



Consiglio Nazionale
delle Ricerche

“La Statistica al CNR al servizio del Paese”

July 5th, 2022



In silico recognition of a prognostic signature in basal-like breast cancer patients

FEDERICA CONTE, PHD

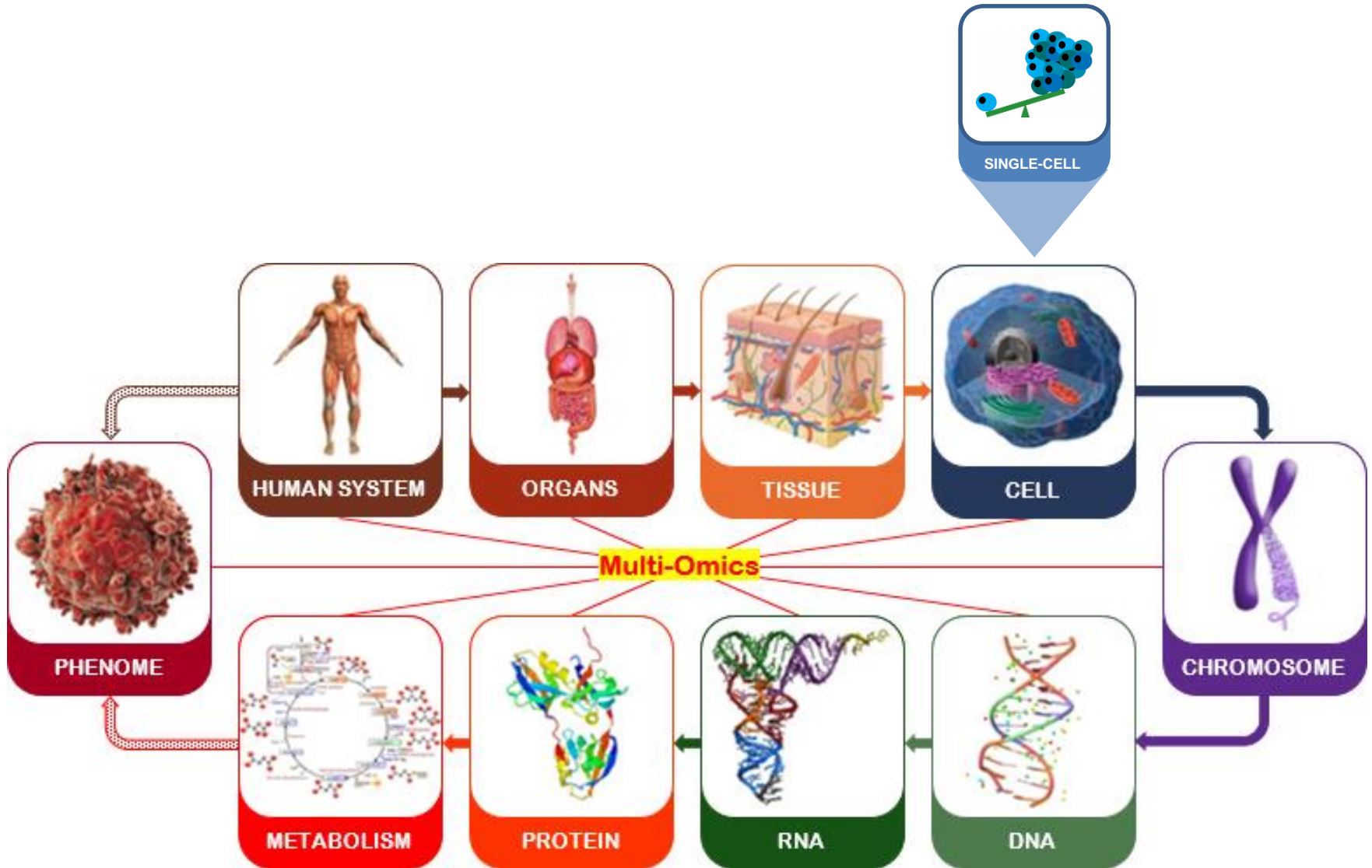
Institute of Systems Analysis and Computer Science (IASI) “A. Ruberti”

