Case Study: OVA1
The 1st proteomics IVD MIA cleared by FDA
Ovarian Cancer

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**Deadly Cancer**

The five-year survival rates for ovarian cancer have lagged behind the overall cancer survival rate:

- All cancers
- Ovarian cancer

Source: National Cancer Institute
Cancer Clues
A new test measures five proteins that increase or decrease in your blood if you have ovarian cancer:

**Apolipoprotein A1**
- Function: Cholesterol Transport
- Likely Change if You Have Cancer: DOWN

**Beta 2 microglobulin**
- The body's immune response
- Likely Change if You Have Cancer: UP

**CA125**
- Released by tumor cells
- Likely Change if You Have Cancer: UP

**Prealbumin**
- Hormone and vitamin transport
- Likely Change if You Have Cancer: DOWN

**Transferrin**
- Iron transport
- Likely Change if You Have Cancer: DOWN

Source: Vermillion Inc.
OVA1: IVDMIA

- Vermillion Inc. licensed the invention, conducted clinical trial and cleared by the FDA for clinical use on September 11, 2009 as the OVA1 test.

- This was the 1st proteomics IVDMIA (In vitro diagnostic multivariate index assays) cleared by the US FDA.
Case Study: Ovarian Cancer

- A 50 years old woman was presented at the Johns Hopkins Hospital clinic. Physical examination revealed masses in the pelvic area. An ultrasonography was performed, however, the result was not diagnostic. Her serum CA125 was 105 U/mL. What was the diagnosis?
OVA1 – Intended Use (FDA)

- The OVA1 test is a qualitative serum test that combines the results of 5 immunoassays into a single numerical score.
- It is indicated for women who meet the following criteria: over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist.
- The OVA1 test is an aid to further assess the likelihood that malignancy is present when the physician’s independent clinical and radiological evaluation does not indicate malignancy.
- The test is not intended as a screening or stand-alone diagnostic assay.
Our Strategies
Cancer biomarker discovery, validation & translation

- Select the right technologies: Protein/Lectin array and/or mass spectrometry.
- Use well characterized clinical specimens – plasma, serum, urine, body fluid, tissue, cell: Pathology.
- Develop bioinformatics tools for data analysis and multiplexing of biomarkers: Engineering.
- Design multi-center case control study with extensive clinical validation to minimize the impact of possible confounding variables: Statistics.
- Discover and identify biomarkers (profile is not sufficient) with biological (clinical) significance: Cancer Biology.
- Translation of biomarker into multiplex clinical diagnostics: Clinical Chemistry.
Title: Protein chips and bioinformatics: Essential tools for biomarker discovery.
Proteomic Approaches to Tumor Marker Discovery: Identification of Biomarkers for Ovarian Cancer.
Do you have the right specimens for biomarker discovery?

- To obtain the right specimens from the right targeted population for biomarker discovery.
- For example, if the goal is to discover biomarkers for aggressive cancer, specimens should be obtained from patients with and without aggressive cancer.
Lesson learned: Do we have the right approach for biomarker discovery and validation?

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<th>Traditional Approach</th>
<th>New Approach</th>
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<tr>
<td>Discovery Study</td>
<td>Small convenient set of specimens (n=10-100)</td>
<td>Large well defined set of specimens (n=100-1000)</td>
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<td>Validation Study</td>
<td>Large, well defined set of specimens (n=100-1000)</td>
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Study Design

(A) Biomarker Discovery and Validation.

(B) Multivariate Predictive Models.
Bioinformatics:
UMSA for Nonlinear Classification

UMSA: Unified Maximum Separation Analysis
Model Evaluation and Comparison: ROC Curves

Independent validation set: stages I/II epithelial ovarian cancer† vs. healthy controls.

- CA125, AUC=0.770
- 3 Markers + CA125, AUC=0.920, p=0.028
- 3 Markers, AUC=0.885, p=0.023
Lesson learned: The intended use define clinical performance and the target population.
The 4B&4G for Biomarker Translation

- (1) To define clearly a specific clinical “intended use” for unmet needs.
- (2) To generate sufficient evidence in preliminary studies to support the investment for a large-scale validation study.
- (3) To select/develop assays with analytical performance suitable for clinical use.
- (4) To conduct clinical trial to demonstrate clinical utility to obtain regulatory approval and gain acceptance by the clinical community.

OVA 1: Choice of Assay

- Discovery assay: SELDI mass spectrometry
- Clinical assay: ELISA
Summary: The 4B & 4G for Successful Biomarker Translation

Translation Clinical Laboratory

Validation Analytical/Clinical

Define Clinical Intended Use

Discovery Research

Define Clinical Intended Use

Discovery Research

Translation Clinical Laboratory

Validation Analytical/Clinical

Define Clinical Intended Use

Translation Clinical Laboratory
The future of cancer diagnostics will most likely come from the advances in clinical proteomics.

Construction of a roadmap for the development of cancer diagnostics: define clinical intended use and understand the characteristics of cancer diagnostics.

Translation of cancer biomarker into clinical laboratory will require close collaboration between researchers, industry, clinicians and clinical chemists.

We learned that the road from biomarker discovery, validation to clinical diagnostics could be long and winding, sometimes frustrating, however, we know that at the end of the road there is a rainbow waiting for us.