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Ninth International Symposium on Hereditary Breast and Ovarian Cancer
9e Symposium international sur le cancer héréditaire du sein et de l'ovaire

ABSTRACTS

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POSTERS

GROUP 1

CLINICALLY RELEVANT PATHOLOGY

P001 : Application of pathology-supported genetic testing incorporating whole exome sequencing in breast cancer research translation: Lifestyle adjustments, change of medication and genetic counselling

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Background: The implementation of genomic medicine is hampered by a disconnect between disease prevention strategies and targeted therapies applied in public health and clinical settings, respectively. To bridge this knowledge gap in the context of breast cancer, a pathology-supported genetic testing (PSGT) platform was used for transitioning of risk stratification from the study population to the individual.

Clinically Relevant Pathology *(Continued)*

Methods: The study population consisted of 116 postmenopausal breast cancer patients at increased risk of osteoporosis due to aromatase inhibitor (AI) therapy. Both tumour histopathology and blood biochemistry levels were assessed to identify actionable disease pathways using whole exome sequencing (WES). Due to the personalised medicine focus of this study, description of trends and relationships between variables were emphasised above statistical testing to quantify associations.

Results: The causes and consequences of inadequate vitamin D levels as a modifiable risk factor for bone loss were investigated in patients with hormone receptor-positive breast cancer. Comparison of lifestyle factors and WES data between cases with vitamin D levels at extreme upper and lower ranges identified obesity as a major discriminating factor, with the lowest levels recorded during winter. Vitamin D levels could not distinguish between patients with normal bone mineral density, osteopenia, or osteoporosis. Genetic studies identified polymorphisms in the vitamin D receptor gene as the most likely contributors to osteoporosis detected in 14 patients at baseline, while genetic variation in the CYP19A1 gene was linked to AI-induced bone loss (>5%). In a patient with invasive lobular carcinoma, genetic counselling facilitated investigation of the potential modifying effect of a rare CDH1 variant co-occurring with BRCA1 c.66dup (p.Glu23ArgfsTer18).

Conclusion: Relevant pathology tests can overcome limitations imposed by small sample size. Validation of PSGT for generation of adaptive patient reports and data reinterpretation during follow-up, represents a new paradigm in application of personalised genomic medicine.

P002 (Rapid Fire Presentation S2-RF1): Improving the diagnosis of serous tubal intraepithelial carcinoma (STIC) using deep-learning

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Background & objective: Accurate diagnosis of Serous Tubal Intraepithelial Carcinoma (STIC), a putative precursor of high-grade serous carcinoma (HGSC), is important for patient care and understanding the pathogenesis of HGSC. However, diagnosis of STIC is not perfectly reproducible among experts, and most pathologists have limited experience with the diagnosis. Clinically, excluding STIC is critical for the safety of patients who opt for risk-reducing salpingectomy with delayed oophorectomy, and data suggest that women with STIC are at increased risk of developing peritoneal carcinoma, raising critical unresolved issues about management and follow-up. Accordingly, we developed an AI model to detect STIC in digitalized whole slide images as a potential aid in diagnosis.

Methods: We collected, digitalized and annotated 91 cases of STIC/STIL, confirmed using p53 and Ki-67 immunohistochemical stains, and 75 tubal fimbria as control samples. An automated two-step deep-learning algorithm based on 1) detecting all tubal epithelium and 2) identifying abnormal epithelium was trained on 71 cases and independently tested on the remaining 20 specimens. Mapped areas of STIC are highlighted for visual review. Discrimination of STIC from normal was assessed by analysis of area under the curve (AUC) in Receiver Operator Characteristic curve analyses.

Results: The two-step model achieved an AUC=0.946 on a per slide level. Visual inspection confirmed accurate detection of lesional areas- by morphology with additional support from immunohistochemistry.

Conclusion: In this pilot study, we demonstrate proof-of-concept that a deep-learning algorithm has the potential to automatically and accurately identify STIC, and may improve the accuracy of this difficult

diagnosis. We are extending work on an additional set of over 350 lesions, defined by consensus panel review, and refining the approach to develop a one-step model. These developments are expected to further improve the performance of this model.

P003 (Rapid Fire Presentation S2-RF2): Chromothripsis and whole genome duplication are both detectable in early-stage high-grade serous carcinoma (HGSC) of upper gynaecological tract; implications for HGSC risk mitigation

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In an effort to better explain the variable presentation of patients with high-grade serous carcinoma (HGSC), we had posited 'catastrophic' model of HGSC pathogenesis, which entails large, genome-scale events, such as chromothripsis, resulting in widespread copy number changes, preceded by p53 dysfunction.

To assess the timeline of genomic catastrophes, we examined 17 cases of HGSC using the Affymetrix Oncoscan Array (217,611-probe SNP microarray). Chromothripsis(-like events) was identified in 11/17 (64.7%) of cases by microarray, defined as ≥10 contiguous, alternating copy number state changes, present in 6/8 (75%) of FIGO stage I and 5/9 (55.6%) stage III cases. Frequency of chromothripsis did not statistically differ with respect to STIC status (5/6 (83.3%) STIC+ vs. 6/11 (54.5%) STIC-), or to site of origin (8/12 (66.7%) for tubal vs. 3/5 (60%) for non-tubal). Site of origin was presumed to be tubal, based on either presence of STIC, and/or endosalpingeal involvement. Tri- or tetraploidy was identified in 5/17 (29.4%) cases, suggestive of genome duplication, present in 3/8 (37.5%) of FIGO stage I and 2/9 (22.2%) stage III cases. Their frequency also did not differ with respect to STIC status (2/6 (33.3%) STIC+ vs. 3/11 (27.3%) STIC-), or site of origin (4/12 (33.3%) tubal vs. 1/5 (20%) non-tubal). Chromothripsis and tri-/tetraploidy were both present in 4/17 (23.5%) cases, including two stage I cases.

Taken together, chromothripsis and genome duplication are both detectable in early and late stage HGSC cases, suggesting that these events may constitute an early event in HGSC pathogenesis. HGSC pathogenesis involving either of these events, i.e., the “catastrophic” pathway, is not restricted to those cases of presumed tubal origin. This pathway is envisioned to differ drastically in its timeline from the yet another, “gradual” pathway, involving gradual accumulation of copy number changes and point mutations; these biological differences call for enhanced risk-mitigation strategies.

P004 : Cancerous involvement of the fallopian tubes of Hereditary Breast Ovarian Cancer syndrome and Lynch syndrome mutation carriers: presentation and clinically relevant pathology

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Objective: Presentation and clinically relevant pathology underlie this detailed report and classification of 43 cases of cancerous fallopian tube (FT) involvement in Hereditary Breast Ovarian Cancer (HBOC) syndrome and Lynch syndrome (LS) mutation carriers accrued to the Creighton Hereditary Cancer Registry (CHCR) from 1959 through 2020.

Clinically Relevant Pathology *(Continued)*

Methods: The CHCR was searched for gynecologic and/or peritoneal cancers in BRCA1 and BRCA2 mutation carriers from HBOC syndrome families and MSH2, MSH6, and PMS2 mutation carriers from LS families. Thirty-six HBOC and seven LS mutation carriers with cancerous FT involvement were identified. Slides from 19 cases, were re-classified using WHO 2020 criteria, and p53 IHC was performed in 15 cancers.

Results: Of 35/36 HBOC-linked tumors accrued as moderate to high-grade carcinomas, 14 were classified as high-grade serous carcinoma (HGSC) (6) or HGSC with solid, endometrial-like, transitional (SET) patterns (8), and 10/10 had p53 staining consistent with a TP53 mutation. The FT locations of tumors were intralumenal (9), fimbrial (9), and varied. Three cancers showed transition from pre-invasive lesions. Metastases were documented in 34/36 HBOC syndrome cases. Three LS-linked tumors registered as endometrioid carcinomas (EC), one mixed endometrioid-clear cell (EC-CCC) and one clear cell carcinoma (CCC) were confirmed, and all showed wild-type p53 IHC staining. Confirmatory endometrioid features (CEF) were documented in 4/7 LS cases: three were associated with endometriosis, and one had synchronous FT and endometrial endometrioid carcinomas. Metastases were noted in two LS cases.

Conclusion: All classified HBOC-linked cancers were HGSC and showed p53 IHC consistent with TP53 mutations. LS-linked cancers contained only EC and/or CCC elements and had wild-type staining. CEF were common in LS cases, but not found in HBOC-linked cancers. WHO 2020 classification supported by p53 IHC are useful initial steps in clinical laboratories to differentiate HGSC and HGSC-SET in HBOC from EC and CCC in LS mutation carriers.

P005 : Short-term patient-derived ovarian cancer organoids for frontline drug sensitivity testing

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Introduction: Platinum-based therapy is the backbone of ovarian cancer treatment, but a subset of patients progresses on platinum and alternatively may benefit from PARP inhibitors (PARPis). Patient-derived organoids (PDOs) may provide rapid drug screening to tailor therapy. This project aims to determine if PDOs can be used to compare response to platinum versus PARPis and if the response prediction using PDOs matches the response in-vivo.

Methods: Preliminary data were generated using three-dimensional cell culture of established ovarian cancer cell lines with known treatment response. Specifically, PEO1, PEO4 and PEO6 cells were grown in an ultra-low attachment environment. Live/dead cell imaging and an apoptosis detection assay were performed to compare the cells' viability and characterize their behavior. Tumor specimens obtained at time of biopsy or surgery were dissociated, then embedded into single-cell suspension in Matrigel. PDOs were grown in ovarian-specific medium.

Results: PEO1 cells displayed the highest aggregation level, PEO6 cells the highest compaction level, and PEO4 cells the lowest aggregation and compaction levels. All three cell lines were found to mimic poorly vascularized tumors by forming a multilayered structure with an outer layer of live cells and an inner layer of apoptotic cells in the center, but at different timings. Building on three-dimensional ovarian cell culture, two PDOs have thus far been successfully generated from patients, one who is treatment naïve and another who progressed on PARPi.

Conclusion: If PDOs mirror the tumor they are derived from, this will allow for individualized therapy. Experiments in which the cell lines and PDOs will be exposed to standard platinum-based therapy

compared to the PARPi, Niraparib, are planned. Testing of three-dimensional cell lines will help validate our protocol given known responses. At the time of interval cytoreductive surgery, the tumor will be analyzed to compare the treatment effect in-vivo versus in PDOs.

P006 : Mutations in BRCA1 and BRCA2 generate distinct ovarian tumour microenvironments and differential responses to therapy

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Ovarian cancer cells harbouring BRCA1/2 mutations are heavily reliant on the poly (ADP-ribose) polymerase (PARP) pathway. Consequently, PARP inhibitors (PARPi) are frequently used as maintenance therapy. Combinations of PARPi and immune checkpoint inhibitors (ICIs) are currently being tested in clinical trials; however, their effects on the composition of the ovarian tumour microenvironment (TME) remain unknown. Here, we assessed how PARPi and anti-PDL1 antibodies influence the composition of BRCA-mutated ovarian TMEs.

First, BRCA-mutated mouse ovarian cancer cell lines were treated with Olaparib, which reduced viability and enhanced PDL1 expression. Next, syngeneic mouse models harbouring intraperitoneal tumours were treated with daily doses of Olaparib, anti-PDL1 monoclonal antibodies or their combination. Immediately following the end of therapy, TME composition was assessed using flow cytometry. In the Brca1-null tumours, Olaparib monotherapy reduced natural killer (NK) cell numbers (5%) but enhanced cytotoxic T cell numbers (7%) and T-cell activation. Anti-PDL1 therapy increased PDL1+ macrophages (30%) and dendritic cells (25-30%). The combination therapy reduced the percentage of activated CD4+, CD8+ and NK cells (4%, 10% and 5%, respectively).

The treatments were less transformative in the Brca2--null tumours; the anti-PDL1 monotherapy reduced CD4+ T cell numbers (7%) and enhanced PDL1 expression similar to the Brca1-null tumours. The combination therapy reduced NK cell exhaustion. Olaparib and the combination treatment improved the median survival of Brca1-null (34.2%) and Brca2-null (37.2%) tumour-bearing mice. Anti-PDL1 monoclonal antibodies improved the survival of mice with Brca1-null tumours (95%) but not Brca2-null tumours. Lastly, in-silico analysis of RNA-seq from BRCA-mutated tumours revealed that these mutations influence the ovarian TME differently, with Brca1-null tumours having enhanced vascularity, PARP pathway activity, and PDL1 expression.
Since BRCA1 and BRCA2 mutations lead to distinct ovarian TMEs, further analysis of BRCA-mutated tumours in response to therapy can catalyze the development of more effective combination therapies in the future.

P007 : Global-screening array for the assessment of homologous recombination deficiency (HRD) in epithelial ovarian cancer

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Genomic instability caused by homologous recombination deficiency (HRD) - in 40-50% of cases due to BRCA1/2 pathogenic variants (PVs) - is a predictive biomarker for the response of different tumors to PARP-inhibitor therapy. In epithelial ovarian cancer (EOC) it is also considered predictive for sensitivity of platinum-based therapies. Currently, diagnostic genomic instability testing is mostly based on the HRD-score by Myriad Genetics.

Clinically Relevant Pathology *(Continued)*

To determine HRD positivity we examined genome-wide copy number variation and loss of heterozygosity (LOH) by genotyping 89 ovarian cancers, 26 of which contained a BRCA1/2 PV, using the Global Screening Array (GSA-24 v3.0+Multi-Disease Content; Illumina). Data analysis was performed with Illumina GenomeStudio 1.6.3 (Genotyping Analysis Module) and NxClinical (Biodiscovery, SNP-FASST2-Segmentation Algorithmus) software. For quantification of HRD a LOH-score based on Swisher et al (2017; PMID: 27908594) and an Aneuploidy Normalized Telomeric Imbalance-Score (ANTI-Score, unpublished) were defined.

The group of BRCA1/2-PV samples had significantly higher median scores than BRCA1/2-wildtype samples. LOH-score and ANTI-scores were concordant (r= 0.83) with each other and with the HRD-Score by Myriad (rLOH/MYRIAD= 0,82; rANTI/MYRIAD=0,86). Based on the lowest scores determined in the BRCA1/2-PV samples, we defined the threshold for HRD-positivity as LOH-score =14 and/or ANTI-score =6. Current investigations focus on the correlation of the scores with the clinical outcome and in depth sequence and epigenetic analysis of BRCA-wildtype samples with positive LOH/ANTI-scores. Applicability of our scores in other tumor entities are tested.

DISPARITIES IN HEREDITARY CANCER GENETICS

P008 : Moving toward health equity in cancer genetics: pilot study of a cancer genetic risk assessment tool within an underrepresented population

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Objectives: Lack of genetic services has been associated with non-White race and public insurance. We evaluated the universal administration of a cancer genetic risk assessment (CGRA) tool in a diverse, US Medicaid-supported gynecology clinic.

Methods: Patients presenting for gynecology appointments were asked to complete a smartphone-based CGRA tool. The tool identified patients meeting nationally-accepted criteria for genetic testing. Eligible patients were offered same-day mainstream genetic counseling and testing as part of their gynecology visit.

Results: The CGRA tool was offered to 180 patients and completed by 127 (71%). Among users, median age was 39 years (interquartile range 31-49); 53 (42%) self-identified as Hispanic, 37 (29%) non-Hispanic Black, 23 (18%) non-Hispanic White, 6 (5%) Asian, 8 (6%) other. 97 (76%) had Medicaid, 10 (8%) Medicare, 14 (11%) other state-sponsored insurance, 6 (5%) other. 37 (29%) were eligible for genetic testing; of those, 18 (49%) elected to complete genetic testing at the time of appointment, 9 (24%) had previously completed testing, 10 (27%) declined. Genetic testing yielded 0 pathogenic variants, 11 variants of uncertain significance, 3 single-copy recessive pathogenic variants, 4 negatives. Four (3%) patients were identified to be eligible for additional cancer screening due to elevated lifetime cancer risks. Of the 17 patients eligible for genetic testing without prior testing who had been seen by a gynecologist or primary care provider in the past 6 months, only 2 (12%) had prior documentation of cancer genetic risk discussion.

Conclusions: In this historically underserved population, nearly a third were eligible for genetic testing and more than half of eligible patients elected to proceed with genetic testing, demonstrating feasibility and interest in CGRA. Most patients who were eligible for genetic testing had recent healthcare encounters without cancer risk discussion, supporting prior literature showing reduced rate of genetic services patients with government insurance.

P009 : Genetics referral of ovarian cancer patients: Referral rates at a publicly Funded Hereditary Cancer Program Between 2010-2019

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Background: Ovarian cancer has a poor 5-year-survivability, with up to 23% of cases being due to pathogenic variants across multiple genes. Because specific variants can influence treatment decisions, genetics referral for all ovarian cancer patients has been recommended since 2010. Despite these guidelines, previous North American reports have demonstrated that referral rates for ovarian cancer patients are dramatically lower than expected.

Methods: To improve referral rates, BC's Hereditary Cancer Program (HCP) has implemented (1) GENONC, a referral pathway beginning with medical oncologist-led genetic testing, and (2) GENOVA, a physician-targeted education program for gynecologic cancers. To assess the impact of these initiatives of referral rates, we identified all patients > 18 years old referred to HCP for ovarian cancer between 2010-2019. Using publicly available provincial data, we calculated annual referral rates and average wait times between diagnosis and referral (time-to-referral). We also compared the proportions of referral sources over the same period.

Results: Referral rates increased between 2010-2019 (68% of cases were referred in 2019, compared with 40% in 2010). Time-to-referral also decreased over time, from an average of 659 days in 2010, to 89 days in 2019. We also observed that most physician-led referrals were initiated by oncologists (81%), but also by family physicians and surgeons (11% and 6% respectively).

Conclusion: This is the first comprehensive review of ovarian cancer referral rates in BC, and the first report examining BC referral rates in context of HCP-led initiatives such as GENONC and GENOVA. Although the majority of referrals were provided by oncologists, family physicians and surgeons were also involved. While referral rates and time-to-referral improved from 2010 to 2019, ovarian cancer is still under-referred to the HCP. Future campaigns should continue to target the above physician groups in order to increase the overall referral rate.

P010 : From referral to results: Developing education resources for ovarian cancer patients and primary care physicians

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Up to 23% of ovarian cancers are caused by pathogenic variants across multiple genes, including BRCA1 and BRCA2. Because genetic results can influence treatment decisions in cancer patients and prompt risk-reducing surgeries in unaffected carriers, current guidelines recommend genetics referral for all ovarian cancer patients. However, both international and BC-specific data suggest that these patients are under-referred to genetic services. Possible contributors may include: (1) that referral eligibility changes rapidly, and physicians may be unaware of updates, and (2) that systemic barriers may lead to reduced referral of diverse populations, particularly patients who do not speak English or who live in rural locations.

To help address these factors, BC's Hereditary Cancer Program (HCP) plans to provide BC and Yukon (BC/YK) physicians with multilingual resources that guide patients and physicians through every step of HCP assessment, from referral to results disclosure. The project will include two components: (1) a multi-platform invitation to BC/YK primary care physicians to join an email list, which will provide updates on HCP eligibility criteria; (2) the development of educational resources for family physician offices. These printable resources will discuss cancer syndromes and genetic testing in plain language and will be translated into BC's commonly spoken languages. They will also include links to HCP's newly developed Support website.

The overall goals of this project are to: (1) increase ovarian cancer referrals among BC/YK patients, (2) increase ovarian cancer referrals among diverse or non-English speaking patients, and (3) provide BC/YK patients and physicians with up-to-date information regarding genetics and hereditary cancers.

To assess the success of this initiative, we will collect ongoing data regarding HCP referral rates and referral sources, patient location (e.g. rural or urban), and patients' preferred languages. We will also use surveys to gather feedback from BC/YK physicians who choose to participate.

P011 : Telegenetics Improves Ovarian Cancer Patient Access to Genetic Counseling and Testing

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Background: Cancer genetic counseling (CGC) and genetic testing (GT) are standard for women with ovarian cancer and results have implications for treatment and prognosis. We explored how implementation of telemedicine would impact barriers to CGC.

Methods: We compared patient age, ethnicity, socioeconomic status (SES) (using Area Deprivation Index (ADI) national rank), and distance to office site for in-person visits (IPV) to tele-genetic visits (TGV) from 03/01/2019-09/30/2022. We also interrogated patient referral and appointment characteristics. Chi-square tests assessed differences in appointments scheduled within two weeks of referral, consultation completion rate, sample collection rate, and sample failure rate. Patient-provider distance (<10 vs =10 miles) and turnaround time for results were summarized with a median (IQR) and analyzed with a Wilcoxon rank-sum test. We will conduct logistic or linear regression for the seven outcomes, controlling for characteristics with p=0.20 in the univariate comparisons.

Results: Of the total 111 patients referred for GC/GT during study time period, 48 had IPV and 63 TGV. Patients with TGV were younger, had lower SES, and lived >10 miles from the service location compared to those with IPV (all p<0.03). However, in the logistic regressions controlling for age, SES and sample type (blood vs saliva), appointment type was not significantly associated with any outcome, but lower SES was associated with a longer distance to the provider (OR=1.09, CI 1.03-1.16).

Conclusions: Telemedicine can impact the demographics of patients and access to GC/GT by reducing barriers for ovarian cancer patients obtaining CGC. The burden of leaving work for multiple appointments, driving, and cost of parking and childcare tends to be heavier on those who have a lower income and who are younger. While studies in larger populations are required to confirm these preliminary findings, tele-genetics can help improve access to timely CGC which can impact clinical outcomes.

P012 : Réseau en oncogénétique de l'est du Québec (ROEQ) : Présentation de la démarche de consultation pour la formalisation du réseau

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Contexte : Sur le territoire du RUISSS-UL, le CHU de Québec–UL, par sa mission de centre tertiaire, dispense la majorité des services pour la clientèle de génétique. Les délais de réponse aux demandes croissantes de consultation et la méconnaissance des indications de référence par les intervenants peuvent amener une disparité régionale pour l'accès au test. Le ROEQ vise une plus grande collaboration entre les équipes pour des soins plus accessibles, mieux organisés et coordonnés. La formalisation de ce réseau d'oncogénétique s'inspire du cadre de référence pour la mise en place des réseaux par siège tumoral ou par thématique du Programme québécois de cancérologie.

Objectif : Les objectifs étaient de 1) faire un portrait des trajectoires de soins et services en oncogénétique (clientèle adulte et pédiatrique) et 2) décrire les principales forces et faiblesses de ces trajectoires.

Méthodologie : La démarche globale de consultation comporte 4 volets : 1) obtenir un portrait statistique grâce aux données administratives et aux bases de données locales des établissements du RUISSS-UL; 2) documenter les pratiques des médecins en lien avec l'oncogénétique avec un questionnaire inspiré du National Cancer Institute Physician Survey on Cancer Susceptibility Testing (Wideroff, Cancer Epidemiol Biomarkers Prev, 2003); 3) recueillir l'opinion de personnes ayant eu accès à une consultation en oncogénétique par un questionnaire téléphonique ou en ligne en collaboration avec le projet C-MOnGene; 4) discuter avec les intervenants et identifier les défis de chacun des milieux par des rencontres dans les 9 établissements.

Conclusion : L'analyse de l'ensemble des données, en étroite collaboration avec la recherche, a permis 1) d'identifier les défis, les opportunités, les perceptions et les interactions des acteurs des milieux vis à-vis du ROEQ; 2) de dégager une vision commune du ROEQ; et surtout 3) de développer un modèle logique pour guider sa mise en œuvre.

P013 : Health system-led direct contact of at-risk relatives for cascade testing: Trial in progress

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Disparities in Hereditary Cancer Genetics *(Continued)*

Background: Cascade screening in at-risk relatives of people with known pathogenic variants is key to the promise of genetic medicine. In the United States, probands with variants suggesting hereditary breast or ovarian cancer (HBOC) syndrome are expected to notify their own at-risk relatives, but many at-risk relatives are never notified. We developed a novel familial genetic risk notification program where genetic counselors offer to contact probands' at-risk relatives directly and are evaluating it in an NIH-funded feasibility trial.

Methods: This prospective study used a single-arm mixed-methods design. We enrolled two groups of participants: probands and relatives of those probands. Eligible probands were currently enrolled members of a U.S. health system with an upcoming appointment for pre-test genetic counseling for HBOC or Lynch syndrome. Eligible relatives were first-and second-degree relatives of probands. For probands with concerning variants identified during testing, the genetic counselor offered to contact any or all at-risk relatives directly to discuss genetic risk and testing. Study outcomes are program reach, acceptability, and limited efficacy, assessed by a combination of medical record, survey, and qualitative interview data.

Results: Preliminary assessments of reach show a 37% of probands approached enrolled in the study (55 of 148), 51% of enrolled probands used the direct contact program (28 of 55), and 44% of eligible relatives were reached via direct contact (44 of 101). Qualitative results suggest the program was acceptable to probands and relatives, reduced burden for probands, notified at-risk relatives who would not otherwise have been notified, and did not cause adverse events. Ongoing analyses will examine cascade testing uptake, genetic testing outcomes, and impacts on family communication.

Conclusions: Our findings will provide new, foundational evidence for the creation of US-based familial notification systems while prioritizing the preferences of patients and families.

P014 : Understanding the knowledge and perceptions of hereditary breast cancer testing (BRCA 1/2) among breast cancer care providers in Nigeria

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Purpose: A greater understanding of hereditary breast cancer prevalence in Nigeria is needed and must occur alongside efforts to understand both patients' and health care practitioners' perceptions and acceptability of genetic testing, and the development of wrap-around genetic counselling, management and support services, all of which are currently lacking in Nigeria.

Aim: To understand the knowledge and perceptions of hereditary breast cancer testing (BRCA1/2), amongst breast cancer care providers in Nigeria

Methods: Breast care health providers (general surgeons, radiation oncologists and radiologists) were invited to complete a questionnaire focused on perceptions, knowledge, and practice of genetic testing in Nigeria. Data analysis was completed in SPSS. Sociodemographic variables were presented in tabular form and the association between categorical variables were assessed using the Chi-Square and non-categorial variables logistic regression (p=0.05).

Results: A total of 121/549 (22%) breast care health providers completed the questionnaire. The sample was relatively evenly split between consultants (58.9%) and senior residents (41.1%). The majority of respondents 94 (77.7%) worked in a public teaching hospital setting and the majority of respondents 116 (95.9%) were in the 31 - 64year age range.

Most of the respondents 85(70.2%) didn't have provisions for genetic counseling nor a pathway for referral 70(57.9%) and almost all reported (97.5%) that a lack of a genetic counselor affects their request for genetic testing.

Only 12 (9.9%) respondents had formal genetic training. Yet 100% of respondents without any form of training are willing to be trained or send a colleague from their institution for training.

Conclusion: We recommend the inclusion of genetic counseling and testing in Nigeria hospitals to improve hereditary genetic testing. It's also important to improve the postgraduate curriculum to include cancer genetics.

MAINSTREAMING GENETIC TESTING

P015 : The unique genetic structure of the South African population reveals strong BRCA1/2 founder effects and a high contribution of non-BRCA risk genes influencing testing strategies

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Translation of genomic knowledge into public health benefits relies on evidence-based recommendations informed by the spectrum of actionable variants occurring globally, which differs between populations. This is relevant to South Africa (SA) as a complex history of migration events resulted in varying degrees of pathogenic SA founder variants detectable using first-tier BRCA1/2 genotyping assays. Numerous negative results resulted in us moving beyond BRCA1/2 screening.

We explored multigene panel testing for genes participating in homologous DNA damage repair, and ultimately searched for truncating variants in clinically predisposing genes in uninformative breast cancer (BC) cases using whole exome sequencing (WES) in a research context. We provide evidence and propose an unconventional cost-effective testing strategy at the intersection of research and service delivery for BC diagnostics in our financially stricken health sector.

2974 BC patients were screened for pathogenic variants in BRCA1/2, with 596 patients investigated using the multigene Oncomine™ BRCA Expanded Panel. Exploratory WES data (n=20) assisted with the validation of the multigene assay and provided insight into its application for variant and gene discovery.

The BRCA1/2-only screen, together with the multigene assay revealed 481 and 93 actionable variants respectively (16.2%, 15.6%), with 28.8% of these representing founder variants. The established non-BRCA1/2 risk genes contributed 33.3% (31/93) to the total percentage. WES revealed two novel protein

truncating variants in the basal cell carcinoma gene PTCH1 and the signal transmission and transduction gene KIT involved in crucial cellular processes, respectively.

The high prevalence of founder variants detected using the NGS-based screens justifies retaining targeted genotyping at the first tier before progressing to costly NGS-based screening. If negative, it can be followed by panel testing when clinically indicated, with WES added in a research context for unresolved cases as an inventive step to provide a constant flow of new knowledge into the diagnostic platform.

P016 : BRCA1 and BRCA2 testing when a familial variant is reported

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Introduction: BRCA1 and BRCA2 (BRCA1/2)-targeted genetic testing is often ordered due to family history of a genetic variant. However, the positive familial test report (proband report), or notation of the gene and known familial variant (KFV), are not always available at the time of ordering. Family members or providers may assume a KFV is within BRCA1/2 but in fact the variant is in a different gene. When a KFV is indicated in provided records, attempts are made to obtain proband reports and modify the initial order if it will not detect the KFV. The purpose of this study was to identify the percentage of patients whose KFV could be identified within the BRCA1/2-targeted initial order at a large clinical reference laboratory.

Methods: This analysis included BRCA1/2-targeted orders: BRCA Panel or BRCA1 and BRCA2 Deletion and Duplication. Orders with a reported KFV were identified. Provided medical records were examined to determine if a proband report, notation of the familial variant, or gene was available. Data were analyzed to determine if and how frequently KFVs would be captured by the original order.

Results: This study identified 1,719 cases with a reported KFV; however, documentation of the KFV or gene was provided in 1,410 cases. Of these documented cases, 1,190 (84.4%) KFVs would have been detected with the original order, while the remaining 219 (15.5%) were outside of BRCA1/2 and the original order needed to be modified to capture the KFV.

Conclusion: In this cohort, 15.5% of KFVs were outside of BRCA1/2 and the original order would not capture the reported KFV. It is critical for ordering providers to obtain proband reports to help ensure appropriate testing is ordered. If unavailable, providers may consider a more comprehensive hereditary cancer panel. This research demonstrates the need for provider education to extend beyond BRCA1/2 when assessing familial variants.

P017 : Pancreatic mainstreaming at Sunnybrook: A tertiary care centre's experience

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Introduction: Identifying germline pathogenic variants in patients with pancreatic cancer can direct cancer treatments and facilitate genetic testing for relatives, leading to increased cancer screening for carriers. Pancreatic cancer is known to have a poor prognosis and wait times to see genetics may prevent patients from accessing testing. The goal of our study was to facilitate mainstreaming (oncologist initiated testing) and measure patient satisfaction.

Method: Patients with newly diagnosed exocrine pancreatic cancer were offered abbreviated genetic counselling and testing by their oncologist. Those interested completed consent, testing, and pre-test and post-test surveys on their experience.

