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Title: Development of a multi-omics diagnostic approach for the early detection of ovarian cancer in asymptomatic women

Objectives:
Ovarian cancer (OC) is the fifth leading cause of cancer-related deaths among women. Unfortunately, for most patients, detection of OC occurs at late stages (III/IV) when the five-year survival rate is <30%. To change this paradigm, screening methods must be developed that are minimally invasive, highly sensitive, and disease specific. We have determined that utilizing multi-omics, which include novel classes of lipid and protein biomarkers with machine-learning, enables the robust detection of ovarian cancer across stages and subtypes, while requiring <500µL of serum.

Methods:
We utilized a multi-omics approach to characterize a clinically annotated cohort comprising serum samples from individuals with ovarian cancer (N=235) and normal donors (N=82). The cohort was obtained from the University of Colorado Gynecologic Tissue and Fluid Bank (IRB #07-935 and 21-4787) and commercial vendors. UHPLC-MS data were generated from 20µL of extracted serum to profile lipids and fatty acids, while manual immunoassays were performed for a panel of protein biomarkers using unextracted serum. Machine learning (ML) model training was performed using the biomarker classes separately and in combination to identify top-performing models, using 20-fold cross validation.

Results:
We profiled a total of 611 features of the lipidome by UHPLC-MS and protein biomarkers by immunoassay. The main molecular drivers contributing to best performing initial OC-specific signatures included a combination of lipids, fatty acids, and proteins together: multi-omic model consistently exhibited highest AUC when compared to individual biomarker classes. The AUC for High Grade Serous OC (HGSOC) was 0.98. At 98.2% specificity, sensitivity was 93.1% for all stages and subtypes of OC (93.8% sensitivity for all subtypes of early-stage (I/II) OC). The sensitivity for early stage HGSOC was 92.6%.

Conclusions:
Early detection of OC is critical to improve patient outcomes, but current screening tools for OC lack early-stage sensitivity and specificity. The application of a multi-omics, machine learning approach for the screening of post-menopausal asymptomatic women offers significantly improved

performance over CA125 for the detection of early-stage HGSOC. Future research will validate the performance of this approach in a large prospective cohort.