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Serum Lipidomics Distinguishes Benign from Malignant Gynecologic Disease, Extending a Novel Biomarker Pipeline to New Indications

Rachel Culp-Hill[1], Charles M. Nichols[1], Moisés Zapata[1], Enkhtuya Radnaa[1], Maria Wong[1], Mattie Goldberg[1], Emily Chang[1], Kim Ekroos[2], Vuna S. Fa[1], Abigail McElhinny[1]

[1]AOA Dx, Denver, CO; [2]Lipidomics Consulting Ltd., Espoo, Finland

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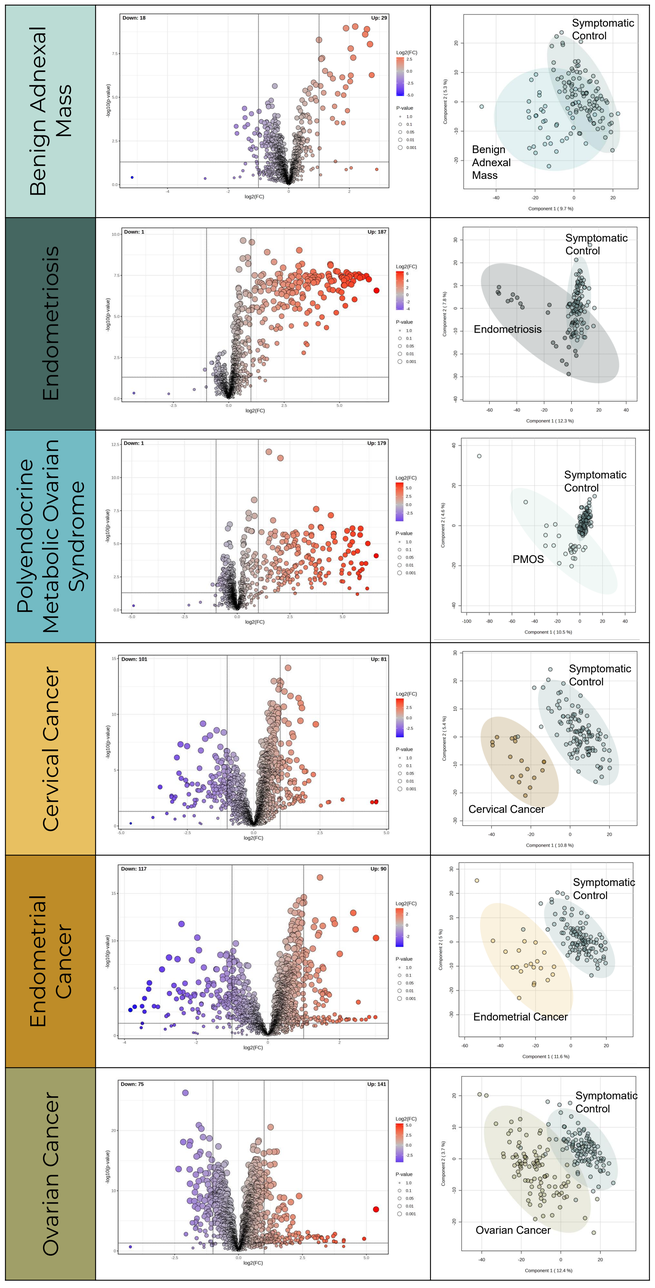
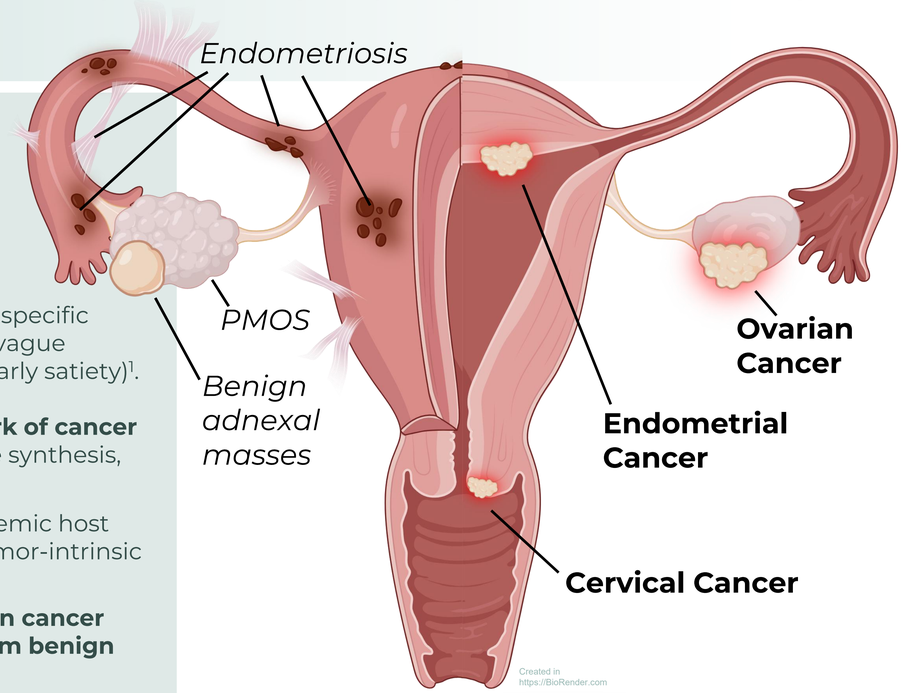