Results: Fifty-eight participants were approached from July 2020 to February 2022 and 39 consented, had testing, and completed surveys. All participants had testing of a set of 11 genes (ATM, BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53) and 29/39 also had testing of CDKN2A. For results, 5.1% had a likely pathogenic/pathogenic variant, 28.2% had a variant of uncertain significance, and 66.7% were negative. Of the 39 participants, 27 completed a pre-test survey and the majority were satisfied with the information provided and discussion length. Fourteen completed a post-test survey and the majority would recommend testing to other patients, while 100% would make the same choice again and none felt the process did them harm.

Conclusion: Through mainstreaming, 39 patients accessed genetic testing and there was a 5.1% positive rate. There were challenges to recruitment including decreased patient loads at the hospital due to the pandemic and drops in survey responses at each time point due to participants in declining health or becoming overwhelmed by paperwork.

Overall, the vast majority of participants expressed satisfaction with their experience and would recommend it to others. If barriers like study paperwork were removed, it seems access to this time sensitive testing could be increased through mainstreaming.

P018 : Mainstreaming genetic testing in the high risk breast clinic at Sunnybrook

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Introduction: Genetic testing criteria in Ontario includes testing for unaffected patients with a minimum 5% risk of a pathogenic mutation. Provincial testing has expanded to offering multi-gene panels. Identification of pathogenic mutations in unaffected women can direct additional cancer screening and risk reduction surgery, as well as help facilitate predictive genetic testing for relatives.

The High Risk Breast Clinic at Sunnybrook follows unaffected women identified as high risk for breast cancer due to their family histories. These women may benefit from being offered genetic testing when affected relatives are unavailable for testing and/or to update previous uninformative BRCA testing.

The goals of our study were: to assess outcomes of genetic testing in eligible women when offered, in conjunction with modified counselling, directly by physicians in the High Risk Breast Clinic; and to measure physician satisfaction and workload with this novel approach.

Methods: Select women at high risk for breast cancer were offered abbreviated genetic counselling and testing by their physician in the High Risk Breast Clinic. Physicians ordering testing completed satisfaction surveys.

Of 157 patients approached between May 2019 and March 2022, 156 had testing. 155 patients had prior genetic counselling and 80 had previous BRCA testing. Testing included either a breast/ovarian gene panel or Ashkenazi Jewish testing.

Results: Of 156 tests, 4.5% were positive, 19.2% had a VUS and 76.3% were negative. Of 7 positive results, 5 were in moderately penetrant genes including ATM, BARD1, BRIP1 and CHEK2, and 2 in high risk genes BRCA2 and PALB2.

Modified genetic counselling, including paperwork, was completed in 14 minutes or less in 130 of 157 patients. Physicians felt clinic time utilization was acceptable (99%) and that patients benefited from physician-directed genetic testing (100%).

Conclusions: Through mainstreaming using a physician-directed protocol, 156 patients accessed genetic testing yielding a 4.5% positive rate. Physicians were able to appropriately identify unaffected women eligible for testing. Physicians expressed a high degree of satisfaction in facilitating genetic testing.

P019 : DNA-First: latest experiences with large scale transition of DNA-diagnostics from clinical geneticists to treating clinicians in breast cancer patients

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Introduction: In the Netherlands, traditionally only clinical geneticists requested DNA-diagnostics for hereditary breast cancer. To facilitate timely test results and decrease patient burden, we have stepwise shifted counselling and requests for these DNA-tests to treating clinicians (a procedure called 'DNA-First') and evaluated the latest experiences of professionals and patients with this large scale transition of care.

Materials and methods: DNA-First was initiated in July 2018 by the departments of clinical genetics from Maastricht University Medical Center and Radboud university medical center, Nijmegen, The Netherlands. DNA-diagnostics consisted of gene panel analysis for BRCA1, BRCA2, PALB2, CHEK2 and ATM; from March 2022 onwards RAD51C, RAD51D, BARD1 and BRIP1 were added. Originally, DNA-First was available only in selected larger regional hospitals for breast cancer patients for whom test results might alter treatment. From October 2021 onwards, all recently diagnosed breast cancer patients with an indication for DNA-diagnostics were eligible. Stepwise all hospitals in the South-East of the Netherlands were invited to participate. In addition, test results were sent to patients as well, instead of clinicians only. In case of a pathogenic variant, patients were directly invited for consultation with a clinical geneticist without the need for separate referral. Experiences with these new procedures of treating clinicians and clinical geneticists (interviews) as well as patients (surveys and interviews) were recently evaluated.

Results: Up to November 2022, 19 hospitals were included, 2229 requests for DNA-diagnostics were made and 248 pathogenic variants were identified (11.1%). The number of requests increased to 90 per month, while retaining the percentage of positive results. Treating clinicians, clinical geneticists and patients were positive about the latest changes in DNA-First.

Conclusion: Large scale transition of DNA-diagnostics for hereditary breast cancer from clinical geneticists to treating clinicians is feasible and acceptable. For more information: see www.DNAfirst.nl.

P020 : Genetic testing for cancer susceptibility: Physicians' attitudes and practices in Eastern Québec, Canada

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Mainstreaming Genetic Testing *(Continued)*

Background: Owing to the advance in genomics and increase in availability, genetic testing for cancer susceptibility is increasingly used to guide prevention and/ or treatment strategies. In a context of a developing network in oncogenetic for Eastern Québec, gaining an accurate portrait of physicians' practices regarding cancer genetic testing would support implementation strategies.

Purpose: We assessed Eastern Québec physicians' attitudes, opinions and practices regarding genetic testing for cancer susceptibility.

Methods: An online questionnaire, inspired from a previous large-scale practice survey, was distributed through nine healthcare institutions to all of their practicing primary care and specialist physicians.

Results: A total of 448 physicians completed the questionnaire. Respondents were female (66.8%), primary care physicians (50.3%) and had a practice seniority between 0 to 15 years (56.5%). In the past 12 months, a proportion of 9.5% reported having ordered genetic tests for at least one patient and 51.3% referred patients to another specialist for cancer susceptibility genetic testing. Only 18.6% felt qualified to recommend genetic testing to adult patients, 19.3% were aware of guidelines regarding genetic testing and 55.7% were interested in training in hereditary risk assessment, genetic testing and patient follow-up. Most (75.4%) agreed that there should be provincial guidelines regarding genetic testing for cancer susceptibility and training tools to support physicians' practice.

Conclusion: These results underline the importance of developing targeted educational programs as well as provincially endorsed and regularly updated guidelines covering the whole spectrum of oncogenetic services. In a context where demands for genetic testing for cancer susceptibility is continuously expanding and already exceeding genetic services capacity, the proper training of primary care and specialist physicians is a pressing priority.

P021 : Oncologist's satisfaction with a mainstreaming education module

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In April 2021 Ontario Health-Cancer Care Ontario implemented Provincial Hereditary Cancer Testing (HCT) criteria for a standardized gene panel list to improve cancer genetic testing services and to ensure equal access to high quality care for patients across Ontario. Other goals included supporting collaboration among providers, increasing capacity, maximizing efficiencies, and optimizing health system resource use. The changes significantly increased the number of patients eligible for HCT, and a key recommendation for implementation was consideration of oncology-initiated testing - 'mainstreaming'- in patients who meet testing criteria based on their own personal cancer diagnosis.

The Hereditary Cancer Team at CHEO, in collaboration with oncologists at The Ottawa Hospital, developed and implemented a mainstreaming program for HCT for prostate, pancreatic, breast, and ovarian cancers. The module included a short presentation and demonstration of the mainstreaming process. After completing the training module, we invited oncologists to evaluate the module and their satisfaction with the process.

The participation rate for the survey was 70% (N= 30/43). Thirty-three percent (10/30) of participants had attended mainstreaming education sessions prior to the training module. Prior to completing the training module, 57% (17/30) of oncologists reported feeling either neutral, not confident, or totally unprepared to

offer mainstreaming genetic testing and 27% (8/30) reported feeling either confident or very confident in their ability to provide mainstreaming services. After completing the module, 97% (29/30) of participants were confident or very confident in providing mainstreaming testing. Similarly, oncologists reported an improvement of their knowledge of the responsibilities of being a mainstreaming provider. Overall, oncologists reported satisfaction with the ease of accessing training, the module content, the clarity of testing criteria, the support being provided by the Hereditary Cancer Team, and the training module length. The module was an effective way to introduce oncologists to mainstreaming testing.

P022 : Unique design and outcome of mainstreaming collaboration

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Advances in oncology treatment have led to an increasing number of patients with a cancer diagnosis requiring timely access to genetic testing for treatment decisions. A well-recognized solution at many centers has been mainstreaming genetic testing into the oncology clinic.

The Inherited Cancer Program at CHEO, in collaboration with oncologists at The Ottawa Hospital (TOH), developed and implemented Genetics to Oncology (G2O), a mainstreaming program for breast, ovarian, pancreatic and prostate cancers. After a ~20 minute onboarding tutorial, oncologists at TOH can arrange next-generation sequencing panel testing from the provincial evidence based list of cancer-site specific genes. Select provincial eligibility criteria are recorded on the laboratory requisition. The analysis takes place through the Genetics Diagnostic Laboratory (GDL) at CHEO. Concurrently, TOH oncologists send a standardized referral to CHEO. Results are reported simultaneously to the ordering oncologist and the Inherited Cancer Program.

If results are negative the patient is not seen at CHEO, however, a consultation letter is sent both to the ordering oncologist and the patient. If a pathogenic variant (PV), likely pathogenic variant (LPV) or variant of uncertain significance (VUS) is detected, the patient or their next of kin is offered an urgent genetic counselling appointment.

From December 2021 to 2022, 42 oncologist have been on-boarded and 308 patients have completed the G2O process. There have been 213 (69%) negative results where ordering providers and patients received a negative result letter only thereby reserving clinic spots for other eligible patients. The genetics clinic saw 94 (31%) patients or patient's next of kin for one appointment to disclose a positive (PV or LPV) or VUS result. Strengths of the CHEO-TOH G2O collaboration compared to other mainstreaming programs include the capture of select provincial eligibility criteria and provision of genetic counselling for every patient with a PV, LPV or VUS.

P023 : Oncologist initiated genetic testing for patients with prostate cancer: The Sunnybrook Odette Cancer Centre experience

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Background: Prostate cancer is the most common cancer among men and is the second leading cause of cancer-related deaths. An estimated 20-30% of men with prostate cancer are reported to have a genetic mutation, of which approximately half are germline and half are somatic. The Odette Cancer Centre, a large tertiary oncologic centre, introduced oncologist-initiated genetic testing, mainstreaming, for prostate cancer patients in April 2021, when eligibility criteria for germline genetic testing expanded.

Methods: We conducted a retrospective chart review on the first year's mainstreaming experience at the Odette Cancer Centre. Between May 1, 2021, and May 30, 2022, 174 eligible prostate cancer patients underwent mainstreaming with a 19-gene panel. Descriptive and inferential statistics were used to compare patients with and without a germline mutation.

Results: Patients were of various ethnic backgrounds, with a median age of 75 (IQR 68.25-80). 14 patients (8%; 95% CI 4-12%) were found to have a deleterious germline mutation. These included pathogenic, likely pathogenic, and highly suspicious findings in BRCA1/2, ATM, CHEK2, PMS2, RAD51C, HOXB13, and BRIP1. Patients with germline mutations were not statistically different from those without a mutation in terms of baseline clinicodemographic features, including age and stage at diagnosis. Of the 14 patients with a germline mutation, none reported a second primary cancer and 8 (57%) reported a first- or second-degree relative with a history of prostate, breast, ovarian, or pancreatic cancer. The median turnaround time for germline results was 91 days (IAR 37-113 days). Of those mainstreamed, 34 (19.5%) had somatic panel genetic testing, among whom 8 (23%) had an alteration in a homologous recombination gene.

Conclusion: We demonstrate the feasibility of a mainstreaming model for germline genetic testing in prostate cancer patients. Personal and family history of cancer cannot reliably stratify patients for the presence of deleterious germline variants.

P024 : Mainstreaming genetic counselling (GC) and testing (GT) in underrepresented populations with triage and remote GC: Germline testing in breast (BC), ovarian (OC), prostate (PC), and pancreatic cancer (PaC) in over 700 Mexican patients (pts).

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Genetics could help guide therapy and prevention in cancer pts, and their relatives. In Mexico, the lack of genetic services has been a barrier to offering GT. Since 2020, we have implemented a triage and a remote system to hasten GT and ensure GC. Here, we report the results of those projects. Eligibility was assessed by NCCN guidelines. We gathered clinical features, cancer family history (CFH), and histopathological features (HF). BRCA1&2 were analyzed in all pts, while others (PC, remote and selected cases) had multigene panel (MGP). Certified laboratories performed GT. We added the data from a previous cohort for statistical analysis.

741 pts underwent GT. 51% had BC, 29% OC, 17% PC, and 3% PaC. 54% had CFH. 51% were candidates because of HF. 30% had metastasis at diagnosis. 71% of GT was prescribed from 2020. 28% had PMG. 20.5% of pts had a pathogenic variant (PV): 50% in BRCA1, 32% in BRCA2, and 7% in PALB2. Founder PV (BRCA1 Del 9-12) was 15% of all PVs, only in BC and OC cases. 17% had variants of uncertain significance (VUS). There was an association between PV and CFH ($p<0.0001$), and HF ($p<0.0005$). MGP increased the diagnostic yield in BC ($p=0.023$) and PaC ($p=0.034$. An association between PV and metastatic disease was noted in PC ($p=0.008$).

We present new models of GC to overcome the lack of GC services in Mexico. 535 pts had accelerated GT in 2 years. 35% or the remote cohort had a PV. Those pts would still be on a waiting list. Also, we found 12% PV in men with PC. Reports of GT in Mexican men are scarce. We identified the need to implement PMG in daily practice. Finally, we identify more VUS with PMG (p>0.0001), which underlines the necessity of GC for all pts.

P025 : Genetic Rapid Easy Access Testing (GREAT) in breast cancer; a hybrid genetic testing experience through the McGill University hospitals

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Background: Between 5 to 10% of breast cancer cases are linked to an inherited germline pathogenic or likely pathogenic (P/LP) variant. To identify these individuals, a rapid and easy access genetic testing and counseling program was initiated at three cancer centers at McGill University, Montreal, Canada for unselected women newly diagnosed with breast cancer. The program aimed to assess the feasibility, acceptability and clinical utility of offering rapid testing of 15 breast cancer susceptibility genes.

Methods: Treating physicians referred female patients with a first diagnosis of invasive breast cancer from 2019 to 2022. Eligible women were offered genetic counseling through an organized, genetic counselor-led clinic and DNA banking. Those who consented were tested via an in-house Next-Generation Sequencing (NGS) panel of 15 genes.

Results: Of 1083 referred patients, 72.8% (788) were eligible and 92.5% (729) of those eligible consented to be tested. P/LP variants were identified in 8.2% (60) of patients including 5.3% (39) in *BRCA1*, *BRCA2* and *PALB2* (B1B2P2) and 2.9% (21) in 6 of the remaining 12 genes (*ATM, BARD1, CHEK2, MSH2, RAD51D, STK11*). Overall, 28.2% (11/39) of positives for B1B2P2 and 81% (17/21) of positives for the other predisposition genes would not have been eligible for genetic testing according to traditional high risk based criteria used in the regular medical genetics service. 71.8% (28/39) of women positive for B1B2P2 had at least one risk reducing procedure following a positive result.

Conclusion: A hybrid genetic testing program in a network of breast cancer centers in Montreal, Canada detected P/LP variants in 8.2% of patients and was widely accepted by patients and their physicians alike. Clinical management decisions were impacted in 72% of positive cases when genetic testing and counseling was easily available around the time of diagnosis.

P026 : Preimplantation genetic testing (PGT) for aneuploidy and hereditary breast cancer (PGT-A/M) for optimal fertility preservation or prevention of vertical transmission

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Objective: Carriers of mutations in BRCA1/2, CHECK2, ATM, Lynch sy and other oncogenes have higher lifetime risk for beast cancer (BC)(65-80%), ovarian (30-45%) and other cancers, with 50% transmission to their offspring. Oocyte and/or embryo cryopreservation is an option for fertility preservation(FP), and when coupled with PGT-A/M for BC-mutations, allowing prevention of vertical transmission(VT). Our objective was to evaluate the outcomes of simultaneous PGT-A/M for BC mutation carriers.

Materials and Methods: We analyzed 42 IVF/PGT-A/M treatment cycles of 29-couples undergoing IVF because of pre-chemotherapy FP(n=12) or BC-mutation carrier status to VT(n=17) at CReATe Fertility Center(CFC), Toronto from 2017-2022. PGT-A/M was performed from a single trophectoderm(TE) biopsy. We compared cycle outcomes and proportion of euploid/mosaic-carrier embryos(EC,MC) to non-carrier(ENC,MNC) in couples with female or male mutation-carriers. Implantation(IR), ongoing pregnancy-rate(OPR) and live-birth rates(LBR) were evaluated. SSPS-software was used for statistical analyses.

Results: Overall 221 blastocysts were biopsied from 42-IVF/PGT-A/M cycles. 23%(n= 51) of all embryos were tested for BRCA1, 49.8%(n=110) for BRCA2, 6.8%(n=15) for CHECK2, 5%(n=11) for PALB2 and2.7%(n=6) for BRIP1. Three couples carried Lynch Sy(MSH2,PMS2) and one-STK11 mutations; overall 6-IVF cycles and 12.7% (n=28) of all embryos. Average female age was 34.6±3.8yrs. Patient characteristics and IVF cycle characteristics were no different between F-carriers and M-carriers couples. PGT-A/M results for all 221 embryos: 35% were PGT-A-abnormal, 21.6% ENC, 31.6% EC, 5.3% MN% C and 6.4% MC. 44.4% of the IVF cycles resulted in no ENC embryos, 22.2%-IVF-cycles had 60-85%-EC and 33.4had the expected 50% ratio of ECvsENC. Total of 24 FET were performed, 21 FETs of ENC embryos and 2-EC embryos. IR was 38%, OPR-33.3% and LBR-28.6%. All 6 babies were born healthy at term.

Conclusion: Simultaneous PGT-A/M for hereditary-BC mutations offers reliable FP in BC patients and VT avoidance in carriers, allowing for informed decision making and family planning for these couples.

P027 : Family history is not predictive of mutation status in breast, ovary, pancreas, and prostate cancer patients undergoing universal germline genetic testing

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An expedited Genetic Testing Station (GTS) workflow was implemented at an academic medical center to facilitate universal germline genetic testing for patients with breast, ovarian, pancreas, and high-risk prostate cancers (HBOC cancers). Between 1/1/2019 and 6/25/2022, genetic counselor assistants collected cancer family history of HBOC cancers and Lynch Syndrome (LS) cancers (colorectal and endometrial) from 2,021 patients referred to the GTS by their oncologists for multi-gene panel testing (712 with breast cancer, 114 with ovarian cancer, 435 with pancreas cancer, and 760 with prostate cancer). Pathogenic/likely pathogenic variant (P/LPV) detection rates were computed for actionable genes, defined as those with National Comprehensive Cancer Network guidelines for HBOC cancers: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53.

Family history (FH) was characterized as follows: No FH of HBOC/LS cancers, FH of any HBOC/LS cancer, FH of HBOC cancers only, FH of HBOC cancers including the patient's presenting cancer type. Percentage of patients with a P/LPV in any actionable gene was computed for each FH category respectively for breast (9.1, 8.4, 8.0, 8.7); ovary (14.3, 16.7, 26.7, 30.8); pancreas (13.5, 10.7, 11.8, 14.0); and prostate (7.4, 9.9, 9.6, 8.5). Odds ratios, 95% confidence intervals, and p-values were computed using Fisher's exact test to compare likelihood of P/LPV for each cancer indication between patients with no FH and those with FH in each of the categories described above.

No significant differences were found, though the presence of ovarian cancer in the family history was most likely to predict the presence of P/LPV in patients with ovarian cancers (OR=2.67; 95%CI 0.45, 14.05; p=.1729). These findings continue to support universal germline genetic testing for patients diagnosed with HBOC cancers.

P028 : An Australian mainstream genetic testing program: data audit and clinicians views about clinical practice

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Introduction: A mainstream genetic testing program for women diagnosed with ovarian cancer and supported by the local Cancer Genetics service (CGS). A limited number of breast and prostate cancer patients had testing arranged by their clinician. The aim of this study was to review the mainstream genetic testing program.

Methods: Eligible patients had genetic testing arranged between February 2015 and August 2019 by the CGS or approved clinicians from five affiliated Sydney-based hospitals. Tumour, family history details, and outcomes of genetic testing were assessed from medical records. Web-based surveys were administered to clinicians.

Results: Genetic testing was arranged for 289 women with ovarian cancer. Before 2017, up to 45% of genetic tests were mainstreamed, compared with 76% of tests after 2017. CGS were more likely to arrange testing for women with a family history of hereditary breast/ovarian cancers (50.7% vs 39.7%), and non-serous pathology (28.2% vs 12.3%). Pathogenic variants were detected in 13.7% of women who had mainstream testing and 20.3% of women tested by the CGS. Women with pathogenic variants (15 BRCA1, 14 BRCA2, 1 PALB2 later identified in research) were appropriately referred for post-test counselling to the CGS. Motivated clinicians requested testing for 18 women with breast cancer. Most (13/14, 93%) who had publicly-funded testing were eligible by age or pathology-based criteria, and 4 women self-funded their test. No pathogenic variants were detected in this cohort. Fifty-four clinicians (70% response rate) participated in the survey. Clinicians were overall satisfied (76%) and viewed the process as time-efficient and accessible for patients.

Discussion: Mainstream genetic testing of eligible participants increased over time, with testing and post-test referral appropriately arranged. This study demonstrated successful implementation of a coordinated mainstream ovarian cancer genetic testing program and clinicians' approval of the pathway. This has implications for future development of mainstreaming programs.

NEW APPROACHES TO THE EARLY DIAGNOSIS OF HEREDITARY CANCERS

P029 (Rapid Fire Presentation S5-RF1): Somatic testing lags far behind germline testing in patients with epithelial ovarian cancer; a missed opportunity

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Objective: Determine frequency of germline and somatic testing for patients with epithelial ovarian cancer (EOC) and whether result was associated with use of PARP inhibitor (PARPi) maintenance therapy.

Methods: Retrospective cohort study of patients with newly diagnosed EOC in a large community-based integrated health system from 1/1/2019-12/31/2020. The primary outcome was performance of somatic testing. Rates of testing were compared pre and post the American Society of Clinical Oncology (ASCO) 2020 guidelines recommending somatic testing for all patients with negative germline testing. Secondary outcomes included use of PARPi therapy and association with genetic result.

Results: 246 patients were diagnosed with EOC: 144 in the pre-ASCO cohort, 102 in the post-ASCO cohort. Median age at diagnosis was 63yrs. 57% were high grade serous cancer and over 50% were stage III/IV. There were no differences between pre- and post-ASCO cohorts. Germline genetic testing was completed in 80.9% of patients with 8.5% having a germline BRCA 1/2 mutation (gBRCAm). Somatic testing was done in 30% of patients, with an additional 11 patients having homologous recombination deficiency (HRD) mutations. There was no difference in proportion of patients who had somatic testing between the pre- and post-ASCO cohorts (26% vs 35%, p=0.13) or in maintenance PARPi use between cohorts (45.5% vs 55.5%, p=0.2). Of stage III/IV patients with serous or endometrioid cancers, 22% were on PARPi maintenance, and gBRCAm was significantly associated with use (36% gBRCAm vs 4% no gBRCAm p<.001), while somatic HRD mutation was not.

Conclusions: Somatic genetic testing was low at 30% and did not significantly increase following the new ASCO guidelines. PARPi use was correlated with gBRCAm but not somatic HRD mutation. Given the significant clinical implications of somatic tumor testing, efforts that have increased adoption of germline testing in this population should be utilized to improve somatic testing rates.

P030 : We are more than our founders: adding to the story of French Canadian cancer risk

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Background: Several founder pathogenic germline variants (PGVs) that predispose to cancer have been reported in the French Canadian population. However, relatively little is known about the outcomes of multigene panel testing (MGPT) in this population. The aim of this study was to describe MGPT outcomes among a French Canadian cohort.

Methods: A retrospective analysis of 5,904 French Canadian probands with cancer undergoing germline genetic testing through a single commercial laboratory ordered by healthcare providers from Canada was conducted. Overall cohort demographic data abstracted from the test requisition form and testing outcomes were analyzed. Descriptive statistics and Fisher's exact test were utilized.

Results: The majority of individuals were female (83.6%), between ages 40-69 years at testing (70.2%), and had 11-30 genes analyzed (76.6%). Over half the cohort (52.5%) had breast cancer. The overall PGV rate was 14.1%. Females with ovarian cancer had a higher PGV rate (17.1%) than individuals with breast cancer (12.7, p=0.0018) and pancreatic cancer (12.0%, p=0.03). PGVs in BRCA1, BRCA2, PALB2, and RAD51D were present in 49.2% of individuals with PGVs, with founder variants accounting for 81.5% of PGVs. FH had the highest PGV rate (5.6% of those tested), with 78.1% of individuals carrying p.Glu432Lysfs*17. PGVs were also common in CHEK2 (1.9%), ATM (1.4%), PMS2 (0.7%), RAD51C (0.6%), and MSH6 (0.5%). The uptake of cascade testing was 26.9%.

Conclusions: Although genes with French Canadian founder PGVs accounted for almost half of the positive results, nearly one-fifth of the PGVs were not founders. Additionally, PGVs from a broad spectrum of genes were observed in this cohort. These results support the use of MGPT in the French Canadian population undergoing hereditary cancer testing.

P031 (Rapid Fire Presentation S5-RF2): Facilitated cascade testing for families with identified variants associated with hereditary gynecologic cancers

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Objectives: We evaluated the feasibility of a facilitated referral pathway for cascade genetic testing for patients with mutations associated with gynecologic cancers.

Methods: This is a prospective cohort study of patients with BRCA1, BRCA2, BRIP1, MSH2, MLH1, MSH6, PMS2, EPCAM, RAD51C, and RAD51D pathogenic variants from March 2019 to November 2022 seen at a gynecologic oncology clinic. Eligible patients were offered a facilitated referral pathway for genetic testing for first and second-degree relatives. The primary outcome was the proportion of patients with a relative who completed genetic testing.

Results: Seventy-six patients were enrolled in our study. The median age of genetic testing was 41 (range 20-68). Fifty-three (70%) were non-Hispanic white, seven patients each were non-Hispanic Black and Asian (9%), six patients were Hispanic (8%), and three patients were other/ unknown (4%). For patients with cancer, the median age at diagnosis was 45 (range 23-66). Forty-four patients (58%) had no history of cancer. Cancer history was as follows: breast, 17 (22%); ovary, 9 (12%); uterine, 2 (3%). Renal, thyroid, and small bowel each had one patient (1%). The most common variant was BRCA1 (38, 50%), followed by BRCA2 (29, 38%), BRIP1 (3, 4%), PMS2 (4, 5%), MSH6 (3, 4%), MLH1, MSH2 (2, 3%), and EPCAM (1, 1%). At one month of enrollment, 44 (57%) of patients had contacted at least one relative for genetic testing, and 12 (13%) of patients had at least one relative that participated in our facilitated referral pathway for genetic counseling. However, only four patients (5%) had at least one relative complete genetic testing; two in our pathway and two outside of our facilitated pathway.

Conclusion: Although over 50% of patients contacted family members regarding genetic testing, only 5% had a relative complete genetic testing. Novel efforts to simplify access for relatives to improve testing are desperately needed.

P032 : Identification of putative PTEN Cis-Regulatory elements by Multi-Omics data integration

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PTEN Hamartoma Tumor Syndrome is a hereditary cancer predisposition syndrome characterized by the appearance of benign and/or malignant tumors affecting multiple organs and is associated with heterogeneous clinical traits, resulting from a germline pathogenic variant (GPV) in PTEN. In the last decade, the number of patients with a suspicious PHTS phenotype without any identified PTEN's GPV variant has increased and is estimated at 20%, raising the question of missing heritability. While PTEN appears to be involved in approximately 20% of tumor non-specific breast cancer and more than 50% of basal-like breast cancer cases, point mutations in this gene are found in only 4-8% of breast cancers. The recent identification of PTEN structural modifications through Alu insertion in the coding region prompted us to continue exploring the allelic heterogeneity by hypothesizing that cis-regulatory region alterations may alter PTEN expression.

PTEN expression is ubiquitous and controlled through a poorly defined promoter and unknown enhancers. Enhancers can target promoters by chromatin approximation in the 3D structure, known to be organized in topologically associated domains (TAD). We propose those differences in PTEN genotype-phenotype can be explained by a loss of expression due to a TAD disruption or alterations of cis-regulatory noncoding regions. By combining ChIP-Seq and Hi-C data from ENCODE database, we found that PTEN is located in a 1Mb TAD, in contact with two 3'-putative enhancers: one of which harboring super-enhancers hallmarks and located in a genetic desert; the other one in RNLS intronic region. Taking together, we suspect PTEN might be in contact with both by an active mechanism of loop extrusion. We aim to verify and confirm their role in PTEN's TAD by our own Hi-C analysis, as well as define their location by Tiled-C analysis to obtain an accurate definition of the PTEN cis-regulation region.

P033 : An ex vivo model of mammary alveologenesis and macrophage infiltration to study BRCA1 mutation induced alterations to the mammary gland during pregnancy and involution

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Breast cancer diagnosed during pregnancy or up to one-year post-partum is termed a pregnancy associated breast cancer (PABC). Up to 30% of females diagnosed with PABC carry a *BRCA1* mutation, while females with *BRCA1* mutations also report difficulties breastfeeding. In BLG-Cre *Brca1*$^{22\text{-}24f/22\text{-}24f}$; *Trp53*$^{+/-}$ transgenic mice, tumourigenesis is preceded by aberrant differentiation towards an alveolar-like cell state, as well as altered immune macrophage infiltration. Thus, it is of interest to study how BRCA1 mutation affects mammary gland development and immune infiltration during pregnancy and involution.

Here, we utilized the BLG-Cre *Brca1*$^{22\text{-}24f/22\text{-}24f}$; *Trp53*$^{+/-}$ mouse model and performed immunofluorescence on formalin fixed paraffin embedded mammary glands of mice at day 18.5 of pregnancy and day 4 of involution to investigate how *Brca1* mutation affects alveologenesis and immune infiltration. We find that transgenic mice have more milk proteins in alveoli at d18.5 of pregnancy compared to their wild-type counterparts. Further, at both day 18.5 of pregnancy and day 4 of involution, transgenic mice have altered immune infiltration. We then validated an *ex vivo* 3D culture system of mammary alveologenesis and macrophage infiltration for future studies in mammary epithelial cells with *Brca1* mutations. We cultured organoids from mammary epithelial cells isolated from virgin BLG-Cre *Brca1*$^{22\text{-}24f/22\text{-}24f}$; *Trp53*$^{+/-}$ mice and stimulated the organoids with lactogenic medium. We confirmed the organoids develop phenotypes associated with alveologenesis, including more growth, development of lipid droplets and binucleated cells, and upregulate the expression of milk transcripts. Finally, we tested if murine derived macrophages

interact with these organoids in co-culture experiments. This study reveals that BLG-Cre *Brca1*$^{22\text{-}24f/22\text{-}24f}$; *Trp53*$^{+/-}$ mice have disturbances to normal processes during pregnancy and involution, and provides an *ex vivo* model for studying how *Brca1* mutation affects alveologenesis in future experiments.

