INTERNATIONAL CONFERENCES ON
VIRAL INFECTIONS, CANCER, VACCINES AND IMMUNOTHERAPY

# VIOLATON OF GENE REGULATION IN COLON CANCER AND ADJUSTANT COLON MUCOSA REVEALED BY COMPARATIVE GENE EXPRESSION AND GENE CORRELATION ANALYSIS

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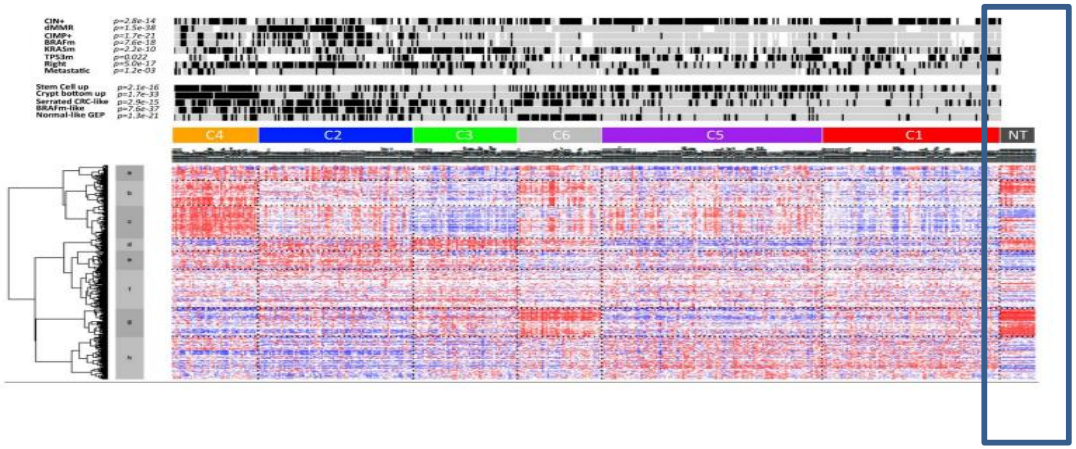
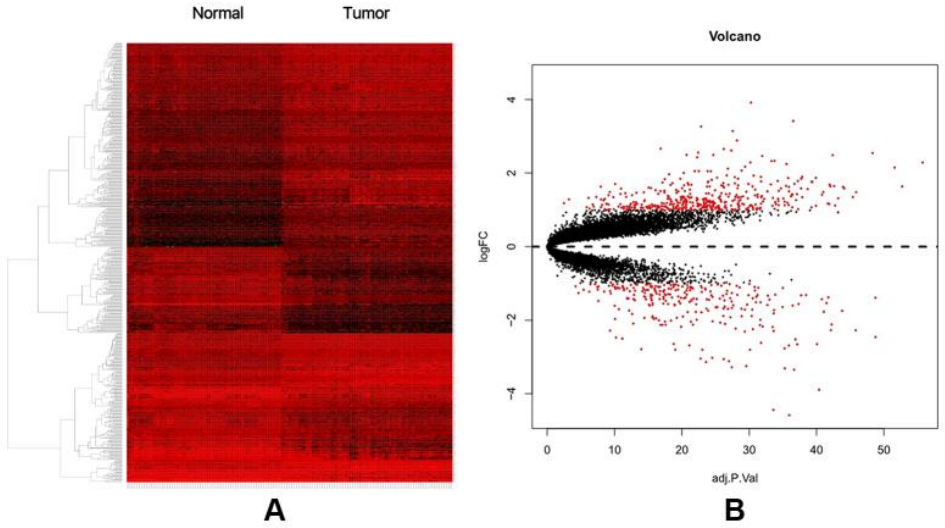
# Gene expression level in cancer cells differs from normal epithelium, of course




Expression profile of normal colon




- *The mechanisms of genes interaction in morphologically identical normal colon tissue of healthy and colon cancer patients differ significantly.*
- *At the same time, there may be no difference in the level of gene expression*

Laetitia Marisa, PLOS 2013; Ding X, Duan H and Luo H (2020) Identification of Core Gene Expression Signature and Key Pathways in Colorectal Cancer. Front. Genet. 11:45. doi: 10.3389/fgene.2020.00045

