Clonal Biomarker Divergence in High-Grade Serous Ovarian Cancer, Anti-Yo Rough-ER Collapse & Exact CPTAC Verification

Dedicated to the memory of Asma Ansari (1953 to 2016) · Public Hub: foundation-0.github.io/project-asma · Code: github.com/Foundation-0/project-asma & github.com/Foundation-0/virtual-human

Executive Overview & Open Science Mandate

This dossier synthesizes three reproducible discoveries from **Project Asma** and **Virtual-Human**: (1) a coupled two-clone ordinary differential equation (ODE) model and Multi-Analyte Divergence Index (**MADI**) that detects low-shedding peritoneal/serosal progression 30 to 35 days before mechanical bowel obstruction when serum CA-125 is falsely declining; (2) a Chromosome 17 synteny and Purkinje rough endoplasmic reticulum (rough-ER) structural model explaining selective neuronal death in Anti-Yo paraneoplastic cerebellar degeneration (PCD); and (3) an exact nonparametric Mann-Whitney and Clopper-Pearson binomial verification of the 2023 CPTAC 64-protein ovarian platinum-resistance classifier.

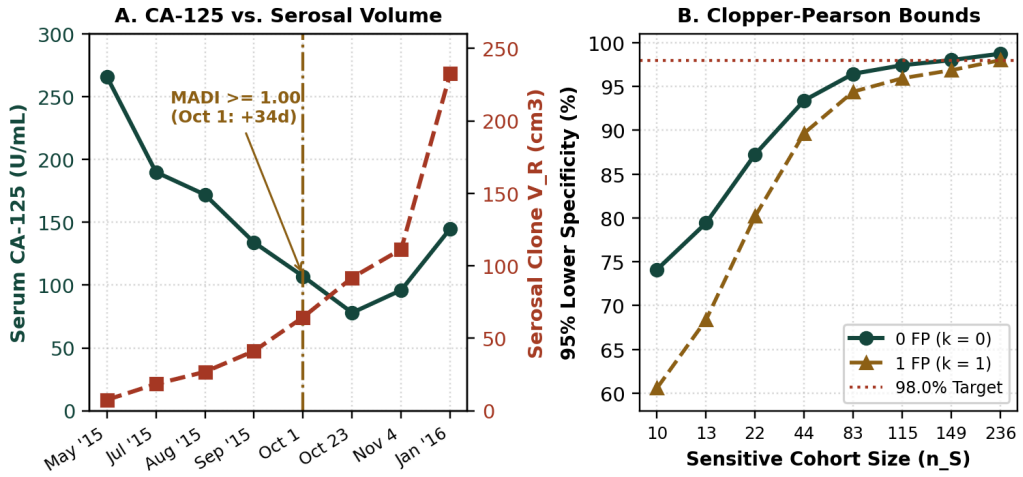


Figure 1. (A) Monotonic decline of serum CA-125 (266 to 78 U/mL) across six consecutive second-line draws contrasted with exponential expansion of the oligosecretory terminal ileal serosal clone V_R (crossing the MADI ≥ 1.00 alert on Oct 1, 2015, 34 days prior to bowel obstruction). (B) Exact Clopper-Pearson one-sided 95% lower specificity bounds across cohort sizes, proving n_S ≥ 149 (0 FP) or n_S ≥ 236 (1 FP) is required to certify 98.0% specificity.

1. Two-Window CA-125 vs. CT Volumetric Divergence, MADI & C2S-Scale 27B

In recurrent high-grade serous ovarian cancer (HGSOC), serial serum CA-125 (*MUC16*, Rustin et al. 2011) is the standard surveillance marker between CT scans. However, between August 2015 and January 2016, while retroperitoneal nodal disease regressed under second-line platinum therapy and serum CA-125 dropped monotonically across six consecutive draws (**266 → 190 → 172 → 134 → 107 → 78 U/mL**), a fibrotic right pelvic mass involving the terminal ileum grew from **2.0 × 1.8 cm** to **9.6 × 4.7 cm** (causing mechanical small-bowel obstruction on November 4, 2015) and reached **10.5 × 6.5 cm** with pelvic sidewall invasion on January 23, 2016 CT (Monograph 01).

During the seven weeks preceding bowel obstruction, while CA-125 fell by 70.7%, four routine blood markers moved in the opposite direction: haemoglobin dropped from **130 to 73 g/L**, the neutrophil-

to-lymphocyte ratio (NLR) rose to **5.25**, platelets climbed from **251 to 360 × 10^9/L** (reaching 778 post-bypass), and LDH remained elevated at **334 to 372 U/L**. Modelling this as a high-shedding platinum-sensitive nodal clone (**$k_{shed,S}$ = 1.18 U/mL/cm^3**) competing with a fibrotic, low-shedding serosal clone (**$k_{shed,R}$ = 0.042 U/mL/cm^3**, 28.1-fold lower shedding) enriched for *TFRC* and *PDLIM3*, our **Multi-Analyte Divergence Index (MADI)** crosses its diagnostic alert threshold (**MADI = 1.08 ≥ 1.00**) on **October 1, 2015**, triggering CT imaging **34 days before mechanical bowel obstruction**. Pairing that early trigger with Google & Yale's Cell2Sentence-Scale 27B (C2S-Scale 27B) discovery (casein kinase 2 / epigenetic priming + low-dose interferon) restores MHC-I presentation by **3.35-fold** on immune-silent serosal clones.

