

ISC: an Integrated Signature Classifier for stage I epithelial ovarian cancer



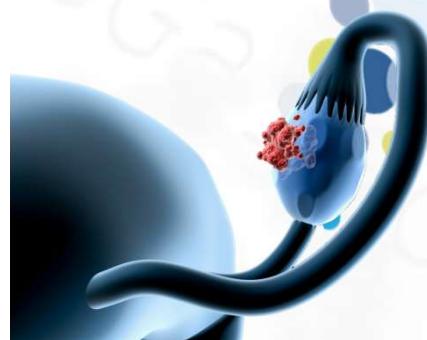
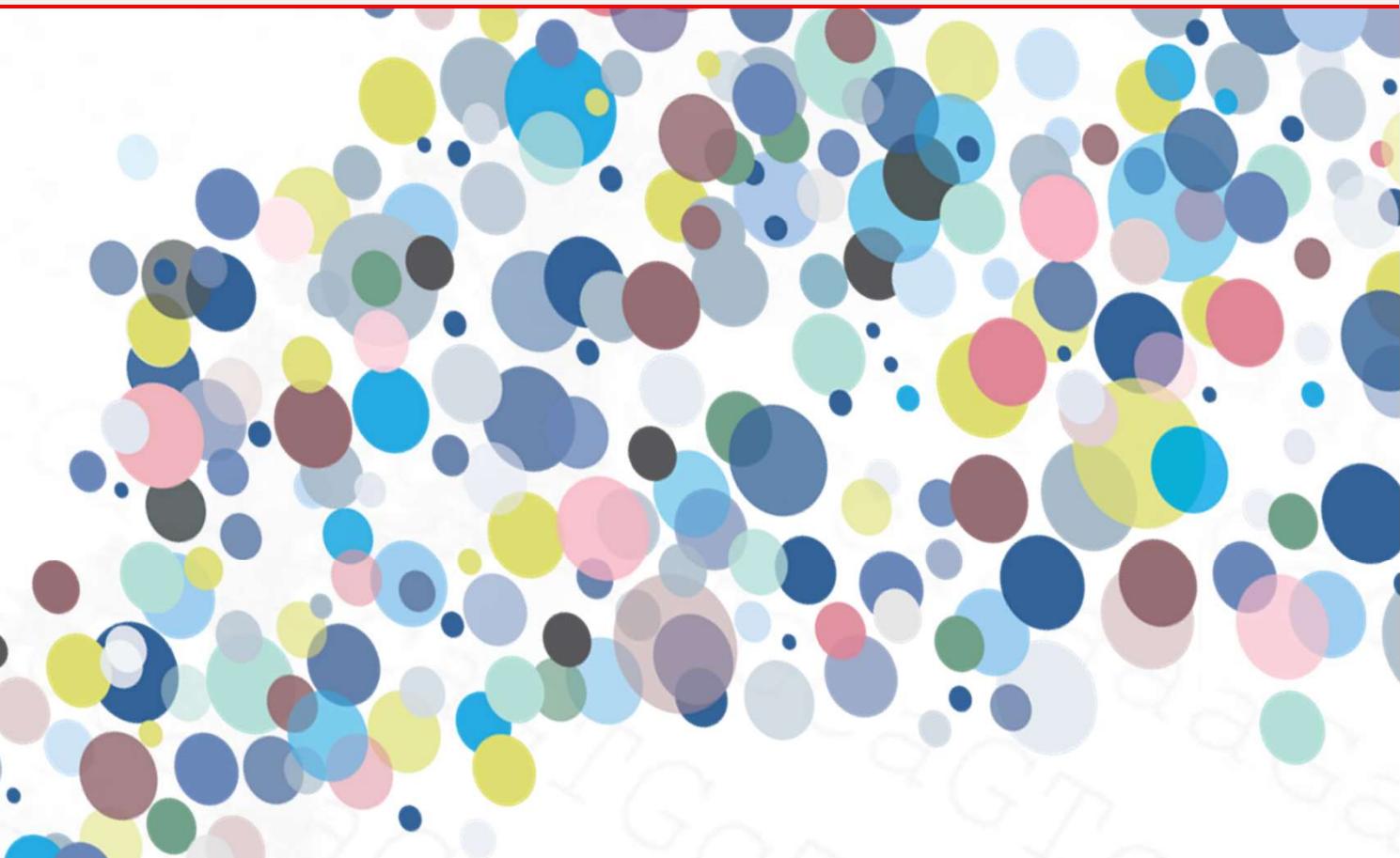
*Sergio Marchini, PhD
Translational Genomic Unit, Department of Oncology
Mario Negri Institute*





Epithelial Ovarian Cancer

Introduction



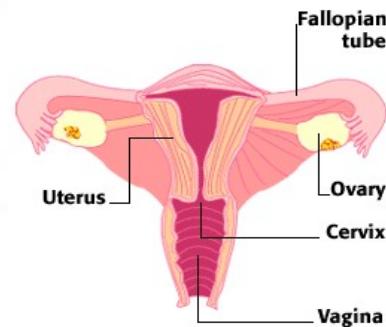
EOC is characterized by a marked clinical, pathological and molecular heterogeneity



