#383 BIOENDOCAR: IDENTIFYING CANDIDATE BIOMARKERS FOR DIAGNOSIS AND PROGNOSIS OF ENDOMETRIAL CARCINOMA USING MACHINE LEARNING AND ARTIFICIAL INTELLIGENCE

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Abstracts

Introduction/Background Endometrial carcinoma (EC) is the most common gynaecological malignancy in the developed world. Currently, no valid non-invasive diagnostic or prognostic methods exist, making diagnosis and treatment rely on histopathological and surgical findings. The clinical study 'Biomarkers for Diagnosis and Prognosis of Endometrial Carcinoma' (BioEndoCar; NCT03533589) addresses this issue.

Methodology A prospective observational case-control study was conducted at six medical centres across Europe. Plasma samples from women with diagnosed EC and controls were examined using non-targeted/targeted metabolicomic and semi-quantitative immune-based proteomic approaches. The blood metabolomics (>850 metabolites) and proteomics (>900 proteins) data together with clinical and epidemiological data, were analysed using advanced artificial intelligence (AI) and machine learning (ML) methods to develop new diagnostic/prognostic models for early EC diagnosis and identifying patients with low/high risk for cancer progression and recurrence.

Results BioEndoCar has recruited more than 440 patients, with strict standard operating procedures for sample collection, processing, and storage. The diagnostic/prognostic models based on all data developed using AI/ML methods showed promising characteristics with a repeated k-fold cross-validation AUC > 0.8. The developed models will undergo further validation using both statistical (AI/ML) approaches to confirm which subset of proteomic and metabolomic data could serve as diagnostic and prognostic biomarkers in endometrial cancer.

Conclusion The BioEndoCar study has completed the initial phase of identifying and validating diagnostic/prognostic models for early EC diagnosis and identifying patients with low/high risk for cancer progression and recurrence using artificial intelligence and machine learning methods. If validated, the models including a subset of proteomic and metabolomic data could serve as a foundation for developing valuable non-invasive tools for the diagnosis and prognosis of EC.

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#432 SPECTRUM OF BRCA1, BRCA2, PALB2, ATM AND TP53 PATHOGENIC VARIANTS IN BREAST AND OVARIAN CANCER PATIENTS OF TATAR AND BASHKIR ETHNIC ORIGIN

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Introduction/Background Tatarstan and Bashkortostan are large republics located nearby Volga river. Although they joined Russia about five hundred years ago, they managed to preserve national authenticity over centuries.

Methodology The study included 132 ovarian cancer (OC) patients and 277 women with breast cancer (BC), who reside in Tatarstan or Bashkortostan and identify themselves as ethnic Tatars or Bashkirs. In order to enrich the analyzed groups by carriers of cancer-predisposing pathogenic variants (PVs), OC were selected on the basis of high-grade serous histology, and BC were represented mainly by early-onset and/or family-historical positive and/or bilateral and/or receptor triple-negative cases. Coding sequences and 5‘- and 3‘-UTRs of BRCA1, BRCA2, PALB2, ATM and TP53 genes were analyzed by next generation sequencing.

Results The frequency of BRCA1/2 mutations was 25/132 (19%) in OC and 43/277 (16%) in BC. BRCA1 PVs accounted for 47/68 (69%) cases with mutation. A significant share of BRCA1 PVs detected in ethnic Tatars and Bashkirs was represented by Slavic founder alleles (c.5266dupC (5382insC): n = 14; C61G: n = 4; c.3700_3704delIGTAA: n = 3; c.4034delA: n = 2; c.3756_3759del: n = 1). Seven patients carried BRCA1 c.5161C>T [Q1721X] allele, which is an ethnic-specific mutation characteristic for this region. There were two recurrent BRCA2 PVs, c.-39-L_39delGA (n = 6) and c.468dupT (n = 4). One patient carried PV in PALB2 (c.221delA). No instances of ATM or TP53 heterozygosity were observed.

Conclusion Despite well-preserved national identity of Tatars and Bashkirs, Slavic BRCA1 founder PVs are common among patients from these ethnic groups. In addition, one BRCA1 and two BRCA2 ethnicity-specific PVs were identified in this study. Recurrent BRCA2 c.-39-L_39delGA allele deserves particular attention, because it is located not in coding but in regulatory region of the gene.

Disclosures The study has been supported by the Russian Science Foundation [grant number 21–75–30015].

#502 ADDITIONAL INHIBITION OF PHOSPHOR-S6 KINASE IMPROVES THE THERAPEUTIC EFFECT OF CARBOPLATIN IN OVARIAN CANCER

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Introduction/Background S6 kinase is a protein kinase that is involved in signal transduction. S6 kinase is thought to play an important role in the compensatory adaptive response of various cancers against anti-cancer drug. We examined whether various
inhibition of phospho-S6 can increase the treatment effect of carboplatin in ovarian cancer.

