction Multi-gene hereditary cancer testing has been shown to have clinical utility, but there is a need for sharing among labs to improve upon existing data and further our understanding of multi-gene panels. Here we examine the frequency of pathogenic and likely pathogenic variants (P/LPVs) found during genetic testing for hereditary cancer genes at a diagnostic laboratory.
Methods We conducted a retrospective analysis of variants identified in 3805 individuals who underwent genetic testing using a 34-gene hereditary cancer panel (APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, RET, SDHB, SDHC, SDHD, SMAD4, STK11, TP53, and VHL) at a diagnostic laboratory. Genetic testing was performed using next-generation sequencing; DNA microarray was used to confirm copy number variants. Clinical presentations were recorded if available.
Results In our cohort, 386 pathogenic and 64 likely pathogenic (450 total) variants were identified in 422 (11%) individuals. Breast cancer genes had the most P/LPVs; 323 (72%) were identified. In ovarian cancer genes, 264 (59%) P/LPVs were identified. In genes not associated with breast or ovarian cancer, 83 (18%) P/LPVs were identified. Of those P/LPVs in breast and/or ovarian cancer genes (n = 353), 216 (61%) P/LPVs were in non-BRCA1/2 genes. Clinical presentations associated with P/LPVs from breast and/or ovarian cancer genes will be presented.
Discussion The results from our multi-cancer panel test indicate that the most frequently reported P/LPVs were in breast and ovarian cancer genes. Of those genes, most P/LPVs were found in non-BRCA1/2 genes collectively, compared to BRCA1/2. Since our cohort included individuals who may not have met clinical criteria for HBOC testing, it is notable that most P/LPVs were identified in breast and ovarian cancer genes, although some of these genes are also associated with other cancers.

P119: Integrated analysis of tumour exome sequencing data from familial high-grade serous ovarian cancer patients to validate novel predisposition genes

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Background High-grade serous ovarian carcinoma (HGSOC) has a significant hereditary component, approximately half of which cannot be explained by known genes. We recently reported enrichment for germline loss-of-function (LoF) variants in 43 candidate genes as well as three proposed genes (*PALB2, ATM* and *MRE11A*) in 516 *BRCA1/2*-negative HGSOC patients[1]. However, since the number of carriers for each gene was small, orthogonal approaches are needed to validate these findings. We therefore conducted tumour sequencing to seek molecular genetic evidence of biallelic inactivation for these genes.
Methods Whole exome and targeted bisulphite sequencing were performed on DNA extracted from archival HGSOC specimens from 91 patients who were heterozygous carriers of germline LoF variants in one of the enriched genes. The data were analysed for evidence of biallelic inactivation, including copy number (CN) loss, somatic point mutations, promoter methylation and mutational signatures.
Results Biallelic inactivation involving the wildtype allele via CN loss was observed in 3/3 *PALB2* cases, and in 3/4 *ATM* cases (2 CN loss and 1 somatic point mutation) but not in any of the *MRE11A* cases (0/2); none of these tumours showed loss of the variant allele. Of the 38 candidate genes represented, 14 demonstrated CN loss of the wildtype allele in at least one tumour from a germline carrier, with three genes (*LLGL2, LOXL2, SCYL3*) displaying this in multiple samples. Conversely, seven candidate genes exhibited loss of the variant allele in multiple tumours, making them less likely to be genuine predisposition genes.
Conclusion Our results for *ATM* and *PALB2* demonstrate the utility of this approach for validating candidate familial cancer genes, providing further support for the latter as an HGSOC predisposition gene[2]. Only a small number of candidate genes demonstrated evidence of wildtype allelic loss to indicate a contributory role to tumorigenesis in germline LoF variant carriers.
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P121: Spectrum of germline mutations within Fanconi anemia-associated genes across populations of varying ancestry

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Background Fanconi anemia (FA) is a rare genetic disorder associated with hematological disorders and solid tumor predisposition. Owing to phenotypic heterogeneity, some patients remain undetected until adulthood, usually following cancer diagnoses. The uneven prevalence of FA cases with different underlying FA gene mutations worldwide suggests variable genetic distribution across populations. In this study, we aim to assess the genetic spectrum of FA-associated

genes across populations of varying ancestries and explore potential genotype–phenotype associations in cancer.

Methods Carrier frequency and variant spectrum of potentially pathogenic germline variants in 17 FA genes (excluding *BRCA1/FANCS, BRCA2/FANCD1, BRIP1/FANCJ, PALB2/FANCN, RAD51C/FANCO*) were evaluated in 3523 Singaporeans and seven populations encompassing Asian, European, African and admixed ancestries from Genome Aggregation Database. Germline and somatic variants of 17 FA genes in seven cancer cohorts from The Cancer Genome Atlas (TCGA) were assessed to explore genotype–phenotype associations.