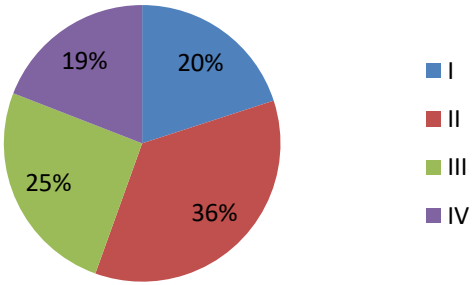
# Patients in the study

- The aim of the study was to assess the level of gene expression in CRC and the surrounding morphologically normal tissue in comparison with the normal colon epithelium of heathy volunteers

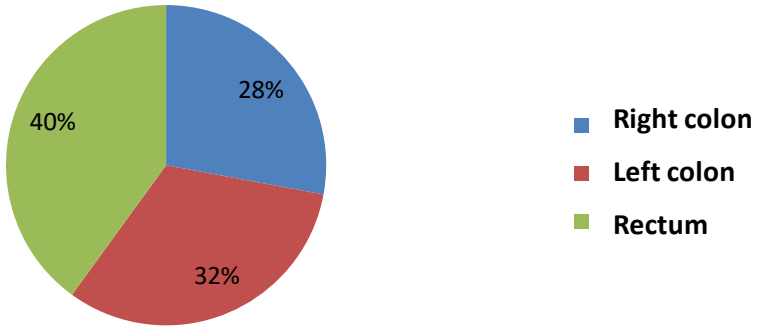
- 376 samples of colon tissue:
  - 77 normal epithelium of healthy volunteers
  - 132 morphologically unchanged colon epithelium of patients with CRC (at least 15 cm from the primary tumor, microscopic analysis)
  - 167 colon cancer (79% by par method) stage I – IV

- Average age: 62.9 ± 10.4 years
- Men – 184 (49.4%)

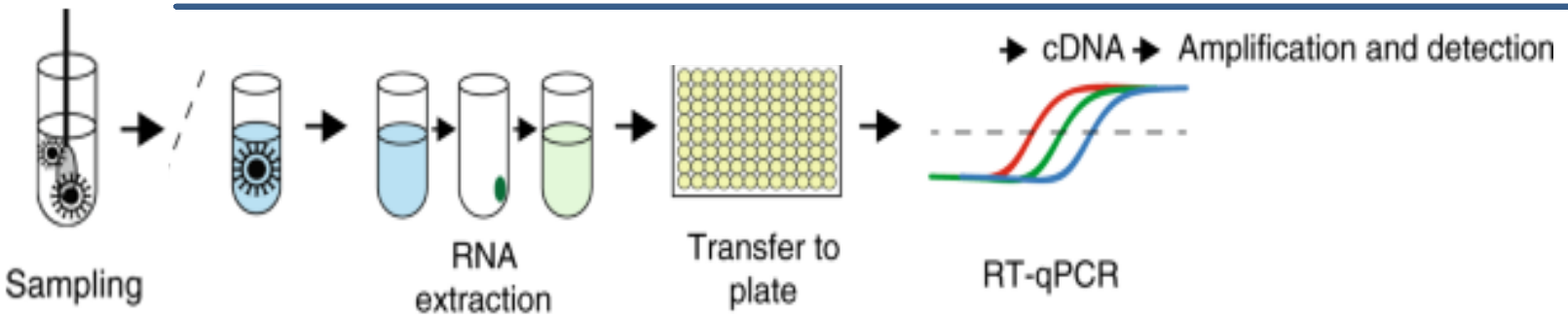
## Stages of the disease




## Tumor localization



# Study design




**Tissue intake** → **Morphology** → **RNA isolation** → **Gene expression PCR**

Important step

- Amount of tumor cells in cancer sample
- Sample quality (absence of necrosis, live cells)
- **Absence of tumor cells in normal colon samples**

