The IWBBIO 2022 (9th International Work-Conference on Bioinformatics and Biomedical Engineering)

Integrative Analysis of Ovarian Serious Adenocarcinoma to Understand Disease Network Biology

Dr. Raza's Lab

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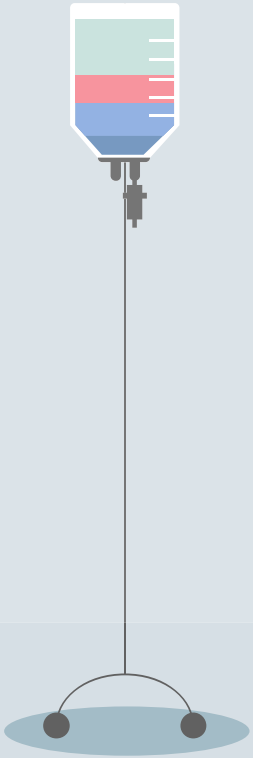


“He who conceals his disease cannot expect to be cured !”

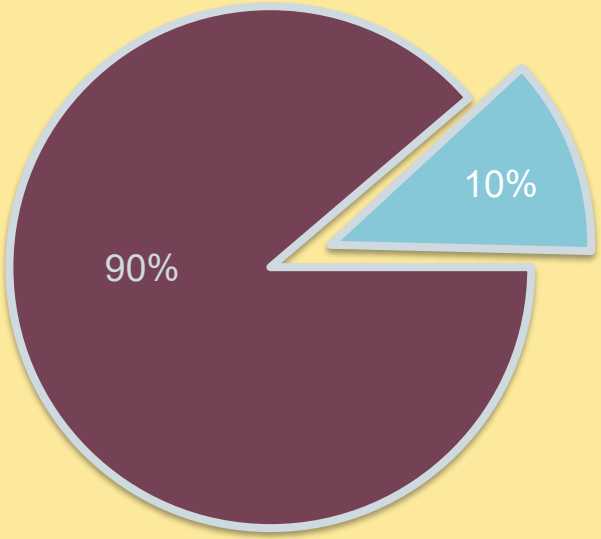
—An Ethopian Proverb

INTRODUCTION

Ovarian Cancer (OC)

- Ovarian cancer (OC) is one of the gynecologic oncologic malignancies in females that leads to lethality annually is a cancer that develops on the surface of the ovary.
- As per the NCRP-ICMR (2013) it is known to be the third leading cause of cancer triggered deaths in females and henceforth is tagged as a ***Silent Killer***.
- Ovarian Cancer has majorly five subtypes, namely - ***High grade serous*** (HGS-OvCa), ***Low grade serous*** (LGS- OvCa), ***Endometrioid***, ***Mucinous***, ***Clear Cell Tumors***.
- High grade serous is the most common types of ovarian cancer (OC) in females in India.