P034 : Blood-based early cancer detection screening for breast cancer: Who should be tested?

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Blood-based early cancer detection (ECD) screening tests present a notable advantage in detecting malignancy at an early stage. Here, we report results from 100 surveyed OBGYNs exploring the clinical utility of a blood-based ECD test for breast cancer (BC) and sought to determine the target population that may most benefit from this testing.

Most survey respondents spent on average 95% of time in clinic and have been in practice for 10-30 years (94%). Majority of the respondents reported interest in utilizing a blood-based ECD assay for patients with pathogenic germline variants in BRCA1/BRCA2 (60%) or with a family history of BC (53%). Both scenarios represent patients at elevated-risk for developing BC (>20% lifetime risk).

These data demonstrate that blood-based ECD may provide a novel screening strategy in elevated-risk populations that complements current screening recommendations (i.e., annual mammography and MRI). Dual imaging is recommended because mammography alone misses ~20% of cases overall and performs more poorly (<50% sensitivity) across certain patient characteristics. However, clinician MRI referral and subsequent patient adherence rates have been reported to be <40%, due to cost and/or accessibility barriers.

Based on the survey findings, we envision several possible clinical scenarios where a blood-based ECD test can help: triage indeterminate findings, inform whether additional imaging is warranted, or determine imaging frequency. In any scenario, blood-based ECD has the potential to improve overall compliance and improve early detection in high risk populations. Any blood-based ECD assay implemented in this manner would require a demonstration of both analytical and clinical validity, in addition to studies of clinical utility, in the target patient population.

P035 : Interim results from a multimodality screening program reveal low recall rates and high rates of adherence to protocol specified visits

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Background: One-size-fits-all screening has proven disadvantageous for high-risk populations, particularly BRCA1 and BRCA2 mutation carriers and individuals of African ancestry (AA) at high risk for aggressive young onset breast cancer. After several studies demonstrated the diagnostic equivalency of abbreviated MRI to the full MRI protocol, we launched the Chicago Alternative Prevention Study for BReast CAncer (CAPSBRACA; clinicaltrials.gov: NCT03729115) to test the hypothesis that state-of-the-art genomic testing to identify women at increased risk, combined with state-of-the-art MRI techniques, could effectively detect and downstage aggressive breast cancers for high-risk women in diverse populations.

Method: Patients are scanned every 6 months with a bilateral breast MRI. The first MRI is a full scan, and subsequent MRI scans are abbreviated MRIs that include an Ultrafast MRI protocol. Major inclusion criteria includes: women over the age of 25 with either a BRCA1, BRCA2, TP53, PALB2, PTEN, CDH1,

STK11 mutation, or a Polygenic Risk Score (PRS) > 30%. AA women under 45 with at least one 1st or 2nd degree relative with breast or ovarian cancer are eligible because PRS scores are not reported for AA women.

Results: Currently the cohort consists of 130 participants c; the accrual goal is 400. There are 44 BRCA1 carriers, 42 BRCA2, 7 PALB2, 4 in other genes, 25 with PRS > 30%, and 8 due to family history. 5 are Asian-American, 18 Black/AA, 96 White/Caucasian, 1 biracial, 2 Latinas, and 8 other/unreported. There have been 14 recall visits; two resulted in breast cancer diagnoses: both were IDC, HR+/HER2-, and in BRCA2 mutation carriers. One diagnosis was detected on MRI only, and one was detected on mammogram with a normal MRI result.

Conclusion: Our study has the potential to address an unmet clinical need for early and accurate detection of aggressive young-onset breast cancers in high-risk women.

P036 : Circulating osteoprotegerin levels and breast cancer risk among women with a BRCA1 mutation: A prospective study

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Background: Upregulation of the receptor activator of nuclear factor κB (RANK)-signaling has been implicated in the pathogenesis of BRCA1-associated breast cancer, and pharmacologic inhibition of this pathway has been shown to suppress brca1-mammary tumorigenesis. Osteoprotegerin (OPG) is the endogenous decoy receptor for RANK-ligand (RANKL) that inhibits RANK/RANKL-signaling. Lower circulating OPG levels have been reported among women with a BRCA1 pathogenic variant (mutation). Whether there is an association between OPG levels and breast cancer is unclear.

Methods: Eligible women from a longitudinal study with a confirmed BRCA1 mutation and blood sample available were included. Self-reported biennial questionnaires collected detailed information on risk factors and cancer incidence. Serum OPG was quantified using an enzyme-linked immunosorbent assay. The exposure was dichotomized into high (>79.2 pg/ml) vs. low (=79.2 pg/ml) OPG levels using the median value in the entire cohort, and continuously per 10-unit increases. Cox proportional hazards models was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of breast cancer by OPG levels.

Results: A total of 662 BRCA1 mutation carriers were included in this prospective analysis with a mean age of 40.3 years (SD 12.1). Over a mean follow-up of 5.6 years (range 0.0-11.9), 49 incident breast cancers were diagnosed. Women with high OPG levels had a lower risk of developing breast cancer (HR 0.57; 95% CI 0.32-1.04; P=0.07) compared to those with low OPG levels. For every 10-unit increase in circulating OPG concentration, there was a significant 9% decreased risk of breast cancer (HR 0.91; 95% CI 0.84-1.00; P=0.04).

Conclusion: These findings suggest an inverse association between OPG levels and breast cancer risk among women with a BRCA1 mutation. Pending validation, circulating OPG levels may improve upon existing risk prediction and enhance our ability to identify women at the highest threshold of cancer risk.

MUTATIONS, VARIANTS, DATABASES

P037 : Reduced risk BRCA1 and BRCA2 variants: insight into classification of concordant variants between two commercial laboratories

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Introduction: The identification and reporting of reduced risk BRCA1 and BRCA2 (RR-BRCA) variants is complex and poses challenges for patient counseling. We sought to compile and compare data for RR-BRCA variants reported by two clinical diagnostic laboratories.

Methods: A list of RR-BRCA variants provided by two laboratories were compared for concordant interpretations. Rationale and data supporting a reduced-risk interpretation were compiled, including unpublished functional and clinical data (where available), and publicly available information including population-, predictive-, and functional data.

Results: Laboratories had different but complementary approaches in identifying RR-BRCA variants. Considerations included 1) the identification of biallelic Fanconi Anemia-affected patients; 2) variant type; 3) incomplete aberrant splicing; 4) identification of NMD-escaping, in-frame splice events; 5) laboratory-validated cancer history weighting models; 6) published reduced risk data; and 7) extrapolation of a reduced-risk interpretation onto close match variants that are expected to have the same effect. Between the two laboratories, 13 variants were consistently identified as potential RR-BRCA variants: for BRCA1, variants included c.5096G>A (p.R1699Q) and variants impacting the canonical c.671 splice acceptor site. For BRCA2, variants included three frameshift (c.658_658delGT, c.9672dupA, c.9699_9702delTATG); two spliceogenic (c.8488-1G>A and c.8488-1G>T); and two missense [c.7878G>C (p.W2626C), c.9302T>G (p.L3101R) variants.

Conclusions: Despite differences in interpretation strategies across two laboratories, consistent results were obtained for 13 RR-BRCA variants providing evidence for a less severe phenotype. As such, these variants may require less stringent management strategies compared to traditional pathogenic BRCA variants depending on individual and family history. Further work to define risk thresholds and categories for reporting RR-BRCA variants will be of great clinical value to personalize cancer risks in conjunction with other clinical and genetic risk factors, including polygenic risk scores. Opportunities to harmonize variant interpretation and standardized reporting will be of great benefit for patients and care teams.

P038 : Integration of functional data to classify BRCA2 missense variants: an ENIGMA project

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The success of precision cancer medicine is predicated on the accurate discrimination between benign and pathogenic germline alleles in susceptibility genes. Variants of uncertain clinical significance (VUS) pose a significant challenge in cancer risk assessment. Functional data derived from validated functional assays have become an important resource to assess the pathogenicity of VUS. We developed a cloud-based environment to integrate and analyze all published functional data for BRCA2 missense VUS according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) classification framework.

We selected 28 published articles describing data for 2,183 missense variants (1,011 reported in BRCAExchange) from 131 individual instances of functional assays (tracks) to assess their functional impact. Functional results were harmonized using the thresholds and classifications described by the original authors and converted to ordinal variables: [0 = no functional impact], [1 = intermediate impact], and [2 = functional impact]. We used a panel of 416 known reference variants (384 benign or likely benign and 32 pathogenic or likely pathogenic) to determine the sensitivity, specificity, and ACMG/AMP odds of pathogenicity of every track. Variants were assigned ACMG/AMP criteria based on the level of evidence.

In this study, we were able to derive unambiguous evidence criteria from functional data for 2,040 BRCA2 missense variants, while 143 variants had discordant results and could not be assigned a functional code. This work illustrates the power of functional data for resolving the majority of BRCA2 VUS.

P039 : The benefit of Probe Capture Enrichment Next Generation Sequencing (NGS) for HBOC testing - CNV analysis

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Introduction: NGS is excellent to detect single nucleotide variants (SNVs). However, detection of copy number variants (CNVs) from NGS data is challenging, for example due to PCR-bias in amplicon sequencing. In Belgium, Hereditary Breast and Ovarian Cancer syndrome (HBOC) testing requires sequencing of 13 genes for SNVs and detection of CNVs (minimal BRCA1/2) using multiplex ligation-dependent probe amplifications (MLPA). Therefore, using NGS data as a first CNV screening step would be of interest to increase the number of genes for CNV detection (followed by MLPA confirmation). Especially NGS using hybridization-capture is more suitable for CNV analysis since it offers high depth and uniformity of coverage.

Methodology: The CMG of Antwerp moved from PCR-based to hybridization-based target enrichment for NGS using a TWIST custom panel (Twist Bioscience) designed for HBOC testing, and sequencing on an Illumina MiSeq. Since the Twist custom panel NGS data allow for CNV analysis, it is of interest to study the number of additional CNVs that are found with this method.

Results: Since January 2022, ±500 samples were run using this new method. In 10 patients (1.5-2%) a CNV was found in a gene other than BRCA1/2. These include five (likely) pathogenic CNVs and two variants of unknown significance (VUS, detected in respectively 3 and 2 unrelated patients). To study the effect of these VUS, segregation analysis and RNA sequencing is currently being performed. Results of these analyses, updated numbers of detected CNVs and accompanying phenotypes will be presented at the conference.

Conclusion: We experienced a benefit of changing to a probe-based enrichment technique for HBOC NGS testing. Since this technique is more suitable for CNV analysis, we found an additional 1.5-2% of CNVs. However, interpretation of certain CNVs remains challenging and requires more data (RNA, segregation, additional families, …) to achieve a different classification than VUS.

P040 (Rapid Fire Presentation S1-RF1): BRCA1 frameshift variants leading to extended incorrect protein termini

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Carriers of BRCA1 germline pathogenic variants are at significantly higher risk of developing breast and ovarian cancer than the general population. The accurate identification of at-risk individuals is crucial for risk stratification and the targeted implementation of risk reducing and therapeutic interventions. Despite significant progress in classification efforts, a significant number of reported BRCA1 variants are variants of uncertain clinical significance (VUS). Variants leading to premature protein termination and loss of essential functional domains are typically classified as pathogenic. However, the impact of frameshift variants that result in an extended incorrect terminus (EIT) is unclear.

We combined functional assessment, structural modeling, clinical and family data to systematically examine 17 naturally-occurring EIT variants previously reported. Consistent with previous reports, our data show that the loss of more than seven wild-type amino acid residues at the C-terminal portion of BRCA1 results in a striking reduction of the protein activity regardless of the EIT produced. Moreover, steady-state protein levels are markedly reduced for most EITs, suggesting that their loss of activity is due to protein instability. Only one variant, c.5578dup (p.His1860ProfsTer20), displayed transcriptional activation (TA) activity in a validated assay and expression levels similar to the wild-type protein. We also show that p.His1860ProfsTer20 interacts with CtIP at levels comparable to the wild-type protein, suggesting that it may constitute a likely benign/benign or a reduced penetrance variant. These results indicate that most, but not all, BRCA1 variants leading to incorrect extended termini are likely to be pathogenic and highlight the need for functional assays of individual variants.

P041 (Rapid Fire Presentation S1-RF2): A comprehensive characterization of missense variants of uncertain significance (VUS) in RAD51C

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Homologous recombination (HR) is an essential pathway to repair DNA double-strand breaks in a faithful manner. Defects in HR can lead to genomic instability and cancer. We have shown that RAD51C is at the heart of two HR-related RAD51 paralogs complexes, forming RAD51C-XRCC3 and RAD51B-RAD51C-RAD51D-XRCC2 complexes. Inherited variants that result in the truncation of the RAD51C and RAD51D proteins, but not variants in the other paralogs, have been linked to predisposition to breast and ovarian cancers.

The relevance of missense variants of uncertain significance (VUS) in RAD51C to cancer is not known in part because their influence on RAD51C function is not established. Using a homology-directed repair (HDR) assay in reconstituted CL-V4B RAD51C-/- cells, we identified 30 non-functional (deleterious) and 144 functional/partly functional (neutral/intermediate) variants. The deleterious variants conferred sensitivity to cisplatin and olaparib and disrupted RAD51C-XRCC3 and RAD51B-RAD51C-RAD51D-XRCC2 complex formation. These findings were confirmed for a subset of variants by olaparib sensitivity and RAD51 foci formation assays of reconstituted human U2OS RAD51C-/- cells and were consistent with the predicted variant effects on ATP binding. In addition, we also implemented deep mutational scans of important domains of the RAD51 paralogs enriched in predicted deleterious missense variants. This approach allows the simultaneous assessment of all possible amino acid substitutions at a given position. Initial efforts were focused on the ATPase region of RAD51C. Briefly, the mutagenesis libraries were cloned into an inducible, recombinase-site containing vector. Landing pad cell lines were generated to allow the systematic integration of the libraries and to ensure the recombination of one variant per cell. Endogenous RAD51C expression was silenced using a 3'-UTR targeting siRNA and cells were challenged with PARP inhibitors. Globally, these approaches, when combined with other data, will contribute to the classification of missense variants in RAD51C which will help to orient clinical decisions.

P042 : Substantially different penetrance of different pathogenic variants in BRCA1 exon 20 (18): not all pathogenic variants are equal

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Introduction: Studies suggest pathogenic missense variants confer lower risks than truncating variants. Identification of missense variant exceptions is critical in providing accurate risk assessment/management recommendations.

Methods: We initially investigated a Manchester family with the BRCA1 c.5243G>A p.G1748D missense variant. 3/7 heterozygous females developed breast cancer <30 years (24,27,28) despite being separated by 8 meioses. Using combined Ambry/Manchester data, we assessed penetrance for breast/ovarian cancer in women with BRCA1 c.5243G>A (n=21) and compared this with other likely pathogenic/pathogenic (LP/P) exon 20 variants including missense (n=103), truncating (excluding the common founder, c.5266dupC), (n=91) and the in-frame exon20 deletion, BRCA1 c.5194_5277del p.His1732_Lys1759del, (n=74). Individuals were censored at: first BRCA1 related diagnosis; death; risk-reducing mastectomy or date of last follow-up (Manchester); or testing date if unaffected (Ambry). Kaplan-Meier incidence curves were generated.

Results: BRCA1 c.5243G>A had similar penetrance to truncating variants [50y:74%-(95%CI=46-95%) versus 62.7%-(95%CI=51-75%), p=NS]. Penetrance was significantly higher than for other missense LP/P variants in exon 20 [50y: 27.6% (95%CI=19-39%), p<0.001] or the exon 20 deletion [50y:46%-(95%CI=33-63%), p=0.02]. All inter-group p-values were significant, except BRCA1 c.5243G>A versus truncating. Notably, the exon 20 deletion had significantly lower penetrance than truncating variants, and higher penetrance than non-codon 1748 missense LP/P variants (p<0.001). While penetrance estimates are not adjusted for ascertainment bias, resulting in potential over-estimation, inter-group comparisons are still valid due to identical ascertainment.

Conclusion: These data suggest that BRCA1 c.5194_5277del and at least some of the exon 20 LP/P missense variants retain partial BRCA1 function and that BRCA1 c.5243G>A is at least a complete loss-of-function variant and may even act as a dominant negative. Further data is needed on all in-frame exon deletions and missense variants so that women can receive more accurate risk estimates for these attenuated phenotypes.

P043 : Prevalence of Hereditary Breast and Ovarian Cancer syndrome in a multi-ethnic Asian population

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Background: Hereditary Breast and Ovarian Cancer (HBOC) syndrome is associated with predisposition to malignancies, primarily breast and ovarian cancers, due to pathogenic germline variants in BRCA1, BRCA2 and PALB2. The reported population prevalence of HBOC syndrome is 1:300-1:500, however, these are estimates from predominantly European populations, whereas the prevalence among non-European populations is less defined. Here, we aim to evaluate the population prevalence of HBOC in Singapore, a Southeast Asian city-state with residents from multi-ethnic Asian populations of East Asian, South Asian and Southeast Asian ancestries.

Methods: The analyzed dataset is derived from a cross-sectional Singaporean population of 9051 individuals, comprising 5502 Chinese, 1941 Indians and 1608 Malays. Whole-genome sequencing was performed on blood DNA and jointly processed on a standardized bioinformatic pipeline. Identified BRCA1, BRCA2, PALB2 variants were curated using the American College of Medical Genetics and Genomics guidelines and carrier frequencies for pathogenic variants were adjusted to each ancestry group size.

Results: We identified 61/9051 carriers of pathogenic germline variants in HBOC genes, translating to a prevalence of 1:148 in Singaporeans. Prevalence was higher among Malays (1:110, 14/1608) compared to 1:157 Chinese (35/5502) and 1:161 Indians (12/1941). Of 49 pathogenic variants detected, 55% (27/49)

occurred in BRCA2, 31% (15/49) BRCA1 and 14% (7/49) PALB2. Recurrent variants were more frequent among Malays compared to a broader variant spectrum among Chinese, whereas PALB2 variants were depleted among Indians. Notably, 0.2% (4/1608) of Malays harbour the BRCA1 c.2726dup variant, a known founder variant among Malay families with history of breast and ovarian cancers.

Conclusion: HBOC prevalence in Asians is higher than global estimates of 1:300-1:500, with variable genetic spectrum among ancestry groups. Clinical professionals serving multi-ethnic populations should be cognizant of ancestry-specific variation in their genetic risk assessment for HBOC and the potential impact of preventive care in the Asian population.

P044 : Mammography screening and risk of breast cancer among women with a hereditary predisposition to breast cancer unexplained by a pathogenic variant in BRCA1 or BRCA2

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Women with a familial predisposition to breast cancer (BC) are offered screening at earlier ages and at more frequent intervals than women from the general population. Assuming there is no lower threshold dose in which radiation exposure does not cause damage, exposure to ionizing radiation may increase their BC risk.

We evaluated the effect of screening mammography procedures in 1,552 familial BC cases unexplained by a pathogenic variant in BRCA1 or BRCA2, identified through French family cancer clinics, and 1,363 unrelated controls. Participants reported their history of screening mammography exposures in a detailed questionnaire. Germline rare pathogenic or predicted pathogenic variants in 113 DNA repair genes were investigated in 82.5% of the women and their association with BC was previously assessed in Girard et al. (Int J Cancer 2019; 144(8):1962).

We found that having been exposed to mammograms measured as never versus ever had no effect on BC risk. However, when considering the number of exposures and the age at first exposure, we found an increase BC risk of 4% (95%CI: 1%-6%) per additional exposure and a 50% increased risk (95%CI: -9%-153%) when first exposed before age 30 as compared to never exposed women. When stratifying women according to the altered gene they carry, we found that the effect of mammogram exposure on BC risk was doubled (OR=2.17, 95%CI:0.92-5.15) for women carrying a variant in a gene associated with an odds ratio (OR) point estimate <0.9, as compared to those carrying a variant in a gene with an OR >1.1 (OR=0.92, 95%CI:0.48-1.75) (pint=0.02).

Further studies are needed to verify our finding. Even though mammographic screening reduces significantly the risk of mortality from BC thanks to early diagnosis, identification of sub-populations that are more or less susceptible to ionizing radiation is clinically relevant.

P045 : Testing diverse populations enables frequency-based variant classification in breast/ovarian cancer genes.

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Background: Variant classification in cancer predisposition genes is challenging. Segregation analysis is limited due to partial penetrance, and variants may be relatively frequent. We examined the utility of variant frequencies in a genetically diverse population for variant classification.

Methods: During 2015-2021 we ascertained consecutively diagnosed non-Ashkenazi (a heterogeneous population) breast cancer (BC) patients in two Israeli medical centers. Panel testing was offered to patients and to un-affected non-Ashkenazi controls. Variant classification was based on ACMG criteria. Variant frequency was compared between affected and un-affected, incorporating family history.

Results: Genetic testing was performed in 743 affected and 810 unaffected women. Pathogenic (P)/Likely pathogenic (LP) variants were identified in 59 (8%) women with BC, including 26 (3.5%) in BRCA1/BRCA2 and 33 (4.4%) in other genes. 4/14 (28%) of BRCA2 variants were not previously reported in public databases.

Rare variants: In 28 BC genes, 9490 rare variants (<.01 gnomAD MAF) were observed. 541/695 (78%) exonic variants were already in ClinVar. Based on frequency (MAF>0.01) in unaffected, low-family history (FH) controls, 43 ClinVar exonic VUSs were downgraded to Likely Benign: 15 using the entire cohort and 28 by using sub-ethnicity frequency. Variants with conflicting interpretations of pathogenicity were downgraded in 9 cases, including CHEK2 c.1427C>T (p.Thr476Met), previously classified as LP/VUS. 68/8949 non-coding variants were located in regulatory regions and significantly enriched in affected with substantial family history, suggesting possible pathogenicity.

Conclusions: Genetic analysis in diverse populations enriches the P/LP variant repertoire and contributes to variant classification. This may be particularly relevant for non-coding variants, whose interpretation by standard tools is limited.

P046 : Induced pluripotent stem cell (iPSC) modeling of breast and ovarian cancer development in women carrying germline BRCA1 mutations

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Rare mutations in the highly penetrant BRCA1 & BRCA2 genes predispose women to breast and ovarian cancer and more than 90% of families in which these cancers occur in multiple individuals from families. iPSC-derived three-dimensional (3D) 'organoid' models have emerged as a powerful tool to recapitulate the physiologically relevant process of disease progression in vitro. This system leverages the self-renewal and multi-lineage differentiation capability of stem cells and their intrinsic self-organization and regenerative ability to form 3D tissue architecture. For breast cancer (BC), subjects with BRCA1 mutations usually develop triple negative subtype of BC (TNBC), which is the most lethal subtype, derived from basal mammary epithelial cells. For ovarian cancer BRCA1/2 carriers usually develop High Grade Serous Cancer (HGSC), which originates in the neighboring fallopian tube epithelia (FTE).

We have derived breast and fallopian tube organoid models from iPSCs of BRCA1mut carriers and BRCA wild type subjects (BRCAwt). BRCA mammary epithelial (ME) organoids express epithelial cell markers and mammaglobin, indicating breast epithelial specificity. BRCA1mut show characteristics of pre-neoplastic disease even though they are derived from heterozygous BRCA1mut carriers; histologically, they resemble ductal in situ carcinoma (DCIS) of the breast. BRCA1mut. Compared to BRCAwt subjects, BRCA1mut FTE organoids exhibit severe cellular abnormalities consistent with neoplastic transformation, and show structural abnormalities, including cellular crowding, loss of polarity, severe atypia, accumulation of p53 and increased proliferation, characteristics BRCA1 mutant early stage BC and HGSC.

Taken together, these novel human-derived ME and FTE organoid models are more faithful physiological representations of BC and HGSC precursor and, using single cell transcriptomics, have enabled us to identify candidate clinical biomarkers associated with early stage BC and HGSC development. These data provide a basis for personalized early detection, prevention and therapeutic analysis of women carrying BRCA1mut and are now being applied to BRAC2 and other high-risk mutations.

P047 : Characterization of epithelial ovarian cancer based on multi-gene tumour testing and homologous RecomBinatiOn Deficiency (HRD) testing (COMBO): A preliminary analysis

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Introduction: We compared the results of multi-gene next generation sequencing (NGS) in paired tumour and germline samples to determine the correlation of pathogenic variants (PV) in epithelial ovarian cancer (EOC).

Methods: Newly diagnosed EOC patients were prospectively recruited at Princess Margaret Cancer Center between December 2021 and October 2022. Tumour tissue and germline DNA testing were performed. A 21-gene NGS panel (BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, RAD51C, RAD51D, BRIP1, ATM, BARD1, CDH1, CHEK2, HOXB13, PALB2, POLD1, POLE, PTEN, STK11, TP53) was used for both tumour and germline samples. Results of tumour and germline NGS testing were compared.

Results: To date, analyses have been completed for 54 individuals. In tumour, a total of 111 reportable variants were identified in 52 samples with a mean of 2 variants/tumour (range: 0-6). 98% of samples had a TP53 variant. Excluding TP53, there were 59 reportable variants in 35 samples with a mean of 1 variant/tumour (range: 0-5). In germline analysis, 30 variants were detected in 24 individuals, 8 of which were pathogenic [BRCA1 (4), BRCA2 (2), ATM (1) and RAD51C (1)]. Overall, 8/22 (36%) PV and 19/37 (51%) VUS identified in tumour were of germline origin. The variant allele fraction (VAF) in tumour ranged from 39-91% for PV and 6-99% for VUS. All germline variants were independently identified in tumour samples.

Conclusion: Multi-gene NGS tumour testing was capable of identifying all clinically relevant germline variants. Although paired multi-gene tumour-germline testing is required to determine variant origin, over 30% of individuals in this study could have avoided germline testing following negative tumour results. These results suggest that streamlining genetic testing for EOC patients via primary multi-gene tumour testing is possible with further investigation.

P048 : Identification of BRCA1 biallelic pathogenic variants in a Fanconi anemia patient and the clinical implications of variant location

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Introduction: Fanconi anemia subtype S (FA-S) is an extremely rare, autosomal recessive disorder caused by biallelic pathogenic mutations in BRCA1 and is characterized by physical abnormalities, developmental delay, and increased chromosomal breakage. The rarity of FA-S is likely due to embryonic lethality and cases resulting in live birth may be the result of some level of retained functional BRCA1 protein.

Clinical Description: A 2-year-old female was referred for genetic consultation due to the clinical presentation of microcephaly, coloboma, duodenal web, colpocephaly, multiple café-au-lait spots, poor growth, and developmental delay. A molecular diagnosis of FA was confirmed by abnormal chromosome breakage testing. Genetic testing by exome and cancer panel identified two BRCA1 pathogenic mutations: c.191G>A (p.C64Y) and c.3991C>T (p.Q1331*). Pathogenic alterations in other FA-associated genes were not identified.

Discussion: BRCA1 c.191G>A is a missense alteration at a cysteine residue critical for protein folding and function. BRCA1 c.3991C>T is a nonsense alteration in exon 11 and is expected to result in nonsense-mediated decay and loss-of-function. Multiple literature-reported FA-S patients also have loss-of-function variants in exon 11. This exon undergoes natural alternative splicing resulting in in-frame transcripts with partial or complete loss of this exon. The proteins resulting from these alternative transcripts may retain partial function. Because these alternative events splice-out the loss-of-function alterations, and may be partially functional, the result may be a hypomorphic effect explaining the enrichment of exon 11 loss-of-function variants in this patient and in other literature FA-S patients.

Conclusions: Two pathogenic BRCA1 alterations, including a loss-of-function variant in exon 11 were identified in a 2-year-old proband with FA-S. The enrichment of pathogenic variants in FA-S patients in alternatively spliced exons, such as exon 11, may be evidence that loss-of-function alterations in these exons are hypomorphic and may have atypical risks relative to traditional pathogenic alterations.

P049 : Analysis of tumour homologous recombination by RAD51 for BRCA1, BRCA2 and PALB2 variant classification

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Background: Accumulation of RAD51 at DNA double-strand breaks is a functional biomarker for DNA homologous recombination repair (HR). The presence of RAD51 is an indicator of HR proficiency (HRP) whereas its absence suggests HR deficiency (HRD). We aim to assess if tumour RAD51 can be a predictor of pathogenicity or benignity for BRCA1, BRCA2 (BRCA1/2) or PALB2 variants, and used as phenotype evidence in germline variant classification.

Methods: Immunofluorescence was used to quantify RAD51, yH2AX and BRCA1 foci in formalin-fixed paraffin-embedded tumours of primary untreated breast and ovary tumours, diagnosed in germline carriers of pathogenic, benign or variants of unknown significance (VUS) in BRCA1/2 or PALB2 genes. For VUS, further analyses were conducted to determine genomic instability score (GIS) using the Myriad myChoice CDx assay as well as HR genes mutation profile and gene-specific LOH (gsLOH). HRD was pre-defined as RAD51 score =10% and GIS =42.

Results: To date, we have assessed 85 tumours carrying 55 germline BRCA1/2 and PALB2 pathogenic variants showing a 93% prevalence of HRD by RAD51. In contrast, the first results from nine tumours carrying six benign variants indicated an 11% HRD prevalence. The HRD occurrence in 28 VUS tumours was 43%. However, low BRCA1 was detected in three tumours with HRD carrying VUS in BRCA2 and PALB2, suggesting that their HRD might be the result of BRCA1 hypermethylation. The GIS from 21 VUS tumours showed a 71% concordance with RAD51. The gsLOH jointly with RAD51, GIS, and HR genes mutation findings, added evidence in favour of pathogenicity for c.2123C>A VUS in BRCA1 and non-pathogenicity for BRCA1 c.3247A>G as well as BRCA2 c.7522G>A, c.9410C>T and c.3398C>T.

Conclusions: An HRP status indicated by RAD51 in VUS tumours with gsLOH, is highly suggestive of non-pathogenicity and this can assist in variant classification.

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P050 : Reinterpretation and subsequent reclassification of germline BRCA1/BRCA2 variants of uncertain significance identified in a single genetic laboratory over a 20-year period

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Background: Identification of variants of uncertain significance (VUS) in BRCA1 and BRCA2 genes is common in testing for genetic susceptibility to hereditary breast and ovarian cancer. This type of result represents a particular challenge for patient management in the era of precision genomic medicine.

VUS reclassification is expected to occur over time. This study aimed to describe data on BRCA1/BRCA2 VUS reclassification from a single clinical laboratory over a 20-year period.