# The same samples, the same genes, different ways of interpreting the result

**44 genes**:

- proliferation and differentiation
- immune response and inflammation
- matrix remodeling and angiogenesis

| Gene | |
|---|---|
| BCL2 | GREM1 |
| MYC | MMP2 |
| BIRC5 | PAPPA |
| NDRG1 | MMP7 |
| CD68 | IL2RA |
| KI67 | IL12A |
| erbB2 | IL7 |
| PTEN | IL15 |
| BAG1 | IL1B |
| CCNB1 | IL10 |
| ESR1 | TPA (PLAT) |
| GRB7 | CD45 (PTPRC) |
| MMP11 | TGFb1 |
| STK15 (AURKA) | CD69 |
| MYBL2 | BAX |
| P16INK4A (CDKN2A) | VEGFA (subunits 165, 189) |
| MMP9 | TLR2 |
| GNLY | TLR4 |
| IGF1 | HLA-G |
| COX-2 (PTGS2) | LGALS1 |
| IGF2 | LIF |
| LIFR | GREM1 |

**Expression analysis: we compared gene expression level in samples (normal_healthy, normal_cancer, cancer)**

**Correlation analysis: we compared correlation coefficients of genes in samples (normal_healthy, normal_cancer, cancer)**

# Gene activity profiles

**proliferation and differentiation**

*MYC, NDRG1, KI67, erbB2, GRB7, PTEN, CCNB1, ESR1, STK15 (AURKA), MYBL2, P16INK4A (CDKN2A), IGF1, IGF2, TGFb1, GREM1, LIF, LIFR*