TYPES OF OVARIAN CANCER



90%

Are epithelial carcinoma

10%

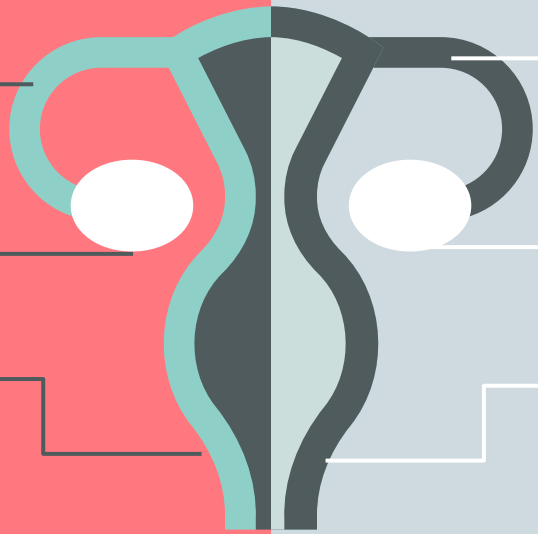
Are germ cell and stromal tumors

FACTORS INVOLVED IN OVARIAN CANCER

Obesity

Growing Age

History of breast cancer

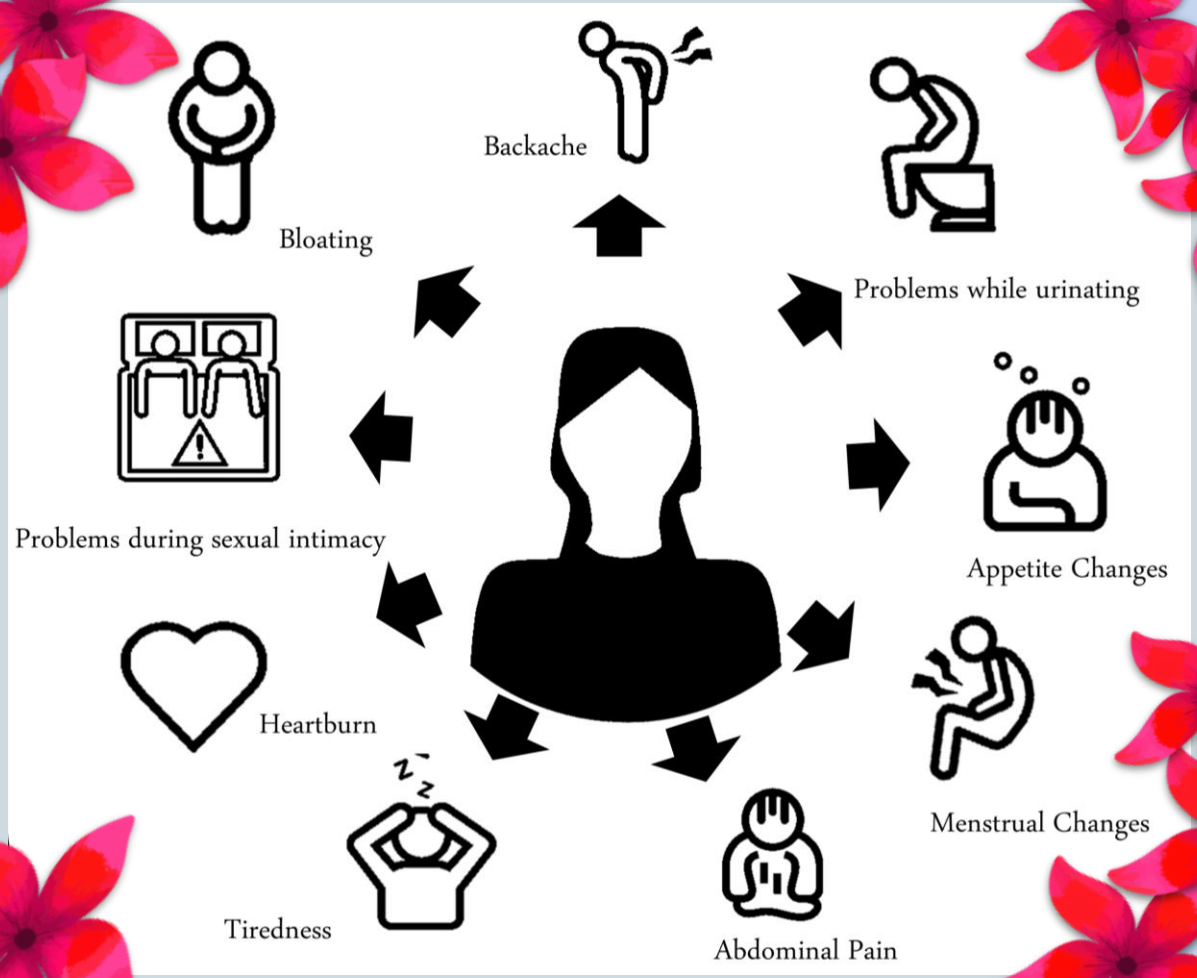


HRT

IVF approaches

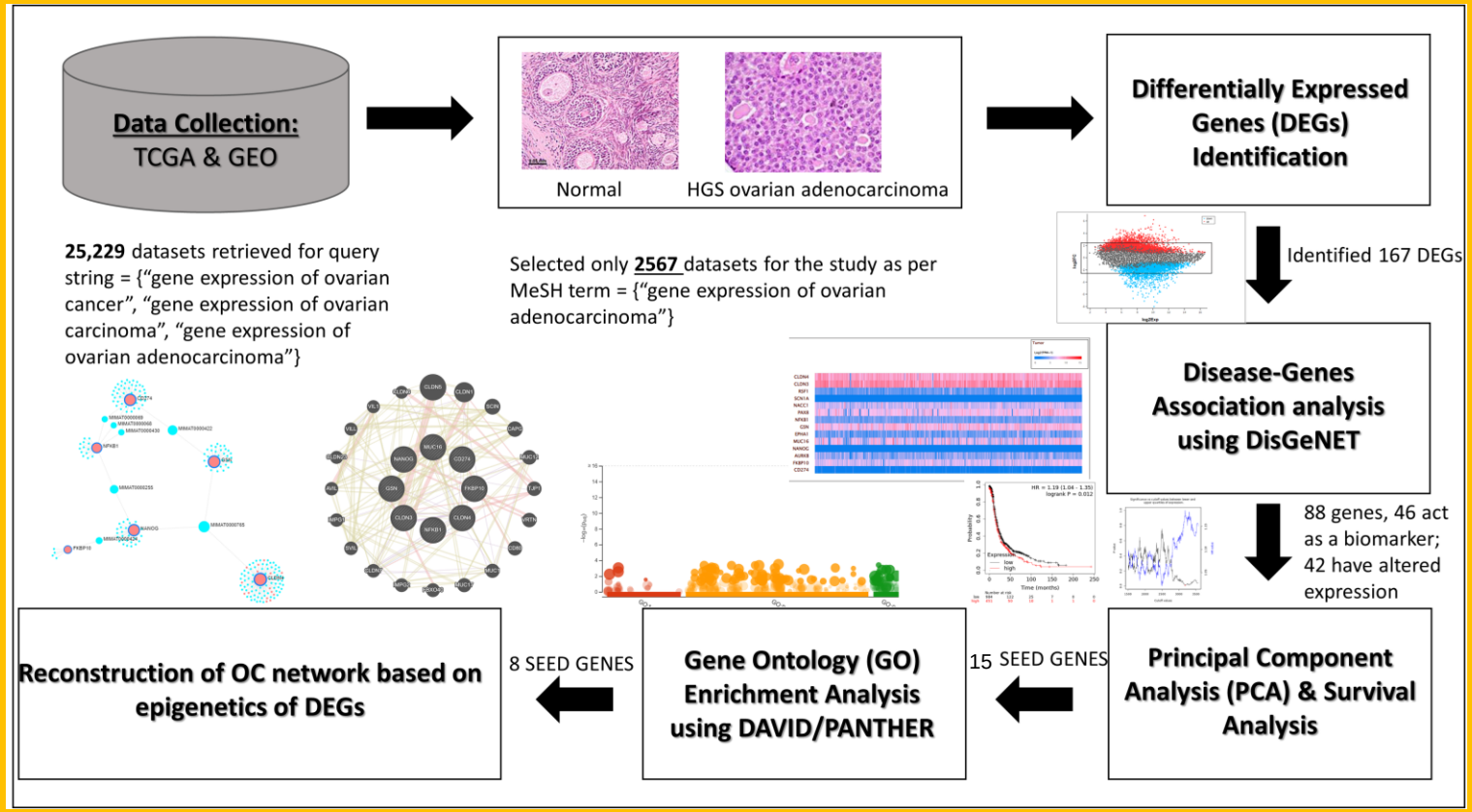
Infertility

COMMON SIGNS



OBJECTIVE

Analysing the behaviour of ovarian cancer (OC) network

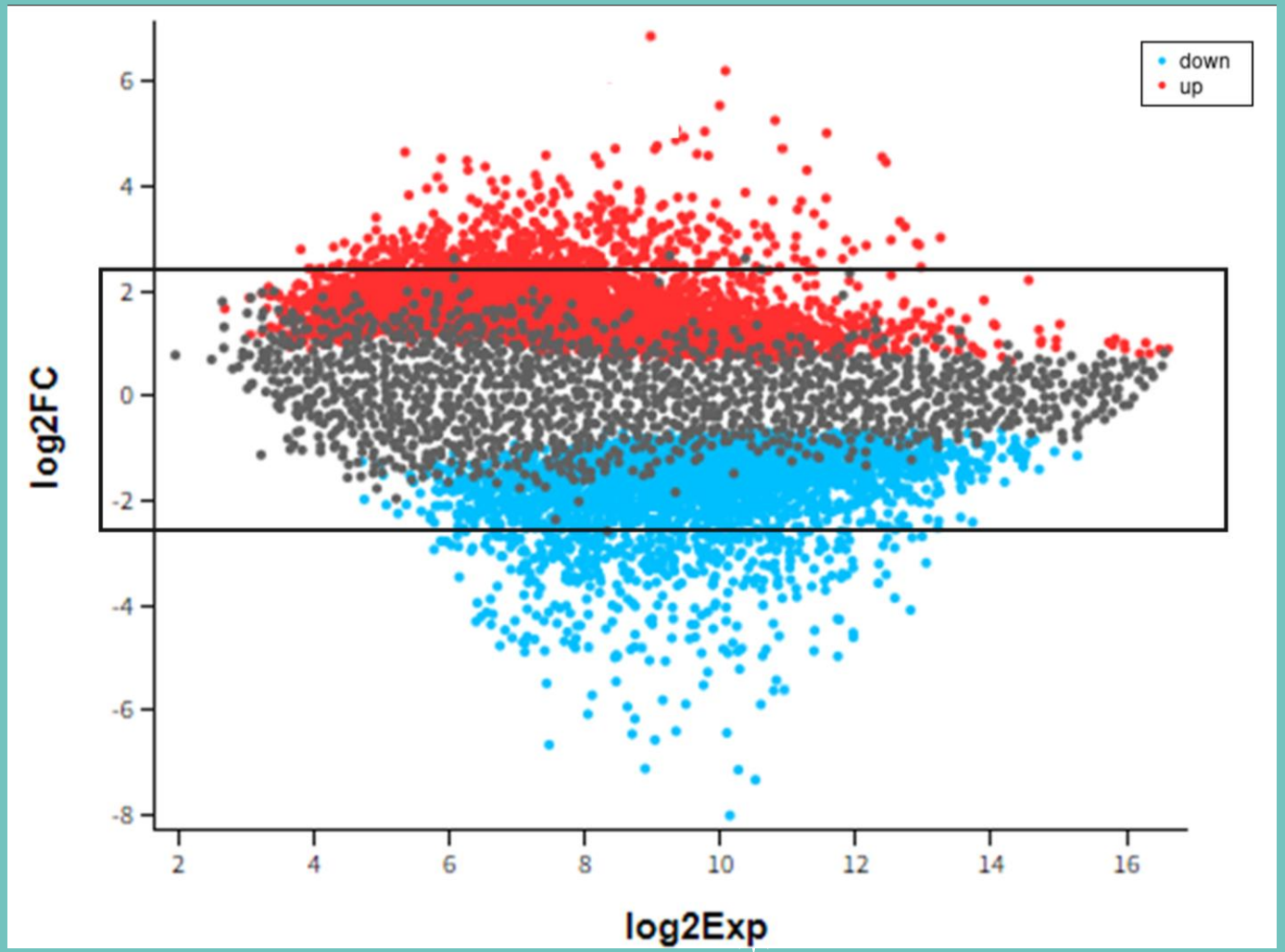


GRAPHICAL ABSTRACT

DATABASES/SOFTWARE/PLUGINS USED

S.No.	NAME	PURPOSE	LINK
1.	The Cancer Genome Atlas (TCGA) database	OVCA gene expression dataset retrieval	https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga
2.	Gene expression omnibus (GEO) database	OVCA gene expression dataset retrieval	https://www.ncbi.nlm.nih.gov/geo/
3.	R Studio (packages used: GeoTcgaData, BiocManager, forcats, stringr,igraph ggplot2,ggrepel,readr, tidyr, survminer, GEOquery, limma, pheatmap, ClustVis, pcaExplorer,OmicsNetR)	