Methods: We reviewed 360 distinct BRCA1/BRCA2 VUS identified in the Laboratory of Molecular Oncology, University Hospitals of Geneva (Switzerland) between 1997 to 2019. Variant assessment included review of distinct lines of evidence (functional, genetic, population, computational, etc.) according to the current American College of Medical Genetics (ACMG) recommendations by two investigators. When a reclassification was confirmed, physicians in charge of index cases were informed by letter. In case of management modification, a follow-up consultation was suggested.

Results: In total, 73/139 (52.5%) BRCA1 variants and 108/221 (48.9%) BRCA2 variants originally classified as VUS were reclassified. Overall, 82.3% (n=149) of reclassifications were downgrades, i.e. VUS to likely benign/benign variants, and 17.7% (n=32) were upgrades, i.e. VUS to likely pathogenic/pathogenic variants. Seventy-five percent of the reclassified VUS were missense variants and 25% were intronic variants. Variant reclassification process resulted in updated reports for more than 200 index cases.

Conclusions: More than half of all BRCA1/BRCA2 VUS were reclassified. The majority of VUS reclassifications, i.e. >80% in this study, are downgrades. This study highlights the importance of periodic reevaluation of BRCA1/BRCA2 VUS to appropriately manage index cases and their relatives. VUS review is a complex process and represents an underestimated additional workload for the laboratory.

P051 : Biallelic BRCA2 mutations and negative chromosome breakage analysis in a patient with adult onset breast and colon cancers

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Biallelic mutations in BRCA2 are associated with Fanconi anemia (FA), a rare disorder characterized by a wide range of clinical features including progressive bone marrow failure, congenital anomalies, cancer predisposition and chemosensitivity. The diagnosis of FA is typically established through chromosome breakage analysis and/or genetic testing for biallelic FA mutations in affected individuals.

We present a case of a 37 year old female with newly diagnosed triple negative breast cancer, a history of stage III colon cancer at age 33, and biallelic BRCA2 mutations. Results of an 84-gene panel were significant for the well-established pathogenic BRCA2 c.2808_2811del (p.Ala938Profs*21) mutation and likely pathogenic BRCA2 c.7964A>G (p.Gln2655Arg) mutation. Her father is deceased at age 50 of lung cancer and her mother tested positive for the BRCA2 c.2808_2811del mutation only, suggesting paternal inheritance of the c.7964A>G mutation. Chromosome breakage analysis was subsequently performed and results were negative. The patient is a nulliparous only child with no known family history of breast, ovarian, prostate or pancreatic cancer. She presented with severe fatigue, pancytopenia, polyneuropathy, neutropenia and diffuse edema with chemotherapy resulting in early termination of treatment for both colon and breast cancers. Her chemosensitivity was historically attributed to her significant history of cocaine and heroin abuse and it is, therefore, unclear whether the BRCA2 mutations contributed. She has no other features of FA.

Hypomorphic mutations are known to correlate with milder clinical phenotype in FA and other recessive disorders. This case suggests the possibility of reduced penetrance of the BRCA2 c.7964A>G variant in both FA and hereditary breast and ovarian cancer syndrome and that the presence of biallelic mutations alone may not be sufficient to clearly establish a diagnosis of FA in patients with atypical manifestations.

P052 : Copy number variants are ovarian cancer risk alleles.

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Known risk alleles for epithelial ovarian cancer (EOC) account for ~40% of the narrow-sense heritability for EOC. We recently identified copy number variants (CNVs) as an important class of genetic variant that contribute to the genetic architecture of EOC. We used single nucleotide polymorphism array data from 13,071 EOC cases and 17,306 controls of European ancestry to identify CNVs associated with EOC and identified significant risk associations with CNVs at known EOC susceptibility gene loci: BRCA1 (P = 1.60x10-21), RAD51C (P = 5.5x10-4) and BRCA2 (P = 7.0x10-4). Four suggestive associations (P<0.001) were identified for rare CNVs at novel risk loci across the genome.

We performed whole genome sequencing in 215 EOC cases and used publicaly available data for >500 EOC cases and >25,000 controls to confirm the frequency of deletions and duplications in known ovarian cancer genes (BRCA1, BRCA2, RAD51C, RAD51D) and replicate several novel risk associated structural variants initially detected using genotyping array data. Deletions were more frequently identified as risk alleles for EOC, but duplications, insertions and inversions that interrupt the coding frame were also identified. The breakpoints of structural variants in BRCA1 were frequently flanked by repetitive elements where single nucleotide polymorphisms created complete homology in regions >35bp, resulting in regions of homology where homology-mediated recombination may create crossing over events that lead to structural variants. Structural variants at both known and novel risk regions are risk alleles for EOC, are potentially pathogenic and contribute to the spectrum of disease-causing deleterious variants.

In ongoing studies in publicly available case control cohorts we continue to identify novel structural variants as risk alleles for EOC with validation using long read sequencing. More fully understanding the complex genetic architecture of architecture will improve our ability to identify those at risk for the disease and offer prevention strategies.

P053 : Germline pathogenic variant of prostate cancer in Singapore

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Genetic testing in prostate CA (PCa) has become more widespread with approval of PARP inhibitors. Carriers of germline BRCA1/2 pathogenic variant (PV) have increased risk of PCa with aggressive phenotypes. However, data in Asia remains limited. In Singapore, PCa is the 3rd most common cancer in males. We report our institution's experience with germline testing of PCa.

Data were prospectively collected from patients referred to Singapore National Cancer Centre, Cancer Genetics Service (CGS). Demographics, first degree relatives (FDR) cancer type, clinical-pathologic data (e.g Gleason score, stage at diagnosis, presence of ductal variant), and PV distribution were collected. Predictors for PV were analyzed using fisher's exact test. Between January 2014 to November 2022, 186 PCa patients were seen at CGS and 154 (83%) underwent germline testing. There were 123 (80.4%) Chinese, 12 (7.8%) Malays, 7 (4.6%) Indians and 11 (7.2%) of other ethnicities. One-hundred and thirty-nine (90.3%) had adenocarcinoma, with 11 (8%) ductal variant. Twenty-nine (18.8%) PCa patients had localized disease at diagnosis, and 97 (63%) Stage IV disease. Twenty-two (14.3%) PCa patients have germline PV, consisting of 10 (45%) BRCA2, 2 ATM, 2 TP53, 1 MSH2, 1 MSH6, 1 FANCA, 1 LZTR1, 1 NF1, 1 VHL, 1 PTPN11 and 1 RAD51D. FDR with cancer were identified in 92 (59.7%) PCa patients. PV were not associated with personal history of cancer, gleason score, ductal variant, age or stage at diagnosis. Ethnicity was observed to have an association for PV ($p = 0.011$). One or more FDR with cancer was not predictive for PV. However, FDR with breast cancer ($p < 0.05$) or ovarian cancer ($p = 0.039$) had increased risk for PV. Ethnicity, FDR with breast and/or ovarian cancer were associated with germline PV in PCa, and testing should be encouraged. Our study highlights the importance of a comprehensive history assessment.

NON-BRCA1/2 GENETIC FACTORS ASSOCIATED WITH CANCER RISK

P054 : Investigating the association of SDHA pathogenic variants with breast cancer risk

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Background: Pathogenic variants in genes encoding the 5 components of the Succinate Dehydrogenase (SDH) protein complex (SDHA, SDHB, SDHC, SDHD and SDHAF2) are known to confer risk to paragangliomas, pheochromocytomas, renal, gastric and pituitary tumours. However, there is preliminary evidence for the possible involvement of SDHx genes in breast cancer. Here, we describe the SDHA germline pathogenic/likely pathogenic variants identified in our breast cancer cohort. We also investigated a possible genotype-phenotype correlation in our breast cancer cohort.

Methods: We performed a review on patients that were tested for the multi-gene panels including SDHx genes under a CLIA/CAP certified lab through the Cancer Genetics Service, National Cancer Centre Singapore between 2014-2022. SDHA germline pathogenic variant carriers were identified and genetic testing results were correlated with patient demographics, cancer/tumour diagnoses, clinical pathological findings, as well as family history of malignancies.

Results: Of 1220 individuals that underwent genetic testing and had a personal history of breast cancer, a total of 8 individuals were seen to carry an SDHx mutation. Four individuals carried a pathogenic variant in the SDHA gene. All four patients developed an Invasive Ductal Carcinoma at an average age of 47.2. Of these four individuals, the c.1A>G pathogenic variant (p.Met1Val) occurred in two unrelated patients. We also observed the occurrence of variants c.1258C>T (p.Gln420*) and c.923C>T (p.Thr308Met) in the remaining patients. The observed SDHA pathogenic variants were not domain specific.

Conclusion: For the SDHA cohort, a genotype-phenotype correlation could not be established. However, our study supports the possible association between pathogenic variants in SDHA and breast cancer. Further segregation and functional analyses will be required to validate the association between pathogenic germline SDHA variants with breast cancer predisposition.

P055 : Yield and effectiveness of breast cancer surveillance in women with PTEN Hamartoma Tumour Syndrome

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Background: Women with PTEN Hamartoma Tumour Syndrome (PHTS, Cowden syndrome) have a 54-76% risk of developing breast cancer (BC) and are therefore offered BC surveillance. However, data supporting BC surveillance guidelines are scarce due to the rarity of PHTS. We aimed to assess the yield and effectiveness of BC surveillance in women with PHTS.

Methods: A retrospective cohort study based on medical record data including women with PHTS aged ≥18 who visited a PHTS expertise centre between 2001-2021 was conducted. BC surveillance consisted of annual magnetic resonance imaging (MRI) and mammography starting at age 25 and 30, respectively, as indicated by the national PHTS guideline.

Results: Sixty-five women visited our centre of whom 39 started BC surveillance and underwent 156 surveillance rounds during 135 follow-up years. The median age at first surveillance examination was 38 years (range: 24-70). Surveillance resulted in detection of BC in 7/39 (18%) women at a median age of 43 years (range: 31-55), and benign breast lesions in 11/39 (28%) women. The cancer detection rate was 45/1000 rounds. Five of 7 women with BC underwent surveillance one-year prior to BC detection, showing no malignancies. Overall sensitivity when excluding BCs detected during prophylactic mastectomy was 100%, whereas sensitivity of mammography and MRI alone was 50% and 100%, respectively. Overall specificity was 82%. Surveillance-detected BCs all had a T1 stage (6/6; 100%) and N0 stage (8/8; 100%), whereas BCs detected outside surveillance more often had a ≥T2 (6/10; 60%) and N+ (6/11; 55%) stage ($p<0.05$). The median age at diagnosis of BCs detected outside surveillance was 40 years (range: 24-59).

Conclusions: These findings indicate that BC surveillance in women with PHTS enables detection of early-stage BC (https://doi.org/10.1002/cncr.34326). The annual interval and starting age of 25 appear appropriate given our results and hence our findings support the current guideline.

P056 : Influence of genetic and non-genetic risk factors in a Brazilian cohort of patients with breast cancer with suspected Hereditary Breast and Ovarian Cancer Syndrome

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Background: There is a substantial variability in cancer risk in patients (pts) who have inherited BC risk genes (BCRG) which may be partially explained by the influence of non-genetic risk factors (NGRF). We aim to assess the prevalence of genetic and non-genetic risk factors (NGRF) in a Brazilian cohort of pts with BC with suspected hereditary breast and ovarian cancer syndrome (HBOC).

Methods: Patients with a diagnosis of BC and suspected HBOC according with NCCN guidelines underwent multigene panel testing (MGPT) included these related to BC:BRCA1, BRCA2, PALB2, BARD1, RAD51C, RAD51D, ATM, CHEK2, CDH1, TP53, STK11, PTEN. Patients were divided into two groups: those without (A) or with (B) pathogenic or likely pathogenic (P/LP) germline mutations in BCRG; Groups A and B were compared for the prevalence of the NGRF: body mass index (BMI), sedentary lifestyle, age at menarche, parity, age at first birth, breastfeeding, use of oral contraceptives, use of hormone replacement therapy (HRT), alcohol consumption and mammographic density.

Results: Between 2017 and 2020, 100 patients underwent germline MGPT testing in a Brazilian tertiary cancer center. Mean age was 39.9 years and the most common histology was invasive carcinoma not otherwise specified 81 (81%), with estrogen-receptor positive 68 (68%) and HER2 negative 86 (86%) disease. Family history of cancer was reported by 59 (59%) of patients. P/LP variants in BCRG were detected in the frequency: BRCA1 (45%), BRCA2 (25%), TP53 (15%), PALB2 (10%), STK11 (5%), BARD1 (5%). The difference in the proportions of NGRF between Groups A and B was not statistically significant. The proportion of patients with BMI ≥ 25 kg/m2, early menarche, nulliparity, age at first birth ≥ 25 years-old and no history of breastfeeding was numerically higher in Group A than in Group B.

Conclusion: This data emphasize the role of NGRF in modifying the risk of BC either in the presence or not of germline mutations in cancer susceptibility genes.

P057 : Prevalence of Lynch Syndrome in patients with breast cancer in the Brazilian population: result of a single-institution cohort

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Background: Lynch Syndrome (LS) is an inherited cancer syndrome well caused by mutations in mismatch repair genes - MMR (MLH1, MSH2, MSH6, PMS2) and large deletions including a 3' end of EPCAM, related to high risk for colorectal cancer and endometrial cancer as well as other malignancies. Data describing the relationship between breast cancer and LS are scarce and have not been previously reported in the Brazilian population. Our study aims to determine the prevalence of LS in patients with breast cancer and suspected hereditary breast and ovarian cancer syndrome (HBOC).

Methods: Patients with breast cancer and suspected HBOC referred for genetic counseling at a Brazilian tertiary cancer center between 2017 and 2020, who meet NCCN guideline criteria for genetic testing were included. A targeted next-generation sequencing (NGS)-based multigene panel testing (MGPT) for hereditary cancer was used to evaluate 138 genes, including ATM, BRCA1, BRCA2, PTEN, RAD51C, RAD51D, STK11, BRIPI1, BARD1, CDKN2A, CDH1, CHEK2, NBN, PALB2, TP53; and also MMR genes (MLH1, MSH2, MSH6, PMS2, EPCAM).

Result: A pathogenic variant in the MSH6 gene was detected in 1 of 100 (1%) patients who underwent MGPT; The patient diagnosed with LS had a triple negative breast carcinoma not otherwise specified diagnosed at age 43, had a family history consistent with HBOC (sister with triple negative breast cancer) and no personal or family history of colorectal and/or endometrial cancer. Immunohistochemistry for MMR proteins from tumor biopsy showed preserved expression for MSH6. The variant detected in MSH6 was c.1519dupA, a sequence change that creates a premature translational stop signal (p.Arg507Lysfs*9).

Conclusion: The prevalence of LS-related germline mutations was 1% in a cohort of Brazilian patients with breast cancer and suspected HBOC. Multigene panel testing can identify patients with LS who present with the HBOC phenotype and who would not be identified by clinical criteria of suspicion for LS or by screening tests for microsatellite instability and/or immunohistochemistry for the MMR proteins

P058 : Genetic risk assessment using multi-gene panel testing in male breast cancer: toward gender-specific precision prevention.

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Germline pathogenic variants (PVs) in BRCA1/2 are associated with high breast cancer (BC) risk in both sexes. Reliable data on actionable PVs in other cancer susceptibility genes are emerging, with implications in terms of BC prevention and treatment. Thus, multigene panel tests are being increasingly used for BC risk assessment, although gender-specific data are lacking.

This study aimed to provide the spectrum, prevalence and risk estimates associated with PV in non-BRCA genes for male BC (MBC), in order to improve BC precision prevention for male patients.

A population-based case-control study, including 725 BRCA1/2-negative MBCs and 1076 healthy male controls, all enrolled in the Italian multicenter study on MBC, was performed using a custom 50-gene panel in NGS. Statistical analyses were performed using chi-square test and logistic regression model.

PVs in genes other than BRCA1/2, mainly PALB2, ATM, BLM, FANCM and CHEK2, were identified in 37/725(5%) MBCs and in 20/1076(1.8%) controls. Overall, PVs were significantly more frequent in MBCs compared with controls and associated with a 3-fold increased MBC risk (5% vs 1.8%, OR: 3.3, 95%CI: 1.7-6.3; p=0.0006). PALB2 PVs were identified in 1% of MBCs and were associated with a 7-fold increased MBC risk (OR:6.8, 95%CI: 1.1-42.9; p=0.04). BLM and CHEK2 PVs were more frequent in cases than in controls (p=0.02 and p=0.03, respectively). PV carriers were more likely to have personal (p=0.01) and family (p=0.006) history of cancers not limited to BC.

Our results highlight the main role of PALB2 PVs in MBC susceptibility and provide risk estimates with possible translational relevance. This study supports the clinical utility of multigene panel testing approach to increase the detection of actionable PVs in MBC patients, particularly in those with family and personal history of multiple cancers. Overall, these results may improve gender-specific BC precision prevention in patients and their relatives.

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P059 (Rapid Fire Presentation S4-RF1): Exome sequencing identifies novel susceptibility genes and defines the contribution of coding variants to breast cancer risk

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Non-BRCA1/2 Genetic Factors Associated with Cancer Risk *(Continued)*

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Genetic susceptibility to breast cancer is conferred by a combination of common variants identified through genome-wide association studies and rarer coding variants with higher disease risks. The latter include protein-truncating variants (PTVs) and rare missense variants in ATM, BARD1, BRCA1, BRCA2, CHEK2, RAD51C, RAD51D, PALB2 and TP53. These variants explain ~20% of the familial relative risk (FRR) of breast cancer but the overall contribution of coding variation is unclear.

To evaluate the role of rare coding variants more comprehensively, we performed a meta-analysis across three whole-exome sequencing datasets in the context of PERSPECTIVE-I&I and BRIDGES projects: 2 datasets from the Breast Cancer Association Consortium with UK Biobank. These included 26,368 female cases and 217,673 female controls primarily of European ancestry. Burden tests were performed for PTVs and rare missense variants. To improve power, we incorporated family history of breast cancer. Associations between PTVs and breast cancer were identified for 6 genes at exome-wide significance ($P<2.5\times10^{-6}$): the five known susceptibility genes BRCA1, BRCA2, CHEK2, PALB2 and ATM; and MAP3K1. Associations were also observed for LZTR1, ATRIP and BARD1 with $P<1\times10^{-4}$. Predicted deleterious rare missense variants combined with PTVs were additionally associated at $P<2.5\times10^{-6}$ for CDKN2A, followed by SAMHD1 ($P<10^{-5}$).

All the novel genes have prior evidence of being tumour suppressor genes. MAP3K1 is a well-established breast cancer GWAS locus; however, the observed PTV association and the GWAS association were independent. We used an empirical Bayes approach to estimate the exome-wide contribution of PTVs to the FRR of breast cancer: under the best-fitting model, the contribution of PTVs beyond previously known genes explains ~1.1% of the FRR, with ~90 genes being associated. We demonstrate that large exome sequencing studies, can identify additional breast cancer susceptibility genes, but that most of the 'missing' heritability is likely to be found in the non-coding genome.

P060 : Biallelic pathogenic variants in CHEK2 predispose to multiple primary malignancies

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Background/objectives: The development of multiple primary malignancies (MPMs) is a hallmark of genetic tumor risk syndromes. Heterozygous pathogenic variants (PVs) in CHEK2, a gene activated upon double-strand DNA breaks, are associated with an increased risk to develop breast cancer (BC). Here, we aimed to elucidate the role of CHEK2-deficiency in the development of MPMs.

Methods: Individuals with biallelic germline PVs in CHEK2 were identified via whole-exome sequencing (WES) of individuals who developed MPMs (n=3/59), genotyping of individuals with early-onset cancer (n=3/787), routine diagnostic testing (n=22) and literature (n=11). WES on DNA extracted from 16 tumors (six tissue types) was performed. For each tumor, mutational signatures and cancer driver genes analyses were performed.

Results: We collected 39 individuals with biallelic germline PVs in CHEK2. The majority were women (n=34; 87%) and the most common cancer type was BC, followed by colorectal cancer (n=10). Overall, 46 breast (pre)malignancies were diagnosed in 31 individuals (79%), of which 12 individuals (38.7%) developed ≥2 breast (pre)malignancies. Twelve other (pre)malignant tumor types (34 malignancies in 17 individuals) were identified. Eleven individuals were diagnosed with at least one (pre)malignancy other than BC and four developed MPMs, but not BC. The median nonsynonymous tumor mutational burden was 1.87 mutations/Mb [range 0.29-16.73]. In 14 malignancies (87.5%), the main mutational signatures observed were SBS1 and/or SBS5, which are associated with aging. None of the tumors presented with SBS3, the signature associated with homologous recombination (HR)-deficiency. Compared to a control cohort of BRCA1- and BRCA2-deficient malignancies, tumors from individuals with biallelic PVs in CHEK2 harbored significantly less frequently somatic PVs in TP53.

Conclusions: Our data suggests that individuals with biallelic germline PVs in CHEK2 develop MPMs. HR-deficiency does not seem to be the underlying mechanism of carcinogenesis in CHEK2-deficient individuals, which suggests PARP-inhibitor therapy might not be beneficial for these individuals.

P061 : RINT1 pathogenic variant carriers in a single institution

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Background: Established genes associated with predisposition to breast cancer includes high penetrant genes, such as BRCA1 and BRCA2, and moderate-low penetrant genes, such as ATM and CHEK2. One candidate gene is RINT1. Some studies have proposed that heterozygous pathogenic variants in RINT1

gene may be associated with an increased risk of breast cancer and possibly Lynch syndrome–spectrum cancers. However, other studies did not support the increased risk of breast cancer. Therefore, the impact of RINT1 gene in cancer predisposition is still undetermined. Here, we report our experience with heterozygous RINT1 pathogenic variants carriers in a single institution.

Methods: We performed a review on patients with germline RINT1 variants who was seen at the Cancer Genetics Service, National Cancer Centre Singapore, between 2014-2022. Demographic, clinical and pathologic characteristics of patients, as well as their family history of cancers were collected and analysed.

Results: Five patients were found to carry a heterozygous RINT1 pathogenic variant, of which four patients carried the same variant (RINT1 c.1966C>T (p.Arg656*)) and one patient carried a different variant (RINT1 c.310C>T (p.Arg104*)). Both were protein-truncating variants. All patients were female and of Chinese (4/5) and Malay (1/5) ethnicities. All patients had invasive ductal breast carcinoma diagnosed, with most patients (4/5) being ER/PR positive and HER2 negative. The median age of diagnosis was 48 (range 39 – 68). All patients had a family history of cancers and three patients having a first-degree relative with breast cancer.

Conclusion: Our finding is consistent with previous literature that suggest an association of heterozygous RINT1 pathogenic variants with breast cancer. Even though further molecular evaluation and segregation studies would be helpful to confirm the association with breast cancer and the exact cancer risk, our study provided additional information to support the inclusion of RINT1 as part of the breast cancer predisposition gene.

P062 : Beyond the colon: Do biallelic variants in NTHL1 predispose to breast cancer?

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Background: Biallelic pathogenic variants (BPVs) in NTHL1 have been identified as a cause of hereditary colorectal polyposis and/or cancer. Extracolonic tumors have been observed in the approximately 20 families described in published literature; however, the full spectrum of the NTHL1-tumor syndrome (NTS) has yet to be fully characterized. We present 33 unrelated cases with BPVs in NTHL1 ascertained from a multigene panel testing (MGPT) cohort.

Methods: A retrospective data review of cases was performed with NTHL1 BPVs detected by MGPT (32-81 genes) between April 2017-September 2022. Proband histories were obtained via test requisition forms and clinical documents submitted to our laboratory. Biallelic PVs include individuals with two PVs in NTHL1.

Results: Thirty-three individuals were found to have BPVs in NTHL1, 21 with reported polyps, 14 with breast cancer (BC), 13 with colorectal cancer, 10 with skin cancer (4 melanoma), 5 with brain tumors, and 3 with no cancer/polyps. Other tumors occurred in less than 10% of the cohort (n=3). BC was the most common cancer, reportedly diagnosed in 14/22 females (63.6%). Of these, 4 females had more than one BC diagnosis. The average age of BC diagnosis was 47.15 years.

Conclusions: Individuals with BPVs in NTHL1 in our cohort exhibit a multi-tumor predisposition. The high rate of breast cancer may be explained by the ascertainment bias inherent in MGPT, but when compared to the frequency of breast cancer in our MGPT cohort (45%), this tumor type is enriched in individuals with BPVs in NTHL1. Compared to the general population, individuals with BPV appear more likely to have multiple primary BCs (22% vs 1-11%) and are diagnosed at younger ages (47y vs 63y). This case series suggests that targeted study may be worthwhile to establish early-onset and/or multiple primary BC as a significant feature of NTS.

P063 : Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) has approximately 20-30% penetrance in individuals carrying loss-of-function mutations in SMARCA4.

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Introduction: Loss- of -function (LoF) alterations in SMARCA4 are associated with a rare and highly aggressive type of ovarian cancer, known as small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), typically diagnosed between childhood and early 40s. SMARCA4 was first reported in association with this phenotype in 2013. With fewer than 1000 patients described in the literature since, penetrance is not well-defined. Here, we aimed to estimate the crude penetrance of SCCOHT.

Methods: From a cohort of individuals undergoing multigene panel testing, we retrospectively curated clinical data reported for carriers of LoF SMARCA4 alterations and their relatives. We estimated the penetrance of SCCOHT in this cohort by dividing the number of affected female carriers by the number of total female carriers in the cohort

Results: We identified 58 female probands with a LoF alteration in SMARCA4. 12 of these individuals were reported to have a clinical history of SCCOHT, diagnosed between the ages of 9 and 39 years of age. An additional 4 patients were diagnosed with ovarian cancers of unspecified subtype between the ages of 15 and 46 years. With a total of 12-16 possible affected individuals, the crude penetrance of SCCOHT in this cohort is approximately 20.7-27.6%. As these individuals are undergoing multigene panel testing for cancer, ascertainment bias may impact this estimate. Of the 42 unaffected female probands, 5 (~11.9%) reported a history of SCCOHT or early-onset ovarian cancer (<40) in a first-degree relative. 9 of the unaffected individuals were under the age of 40, thus are within the age range to still be potentially impacted by this disease.

Conclusions: Based on our data, crude penetrance of SMARCA4-associated SCCOHT is 20-30%. This information is critical for the management of these patients and their family members when considering the potential for risk-reducing options and planning.

P064 : Meta-Analyses on 270,662 cases and controls and CRISPR/Cas9-based assay to test the effect of FANCM truncating variants on breast cancer risk

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Case-control association studies have indicated that germline protein truncating variants (PTVs) in the FANCM gene are associated with increased risk for ER-negative and triple negative breast cancer (TNBC). Moreover, our results from clinical, genetic and functional studies suggested that N-terminus FANCM PTVs (such as p.Arg658*), with respect to C-terminus PTVs (such as p.Gln1701* and p.Gly1906fs*12), may be associated with a higher breast cancer risk and with more severe cellular phenotypes.

In this study, we conducted a large meta-analysis totaling 146,175 breast cancer cases and 124,487 controls. The most frequent PTVs were tested individually, while the rare PTVs were analyzed using a burden approach grouping the variants all together or by their gene position. Stratified analyses for breast cancer subtypes were also performed. We also conducted a CRISPR/Cas9-based assay in the haploid HAP1 cell line. In this assay, all FANCM domains were tested for their resistance to gene knock-out (KO) by DNA editing.

In the single PTV meta-analysis, the N-terminus p.Arg658* was found associated with the risk of ER-negative (OR=2.03, 95% CI 1.02-4.04, P=0.043) and TNBC (OR=3.29; 95% CI 1.47-7.35, P=0.004), while less convincing associations were observed for the p.Gly1906Alafs*12 with these subtypes, and no association was found for the p.Gln1701*. In the meta-analysis of the burden tests, the PTVs located in the gene N-terminus (upstream aa position 1674) resulted associated with the ER-negative (OR=1.99, 95% CI 1.38-2.88, P=0.0002) and TNBC (OR=2.46, 95% CI 1.51-4.00, P=0.0003). No significant associations were detected for the PTVs located in the gene C-terminus (downstream aa position 1675). The functional assay results indicated that DNA editing causing gene KO in the FANCM C-terminus domains were tolerated while these events were not tolerated in the N-terminus domains.

Our genetic and functional results confirm that N-terminus FANCM PTVs are moderate-risk factors for ER-negative and TNBC subtypes.

P065 : Integrated germline and tumour sequencing analysis identifies LLGL2 as a potential high-grade serous ovarian cancer predisposition gene

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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 previously reported enrichment for germline loss-of-function (LoF) variants in 43 candidate genes identified in 510 BRCA1/2-negative HGSOC patients[1] and demonstrated biallelic somatic inactivation of one candidate gene (LLGL2) in multiple tumour samples from germline LoF variant carriers using exome and bisulphite sequencing[2]. However, since the number of LLGL2 variant carriers was small, additional orthogonal evidence was sought to validate these findings.

Methods: Paired germline and tumour DNA whole genome sequencing (WGS) along with LLGL2 immunohistochemistry (IHC) on sectioned tumour blocks was performed on archived material from four HGSOC patients who were heterozygous carriers of germline LoF or predicted pathogenic missense variants in LLGL2; all had prior evidence of tumour biallelic inactivation[2]. Case-control analyses using local control data from the Medical Genomics Reference Bank (MGRB)[3] and Lifepool[4] were also performed.

Results: WGS and IHC showed molecular genetic and staining features consistent with partial or complete loss of expression of LLGL2 protein in 3/4 tumours, compared to tumours with an intact LLGL2 allele. Case-control data showed a higher frequency of rare LLGL2 LoF variants in the HGSOC cases versus local controls, consistent with the magnitudes observed versus GnomAD.

Conclusion: Our data is consistent with LLGL2 being a novel HGSOC predisposition gene, albeit one difficult to validate due to the rarity of inactivating germline variants in HGSOC patients. Further work is underway using in vitro cell culture models to evaluate the mutational signature and functional consequences of inactivating variants within this gene.

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P066 : Using the homologous recombination deficiency mutational signature to discover Non-BRCA1/2 breast cancer susceptibility genes

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Hereditary Breast Cancer (HBC) accounts for 5-15% of all Breast Cancer (BC) cases. Approximately 50% of HBC can be explained by germline variants in well-established Breast Cancer Susceptibility Genes (BCSG) like BRCA1/2, PALB2, BARD1, among others. However, the remaining HBC cases are still unexplained. We hypothesize that the missing heritability is partly explained by germline variants in underexplored genes not yet established as BCSG.

Methods: We devised an innovative computational framework that identifies genes enriched with somatic mutations in tumors having the COSMIC Mutational Signature 3 (SBS3), then analyzes the germline of these patients to identify non-BRCA1/2 candidate BCSG. We analyzed the exomes of the BC cohort of The Cancer Genome Atlas (TCGA) and utilized the algorithm SigMA to analyze SBS3 due to its unique machine-learning boosted capacity to accurately detect SBS3 specifically in exomes.