CNR - Roma

Revolution in Biomedical Research



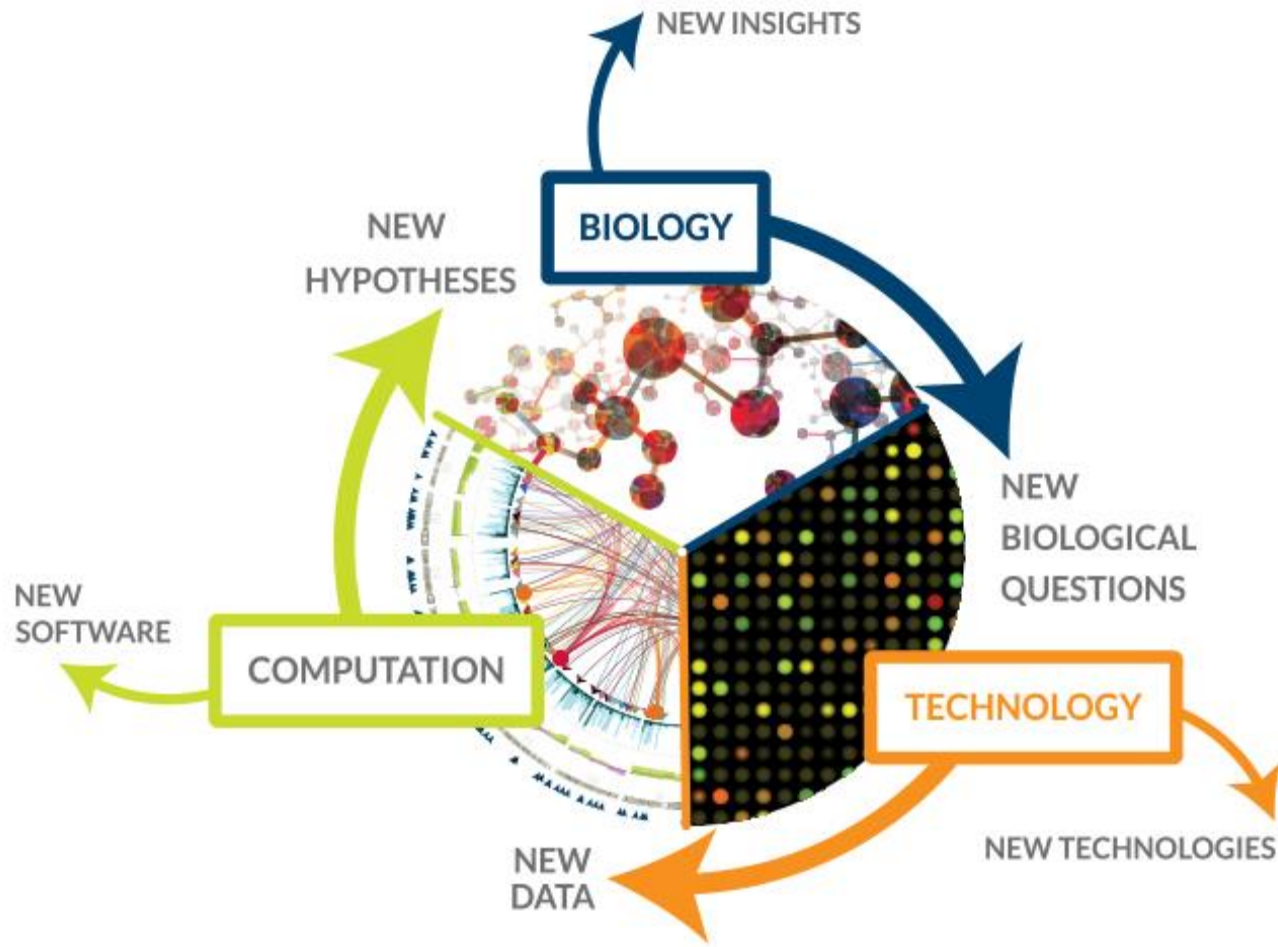
Biological Big Data



Biological Big Data



To face this massive amount of data



Challenges for the future

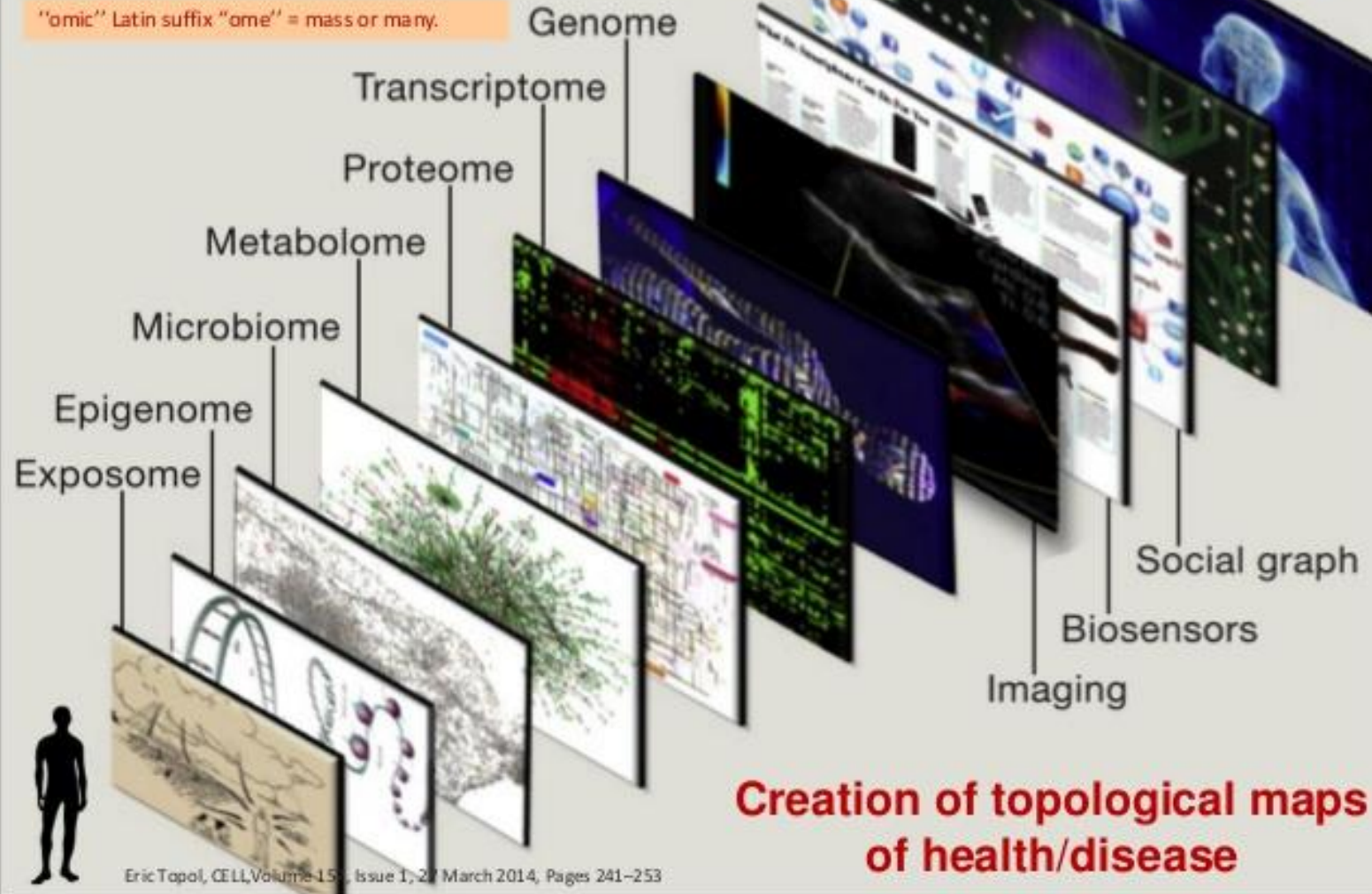


1) Accept the complexity

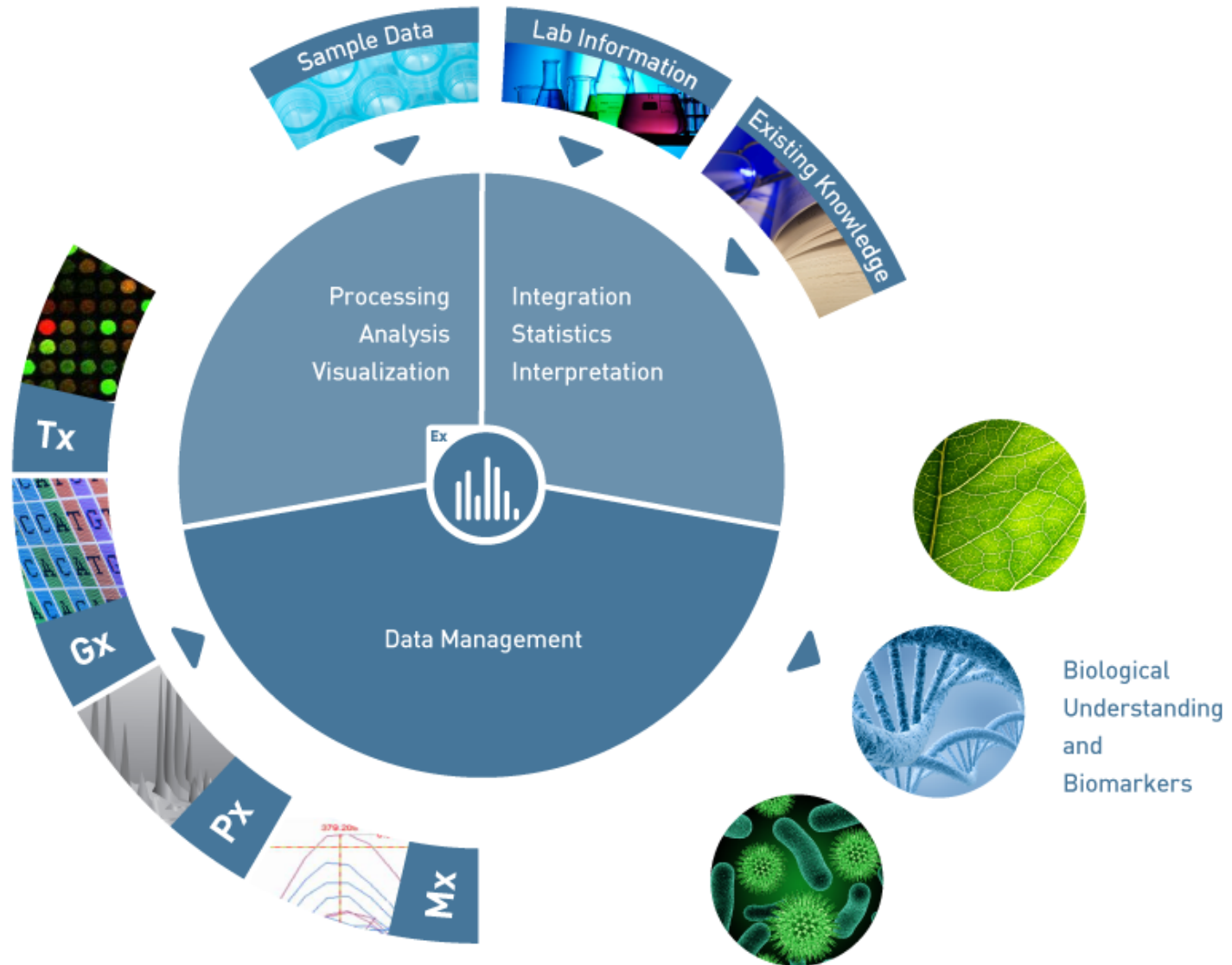
PRECISION MEDICINE:

Integrating multi-omics, clinical and real world data

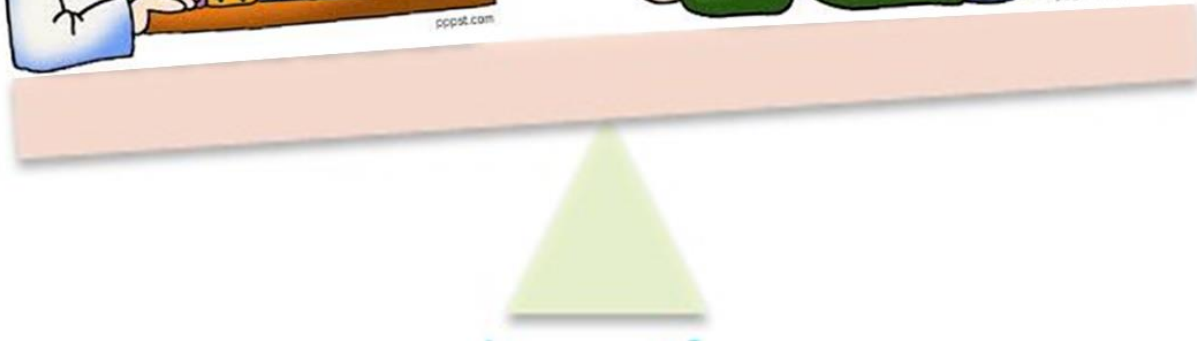
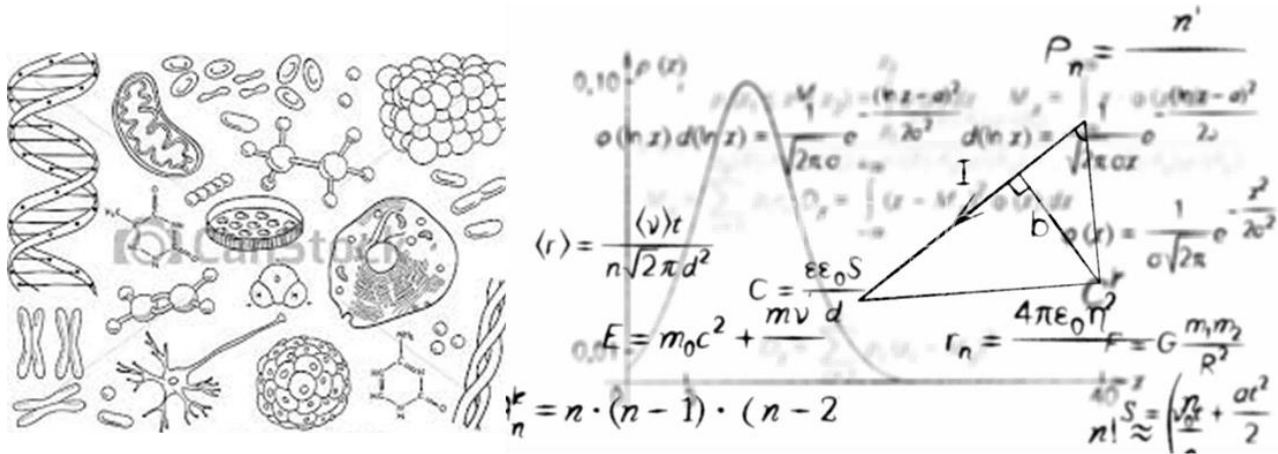
"omic" Latin suffix "ome" = mass or many.



2) Integrate data from different sources



3) Find a common language





PLOS ONE

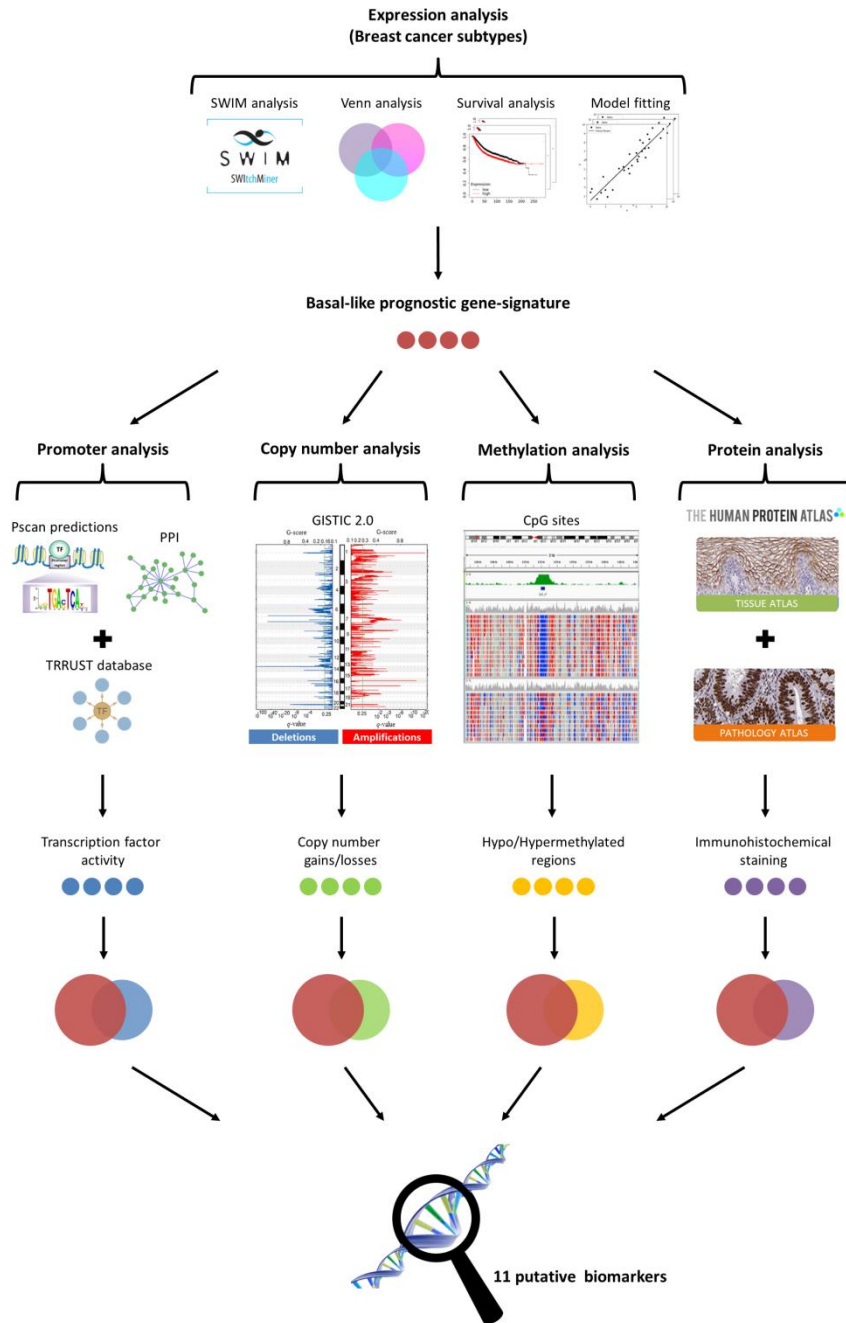
RESEARCH ARTICLE

In silico recognition of a prognostic signature in basal-like breast cancer patients