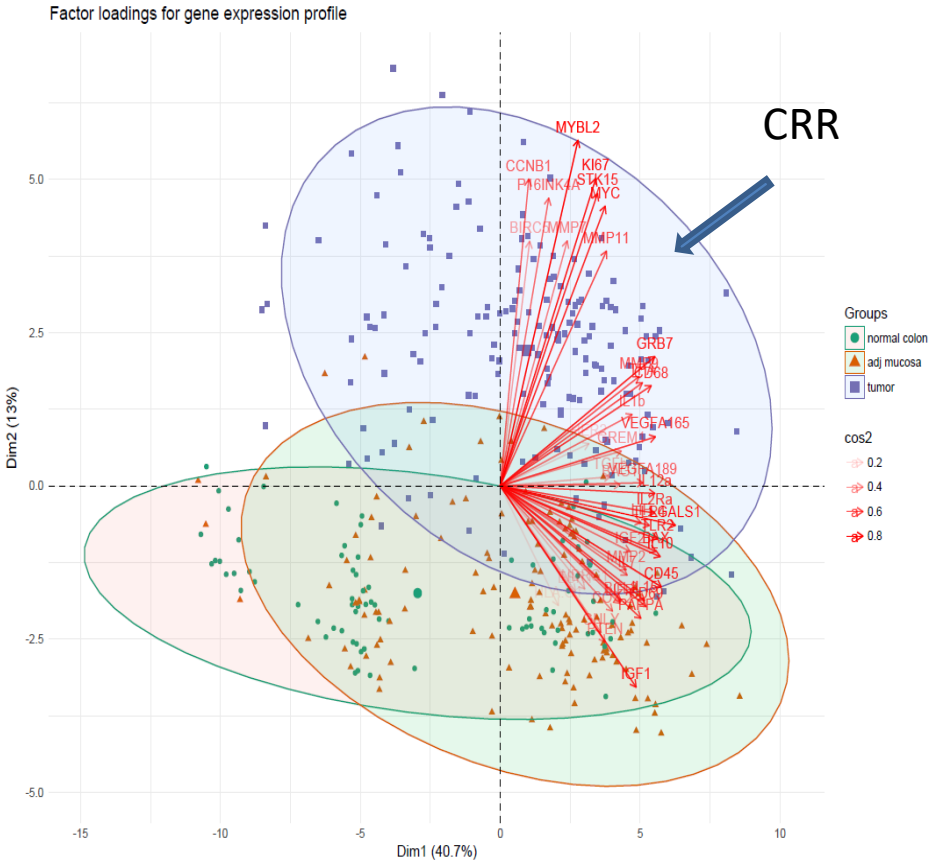
**immune response and inflammation**

*CD68, GNLY, COX-2 (PTGS2), IL2RA, IL12A, IL7, IL15, IL1B, IL10, CD45 (PTPRC), CD69, TLR2, TLR4, TPA (PLAT), HLA-G*

**matrix remodeling and angiogenesis**

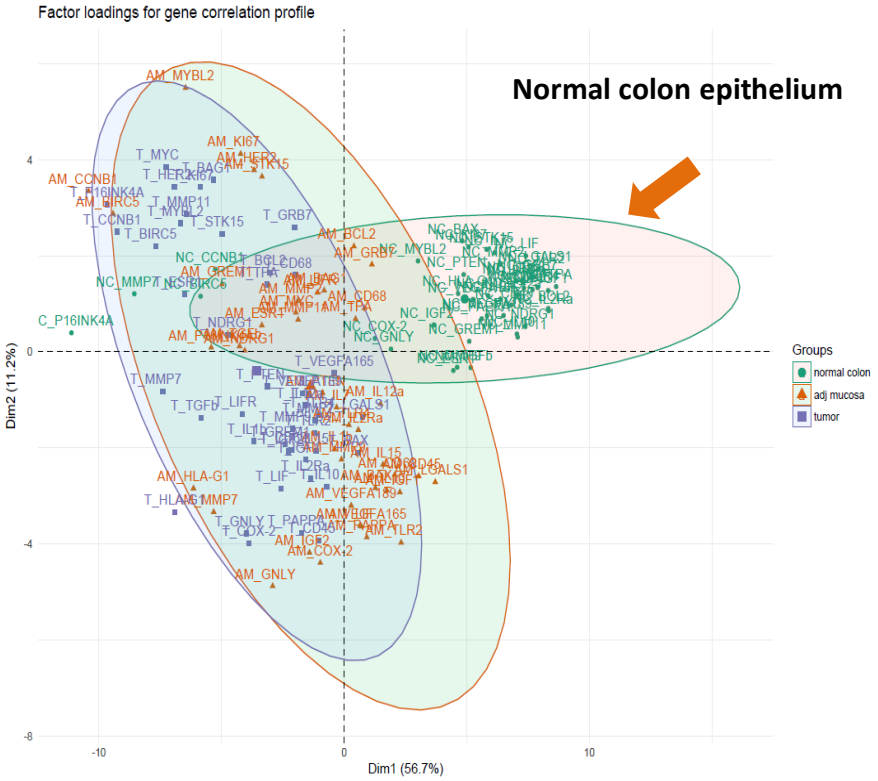
*VEGFA* (subunits 165, 189), *MMP11*, *MMP2*, *MMP7*, *PAPPA*, *LGALS1*

