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

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AACR ANNUAL MEETING 2025 CHICAGO

## Key Takeaways

- Ovarian cancer (OC) is often diagnosed at late stages, and current screening methods have not reduced mortality.
- Lipids can be used as novel biomarkers to enable detection of early-stage disease. We have determined that combining lipids with protein biomarkers is a powerful diagnostic approach.
- We are evaluating a serum-based blood test to detect OC earlier in the asymptomatic population. This novel machine learning (ML)-based multi-omic model achieves high AUCs in early-stage OC.
- ML + multi-omics shows improved performance over current methods, allowing for earlier cancer detection and improving patient outcomes

## Current OC screening does not significantly impact mortality

**Most cases are diagnosed at late stage:** >70% of patients are diagnosed with late-stage ovarian cancer (OC), with a 5-year survival between 10-30%[1]

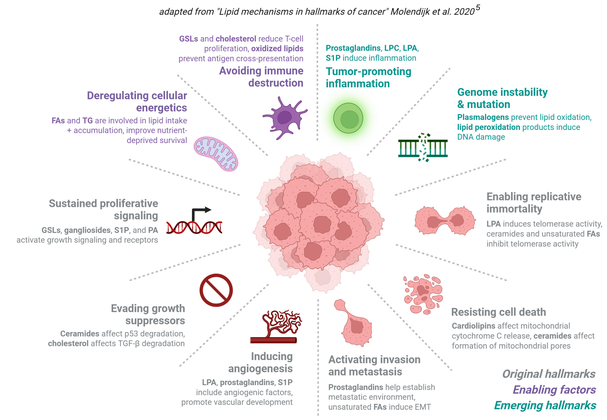
**No mortality benefit:** Large trials show that CA125 with transvaginal ultrasound, the current standard of care for OC screening, does not significantly reduce deaths.[2, 3, 4]

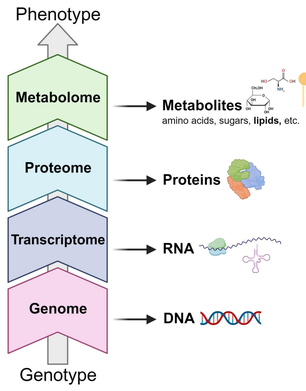
**Risks of screening:** High false-positive rates lead to unnecessary surgeries with a 15% complication rate.

**New approaches are needed:** Current screening methods fail to significantly reduce deaths. Future efforts must focus on more effective screening strategies.

## Altered lipid metabolism is a known cancer hallmark

*adapted from "Lipid mechanisms in hallmarks of cancer" Molendijk et al. 2020[5]*



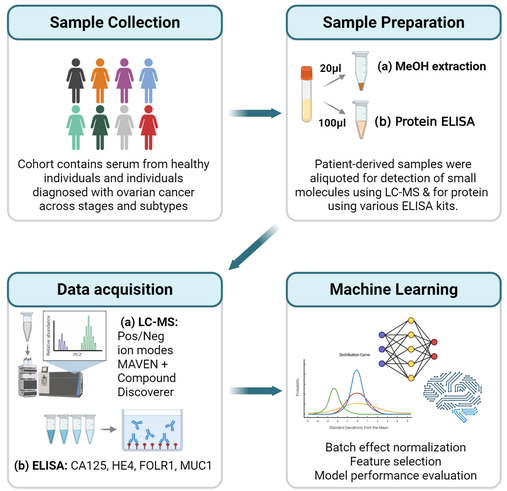




Metabolomics, including lipidomics, closely reflects phenotype, capturing real-time physiological changes.

MS-based lipidomics **enables detection of subtle metabolic shifts**, offering a powerful tool for <u>early</u> cancer detection.

Lipid biomarkers can improve diagnostic accuracy and complement existing methods.