Federica Conte¹, Pasquale Sibilio^{1,2}, Anna Maria Grimaldi³, Marco Salvatore³, Paola Paci^{1,4}*, Mariarosaria Incoronato³

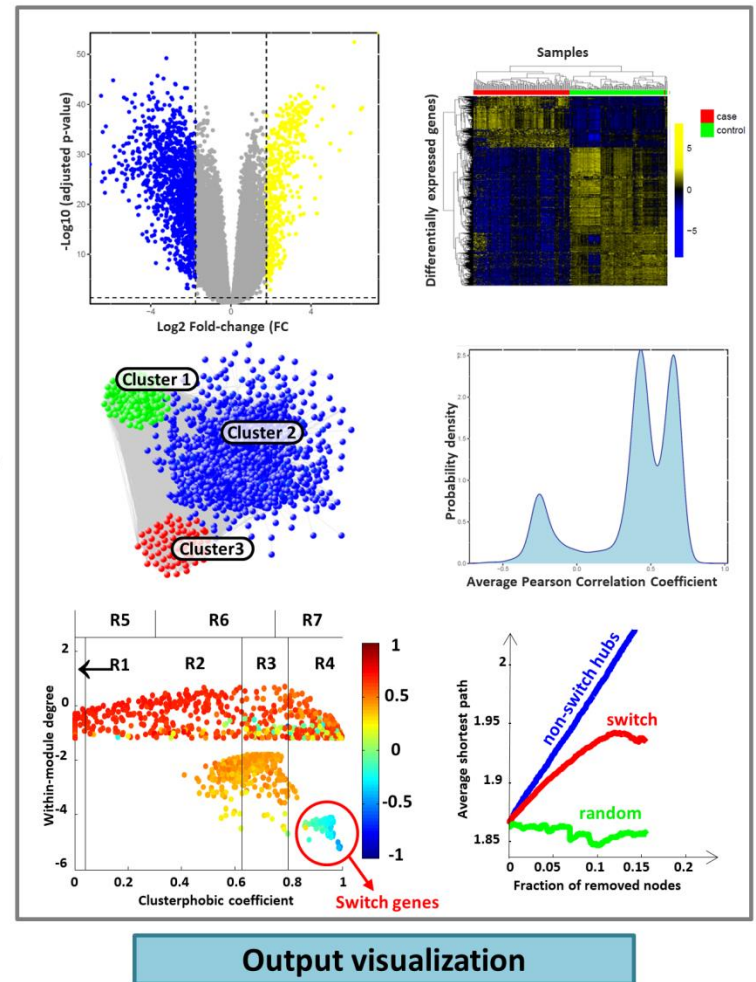
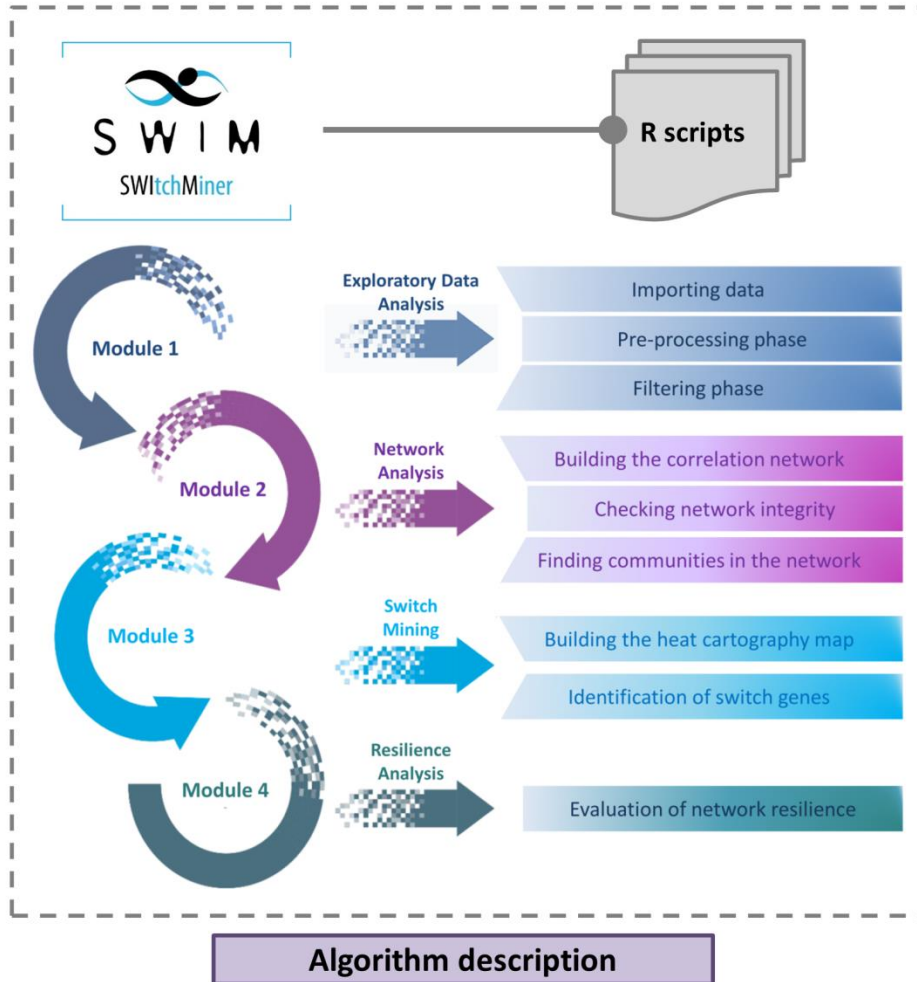


Bioinformatics pipeline

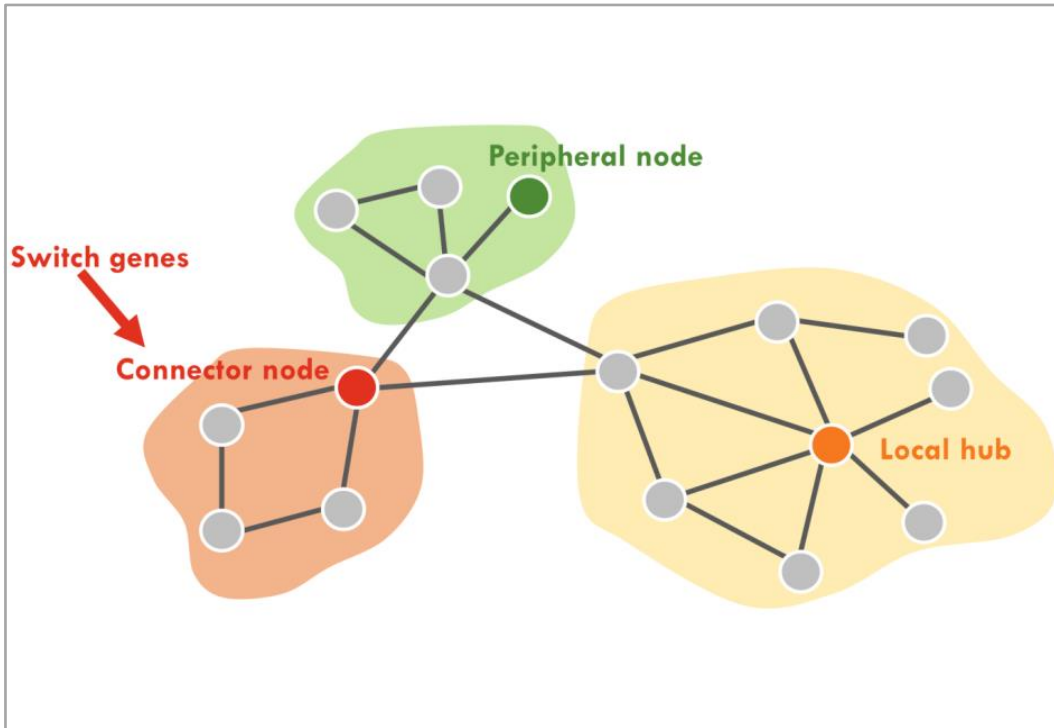


SWIM analysis

<https://github.com/sportingCode/SWIMmeR.git>



Switch genes



- ❖ They show **coherent patterns of correlation** suggesting they may be co-regulated or **functionally related**
- ❖ They form **localized connected subnetworks** in the correlation network
- ❖ They are **not local hub** within their own module
- ❖ They are important **connector nodes** able to convey information between modules of the correlation network

Genetic, epigenetic and genomic effects on variation of gene expression among grape varieties

Gabriele Magris^{1,2}, Gabriele Di Gaspero², Fabio Marroni^{1,2}, Sara Zenoni³, Giovanni Battista Tornielli³, Mirko Celii^{1,2}, Emanuele De Paoli¹, Mario Pezzotti³, Federica Conte^{4,5}, Paola Paci^{4,5} and Michele Morgante^{1,2,*}

Plant Physiology

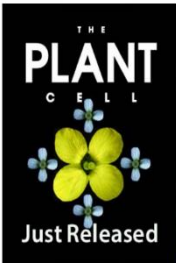
Ripening Transcriptomic Program in Red and White Grapevine Varieties Correlates with Berry Skin Anthocyanin Accumulation

Mélanie Massonnet, Marianna Fasoli, Giovanni Battista Tornielli, Mario Altieri, Marco Sandri, Paola Zuccolotto, Paola Paci, Massimo Gardiman, Sara Zenoni, Mario Pezzotti
Published August 2017. DOI: <https://doi.org/10.1104/pp.17.00311>

Distinct transcriptome responses to water limitation in isohydric and anisohydric grapevine cultivars



Silvia Dal Santo^{1†}, Alberto Palliotti^{2†}, Sara Zenoni¹, Giovanni Battista Tornielli¹, Marianna Fasoli^{1,3}, Paola Paci⁴, Sergio Tombesi², Tommaso Frioni², Oriana Silvestroni⁵, Andrea Bellincontro⁶, Claudio d'Onofrio⁷, Fabiola Matarese⁷, Matteo Gatti⁸, Stefano Poni⁸ and Mario Pezzotti^{1*}



Integrated Network Analysis Identifies Fight-Club Nodes as a Class of Hubs Encompassing Key Putative Switch Genes That Induce Major Transcriptome Reprogramming during Grapevine Development

Maria Concetta Palumbo^{a,1}, Sara Zenoni^{b,1}, Marianna Fasoli^b, Mélanie Massonnet^b, Lorenzo Farina^c, Filippo Castiglione^a, Mario Pezzotti^b and Paola Paci^{d,e,2}



HUMAN DISORDERS

2021

FEBS
Letters



Gene network analysis using SWIM reveals interplay between the transcription factor-encoding genes HMGA1, FOXM1, and MYBL2 in triple-negative breast cancer

Giulia Fison^{1,2}, Silvia Pegoraro³, Federica Conte¹ , Guidalberto Manfioletti^{3,1} and Paola Paci^{1,4,†}