Differentially expressed genes (DEGS) identification, inspection of clinical variables, sample clustering and principal component analysis (PCA), network visualization	https://www.r-project.org/
4.	Kaplan Meier (KM) survival estimation webserver	Prediction of survival estimates of the seed genes.	https://kmplot.com/analysis/index.php?p=background
5.	Cytoscape software (plugins used: DisGeNET, BINGO, GeneMania & EnrichmentMap)	Network visualization, disease-gene associations, gene ontology (GO) representation in network, gene regulatory network re-construction and pathway enrichment	https://cytoscape.org/

SCATTER PLOT

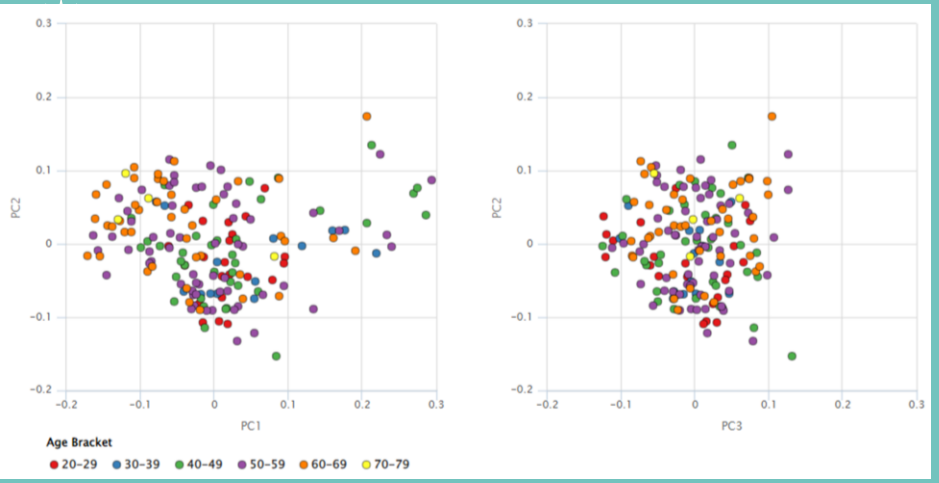


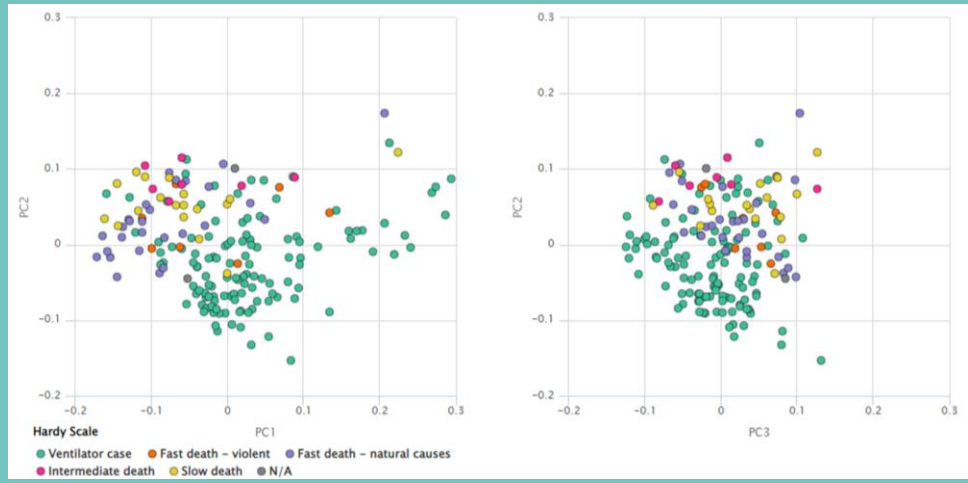
Here, the red-colored dots represent **up-regulated** (over-expressed) genes while dots in blue represent **down-regulated** (under-expressed) genes in serous ovarian adenocarcinoma. The grey dots represent those genes that maintain a normal level of expression.