Epithelial Ovarian Cancer

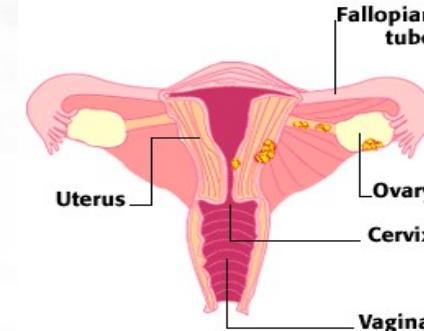
Introduction

TUMOR STAGE: the main prognostic parameter



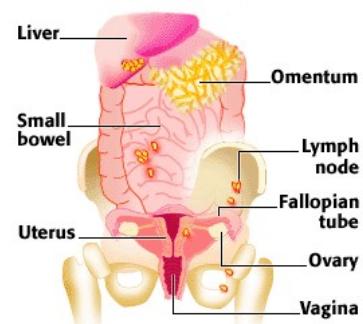
Stage I

Limited to one or both ovaries: **10%**



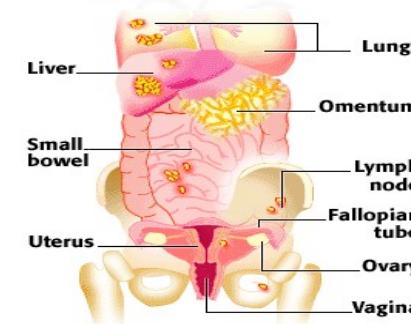
Stage II

Invades the pelvic region: **5-8%**



Stage III

Extends into the abdominal organs: **45%**



Stage IV

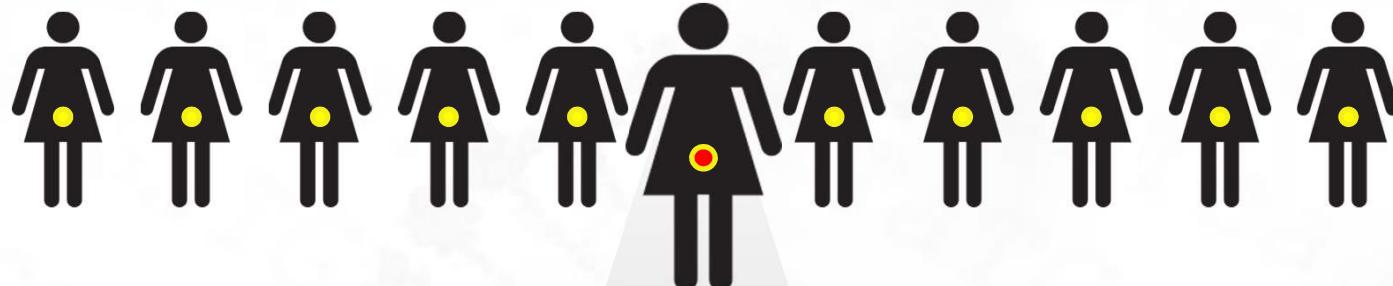
Metastasis to the lung, liver: **25%**



Stage I EOC

Introduction

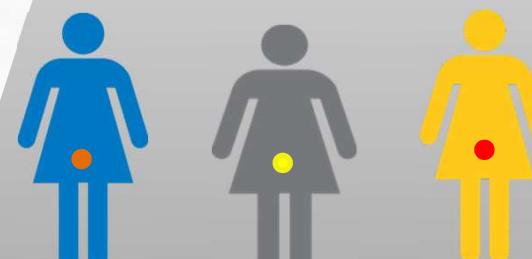
EOC



Stage I

Histological classification

HG-Serous LG-Serous



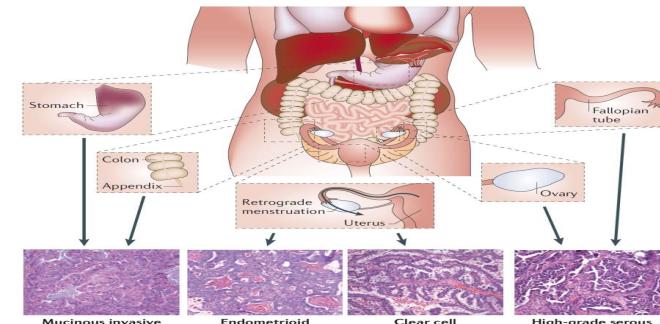
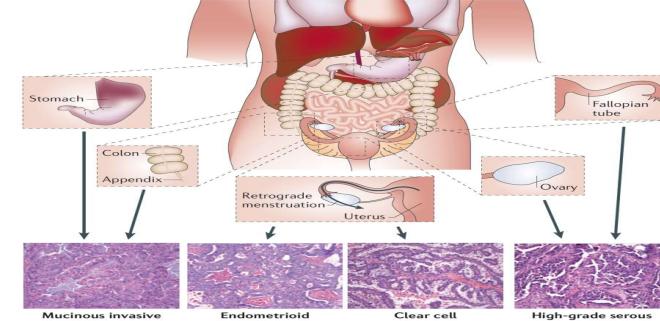
Mucinous Endometrioid Clear cells



EOC : a misleading term

Introduction

- Many EOCs derived from non ovarian tissues.
- Different histological subtypes are independent diseases.
- Taking a rigorous view, the ovarian histotypes should be regarded as **distinct diseases**, as their cell of origin, epidemiology and driver mutations are quite different.



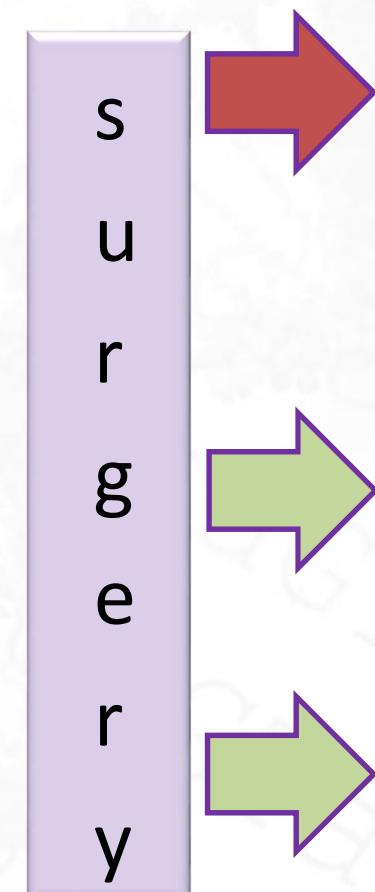
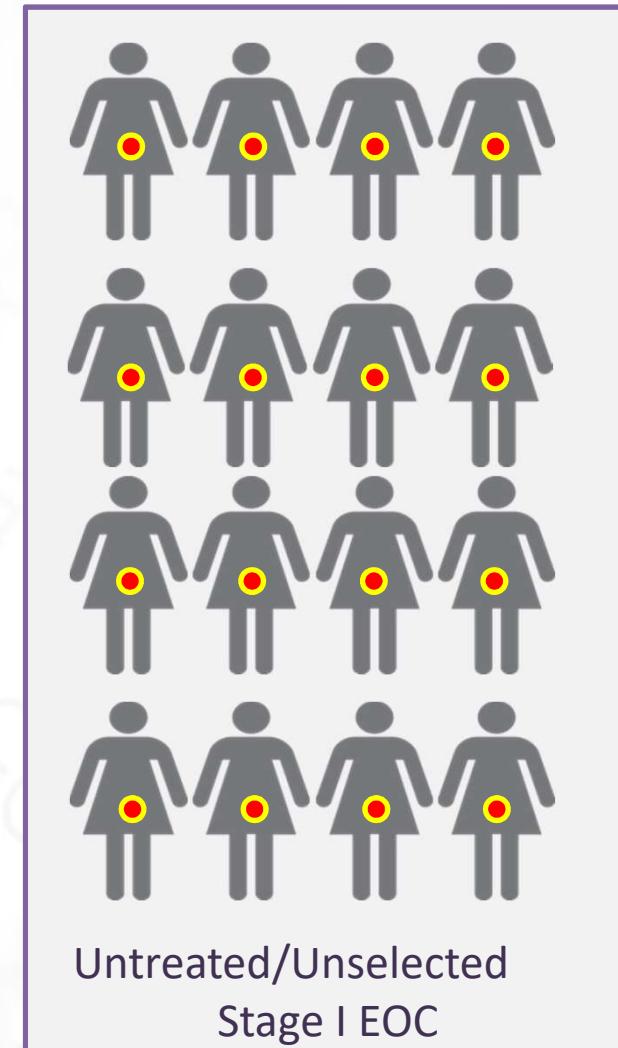
Nature Reviews in Cancer:11 October 2011 719-725

EOC is not a single disease but a **collection of diseases** sharing the loco regional dissemination to the ovary and related pelvic organs.



EOC: clinical outcome

Introduction





EOC: open questions

Introduction

1st question:
why 20% of stage I EOC patients relapse?



Accordingly to the ESMO guideline in stage I, **TUMOR GRADE** is the **only- not sufficient-** variable associated with PFS.