2020

SCIENTIFIC REPORTS

Integrated transcriptomic correlation network analysis identifies COPD molecular determinants

Paola Paci^{1,†}, Giulia Fison¹, Federica Conte¹, Valerio Licursi², Jarrett Morrow³, Craig Hersh³, Michael Cho³, Peter Castaldi³, Kimberly Glass³, Edwin K. Silverman³ & Lorenzo Farina⁴

2019

Endocrine

International Journal of Basic and Clinical Endocrinology

BRAF^{V600E}-mutant cancers display a variety of networks by SWIM analysis: prediction of vemurafenib clinical response

Rosa Falcone¹ , Federica Conte^{1,2,3} , Giulia Fison^{1,2,3} , Valeria Pecce¹, Marialuisa Sponziello¹ , Cosimo Durante¹ , Lorenzo Farina^{1,4} , Sebastiano Filetti¹, Paola Paci^{1,2} , Antonella Verrienti¹

2018

SCIENTIFIC REPORTS

Computational identification of specific genes for glioblastoma stem-like cells identity

Giulia Fison^{1,2} , Federica Conte^{1,2}, Valerio Licursi¹, Sergio Nasi^{3,4} & Paola Paci^{1,2}

2018

BMC Bioinformatics

RESEARCH

SWIM tool application to expression data of glioblastoma stem-like cell lines, corresponding primary tumors and conventional glioma cell lines

Giulia Fison^{1,2}, Federica Conte^{1,2} and Paola Paci^{1,2*}

2017

SCIENTIFIC REPORTS

SWIM: a computational tool to unveiling crucial nodes in complex biological networks

Paola Paci^{1,2}, Teresa Colombo³, Giulia Fison¹, Aymone Gurtner³, Giulio Pavesi⁴ & Lorenzo Farina⁵

2016

GNB 2016

V CONGRESSO
GRUPPO NAZIONALE DI BIOINGEGNERIA

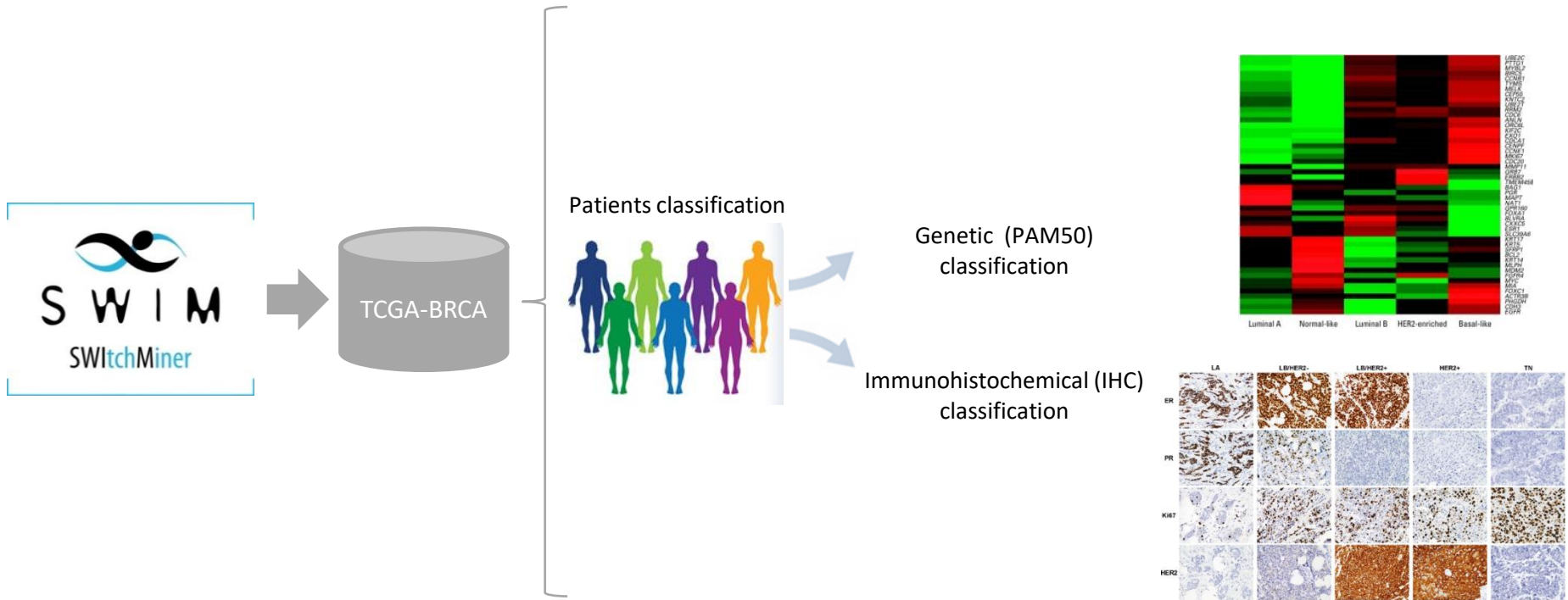
20 - 22 Giugno 2016, Napoli



Integrated network analysis for studying human lung squamous cell carcinoma

G. Fison^{1,*}, F. Conte^{1,*}, T. Colombo¹, L. Farina², and P. Paci¹

SWIM-based analysis of BC subtypes



International Journal of
Molecular Sciences

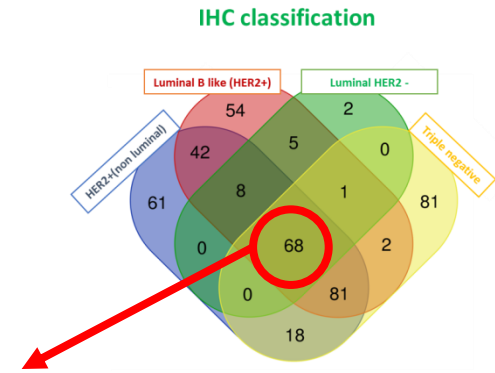
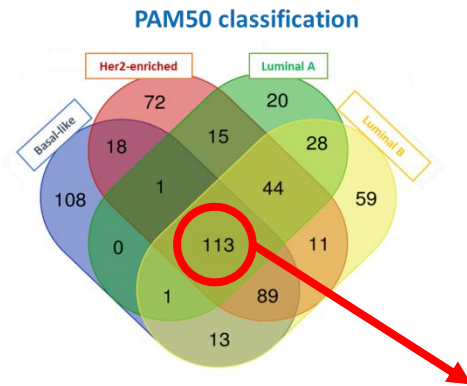


Article

The New Paradigm of Network Medicine to Analyze Breast Cancer Phenotypes

Anna Maria Grimaldi ^{1,†}, Federica Conte ^{2,†}, Katia Pane ^{1,†}, Giulia Fison ²,
Peppino Mirabelli ¹, Simona Baselice ¹, Rosa Giannatiempo ³, Francesco Messina ³,
Monica Franzese ¹, Marco Salvatore ¹, Paola Paci ^{4,*} and Mariarosaria Incoronato ^{1,*}

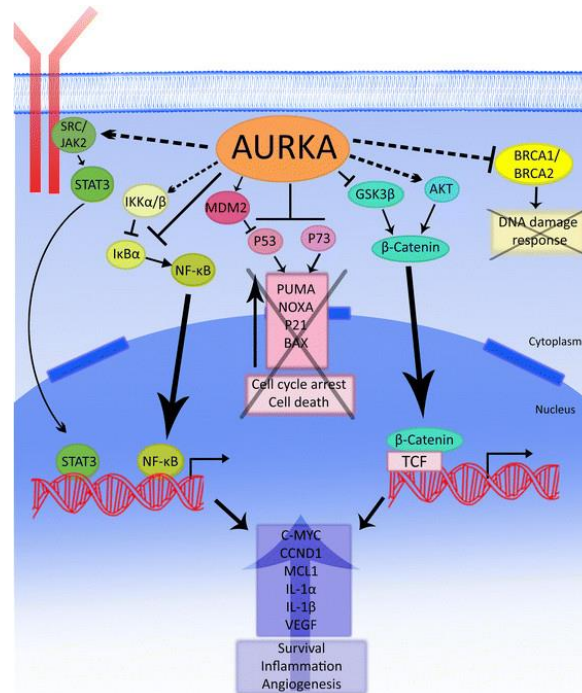
Common switch genes among BC subtypes



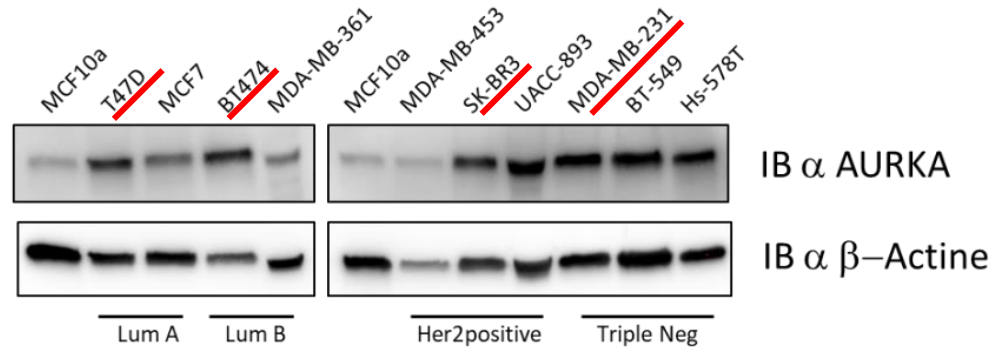
| Gene name | Gene description | Location | Type(s) | Gene stable ID |
|---------------|---|-----------|-------------------------|-----------------|
| <i>AURKA</i> | aurora kinase A | Nucleus | kinase | ENSG00000087586 |
| <i>CCNB1</i> | cyclin B1 | Cytoplasm | kinase | ENSG00000134057 |
| <i>CCNB2</i> | cyclin B2 | Cytoplasm | other | ENSG00000157456 |
| <i>CDC20</i> | cell division cycle 20 | Nucleus | other | ENSG00000117399 |
| <i>CDC45</i> | cell division cycle 45 | Nucleus | other | ENSG00000093009 |
| <i>CDK1</i> | cyclin dependent kinase 1 | Nucleus | kinase | ENSG00000170312 |
| <i>ESPL1</i> | extra spindle pole bodies like 1, separase | Nucleus | peptidase | ENSG00000135476 |
| <i>NEK2</i> | NIMA related kinase 2 | Cytoplasm | kinase | ENSG00000117650 |
| <i>PLK1</i> | polo like kinase 1 | Nucleus | kinase | ENSG00000166851 |
| <i>PTTG1</i> | PTTG1 regulator of sister chromatid separation, securin | Nucleus | transcription regulator | ENSG00000164611 |
| <i>RAD54L</i> | RAD54 like | Nucleus | enzyme | ENSG00000085999 |

Aurora Kinase A (AURKA)