# Gene expression landscape of different tissues



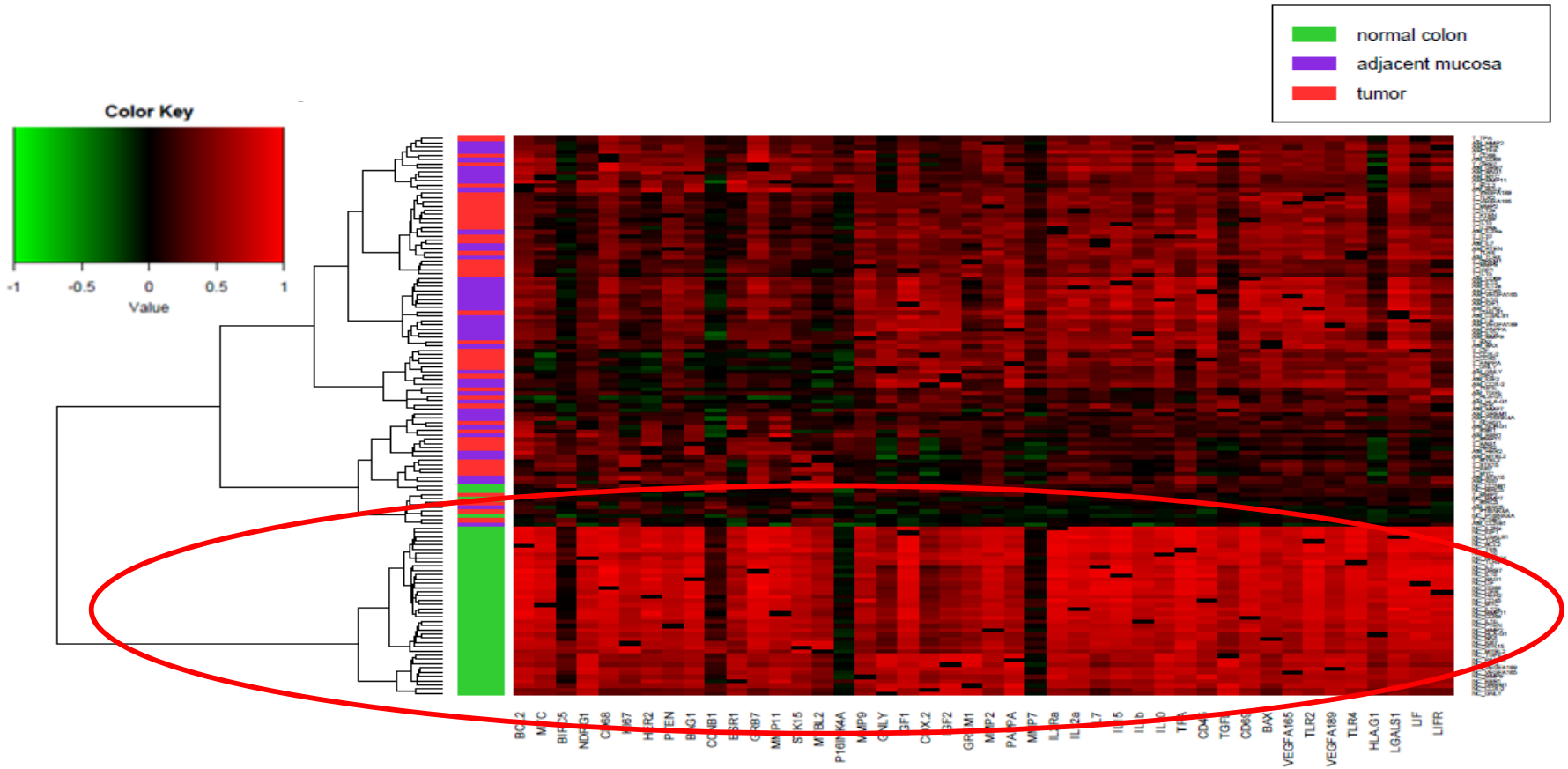

- The tumor is characterized by high activity of division, invasion genes, angiogenesis…
- Normal epithelium of healthy and cancer patients does not differ