Non-BRCA1/2 Genetic Factors Associated with Cancer Risk *(Continued)*

Results: As proof of principle, we confirmed genes significantly associated with SBS3 ($p < 0.05$) to include BRCA1, BRCA2, as well as TP53 (already expected for BRCA1/2). Interestingly, TP53 was the top ranked gene associated with SBS3, markedly above BRCA1/2. We performed a breakdown of clinical subtypes and observed that only TP53 and BRCA1 reached significance in the basal/Triple Negative Breast Cancer (TNBC) subtype, respectively. No other gene reached significance in the ER+ and HER2+ subtypes. Of note, almost all TP53-mutated cases were basal subtypes. We are currently analyzing the germline of all tumors bearing SBS3 and identified mutations in well-known TNBC-associated genes (BRCA1, PALB2, BARD1), as well as in RAD51B. So far, we identified possible candidate genes from the FANC family such as FANCI (recently associated with ovarian cancer). Our next step is to investigate further the germline of these samples, second hit events in their tumors, methylation, and expression, which we hope can provide supporting evidence of their candidacy as possible BCSG.

P067 : Challenges of counselling and managing patients with pathogenic variants in multiple germline cancer susceptibility genes

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Identification of families with a hereditary cancer syndrome is crucial for providing risk assessment, risk reduction and cancer treatment options. While BRCA1/2 pathogenic variants account for a large percentage of detected variants, the adoption of multi-gene panel testing in clinical practice has permitted the identification of families with pathogenic variants in genes other than BRCA1/2. Additionally, there are increasing reports of families with pathogenic variants in more than one hereditary cancer gene. With limited information about the clinical impact for double PV carriers, this poses challenges for clinicians.

We present two cases of individuals found to have two pathogenic variants in hereditary cancer predisposition genes using multi-gene panel testing. The first case involves a 50-year-old female diagnosed with triple-negative breast cancer and a strong family history of pre-menopausal breast and bilateral breast cancer. Previous genetic testing performed in the family was negative for BRCA1/2. Updated testing performed in 2022 identified the presence of 2 pathogenic variants: PALB2 c.2325dup p.(F776Ifs*26) and CHEK2 c.1555 C>T p.(R519*). The second case involves a 30-year-old female diagnosed with rectal cancer. Two pathogenic variants were identified in CHEK2 c.1100delC (p.Thr367MetfsX15) and NTHL1 c.268C>T (p.Gln90Ter), although a second variant was not identified in NTHL1, an autosomal recessive gene.

The first case highlights the importance of retesting families who tested negative for BRCA1/2 with updated multi-gene panels. In both cases, genetic counselling was provided, but cancer management guidelines for double PV carriers are not available. Clinical decision making is limited to published guidelines for single mutation carriers and was used in combination with the person's medical and family history. Ongoing follow-up of these cases will be crucial in our understanding of management for double-variant carriers, which are likely to grow in number with increased multi-gene panel use in clinical practice.

GROUP 2

CLINICAL ISSUES FOR MANAGEMENT

P068 : Germline genetic testing in Canadian patients identifies those with potential benefit from PARP inhibitor treatment

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Background: Identification of pathogenic germline variants (PGVs) in homologous recombination repair (HRR) genes among patients with breast (BC), ovarian (OC), pancreatic (PaC), and prostate cancer (PrC) is critical to identify those who might benefit from targeted therapies such as PARP inhibitors. Although PGV rates have been reported in the literature, evaluation of these rates in a specific region can help to inform counseling patients undergoing genetic testing. The aim of this study was to describe germline genetic testing outcomes among a Canadian cohort.

Methods: A retrospective analysis of 27,863 probands with cancer undergoing germline genetic testing through a single commercial laboratory ordered by healthcare providers from Canada was conducted. Overall cohort demographic data were analyzed, and further analyses were limited to individuals with BC, OC, PaC, and/or PrC. Descriptive statistics, Chi square with Yates correction, and Fisher's exact test were utilized.

Results: The majority of individuals were female (78.4%), between ages 40-69 years at testing (64.2%), and of white (34.6%), unknown (27.0%), and French Canadian (21.2%) self-reported ethnicity. The overall PGV rate was 14%, 13% in BC, 18% in OC, 13% in PaC, and 15% in PrC cases. Cases potentially eligible for PARP inhibitor therapy based on BRCA1/2 status (BC, OC, PaC) and BRCA1/2 or ATM (PrC) were 6.1% (BC), 9.6% (OC), 4.6% (PaC), and 7.5% (PrC). Overall, 78.4% of PGVs were in HRR or DNA damage repair (DDR) genes.

Conclusions: Among a cohort of Canadian patients with cancer undergoing germline panel testing, PGVs were identified in 14%. More than three-fourths of the PGVs were in HRR/DDR genes, which could have potential to influence treatment options such as treatment with a PARP inhibitor or enrollment in a clinical trial.

P069 : Roughly 6% of Canadians tested through proactive genetic screening have a hereditary cancer syndrome

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We assessed the prevalence of hereditary cancer predisposition syndromes and associated cancer risks in a Canadian cohort who elected to have proactive genetic testing. In total 1,032 Canadian individuals underwent testing that included 58 or 62 cancer risk genes, from June 2017 to June 2022. 44% of individuals were reported to be healthy with no family history of cancer, 1% had a personal history of cancer, 9% had a family history of cancer, 1.2% reported both a personal and family history of cancer, and no history information was provided for 44%. For Provinces that have qualifying guidelines for germline cancer genetic testing, this ostensibly healthy cohort would not have met those criteria.

The molecular diagnostic yield for a hereditary cancer syndrome was nearly 6% for the whole cohort, which increased to 24% for those with a personal history of cancer regardless of family history, and 11% in individuals with only a family history of cancer (Chi-square p < 0.001). CHEK2, ATM, APC p.I1307K, BRCA2, and BRCA1 accounted for roughly 50% of the molecular diagnoses. In individuals with a molecular diagnosis, 41% had a high risk of cancer (>50% lifetime risk), 43% had a moderate risk (20-50% lifetime risk), 8% had a low risk (<20% lifetime risk), and 8% had either a risk for a rare cancer type or an undefined elevated risk. 72% of individuals with a molecular diagnosis had a pathogenic variant in a DNA damage response and repair (DDR)/ homologous recombination repair (HRR) gene and 89% were in genes for which there may be Provincial or National expert opinion on management.

This study indicates that approximately 6% of Canadians who may not meet Provincial or National guidelines for genetic testing may indeed carry a hereditary cancer syndrome, which supports testing in the low risk population.

P070 : Impact of public insurance coverage for HBOC from 2020 in Japan

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Introduction: In Japan, public insurance for HBOC had just been covered from 2020. Its adaptation is a limit to those who had previous cancer history, but it has increased demand for RRSO in Japan. We aimed to evaluate the impact of insurance coverage on RRSO.

Subjects: In this retrospective analysis of 212 cases of RRSO performed at our hospital, the annual frequency was compared between pre- and post-insurance groups.

Results: The annual rate of RRSO increased 5.6 times in post-group. Breast cancer (BC) surgery or RRM was performed along with RRSO in 29.2% of cases overall, with rates of 8.7% and 45.8% in the pre- and post- groups, and with rates in women <45 years old of 22.3% and 45.8%, respectively. The rate of individuals at risk for HBOC without cancer was 12.8% and 9.3%, respectively. The following between-group differences were also identified: age at genetic testing, 49.4 and 46.4 years for the pre- and post-groups; the periods from cancer diagnosis to genetic testing, 6.92 and 0.4 years; and the periods from HBOC diagnosis to RRSO, 1.84 and 0.64 year. Overall, there was no onset of peritoneal cancer over a median post-RRSO observation period of 20 months; the rate of BC recurrence or secondary cancer at 5.6% (gBRCA1, 7; gBRCA2, 5), with a rate of mortality of 0.5% at 2.5 years post-RRSO.

Conclusion: In Japan, provision of insurance coverage for HBOC increased the frequency of RRSO for BC. But the needs for individuals at risk for HBOC without previous cancer history cannot be met due to current limitations in insurance for this group in Japan.

P071 : Prospective pancreatic cancer in a large Norwegian cohort of confirmed BRCA1/BRCA2 carriers

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Background: BRCA1 and BRCA2 (BRCA1/2) mutation carriers have increased risk of pancreatic cancer (PC), but the size of the risk is uncertain. Better estimates are needed to consider whether carriers should be recommended surveillance. We explored the incidence rate and cumulative risk of PC in a large, prospective cohort of confirmed BRCA1/2 carriers.

Material and Methods: Carriers of pathogenic variants in BRCA1/2 without a diagnosis of PC prior to genetic testing were identified in the clinical registry at Section for Hereditary Cancer, Oslo University Hospital. Data were collected on date of birth, gender, gene and date of mutation testing. Cancer diagnoses were collected from the Cancer Registry of Norway (CRN). Standardized incidence ratios (SIRs) were derived from national age-, sex- and period-specific reference rates (CRN data). The Kaplan-Meier method was used to calculate cumulative risk.

Results: Among 2681 BRCA1 carriers, we observed 12 cases versus 4.7 expected, and in 1476 BRCA2 carriers, we observed 9 cases versus 1.9 expected from the reference rates. Elevated risks were most clearly seen in female BRCA2 carriers (SIR 6.5, 95% CI 2.8–12.9, 8 cases) and male BRCA1 carriers (SIR 5.5, 95% CI 2.5–10.5, 9 cases). For these two groups, cumulative risk at 70 years was 1.2 % and 2.5%, respectively, compared with 0.5% and 0.7% in all Norwegian females and males (observed until age 70, 2017–2021, CRN data).

Conclusions: In our prospective study, confirmed BRCA1/2 carriers had, overall, three times more cases of PC than expected. Cumulative risk of PC in the groups producing 81% of the observed cases remained quite low at 70 years, but the number of cases was limited and more data are needed to obtain precise estimates. Whether subgroups of BRCA1/2 carriers may have a sufficiently high risk to be recommended screening should be addressed in future studies.

P072 : Tamoxifen and the risk of breast cancer in women with a BRCA1 or BRCA2 mutation

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Chemoprevention with a selective estrogen receptor modulator (SERM) (tamoxifen or raloxifene) is a non-surgical option offered to high-risk women to reduce the risk of breast cancer. The evidence for tamoxifen use is based on trials conducted among predominantly postmenopausal women from the general population and on studies of contralateral breast cancer in women with a pathogenic variant (mutation hereafter) in BRCA1 or BRCA2. Tamoxifen has not been assessed as a primary prevention option in women with an inherited BRCA mutation.

We conducted a prospective analysis of tamoxifen chemoprevention and the risk of breast cancer in women with a BRCA1 or BRCA2 mutation. Data on tamoxifen (and raloxifene) use was collected by questionnaire and updated biennially. Information on incident cancers was collected by self-report and was confirmed by medical record review. In a matched analysis, we estimated the hazard ratio (HR) and

95% confidence intervals (CI) for developing a first primary breast cancer associated with tamoxifen or raloxifene use, using Cox proportional hazards analysis. There were 4,578 unaffected women in the cohort of whom 137 reported tamoxifen use (3%), 83 reported raloxifene use (2%) and 12 used both drugs (0.3%). Women who used tamoxifen or raloxifene were matched 1:3 with women who used neither drug, on year of birth, country of residence, year of study entry and gene (BRCA1 or BRCA2). We generated 202 matched pairs.

After a mean follow-up of 6.8 years, there were 22 incident breast cancers diagnosed among tamoxifen/raloxifene users (10.9% of users) and 71 cases diagnosed among non-users (14.3% of non-users; HR = 0.64; 95%CI 0.40-1.03; P = 0.07). Chemoprevention may be an effective risk-reduction option for BRCA mutation carriers, although further studies with longer follow-up are necessary.

P073 (Rapid Fire Presentation S7-RF2): Bilateral oophorectomy and all-cause mortality in women with BRCA1 pathogenic variants

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Purpose: Preventive oophorectomy is offered to women at high-risk of cancer due to a pathogenic variant (mutation) in BRCA1; however, the impact of oophorectomy on all-cause mortality has not been clearly defined.

Methods: In this prospective analysis, we included 3,177 women with a BRCA1 mutation who were cancer-free at enrollment. Detailed information on exposures, incident disease and vital status was obtained via biennial questionnaire. Women were followed from age 35 to 75 years for incident cancers and deaths. Cox proportional hazards regression was used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality and cancer-associated mortality associated with bilateral oophorectomy (time-dependent).

Results: A total of 2,106 (66.3%) women underwent a preventive oophorectomy. After a mean follow-up of 9.3 years, 671 of 3,177 (21.1%) women developed 709 incident cancers of whom 197 died; 55 died of ovarian or fallopian tube cancer, 48 died of breast cancer, 15 died of peritoneal cancer, and 79 died of other causes. The age-adjusted HR associated with oophorectomy was 0.17 for ovarian, fallopian tube or peritoneal cancer mortality (95% CI 0.10-0.29; P < 0.0001), was 0.48 for breast cancer mortality (95% CI 0.25-0.92; P = 0.03) and was 0.28 for all-cause mortality (95%CI 0.20-0.38; P < 0.0001). The all-cause cumulative mortality to age 75 for women who had an oophorectomy at age 35 was 26%, compared to 65% for women who did not.

Conclusions: Among women with a BRCA1 mutation, oophorectomy is associated with a highly significant reduction in all-cause mortality.

P074 : Sexual distress in Hereditary Cancer Clinic: Are we doing enough?

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Introduction: Decision making for risk-reducing surgery is influenced by many factors, including sequelae of surgical menopause and sexual health. This study aims to describe sexual distress in gynecologic patients with hereditary cancer syndromes to provide intervention and improve well-being.

Methods: We performed a cross-sectional study of new surgical consultation referrals and follow-up patients who are deciding about or already completed risk-reducing surgery. The primary outcome of sexually-related personal distress was classified by a Female Sexual Distress Survey—Revised (FSDS-R) score of 11 or above. Additional investigator-generated questions examined sexual health education experiences and preferences.

Results: Seventy-seven (of 89) eligible patients completed the survey (86% response rate). All of these individuals carry a pathogenic variant in BRCA1 (n= 20), BRCA2 (n=29), and others(n=27). The median age of respondents was 45-years-old and 70% were pre-menopausal (n=52). Only 23% currently used prescription female hormones. Nineteen patients had a personal history of breast cancer. Twelve patients previously underwent risk-reducing bilateral salpingo-oophorectomy; four of whom had a history of breast cancer. Fifty-seven (76%) were sexually active.

The median FSDS-R score was 10(IQR 15). Overall, 43.6% of subjects reported sexually-related personal distress. Patients with a history of breast cancer experienced less sexual distress compared to those without any history of cancer (29.4% vs 47.3%, respectively). Age, menopausal status, and hormone use were also not significantly associated with distress.

At intake, 76.7% of respondents felt 'neutral', 'somewhat,' or 'strongly disagreed' that a healthcare provider adequately informed them about sexual function side effects of treatment. 46.3% reported interest in speaking with their gynecologic oncologist, over their breast surgeon, Ob/Gyn, or general practitioner. 45.5% and 31% desired consultation with a sexual health specialist and psychologist/counselor, respectively.

Conclusion: While almost half of respondents experienced sexually-related personal distress, many welcomed more counseling on the sexual side effects of treatment, particularly from gynecologic oncologists and sexual health counselors over other specialists.

P075 : Upgrade rates at surgical excision for high-risk breast lesions on core needle biopsy in germline mutation carriers

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Background: While upgrade rates for high-risk breast lesions (HRL) identified on core needle biopsy (CNB) are well-established in the general population, minimal data exist for germline mutation carriers.

Methods: Using institutional databases at Dana-Farber Brigham Cancer Center and the University of Michigan, we identified patients with germline mutations in a breast cancer predisposition gene and history of atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA) or lobular neoplasia (LN; atypical lobular hyperplasia [ALH] or classic lobular carcinoma in situ [cLCIS]) on CNB. Patients with prior or concurrent ipsilateral breast cancer were excluded. Upgrade rates with Wilson confidence intervals were calculated for each HRL.

Results: 64 women with 77 HRLs were included. Germline mutations were present in high-penetrance genes in 64% (n=13 BRCA1, n=22 BRCA2, n=6 PALB2) and moderate-penetrance genes in 36% (n=11 CHEK2, n=9 ATM, n=1 RAD51D, n=1 STK11, n=1 BRIP1). Among 49 ADH lesions on CNB, 92% underwent excision and 13.3% (6/45, 95%CI: 6.3-26.2%) were upgraded. Among 24 LN lesions (n=15 ALH, n=9 cLCIS) on CNB, 58% underwent excision and 7.1% (1/14, 95%CI 1.3-31.5%) were upgraded. The remaining 10 patients with LN were observed, with no same-site cancers at a median follow-up of 3.7 years. Among 4 FEA lesions, all were excised with zero upgrades. All upgraded cancers were estrogen receptor positive: 5 ductal carcinoma in situ and 2 pT1N0 invasive carcinomas. Of the total 52 patients managed with surgery, 85% had excisional biopsy as initial management and 15% had bilateral mastectomy. Chemoprevention was initiated in 26% of eligible patients.

Conclusions: Upgrade rates for ADH on CNB in germline mutation carriers are consistent with reported rates in the general population. Although the sample size for LN was limited, observation in the setting of radiologic-pathologic concordance appears to be safe, yet larger studies in this high-risk cohort are warranted.

P076 : Does concomitant hysterectomy impact menopausal symptoms in premenopausal BRCA1/2 pathogenic carriers undergoing risk reducing salpingo-oophorectomy?

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Background: Prevention of high-grade serous carcinoma in women with a pathogenic variant (mutation) in the BRCA1/2 genes includes prophylactic bilateral salpingo-oophorectomy (PBSO). There is debate on whether concomitant hysterectomy should be recommended, with benefits including a decreased risk of endometrial carcinoma and the ability to use estrogen-alone menopausal hormone therapy (MHT). The

latter is thought to be associated with better menopause-specific quality of life (MENQOL) outcomes with improved breast cancer risk.

Objective: To determine if BRCA1/2 mutation carriers undergoing premenopausal PBSO with concomitant hysterectomy have improved MENQOL compared with those women with an intact uterus.

Methods: Eligible participants were identified from a research program embedded within a familial ovarian cancer clinic with specialized aftercare. Data collected included completion of the validated MENQOL-intervention questionnaire, prior to surgery and one-year following surgery. Change in menopausal symptoms after oophorectomy, by hysterectomy status, and by MHT use were compared using a paired or Student's t-test.

Results: We included 148 women who underwent a PBSO prior to menopause; 76 (51%) underwent concomitant BSO-hysterectomy and 72 (49%) underwent BSO alone. Among women who did not use MHT (n = 62), the change in vasomotor symptoms (P = 0.04) and in sexual function (P = 0.01) worsened for those with hysterectomy vs. no hysterectomy. There was no difference in physical or psychosocial symptoms (P ≥ 0.05). Among women who did use MHT (n = 86), vasomotor symptoms worsened for those with hysterectomy compared to no hysterectomy (P = 0.0003). There was no difference in sexual function, physical, or psychosocial symptoms (P ≥ 0.05). Overall, women did not experience a decline in quality of life regardless of MHT use and/or hysterectomy status.

Conclusion: At one-year post-surgery, there was no difference in MENQOL scores based on hysterectomy status. The worsening vasomotor domain with hysterectomy requires further study.

P077 : Prophylactic surgery and use of hormone replacement therapy in Norwegian BRCA1/2 mutation carriers

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Background: Risk-reducing salpingo-oophorectomy (RRSO) and bilateral risk-reducing mastectomy (BRRM) reduce the risk of ovarian and breast cancer in BRCA1/2 carriers by at least 90%. In Norway, carriers are recommended RRSO from 35 years of age, and hormone replacement therapy (HRT) unless contraindications. The uptake of RRSO and BRRM among Norwegian BRCA1/2 carrier and the use of HRT is unknown. We also do not know if they receive sufficient pre-surgical information.

Aims: The main aim is to determine the uptake of RRSO and BRRM among Norwegian BRCA1/2 carriers. Our secondary aims are to explore if the women receive sufficient pre-surgical information, and HRT use after surgery.

Method: We currently conduct a prospective cohort study where we invite all female BRCA1/2 carriers in the South-Eastern Norway Health Authority Trust to participate. Inclusion started in March 2022 and is ongoing. We present interim analyses of questionnaire data.

Results: Until December 2022, 324 BRCA1/2 carriers had answered the questionnaire. Among these, 256 (79%) had undergone RRSO, and 233 (72%) BRRM. Mean age at RRSO was 42.8 (standard deviation (SD) 8.8), and 46.4 (SD 9.2) years among BRCA1 and BRCA2 carriers, respectively. We performed sub analyses among the HRT eligible women under the age of natural menopause (≤ 52 years), with no

history of breast cancer (n=84): in total 69 (82%) used HRT. Common reasons for not using HRT were "no postmenopausal complaints", "worried about breast cancer", and "the doctor advised against it". After RRSO, about one third considered the pre-surgical information about HRT satisfactory, while one third answered not sufficient. They especially requested information concerning cardiovascular and cognitive effects after RRSO.

Conclusion: The uptake of RRSO in Norwegian BRCA1/2 carriers is high. The proportion of HRT users after RRSO is increasing; however, many women reported insufficient pre-surgical information about late effects from RRSO.

P078 : Risk of contralateral breast cancer after radiotherapy in breast cancer patients with a germline-BRCA1/2- pathogenic variant

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Background: Radiation-induced secondary breast cancer may be a concern after radiotherapy for primary breast cancer (PBC), especially in young germline (g)BRCA-associated breast cancer patients with already high baseline contralateral breast cancer (CBC) risk and potentially increased genetic susceptibility to radiation.

Aim: To investigate whether adjuvant radiotherapy for PBC increases the risk of CBC in gBRCA1/2-associated BC patients.

Methods: gBRCA1/2 pathogenic variant carriers diagnosed with PBC were selected from the prospective International BRCA1/2 Carrier Cohort Study. We used multivariable Cox proportional hazards models to investigate the association between radiotherapy (yes versus no) and CBC risk. We further stratified for BRCA status and PBC age (<40 and >40 years).

Results: Of 3,602 eligible patients, 2,976 (64%) received adjuvant radiotherapy. Median follow-up was 9.6 years. Patients in the radiotherapy group had stage III PBC more often compared to patients in the non-radiotherapy group (15% versus 3%, p<0.001), received more often chemotherapy (81% vs. 70%, p<0.001) and endocrine therapy (50% vs. 35%, p<0.001). The radiotherapy group had an increased risk of CBC compared to the group without radiotherapy (adjusted HR: 1.44, 95% CI: 1.12-1.86), although less pronounced in gBRCA1 (HR: 1.29, 95% CI:0.93-1.77) than in gBRCA2 pathogenic variant carriers (HR: 1.77, 95% CI: 1.13-2.77; p-value for interaction= 0.39). In the combined gBRCA1/2 group, patients irradiated before and after age 40 at PBC diagnosis showed a similar risk increase (HR: 1.38, 95% CI: 0.93-2.04 and HR: 1.56, 95% CI: 1.11-2.19, respectively).

Discussion/conclusion: gBRCA1/2 pathogenic variant carriers are at increased risk of developing CBC after receiving radiotherapy for PBC. Those opting for surveillance instead of prophylactic contralateral mastectomy may benefit from tailored radiotherapy regimens minimizing contralateral breast dose, to reduce CBC risk and improve long-term prognosis.

P079 : Survival of BRCA1/BRCA2-associated pT1 breast cancer patients, a cohort study

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Background: Intensive screening in BRCA1/2 mutation carriers aims to improve breast cancer (BC) prognosis. However, long-term outcome of BRCA1/2 patients with small tumors is unclear.

Aim: To evaluate whether smaller tumor size is associated with improved overall survival within pT1a-c BC patients with a germline BRCA1/2 mutation, and to assess frequency of lymph node involvement by tumor size.

Methods: BRCA1/2 mutation carriers, diagnosed with pT1a, pT1b or pT1c BC, were selected from the Dutch national HEBON cohort. Primary outcome was 10-year overall survival (OS) in node negative

pT1a, pT1b and pT1c BC patients. Secondary outcome was the proportion with lymph node involvement per pT1a-b-c group. For survival analysis, Kaplan-Meier method and Cox proportional hazards models were used to calculate survival rates and hazard ratios for OS, respectively.

Results: 963 women with pT1 BRCA1/2-associated BC diagnosed between 1990 and 2017 were included, of whom 679 had pN0 BC. After a median follow-up of 10.5 years, 10-year OS in patients without chemotherapy was 77.1% in pT1cN0 and lower than for pT1aN0 (91.4%, p=0.119) and pT1bN0 (90.8%, p=0.024). OS was better with than without chemotherapy for pT1cN0 (91.6% vs. 77.1%, p=0.001; hazard ratio, 0.56, 95% confidence interval: 0.21-1.48). Lymph node involvement was 24.9% in pT1c, 18.8% in pT1b, and 8.6% in pT1a.

Conclusion: Smaller tumor size is associated with better OS and less lymph node involvement in pT1 BRCA1/2-associated BC patients. The results suggest that early detection in BRCA1/2 mutation carriers of pT1a/b BC may reduce mortality and the need for systemic therapy.

P080 : Fragmented systems of care: an overview of Canadian health system care models for hereditary cancer syndromes

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Hereditary cancer syndromes (HCS) are one of the most prevalent inherited diseases, accounting for 5-10% of all cancers. Patients and family members with a confirmed genetic diagnosis of a HCS require lifelong screening and follow-up due to an increased risk for malignancies in several organ systems. However, there is limited data on the accessibility and coordination of HCS care across health jurisdictions in Canada. The purpose of this study is to compare and explore the indirect socioeconomic and psychosocial impacts of HCS in British Columbia, Ontario, and Newfoundland & Labrador.

Care system dimensions examined included an overview of populations and regions served, structure of genetic service delivery, genetic testing eligibility, panel sizes, coordination of follow-up care, and gaps in care. Access to and coordination of HCS care across all 3 provinces is fragmented, which may result in socioeconomic, psychosocial and health implications for HCS families.

First, inconsistencies in genetic testing referral criteria and management recommendations for carriers across Canada means that there is variation in access to HCS medical services (e.g., genetic testing, screening). Strict and varied eligibility criteria across the provinces further impairs accessing testing. Secondly, all provinces face a genetics workforce shortage and long wait times to access publicly funded testing. Thirdly, the lack of provincially-organized screening and surveillance programs in the 3 provinces leaves at-risk individuals and their family physicians to navigate the system of care alone. This results in inequities in medical outcomes, which are amplified for underserved populations and rural communities.

Lastly, genetic testing offerings (e.g., gene panels) across the 3 provinces vary which means that at-risk individuals living in different jurisdictions will have inconsistent genetic diagnoses. Further investigation is needed to better examine these impacts to inform evidence-based practice for a more coordinated and patient-centered health care system for families affected by HCS.

P081 : Partnering with patients to explore the psychosocial and socioeconomic impacts of hereditary cancer syndromes

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Patient oriented research aims to improve patient outcomes and the quality of research by focusing on patient-identified priorities and engaging patients as partners. Methods for meaningful patient engagement and the role of patient partners in genomics health research are not well described.

To describe the engagement of patient partners in a Canadian grant exploring the socioeconomic impacts of hereditary cancer syndromes (HCS), six patient partners living with HCS were recruited. Regular meetings among study PIs, staff and patient partners provide consistent communication and co-development opportunities, but they are also given opportunities to review study material on their own time for equitable involvement. Patient partners were invited to engage across all phases of the study: grant application, study design, recruitment, data analysis, and knowledge dissemination. Offering choice in level of involvement is best practice for patient engagement because it allows flexibility around their contributions. As this study involves qualitative interviews about sensitive topics, patient partners' lived experiences have informed study materials. To date, patient partners provided feedback on the content and length of interviews, probing questions, and the language to be used. Feedback on early iterations of the interview guide revealed a bias towards negative language about the impact of HCS. Partners reminded the team that there were positive impacts as well and cautioned about the use of exclusively negative language. Patient partners also took part in mock interviews to finalize the interview guide and provide a training opportunity for students and study staff. To date, patient partners provided important insights on the study population and methods. Ultimately, our aim is to build a rigorous patient oriented research program in hereditary cancers, informed by patient voices, from which lessons learned are shared and the care of families affected by HCS is improved.

P082 (Rapid Fire Presentation S4-RF2): Universal whole genome tumour and germline sequencing of newly diagnosed breast cancer

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Background: Following diagnosis of breast cancer (BC), identification of germline mutations in hereditary breast cancer (HBC) genes can have profound benefits in terms of treatment decisions and managing future cancer risk. In addition, sequencing of the BC can reveal clinically relevant insights, such as homologous recombination deficiency (HRD)and mutational signatures, into effective treatments beyond those revealed by germline sequencing. We hypothesised that current standard of care where only some women diagnosed with BC are offered germline and/or tumour sequencing is suboptimal because it fails to exploit critical vulnerabilities that would be identified if this information was available for all patients. The MAGIC study is the first prospective trial in Australia of unselected invasive BCs in general practice combining germline and somatic sequencing.

Methods: An Australian multi-centre prospective study of 150 consecutive newly diagnosed with nonmetastatic BCs. Germline whole genome sequencing was performed and analysed for actionable HBC gene mutations. Whole genome tumour sequencing was performed on DNA extracted from a formalin fixed paraffin embedded diagnostic tumour and the data analysed for actionable somatic mutations as well as scoring for homologous recombination deficiency and mutational signatures.

Results: A total of 12 carriers (8.6%) with actionable germline mutations were identified in BRCA1 (n=2), BRCA2 (n=1), PALB2 (n=3), CHEK2 (n=2), ATM (n=2) and PMS2 (n=2) and most would have been missed using current guidelines. Somatic sequencing identified BRCA-like genomic features in 15% of tumours from patients without a germline HBC gene mutation.

Conclusion: Universal germline HBC gene testing was viewed favourable by both patients and clinicians and is the most appropriate method for detecting carriers as the majority are missed using current guidelines. Tumour sequencing identified a significant proportion of cases beyond germline HBC gene carriers who may have selective therapeutic sensitivity to PARP-inhibition. Recruitment is ongoing with ~500 new cases per annum.

P083 : Progression-free survival and overall survival after BRCA1/2-associated epithelial ovarian cancer: a matched cohort study

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Introduction: Germline BRCA1/2-associated epithelial ovarian cancer has been associated with better progression-free survival and overall survival than sporadic epithelial ovarian cancer, but conclusive data are lacking.

Methods: We matched 389 BRCA1-associated and 123 BRCA2-associated epithelial ovarian cancer patients 1:1 to sporadic epithelial ovarian cancer patients on year of birth, year of diagnosis, and FIGO stage (<=IIA/>=IIB). Germline DNA test was performed before or after epithelial ovarian cancer diagnosis. All patients received chemotherapy. We used Cox proportional hazards models to estimate the associations between mutation status (BRCA1 or BRCA2 versus sporadic) and progression-free survival and overall survival. To investigate whether DNA testing after epithelial ovarian cancer diagnosis resulted in survival bias, we performed additional analyses limited to BRCA1/2-associated epithelial ovarian cancer patients with a DNA test result before cancer diagnosis (n=73 BRCA1; n=9 BRCA2) and their matched sporadic controls.