Results Germline variants in *FANCA* were consistently more frequent in all populations. Similar trends in carrier frequency and variant spectrum were detected in Singaporeans and East Asians, both distinct from other ancestry groups particularly in the lack of recurrent variants. Our TCGA dataset exploration suggested higher germline and somatic mutation burden between *FANCA* and *FANCC* with head and neck and lung squamous cell carcinomas, as well as *FANCI* and *SLX4/FANCP* with uterine cancer, but is insufficiently powered to detect any statistical significance.

Conclusion Our findings highlight the diverse genetic spectrum of FA-associated genes across populations of varying ancestries, emphasizing the need to include all known FA-related genes for accurate molecular diagnosis of FA.

P122: Rare heterozygous NTHL1 c.268C>T; p.Gln90Ter mutation in women with high-grade serous ovarian carcinoma

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It has been proposed that germline mutations in homologous recombination (HR) and Fanconi Anemia (FA) DNA repair genes RAD51C, RAD51D, and BRIP1 along with BRCA1 and BRCA2 confer increased risk to ovarian cancer (OC). Recurrent BRCA1, BRCA2, and RAD51D germline mutations account for a significant proportion of OC cases in the French Canadian (FC) population of Quebec due to common ancestors. However, we observed that 20–30% of FC families with at least two OC cases are BRCA1/BRCA2 mutation-negative which prompted our investigation of new candidate OC predisposing genes.

Whole exome sequencing (WES) and bioinformatic analyses were performed on the germline of 21 familial FC OC cases. Given the role of known HR-FA genes in OC predisposition, we used candidate gene approach focusing on potentially damaging rare alleles found in DNA repair pathway genes. We identified heterozygous carriers of NTHL1 c.268C>T;p.Gln90Ter in two OC cases from the same family. Genotyping NTHL1 c.268C>T in three independently ascertained FC cohorts of unselected OC cases, identified 2/439 (0.6%) and 1/258 (0.4%) heterozygous carriers. The carrier frequency among high grade serous OC cases was significantly different from cancer-free FC controls (0.6%; 3/482 vs. 0.05%; 1/1917, $p = 0.03$). Tumor profiling revealed loss of the wild-type allele in both left and right ovarian tumors from two carriers. WES analysis on those tumors showed the associated mutational signature. Further WES analysis of c.268C>T carriers did not reveal the presence of rare of other potentially pathogenic alleles in known or suspected OC predisposing genes. Biallelic NTHL1 c.268C>T carriers in non-FC populations have been described with multi-tumor phenotype that predominantly feature colorectal and breast cancers. Though NTHL1 c.268C>T does not account for a significant proportion of unexplained heritable OC in the FC population, our findings suggest the intriguing possibility that heterozygous carriers of may have had an increased risk to OC.

PSYCHO-ONCOLOGY

P128: Impact of genetic counseling and genetic testing on families at high-risk for hereditary breast and ovarian cancer predisposition syndrome

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The aim of this study is to evaluate the impact of genetic counseling (GC) and genetic testing (GT) in 60 families at-risk for hereditary breast and ovarian cancer from the Department of Oncogenetics in a Brazilian hospital.

This is a prospective study of mixed methods, which have four moments: M1- Before the GC, in which the draw of pedigree, genogram, and ecomap is done and, psychosocial questionnaires (PQ) were carried out; M2- After GC session and blood draw for GT, the application of PQ; M3- After GT, with the application of PQ and M4- Performed 6 to 12 months after the GT result, which became a new draw of the pedigree, genogram, ecomap, and reapplication of PQ questionnaires.

The qualitative analysis was performed through Content Thematic Analysis. Of the 60 women included, 16 have pathogenic germline variants (PV) in the genes BRCA1, BRCA2, or TP53, 41 had negative genetic test result (WT) and 3 had variant of unknown clinical significance (VUS). The cancer risk perception changed throughout the moments ($p < 0.05$) and, in M4, the higher risk perception has relation with the greater the search for religiosity ($p = 0.015$). Individuals with VUS have high levels of concern to the development of cancer and have a high perception of health beliefs on the barriers scale for doing preventive exams. Symptoms of depression increased over time in individuals WT, PV and VUS ($p = 0.006$). Qualitative data show that the genetic test holds up negative relationship among family members, but despite this, there is the promotion of communication, with 68.7% of the families of MT patients. It was possible to identify the impact of GC and GT at families. The obtained information is of great importance allowing the professionals to understand individual perceptions and family dynamics, supporting a personalized assistance.