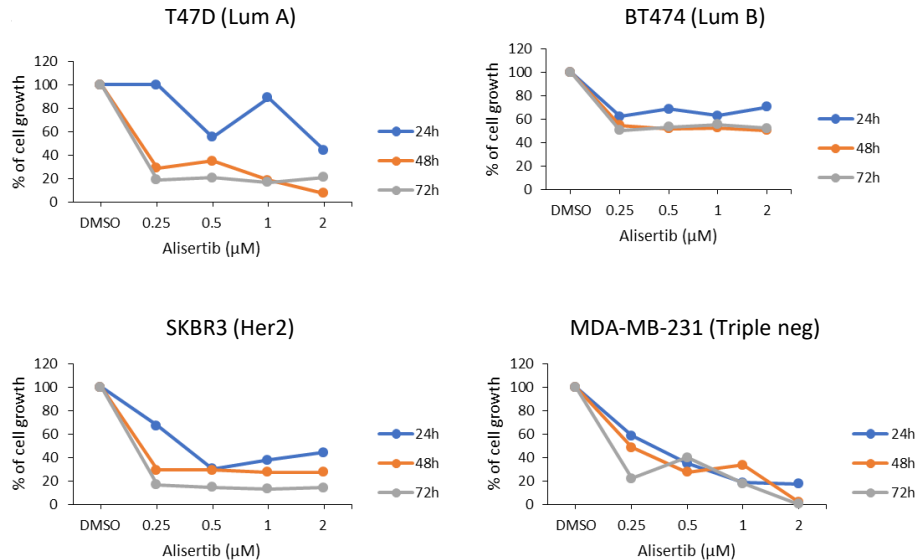
- ❖ It is a kinase with a key role in cell division and cell-cycle progression
- ❖ It is critical for proper formation of the mitotic spindle and chromosomal segregation
- ❖ It is deregulated in many human cancers
- ❖ It collaborates with numerous tumor suppressors (e.g., p53, BRCA1, BRCA2)
- ❖ It is suggested as a priority pharmaceutical target for the treatment of cancers



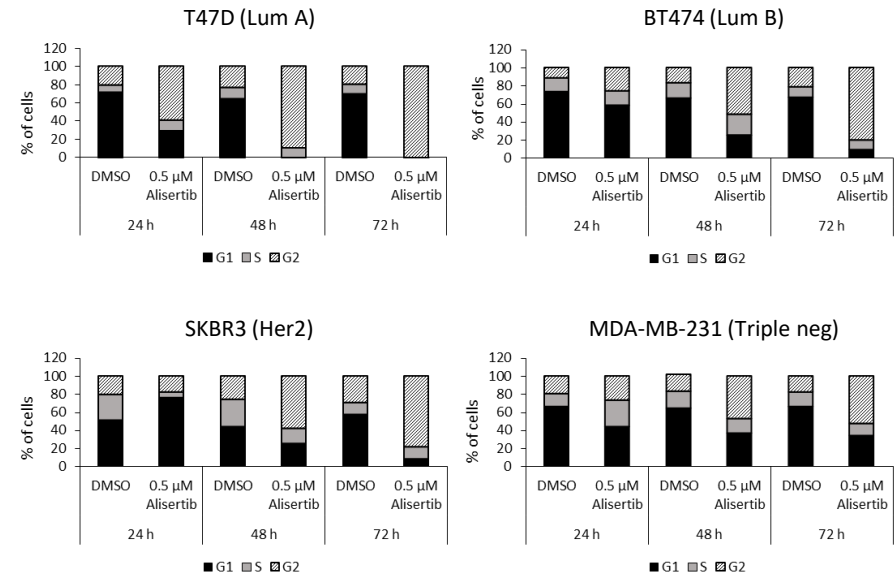
AURKA protein: experiments in BC cell lines



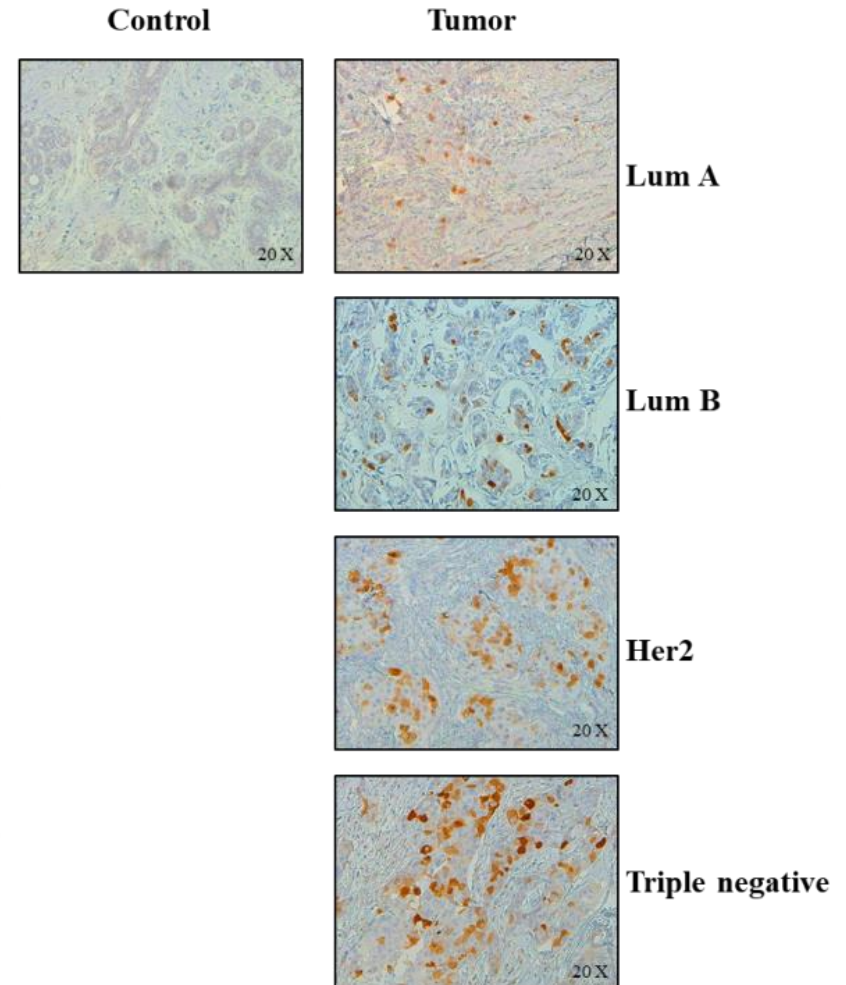
cell growth



cell cycle

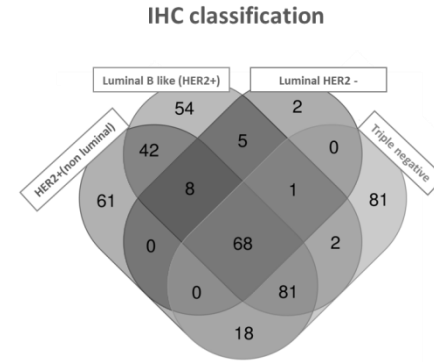
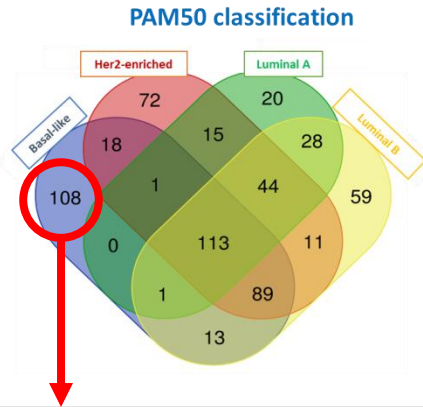


AURKA protein: experiments in BC tissues

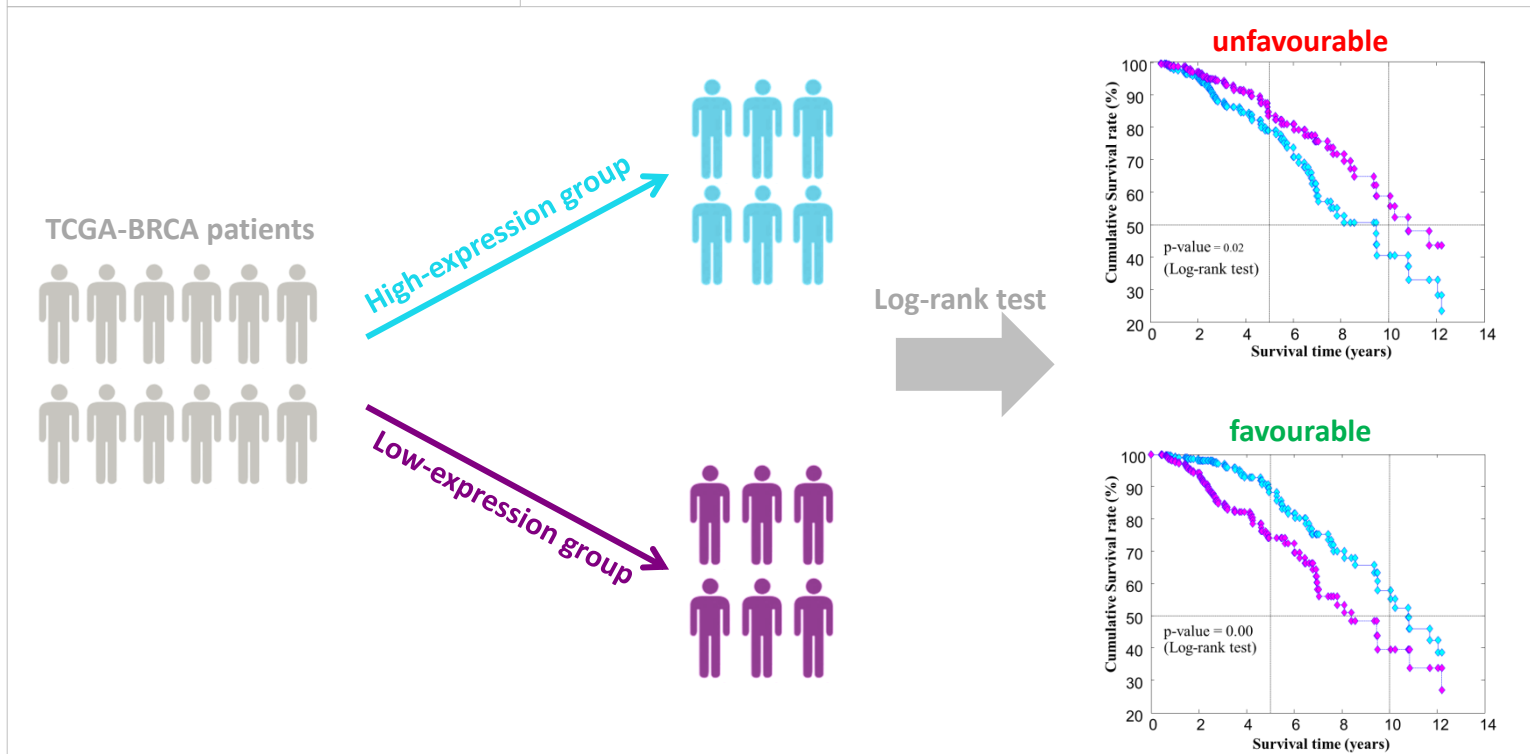


| Breast specimens | Number of samples |
|------------------|-------------------|
| Control | 4 |
| Luminal A | 6 |
| Luminal B | 5 |
| Her2-enriched | 8 |
| Triple negative | 4 |