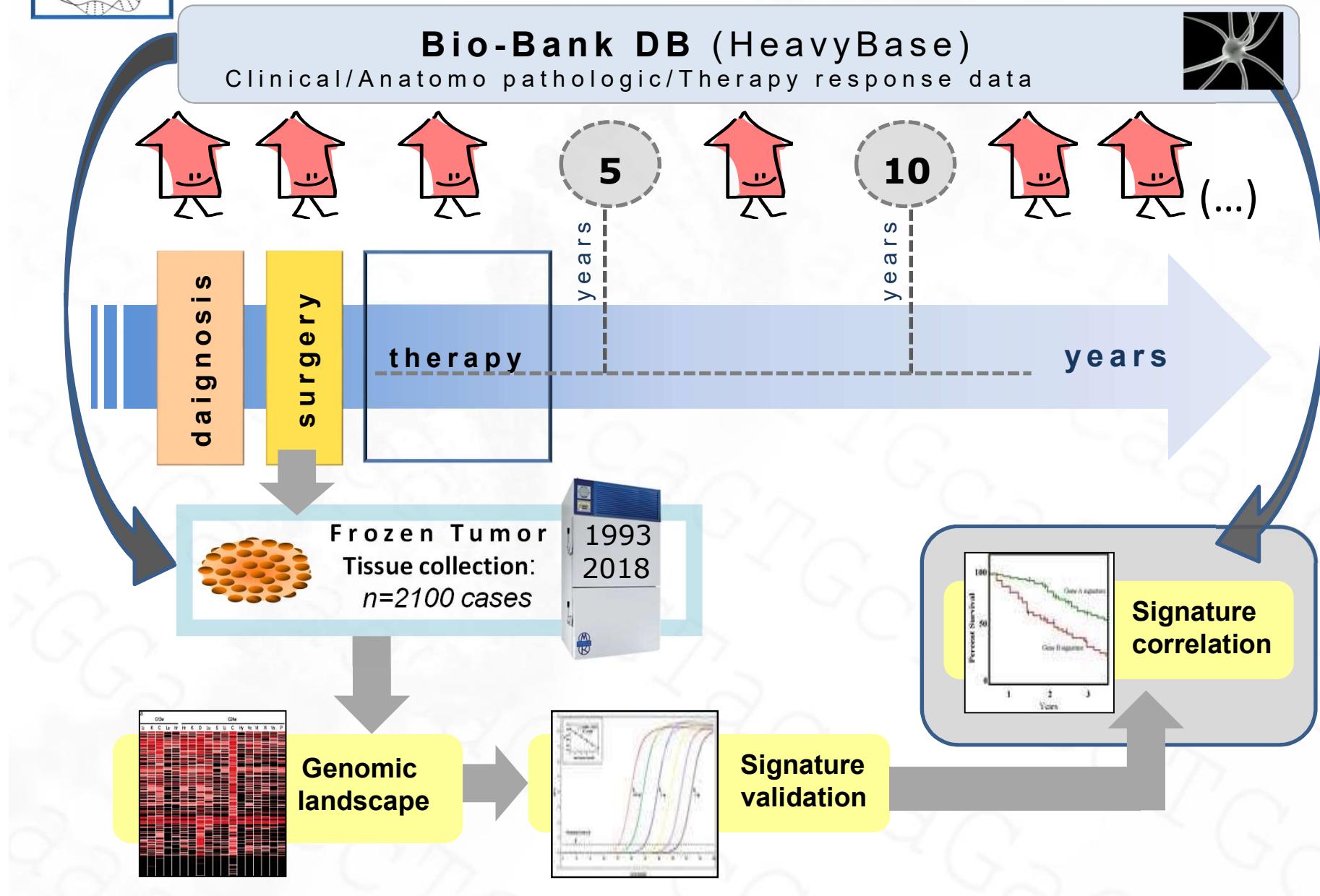


2nd question:
can molecular information add “something” to clinical parameters?



Pandora

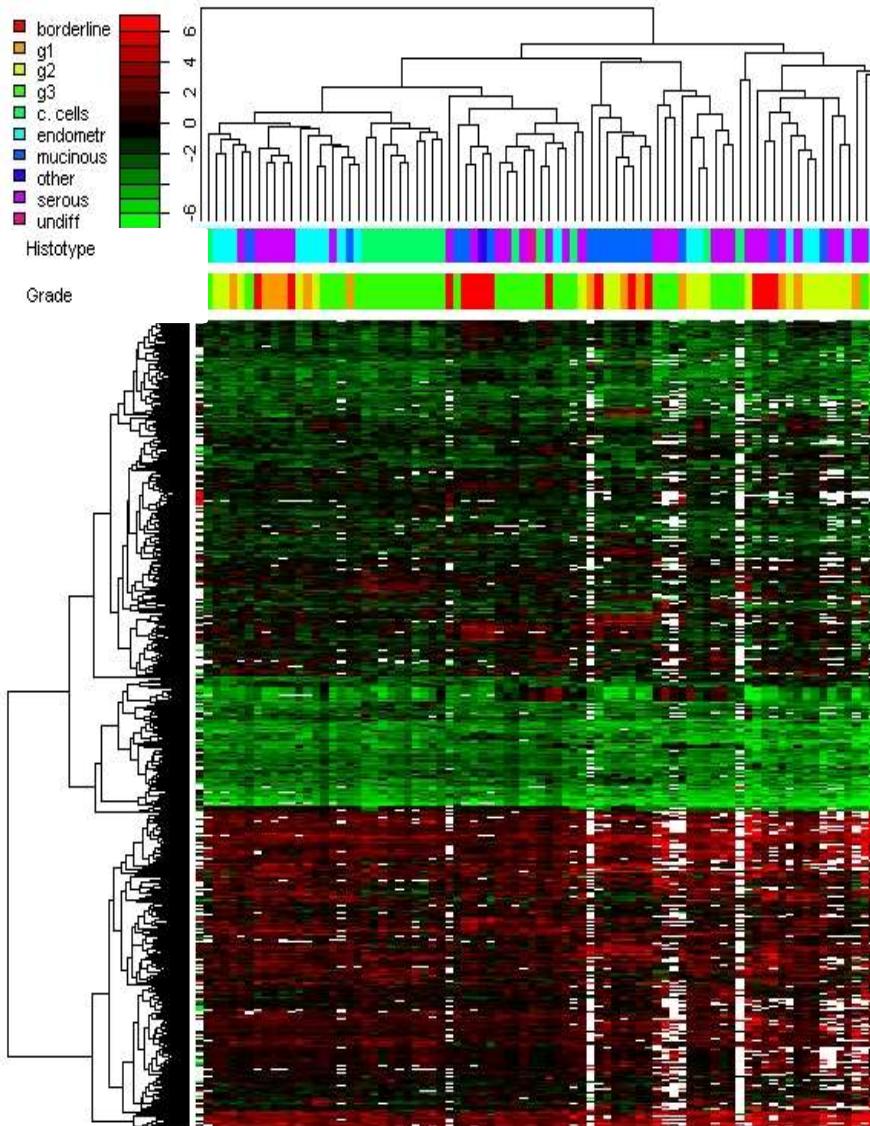
The Ovarian Cancer Tumor Tissue Collection



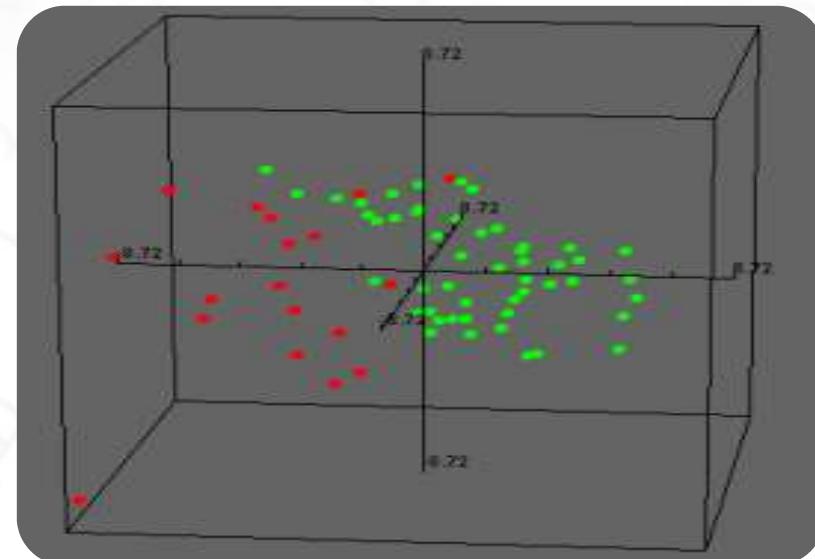


Stage I EOC: expression profile

Relapsing vs not relapsing



- Unsupervised cluster analysis revealed a complex molecular scenario.
- Looking for those differences between **relapsing** and **not relapsing** cases, we observed two different molecular profiles.