Results: The median follow-up was 4.4 years (range 0.1-30.1). During the first three years after epithelial ovarian cancer diagnosis, progression-free survival was better for BRCA1 (HR 0.88, 95% CI 0.74-1.04) and BRCA2 (HR 0.58, 95% CI 0.41-0.81) patients than for sporadic patients. Overall survival was better during the first six years after epithelial ovarian cancer for BRCA1 (HR 0.7, 95% CI 0.58-0.84) and BRCA2 (HR 0.41, 95% CI 0.29-0.59) patients. After surviving these years, survival benefits disappeared or were in favor of the sporadic patients.

Conclusion: For epithelial ovarian cancer patients who received chemotherapy, we confirmed survival benefit for BRCA1 and BRCA2 germline pathogenic variant carriers. This may indicate higher sensitivity to chemotherapy, both in first line treatment and in the recurrent setting. The observed benefit appears to be limited to a relatively short period after epithelial ovarian cancer diagnosis.

P084 (Rapid Fire Presentation S7-RF4): Novel blood-based biomarker to monitor neoadjuvant therapy outcome In triple-negative breast cancer patients

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Purpose: We have identified Nw-hydroxy L-Arginine (NOHA) as a highly sensitive and specific blood-based biomarker of estrogen receptor status in breast cancer patients, i.e, <4 nM, from 4-8 nM, and above 8nM signifies ER-, ER+ and no cancer, respectively (U.S. Utility Patent 10,073,099). Here, we examined the clinical utility of NOHA to monitor neoadjuvant therapy response among triple-negative breast cancer (TNBC) patients, relevant to BRCA1-associated breast cancer.

Methods: Participants included 24 newly diagnosed TNBC patients scheduled to undergo neoadjuvant systemic therapy. 3 ml of whole blood were collected at five specific time points: i) pre-chemotherapy, ii) post-cycle two, iii) post-cycle four, iv) post-final cycle (i.e., pre-surgery), and v) following surgery. Collected whole blood was processed for plasma isolation, and assessed for NOHA by competitive ELISA method, utilizing a proprietary monoclonal antibody. The NOHA ELISA assay results were compared with LC-MS NOHA measurement for experimental validation. Statistical difference was set at $p<0.01$, with two repetitive samples for each tested criteria/condition

Results: Plasma NOHA levels above 4nM were considered indicative of treatment effectiveness. NOHA levels among all enrolled patients showed a robust correlation with their initial disease burden and were sensitive in predicting clinical and pathologic responses to neoadjuvant therapy. Sensitivity of the ELISA assay was comparable to LC-MS results.

Conclusions: This study suggests NOHA clinical utility in monitoring clinical and pathologic responses to TNBC neoadjuvant therapy. It provides the foundational knowledge for future delineation of NOHA to guide TNBC screening, surveillance and management; relevant to individuals with BRCA1 mutations.

Keywords: TNBC, BRCA1, treatment outcome, NOHA, biomarker

P085 : Comprehensive care model for patients with hereditary cancer risk

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Background: As the cohort of individuals with a positive genetic test for BRCA1/2 continues to grow it becomes more challenging to provide coordinated cancer screening and risk management for these patients. While follow up care for BRCA1/2 carriers is often managed in a siloed approach by multiple specialists, alternative service delivery models have been designed to support the demand for a comprehensive approach to hereditary cancer risk management and follow-up.

Methods: This study describes a comprehensive model of hereditary cancer follow-up adopted by a single referral service in Northern California. After receiving positive genetic test results from Cancer Genetics Program at UCSF, patients are referred to the Nurse Practitioner directed Hereditary Cancer Clinic (HCC) which coordinates cancer screening and risk management based on the patient's hereditary cancer risk, age, and phase of life. Data was collected from a database of patient visits at the University of California San Francisco from 2020 to 2022 and a chart review was conducted on a subset of 100 female BRCA1/2 patients to determine the effectiveness of the care model as measured by adherence to National Comprehensive Cancer Network (NCCN) screening guidelines.

Results: Between 2020 and 2022 483 BRCA1/2 patients were seen in the HCC for follow-up. The chart review of 100 patients with visits between 1/2022 – 4/2022 revealed that approximately 90% of patients had exams and imaging performed within 2 months of the NCCN recommended intervals for screening.

Conclusions: This innovative and collaborative model of follow-up has been successfully performed in our institution with high patient acceptance and adherence. The high rate of BRCA1/2 patients in follow-up consistent with NCCN guidelines is due in part to an optimized visit approach that can be leveraged to ensure adherence to screening guidelines and to maximize the opportunity for early cancer detection and/or prevention.

P086 : BRCA carriers after risk reducing bilateral salpingo-oophorectomy: menopausal hormone therapy knowledge gaps, and the impact of physicians' recommendations

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Objectives: Female carriers of BRCA1/2 gene mutations are at an increased lifetime risk for breast and ovarian cancers. They are recommended to undergo risk-reducing surgery, including bilateral salpingo-oophorectomy (RR-BSO), upon completion of childbearing. RR-BSO surgery decreases morbidity and mortality but results in early menopause. Menopausal Hormone Therapy (MHT) alleviates the menopausal symptoms, but it is under-utilized despite being shown as safe for carriers.

Aim: We aim to evaluate the factors associated with decision-making regarding MHT use following RR-BSO in healthy BRCA mutation carriers

Methods: Female carriers aged<50 years at the time of the surgery, who underwent RR-BSO and followed in a multidisciplinary clinic completed online multiple-choice and free-text questionnaires, concerning their quality of life, sexual function, MHT decision process and MHT use.

Results: 142 women met the inclusion criteria and filled the questionnaire. 83 were MHT-users, and 59 were non-users. MHT-users underwent RR-BSO earlier than non-users (40.82±3.91 vs. 42.88±4.34; p<0.0001). MHT usage was positively associated with MHT explanation, OR 4.318, 95%CI[1.341-13.902, p=0.014], and knowledge regarding the safety of MHT and its positive effects on general health OR 2.001, 95%CI[1.443-2.774, p<0.0001].

MHT users and non- users retrospectively evaluated their comprehension of RR-BSO consequences as significantly lower compared to their self-evaluation prior to surgery (p<0.001 for both groups).

Conclusion: Post-RR-BSO outcomes, including the effects on women's quality of life and its possible mitigation through MHT use, need to be addressed pre-surgery by healthcare providers.

P087 : Race and language related disparities in genetic counseling among ovarian cancer patients

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Introduction: Approximately 15% of ovarian cancer (OC) patients carry a pathogenic germline BRCA1/2 variant. Since 2010, NCCN guidelines recommend universal germline testing in all OC patients. Despite this, testing rates in practice are reportedly poor varying from 10 to 30%. We analyzed one academic center’s electronic health record (EHR) to determine differences in proportions of genetic counseling (GC) referrals related to patient characteristics including race and primary language.

Methods: A large single institution tertiary care center EHR database was reviewed for patients linked to OC diagnosis codes with a documented date of diagnosis (dx) between the years 2010 and 2022. These patients were analyzed for GC referral orders within a year of their date of diagnosis. Chi-square tests were performed separately to examine the relationship between patient’s race and primary language with the receipt of GC referral.

Results: A total of 1553 patients met inclusion criteria with the majority being white 1324 (85%) and English speaking 1443 (92%). Overall, 402 (0.19%) were referred to GC. GC referral rates were notably lower among people of color at 39 (17%) vs 374 (21%) (p<0.05), as well as non-English speakers at 12 (10%) vs 403 (27%) (p<0.05).

Discussion: This examination of one EHR identified a statistically significant difference in the rates of GC referral with respect to patient’s race as well as preferred primary language. Increased physician awareness of such existing healthcare gaps is crucial to identify mitigation strategies. Resource utilization including optimization of translator support and development of culturally cognizant provider communication are possible strategies to help bridge this gap. Of note, the above results are limited by missing data such as the receipt of GC at an outside institution or EHR data entry error and require further validation by chart review.

P088 : Clinical predictors associated with participation in the preventive clinical trial with Denosumab (BRCA-P) for healthy women with a pathogenic germline variant in BRCA1 gene

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Background: BRCA-P clinical trial (CT) is a phase III study evaluating the Denosumab effect in reducing breast cancer (BC) risk among healthy women harboring a BRCA1 pathogenic variant. However, uptake to preventive CT is low. We conducted a cross-sectional study to identify the reasons to participate or decline in BRCA-P CT.

Material and methods: All eligible women to BRCA-P CT among the five Spanish centers were invited to participate. Participants fulfilled a RedCap questionnaire after being offered enrollment in the CT with questions addressing potential barriers to enrollment to be answered with a Likert-5 scale. Demographic data, BC risk perception, and cancer worry according to the Cancer Worry Scale (CWS) were compared between women enrolled in the CT (controls) and those who refused to participate (cases). Univariate logistic analysis was performed to estimate the association between the predictors and enrollment in the BRCA-P trial.

Results: So far, 39 women were included. Overall, 13 participants were controls and 26 were cases. We observed statistical differences in the menopausal status (premenopausal 73% in cases vs 31% in controls, p=0.015), university degree (85% cases vs 46% control, p=0.017) and CWS mean score (mean score=12.30 in cases vs 10.15 in controls vs, p=0.051). The main reasons to refuse participation in the CT were: 1. concerns about adverse events (n=19, 73%), 2. duration of the CT (n=10, 38%), 3. pregnancy planning (n=9, 35%), and 4. consideration of risk reduction mastectomy in the next 5 years (n=7, 27%).

Conclusions: Premenopausal women, graduates, and those with a higher cancer worry score were more likely to refuse participation in BRCA-P CT, mostly related to the concern about adverse events. With these data, clinical investigators face the challenge of balancing the pros and cons of preventive drugs, so that participants can make an informed decision.

P089 : Retrospective study on the risk of breast cancer after ovarian cancer in carriers of a pathogenic variant in BRCA1/2.

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Background: Breast and ovarian cancer risk in carriers of BRCA1/2 pathogenic variants is well known. However, risk of breast cancer following ovarian cancer diagnosis is not well established in current models and there is no current consensus on clinical recommendations. The aim of this study is to determine the risk of breast cancer after ovarian cancer among general population and in a large cohort of BRCA1/2 patients.

Methods: This is an observational retrospective analysis in which patients carrying a pathogenic variant in BRCA1/2 diagnosed with breast cancer after ovarian cancer are evaluated from data based on the Girona Population Based Cancer Registry for the period 1990-2018 and the Hereditary Cancer Catalan Network Registry (XICOS) from 1990 to 2022.

Results: In the Girona Cancer Registry 1.390 cases of ovarian cancer were identified, of which 27 cases developed metachronous breast cancer (2%). In the XICOS Registry, 48/643 (7.46%) cases of metachronous breast cancer after ovarian cancer were identified (30/401 in BRCA1 and 18/242 in BRCA2). The mean age at diagnosis for ovarian cancer was 53 years old (38-72) and for breast cancer was 61.5 years old (41-77). 54% of patients were diagnosed by screening mammography and 19% by breast magnetic resonance (MRI). The mean time between the two diagnoses was 103 months (8-338). Ten out of 48 died (21%), 5 due to ovarian cancer recurrence, 1 from breast cancer recurrence/progression and 4 from other causes.

Conclusion: The risk of metachronous breast cancer after ovarian cancer in our series is 7.5%. With the improvement in survival, partly due to new ovarian cancer treatments, there is a need to profile the risk of subsequent breast cancer to optimize preventive management in terms of early detection and risk-reducing strategies in these patients. Risk-reducing recommendations for breast cancer after an ovarian cancer diagnosis remain challenging.

P090 : Hereditary breast and ovarian cancer predisposition management for asymptomatic patient carrier of a BRCA mutation

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Introduction: Specific inherited mutations in a BRCA gene increase the risk of female breast and ovarian cancers and male breast and prostate cancers. Despite the existence of medical guidelines for the management of an asymptomatic BRCA mutation carrier, how to manage cancer risk is frequently unclear and patients experienced a sense of disorientation leading a loss of follow up. The aim of our study is to compare the Hereditary Breast and Ovarian Cancer (HBOC) syndrome management in the world for unaffected BRCA carriers.

Methods: An online survey was created and sent to at least 200 healthcare professionals around the world. It contains questions about cancer prevention, control continuum and the implication of Genetic Counsellors in the management of asymptomatic BRCA carriers.

Results: 47 health professionals from 13 countries participated in our study. 45 respondents declared that there are guidelines in their own country concerning the management of BRCA carriers. Women are recommended mammograms (100%), MRIs (100%), breast ultrasound (85%), serum CA-125 (61,7%), transvaginal ultrasound (59,6%), chemoprevention (61,7%), bilateral risk-reducing mastectomy (100%) and risk-reducing salpingo-oophorectomy (100%). Men are recommended only prostate surveillance (87,2%). Our study concerns also the frequency, the age of beginning and stopping of surveillance and prevention.

Conclusions: Guidelines for HBOC syndrome management are different in the world. Some countries recommend risk-reducing for cancer prevention and others recommend an early detection. The age of beginning and stopping are also different. It would be necessary that each country has the same guidelines concerning the HBOC syndrome management.

P091 : Hereditary breast and ovarian cancer predisposition management for asymptomatic patient carrier of a BRCA mutation

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Conclusions: Guidelines for HBOC syndrome management are different in the world. Some countries recommend risk-reducing for cancer prevention and others recommend an early detection. The age of beginning and stopping are also different. It would be necessary that each country has the same guidelines concerning the HBOC syndrome management.

P092 : Contributions du savoir expérientiel dans la trajectoire en oncogénétique : Résultats préliminaires

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Contexte : L'intégration de patientes accompagnatrices (PAs) à la trajectoire en oncogénétique améliore l'expérience des patientes par l'apport du savoir expérientiel.

Objectif : Cette étude vise à 1) décrire la contribution perçue de PAs intégrées dans deux contextes de soins en lien avec le cancer du sein : l'oncogénétique et l'oncologie et; 2) évaluer si ces contributions varient selon le contexte de soins.

Méthode : Les participantes ont rencontré une PA dans le cadre d'une démarche en oncogénétique (G1) ou dans le cadre d'un diagnostic de cancer du sein (G2). Les accompagnements étaient offerts par l'équipe clinique et se déroulaient par téléphone, visioconférence ou en personne. Les caractéristiques socio-démographiques et cliniques, l'expérience de l'accompagnement, la détresse psychologique (K6), la capacité à faire face au cancer (CASE) et la contribution des PAs ont été évalués par un questionnaire en ligne. Les proportions de femmes ayant rapporté les divers rôles joués par la PA ont été comparées à l'aide de rapports de prévalence (RP) ajustés.

Résultats : Les analyses incluent 150 participantes (n G1=40, n G2 =110). Partager son expérience (G1=72% ; G2=80%), offrir du soutien (G1=62% ; G2=76%), être à l'écoute du patient (G1=51%; G2=61%) et donner de l'information (G1=61%; G2=70%), sont les rôles rapportés par une majorité de participantes dans les deux groupes. Les participantes du groupe 2 étaient significativement moins nombreuses à percevoir que les PAs contribuent aux processus de décision que les participantes du groupe 1(17% versus 38% ; RP=0.45 ; p=0.01).

Conclusion : Le savoir expérientiel peut contribuer au processus de décision parfois complexe des femmes consultant en oncogénétique. Les variations observées entre les deux trajectoires suggèrent également qu'il est souhaitable que la définition du rôle des PAs, leur formation et leur encadrement soient adaptés au contexte clinique dans lequel elles sont intégrées.

P093 : Walking the tight rope: Fertility preservation among previvors

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Fertility-related issues are some of the biggest areas of concern and medical-related anxiety patients who are diagnosed with Hereditary Cancer Syndromes (HCS), also known as previvors. Currently, guidelines for fertility preservation are limited in patients with Hereditary Breast and Ovarian Cancer syndrome (HBOC). The Society of Gynecologic Oncology and the American Society for Reproductive Medicine recommends patients diagnosed with HCS receive early referral to a reproductive endocrinologist.

This study aimed to examine trends in fertility among patients who are high-risk with HCS. This was a review of all patients who presented at single institution for fertility preservation in the setting of diagnosis of HCS or identified as high-risk for HCS. Patients were included and considered high-risk if tested positive for BRCA1, BRCA2 or had a strong family history of cancer, defined as >3 family members diagnosed with HBOC without a known mutation. HCS patients were matched in a 1:1 fashion to a control group undergoing fertility preservation without a diagnosis of infertility. All analysis was done using SPSS version 9.4 (SAS Institute, Cary, NC).

Between August 1st, 2016 and August 1st, 2022, 66 high-risk patients were identified. Out of these patients, 44 (66.7%) had HBOC and 22 (33.3%) had a strong family history for HCS. Out of all patients who presented to a single institution, 47 (66.2%) ultimately underwent egg freezing whereas 24 (33.8%) had embryo freezing. The median age of presentation of all high-risk patients was 33.06 (range of 24.17-42.36) with median age of 29.9 (range 28.79-38.41) for BRCA1 and 33.32 (range 24.17-41.4) for BRCA2 patients.

In terms of patient demographics, 37 (52.1%) identified as white, 39 (55.0%) as single and median BMI was 23.28 (range 18.02-39.5). Among all high-risk patients, median anti-mullerian hormone (AMH) was 1.85 (range 0.16-10.2) and 2.09 (range 0.16-10.2) specifically for HBOC patients. Median number of days for high-risk patients from initial presentation to the start of their fertility treatment was 117 days (range 10-1522 days). Patients diagnosed with BRCA1 presented for fertility consultation at an earlier age compared to control patients (p=0.007 respectively). Patients with a strong family history without a known mutation were more likely to start fertility treatment in less time compared to the control group (average 112 vs 334 days, p=0.045). For patients with known HCS, there was no difference in time from consultation to beginning of fertility treatment compared to controls, AMH levels, or number of embryos stored compared to control patients (p>0.05). BRCA1 patients had more eggs stored compared to the control group (21.5 vs 7.2, P=0.001). Patients with HCS did not undergo expedited fertility treatment compared to the general population. Patients diagnosed with BRCA1 had more eggs stored which is likely due to earlier age of presentation. Patients with BRCA1 presented for fertility consultation at a younger age, yet, BRCA2 patients and patients with a strong family history for HCS presented at the same age as the general population. Given the known cancer prevention benefit and recommendation of risk-reducing surgery, future studies should focus on guidelines for fertility preservation for high-risk patients for HCS.

P094 : Clinical utility of genomic sequencing for breast cancer patients: a retrospective chart review

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Background: Identification of hereditary breast and ovarian cancer syndromes (HBOC) is important to detect families who can benefit from preventive surgeries and surveillance that reduce morbidity and mortality. However, most patients with query HBOC receive uninformative results from panels and are unable to access risk-reducing strategies. Genomic sequencing (GS) may reduce the diagnostic gap in this population:however, most studies evaluating GS utility use small cohorts or only report high-penetrance pathogenic/likely pathogenic (P/LP) variants.

Aims & Methods: We analyzed the yield of all cancer GS results in a cohort of breast cancer patients with prior uninformative panels, who underwent GS as part of an RCT. Charts were reviewed to extract demographics, clinical history, genomic results, recommendations and follow-through.

Results: 276 patients were eligible and included. Participants were mostly female (240), of European descent (158) with breast cancer history (240). Twenty-five patients (9.1%) received ≥1 P/LP variant, 246 patients (89%) had ≥1 VUS and 27 (10%) were negative.

Most P/LP variants (20/26) were in low/moderate risk cancer gene: more than one third (9/26: 35%) were in breast or ovarian cancer genes (ERCC3, ERCC5, CHEK2, RECQL, BRIP1, FANCM). Only BRIP1 and CHEK2 received recommendations based on NCCN guidelines. Recommendations for low penetrance

genes were made ad-hoc:patients with RECLQ and FANCM received clinical evaluations, while patients with ERCC3 and ERCC5 received no further evaluations.

663 cancer VUS were identified: mean number was 2.7/patient and was higher in patients of Non-European ancestry versus European (3.5 vs. 2.5, $p<0.05$).

Conclusion: We identified modest clinical utility of GS for HCS at the cost of a high frequency of VUS.

The variability in management highlights a need for guidelines to standardize management of patients with low/moderate risk results. To optimize use of GS, future research is needed to evaluate the clinical utility of GS as a first-tier test.

POLYGENIC RISK SCORES IN PRACTICE

P095 : Clinical outcomes in a high-risk population: The Gilda Radner Hereditary Cancer Program

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Ovarian cancer has a complex genetic architecture. Inherited BRCA1 and BRCA2 mutation carriers' risk of developing ovarian cancer is 35%-70%. Late detection and low survival rate of ovarian cancer, prompts the need for disease prevention. The Gilda Radner Hereditary Cancer Program provides enhanced screening and research participation for individuals at high risk for hereditary cancer. Participants provide DNA, plasma, serum, lymphoblastoid cell lines, medical history, family history and epidemiologic risk factor data.

Among the predominantly female BRCA+ cohort, 14 men were BRCA+, the average age was 49 years old, 163 had ovarian cancer, 269 breast cancer, and 36 other types of cancer. We performed genotyping and whole genome sequencing in the cohort. A significant percentage of patients within our study are carriers of deleterious mutations in BRCA1 or BRCA2 (BRCA+; 57%), or other known risk genes (10.7%) and 44% of genotyped patients are of Ashkenazi Jewish descent. PRS calculations for breast and ovarian cancer demonstrate that BRCA+ participants have similar PRS profiles to non-BRCA+ carriers. Ashkenazi Jewish individuals with and without cancer had a significantly higher PRS for both breast and ovarian cancer, indicating a unique PGS evaluation range may be needed for certain ancestral groups. Prophylactic surgeries to prevent breast and ovarian cancer were performed in 697 participants (170 had prophylactic mastectomy, 527 had prophylactic bilateral salpingo-oophorectomy (BSO), most of whom were BRCA+. Of those BRCA+ participants 390 had a BSO, 95% had a prophylactic mastectomy.

In ongoing studies, we will focus on how genetic risk factors interact with epidemiologic risk factors in disease development using iPSC derived organoids for the study of breast, ovary, prostate, and pancreatic cancer. This vast and robust resource of information continues to help shape how we diagnose, counsel, and treat families at risk for inherited cancer.

P096 : The effect of adding polygenic risk score and life-style/hormonal information to mutation status and family history-based risk prediction in CHEK2 c.1100delC families

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Introduction: The c.1100delC mutation in the CHEK2 gene is a well-established BC moderate risk variant explaining the occurrence of about 5% of non-BRCA1/2 Dutch BC families. Close relatives of identified carriers are eligible for genetic counseling and risk-based screening advice. The latest version of BOADICEA model considers pathogenic variants in CHEK2, polygenic risk score (PRS) and a residual familial polygenic component. We aimed to study the effect of adding PRS313 to CHEK2 c.1100delC and family history (FH) on screening recommendations using CanRisk.

Methods: 117 healthy women counseled for CHEK2 c.1100delC (58 carriers and 59 non-carriers) at ErasmusMC or AVL-NKI and participating in HEBON were included. DNA samples were genotyped with the GSAMDv3-array. All known first to third-degree relatives of the genotyped individuals were considered. Lifetime BC risk was calculated with BOADICEA v6 through the CanRisk webtool and categorized according to IKNL guidelines (population level <20%; moderate-risk >20-30%; and high-risk >30%).

Results: After adding PRS313 to CHEK2 c.1100delC status and FH, 29% of carriers and 34% of non-carriers changed risk category. Five out of 58 (9%) carriers and 12/59 (20%) non-carriers increased risk group requiring more intensified screening (3 carriers and 4 non-carriers shifted from moderate to high-risk). Additionally, 12/58 (20%) carriers and 8/59 (13%) non-carriers changed risk group downward leading to a less intensive screening (3 carriers and 6 non-carriers reached the population level category). When PRS313 and life-style/hormonal factors were added to CHEK2 status and FH, an additional improvement in risk stratification was observed (31% of carriers and 37% of non-carriers changed risk category and screening recommendations).

Conclusion: The addition of PRS313 to CHEK2 mutation status and FH resulted in shifts in BC risk prediction and screening advice for a substantial number of women. There may be clinical utility in adding PRS313 to diagnostic CHEK2 testing from age 35.

P097 : At least I know what to do: Qualitative analysis of women's reactions when learning they are at high risk in a personalized breast cancer risk assessment study

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Polygenic Risk Scores in Practice *(Continued)*

Background: Risk-stratified breast cancer (BC) screening has the potential to improve the benefit-to-harm ratio and cost-effectiveness of screening. PERSPECTIVE I&I (Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation) evaluates the acceptability and feasibility of a risk-based approach to BC screening at population level. Implementing such an approach brings its own challenges, including risk communication. This analysis describes the reactions of women when learning that they are at high BC risk.

Methods: Participants were unaffected, consented women aged 40-69, identified as being at high risk in the Québec cohort using the multifactorial CanRisk BC risk prediction tool including a polygenic score. The high-risk category corresponds to a BC lifetime risk of = 25%. The study nurse contacted these women by phone to communicate their risk level and to discuss the proposed screening action plan, a copy of which was also sent to their healthcare provider (HCP). A phone script inspired by the “Breaking Bad news SPIKES protocol” was developed to guide the risk communication. Notes were taken by the nurse and a data collection form was completed afterwards. A thematic analysis was performed.

Results: Among the 1,678 women for whom risk was calculated, 127 (7.6%) were at high risk of developing BC. Most were not surprised to be at high risk. The information about the risk level was generally well understood, but some expressed the desire to know more. The action plan was considered reassuring. Concerns were expressed by few women about the implementation of the screening action plan by their HCP. Excerpts summarizing the risk communication will be presented.

Conclusions: Our observations suggest that informing women that they are at high risk of BC is generally well received and highlight some considerations for implementing a risk-stratified BC screening approach at population level.

NEW DEVELOPMENTS IN HBOC MANAGEMENT

P098 : Navigating the healthcare system with a BRCA mutation: What do patients value?

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Objectives: There is a dearth of literature on patient-reported needs and preferences of patients with BRCA mutations with regard to preventative healthcare services and psychosocial, financial, and logistic support. We conducted a patient-advocate led pilot survey to address this gap.

Methods: People self-identifying as having BRCA1 or BRCA2 mutations completed an anonymous online survey focusing on care preferences. The 20-question survey was distributed via email through patient advocate and survivor networks.

Results: Thirty individuals visited the survey website, and 27 (90%) self-identifying BRCA mutation carriers completed the survey. Median age of respondents was 45 years (interquartile range, 39-67.5 years); 23 (85%) identified as non-Hispanic White, 3 (11%) as Hispanic White, and 1 (4%) as non-Hispanic black. All were women; 13 (48%) reported a history of breast or ovarian cancer. Most respondents valued the following components of BRCA-related care: a single provider managing BRCA-related needs (26, 96%),

centralized care at one institution (26, 96%), streamlined care with appointments on the same day (25, 93%), and access to clinical trials (24, 89%). Participants reported prioritizing that the specialists who managed the following aspects of care had expertise in BRCA: ovarian and breast cancer screening (27, 100%), menopause symptoms (25, 100%), risk-reducing breast or pelvic surgery (22, 96%), and interpretation of breast imaging (25, 93%). Twenty-one (77%) reported they would be interested in receiving care at a comprehensive hereditary genetic center if the option were available.

Conclusion: A majority of BRCA mutation carriers expressed desire for a single provider or center to coordinate BRCA-related needs and that providers managing cancer screening, risk-reducing surgery, and menopause symptoms have expertise in treating patients with BRCA mutations. Healthcare centers should strongly consider these needs and preferences in order to provide comprehensive patient-centered care for this high-risk population.

P099 : SALSA® digitalMLPA™ assay for simultaneous analysis of copy number and methylation status of BRCA1/2, PALB2 and RAD51C/D genes in germline and somatic DNA

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PARP inhibitors are approved for the treatment of BRCA-mutated cancers, including metastatic breast and epithelial ovarian carcinomas. These tumours may exhibit homologous recombination (HR) deficiency caused by germline/somatic alterations and/or promoter hypermethylation of BRCA1/2 genes. Recent studies highlighted potential clinical relevance of other HR genes (PALB2 and RAD51C/D) in guiding therapeutic interventions, creating a need to implement routine somatic testing for effective patient care.

A new SALSA® digitalMLPA™ Probemix DM014 was designed to analyse methylation and copy number alterations (CNAs) in BRCA1/2, PALB2 and RAD51C/D genes in cancer cell lines and germline DNA. Validation of results against public databases and by independent assays (SALSA® digitalMLPA™ Probemix D001 Hereditary Cancer Panel 1 and SALSA® MLPA® Probemix ME053 BRCA1-BRCA2-RAD51C) is ongoing.

A complete BRCA1 heterozygous deletion (HetDel) was detected in breast (HCC-1143, SK-BR-3, EFM-19) and pancreatic (PANC-1) cells, and BRCA1 gain was found in ovarian (FU-OV-1) and hepatic (HEP-G2) cells. Co-occurring CNAs in BRCA2 were found in breast (EFM-19; BRCA2 gain), prostate and pancreatic cells (DU-145, LNCAP, PANC1; BRCA2 HetDel). PALB2 gain was found in breast (MCF-7) and hepatic (HEP-G2) cells, and a complete PALB2 HetDel was detected in breast (HCC-1143, MDA-MB-231) and prostate (DU-145) cells. RAD51C/D co-occurring CNAs were detected in breast (MCF-7, HCC-1143, SK-BR-3 and EFM-19), with high-level amplification of RAD51C in MCF-7 cells. CNAs from germline samples were confirmed with SALSA® digitalMLPA™ Probemix D001 Hereditary Cancer Panel 1. BRCA1/2 methylation ratios confirmed the unmethylated status of all cell lines tested. RAD51C hypermethylation was detected in a triple-negative breast cancer cell line (CAL-51).

SALSA® digitalMLPA™ Probemix DM014 contains probes targeting clinically relevant breast/ovarian cancer genes and allows simultaneous detection of CNAs and methylation in samples from germline or somatic origin. Further testing with fresh frozen/FFPE tissue samples is required to assess its clinical and diagnostic utility.

P100 : The multi-omics based immune landscape of BRCA1/2-positive and negative male breast tumors

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Compared with female breast cancer, male breast cancer (MBC) is rare and displays biological and clinical peculiarities. Gender-specific data on predictive molecular biomarkers are lacking, thus cutting out male patients from targeted treatments.

Here, we characterized the multi-omics immune landscape of MBC, in order to provide insights into immune-genetic properties of MBCs in relation to BRCA1/2 status and pathological features, that may help improving the selection of patients responsive to immunotherapy.

Genomic and transcriptomic data of 66 male breast tumor samples, including 20 with germline BRCA1/2 PVs, were obtained by gene panel sequencing and RNA-sequencing. Tumor mutational burden (TMB), Microsatellite Instability (MSI), PD-1 and PD-L1 gene expression, immune scores and immune cell infiltration profiling were evaluated.

High TMB (>10 mut/Mb) was reported in 6 (9%) MBCs, and high MSI (>10%) in 10 (15%) MBCs. Transcriptome-based immune score values ranged from 0 to 94.5 (median=15). Immune scores were positively correlated with PD-1 ($p=0.04$) and PDL-1 ($p<0.00001$) expression, but not with TMB or MSI values.