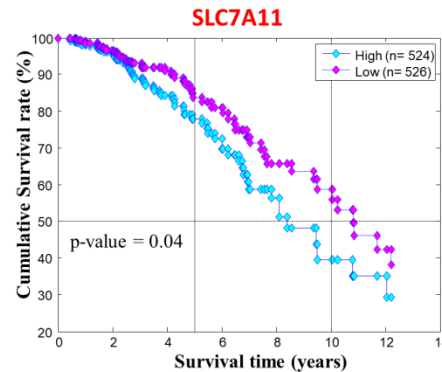
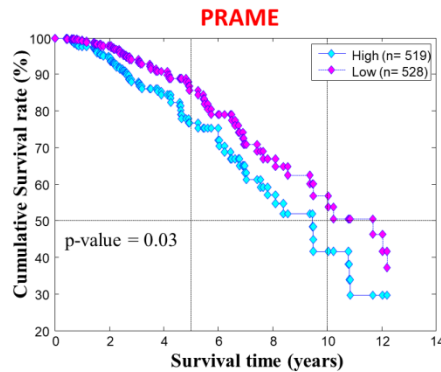
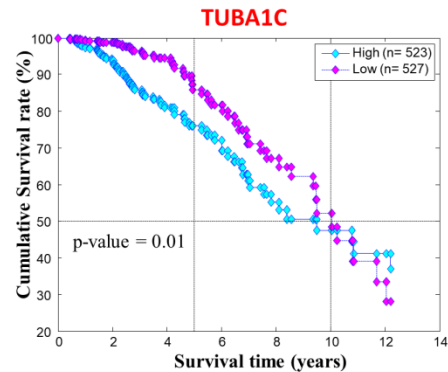
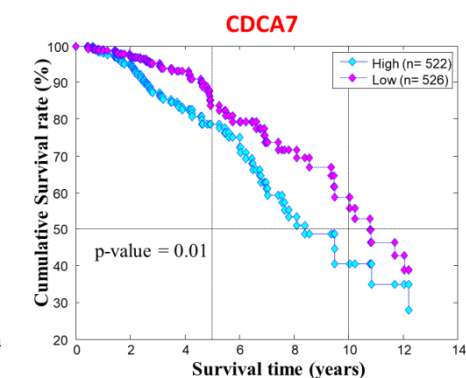
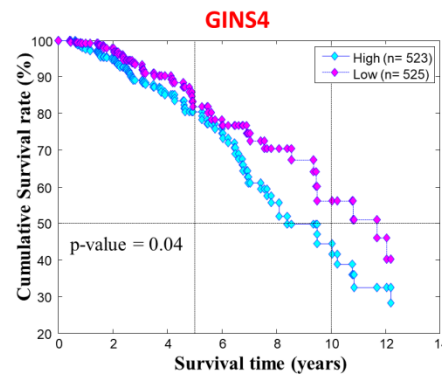
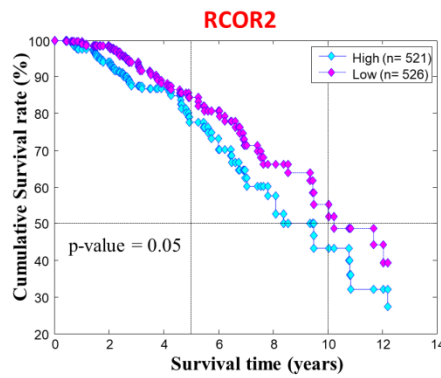
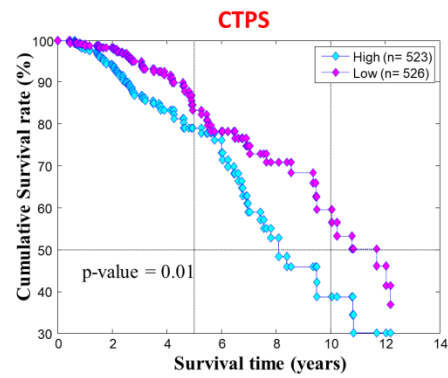
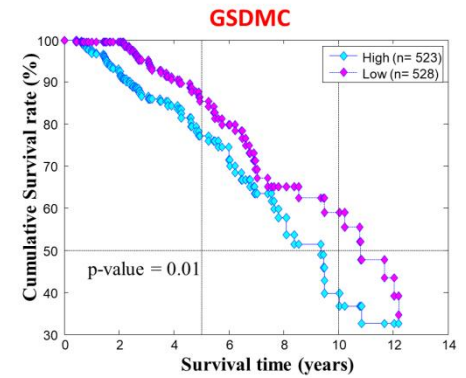
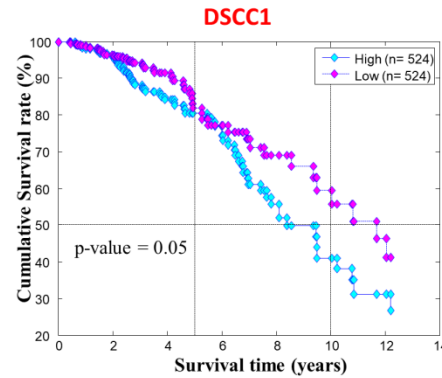
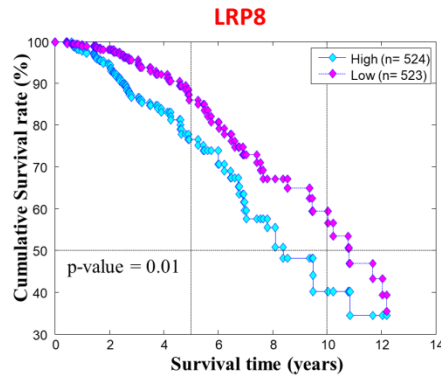
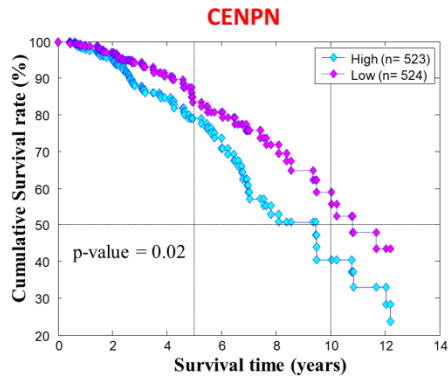
Basal-like specific switch genes