P129: In their own words—written narratives of hereditary breast and ovarian cancer

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Background In genetic counseling we listen to fragments from family stories and how life experiences influence the choice of treatments and risk perception. These stories are seldom fully told in the setting of a genetic counseling session. Previous qualitative research on experience of hereditary cancer has been done through interviews. In this study we asked patients to write their own story. A narrative might allow a person to tie changes in his/ her life into a story that might give an understanding of various events and how these are interpreted and made meaningful.
Aim To elucidate how individuals with a pathogenic BRCA variant tell their story of cancer in their family. Do their experiences affect their perception and understanding of a genetic variant and its cancer risk?
Material Fifty patients with a pathogenic BRCA variant were invited to write their narrative about cancer in their family. In the invitation we included a writing guide to help them get started with the writing process. Six patients returned their narratives.
Method To analyze the narratives we used a previously described qualitative content analysis.
Results The main themes identified: (1) experiences of cancer are intertwined with a larger family history, (2) experience with insecurity and bodily vulnerability, (3) finding a new direction in life with cancer risk.
Conclusion Through the written narratives we gained a better understanding of how perceptions of a genetic variant and cancer risk can be affected by and intertwined with experiences from one's family. This emphasizes the importance of active listening in the genetic counseling session, which could be at stake when the complexity of genetic testing and information load is steadily increasing along with a demand of increasing efficiency in the cancer genetic clinic.
Keywords BRCA-genes, written narratives, cancer risk, genetic counseling.

RISK ASSESSMENT AND GENETIC COUNSELLING ISSUES

P130: Flipping the model: a novel approach to expand access and increase capture of ovarian cancer patients for genetic testing

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Background Genetic testing for ovarian cancer patients is essential to consideration of PARP inhibitor therapy. To improve access, we piloted a Genetic Testing Station (GTS) which allowed patients to have a drop-in, same-day genetic testing visit facilitated by Genetic Counselor Assistants (GCAs) under the supervision of Genetic Counselors (GCs).
Methods The GTS was implemented in December 2018 and operated through February 2020. Gynecologic Oncologist offered ovarian cancer patients a same-day GTS visit with a GCA, where the patient received education via videos designed by GCs. The patient also provided consent, a brief family history, and a sample for a standardized 133-gene panel. Results were provided by a telehealth or clinic visit with a GC. We compared uptake of genetic testing post-GTS, and also time from referral to delivery of testing results. Patients were retrospectively identified by querying the medical record for ovarian cancer patients seen 12 months prior to and 18 months after GTS implementation.
Results A total of 482 patients pre-GTS were compared to 625 patients post-GTS. Genetic testing increased from 68.5% to 75.66665% ($p = 0.012$) after implementation of the GTS, with the majority of the increase in patients with epithelial histologies (80% vs 89% in pre-GTS vs post-GTS, $p = 0.005$). Time from referral to genetic testing to obtaining results was evaluated in the post-GTS cohort, comparing patients who had traditional counseling to those who utilized the GTS. The time to obtaining results was shorter in the GTS group at 21 days (95% CI [10, 34]) compared to 56 days (95% CI [41,76]) in the traditional genetic counseling group.
Discussion The GTS reduces barriers to care and facilitates discussion of precision treatment and prevention strategies with patients and their families in a timely fashion while optimizing Genetic Counselor clinic time. Post-COVID, access improvement remains integral to improving uptake of genetic testing.

P133: Putting together the pieces: challenges in the clinical interpretation of mosaic TP53 pathogenic variants

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Background Multi-gene panel testing (MGPT) with next generation sequencing (NGS) is routinely used to identify germline pathogenic variants (PVs) causative of hereditary cancer. Many breast cancer patients undergo MGPT to inform therapeutic decision-making. The inclusion of the TP53 gene on MGPT poses challenges, as NGS coverage may detect low-level TP53 mosaicism. Distinguishing germline TP53 PVs, associated with Li-Fraumeni syndrome (LFS), from somatic TP53 PVs, which may be associated with clonal hematopoiesis of indeterminate potential (CHIP), is critical. We present two cases of mosaic TP53 PVs identified on MGPT and their diagnostic outcomes.
Case Discussion
Case 1 23 year-old female with unilateral breast cancer (IDC, ER+/PR+/Her2−) and family history of male breast cancer (paternal uncle). NGS (peripheral blood) revealed a TP53 PV (c.1024C>T; p.Arg342*) at 10% allele frequency. Site-specific analysis via Sanger sequencing (skin fibroblasts) was negative. Paired somatic and germline analyses (tumor and peripheral blood) demonstrated TP53 c.1024 C>T with loss of a second TP53 allele. This patient likely has true mosaic LFS and is following screening protocols as outlined in professional guidelines.
Case 2 55 year-old female with unilateral breast cancer (IDC, ER+ PR+ Her2−) and family history of ovarian and colon cancers (mother and maternal grandfather, respectively). NGS (peripheral blood) revealed a TP53 PV (c.673-2A > G, splice acceptor) at 10% allele frequency. NGS (skin biopsy) was negative, suggesting that this PV