## LC-MS for lipidomics + ELISA-based protein panel + Machine Learning

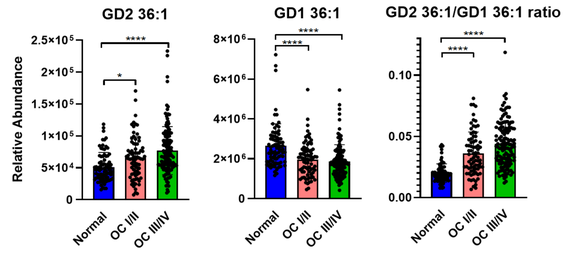



## Cohort Design

We conducted a blinded multi-omics analysis of a clinically annotated cohort. Serum samples were obtained from the University of Colorado Gynecologic Tissue and Fluid Bank + commercial vendors.

| Diagnosis | Group | Cohort |
|---|---|---|
| Cancer | All OC | 218 |
| | Early-stage OC | 82 |
| | Late-stage OC | 136 |
| | Borderline | 25 |
| Non-Cancer | Normal | 82 |
| **Grand Totals** | | **325** |

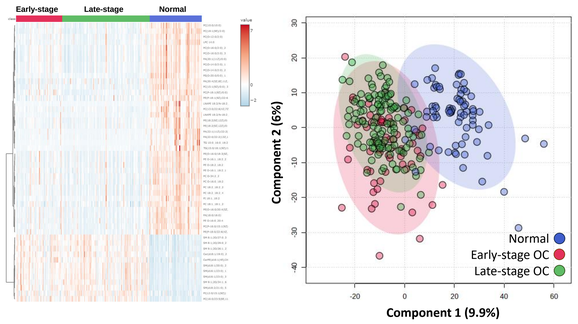
## Gangliosides are altered in ovarian cancer serum




LC-MS analysis shows **gangliosides** (glycosphingolipids) **are significantly altered in both early- and late-stage OC** when compared to normal serum.

Interestingly, the ratio of GD2 36:1 to GD1 36:1 showed <u>increased signal</u> compared to those species alone.

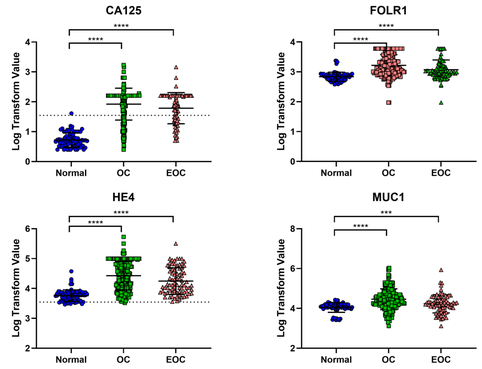
## OC serum shows distinct lipidomic profile compared to normal




As shown in the heatmap (left) there are a wide range of significantly altered lipid classes and individual species in both early- and late-stage OC.

PLSDA comparing normal v. early- and late-stage OC (right) shows **clear lipid profile differences**.

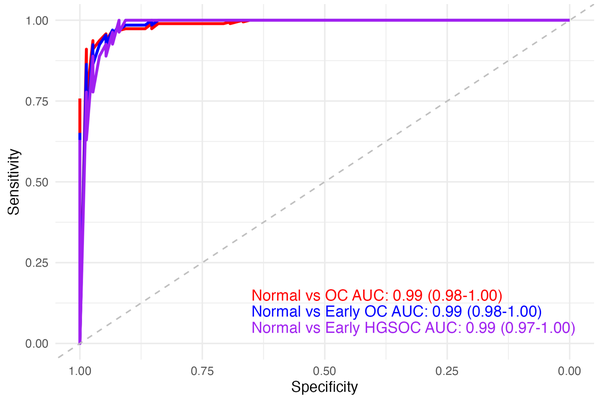
## Protein biomarkers differ in OC but lack early-stage diagnostic power




Levels of **CA125** and **HE4** (currently used in the clinic) as well as **FOLR1** and **MUC1** (promising diagnostic targets) were **elevated in OC and early-stage OC** when compared to normal.

Despite increased levels, wide ranges and modest differences highlight the challenges and limitations of using any of these proteins as stand-alone biomarkers.

## Multi-omic modeling distinguishes OC & early-stage OC




| Group Comparison | Sensitivity | Specificity |
|---|---|---|
| Normal v. all OC stages | 93.1% | 98.2% |
| Normal v. Early-stage OC | 93.8% | 98.2% |
| Normal v. Early-stage HGSOC | 92.6% | 98.2% |

The main molecular drivers contributing to the best performing OC specific signatures included a combination of lipids, fatty acids, and proteins together.

A **multi-omic model consistently exhibited highest AUC** when compared to individual biomarker classes.

**References**

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