Research Project Proposal:
Integrative analysis of transcriptional, mutational and DNA structural profiles in ovarian cancer of chemotherapy sensitive vs. resistant patients

Sara Sansone
sara.sansone@mail.polimi.it
Track CSE - Data, Web and Society
Genomic Computing

• Genomic computing is a new science focused on understanding the functioning of the genome.

• The aim is to make fundamental discoveries in biology and medicine.

• The challenge is to answer to relevant questions for biological and clinical research.
Research topic

Relative 5-year survival for invasive epithelial ovarian cancer
• Ovarian cancer
Research topic

- Ovarian cancer
- HGS-OC: high-grade serous ovarian adenocarcinoma
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- Ovarian cancer
- HGS-OC: high-grade serous ovarian adenocarcinoma
- Treatment: surgery and cytoreduction followed by chemotherapy
Research topic

Problem with the treatment?

Relative 5-year survival for invasive epithelial ovarian cancer
Problem with the treatment?

- Relapse is likely to occur within a median of 16 months
Resistance to chemotherapy

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• relapse within 6 months since the end of treatment: resistant;

• relapse after 12 months since the end of treatment: sensitive;
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- relapse within 6 months since the end of treatment: *resistant*;

- relapse after 12 months since the end of treatment: *sensitive*;

- relapse after 36 months since the end of treatment: *sensitive long term*. 
Relevance of the research project

• It is crucial to find a mechanism that allows to identify and discriminate resistant and sensitive patients, at the time of diagnosis.
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• New treatment options, which consider achievements in understanding of the pathophysiology of ovarian cancer, will then be needed to improve outcomes.

• This study involves the analysis of resistance to chemotherapy in ovarian cancer patients, based on their transcriptional, mutational, and DNA structural profiles.
Aim of the research

• We will study the possibility of building a classifier able to predict the chemotherapy resistance of a patient affected by high grade serous ovarian cancer.
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• The ultimate aim is the identification of a molecular signature (most likely the expression of a restricted list of genes) that could be used to predict the response to therapy (sensitive / resistant) at the time of diagnosis, starting from the Copy Number Alteration (CNA) profiles of the patients.
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• The hope is that this classifier will achieve an accuracy of at least 80%.
Used technologies

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• GISTIC 2.0: it identifies regions of the genome that are significantly amplified or deleted across a set of samples.
Research plan

• Data extraction
Research plan

- Data extraction
- Data analysis
Research plan

• Data extraction
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• Implementation
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• Validation
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- Check the Progression-free Survival column to discriminate sensitive and sensitive long term (PFS months > 36).

- Obtain three sets of data (one for each type of patients) after executing three different query on GMQL (GenoMetric Query Language).
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The possibility to use the tool GISTIC 2.0 to identify those relevant regions will be considered.
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- A classifier that uses relevant CNA regions in order to identify a set of genes, whose expression will then be used to classify patients.

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After creating the data set, we will use some known classifier, e.g. Random Forest, K-Nearest Neighbours or AdaBoost.
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In order to identify the best model, a 10-fold cross validation will be executed for each proposed classifier.

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At the end, a test of the obtained model will be done using in-house data, which are never used during the training phase.
Implementation steps done so far

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    - As a features selection tool for a classifier that uses gene expression data (using as features the genes that were mapped on those regions).
  - We discovered that the regions identified by GISTIC were not able to correctly discriminate the three classes.

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We identified regions that have different CNA across the three set of samples (Resistant, Sensitive, Sensitive Long Term), starting from their values on the whole genome.
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We tried first to discriminate the two classes that are more different, i.e. Resistant and Sensitive long term.
Preliminary relevant results

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- Average precision: 0.75.
- Average recall: 0.77.
- Average accuracy: 0.68.
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In order to improve the previous results, we normalized the values of expression of the selected 8875 genes in the dataset.
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Then, we run again a 10-fold cross validation, using AdaBoost as classification algorithm, and we got the following performance:
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Then, we run again a 10-fold cross validation, using AdaBoost as classification algorithm, and we got the following performance:

- Average precision: 0.84.
Preliminary relevant results

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- Average precision: 0.84.
- Average recall: 0.88.
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Then, we run again a 10-fold cross validation, using AdaBoost as classification algorithm, and we got the following performance:

- Average precision: 0.84.
- Average recall: 0.88.
- Average accuracy: 0.79.
Future steps

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• In this way, we will obtain as features less genes, which are more meaningful for the discrimination of the two classes.

• We will apply the same procedure in order to classify also Resistant against Sensitive and finally putting all the classes together.

• This will hopefully lead us to a classifier with the desired performance.
Bibliography