was confined to blood. The patient's older age of onset and absence of LFS spectrum cancers suggests CHIP. She was managed clinically by breast oncology.

Conclusions Significant differences in phenotype and clinical management between CHIP and mosaic LFS prompt the need for additional analyses of low-level TP53 mosaicism. Challenges presented by NGS testing will undoubtedly continue to increase, highlighting the need for discussion amongst genetics professionals to address current challenges in results interpretation and post-test genetic counseling.

P135 Rapid Fire Presentation: The BRCA Founder OutReach (BFOR) study: a novel digital heath initiative ongoing in the Ashkenazi Jewish population

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Background NCCN guidelines endorse consideration of BRCA founder mutation testing in Ashkenazi Jewish (AJ) individuals irrespective of personal/family history. Barriers to BRCA population screening include access, counseling availability, and care provider readiness to participate in this process. The BRCA Founder OutReach (BFOR) study evaluated a digital approach to genetic testing using a medical model and risk-adapted follow-up.

Methods The BFOR study (bforstudy.com) was open in four US cities to insured individuals 25 or older with at least one grandparent of AJ ancestry. Participants received pretest education, provided consent, and completed questionnaires via a chatbot-based online interface. Participants chose to receive results from their primary care provider (PCP) or BFOR staff. Nominated PCPs could accept or decline this invitation. Participants received BRCA AJ fonder mutation testing at local phlebotomy centers. Personal/family history of potentially BRCA-associated cancers was assessed to flag those who may be eligible for additional testing. Participants will be surveyed for up to 5 years; a subset of PCPs were also surveyed.

Results As of March 2020, 5193 participants consented to the study and 4109 participants completed genetic testing (median age: 54). Genetic knowledge after interactive consent was high (mean score 90% questions correct). Overall satisfaction with the digital tool was moderate (mean 7.2 on 0–10 scale) and was negatively correlated with age ($r2 = -0.08$; $p < 0.001$, age range 25–93). 35.1% of participants selected a PCP to disclose results and 40.5% of PCP invitations to disclose results were accepted. 36.7% of participants who tested negative were flagged for a significant personal/family history of cancer. 138 mutation carriers (3.4%) were identified. Participants' medical and psychosocial outcomes as well as acceptance of this model by both lay and medical communities are being evaluated.

Conclusion An internet-assisted digital tool effectively provides access to pretest education, genetic testing, and medical follow-up for targeted populations.

P136: Is it somatic or germline? A case report of a TP53 variant identified in hereditary cancer panel testing

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Pathogenic variants (PVs) in the TP53 gene cause Li-Fraumeni syndrome (LFS), a cancer predisposition syndrome associated with high risk for a diverse spectrum of malignancies. A recent study found that nearly 40% of PVs in TP53 on Next-Generation Sequencing (NGS) cancer panels are likely somatic with a low allele frequency, between 10 to 30% (Coffee 2017). With follow up testing, the majority of likely somatic PVs were confirmed to be acquired aberrant clonal expansions, not germline mutations (Weitzel et al. 2018).

We report a case of a 60-year-old woman with breast cancer at age 45 undergoing testing for an 18 gene NGS cancer panel. Lymphocyte testing revealed a PV (c.155_164del; p.Gln52LeufsTer68) in TP53 with an allele frequency of 36%. This variant was confirmed by Sanger sequencing. While the allele frequency was above the cut-off for likely somatic PVs, follow up testing was done to verify if the PV was germline. DNA extracted from skin biopsy in the proband was Sanger sequenced. Lymphocyte testing was also done in her identical twin sister (zygosity confirmed). These tests did not identify the same PV in TP53, indicating it was somatically acquired. This case demonstrates that PVs in TP53 with an allele frequency of over 30% can be somatically acquired. Given the intense surveillance required in LFS and the common occurrence of somatic PVs in TP53, germline PVs in TP53 should be verified by testing other tissues and/or family members prior to making medical management decisions. We propose follow up testing should not be limited to PVs in TP53 with allele frequency under 30%. When interpreting apparent germline PVs in TP53, clinicians should consider the complete clinical picture, including personal cancer history, family history, and the availability of follow up testing.