Kaplan-Meier survival analysis

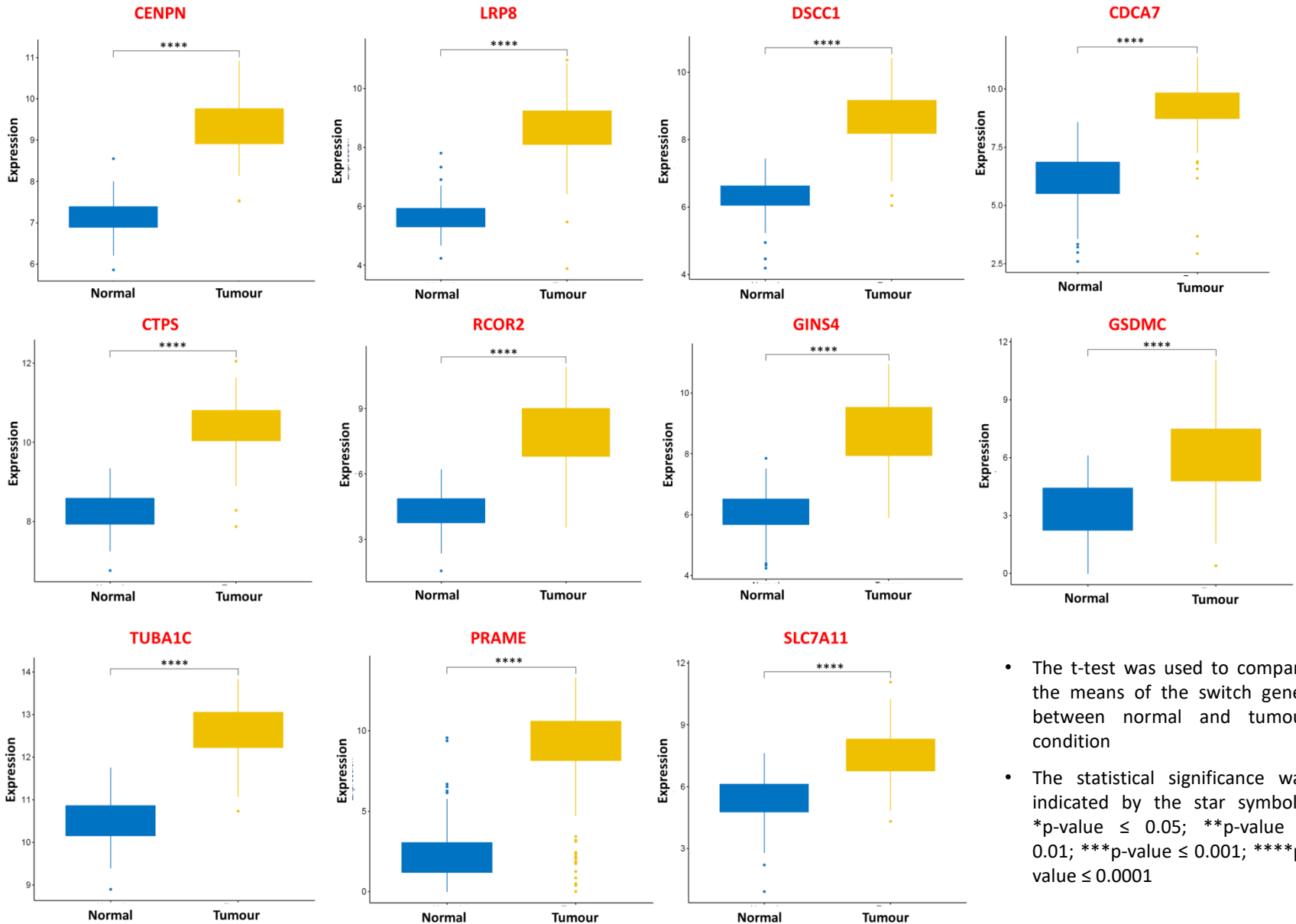


Prognostic value of the basal-like specific switch genes



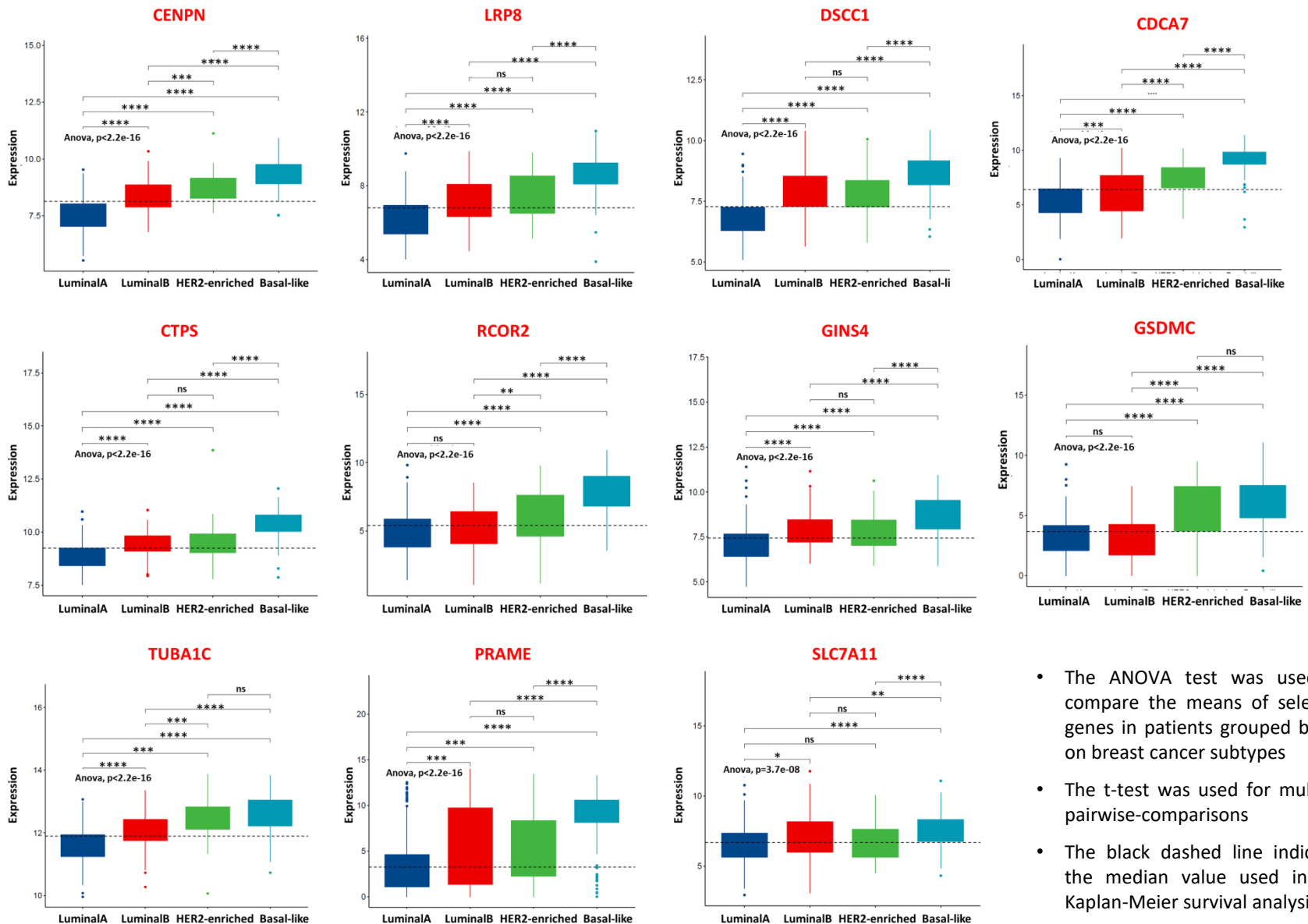
- Low- and High- groups refer to patients with expression levels lower and greater than the 50th percentile
- The survival outcomes of the two groups were compared by the log-rank test
- The clinical relevance of the switch genes was confirmed using other BC datasets collected in the Kaplan-Meier plotter website

Overexpression of the basal-like prognostic biomarkers



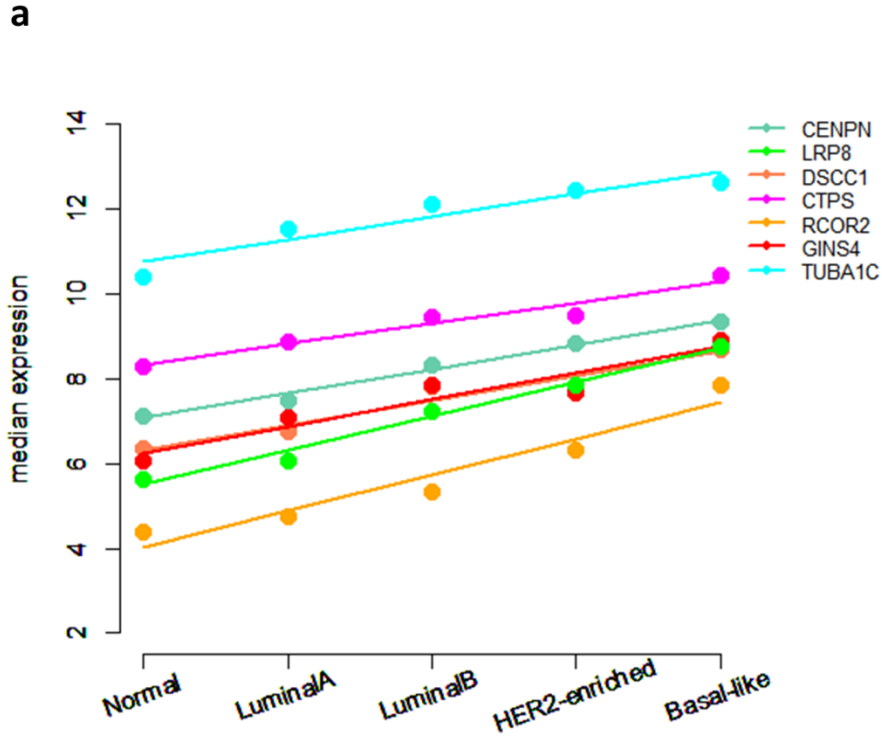
- The t-test was used to compare the means of the switch genes between normal and tumour condition
- The statistical significance was indicated by the star symbols: *p-value \leq 0.05; **p-value \leq 0.01; ***p-value \leq 0.001; ****p-value \leq 0.0001

Overexpression of the basal-like prognostic biomarkers

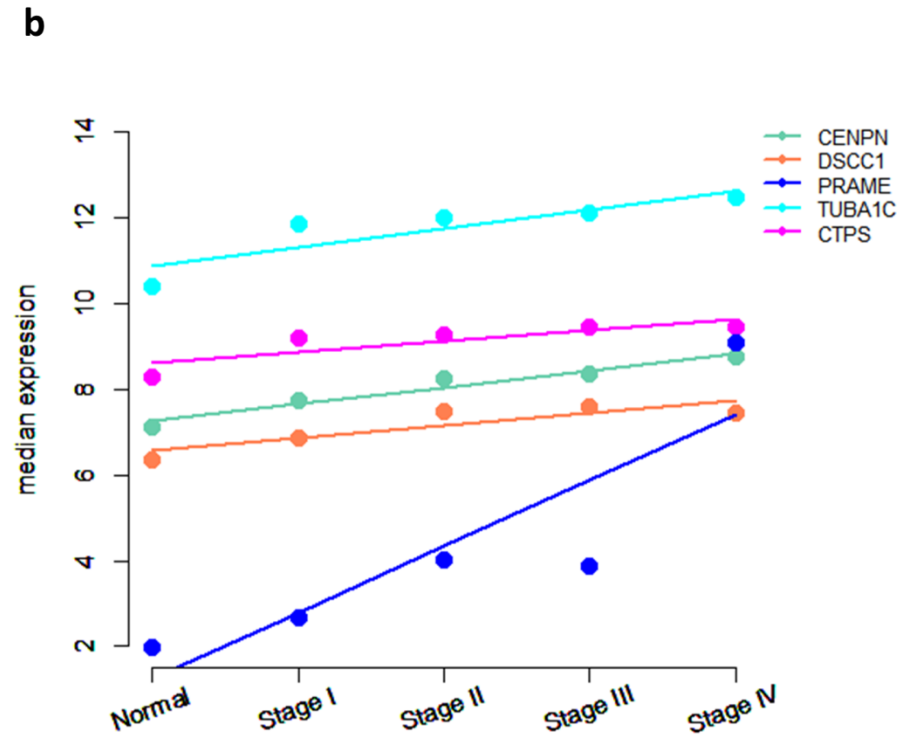


- The ANOVA test was used to compare the means of selected genes in patients grouped based on breast cancer subtypes
- The t-test was used for multiple pairwise-comparisons
- The black dashed line indicates the median value used in the Kaplan-Meier survival analysis

Linear regression model fitting

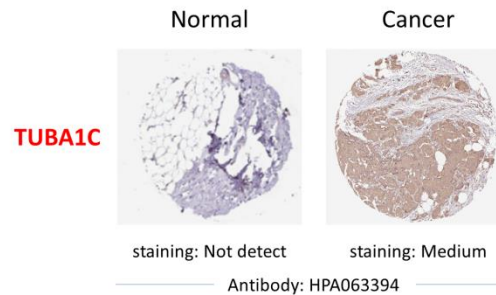
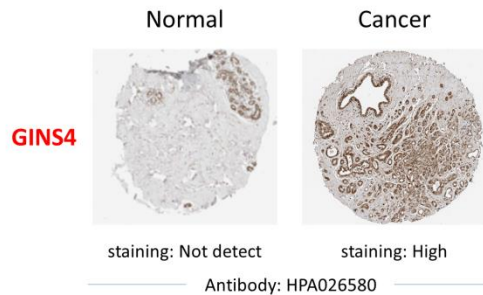
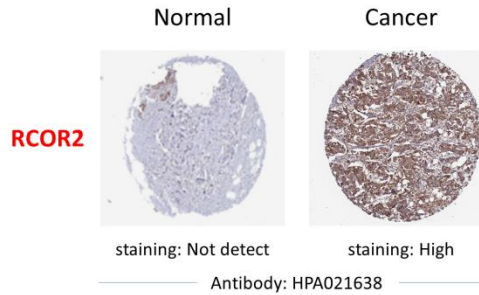
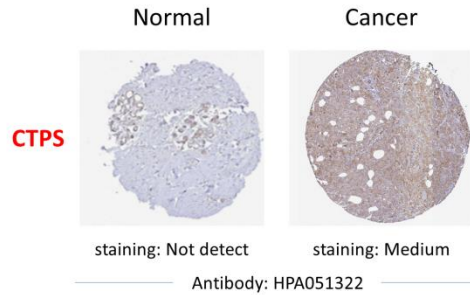
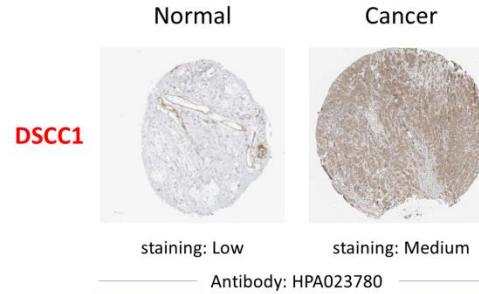
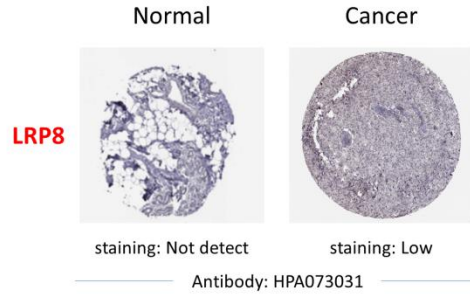