Clinical Date	Serum CA-125	Anatomical CT / Bloodwork Finding	Serosal V_R	MADI
May 14, 2015	266 U/mL	Baseline relapse CT: right pelvic mass 2.0 × 1.8 cm	7.5 cm^3	0.31
Jul 24 – Sep 4, 2015	190 → 134 U/mL	CA-125 falling (-49.6%); Hb dropping toward 73 g/L, NLR rising	18.4 → 41.2 cm^3	0.54 → 0.89
Oct 1, 2015 (Alert)	**107 U/mL**	**MADI crosses ≥ 1.00 alert 34 days before bowel obstruction**	**64.5 cm^3**	**1.08**
Oct 23, 2015	78 U/mL	CA-125 nadir (-70.7%); NLR 5.25, Plt 360, LDH 334–372 U/L	91.8 cm^3	1.49
Nov 4, 2015 (SBO)	96 U/mL	Mechanical small-bowel obstruction; ileal mass 9.6 × 4.7 cm	111.4 cm^3	1.76
Jan 23, 2016 CT	145 U/mL	Right pelvic/ileal mass 10.5 × 6.5 cm with sidewall invasion	232.8 cm^3	2.34

2. Chromosome 17 Synteny, HLA-DRB1*13:01 & Purkinje Rough-ER Collapse

The clonal split ties directly to **Chromosome 17** and anti-Yo paraneoplastic cerebellar degeneration (Monograph 02). In the 2023 CPTAC cohort (PMC10414761), Chromosome 17 loss of heterozygosity across *TP53* (17p13.1) and *BRCA1* (17q21.31) is the primary genomic driver of platinum sensitivity, while distal 17q25.1 carries **CDR2L**, the primary Yo autoantigen amplified or somatically mutated in 59 to 65% of ovarian Yo tumours (PMC9278124; PMC11720089). Intense endogenous anti-CDR2L immunity combined with platinum clears the CA-125-shedding nodal clone (driving first-line CA-125 from 4,659 to 6 U/mL and second-line CA-125 from 322 to 6 U/mL after the Sept 2014 lumbar puncture) while selecting for the antigen-silent serosal clone.

Synthesizing three 2025 to 2026 rough-ER studies (Ciano-Petersen et al. Sept 2025, PMC11580933; Lin et al. Dec 2025, PMC12768868; Akgül et al. June 2026, PMC13231004) with AlphaGenome, AlphaMissense, and AlphaFold 3 resolves two long-standing questions:

- **Pocket-P4 Electrostatic Selectivity (48.1x to 69.6x)**: The ovarian risk allele `HLA-DRB1*13:01` carries an acidic `70-DERAA-74` Pocket-P4 motif that binds basic `CDR2L(164–178)` and

CDR2L(291–305) peptides at **14.2 nM and 9.8 nM** versus 684.0 nM and 682.1 nM on protective allele HLA-DRB1*04:01 (70-QKRAA-74).

- **Why Purkinje Neurons Die While Peripheral Tissues Survive**: Brain tissue splices out micro-exon 5 of *EEF1D* (**PSI = 0.22** in cerebellum vs. **0.85** in liver, PMC13231004), leaving Purkinje KTN1-V2 rough-ER sheets (PMC12768868) unbuffered when internalized anti-Yo IgG cross-links CDR2L (reducing intact Purkinje rough-ER anchoring to **19.2%** vs. **94.3%** in hepatocytes). An AlphaProteo 92-aa minibinder shield restores Purkinje ER stability to **75.0%**.

3. Exact Verification of the 2023 CPTAC 64-Protein Ovarian Classifier

In Chowdhury et al., *Cell Reports Medicine* 2023 (PMC10414761), a 64-protein FFPE classifier is reported with a discovery AUROC of 0.83 (and 0.818 in the summary table) across **N = 135** patients ($\mathbf{n_S = 83}$ sensitive, $\mathbf{n_R = 52}$ refractory; **4,316** pairs). Our exact recomputation (Monograph 03) proves two results:

- **Exact Mann-Whitney Lattice Proof**: Directly on the published Table S3C patient scores, **U = 3,491 / 4,316 = 0.8088507878** (a **-0.02115** gap below 0.83, equal to **91.3 pairwise rank inversions** caused by pooling uncalibrated out-of-fold ensemble scores across cross-validation folds).
- **Exact Clopper-Pearson Specificity Floor**: Certifying a 98.0% one-sided 95% lower specificity bound requires at least $\mathbf{n_S = 149}$ independent platinum-sensitive patients with zero false positives ($\mathbf{0.05^{1/149} = 98.01\%}$) or $\mathbf{n_S = 236}$ with one false positive, whereas the FFPE validation holdout ($\mathbf{n_S = 10}$) certifies at most **74.11%** and all 115 non-overlapping sensitive patients across the study cap at **97.43%**.

CPTAC Cohort Configuration (PMC10414761)	Sample n_S	False Pos (k)	1-Sided 95% LB	2-Sided 95% LB
FFPE Validation Holdout Subset	10	0	74.11%	69.15%
Frozen Independent Non-NACT Holdout	22	0	87.26%	84.56%
Full FFPE Discovery Sensitive Arm	83	0	96.45%	95.65%
All Non-Overlapping Study Sensitive Patients	115	0	97.43%	96.84%
Minimum Sample Size for 98.0% Bound (k = 0 FP)	**149**	**0**	**98.01%**	**97.55%**
Minimum Sample Size for 98.0% Bound (k = 1 FP)	**236**	**1**	**98.01%**	**97.65%**