# Gene correlation landscape of different tissues



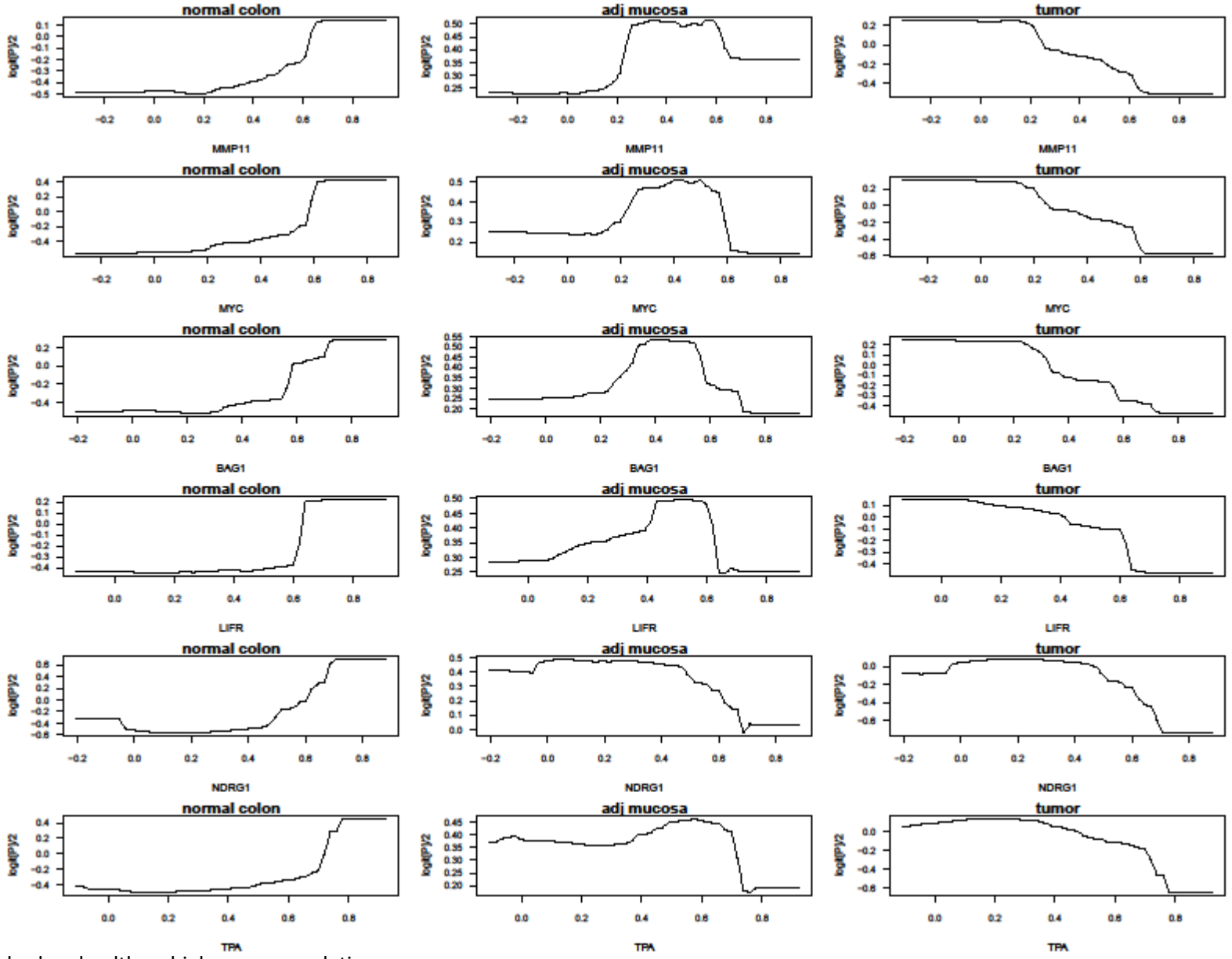

- According to the correlation profile, the normal epithelium of healthy volunteers has unique characteristics
- Correlation profile of morphologically unchanged epithelium and cancer tissue of cancer patients do not differ

**According to the levels of gene correlation, the normal epithelium of healthy volunteers differs significantly from normal epithelium from cancer and cancer**



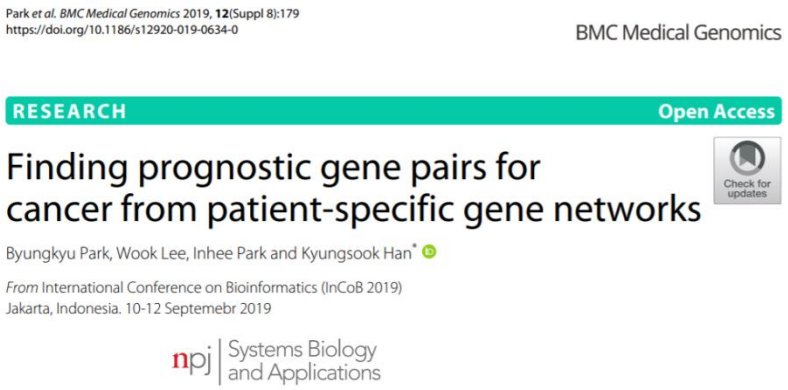

**If the morphologically unchanged colon epithelium of patients with CRC differs so much from the epithelium of healthy volunteers, is it possible to use the model for early diagnosis of "molecular malignancy"?**

# Random forest tissue classification of tissue type




- Normal colon_healthy – high mean correlation
- Normal colon_cancer patients – intermediate correlation
- Colon cancer – low positive and negative correlation

# Studies with same approaches


Park et al. BMC Medical Genomics 2019, 12(Suppl 8):179
https://doi.org/10.1186/s12920-019-0634-0

