Ovarian Cancer-Biomarkers

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Stoller Biomarker Discovery Centre

- Arginine (R)
- Glutamic acid (E)
- Serine (S)
- Threonine (T)
- Pyrrolysine (O)
- Leucine (L)
Ovarian Cancer—Biomarkers for Early Detection

- Ovarian cancer (OC) has the highest mortality rate of the gynaecological cancers.

- In 2010, 7,011 women in the UK were diagnosed with ovarian cancer.

- In 2011, there were 4,272 deaths from ovarian cancer in the UK.

- Majority of women are diagnosed with late stage disease (III/IV) and have a 5 year survival rate of <40%.

- An urgent and unmet need to improve the screening for the early detection of OC.
Ovarian Cancer (C56): 2002-2006
Five-Year Relative Survival (%) by Stage, Adults Aged 15-99, Former Anglia Cancer Network

Original data source:
Prepared by Cancer Research UK
The National Cancer Registration Service, Eastern Office. Personal communication.
http://ecric.org.uk/
Clinical Biomarkers- Current State of Play


Clinical Biomarkers in Ovarian Cancer

FDA approved Biomarkers for Ovarian cancer


http://ova-1.com/physicians/how-ova1-works

http://edrn.nci.nih.gov/resources/highlights
Problems in biomarker discovery for early detection

Problem 1
The use of case-control sets from patients already clinically diagnosed with cancer produces clinical biomarkers that are concurrent with their clinical disease and does not allow you to determine if the disease can be identified early with a given biomarker.

Access to appropriately designed studies:
- Context for clinical application should drive the study design.
- Appropriate matched controls
- Appropriate study size for statistical power
- Pre-clinical as well as clinical samples
- Appropriate sample handling, storage and data management
Solution 1
UKCTOCs: Early Detection, Risk Stratification and Diagnosis of Ovarian Cancer

- **UKCTOCS** (The United Kingdom Collaborative Trial of Ovarian Cancer Screening) involving 202,000 participants in 13 collaborating UK centres. (£26 million MRC)

- **PROMISE 2016** (Predicting Risk of Ovarian Malignancies, Improved Screening and Early Detection). A research programme aimed at halving the number of deaths from ovarian cancer. (£3 million, Eve Appeal, CRUK)

- With serial samples for >50,000 women spanning a 10 year period.
- Can follow the trajectory of potential biomarkers from pre-clinical samples
Problems in biomarker discovery for early detection

Problem 2
Working with Serum!

In Data Dependent Acquisition (DDA) – Only the most abundant ions are selected for fragmentation. Leaving many potential ions unexplored.

In Data Independent Acquisition (DIA) – All of the potential ions are fragmented.

Sequential window acquisition of all theoretical fragment-ion spectra mass spectrometry (SWATH MS) is a form of DIA.

SWATH MS operates by rapidly cycling through sequential isolation m/z windows over the whole LC elution range.

SWATH MS generates, a complete permanent record of the fragment ion spectra of all the components in a biological sample within a predetermined m/z versus retention time window. This can be re-mined time and again based on new hypotheses.
## A priori knowledge

<table>
<thead>
<tr>
<th>Accession</th>
<th>Description</th>
<th>Potential Biomarker for</th>
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<td>ADIPO_HUMAN</td>
<td>Adiponectin OS=Homo sapiens GN=ADIPOQ PE=1 SV=1</td>
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### Table

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<th>Peptide</th>
<th>Q1</th>
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</table>

### Spectral Library

Retention time (mins)

### SWATH Digital Map

Full retention time profile of single SWATH window

### Biomarker Signature Validation

ELISA, nanopro or Selected Reaction Monitoring
Volcano plot of differential expression in pools

- log₀ adjusted p-value
- log₂ expression ratio with respect to controls

- not. sig. diff. expr.
- sig. diff. expr.
- p-value as plot
- p-value < 10⁻¹⁵
Protein expression in longitudinal samples for Type I

Loess linear regression plot

Loess linear regression plot

Non-linear modelling

p-value = 0.0031
Comparison of Expression of CA125 and PROZ Type I
Protein expression in longitudinal samples for Type II

Loess linear regression plot

Loess linear regression plot

Non-linear modelling

p-value = 0.1098
Comparison of Expression of CA 125 and PROZ Type II

![Comparison of CA 125 and PROZ Type II](image)
Comparison of PROZ Thresholds for Type I & Type II
Construction of risk estimation models.

I) Type I

II) Type II
SWATH Maps - Diagnostic Tools

Ovarian Cancer

Breast Cancer

Prostate Cancer

Healthy
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