DISEASE-GENE ASSOCIATION USING DiSGeNET

S.No.	Seed Gene	Association	Score
1.	*CLDN3*	Biomarker	0.02
2.	*CLDN4*	Biomarker	0.11
3.	*RSF1*	Altered Expression	0.02
4.	*SCN1A*	Biomarker; Altered Expression	0.3
5.	*NACC1*	Biomarker, Altered Expression	0.01
6.	*PAX8*	Biomarker	0.1
7.	*NFKB1*	Biomarker	0.01
8.	*GSN*	Biomarker, Altered Expression	0.1
9.	*EPHA1*	Biomarker	0.02
10.	*MUC16*	Biomarker	0.3
11.	*TP53*	Biomarker	0.1
12.	*NANOG*	Altered Expression	0.01
13.	*AURKB*	Altered Expression	0.3
14.	*FKBP10*	Altered Expression	0.01
15.	*CD274*	Altered Expression	0.02

PRINCIPAL COMPONENT ANALYSIS (PCA)





a) PCA representing an incidence of ovarian serous adenocarcinoma based on the age bracket of a female.

b) PCA representing the severity of patients based on *Hardy-Weinberg's* equilibrium.

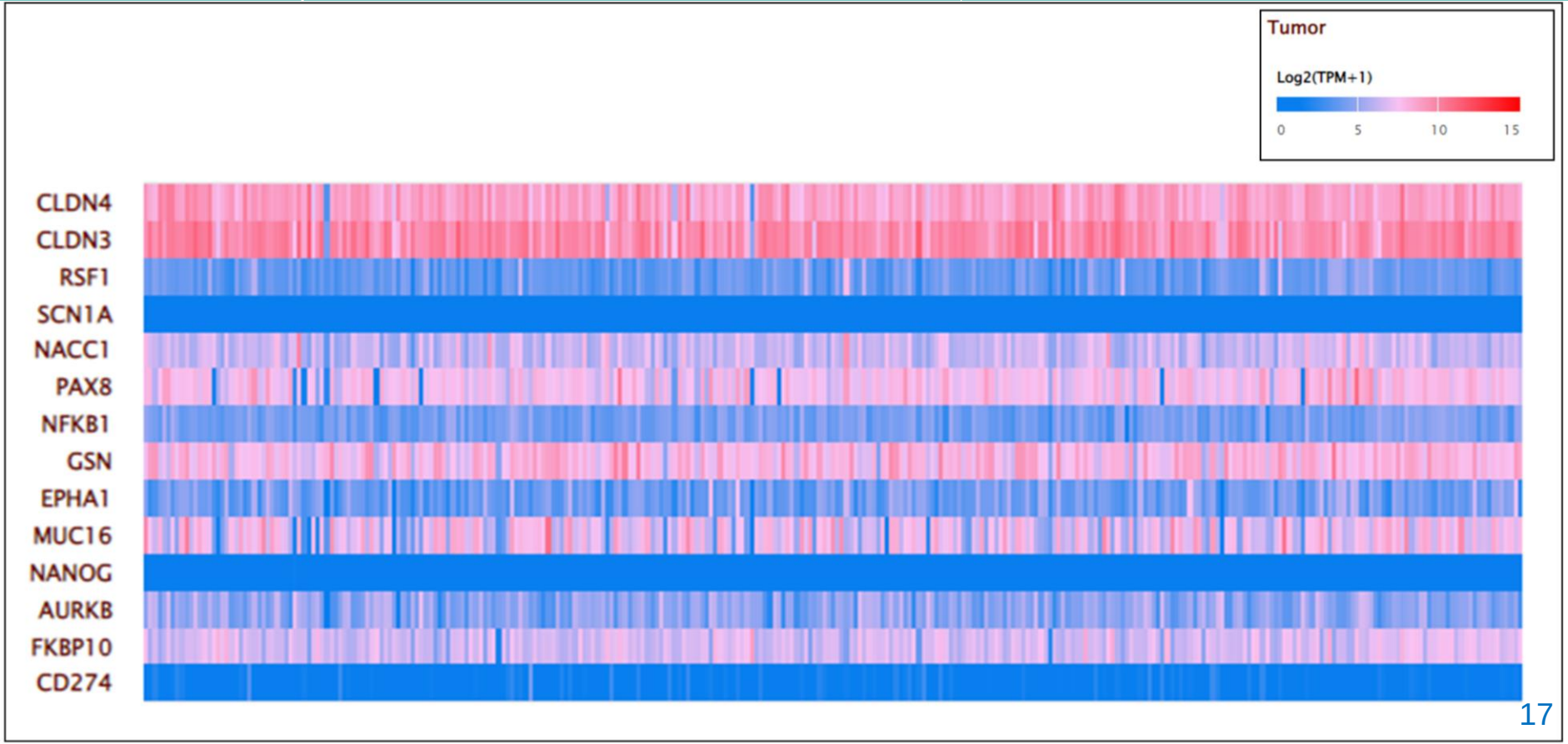
PRINCIPAL COMPONENT ANALYSIS (PCA)

c) PCA representing autolysis of genes involved in ovarian serous adenocarcinoma.