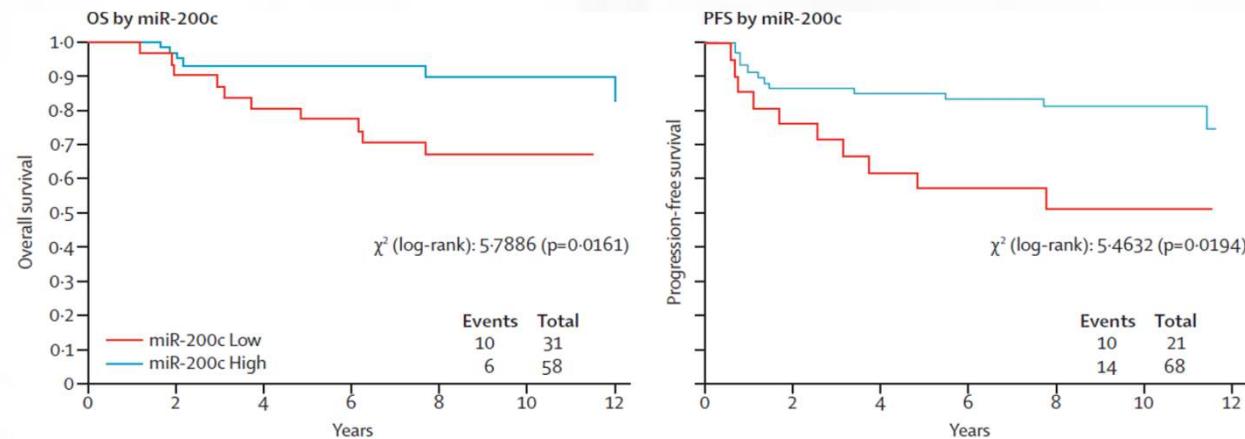
Marchini S., et al. Clinical Cancer Res. 2008



Expression profiles

miR-200c

Cohort A

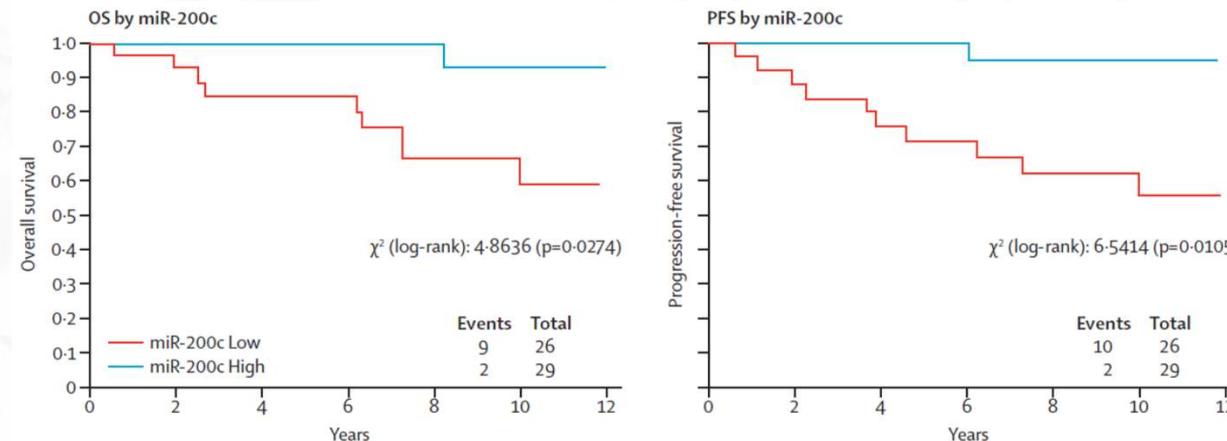


Association between miR-200c and the survival of patients with stage I epithelial ovarian cancer: a retrospective study of two independent tumour tissue collections



Sergio Marchini*, Duccio Cavalieri*, Robert Fruscio, Enrica Calura, Daniela Garavaglia, Ilaria Fuso Nerini, Costantino Mangioni, Giorgio Cattoretti, Luca Clivio, Luca Beltrame, Dionysios Katsaros, Luca Scarampi, Guido Menato, Patrizia Perego, Giovanna Chiorino, Alessandro Buda, Chiara Romualdi, Maurizio D'Incalci

Cohort B





Stage I EOC: additional questions

New challenges

As we demonstrated that transcriptional programs shape the balance between **relapsing** and **not relapsing** stage I EOC cases, we next questioned :

- 
- Is *miR-200c-3p* part of a more complex and yet uncovered transcriptional program, that drives poor prognosis in stage I EOC?

To **answer** to these questions, we required:

- new data
- increase the sample size
- new bioinformatics tools

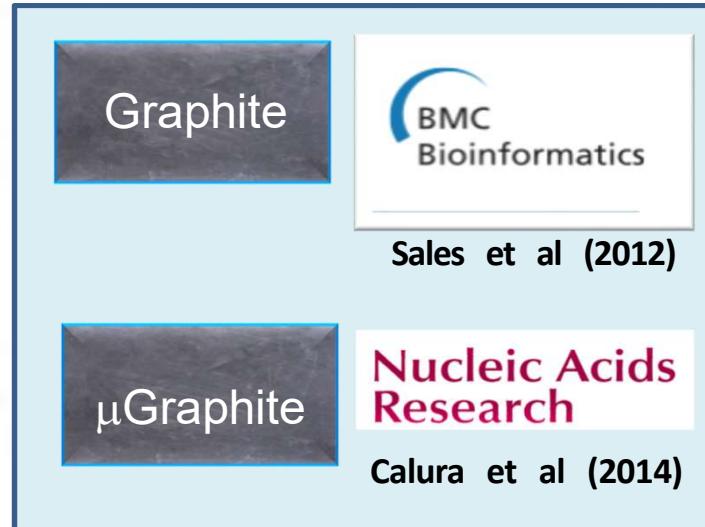




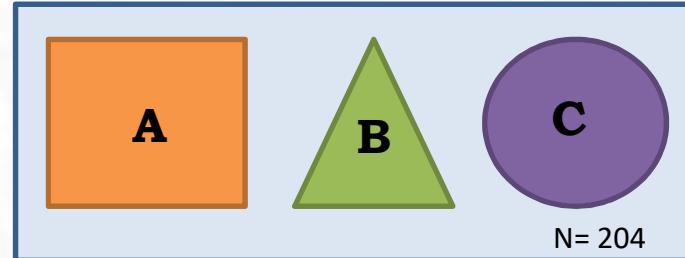
Stage I EOC: additional questions

The issues to resolve

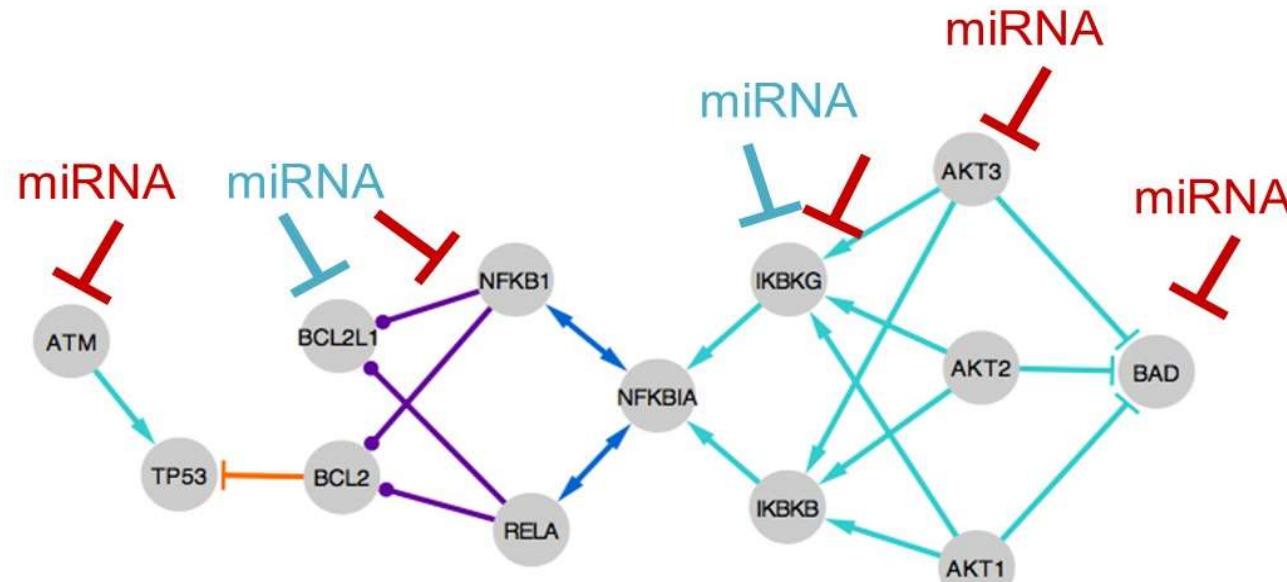
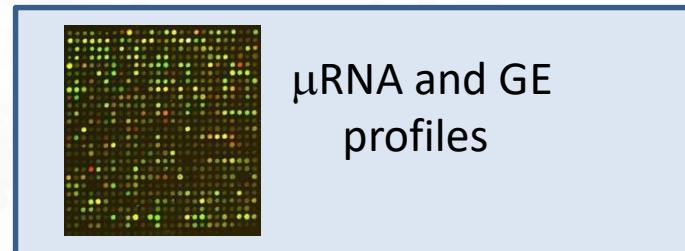
Tools



Biobanks



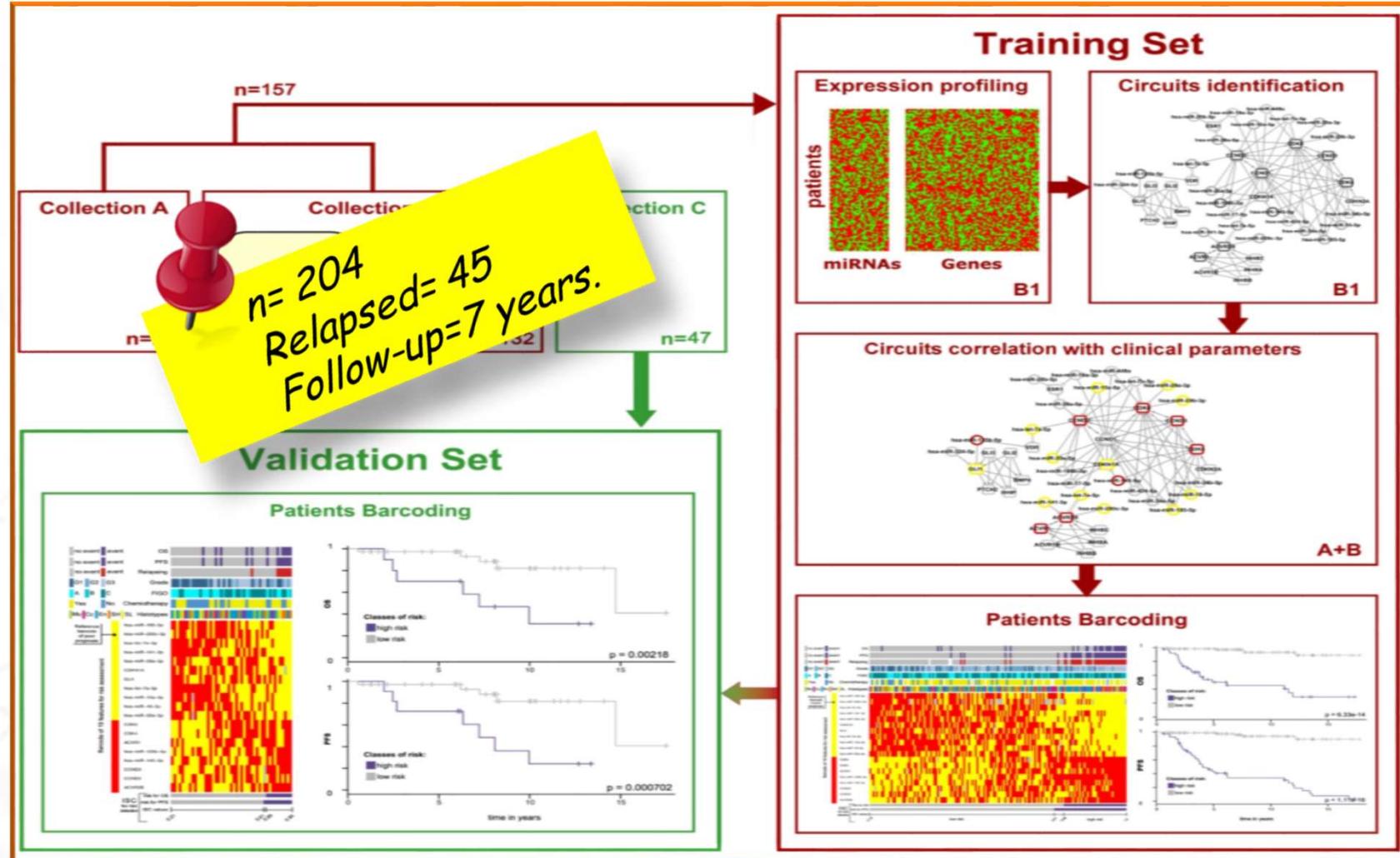
Data





Stage I EOC

Why some stage I patients relapse?