R-squared ≥ 0.9

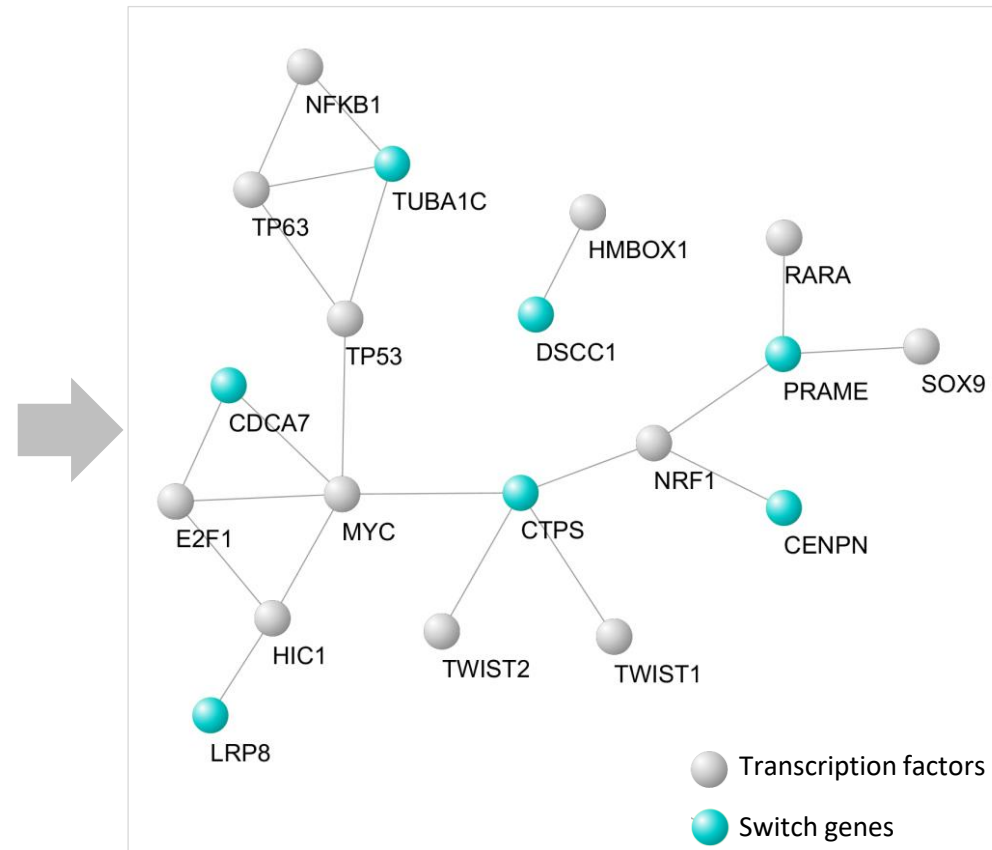
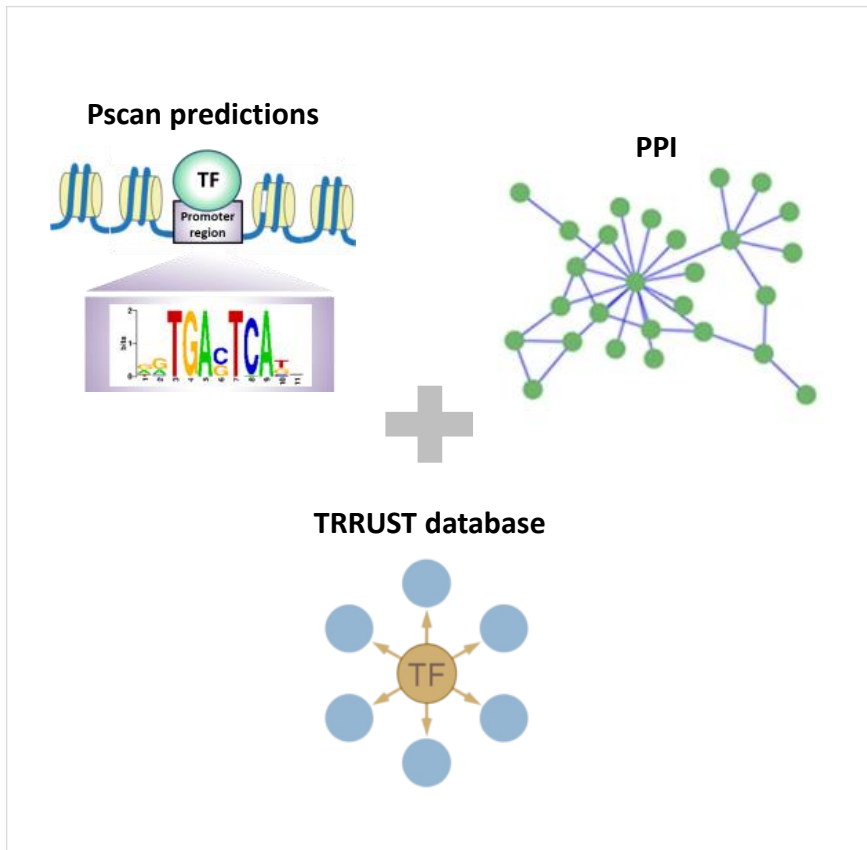


R-squared ≥ 0.7

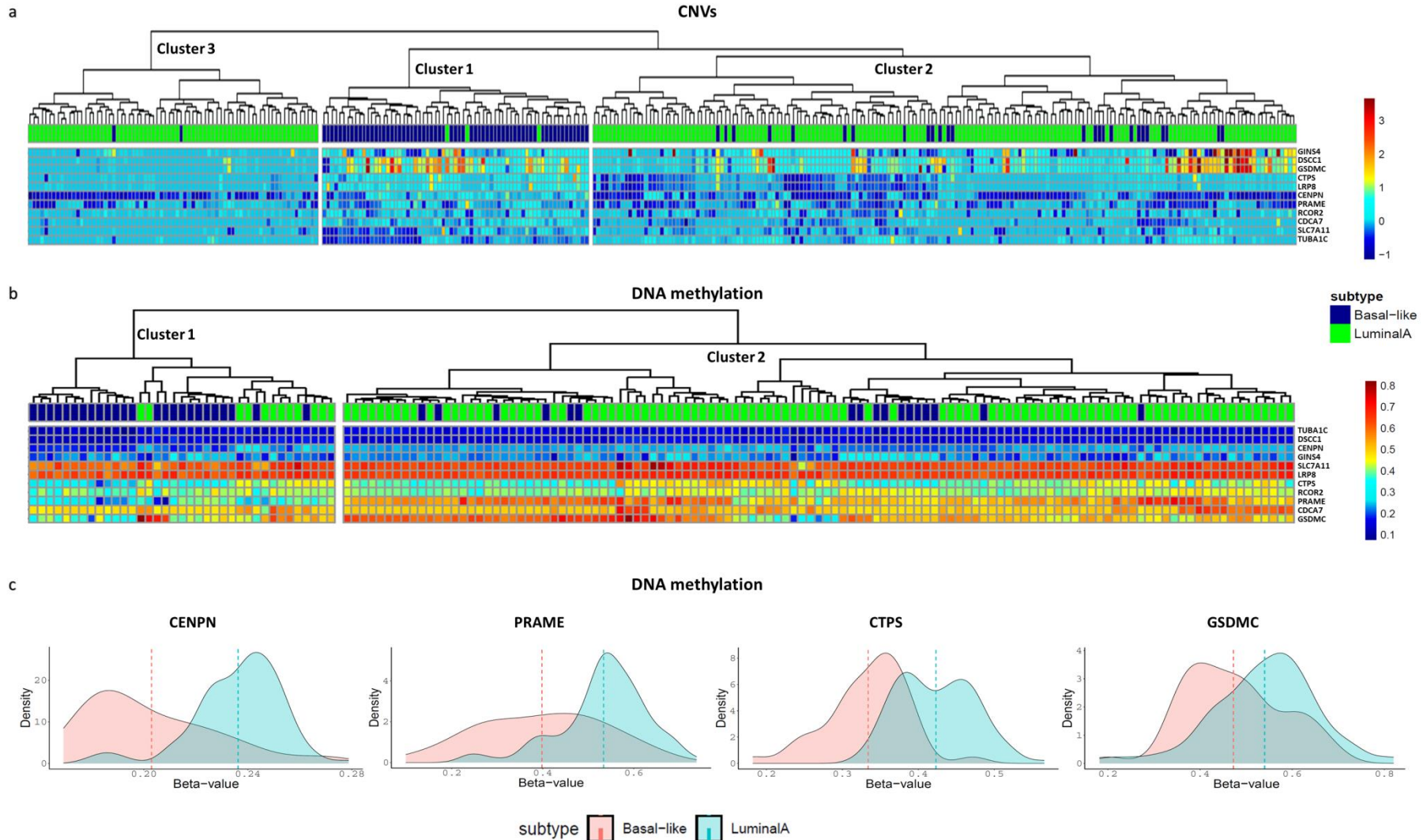
Protein expression levels



Gene regulatory network of the basal-like prognostic biomarkers



Genomic and epigenomic alterations of the basal-like prognostic biomarkers



Conclusions

Basal-like gene signature

| | DNA | | | RNA | | | | | Protein |
|---------|----------------------------|-----------------------|-------------|--------------|--------------------------------|----------------|---------------------------------------|-------|----------------------|
| | TFs | CNVs | Methylation | SWIM | KM analysis (log rank p-value) | | model fitting (index R ²) | | IHC staining |
| | TRRUST/Pscan/PPI | TCGA | TCGA | TCGA | TCGA | other datasets | subtype | stage | HPA |
| CENPN | <i>NRF1</i> | amp in BL/del in LumA | hypo in BL | switch genes | 0.02 | 4.9E-6 | 0.99 | 0.96 | not available* |
| LRP8 | <i>HIC1</i> | amp in BL/del in LumA | - | switch genes | 0.01 | 2.4E-4 | 0.98 | 0.63* | more expressed in BC |
| DSCC1 | <i>HMBOX1</i> | amp in BL | - | switch genes | 0.05 | 3.5E-8 | 0.95 | 0.78 | more expressed in BC |
| CTPS | <i>MYC, TWIST1-2, NRF1</i> | amp in BL/del in LumA | hypo in BL | switch genes | 0.01 | 8.2E-5 | 0.94 | 0.72 | more expressed in BC |
| RCOR2 | - | - | - | switch genes | 0.05 | 4.3E-3 | 0.93 | 0.47* | more expressed in BC |
| GINS4 | - | - | - | switch genes | 0.04 | 6.4E-3 | 0.90 | 0.68 | more expressed in BC |
| TUBA1C | <i>TP53, NFKB1</i> | del in BL | - | switch genes | 0.01 | 1.3E-6 | 0.89 | 0.76 | more expressed in BC |
| PRAME | <i>NRF1, SOX9, RARA</i> | amp in BL/del in LumA | hypo in BL | switch genes | 0.03 | 9.9E-6 | 0.83 | 0.76 | not available* |
| SLC7A11 | - | - | - | switch genes | 0.04 | 0.03 | 0.80 | 0.46* | not available* |
| CDCA7 | <i>MYC, E2F1</i> | amp in BL | - | switch genes | 0.01 | 1.3E-4 | 0.73 | 0.32* | not available* |
| GSDMC | - | amp in BL | hypo in BL | switch genes | 0.01 | 4.9E-4 | 0.64* | 0.05* | not available* |

Abbreviations: TFs, Transcription Factors; CNVs, Copy Number Variations; KM, Kaplan-Meier; IHC, Immunohistochemistry; PPI, protein-protein interactions; TCGA, The Cancer Genome Atlas; HPA, Human Protein Atlas; BC, Breast Cancer; BL, Basal-like; LumA, Luminal A; amp, amplified; del, deleted; hypo, hypomethylated. Asterisk (*) was used to highlight values not satisfying the chosen thresholds as well as not available data.



THANK
YOU

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