Figure 2 (above): Lipidomic profiling across benign and malignant gynecologic conditions. Volcano plots (left) show differentially abundant lipids (log2FC vs. −log10 p) for each condition vs. symptomatic controls; PLS-DA scores plots (right) show corresponding group separation. Benign adnexal mass: 18 lipids significantly decreased, 29 increased, with modest separation from controls. Endometriosis: 1 decreased, 187 increased, with partial overlap but clear separation. PMOS: 1 decreased, 179 increased, with clear separation. Cervical cancer: 101 decreased, 81 increased, with complete separation. Endometrial cancer: 117 decreased, 90 increased, with complete separation. Uterine cancer: 97 decreased, 104 increased, with complete separation. Ovarian cancer: 75 decreased, 141 increased, with slight overlap.

BACKGROUND

- Distinguishing benign from malignant gynecologic conditions is a major unmet clinical need: endometriosis, polyendocrine metabolic ovarian syndrome (PMOS), and benign adnexal masses share nonspecific symptoms with gynecologic cancers (vague abdominal and pelvic pain, bloating, early satiety)[1].
- **Altered lipid metabolism is a hallmark of cancer biology**, supporting tumor membrane synthesis, energy production, and signaling[2-4].
- Circulating lipid changes reflect a systemic host response to tumor growth, not just tumor-intrinsic reprogramming[5].
- We have previously shown that **ovarian cancer shows a distinct lipidomic profile from benign conditions**[6,7].
- We have built a **pipeline to downselect discovery-phase lipid biomarkers** into a targeted, clinically deployable assay, with the capacity to expand beyond ovarian cancer.
- Goal: apply discovery-based lipidomic profiling across a broad panel of benign and malignant gynecologic conditions to identify lipid biomarker candidates, the first step in expanding the application of the downselection pipeline to new cancer types.



Discovery-based lipidomics reveals candidate biomarkers that distinguish malignant from benign gynecologic conditions, the first step in extending our OC-proven pipeline to new indications.