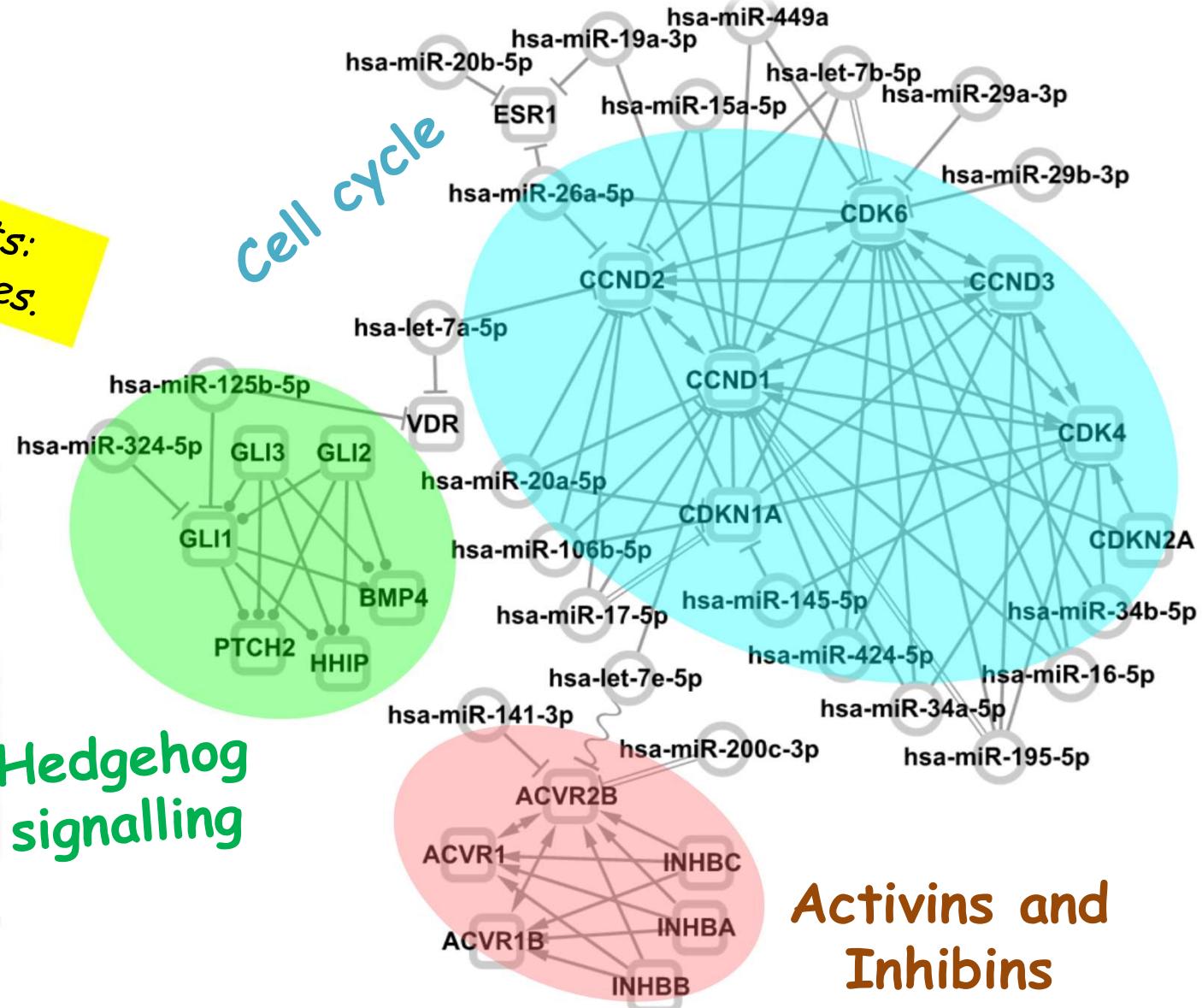
Stage I EOC

Why some stage I patients relapse?

44 elements:
23 miRNA+21 genes.

Hedgehog
signalling

Activins and
Inhibins





Stage I EOC

Why some stage I patients relapse?

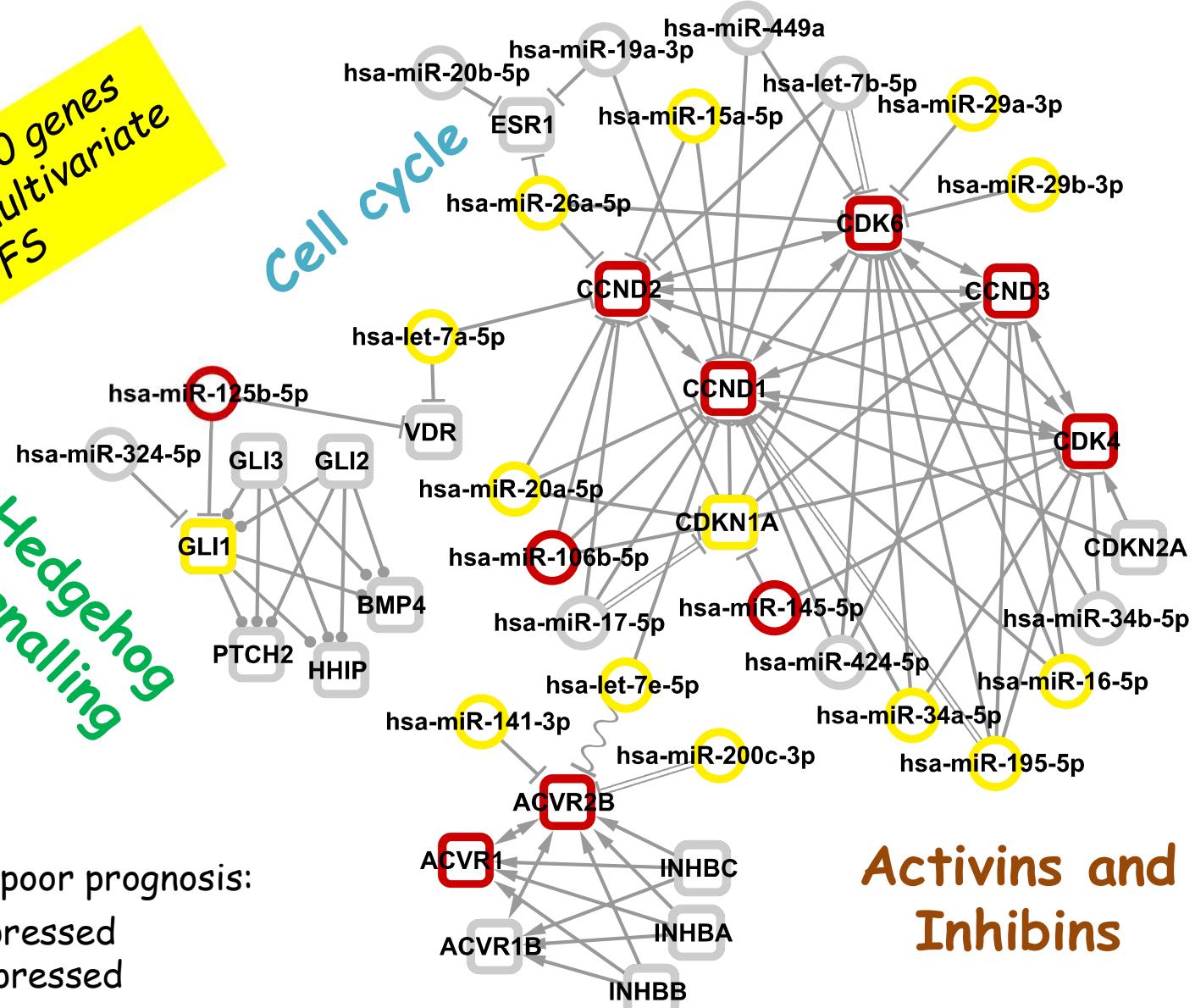
16 μ RNA+10 genes
associate in multivariate
to OS and PFS

Hedgehog
signalling

In patients with poor prognosis:

- Low expressed
- high expressed

Activins and
Inhibins





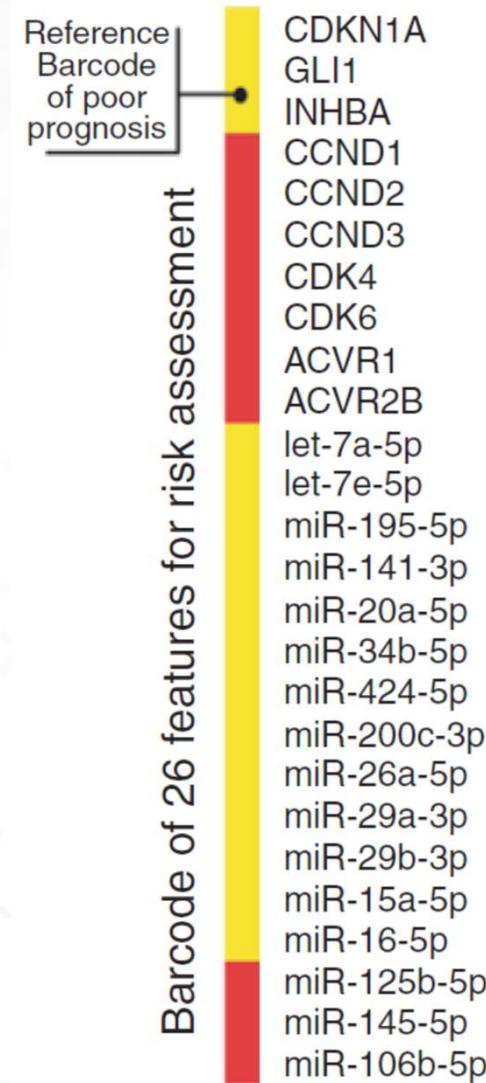
Stage I EOC

Why some stage I patients relapse?

We identified 16 miRNAs and 10 genes with prognostic value that compose a **barcode** specific for each patient, useful to evaluate the patient-specific level of risk.

We elaborated an **index** representing the activation state of the studied circuit in each patient.

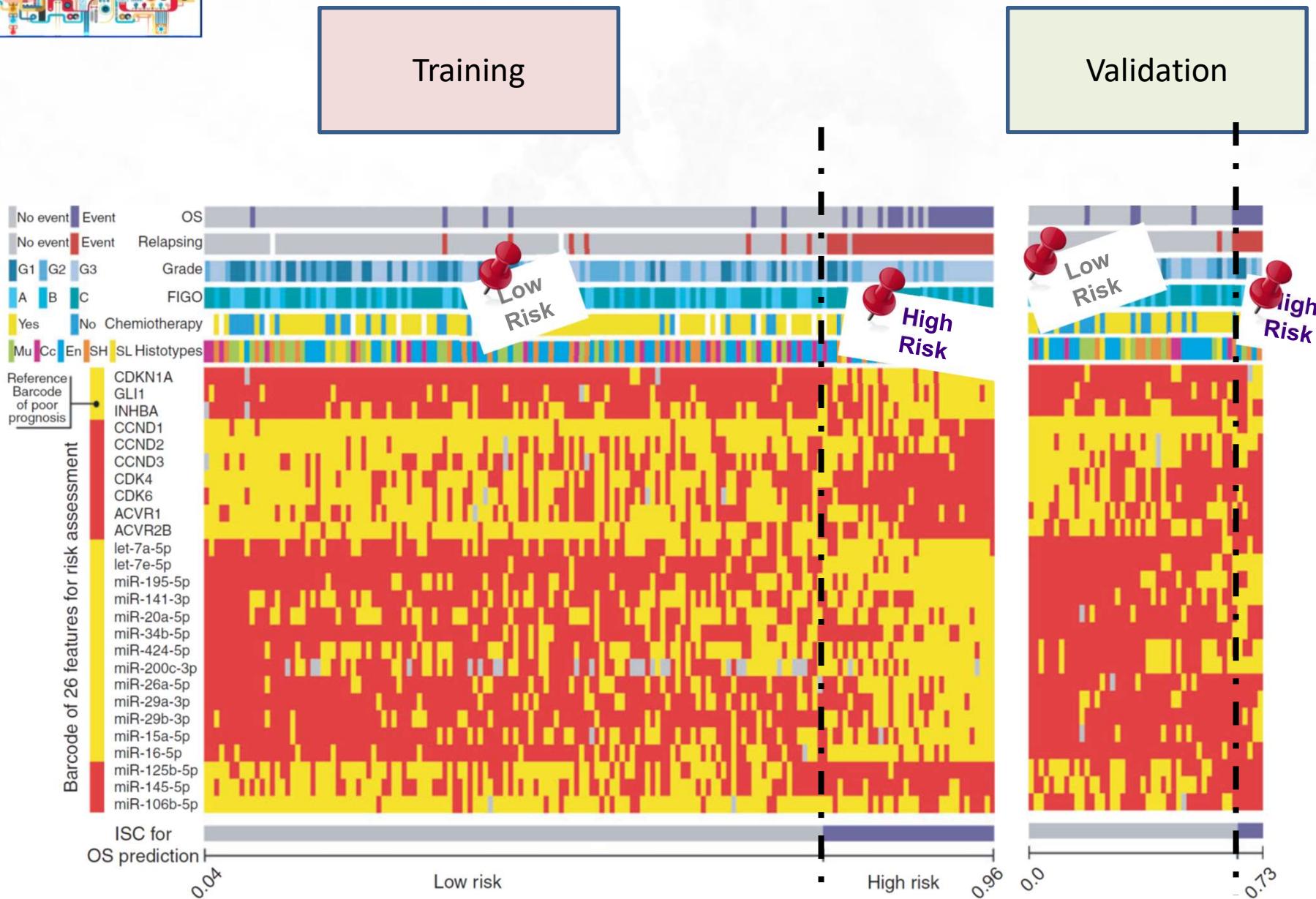
The index has been used to efficiently stratify patients in **high, medium or low risk classes** resulting in a prediction of patients outcome with a **sensitivity=88% and specificity=91%**.