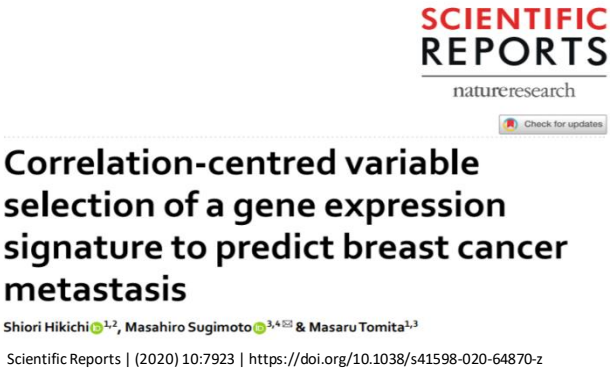
BMC Medical Genomics

RESEARCH Open Access

Finding prognostic gene pairs for cancer from patient-specific gene networks

Byungkyu Park, Wook Lee, Inhee Park and Kyungsook Han*

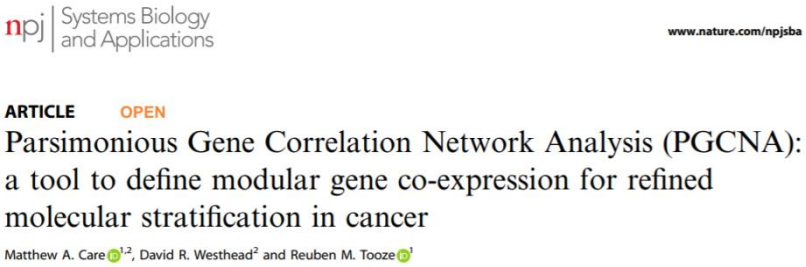
From International Conference on Bioinformatics (InCoB 2019)
Jakarta, Indonesia. 10-12 Septemebr 2019


SCIENTIFIC REPORTS
nature research

Correlation-centred variable selection of a gene expression signature to predict breast cancer metastasis

Shiori Hikichi[1,2], Masahiro Sugimoto[3,4] & Masaru Tomita[1,3]

Scientific Reports | (2020) 10:7923 | https://doi.org/10.1038/s41598-020-64870-z

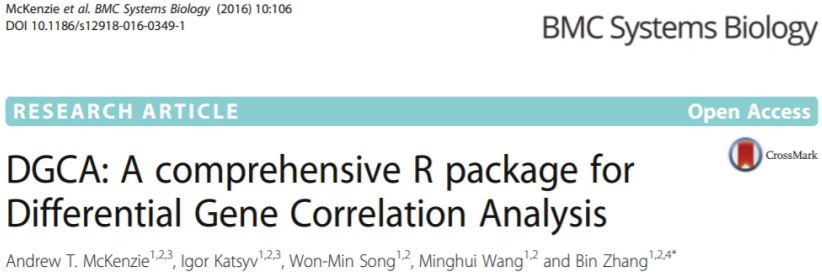

npj | Systems Biology and Applications

www.nature.com/npjsba

ARTICLE OPEN

Parsimonious Gene Correlation Network Analysis (PGCNA): a tool to define modular gene co-expression for refined molecular stratification in cancer

Matthew A. Care[1,2], David R. Westhead[2] and Reuben M. Tooze[1]


McKenzie et al. BMC Systems Biology (2016) 10:106
DOI 10.1186/s12918-016-0349-1

BMC Systems Biology

RESEARCH ARTICLE Open Access

DGCA: A comprehensive R package for Differential Gene Correlation Analysis

Andrew T. McKenzie[1,2,3], Igor Katsyv[1,2,3], Won-Min Song[1,2], Minghui Wang[1,2] and Bin Zhang[1,2,4*]

- Studies using a similar approach - prognostic models based on the study of tumor material only
- Publications of algorithms for multiparametric correlation analysis
- There are no studies using morphologically normal epithelium

# Conclusions and Future directions

- **Investigation of the possibility of early diagnosis of "molecular malignancy/progression" of CRC and other solid tumors**
- Extrapolation of the model to other types of tumors
- Investigation of the possibility of developing prognostic/predictive models of drug resistance?
- Investigation of the fundamental mechanisms of interaction between the tumor and the microenvironment

# Thank you

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