

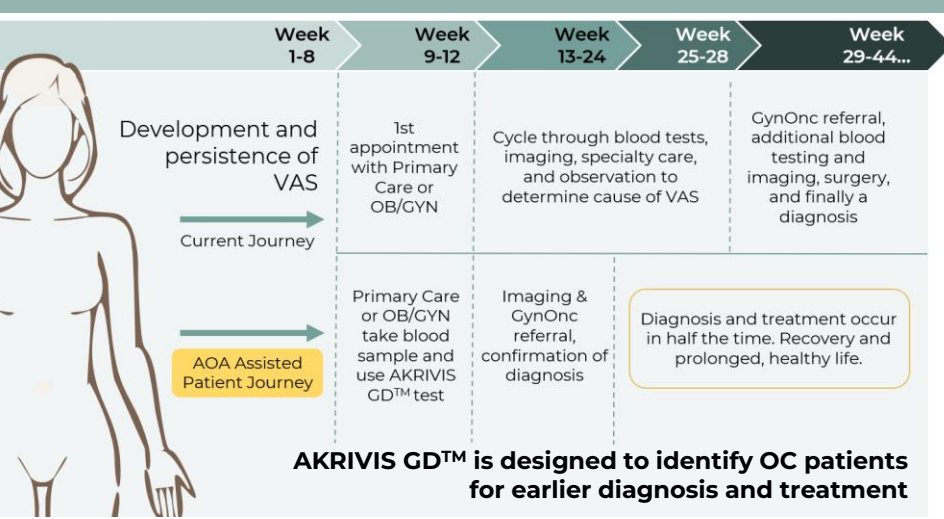
A Novel Serum-Based Multi-Omic Machine Learning Model Improves Early Detection of Ovarian Cancer in the Symptomatic Population

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Background and Rationale

- 80% of OC is diagnosed at late stage, with 5-year survival <30%
- Prevalence of OC is 88-fold higher in women with signs and symptoms (VAS) as compared to asymptomatic women
- Current diagnostic tools lack sufficient sensitivity and specificity for early-stage OC detection
- Binary classification is limited: benign masses drive false positives, reduce specificity
- Ordinal modeling preserves disease-state information during training, improving cancer vs. non-cancer separation across the full disease continuum

Patient Journey to OC diagnosis



Patient Samples & Study Objective

Serum samples were collected from symptomatic women across multiple prospective clinical studies and biobanks in the US and UK, supplemented with commercial vendor samples, to reflect the intended-use population. The study population reflects the real-world clinical landscape a diagnostic test would encounter, spanning five groups:

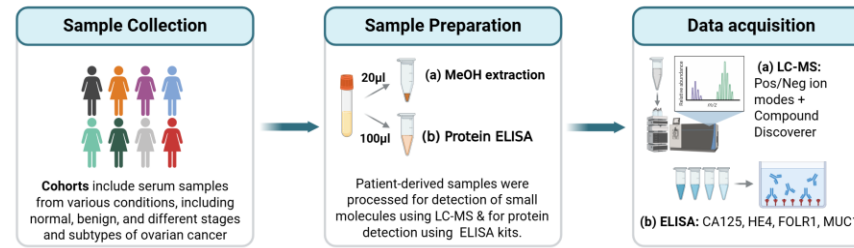
Group	Description
Assumed Healthy	No known malignancy; no OC-aligned symptoms
Symptomatic Normal	Sought care for symptoms; no malignancy identified
Benign Gynecological Conditions	Confirmed non-malignant diagnoses including benign masses, cysts, and growths
Borderline Ovarian Tumors	Non-invasive epithelial neoplasms with intermediate behavior between benign cysts and malignant OC
Ovarian Cancer (Stage I-IV)	Epithelial (serous, mucinous, endometrioid, clear cell, mixed) and non-epithelial subtypes

Symptomatic patients represent the majority of this population.

Objective:

Develop a test with high sensitivity to **rule out** OC in women with signs and symptoms.

Study Design & Methods



Ordinal Histologic Category	N
1. Assumed Healthy	353
2. Symptomatic Normal	191
3. Benign Gynecological Conditions	313
4. Borderline Tumors	48
Ovarian Cancer (Stages I-IV)	384
5. Ovarian Cancer — Stage I	114
6. Ovarian Cancer — Stage II	46
7. Ovarian Cancer — Stage III	182
8. Ovarian Cancer — Stage IV	42
Grand Total	1289

Analytical Pipeline

Serum → Lipids + Proteins → Feature Selection → Ordinal Model → Risk Score (0-100)

Bootstrap + Monte-Carlo CV (n=2,000)

Feature Selection

34 features selected as strongly statistically and biologically associated with OC (p < 0.00001 per feature).