P137: Traceback: identification and genetic counseling and testing of mutation carriers through family-based outreach

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Women with pathogenic BRCA1/2 mutations have a substantially increased risk of developing breast and ovarian cancer. The National Comprehensive Cancer Network (NCCN) recommends risk assessment and genetic testing for all women diagnosed with ovarian cancer. However, studies have shown that < 30% of eligible women undergo genetic testing. It is estimated that only 48,700 of over 348,000 women who are BRCA1/2 mutation carriers have been identified; 220,000 of these carriers have not been diagnosed with cancer.

To address these missed opportunities for risk management, the National Cancer Institute (NCI) published a Funding Opportunity Announcement (FOA) to support research projects using a Traceback approach to identify and genetically test previously diagnosed but unreferred patients with ovarian cancer and their relatives. The overall goal of Traceback is to increase identification of families at

risk for breast or ovarian cancer, who may benefit from available screening and risk reduction approaches.

A total of three grants, which have complementary Traceback approaches within different clinical and population contexts, were selected for funding and are expected to be awarded in 2020. These proposals include: the development and evaluation of communication strategies to identify and offer genetic testing to survivors and family members identified within Healthcare System Research Network registries; the use of a "citizen scientist" approach and testing of targeted message-based versus standard outreach approaches to inform and offer genetic testing to survivors and family members; and leveraging of coordinated tumor registries within a hospital system to identify previously diagnosed, deceased patients, test their tumors, and reach out to their family members to offer testing. Because Traceback approaches involve ethical, legal and societal implications (ELSI) related to communication, consent, return of results, and community engagement, these proposals each include an aim to identify and explore ways to overcome these ELSI issues.

P138: Value of multiple-gene panel retesting of families with BRCA1/2 mutation-negative hereditary breast and ovarian cancer (HBOC)

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Introduction Despite the use of clinical eligibility criteria and mutation predictive models, a great proportion of families are negative for germline mutations in BRCA1/2genes. Traditionally, risk assessment of inconclusive results included the recommendation of high-risk surveillance protocol, the update of incident cancer cases in the family and the consideration of additional testing to rule out the possibility of phenocopy. More recently, next generation sequencing multigene panels have become a standard practice in cancer genetics clinics worldwide. We addressed the value of multigene panel retesting of BRCA1/2negative HBOC families in our institution.
Methods After genetic counseling session and informed consent, a total of 160 individuals (140 probands and 20 extra cancer-affected relatives) from distinct BRCA1/2 negative families were retested using a panel containing 11 breast and ovarian cancer susceptibility genes (BRCA1/2, PALB2, ATM, CHEK2, PTEN, TP53, STK11, BRIP1, RAD51C, RAD51D). According to the BOADICEA model(versión BWA V4 beta) the remaining probability of BRCA1/2 or PALB2 mutations was 6% (0.1–76). In 42 cases (26%) the reason for considering retesting was the addition of any incident cancer diagnosis. In 8 families, prior study had been performed with a low sensitivity screening technique (dHPLC).
Results Overall, 4 pathogenic (2 BRCA2, 1 CHEK2, 1 MSH2) and 8 likely pathogenic variants (1 BRCA2, 4 CHEK2 and 3 ATM) were found. The prevalence of clinically relevant variants was 7,5%. The detection rate among 19 families with a $> 10\%$ remaining probability of mutation in BRCA1/2 and PALB2 genes was 26%. Three clinically significant variants in BRCA2 were detected in 2 families and 1 cancer updated family (BOADICEA remaining probability of 59, 61 and 12%, respectively). Cascade testing was subsequently done in 20 relatives resulting 10 mutation carriers and 10 true negatives.
Conclusion Our results support the value of updating cancer incident cases and considering expanded panels in selected families.

P139: Challenges with conflicting interpretations of pathogenicity of the CHEK2 c.1427C>T variant

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Clarity of genetic test results is a critical component of accurate cancer risk assessment and appropriate medical management. While guidelines for variant interpretation are available, conflicts amongst laboratories occur frequently due to lack of standardization. We describe two patients impacted by discrepant classifications of the CHEK2 c.1427C>T variant.