**Methodology** We used a western blot analysis to pS6 expression after carboplatin treatment and addition of BX795 which is pS6 inhibitor on ovarian cancer cells. We used a cell viability assay to examine whether addition of BX795 to carboplatin can increase the therapeutic effect of carboplatin on ovarian cancer cells. C57BL/6 mice were injected intraperitoneally with ID8 mouse ovarian cancer cells. Thirty days after the injection of ID8 cells, mice were treated with PBS (control group), carboplatin, BX795, and carboplatin + BX795. All of these drugs were subcutaneously injected into the nuchal region of the mice. For each mouse, body weight, waist length, and ascites amount were measured.

**Results** Carboplatin induced the upregulation of pS6 in ovarian cancer cells. BX795 as inhibitor induced the downregulation of pS6 with concentration-dependent pattern on cancer cells. Combination of carboplatin and BX795 induced stronger inhibition of pS6 in ovarian cancer cells compared with carboplatin only. Compared to carboplatin only, additional treatment of BX795 to carboplatin brought the bigger decrease of viability on ovarian cancer cells. However, there was no significant difference between PBL, carboplatin, BX795, and carboplatin + BX795 treatment groups on mean body weight, mean waist length, and mean ascites amount at the sacrifice day.

**Conclusion** Addition inhibition of pS6 by BX795 increased the therapeutic efficacy of carboplatin on ovarian cancer cells. However, increase of therapeutic effect of carboplatin was not shown on mouse model.

**Disclosures** There was no funding for this research. The Authors declare no conflicts of interest.

### #535

**DIAGNOSTIC ACCURACY OF HUMAN AND HUMAN PAPILLOMAVIRUS DNA METHYLATION TESTING IN CERVICAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS**

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Abstracts

Introduction/Background Cervical cancer is the fourth most common malignancy in women worldwide. Current cervical screening programmes use a primary screening test of high-risk HPV (hr-HPV) testing or cytology to identify at-risk women. hrHPV testing has a high sensitivity but low specificity for high-grade CIN and Cancer. As a result, DNA methylation testing has been suggested as a triage test for hrHPV positive women. As yet, there is no consensus on the most accurate methylation markers for use in screening. We conducted a systematic review and meta-analysis to determine the diagnostic test accuracy of human and HPV DNA methylation markers.

**Methodology** MEDLINE, EMBASE, and ongoing trial registries were systematically searched from inception to February 2023. DNA methylation diagnostic test accuracy studies using histopathology as a reference standard were included. Sensitivity and specificity data were extracted: a bivariate random-effects model was applied to calculate pooled estimates and corresponding heterogeneity, which was explored in a series of sensitivity analyses.

**Results** Twenty-eight studies including 6,956 women were meta-analysed, producing pooled estimates for genes C13orf18, EBP41L3, FAM19A4, HPV16: L1, JAM3, PAX1, SOX1, and ZNF582. PAX1 was the most accurate marker of CIN2+ with a pooled area under the curve (AUC) of 0.93 (95% confidence interval (CI) 0.90–0.95) and pooled AUC of 0.87 (95%CI 0.84–0.90) for CIN3+. HPV16: L1 was the second best marker of CIN2+; pooled AUC 0.83 (95%CI 0.80–0.86). JAM3 was the most accurate marker of CIN3+; pooled AUC 0.88 (95%CI 0.85–0.91).

**Conclusion** PAX1 methylation testing appears to be the most accurate methylation marker for high-risk CIN and Cancer. Specificity may surpass cytology allowing the potential to triage patients more effectively to colposcopy or conservative management. Our analysis has also elucidated several other genes which show promise for use in methylation marker panels, combined panels may provide greater accuracy than stand-alone methylation markers.

**Disclosures** No disclosures

#### #597

**POSSIBLE EPIGENETIC CHANGES THAT COULD DRIVE PLATINUM RESISTANCE IN HIGH GRADE SEROUS OVARIAN CARCINOMA: DATA FROM AN IN-VITRO TREATMENT MODEL**

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Abstracts

**Introduction/Background** The prognosis and therapeutic options for patients with platinum-resistant ovarian High Grade Serous Carcinoma (HGSC) remain poor. BtiRoc-1 data already indicate that genomic alterations alone cannot explain acquired platinum resistance in many cases. Thus, epigenetic changes may play a key role.

**Methodology** We utilised both established cell lines and primary cell cultures derived from the ascites of HGSC patients. Following cell characterisation (p53, PAX8 immunohistochemistry), cells were then pulsed with four cycles of carboplatin (50 μM, 6 hours exposure) with a week of recovery between each cycle. Transcriptomic (RNAseq) and chromatin accessibility (ATACseq) assays were performed. Cells were also imaged using STORM (Stochastic Optical Reconstruction Microscopy) and underwent methylation assay (850k by Illumina).

**Results** All data from primary cell cultures were compared with data from platinum-resistant established cell lines (OvCar4 and IVR01). The highest number of enriched genes seems to occur after the first cycle, with a lower number of progressively enriched genes across all other ones. Both established cell lines and primary cell cultures up-regulate the inflammatory and stress response after the earliest cycles. Cell locomotion and migration processes were largely upregulated across all different primary cell cultures, suggesting cancer’s progression-related processes. Those biological processes were not upregulated in the established cell lines. Chromatin’s arrangement pathways were enriched at latest cycles in primary cell cultures. ATACseq showed an increased accessibility in the AP1 Transcription Factor Family (AP1-TF) across all the relevant pathways.