



Abstract 2022-RA-1697-ESGO Figure 1

**Conclusion** Low ALI was associated with higher perioperative complications and poorer survival in ovarian cancer. The utility of preoperative ALI as a prognostic marker in ovarian cancer should be assessed in prospective studies.

#### 2022-RA-1709-ESGO A PREDICTIVE MODEL FOR DETECTION OF EPITHELIAL OVARIAN CANCER BASED ON METHYLATION LANDSCAPE

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**Introduction/Background** More than 75% of individuals with ovarian cancer (OC) are diagnosed at an advanced stage, given that early-stage disease is usually asymptomatic. Epigenetics studies are emerging in cancer research and diagnostics with encouraging outcomes. Recent developments in large-scale DNA methylation profiling have shown that those changes are at the very early stage of carcinogenesis, indicating that the detection of such markers would drastically increase patient outcome. In OC, that would potentially represent early detection for the majority of patients. Here, we (1) investigated a large-scale methylation landscape of OC, (2) devised a predictive model based on the discovered targets, and (3) sought to validate its performance on independent external cohorts.

**Methodology** Fresh-frozen tissues were collected from 29 OC patients and 14 benign pelvic mass patients. Samples were submitted to global DNA methylation profiling, comprised of ~850,000 targets. For the design of the predictive model we performed: (1) univariate linear model; (2) LASSO-penalized multivariate analysis; (3) cross-validation; and (4) group assignment by centroid approach followed by principal component analysis (PCA). The predictive model was trained with our own samples and validated in 2 external cohorts.

**Results** We identified 21 targets that showed a clear distinction for the OC patient group, with clustering analysis showing two independent groups. Furthermore, the two main components explained 66% of the variance shown by PCA. The validation of our model in 2 independent cohorts showed classification concordance of 81.1% and 85.2%, respectively.

**Conclusion** Our current findings showed that OC presents an unique methylation landscape represented by a signature of 21

targets. Our predictive model algorithm showed considerable concordance with external cohorts. Noteworthy, due to the relatively small cohort used to train our model, we are currently collecting more samples to further improve its prediction efficiency, which may be relevant in diagnostic settings.

## Trophoblastic diseases

#### 2022-RA-701-ESGO ELUCIDATING MECHANISMS UNDERLYING METHOTREXATE RESISTANCE VIA QUANTITATIVE PROTEOMICS ANALYSIS OF GTN PATIENT SAMPLES AND CHORIOCARCINOMA CELL LINES: A CRUCIAL ROLE FOR SERINE METABOLISM

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**Introduction/Background** Choriocarcinoma is an aggressive type of Gestational Trophoblastic Neoplasia (GTN). Patients with low-risk GTN following a molar pregnancy frequently commence therapy with single-agent methotrexate (MTX). Unfortunately, many develop resistance (MTX-R) and require either another single agent or more toxic combination agent chemotherapy to achieve remission. Understanding the molecular mechanisms of MTX-R may identify interventions to prevent or reverse this.

**Methodology** We employed proteomics profiling to identify changes that accompany MTX-R in post molar GTN patient samples and in choriocarcinoma cell lines that were either MTX sensitive (MTX-S) or resistant (MTX-R).

**Results** Quantitative mass spectrometry (MS) analysis revealed that the de novo serine synthesis pathway was one of the most downregulated pathways both in the MTX-R patients and in the resistant choriocarcinoma cell line. Decreased glucose-derived serine synthesis is supported by our findings that choriocarcinoma MTX-R cells have a less active glycolytic pathway. Concomitant de novo serine synthesis inhibition and serine deprivation from the growth medium promoted MTX-R in cell lines. Moreover, examination of the expression levels of 1-Carbon metabolism enzymes suggested a different utilization of serine, the major 1-Carbon donor, between sensitive and resistant cells. In particular, MTX-R cells may be channeling serine into pathways crucial for cell survival, such as the synthesis of glutathione (GSH), as indicated by the increased levels of this metabolite in resistant cells.

**Conclusion** Upon MTX-R, choriocarcinoma cells favor redirection of serine to GSH production and this may help with combating chemotherapy-induced reactive oxygen species (ROS) accumulation and hence participate in the resistant phenotype. In contrast, MTX-sensitive cells utilize serine for nucleotide synthesis and the maintenance of proliferation. Hence, targeting upstream pathways or molecules that block the synthesis of serine in combination with or without MTX treatment could improve therapeutic response in patients with MTX resistance.