The first patient is an unaffected 35 yo female of Iranian descent from a consanguineous family with a history of breast and ovarian cancers. Results of a multi-gene panel at Laboratory 1 were significant for homozygous CHEK2 c.1427C>T variants, classified as Likely Pathogenic. Her parents were, therefore, obligate carriers of this variant, yet her mother's results at Laboratory 2 were negative. Laboratory 2 later confirmed they detected the CHEK2 c.1427C>T variant but classified it as Likely Benign. Counseling regarding cancer risks and appropriate management strategies was challenging, given the conflicting and limited data.

The second patient is a 76 yo male with a history of melanoma at 55 and 75, bladder cancer at 65, leukemia at 71, renal cancer at 74 and prostate cancer at 75. Results of a multi-gene panel at Laboratory 3 were significant for the CHEK2 c.1427C>T variant, classified there as Uncertain. Searches on the public database, ClinVar, and of current literature revealed wide discrepancies in classification of this variant, ranging between Likely Pathogenic to Likely Benign. While there are no implications for this patient's medical management, it remains unclear whether testing for his children and siblings is indicated.

In both cases, conflicting interpretations of pathogenicity of the CHEK2 c.1427C>T were not readily apparent and required more extensive evaluation by the clinical genetics team. These significant challenges not only highlight the importance of results interpretation by providers experienced in genetics but also the need for consistency in variant classification methods and data sharing amongst laboratories to improve patient care.

P140: Compatibility of the NCCN BRCA1/2 testing criteria for Japanese patients undergoing germline BRCA1/2 testing

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Background We examined the applicability of the BRCA1/2 Testing Criteria of the NCCN-Guidelines Ver. 2, 2021 for Japanese patients undergoing germline BRCA1/2 testing.
Patients and Method Medical records of the patients visiting the outpatient clinic for cancer prevention & genetic counseling and the breast cancer clinic from Jan. 2003 through Nov. 2020 were retrieved and 275 patients undergoing BRCA1/2 DNA testing were examined for their compatibility with the NCCN BRCA1/2 Testing Criteria.
Result Of 275 patients, 35 patients had wild type BRCA1/2 and 29 patients had pathogenic/likely pathogenic (P/LP) variants either in BRCA1/2. Patients compatibility with the Testing Criteria was

compared between 2 groups, i.e., 240 patients with wild type vs. 35 patients with P/LP BRCA1/2 variants.

(i) Breast cancer (BC) diagnosed at age less than 45 y/o: 78/240 vs. 20/35 (p = 0.007)
(ii) BC diagnosed at 46–50 y/o with a second BC diagnosed at any age or one more closed blood relative with BC: 18/240 vs. 3/35 (p = 0.738)
(iii) BC diagnosed less than 60 y/o with TNBC: 24/240 vs. 6/35 (p = 0.241)
(iv) BC at any age, with one more blood relative with breast, ovarian, pancreatic cancer, and male breast cancer or three or more total diagnoses of BC in patient and/or blood relatives; 71/240 vs.22/35 (p = 0.000)
(v) Epitherial ovarian cancer: 33/240 vs.6/35 (p = 0.605)
(vi) Male BC: 0/240 vs.0/35
(vii) Exocrine pancreatic cancer: 20/240 vs.2/35 (p = 1.000)
(viii) Metastatic prostate cancer: 0/240 vs. 0/35

Discussion 220/275 (80.0%) patients undergoing BRCA1/2 DNA testing fulfilled the NCCN criteria and all patients with pathogenic BRCA1/2 variants were compatible with the criteria.
Conclusion NCCN-criteria is compatible with Japanese HBOC.

P144: Cervical cancer in individuals with hereditary breast and ovarian cancer—a correlation?

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Cervical cancer is both the fourth-most common cause of cancer and the fourth-most common cause of death from cancer in women worldwide. The life time disease risk is estimated at 1 in 130 (0.8%) in Germany. Cervical carcinomas are mainly caused by persistent infections with human papillomavirus (HPV), particularly with HPV strains 16 and 18. Most HPV infections are no more detectable after 1–2 years. In contrast, there is an increased risk for development of a high-grade dysplasia if HPV infections persist. Genetic factors have been discussed to play a role for HPV persistence and progression from low grade dysplasia to malignancy.

We investigated, whether genes associated with hereditary breast and/or ovarian cancer predispose to cervical cancer. Therefore we screened a total of 2016 patients with breast or ovarian cancer with at least a 10% prior probability of carrying a BRCA1/2 mutation based on clinical criteria as age of manifestation, family history and contralateral disease regarding mutations in one of the following cancer susceptibility genes: BRCA1, BRCA2, ATM, CDH1, CHEK2, PALB2, RAD51C, RAD51D, TP53, PTEN, BRIP1, MSH2, MSH6, PMS2, MLH1 and STK11.