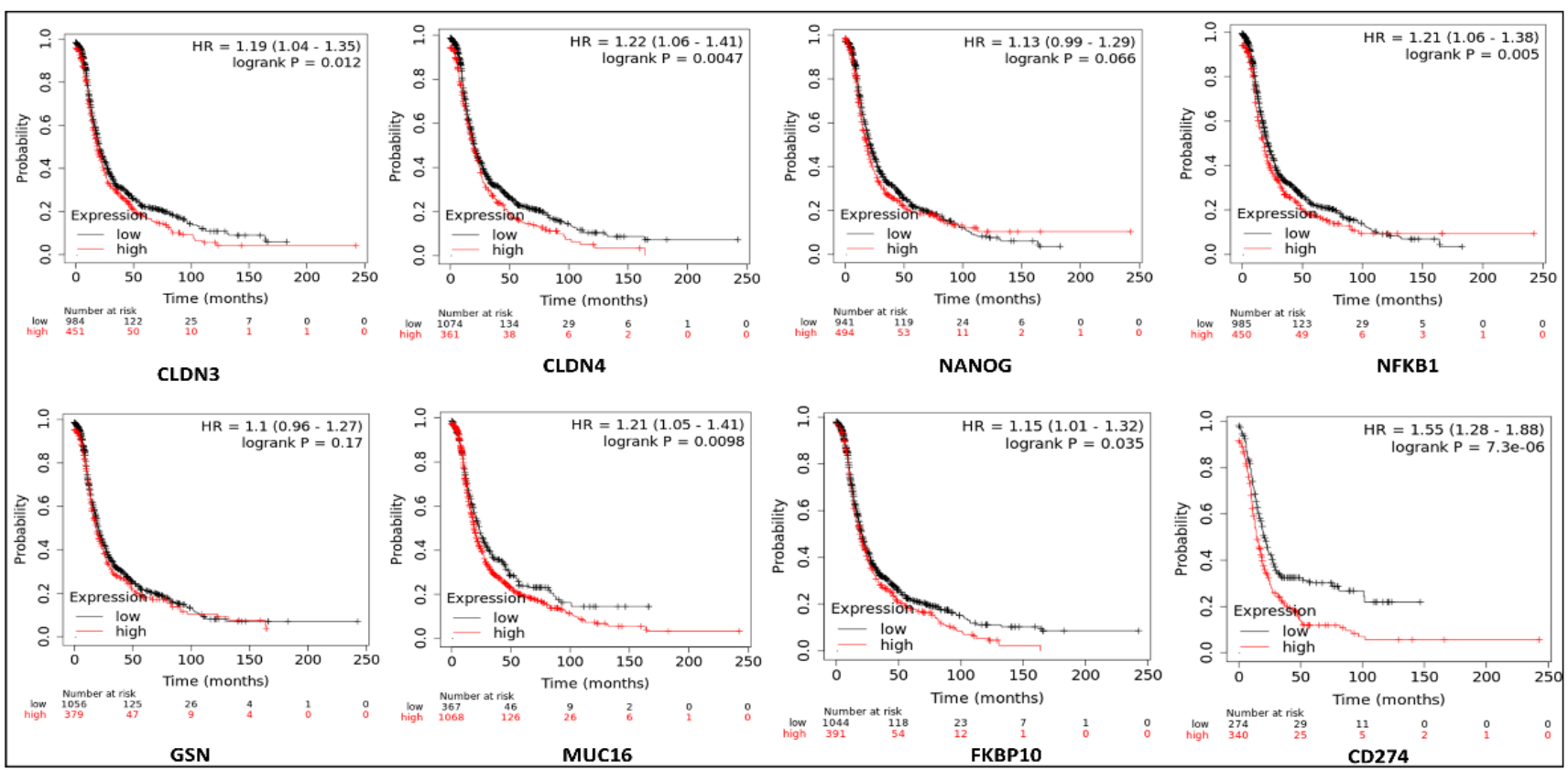
MEDIAN SURVIVAL ESTIMATES FOR 15 SEED GENES

S.No.	Seed Gene	Description	Low expression cohort (months)	High expression cohort (months)
1.	*CLDN3*	Claudin 3	20.63	18.83
2.	*CLDN4*	Claudin 4	20.2	19.0
3.	*RSF1*	Remodeling and spacing factor 1	18.0	15.0
4.	*SCN1A*	Sodium voltage-gated channel alpha subunit 1	18.0	21.29
5.	*NACC1*	Nucleus Accumbens Associated 1	18.27	16.0
6.	*PAX8*	Paired box gene 8	18.79	22.5
7.	*NFKB1*	Nuclear factor kappa B subunit 1	21.13	17.9
8.	*GSN*	Gelsolin	20.53	18.43
9.	*EPHA1*	Ephyrin type A receptor 1	18.23	22.02
10.	*MUC16*	Mucin 16	23.24	19.0
11.	*TP53*	Tumor protein P53	17.43	21.29
12.	*NANOG*	Nanog Homeobox	21.13	18.2
13.	*AURKB*	Aurora Kinase B	18.93	20.63
14.	*FKBP10*	FKBP Prolyl Isomerase 10	20.47	19.0
15.	*CD274*	CD274 molecule	20.0	14.37