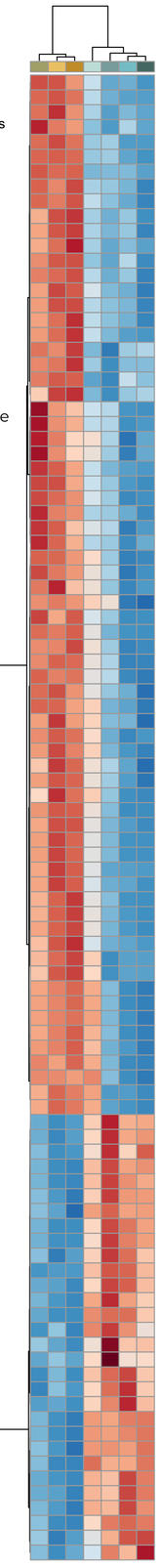
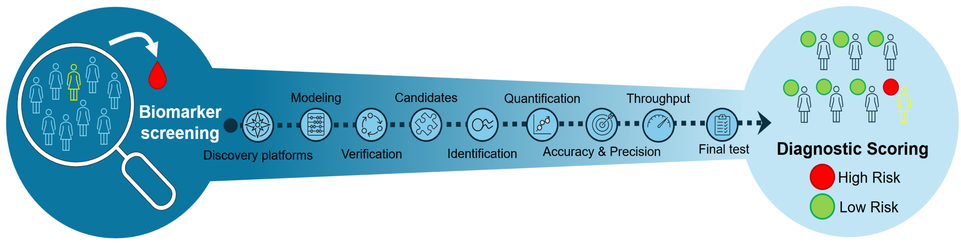


Figure 3 (right): Hierarchical clustering of lipid features across gynecologic conditions. Heatmap of the top 100 features by ANOVA of row-wise z-scored lipid abundance across all sample classes, with hierarchical clustering (Euclidean distance, Ward's method) applied to samples and lipids. Rows are annotated by lipid class. Red = increased, blue = decreased abundance.

Figure 1 (below) : End-to-end biomarker development pipeline. Blood samples from patient cohorts are analyzed using discovery lipidomic platforms, generating candidate lipid features. Each candidate advances through sequential stages: computational modeling and verification narrow the pool to high-confidence candidates; structural identification confirms lipid identity; quantification establishes accuracy and precision; and a high-throughput test format enables clinical deployment. This staged process moves discovery-phase features to a novel biomarker panel with confirmed identifications suitable for diagnostic risk scoring (high vs. low risk).



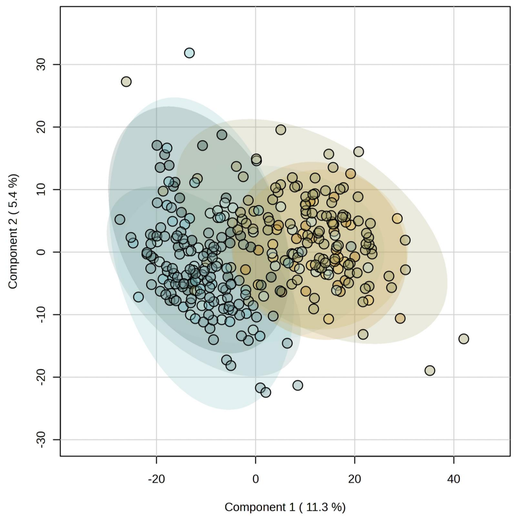
METHODS

1. **Sample Collection**
   Serum specimens were prospectively collected and supplemented with samples from commercial vendors to build a cohort enriched for early-stage disease
2. **Sample Preparation + Data Acquisition**
   Samples are processed using a methanol extraction. Data is acquired by LC-HRMS (Thermo Vanquish + Exploris 240) with data-dependent acquisition (DDA).
3. **Feature Extraction, Annotation, Analysis**
   Compound Discoverer software (Thermo Scientific) and MetaboAnalyst

BENIGN CONTROL GROUPS	N
Symptomatic controls Symp. individuals with confirmed absence of malignancy	114
Benign adnexal masses	37
Endometriosis	33
Polyendocrine Metabolic Ovarian Syndrome	29

GYNECOLOGIC CANCERS	N
Ovarian Cancer	106 (66 early, 40 late)
Endometrial Cancer	23 (early-stage only)
Cervical Cancer	20 (early-stage only)

Figure 4 (below): Aggregate lipidomic separation of all benign and all malignant gynecologic conditions. PLS-DA scores plot pooling all benign conditions (blue) and cancer conditions (yellow). Partial separation is observed, suggesting lipid biomarkers have the potential to distinguish benign from malignant gynecologic conditions.



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