We identified a disease causing mutation (ACMG4 or 5) in a total of 410 patients (20.33%). Six of them (1.46%) had a prior diagnosis of cervical cancer besides breast cancer. One BRCA1 and one ATM mutation was identified in one individual each as well as MSH2 and CHEK2 mutations in two patients each. Of the 1606 cancer patients without an identifiable disease causing mutation nine individuals were diagnosed with cervical cancer (0.56%). Although this difference was statistically not significant in our study group (p = 0.097) it indicates a possible moderately increased risk and the need to validate this observation in larger cohorts.

P145: Implementation of online learning module for hereditary breast and ovarian cancer

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Almost 50% of referrals made to the Hereditary Cancer Program within the Regional Genetics Program at CHEO are women who have not been diagnosed with cancer (unaffected) but have a family history of breast and/or ovarian cancer. We have not been able to successfully see patients referred to our service within the triaged timeline (priority level) with our current resources. In order to see all patients within their assigned priority level, we needed to find efficiencies in performing genetic assessments for this population. Previously we had been seeing these unaffected women in a group setting. Through our quality improvement (QI) initiatives at CHEO and with support from an industry partner we have developed and made available an online learning module (e-Learning module). These patients are able to view the module on their own time and decide whether they wish to proceed with a genetic counselling telephone appointment. Implementation of this intervention involved assessment of our workflow, identifying barriers to communication, constructing a bilingual (English/French) and electronic family history questionnaire, developing a strategy for triaging patients on our wait-list and new referrals, and assessing patient satisfaction.

Within the first 8 months of implementation, we have increased the percentage of patients seen within their triaged priority level (37% to 88%). Our wait list for the entire Hereditary Cancer Program has decreased by 14% from June 2019 to December 2019. Overall, patients found the information presented in the e-Learning module to be valuable (96.3%). Through this quality improvement project we have found an efficient method to meet the needs of our largest referred patient population.

P146: Facilitated referral pathway for genetic assessment of women with ovarian cancer in a public vs private hospital: differential uptake of testing and psychological impact

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Objectives This study compared rates of genetic counseling (GC), genetic testing (GT) and patient-reported stress, anxiety, and depression among patients at a private hospital (PrH) and public hospital (PuH) on a facilitated referral pathway (FRP) for GC and GT.
Methods In this prospective study from 10/2015 to 5/2019, patients with epithelial ovarian cancer diagnosed at a PrH and PuH were offered a uniform FRP. Patients were contacted by a genetics

navigator for a timely appointment for GC and GT. English-speaking patients completed quality of life (QoL) instruments (Impact of Events Scale, State-Trait Anxiety Questionnaire, Hospital Anxiety and Depression Scale) pre-and post-GC. The primary outcome was rate of GC. Data were analyzed using Chi-square, Mann–Whitney U, and logistic regression.

Results One-hundred and ten patients were included (PrH-83, 75.5%, PuH-27, 24.5%). The majority of patients at the PuH were uninsured or on public insurance, less likely to be English-speaking ($p = 0.004$) and be non-white ($p = 0.010$). Patients at the PuH were less likely to undergo GC compared to PrH patients (18, 66.7% vs. 70, 79.5%, $p = 0.046$). When adjusting for age, race, primary language, or tumor site, referring hospital was not associated with uptake of GC (OR 2.90, 95% CI 0.87–9.73) or GT (OR 1.77, 95% CI 0.57–5.51). There were no differences in the uptake of GT once GC occurred. There were no differences in GT results based on the hospital setting; 16 (19.3%) had a pathogenic variant and 28 (33.7%) had a variant of uncertain significance. There were no significant differences in QoL between the two hospitals and when compared prior to and following GC.

Conclusions Despite a dedicated genetics navigator in a FRP, patients at the PuH were less likely than those at the PrH to accept GC. However, this difference disappeared when controlling for race and language. Outreach is needed to increase access to GT for underserved patients.

P147: Leveraging health information technology to collect family cancer history: a systematic review and meta-analysis

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Objectives Collection of a comprehensive family cancer history (FCH) can identify individuals at-risk for hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome (LS). However, there are no formal guidelines for FCH collection across medical systems. The aim of this study is to evaluate the literature on existing strategies whereby providers utilize information technology (IT) to assemble FCH.