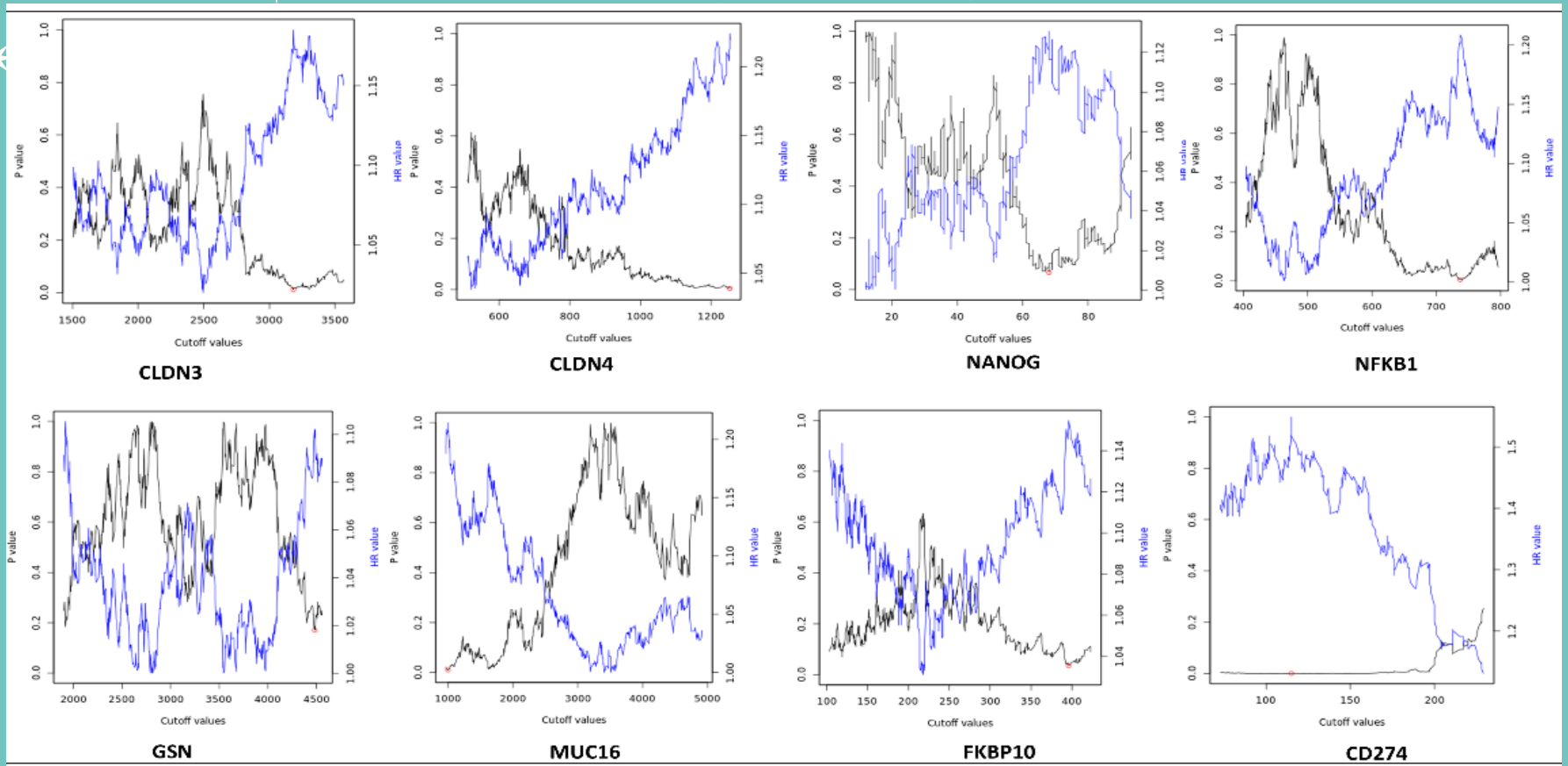
EXPRESSION PATTERNS OF SEED GENES IN THE FORM OF HEATMAP



KAPLAN MEIER SURVIVAL CURVES FOR TOP 8 GENES

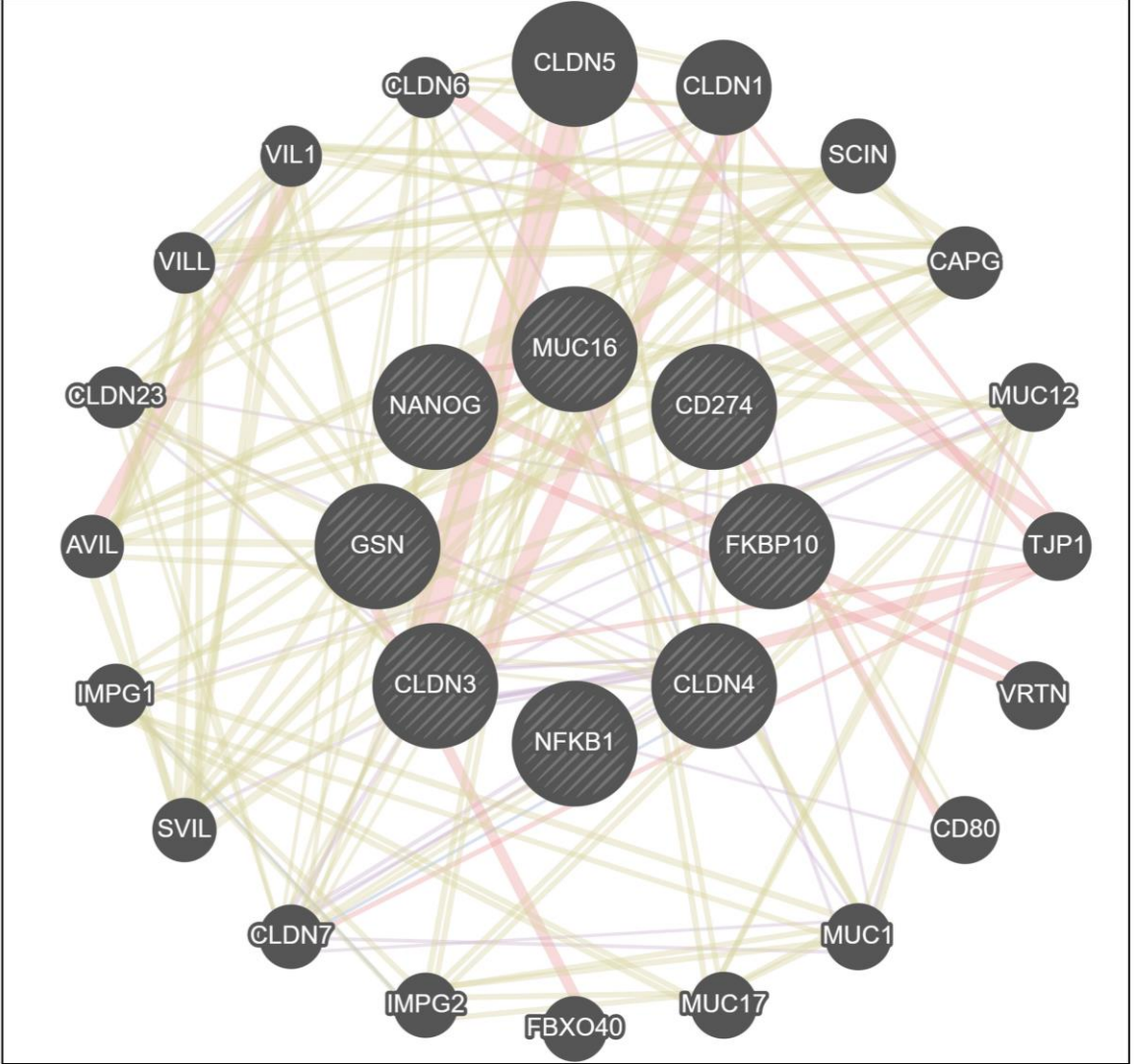


KM Significance vs Cut-Off Values between Upper & Lower Quartiles of Expression



GENE ONTOLOGY ENRICHMENT OF TOP 8 GENES

GENE ONTOLOGY (GO)				
Seed Gene	**Biological Processes**	**Molecular Functions**	**Cellular Localization**	**Pathway Collection**
CLDN3	Response to stimulus, Wound healing, Cell adhesion, Macromolecular metabolic process, biological adhesion, Positive regulation of biological process, Positive regulation of metabolic process, response to cytokine, regulation of peptidase activity, Tight junction assembly, Positive regulation of cell motility	Binding, Protein Binding, DrugBinding, Chloride channel activity, cis-trans isomerase activity, DNA binding transcription repressor activity, Actinin binding	Membrance enclosed lumen, Apicolateral plasma membrane, Organelle lumen, Lateral plasma membrane, Tight junction, Anchoring junction, Endomembrane system, Bicellular tight junction, Cellular component	Proteins with altered expression in endometrial cancer, proteins involved in endometriosis, Coagulation, Apoptosis, Inflammatory response, TNF-Alpha signalling via NF-kB, Cancer immunotherapy by PD-1 blockade WP4585, Interactions between immune cells and microRNAs in tumor microenvironment WP4559
CLDN4				
NFKB1				
GSN				
MUC16				
NANOG				
FKBP10				
CD274				