Compared with non-BRCA1/2 MBCs, BRCA1/2-associated MBCs showed higher TMB values ($p=0.04$), a higher fraction of CD4+ memory activated T cells ($p=0.04$), a lower fraction of activated mast cells ($p=0.03$) and eosinophils (0.004).

Estrogen receptor negative status was associated with high TMB ($p=0.02$), high PD-L1 expression ($p=0.03$) and high immune scores ($p=0.008$). High TMB was associated with a worse overall survival ($p= 0.0001$).

In conclusion, the multi omics-based evaluation of immune-related biomarkers, matched with germline genetic profiling, may open to future characterizations of actionable strategies suitable for men with breast cancer.

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P101 : Genetic analysis across nine cancer types expands the risk profile for BRCA1/2 pathogenic variants

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Introduction: The association with BRCA1/2 in breast, ovarian, prostate, and pancreatic cancers are widely recognized. We recently reported that BRCA1/2 pathogenic variants were associated with the risk of biliary tract, gastric, and esophageal cancers by analyzing >100,000 individuals across 14 common cancer types. These results indicated the potential for implementing early screening tests and expanding

indications for PARP inhibitors. However, there are still other cancer types, which account for about 20% of all cancers. These cancers still have insufficient evidence for clinical significance due to the difficulty in collecting samples. To overcome this limitation, we focused on nine other cancer types based on the self-patient report in BioBank Japan and evaluated the association between BRCA1/2 and the risk of these cancer types.

Method: A total of 3,588 patients with the nine cancer types and 38,153 controls were analyzed. All coding regions in BRCA1/2 were sequenced. Pathogenic variants registered in ClinVar or loss-of-function variants were considered pathogenic. The frequency of pathogenic variant carriers in BRCA1/2 was compared between patients with each cancer type and controls using Fisher's exact test.

Result: The total proportion of pathogenic variant carriers was 1.41% in patients and 0.25% in controls. New associations were identified for three cancer types: bladder cancer (P = 1.1×10-6; OR, 6.1), head and neck cancer (P = 3.7×10-6; OR, 6.5) in BRCA2, and thyroid cancer (P = 1.8×10-4; OR, 11.1) in BRCA1. Also known association was identified for skin cancer including malignant melanoma in BRCA2 (P = 5.8 × 10-4; OR, 8.0).

Conclusion: The results of this self-patient report-based case-control study suggest that pathogenic variants in BRCA1/2 are newly associated with the risk of three cancer types. These results could expand the clinical utility of genetic testing of BRCA1/2 to these three cancer types.

P102 : How can clinical genetics better support BRCA1/2 carriers undergoing risk-reducing bilateral salpingo-oophorectomy? A pilot study.

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Background: In the UK, gold standard tubo-ovarian cancer risk management in carriers of a pathogenic BRCA1/2 variant is risk-reducing bilateral salpingo-oophorectomy (RRBSO). Potential drawbacks of premenopausal RRBSO include surgically induced menopause and changes in sexual function. Patients have reported gaps in specialist advice pre-surgery and feeling surprised and unprepared for dealing with post-surgical sequelae. Clinical Genetics may be well placed to provide support and patient-facing resources to complement shared decision-making with a gynaecological surgeon.

The aims of this study were to: 1) gain insight into the experiences of BRCA1/2 carriers who have undergone RRBSO, particularly regarding menopausal symptoms and sexual function, and 2) gather opinions about support provided by Clinical Genetics and how this may be improved.

Methods: Potential participants were identified using the South West Thames Genetics Service BRCA Carrier Register. Data collection via an online questionnaire included multiple choice and free text questions which were analysed thematically.

Results: Questionnaires were completed by 16/42 invited (37.7% response rate). Pilot data identified key themes including conflicting or lacking information about the emotional and physical impact of RRBSO and the need for access to menopause specialists. Data from this project, along with input from a menopause specialist, contributed to development of an information resource/checklist for patients to bring to clinic. This includes information on RRBSO and important considerations when preparing for surgery. The resource aims to facilitate shared decision-making with health care professionals.

Conclusions: The questionnaire responses suggest follow-on qualitative interviews would provide rich data to inform future work. The checklist has been implemented in clinic and incorporated into an interactive personalised online decision aid as part of a wider project and initial positive feedback has been received in public involvement work. Further qualitative research is planned to inform the implementation, impact and evaluation of this patient resource.

P103 : Mediterranean Diet and quality of life in female gBRCA1/2 mutation carriers

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Objective: Inflammation plays an important role in cancer development and elevated inflammatory markers have been associated with adverse cancer outcomes. Diet modulates inflammation; however, it remains unknown whether the inflammatory potential of diet is associated with health-related quality of life (HRQoL). This study aimed to investigate the association between Mediterranean Diet (MD), dietary inflammatory index (DII) and metabolic syndrome (MetS) with different aspects of HRQoL in gBRCA1/2 mutation carriers.

Methods: We included 312 participants from the ongoing prospective randomized controlled LIBRE trial. Data from the EPIC food frequency questionnaire was used to calculate the DII and adherence to MD was captured by the 14-item PREDIMED questionnaire. HRQoL was measured by the EORTC QLQ-C30 and LOT-R questionnaires. Blood samples, anthropometric measurements and vital parameters were obtained from all participants. Linear and logistic regression models were performed to assess the possible impact of diet and metabolic syndrome on HRQoL.

Results: Of all women (mean age: 43.5 years), 59.6% had a previous diagnosis of cancer. Cancer-diseased women had a significantly lower DII than non-diseased women ($p = 0.01$). A low DII was associated with higher adherence to MD ($p < 0.001$). Women with higher adherence to MD showed a more optimistic outlook on life ($p = 0.01$), whereas women with MetS had higher odds of having a pessimistic outlook on life ($p = 0.03$). Among cancer-diseased women, DII was associated with role function ($p = 0.032$), cognitive function ($p = 0.003$), social function ($p = 0.012$), fatigue ($p = 0.046$), dyspnea ($p = 0.029$) and appetite loss ($p = 0.007$).

Conclusion: Adherence to MD is linked to a more anti-inflammatory diet, better HRQoL and reduced MetS incidence among gBRCA1/2 mutations carriers.

POPULATION-BASED TESTING FOR HBOC-RELATED GENES

P104 (Rapid Fire Presentation S9-RF2): Early insights from the DNA screen study, an Australian pilot study of population genomic screening

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Hereditary Breast and Ovarian Cancer (HBOC), Lynch Syndrome (LS) and Familial Hypercholesterolemia (FH) cause a high burden of early onset hereditary disease. Genomic factors that increase disease risk are well established for these syndromes. Yet, in Australia, access to genetic testing currently relies on a personal or family history of disease. These criteria are inadequate as they fail to detect most high-risk individuals. These individuals are unaware of their predisposition and never engage with the healthcare system to access prevention.

Population genomic screening has the potential to overcome the limitations of criteria-based testing in the context of these conditions, thus enabling disease prevention and early detection, rather than late-stage treatment.

The DNA Screen study has assembled a team of internationally recognized leaders in genomics, oncology, epidemiology, clinical genetics, implementation science and health economics to demonstrate proof-of-concept for population genomic screening for HBOC, LS and FH. Our study will assess the acceptability, scalability and cost-effectiveness of offering this test to young adults in the Australian public healthcare system.

DNA Screen will be established as cohort study of 10,000 young adults recruited from the Australian population, aged 18-40 years old, who are offered germline DNA screening via a highly targeted gene-panel. The recruitment strategy was carefully designed, working closely with consumer and patient group partners, and aims to be nationally representative (in terms of geography, gender, rural/urban areas, culturally and linguistically diverse populations, including First Nations participants).

This presentation will provide early insights from the DNA Screen, following its official launch in August 2022. Following a carefully prepared media release, the study saw 10,000 registrations (its ultimate target) in the first 24 hours and 20,000 in the first week. We will present the strengths and challenges for implementing a preventative genomic screening program at this scale.

P105 : Cost-utility of universal screening for common BRCA variants among Ashkenazi Jewish women: real-life analysis

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Population-Based Testing for HBOC-Related Genes *(Continued)*

Objectives: Identifying carriers of pathogenic BRCA1/BRCA2 variants can reduce cancer morbidity and mortality through surveillance and prevention. Universal testing for founder BRCA1/BRCA2 variants, found in 2.5% of Ashkenazi Jews (AJ), fulfills WHO disease screening criteria. We analyzed the cost-effectiveness of BRCA1/BRCA2 population screening (PS) in AJ, as an alternative to two existing strategies: cascade testing (CT) in carrier's relatives (≥25% carrier probability) and international family history (IFH)-based guidelines (corresponding to ≥10% carrier probability).

Methods: We used a decision analytic model to estimate life years gained, quality-adjusted life-years (QALY) gained, and incremental cost-effectiveness ratio (ICER) for PS vs. CT and IFH strategies. The analysis was conducted from a payer-perspective using lifetime horizon, based on actual costs.

Results: Per 1000 women, the model predicted 21.6 QALYs gained, a lifetime decrease of 3 breast cancer (BC) cases and 4 ovarian cancer (OC) cases for PS vs. CT, and 6.3 years gained, a lifetime decrease of 1 BC and 1 OC cases comparing PS vs. IFH.

PS was less costly compared with CT (-3097 USD/QALY). PS was more costly than IFH-based testing (+42,261 USD/QALY), yet was still cost-effective, from a public health policy perspective. These comparative results are qualitatively robust to sensitivity analysis; PS was the most effective strategy in all analyses.

Conclusions: PS was the most effective screening strategy for breast and ovarian cancer prevention. PS is highly cost-effective, less costly than CT and more costly than IFH. Founder BRCA variant testing should be available to all AJ women, irrespective of family history.

P106 : First population pilot study to determine the prevalence of the recurrent BRCA1 c.68_69del pathogenic variant in a Spanish Roma community.

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The prevalence of BRCA1 germline mutations varies between different geographical zones, races, and ethnic groups. Founder mutations are described in certain populations, such Ashkenazi-Jewish. The BRCA1 c.68_69del, which causes hereditary breast and ovarian cancer syndrome, has a frequency of 1% in this population, accounting for up to 20% of breast cancers below the age of 50. This pathogenic variant has also been described in Roma population (RP), although its exact prevalence remains unknown.

RP represent the largest and most widespread ethnic minority of Europe. In 2012, 11,260,300 Roma individuals were estimated to live in Europe: Spain was the fourth European country with more individuals accounting with 500,000-1,000,000. Current evidence points out to RP common origin to the Indian subcontinent and their arrival in Eastern Europe 1,000 years ago. This makes RP potential candidates to have experienced "genetic founder effect" and, in fact, some studies have already suggested it.

Low participation of the RP in preventive Spanish public health system interventions is well known. For this reason, an action plan was implemented in 2014 to promote participation in genetic studies by facilitating RP access to Genetic Counselling Unit in ICO Badalona. Since then, the number of carrier studies among RP has increased up to 11-fold in half time (1999-2013 versus 2014-2020). Interestingly, 24% of BRCA1 c.68_69del families identified in ICO between 1999-2020 belonged to Roma ethnicity. We aim to determine if the BRCA1 c.68_69del variant prevalence is as high as 1% among RP from Badalona, suggesting potential founder effect.

In collaboration with the primary health care of this area, we present the design and implementation of a prospective community-based study. It started in September 2022 and, up to January 2023, 1 out of 29 Roma participants has been identified to be BRCA1 c.68_69del healthy carrier. Preliminary results will be presented.

P107 : MicroRNAs for characterizing and predicting BRCA mutations in women

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Background: Women with BRCA1 or 2 mutations are at higher risk for developing breast and ovarian cancer. Cancer screening and prevention strategies can help reduce the morbidity and mortality in these patients but identifying patients to prompt testing remains a challenge. We propose identifying BRCA mutant carrier patients through a novel test using microRNA (miRNA) and clinical data.

Methods: 100 women with a BRCA1 or 2 mutation (BRCA-mut) and 1731 non-BRCA women (BRCA-wt) were analyzed in regard to clinical data (e.g. age, race, cancer status, menopausal status, family history) and serum profiles of 179 different miRNAs. Using machine learning techniques, the patients' miRNA and their clinical variables were mapped to two-dimensional space using a joint lasso approach. Afterwards, a simple neural network model was trained to classify patients as BRCA (either 1 or 2) mutant or non-BRCA mutant.

Results: In our study, BRCA-mut and BRCA-wt have significantly different demographics and medical history. BRCA-mut patients were significantly older (mean age of 53 vs. 50 years, $p= 0.02$), white (96% vs. 79%, $p< 0.001$), postmenopausal (70% vs. 47%, $p< 0.001$), and had a family history of ovarian (11% vs. 2%, $p= 0.005$) and breast cancer (36 % vs. 9% $p< 0.001$). Serum miRNA expression was significantly altered in 142 miRNAs in BRCA-mut vs. BRCA-wt patients with the strongest effect for miR-629-5p, miR-361-5p and miR-373-5p. Using the miRNA expression and clinical data we established a novel classification model to predict the BRCA status with an AUC and classification accuracy scores exceeding 99% after a 10-fold cross-validation.

Discussion: BRCA-mut patients show a different expression profile in circulating miRNAs. Combining miRNA data and easily accessible clinical data, we present a highly accurate test for BRCA mutation status prediction, which could be an inexpensive and fast way of screening individuals prior to conventional genetic testing.

P108 : Attitudes and views of healthcare professionals on a risk-stratified breast cancer screening approach: A pan-Canadian cross-sectional survey

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Background: While a risk-stratified approach seems promising to increase the effectiveness of breast cancer (BC) screening, its integration requires the buy-in of all stakeholders, particularly from those who would have a prominent role, the healthcare professionals.

Purpose: We surveyed Canadian healthcare professionals' attitudes and views on the integration of a risk-stratified BC screening approach into current Canadian healthcare systems.

Methods: An anonymous online questionnaire was disseminated through Canadian healthcare professionals associations between November 2020 and May 2021. Variables collected included attitudes towards BC screening recommendations based on individuals' risk of cancer, scope of practice and perceived readiness and comfort related to the implementation of this approach. Their views on aspects of the healthcare system that should be enhanced and the healthcare professional group that should be leading the integration of a risk-stratified BC screening approach were also collected.

Results: A total of 593 healthcare professionals completed the survey. Close to 90% of respondents agreed with the recommendations of increasing the frequency and initiating BC screening at a younger age for women found to be in the high risk group. However, only 9% agreed with the recommendation of not offering BC screening for women in a very low risk group. Respondents indicated that primary care physicians and nurse practitioners should play a leadership role in the implementation of the risk-stratified BC screening approach. Moreover, the enhancement of access to a primary care physician and/or a nurse practitioner was identified as the main aspect for a successful implementation of this approach.

Conclusion: This survey provided key information, including the identification of structural enhancements needed to support future implementation of a risk-stratified BC screening approach into Canadian healthcare systems.

P109 : Population screening for the three Ashkenazi founder mutations in BRCA1/2 genes in Israel

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Population-Based Testing for HBOC-Related Genes *(Continued)*

Introduction: Population screening for three pathogenic founder mutations in the BRCA1/2 genes has been implemented for Ashkenazi Jewish (AJ) females in Israel since 2020. This act has been taken due to the high prevalence of 2.5% for these mutations, reported to account for 95% of the BRCA1/2 pathogenic variants found in AJ, and absence of family history previously reported in half of mutation carriers.

Aims: To characterize personal and familial history and demographic information of carriers identified via the population screening.

Methods: The cohort consisted of women who were tested in Maccabi Health care, the second-largest HMO in Israel, between 10/2021-11/2022. Data was collected from Maccabi's central lab. All carriers were referred to posttest genetic counseling.

Results: During 13 months, 19,000 women were tested and, 420 carriers (2.2%) were identified. Data is available for 330 Of carriers; 32.3%, 13.3% and 54.1%, carried the BRCA1 c.68_69del, the BRCA1 c.5266dup, and the BRCA2 c.5946del mutations, respectively. Only one woman carried two mutations. Age of carriers ranged from 20 to 83 years, with an average age of 40 years (median 39 years). Though the screening was recommended for women who were not diagnosed with BRCA1/2- related cancer, 11 (3.3%) of the carriers had breast/ovarian cancer. Of 308 asymptomatic carriers 27 (9%) women were >60yo and 12 (4%) were >70yo. Interestingly, 249 (82.2%) of carriers reported a positive family history of cancer, of them 80% had BRCA1/2-related cancers.

Conclusions: BRCA1/2 population-based screening allows rapid identification of female carriers. Providing surveillance and preventive measures for all newly diagnosed carriers, becomes a real challenge for the health care system. Posttest counseling revealed that the majority had a family history. This might reflect the motivation to be tested, studies regarding carriers' satisfaction, the medical and emotional effects on BRCA1/2 screening-detected carriers are being performed.

P110 : One continent, one vision: integration of whole exome sequencing at the intersection of research and service delivery, as a necessity for underrepresented African populations

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Clinical service delivery and prognostic genomic research integration may bridge implementation gaps associated with interdisciplinary investigations. Although not customary in Africa, the framework for public health genomics published in February 2021 states that research and healthcare should ideally remain interconnected to address the underrepresentation of genetic research in African populations. Here we demonstrate the clinical utility of prognostic whole exome sequencing (WES) in two South African breast cancer (BC) patients treated at the intersection of research and service delivery.

Blood samples were collected after pre-test counseling. Targeted genotyping for founder variants was performed, followed by multigene panel testing in parallel with exploratory research-based WES. The parallel genomic investigations served for validation of the multi-gene panel.

Population-Based Testing for HBOC-Related Genes *(Continued)*

Case 1 involved a postmenopausal patient with a low initial familial risk based on a brother affected with colon carcinoma. A grade III infiltrating lobular carcinoma was diagnosed at age 58, with infiltrating triple-negative carcinoma occurring at 59 years. Both the targeted gene panel and WES revealed the presence of a single actionable variant detected in CHEK2 c.283C>T,p.Arg95Ter, based on non-functionality, confirmed in terms of kinase activity and dimerization.

Case 2 was a patient diagnosed with infiltrating lobular carcinoma at age 53, metastasizing to the bone and liver. This patient reported a strong family history of breast and prostate cancer. WES revealed a truncating variant in the basal cell carcinoma gene PTCH1 c.4187delG,p.Gly1396AspfsTer56, partaking in the Hedgehog signaling pathway. Truncating variants in this tumor suppressor has the potential to activate breast carcinogenesis by reducing the expression of PTCH1. This gene was not covered in the multi-gene panel.

Collectively, the insights gained from these cases illustrate the successful integration of research-based WES into clinical practice, enabling individualized risk stratification for the application of personalized medicine in Africa.

P111 (Rapid Fire Presentation S9-RF1): Genetic contribution of BRCA1 in hereditary breast and ovarian cancer in Senegalese women

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BRCA1 and BRCA2 are the most incriminated genes in inherited breast/ovarian cancers. Several pathogenic variants of these genes conferring genetic predisposition have been described in different populations but rarely in sub-Saharan Africa. The objectives of this study were to identify pathogenic variants of the BRCA genes involved in hereditary breast cancer in Senegal and to search for a founder effect. We recruited after free informed consent, 51 unrelated index cases diagnosed with breast cancer and each having a family history. Mutation screening of the BRCA1 gene identified a duplication of ten nucleotides 815_824dupAGCCATGTGG, (p. Thr276Aiafs) (NM_007294.3) located in exon 11 with allelic frequency estimated at 27.7%. Haplotypes analysis highlights a shared haplotype encompassing 400 kb between D17S855 and D17S1325. This haplotype was not detected in none of 15 healthy controls. Estimation of the age of the pathogenic variant suggested that it occurred approximatively 1400 years ago confirming its founder effect in West Africa. Genetic testing of the variant in women with family history of breast cancer have been implemented for prevention and counseling.

RISK ASSESSMENT AND GENETIC COUNSELLING ISSUES

P112 : Opportunities and barriers to the uptake of a digitalised breast cancer Family History Assessment Pathway

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In the UK, breast cancer family history risk assessment (FHx) for unaffected women has historically required manual data collection followed by assessment to published written protocols1,2. This time and resource intensive process has led to variable and inequitable implementation of FHx across our region of ~4 million people. We developed a streamlined digital pathway to address this; a patient-facing online family history collection tool (Family History Questionnaire Service [FHQS]3) followed by risk assessment using the CanRisk v2/BOADICEA v64 web-based statistical programme.

From 1st October 2019, >4,000 patients referred to Clinical Genetics completed FHQS. Audit showed response rate consistent/better than previous pathways (~69%) whilst reducing clinician time for assessment (~10 mins vs 30 mins). Personalised assessment using CanRisk4 considering additional parameters, e.g., parity, menarche and genetic test results led to fewer screening mammograms recommended compared to Institute of Cancer Research (ICR)1 assessment (362 fewer mammograms for 239 patients).

From July 2022, we piloted this pathway in three breast screening units assessing acceptability and scalability of use outside Clinical Genetics. Of 175 patients invited, 121/175 (69%) were assessed: 48/121 (40%) were population risk, 66/121 (54%) moderate risk, and 7/121 (6%) high risk, in line with national guidelines2. 54/175 (31%) patients invited did not respond. The FHQS pathway streamlined rejection of population risk patients by asking triaging questions mapped to screening guidelines. The tool can be scaled for use with affected breast cancer patients.

Reported barriers to completion, elicited through telephone calls to patients, included patient knowledge about family history and misplaced invitation leaflets. English was the main spoken language – further work will explore whether the pathway reaches under served populations.

The digital FHQS/CanRisk pathway provides an innovative pathway to reduce the FHx resource burden. In future, health economics and pathways to scale assessment to the unmet need in the community will be evaluated.

1) Protocol 1 mammographic screening 20131101.pub (icr.ac.uk)
2) Overview | Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer | Guidance | NICE
3) St George's Family History Questionnaire Service (fhqs.org)
4) Welcome to CanRisk

P113 : Patient-reported utility of breast cancer results from genomic sequencing

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Risk Assessment and Genetic Counselling Issues *(Continued)*

Background: Genomic sequencing (GS) holds great promise to improve clinical utility for patients with suspected breast and ovarian cancer syndromes (HBOC), most of whom remain undiagnosed after panels. Although GS may increase HBOC detection, it also generates a large volume of non-diagnostic results (e.g., variants of uncertain significance; VUS), whose impact on patients is largely unknown. This limits our understanding of all possible benefits and harms of GS on patients.

Aims & Methods: Explore patient-reported utility of primary/secondary VUS and low/moderate risk result among patients who received GS for breast cancer within an RCT. Thematic analysis employing constant comparison was used.

Results: 25 patients participated: female (22), >50 years (18), European or Ashkenazi Jewish (17) with breast cancer (20), and who received a variety of results including: primary & secondary VUS and pathogenic low/moderate risk variants.

Patients' perceptions of the utility of cancer GS results hinged on whether they triggered clinical action.

For example, when patients were enrolled into high-risk breast cancer screening for low/moderate risk breast cancer genes, they perceived the results to be very 'useful' and 'reassuring' and of moderate-high utility. In contrast, patients receiving low/moderate risk or primary VUS results without clinical action perceived results as 'concerning', leading to harms such as hypervigilance about breast cancer symptoms. Lastly, patients receiving secondary VUS interpreted their results as 'negative'; they began to refocus on other aspects of their life and 'move forward'.

Overall, having a supportive family or primary care provider enhanced perceptions of utility while unsupportive families or providers diminished utility.

Conclusion: From patients' perspectives, GS for cancer may add limited utility and potentially cause harms. These findings of preliminary experiences of harms and limited utility warrant further evaluations in addition to practice interventions to support patients receiving low/moderate risk results and primary VUS from GS.

P114 : Mutation spectrum comparison between benign breast lesion cohort, unselected cancer cohort and high risk breast cancer cohort.

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Background: Mutation study for high-risk breast and ovarian cancer (HBOC) has been extensively studied in patients of different ethnicities. Here we compared the germline mutation rate and spectrum of patients with benign breast diseases or breast cancers, with and without other risk factors.

Methods: Three cohorts of Asian patients were recruited. The first cohort (benign breast lesions cohort (NC), N=101) comprised of 101 patients with benign breast diseases such as fibroadenoma, cysts, fibroadenomatoid hyperplasia and intraductal papilloma. The second cohort (unselected cancer cohort (CC), N=307) was from general recruitment of patients with breast cancer at breast surgery clinics. The third cohort (high risk cohort (HR), N=3935) comprised of high risk breast cancer patients fulfilling the NCCN genetic testing criteria and are recruited at our genetics clinic. A 30-gene panel for hereditary breast cancer was performed on the above mentioned cohorts.

Results: The germline mutation rates of HR, CC and NC cohort were 11.94%, 6.51% and 7.92%, respectively. In CC cohort, 29.3% (90/307) patients actually fulfilled the NCCN genetic test criteria. The mutation rate for this group of patients was 11.11%, similar to that of the HR cohort, while the mutation rate for those not fulfilling testing criteria was 4.61%, similar to that of the NC cohort. High penetrance genes (BRCA1/2, CHEK2, PALB2, PTEN and TP53) mutations were only found in HR (6.67%) and CC (2.76%) cohort but were not found in NC cohort. ATM, BRIP1, RAD51C and RAD51D mutations were identified in all cohorts. RAD51C and RAD51D mutations showed conflicting penetrance. An unexpected high mutation rate of 2.0% was found in NC cohort but it was only 0.3% and 0.5% in HR cohort and CC cohort respectively.

Conclusions: Our results indicate a clinical need to enhance genetic screening of unselected breast cancer patients to identify the high risk patients.

P115 : "Better than Google": evaluation of Rosa chatbot

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Genetic testing has become an integrated part of health care for patients with breast or ovarian cancer, and the increasing demand of genetic testing is accompanied by an increasing need of easy access to reliable genetic information for patients. We therefore developed an app (Rosa), a virtual assistant able to perform human-like digital conversations about genetic BRCA-testing, using chatbot technology.

Before implementing this new information service in daily clinical practice, we wanted to evaluate the utility, clinical usefulness, and trust in chatbot technology among potential users. As part of the evaluation, we invited healthy individuals at risk of hereditary breast and ovarian cancer to test Rosa before and after genetic counseling. Among these, 16 individuals shared their experience through in-depth interviews over video. They were recruited from all genetic departments in Norway and were selected to secure a varied sample with regard to age, gender, and risk of having a BRCA pathogenic variant. Results from this qualitative study will be presented.

The overall finding was that Rosa was very welcomed by the participants. They appreciated the 24/7 availability and that they could have access wherever they were. Furthermore, the fact that Rosa was created by health care professionals made them feel safe that they received medically correct information. It was referred to as an alternative to Google, only better, since it provided more specific and reliable answers to their questions.

After additional testing of Rosa by patients diagnosed with breast or ovarian cancer, we aim at having an information service about hereditary breast and ovarian cancer that is easily accessible, dynamic and reliable. We believe that the introduction of this chatbot in clinical practice can contribute to uniform information for everyone, regardless of residence and access to specialized healthcare personnel.

P116 : Improving criteria for personalized risk assessment among women referred to the high risk Ontario Breast Screening Program (OBSP) irrespective of family history

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Background: The Ontario Breast Screening Program (OBSP) screens women ages 50 to 74 with mammography and since 2011 high risk women ages 30 to 69 with mammography and MRI. Women with a family history suggestive of a hereditary cancer syndrome are referred for genetic assessment to determine high risk screening eligibility. Building on OBSP infrastructure, women ages 40-69 who had a mammogram were recruited to the PERSPECTIVE I&I (Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation) project. This analysis examines the impact of including additional risk factors for identifying high risk women on the current referral criteria.

Methods: Participants' 10-year breast cancer (BC) risk was estimated using the validated multifactorial CanRisk prediction tool that includes family history information, a polygenic risk score (PRS), breast density and established lifestyle/hormonal risk factors. Those at high risk (BC lifetime risk of = 25%) were offered an appointment with the study genetic counsellor to discuss their risk level and proposed screening action plan. High risk participants were advised to speak with their healthcare provider to request referral to their respective OBSP site. Clinical care pathways were developed to support OBSP sites with referrals.

Results: Among 2,111 participants, 46 (2.2%) were identified as high risk. Most high risk women (78.3%) communicated with the genetic counsellor and 66.5% visited their healthcare provider and were referred to the High Risk OBSP. Almost half of those at high risk (45.7%) did not meet the current High Risk OBSP referral criteria because of minimal or no family history of cancer and 61.9% had both a higher PRS and extremely dense breasts.

Conclusions: Referral criteria to the High Risk OBSP could be expanded beyond family history. Multifactorial risk prediction including the PRS and breast density may identify a higher proportion of women at high risk.

P117 : Collecting breast cancer risk factor information for risk-stratified breast cancer screening: Lessons learned from the PERSPECTIVE I&I project

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Background: Internationally, there is considerable interest in moving from an age-based approach to breast cancer screening towards one that is risk-based. I n Ontario and Québec, unaffected women ages 40–69 who had a previous mammogram were recruited to participate in risk-stratified breast screening within the Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation (PERSPECTIVE I&I) project. Understanding the feasibility of collecting detailed risk factor data is essential before implementing breast cancer risk assessment at the population level.

Methods: Participants completed an entry questionnaire that collected detailed breast cancer risk factor information along with sociodemographic and other health information. The questionnaire could only be completed online in Québec, but Ontario participants could complete online, by paper or telephone. The study team verified missing or unusual risk factor information with participants by telephone. Participant characteristics associated with validation of risk factor information and mode of questionnaire completion were assessed, along with preferences for mode of questionnaire completion in Ontario.

Results: Overall, 3,789 women completed risk assessment (n=2,111 Ontario; n=1,678 Québec). In Ontario, 72.8% and 27.2% completed the questionnaire online and on paper/telephone, respectively. Those who completed on paper/telephone were older (p=0.0077), more likely to be members of a visible minority (p=0.0004), have lower educational attainment (p<0.0001), and not working (p=0.026). Substantial proportions of participants required validation of their risk factor information in Québec (41.8%) and Ontario (28.6%). At both sites, participants requiring validation had significantly lower educational attainment. In Ontario, they were also younger (p=0.04), and more often born outside of Canada (p=0.031) and not working (p=0.0025).

Conclusions: More intensive data collection processes were required for many participants. These findings provide important insights for the development of data collection processes that will minimize disparities in access to breast cancer risk assessment at the population level.

P118 : Parent-of-origin-aware genomic analysis in BRCA1 and BRCA2.

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Introduction: Parent-of-origin-aware genomic analysis (POAga) using Oxford Nanopore Technologies long-read sequencing combined with Strand-seq is a novel method enabling assignment of variants to each biological parent with 99% accuracy using only the blood sample of the child. We have previously combined DNA methylation and DNA sequence from long nanopore reads with single-cell DNA template strand sequencing (Strand-seq) data from publicly available samples and datasets and correctly inferred parent-of-origin (PofO) for all autosomes with an average mismatch error rate of 0.31% for single nucleotide variants (SNVs) and 1.89% for indels. Understanding PofO can improve variant assessment and enable focused and efficient cascade genetic testing, especially when variant segregation is not

otherwise possible due to relatives that may be deceased, unavailable, or decline genetic testing. In consideration of Hereditary Breast and Ovarian Cancer (HBOC) being one of the most prevalent high-penetrant cancer susceptibility syndromes, we examined the use of POAga to assign variant-PofO in BRCA1 and BRCA2.