Methods A systematic search of online databases (PubMed, EMBASE, MEDLINE, and the Cochrane Library) between 1980 and 2020 was performed. Meta-analysis was used to estimate pooled results across studies. Statistical heterogeneity was assessed through the chi-square test (i.e., Cochrane Q test) and the inconsistency statistic (I2). A random effects analysis was used to calculate the pooled proportions and means.

Results The comprehensive search produced 4005 publications and 21 studies met inclusion criteria. Fifteen distinct IT tools with four strategies were identified: electronic survey prior to visit (12, 57.1%), electronic survey via tablet in the office (3, 14.3%), electronic survey via kiosk (3, 14.3%) and animated virtual counselor (1, 4.8%). Among the 32,404 included patients, 77.0% completed the FCH tool (CI 0.57, 0.97). The time required for survey completion was 35.2 min (CI 14.3–56.2). Five studies included a standard patient interview for FCH collection and the IT tool; all demonstrated very good agreement between collected data. Five (33.3%) of the IT FCH tools had the capacity to interface directly with the patients' electronic medical record. Seven studies included qualitative assessment of patient satisfaction with the tool, all demonstrating high levels of satisfaction.

Conclusion Our review found that electronic FCH collection can be completed successfully by patients in a time efficient manner with high rates of satisfaction among patients and providers. Increasing the utilization of health IT for FCH collection has the potential to improve detection rates of HBOC and LS.

P153: Breast cancer patients' experiences with mainstreamed genetic testing in two hospitals in South Eastern Norway—preliminary results

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Background In South Eastern Norway, genetic testing of *BRCA1* and *BRCA2* is mainstreamed into regular oncological care. Testing is offered directly to breast cancer (BC) patients by surgeons and oncologists. Only patients who test positive for a pathogenic BRCA variant or have a family history of cancer, are referred to genetic counseling. The aim of this study was to gain knowledge on how BC patients experience this health care service.

Methods Thirty women, diagnosed with BC during the first half of 2016 or 2017 at one regional and one university hospital, and who had been tested by their treating physician were invited. Twenty two (73%) consented to inclusion, and qualitative individual interviews were undertaken with all of them. The data were analysed using a thematic approach.

Results Being diagnosed with BC was a shock that created a need for and an obstacle to absorbing and remembering information. A feeling of trust in the health care providers facilitated communication in this chaotic period. The women regarded genetic testing as important for themselves, their cancer treatment and their relatives. The participants' experience of how genetic testing was offered, the amount of information they received and how they had received the test result varied. Not all patients had been offered testing, and some had asked for the test themselves. The participants emphasized the importance of having routines to secure that all eligible patients were given the opportunity of being tested.

Conclusions Based on the findings in this qualitative study of BC patients' experience with mainstreamed genetic testing, we conclude that access to testing during diagnosis and treatment had been important to these women. Their varied experiences regarding when and how they had been offered testing indicate that there may be a need to strengthen and unify routines for this health care service.

P154: Extending the reach of cancer genetic counseling to the safety net: genetic counseling perspectives across three modes of delivery

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Introduction There are too few Genetic Counselors (GCs) to meet growing demand, and genetic counseling is unavailable in most safety net health care settings. This inequity represents an example of how medical advances can exacerbate health disparities. Delivery of genetic counseling services remotely could increase access for underserved populations. Here we examine what is lost and gained with three modes of genetic counseling in a multi-lingual, low health literacy population from the genetic counselor perspective; and propose strategies to help address challenges identified.

Methods Using mixed methods, we conducted a multicenter partially randomized trial with high-risk English, Spanish, and Cantonese speaking patients assigned by (1) patient´s preference or (2) randomization to three counseling modes: (a) in-person, (b) phone, or (c) video. 30 participants underwent in-depth qualitative interviews and analyses triangulating all forms of data following their initial genetic counseling session. Two genetic counselors completed a detailed review of 27 transcripts from both the genetic counseling session and the patient interview. The GCs' reflections were recorded and summarized.

Results Genetic counselors saw benefits and limitations with each mode. Telephone counseling provided the most convenience and schedule flexibility, though there were often distractions for both patients and GC's, and it was more difficult to provide emotional support without face to face contact. GC's noted reduced engagement, feeling rushed and fatigue, especially when appointments were scheduled back-to-back and/or when using an interpreter. Genetic counselors found video visits similar to in-person with regard to ease of building rapport and establish meaningful connections. When serving low-income patient populations remotely, greater counselor satisfaction may be achievable by use of plain talk and teach back, and avoiding excess information. In addition, heightened awareness of the limitations of phone should prompt more focused efforts to establish rapport when counseling by that mode. Finally, patients and counselors will benefit from explicit emphasis on key take-away messages.