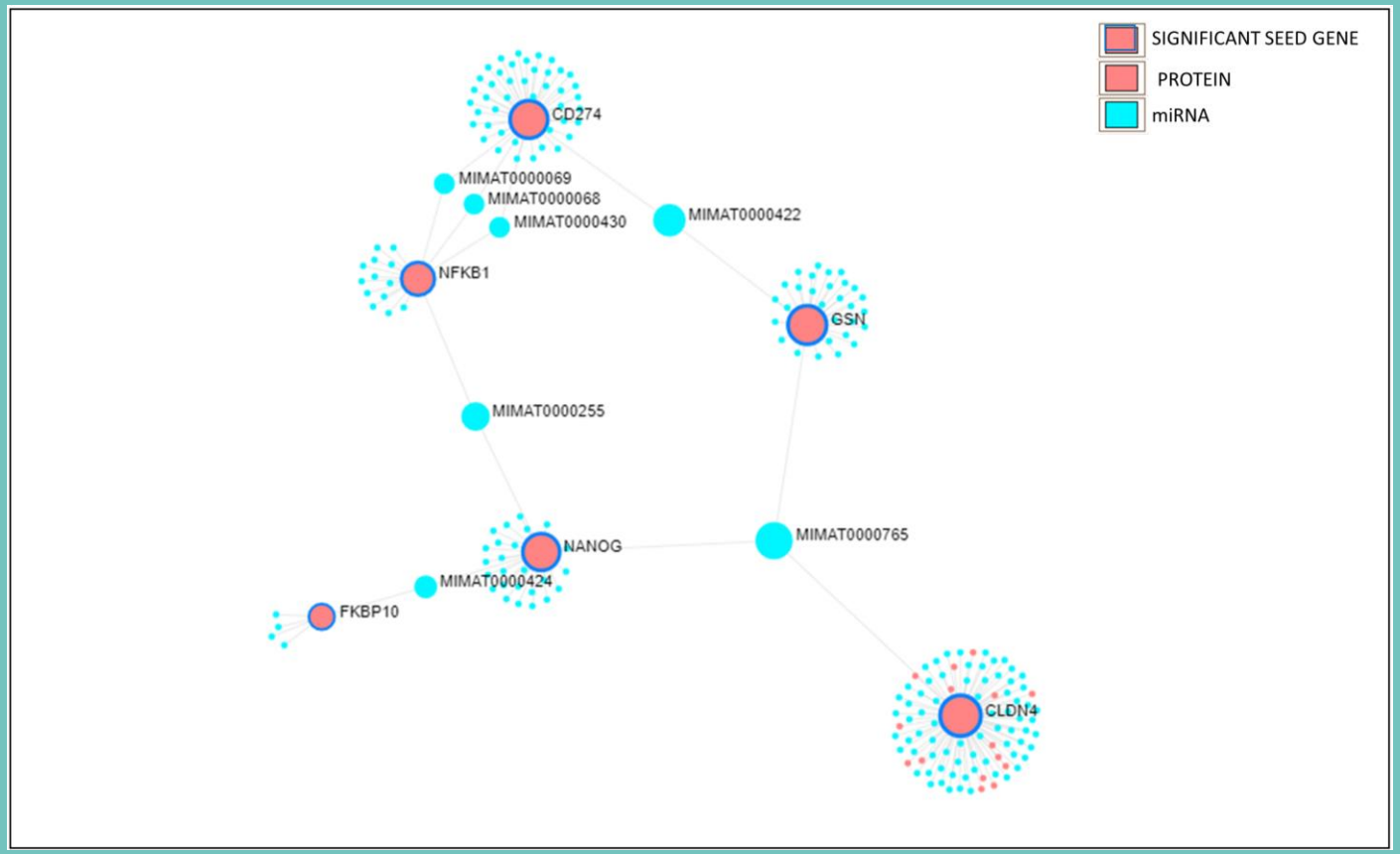
GENE REGULATORY NETWORK(GRN) CONSTRUCTION

To simplify the network, we used ***label propagation algorithm*** (LPA) to visualize the GRN.