Stage I EOC

OS prediction by ISC



Stage I EOC

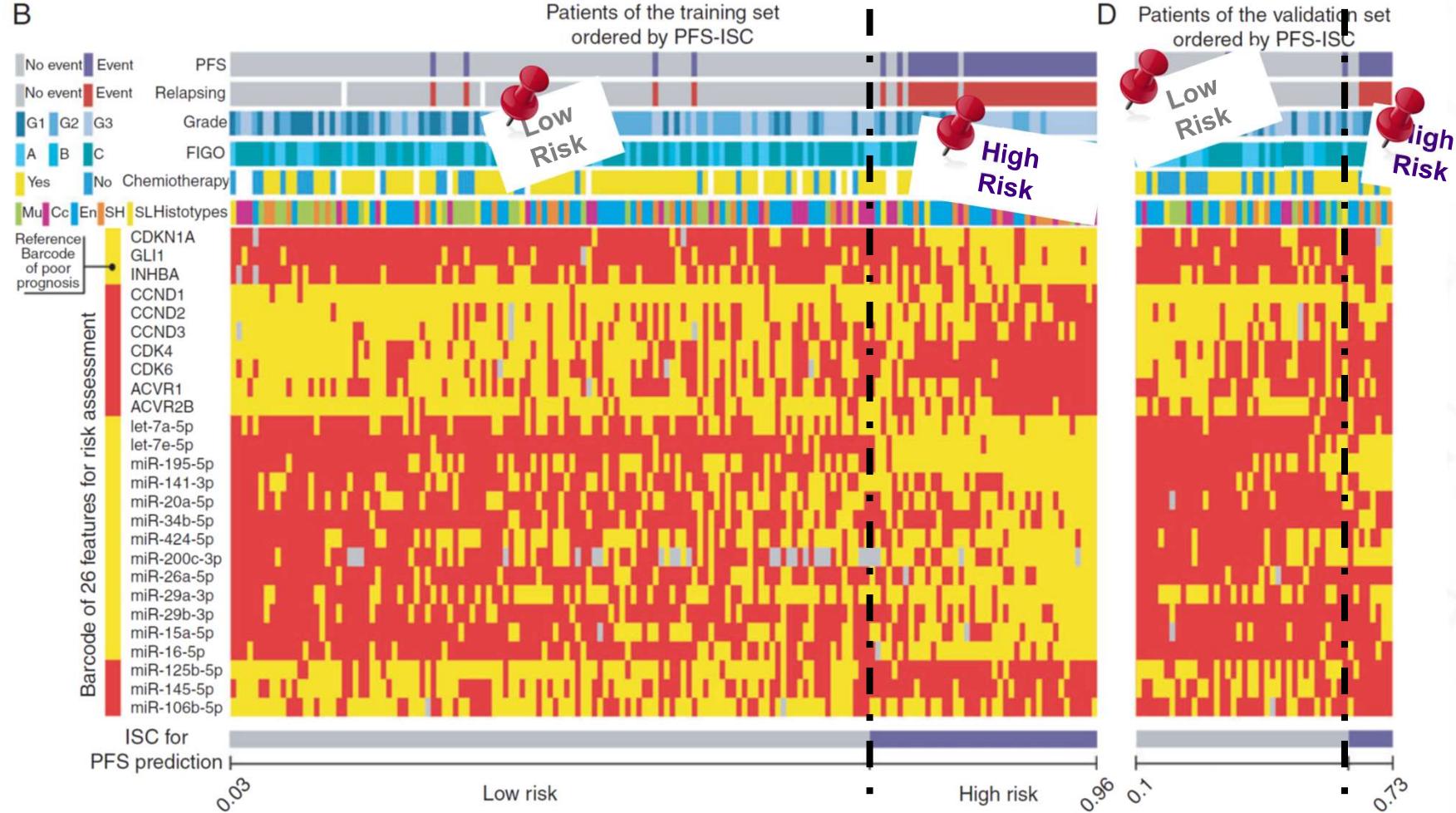
PFS prediction by ISC



Training

Validation

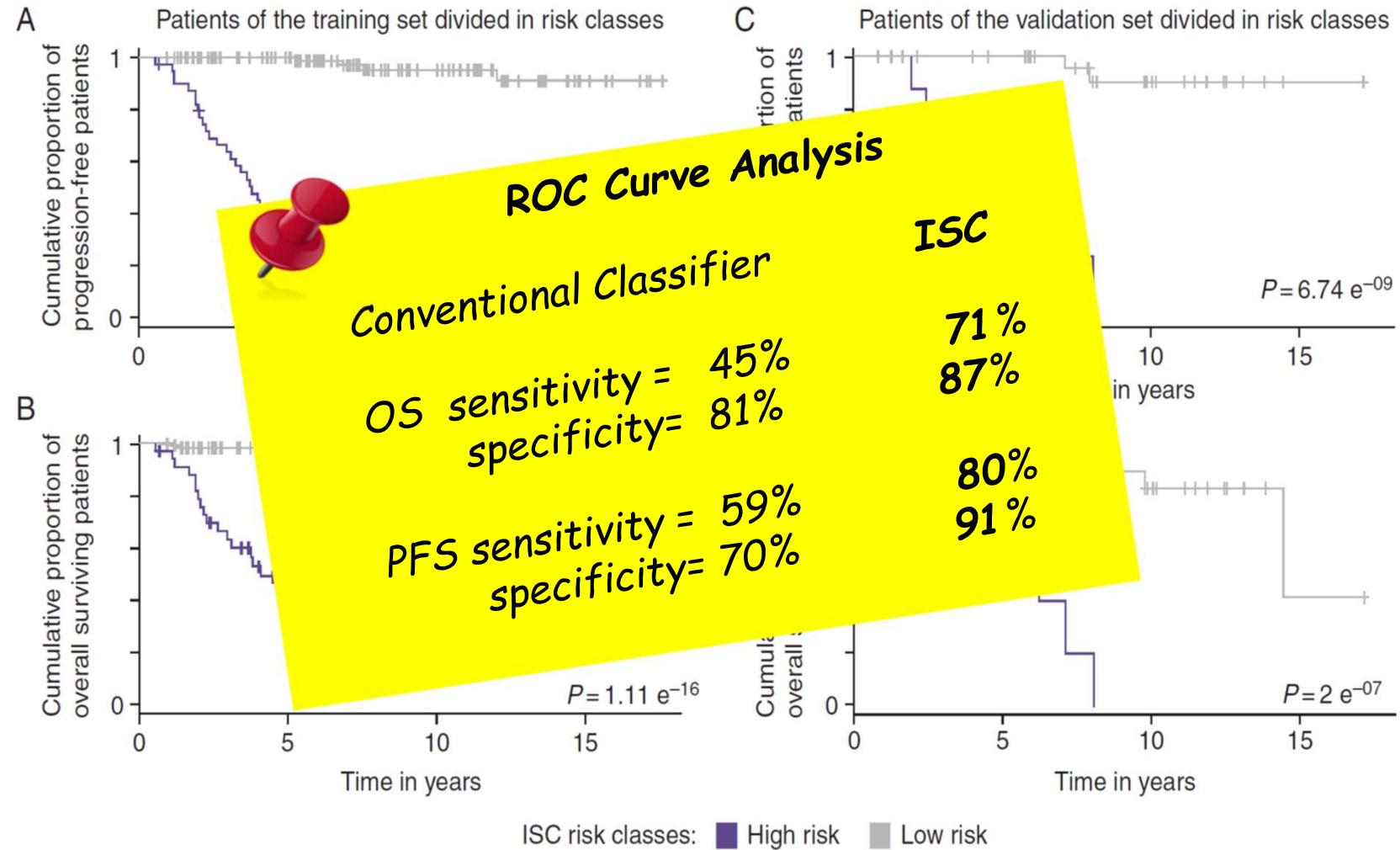
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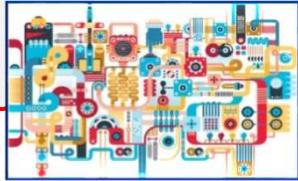




Stage I EOC

KM curves





Stage I EOC: ISC

Take Home message

In stage I EOC, defects in transcription regulation are associated with poor prognosis.

Defects are not widespread across the transcriptome, but are functionally related.

ISC expression level can be used in addition to clinical parameters to improve stage I tumor prognosis.

One of these functional signatures is based on 26 elements, called ISC, which are differentially expressed between relapsing and not relapsing patients.



DEPARTMENT OF ONCOLOGY

Antitumoral Farmacology group

Maurizio D'Incalci
Sergio Marchini
Lara Paracchini
Luca Beltrame
Luca Clivio

San Gerardo Hospital

Monza
Robert Fruscio,
Rodolfo Milani,
Tiziana Dell'Anna,
Giorgio Cattoretti



Fondazione
Cassa di Risparmio di Padova e Rovigo

Thanks!



UNIVERSITÀ
DEGLI STUDI
DI PADOVA

BIOLOGY DEPARTMENT

Computational Biology Group

Chiara Romualdi
Paolo Martini
Gabriele Sales



UNIVERSITÀ
DEGLI STUDI
DI BRESCIA

“Angelo Nocivelli” Institute
of Molecular Medicine

Enrico Sartori
Antonella Ravaggi
Eliana Bignotti
Germana Tognon

UNIVERSITÀ
DEGLI STUDI
DI TORINO
ALMA UNIVERSITAS
TAURINENSIS



Azienda Ospedaliera
S.ANNA

Dionyssios Katsaros

fondazione
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