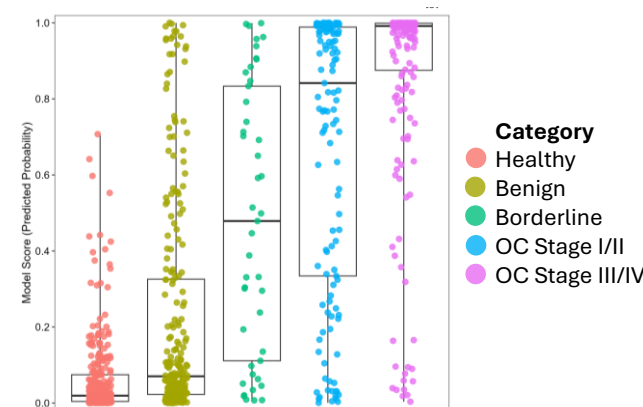
Why Ordinal Modeling?

Conventional binary models collapse all disease stages into cancer vs. non-cancer, discarding biological gradation and reducing sensitivity for early-stage disease.

Ordinal logistic regression preserves the disease continuum:
Benign → Borderline → Early OC (I/II) → Late OC (III/IV)

This approach captures progressive lipid changes across disease stages. The heatmap (center column) demonstrates systematic shifts in lipid classes from benign to late-stage OC, validating the biological rationale for ordinal modeling.

Results: Binary Modeling Approach



0.911
AUC
(95% CI: 0.91-0.95)

87.2%
Sensitivity
(95% CI: 83.1%-90.7%)

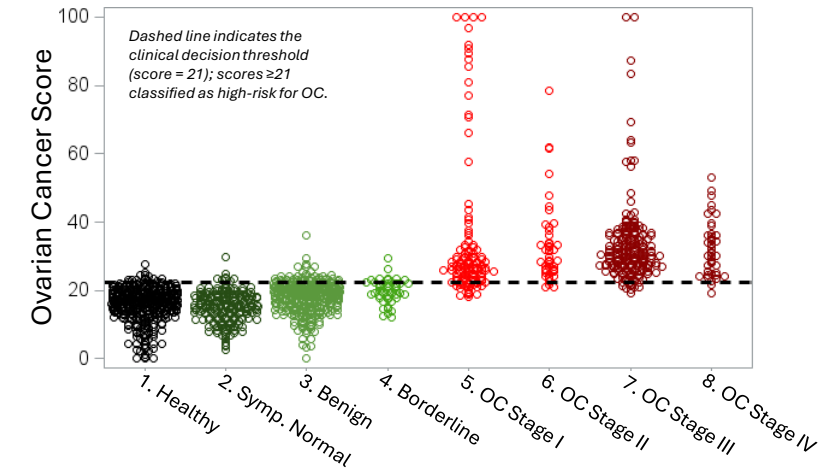
80%
Specificity
(95% CI: 76.5%-83.2%)

Results: Ordinal Modeling Approach

0.960 AUC **91.7%** Sensitivity **91.3%** Specificity

Bootstrap 95% CI: AUC 0.948-0.972
Sensitivity 88.4-94.2%
Specificity 89.2-93.0%

Ovarian Cancer Risk Score Across Clinical Groups



Group	Specificity	Lower 95%	Upper 95%
Assumed Healthy	95.2%	92.4%	97.2%
Symptomatic Normal	95.8%	91.9%	98.2%
Benign Gynecological Conditions	85.6%	81.2%	89.3%
Borderline	81.3%	67.4%	91.1%
Negatives	91.3%	89.2%	93.0%

Group	Sensitivity	Lower 95%	Upper 95%
OC Stage I	83.3%	75.2%	89.7%
OC Stage II	93.5%	82.1%	98.6%
OC Stage III	95.6%	91.5%	98.1%
OC Stage IV	95.2%	83.8%	99.4%
Positives	91.7%	88.4%	94.2%

Conclusions

- This multi-omic model demonstrates **high sensitivity for OC detection** across a complex, real-world symptomatic population spanning benign gynecological conditions, borderline tumors, and OC stages I-IV.
- Compared to our prior binary classification approach, **ordinal modeling improves specificity while preserving sensitivity** by retaining disease-state information during training, enabling better separation between cancer and non-cancer without collapsing the biological continuum.
- These results represent a **proof of concept** that ordinal modeling yields a more clinically deployable diagnostic — with a continuous risk score that remains interpretable as a binary high/low risk output.
- Current development is focused on analytical validation of key features for performance in a clinical diagnostic assay.

Disclosures: Authors are employees or affiliates of AOA Dx. Research ongoing.