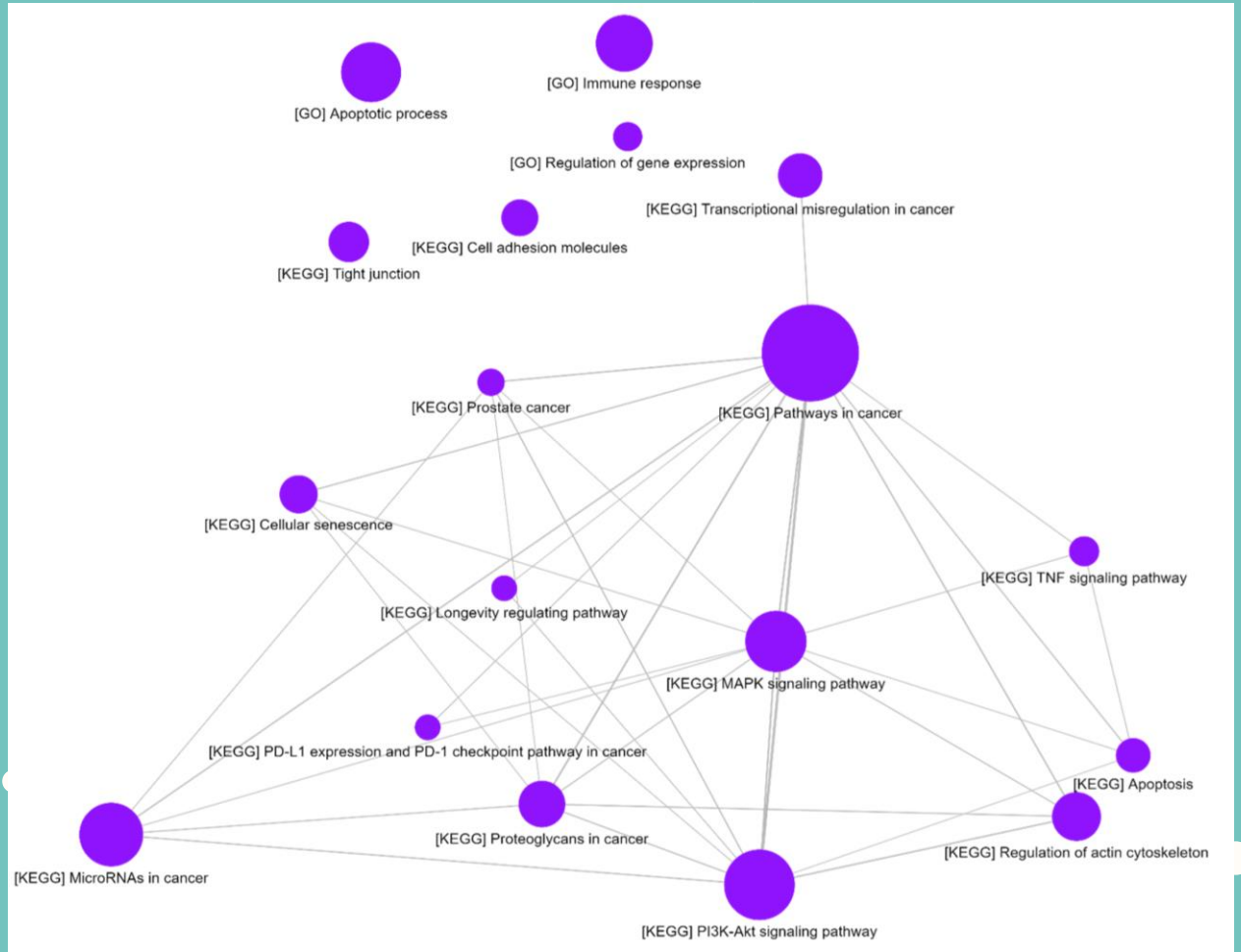
SUB-NETWORK TOPOLOGY

Gene Name	Degree	Betweeness	P-value
CLDN4	88	14703	3.36e-43
GSN	31	10264.75	2.28e-08
CD274	47	8770.75	8.89e-22
NANOG	28	7695.75	2.32e-13
NFKB1	17	4012.75	3.01e-09
FKBP10	5	842	8.94e-11

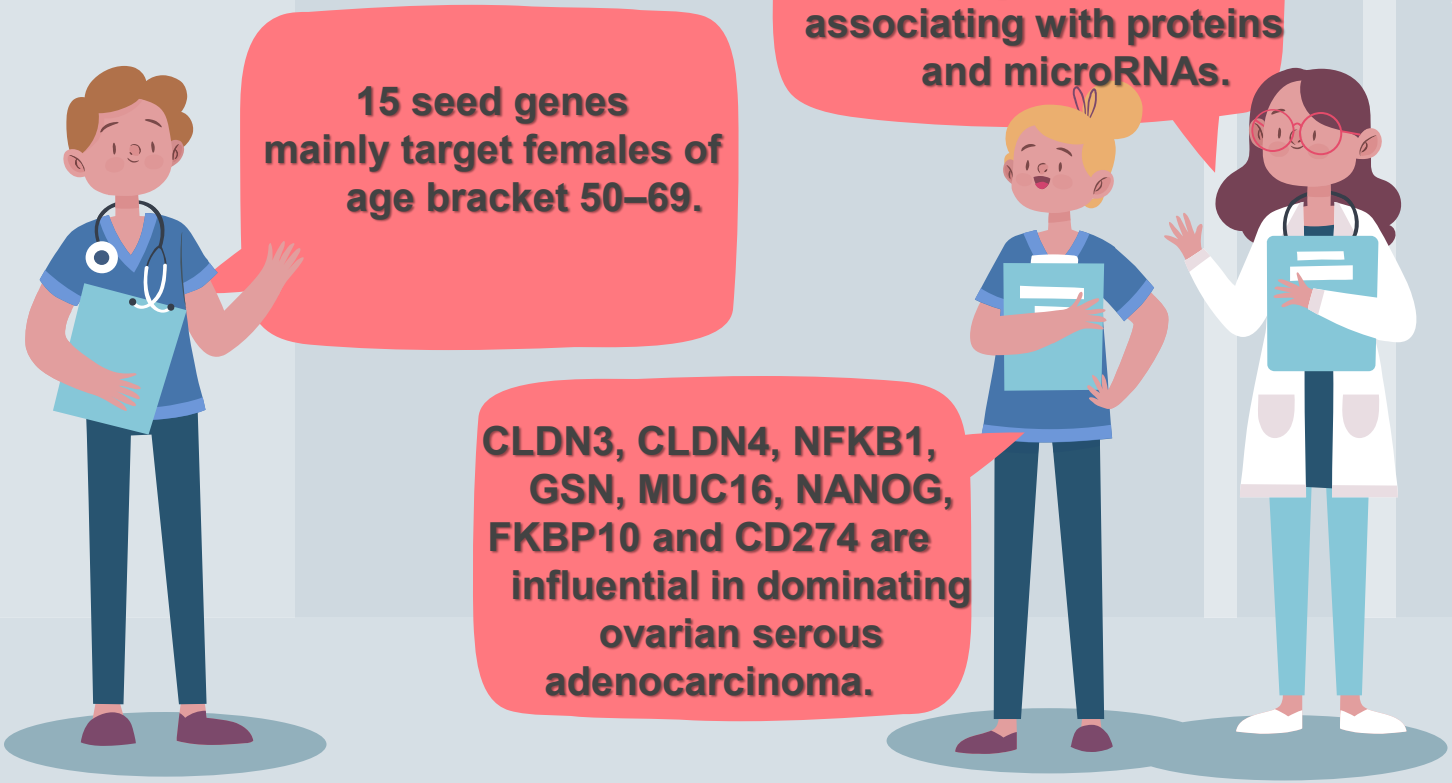
SUBNETWORK OF THE 6 HUB GENES – CD274, NFKB1, NANOG, FKBP10, GSN, CLDN4.



SIGNIFICANT PATHWAYS WHERE THE 6 HUB GENES ARE INVOLVED



SUMMARY


15 seed genes mainly target females of age bracket 50–69.
CLDN4, GSN, CD274, NANOG, FKBP10 and NFKB1 showed a strong sub-network associating with proteins and microRNAs.
CLDN3, CLDN4, NFKB1, GSN, MUC16, NANOG, FKBP10 and CD274 are influential in dominating ovarian serous adenocarcinoma.

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Thank
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