Methods: DNA methylation and DNA sequence from long nanopore reads with Strand-seq data from publicly available samples and datasets of five parent-child trios, was analyzed as previously described. Strand-seq was used to phase nanopore reads, which were used to phase nanopore-detected DNA methylation, SNVs, and indels. Each haplotype was assigned PofO by examining phased DNA methylation at an assembled catalogue of imprinted differentially methylated regions. The rate of correct PofO assignment for heterozygous SNVs and indels in BRCA1 and BRCA2 was determined.

Results: 99.9% (954 of N=955) heterozygous SNVs and 100% (N=75) of heterozygous indels, were correctly assigned PofO in BRCA1 and BRCA2 in five trios with diverse genetic backgrounds.

Conclusion: With appropriate validation, POAga in BRCA1 and BRCA2 stands to provide a powerful new dimension to genomic analysis that could improve variant curation and transform cascade genetic testing and risk assessment within HBOC families.

P119 : Increasing access, reducing barriers, and improving efficiency through genetic counselor oversight of same day genetic testing services

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Underutilization of genetic testing for hereditary cancer in patients meeting established criteria is due to multiple factors, including suboptimal identification of eligible individuals and limited access to genetics professionals. Novel service delivery models aid to increase identification of eligible patients and provide access to genetic testing, but outcomes data on clinical volumes and mutation identification from these programs in community healthcare settings are limited.

We implemented two novel service delivery models across five clinical sites in a community healthcare system in Southern California. Overseen by a genetic counselor (GC), these programs utilize two pathways of patient identification, both leading to pre-test educational video with same-day sample collection facilitated by a genetics assistant (GA). One pathway utilizes an artificial intelligence (chatbot) questionnaire at mammography encounter and the other identifies cancer patients through an anatomic and molecular pathology screening program and/or an oncology provider.

All histories are reviewed, and results disclosures overseen by a GC. Implementation was staggered from 2020-2021, with all sites engaged in January 2022. From 2019 (pre-implementation) to 2022 (post-implementation) clinical volumes per full-time genetic counselor (FTE GC) increased by 80.5% (n=329/GC, 2019; n=594/GC, 2022 projected from quarters 1-3 data). Over that same period, individuals identified with actionable pathogenic/likely pathogenic variants per FTE GC increased by 34.9% (n=43/GC, 2019; n= 58/GC, 2022 projected from quarters 1-3 data) Pathogenic/likely pathogenic variants within genes considered clinically actionable per current 2022 standards included AIP, APC, ATM, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EGFR, EPCAM, FH(HLRCC), FLCN, HOXB13, LZTR1, MAX, MITF, MLH1, MSH2, MSH6, MUTYH(biallelic), NF1, NF2, PALB2, PTEN, PMS2, POLE, POT1, PTCH1, RAD51C, RAD51D, RET, SDHA, SDHB, SDHD, SDHAF2, STK11, TP53, TSC1, VHL. Genes excluded from analysis included MUTYH(heterozygotes), NTHL1(heterozygotes),

BLM(carriers), RAD50,NBN. Novel service delivery models with same-day genetic testing, pre-test educational video and utilization of a GA increase genetic testing and critically identify additional individuals with actionable findings. This serves as a model for improved efficiency and access.

P120 : Female breast cancer prognosis in PTEN Hamartoma Tumor Syndrome – a European cohort study

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Introduction: PTEN Hamartoma Tumor Syndrome (PHTS) is rare with a diverse phenotypic spectrum, including female breast cancer (BC) risks up to 76%. For sporadic BC, the 5- and 10-year survival are about 88% and 80%, respectively. For stages I-IV, the 5-year survival are 99%, 92%, 77% and 31%, and the 10-year survival are 95%, 83%, 58% and 7%, respectively. We aimed to provide a PHTS-specific BC prognosis.

Methods: A European cohort study including PHTS patients recruited via genetic centers and patient societies from over 20 centers in 13 countries. Data from medical files, registries and/or questionnaires was collected. The 5- and 10-year overall survival (OS) of the first primary BC was analyzed using Kaplan-Meier analyses from BC diagnosis onwards to death or last follow-up.

Preliminary results: Overall, 187 BCs were diagnosed in 123 females (72% indexes). The median age at first BC was 41 years (IQR:36-48). The stage was available for 98/123 diagnoses: 32% stage 0, 28% stage I, 26% stage II, 12% stage III and 3% stage IV. The 5- and 10-year OS was 91%(95%CI:86-97) and 84%(95%CI:77-93), respectively. The median OS was 25 years. The 5-year OS per stage was 100%(95%CI:100-100), 95%(95%CI:87-100), 92%(95%CI:82-100), 71%(95%CI:48-100), and 33% (95%CI:7-100), respectively. The 10-year OS per stage was 94%(95%CI:83-100), 87%(95%CI:72-100), 78%(95%CI:61-100), 61%(95%CI:37-100), and 0% (95%CI:0-0), respectively.

Discussion and conclusion: These preliminary results indicate that the 5- and 10-year OS for primary BC in PHTS is likely similar to sporadic BC. Further evaluation of breast and other PHTS-related cancer prognoses and potential influencing factors (e.g. survival bias, year and age of diagnosis, tumor characteristics, treatment) is ongoing and will be available soon.

Funding: PTEN Research UK

P121 (Rapid Fire Presentation S7-RF3): Describing the real world experience of implementing a pre-test genetic counselling portal within a provincial hereditary cancer program

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Objective: To improve access to genetic testing and optimize efficiency, an online patient-led portal was developed at the Hereditary Cancer Program in British Columbia. The portal consists of an educational video, personal and family history questionnaires, patient-reported outcome measures, and provides genetic testing consent and requisition forms.

Methods: Inclusion criteria are adult (≥ 19 years of age), English-speaking patients whose personal or family history of cancer meets provincial criteria for index or carrier genetic testing. Exclusion criteria includes patients requiring extra psychosocial support. Test results are triaged to disclosure by letter or 1-1 appointment with a clinician.

Results: To date, 89% (n=4736/5322) of patients have responded to a portal invite with 82% (n=3877/4736) accepting this model. Reasons to decline: 1.2% no technology access, 1% insufficient digital literacy, 0.1% privacy and security concerns, 6.5% preferred appointment with a clinician. Average time from date of enrollment to test order was eight days for patients who have completed the portal (n=2315). From an initial patient data set (n=1522), 80% self-identified as female, 19% as male, 1% as other with 94% between ages 30-79. Most patients indicated high satisfaction as 98% (n=1499/1522) would complete genetics services using a portal again, 89% (n=1351/1522) indicated it was easy to complete the online forms, and 87% (n=1327/1522) indicated their overall experience was good or excellent. Forty percent of results have been disclosed by letter. Patient reported outcome measures show no significant difference in scores compared to 1-1 genetic counselling and other alternative models of service delivery.

Conclusion: Early data indicates a pre-test patient-led genetic counselling portal is feasible and acceptable to patients at risk of hereditary cancer while reducing wait times for genetic testing. Improved efficiencies will allow increased capacity to provide individualized service for diverse minority populations and families living with hereditary cancer risk.

P122 : Concurrent uterine surgery and uptake of hormone replacement therapy in patients undergoing bilateral salpingo-oophorectomy for risk-reducing or therapeutic indications

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Risk-reducing bilateral salpingo-oophorectomy (BSO) is recommended to those with pathogenic variants at risk for ovarian and breast cancer, or with a strong family history. BSO can also be performed therapeutically for patients with a history of hormone receptor-positive (HRP) breast cancer. The indications for concurrent hysterectomy or endometrial sampling are controversial, and uptake of hormone replacement therapy (HT) in eligible patients after surgery is variable. We aimed to analyze factors associated with operative choice in patients undergoing BSO for risk-reducing or therapeutic indications, to describe trends in concurrent uterine surgery, and to evaluate uptake of post-operative HT.

We performed a 10-year retrospective study of patients at one institution who underwent BSO for risk-reducing or therapeutic purposes. A multinomial regression analysis of patient and case-specific characteristics was performed to determine associations with surgery type (BSO alone, BSO and hysterectomy, or BSO and endometrial sampling). Patterns of HT uptake post operatively were also described.

Our study sample included 644 patients, of which 103 (16%) had a pathogenic variant as well as hormone receptor-positive breast cancer history, 254 (39%) had a variant alone, 176 (27%) had a hormone receptor-positive breast cancer history alone, and 111 (17%) underwent BSO for family history alone. The

majority of pathogenic variant carriers were BRCA1 (141, 39%) or BRCA2 carriers (173, 48%). In a multinomial regression analysis, there was a significant association between Black race (RR=3.54, CI=1.51-8.30, p=.004), history of HRP breast cancer (RR=1.86, CI=1.08-2.18, p=.03), and surgeon (Surgeon 1, RR=2.38, CI = 1.33-4.24, p=.003) with concurrent hysterectomy. Of the 365 patients without a history of HRP breast cancer, 76 (21%) initiated systemic HT postoperatively. Over the 10-year period, the rates of concurrent hysterectomy declined while those of endometrial sampling increased.

Continued work is required to understand risks and benefits in order to standardize treatment recommendations for concurrent surgery and HT in the risk-reducing and therapeutic BSO population.

P123 : Attitudes of BC/Yukon hereditary cancer patients to a supported direct-contact approach for informing relatives about genetic testing

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Introduction: Most hereditary cancer programs use a family-mediated approach to tell relatives about cascade carrier testing. To improve testing uptake, some have implemented a direct-contact approach whereby the program contacts family members to share the option of genetic testing, typically in parallel to patients notifying their family. To ensure that the implementation of such an approach is acceptable to patients, a comprehensive understanding of their preferences, concerns and expectations is required. The purpose of this study is to explore the attitudes of hereditary cancer patients from a Canadian provincial program on a supported direct-contact approach.

Methods: Individuals carrying a pathogenic variant in a hereditary cancer gene were identified; purposive sampling guided the selection of participants to support diversity. Semi-structured interviews were conducted by three of the investigators via Zoom or telephone. Interviews were recorded, professionally transcribed, de-identified, and reviewed for accuracy. Transcripts were coded by two analysts, with thematic analysis currently underway.

Results: Fifteen participants were interviewed; 11 females and 4 males between ages 35 and 70 years. Interviews ranged from 19 to 60 minutes. In response to reported challenges communicating hereditary cancer risk information with relatives, many participants were supportive of enhanced assistance from hereditary cancer programs. Variation in preferences for a supported direct-contact approach centered around timing and level of genetic counsellor involvement, as well as the detail and format of information provided to family members.

Anticipated Outcomes: Based on our program's experience in supporting direct contact for several families in British Columbia, a draft clinical guideline was developed for use by all medical genetics services in our provincial health authority. Results from this study will inform the final version of the guideline and lead to implementation of a patient values-informed supported-direct contact approach to facilitating cascade carrier testing in our province.

P124 : Genetic counseling services for hereditary breast and ovarian cancer: Patients' experience and satisfaction

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Background: In a context of scarce resources and growing demands, some patients do undergo genetic testing for hereditary breast and ovarian cancer (HBOC) without participating in a formal genetic counseling session. This situation is more frequent for patients who are on a fast-track pathway where clinicians need the result of the genetic test to guide a clinical decision.

Purpose: We assessed whether participating in a formal genetic counseling session had an impact on patients' experience and satisfaction with the genetic testing process for HBOC.

Methods: A random sample of patients who underwent genetic testing for HBOC at the CHU de Québec-Université Laval between 2017 and 2021 were invited to respond to a 35-question survey. Experience and satisfaction with the testing process were assessed using a modified version of the Royal Marsden Satisfaction Questionnaire

Results: In total, 501 patients completed the survey. Of these, 378 (75.4%) participated in a genetic counseling session, 109 (21.8%) did not participate, and 14 (2.8%) did not remember. Compared to those who participated in a formal genetic counseling session, patients who did not participate were less likely to report having received information material prior to the test and less likely to have been informed: i) that further discussions with the team was possible before taking a decision, ii) how the test result may impact their treatment and follow up, iii) that it may have implications for family members, and iv) how and when they may expect to receive their result. Nevertheless, overall satisfaction with the process was high and did not differ between groups.

Conclusion: These results seem to indicate that participating in a formal genetic counseling session do add quality to the care of patients who undergo the genetic testing process for HBOC.

P125 : Mosaic TP53 pathogenic variant identified in a woman with 4 cancers including ovarian and breast tumors.

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Introduction: Li-Fraumeni syndrome (LFS) is an autosomal dominant hereditary cancer syndrome due to germline TP53 pathogenic variants (PV) with very high lifetime cancer risks. Distinction between TP53 germline variants and mosaicism status is not trivial. Here we describe the case of a female patient with 4 distinct tumors and a TP53 mosaic PV.

Case description: A 46 year-old Caucasian patient developed a basal cell carcinoma at 36, a borderline ovarian tumor at 42 and an invasive breast cancer at 45. A maternal aunt and a cousin developed breast cancer at 67 and 63, respectively. According to international guidelines, criteria were not met to offer genetic testing at that time. Two years later, the patient developed an acute myeloid leukemia. Somatic genetic testing on a bone marrow sample identified a TP53 PV (c.535C>T/p.His179Tyr) at a 53.9% allele frequency (AF).

To confirm the hypothesis of a germline heterozygous variant, direct testing was performed from a buccal swab and showed a 40.6% AF. The patient was readdressed to our unit for genetic counseling with a LFS diagnosis. As personal and family history was not fully suggestive of LFS, and as buccal swab is known to be at risk of leukemic cells contamination, we decided to perform targeted TP53 testing on other tissues. With the patient's consent, we were able to retrieve non-cancerous tissue samples from surgeries preceding the leukemia diagnosis: stomach (AF: <20%), uterus (AF: <20%) and other cancerous tissue samples: breast (AF: 25%) and ovary (AF: 4%). Based on these results, we concluded that this patient demonstrated a constitutional mosaicism for the TP53 c.535C>T/p.His179Tyr PV.

Conclusion: LFS is no longer a straightforward diagnosis as next generation sequencing can reveal TP53 PV with low minor AF. This case shows the importance of multi-tissue testing to confirm mosaicism for a TP53 PV.

P126 : New effective genetic approaches are needed for male and elderly female relatives in HBOC family

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In Japan, the number of cancer patients diagnosed with HBOC has increased since BRCA1/2 genetic testing, surveillance for breast and ovarian cancer and risk-reducing surgery became covered by national health insurance in 2020. However, not many relatives come to the clinic for genetic counseling. Therefore, this study assessed clinical features of HBOC probands and factors influencing the rate of receiving genetic counseling among relatives, with the aim of searching effective possible ways to improve the rate of genetic counseling visits by at-risk relatives.

Clinical data on 133 HBOC probands who visited Hyogo Cancer Center between February 2013 and September 2022 was analysed. We also collected the data on relatives of 84 HBOC families. Among HBOC probands, 7 were male and 126 were female, including 60 females with breast cancer, 42 with ovarian cancer, and 24 with more than two HBOC-related cancers. The first BRCA-related cancer was breast cancer for 76 (60%) female probands at the median age of 44 years, and ovarian cancer for 48 (38%) at the age of 53 years. About one-third of the first-degree relatives aged 20 to 75 years in HBOC families received genetic counseling, ranging from 18% of male relatives to 40% of female relatives. The rate of receiving genetic counseling was 60.9% for female relatives in their 20's to 40's and 13.6% in their 50's or later, respectively.

Our result shows relatively lower rate of receiving genetic counseling among male relatives and also among female relative aged 50 and over.

Since about half of the HBOC female probands are diagnosed with first BRCA-related cancer in their 50's or later, knowing one's own genetic information may be useful for cancer prevention even in relatively elder female relatives. More convenient ways to access genetic counseling or to collect correct information about the disease are urgently needed.

P127 : Examining the association between ambient exposure to nitrogen dioxide and breast cancer risk among high-risk Canadian women

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Introduction: Air pollution, specifically nitrogen dioxide (NO2), is a carcinogen that was recently associated with an increased risk of breast cancer among women with an elevated familial risk. Whether such an association exists among women with a pathogenic variant (mutation) in the BRCA1 or BRCA2 genes is unknown. Thus, we conducted a prospective analysis of annual NO2 exposure and breast cancer risk among BRCA mutation carriers residing in Canada.

Methods: We identified BRCA mutation carriers from a longitudinal study which collects detailed information on various exposures and incident disease via biennial questionnaire. Women were eligible if they provided a postal code, did not have a preventive mastectomy or cancer at enrollment, and completed at least one follow-up questionnaire. Annual NO2 concentrations (ppb) at enrollment address were obtained through linkage to the Canadian Urban Environmental Health Research Consortium

(CANUE). Hazard ratios (HR) and 95% confidence intervals (CI) for the association between NO2 and risk were estimated using Cox regression.

Results: This analysis included 1,129 women. After a mean follow-up of 7.1 years, 125 incident breast cancers were identified. The median annual NO2 concentration was 13.0 ppb (range 0.2 – 43.8), indicating low overall exposure in the cohort. There was a significant association between increasing NO2 exposure and breast cancer risk; each 8-ppb increase was associated with a 21% increased risk (HR= 1.21, 95%CI 1.01 – 1.43; P-trend =0.04). Although not statistically significant, women in the highest vs. lowest quartile of NO2 had a 51% increased risk (95%CI 0.92 – 2.51). Multivariate analyses are ongoing.

Significance: This is the first report of NO2 exposure and BRCA-breast cancer risk and suggests that environmental exposures may impact breast cancer risk among high-risk women. We will continue to leverage administrative databases to delineate the relationship between environmental toxins and breast cancer risk.

THE BREAST CANCER GENES

P128 : Importance of germline follow-up for BRCA1, BRCA2, and PALB2 pathogenic variants identified on somatic testing

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Tumor genetic testing may identify likely pathogenic or pathogenic (LP/P) variants that are of germline origin. According to the European Society of Medical Oncology (ESMO, 2020), LP/P somatic variants in BRCA1, BRCA2, and PALB2 are confirmed in the germline between 65-80% of the time. Since 10/2020, the NYULH High-Risk Cancer Genetics Program received alerts and notified providers of patients who had somatic mutations of potential germline origin in known hereditary cancer genes, based on ESMO guidelines. Providers were recommended to refer the patient to genetic counseling services.

In total, 176 individuals had BRCA1, BRCA2, and/or PALB2 somatic LP/P variants. The genetic counseling referral rate was 59%, and 43% of individuals have thus far completed genetic testing. The germline positivity rate was 66%. Fifty-nine percent had at least one corresponding BRCA1, BRCA2, and/or PALB2 LP/P variant. Nine percent had either an additional or a single LP/P variant in another high or moderate risk hereditary cancer predisposition gene. The cancer diagnoses for BRCA1, BRCA2, and PALB2 single or double mutation carriers included ampullary, ovarian/fallopian tube, breast, prostate, lung, pancreas, bile duct, colon, and liver cholangiocarcinoma.

We demonstrated a feasible process to detect BRCA1, BRCA2, and PALB2 somatic LP/P alterations, which require follow up germline genetic testing and display a high rate of germline confirmation. Further, 9% of individuals with one or more LP/P germline mutations harbored a mutation in a hereditary cancer predisposition gene that was unrelated to BRCA1/2 or PALB2 and could result in management changes beyond initial expectations for the individuals and their family members. Despite notification and recommendations to providers to refer to genetic services, referral rates remained low (<60%). This observation suggests a streamlined or automated germline genetics referral workflow for these patients may be considered to ensure proper risk assessment and care.

P129 (Rapid Fire Presentation S7-RF1): Early salpingectomy with delayed oophorectomy as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 pathogenic variant carriers - Update of the TUBA-WISP II study

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Introduction: The detrimental consequences of premature menopause caused by risk-reducing salpingo-oophorectomy (RRSO) together with the hypothesis that high-grade serous carcinoma (HGSC) originates in the fallopian tubes, makes an early risk-reducing salpingectomy (RRS) with delayed oophorectomy (DO) an attractive strategy.

Methods: The prospective international TUBA-WISP II study compares the novel RRS with DO to the current standard RRSO among BRCA1/2 pathogenic variant (PV) carriers on safety. Women choose between RRSO between the age of 35-40 (BRCA1) or 40-45 (BRCA2), and RRS after child bearing until age 40 (BRCA1) or 45 (BRCA2) with DO until age 45 (BRCA1) or 50 (BRCA2).

Preliminary Results: The first 1000 of the aimed 3000 BRCA1/2-PV carriers have been included of which 51.9% carriers a BRCA1-PV and 48.1% a BRCA2-PV. Ratio between RRS with DO and RRSO is 74.2% versus 25.8%. Mean (standard deviation (SD)) age at inclusion is 36.6 (3.6) years for women who chose RRS with DO and 38.7 (3.1) years for women who chose RRSO ($p<0.001$). Thus far (November 1, 2022), 894 women underwent their first surgery. Among the women who underwent RRS (n=653), we detected two serous tubal intraepithelial carcinoma (STIC)s (0.3%) and three HGSCs (0.5%). Among the women who underwent RRSO (n=241), three STICs (1.2%) and three HGSCs (1.2%) were detected. Two women had atypical cytology and one malignant cytology without other abnormalities. No ovarian carcinoma have been diagnosed after first surgery.

Discussion: The study will continue aiming to investigate whether RRS with DO is as effective as RRSO in preventing ovarian cancer in women at high inherited risk.

P130 : Multi-Gene panel (MGP) testing for pathogenic germline variants (PGVs) among older patients with breast cancer

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Introductions: The availability and affordability of germline genetic testing result in a wider utilization of these tests in daily clinical practice. However, adherence to international guidelines is low, especially when encountering older patients, where testing is usually not offered.

Methods: Consecutive, newly diagnosed patients with breast cancer aged ≥ 65 years and eligible for germline genetic testing, as per the National Comprehensive Cancer Network (NCCN) guidelines, were invited to participate. Patients were offered the standard guideline-based 20-gene, or an expanded 84-gene panel. Genetic testing was performed using a peripheral blood sample (Invitae Corp., San Francisco, CA, USA).

Results: Between March 2021 and June 2022, 117 patients were enrolled. Mean (SD) age at breast cancer diagnosis was 70.4 (4.3), range 65-81 years. Majority (n=104, 88.9%) had early-stage disease and 12 (10.3%) were male. Patients were tested based on NCCN criteria; 51 (43.6%) with 20-gene panel while the remaining 66 (56.4%) patients had expanded 84-gene panel testing. Family history of breast, ovarian, pancreatic or prostate cancer was the most common indication for testing (n=97, 82.9%). Male breast cancer (n=12, 10.3%) and triple-negative disease (n=8, 6.8%) were less common indications. Among the entire study cohort, 15 (12.8%) had pathogenic variants. Genes involved were BRCA1/2 (n=5), ATM (n=4), CHEK2 (n=4), PALB2 (n=1) and BRIP1 (n=1) and all were actionable. All identified pathogenic variants were included in the restricted 20-gene panel. VUS were identified among 17 (33.3%) patients tested with 20-gene panel compared to 35 (53.0%) patients who underwent expanded 84-gene panel testing.

Conclusions: This study demonstrated that the rate of pathogenic variants among older patients with breast cancer is high enough to justify screening of eligible patients. However, all identified variants were within the guideline-based 20-multi-gene panel. Expanding the testing using an 84-gene panel did not improve detection rate but increased rates of VUS.

P131 : Expanded versus limited multi-gene panel (MGP) testing for pathogenic germline variants (PGVs) among young adults with breast cancer

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Background: Breast cancer in adolescents and young adults (AYAs) is more likely to result from cancer predisposition syndromes, therefore germline genetic testing is an integral part of risk assessment, cancer prevention and therapeutic interventions. In this study, we investigate the pattern and prevalence of actionable pathogenic germline variants (PGVs) using 'restricted' and 'expanded' multi-gene panels (MGPs) in young breast cancer patients.

Methods: This was a prospective study in which all breast cancer patients, aged 30 years or younger, regardless of their personal or family history, or tumor characteristics, were invited to participate. Genetic testing was done using a 'restricted' BRCA1/BRCA2-only or 20-gene panel, or an 'expanded' 84-gene panel and was performed at a reference laboratory (Invitae Corp., San Francisco, CA, USA). Variants were classified as benign/likely benign (negative), pathogenic/likely pathogenic (positive) and variant of uncertain significance (VUS).

Results: Between December 2019 and June 2022, a total of 226 patients were enrolled. Median age at diagnosis was 29 (18-30) years. Majority (n=165, 73.0%) were tested using the 'restricted' BRCA1/BRCA2-only (n=86) or 20-gene panel (n=79), while 61 (27.0%) others had an 'expanded' 84-gene panel. Overall, 56 (24.8%) patients were positive; 32 (19.4%) among the group of patients tested with the 'restricted' panels and 24 (39.3%) among those tested with the 84-gene panel. PGVs in genes other than BRCA1 and BRCA2, like ATM, BRIP1, CHEK2, TP53, MLH1, NF1,and WRN, accounted for 37.5% of the variants identified in the 'expanded' panel and 15.2% in the 'restricted' panel. VUS rate was significantly higher with the expanded compared to the restricted panel; 39.3% versus 15.8%, p=0.001.

Conclusion: Almost one in four young patients (≤ 30 years) with breast cancer harbor actionable PGVs. The expanded-gene panel was able to identify actionable variants that would have been missed with the more restricted panels.

P132 : Yield and implications of multi cancer gene panel testing (Mcgpt) in a single center cohort in the mid-south of Israel

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Introduction: Hereditary breast/ovarian cancer (BOC) is associated with germline mutations in multiple genes, BRCA1 and BRCA2 (BRCA1/2) being the predominant ones. Some recurring mutations in these genes were reported in populations in Israel. The common workup for a BOC patient is a two-step approach where initially these mutations are genotyped followed by multi cancer gene panel testing (MCGPT) for eligible patients (i.e., subjects having a 10% or greater probability of carrying a BRCA1/2mutation in an established model).

Aim: To assess the yield of MCGPT in a series of BOC patients in a center in the mid-south of Israel.

Methods: Data of individuals who underwent testing at between January 1st 2015 to December 31st 2022 was reviewed. MCGPT was done primarily using two commercial panels.

Results Overall, 155 patients underwent MCGPT. The majority (91.8%) were breast cancer patients. Twenty one subjects (13.6%) were identified with a pathogenic variant (PV). Ten PVs were diagnosed in breast cancer risk genes (ATM, CHEK2, NF1 and TP53), with one patient harboring mutations in two genes. Five subjects had a PV in low penetrance genes, for which there is currently insufficient evidence of an association with BOC (MUTYH heterozygotes, RECQL4). Two additional subjects were diagnosed with PVs in cancer predisposition conditions (APC and FH) other than BOC. The remainder six subjects (28.6%) carried a heterozygote mutation in genes seemingly unrelated to BOC risk (CFTR, FANCA, SBDS), but having familial implications for recessive conditions. None of the subjects carried a BRCA1/2 mutation.

Conclusions: The currently used scheme of first-pass genotyping in Israel seems to have a limited mutation detection rates. However, large panels may not be clinically relevant in a familial cancer clinic setting. The challenge is to optimize mutation risk models and the currently used panels to accommodate analysis of clinically relevant and actionable genes.

P133 : A Cell-Based Reporter to screen for modifiers of BRCA1 protein expression

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The breast cancer susceptibility gene 1 (BRCA1) is a critical tumour suppressor involved in double-strand break repair through homologous recombination (HR). Clinical assessments show that BRCA1-mutation carriers have reduced BRCA1 expression, which leads to compromised DNA-damage repair. We and others have reported that BRCA1 expression can be modified through intracellular and extracellular factors, and thus, modulating BRCA1 expression may alter tumour onset and progression. We hypothesize that an agent that increases BRCA1 protein expression will mitigate the oncogenic consequences of an inherited BRCA1 mutation. We also propose that BRCA1 repression may promote “Synthetic BRCAness”, which can sensitize cancer cells to PARP-inhibition (PARPi) and other chemotherapies. We hypothesize that compounds that decrease BRCA1 protein expression can sensitize HR-competent cancers to PARPi.

In this project, we aim to identify novel chemical modifiers of BRCA1 expression. To achieve this we generated and validated novel and unique BRCA1-reporter cell lines which were subsequently used to conduct a pilot screen (64 epigenetic-modifying drugs) and two high-content screens (6,000 compounds each). We identified several compounds that modified BRCA1 protein expression (B-score >3*SD). The epigenetic drug library yielded five repressors and two activators, and the high-content screens identified 401 repressors and 82 activators.

Validation studies have confirmed that the activator drug, aloxistatin, can increase BRCA1 protein expression and function in breast cells in a dose-dependent manner. We have also assessed two down-regulators of BRCA1 from the epigenetics screen (panobinostat, (+)-JQ1) and 7 compounds from the first large screen. Each of these nine compounds can synergize with olaparib to reduce breast cancer cell growth and increase DNA damage. Validation in other breast cancer cells and mouse models are in progress.

Overall, these findings highlight the utility of our novel reporter cells in identifying BRCA1-modulating compounds which may ultimately be useful for the prevention and treatment of BRCA1-associated cancers.

P134 : A novel mammary progenitor population regulated by fatty acid metabolism

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Introduction: Primary risk reduction options for women at high-risk of developing breast cancer remain centered on radical prophylactic mastectomy. There is an urgent need to understand what cell populations in the high-risk breast uniquely predispose these women to breast cancer to drive the development of less invasive primary prevention methods.

Methods: We undertook phenogenomic profiling of primary high-risk human breast specimens using single-cell RNA-sequencing multiplexed with lipid-tagged indices (MULTI-seq). This dataset is currently representative of 15 patients across risk groups (BRCA1, BRCA2, non-carrier control). All samples were age and reproductive phase matched using histology based staging and clinical data. Immunohistochemistry, imaging flow cytometry, and colony forming assays were used to validate and mechanistically explore observations from the MULTI-seq dataset.

Results: Visualization of the MULTI-seq dataset revealed robust heterogeneity across risk groups, with a substantial reduction in a novel luminal progenitor (LP) population in BRCA1/2 carriers compared to non-carriers. This cell population is exclusively marked by a metabolic protein known to be regulate fatty acid metabolism. Trajectory inference positions this novel progenitor as the root of aberrant epithelial differentiation in BRCA1/2 mutations carriers. Concomitant alterations in fatty acid metabolism were identified within these cells through flux estimation analysis, suggesting metabolic dysregulation of this progenitor population.

Conclusions: We have identified a novel LP population that may serve as the root of aberrant differentiation within the breast epithelial hierarchy of high-risk BRCA1/2 mutation carriers. Dysregulated metabolism in BRCA1/2 mutation carriers may drive this phenotype leading to a cell state unique to the high-risk breast.