Master UGA SSD 2024-2025
M1 - Supervised Project

Prognostic biomarkers in colon cancer

Supervisors: Ekaterina BOUROVA-FLIN[1] et Séverine VALMARY-DEGANO[1,2]

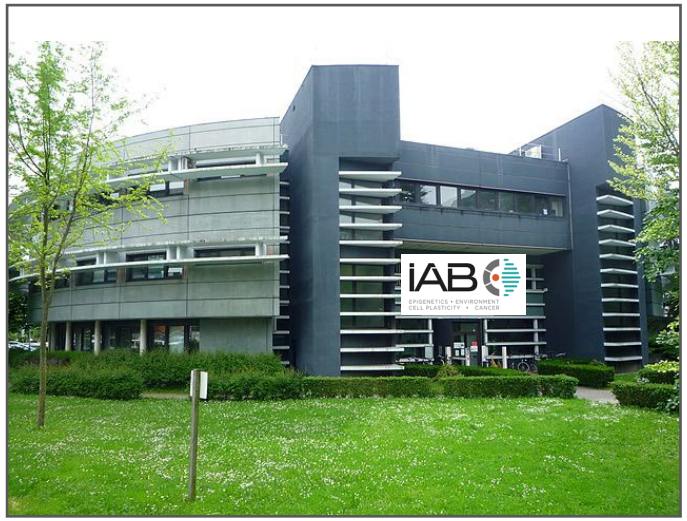
[1] Team “Epigenetic Regulations”, Institute for Advanced Biosciences (IAB), Grenoble
[2] Centre Hospitalier Universitaire Grenoble Alpes (CHUGA)

21/10/2024

Outline

Outline

Institute for Advanced Biosciences



UGA, INSERM, CNRS

3 departments
19 teams
300 people

Signaling through Chromatin

Team « Epigenetic Regulations »

Saadi Khochbin
(Team Leader)

18 permanent staff
- biologists
- computer engineers
- medical doctors

4 PhD students
3 Master students

EpiMed

Bioinformatic facility « EpiMed »

Outline

Epigénétique

20-ème siècle – La génétique

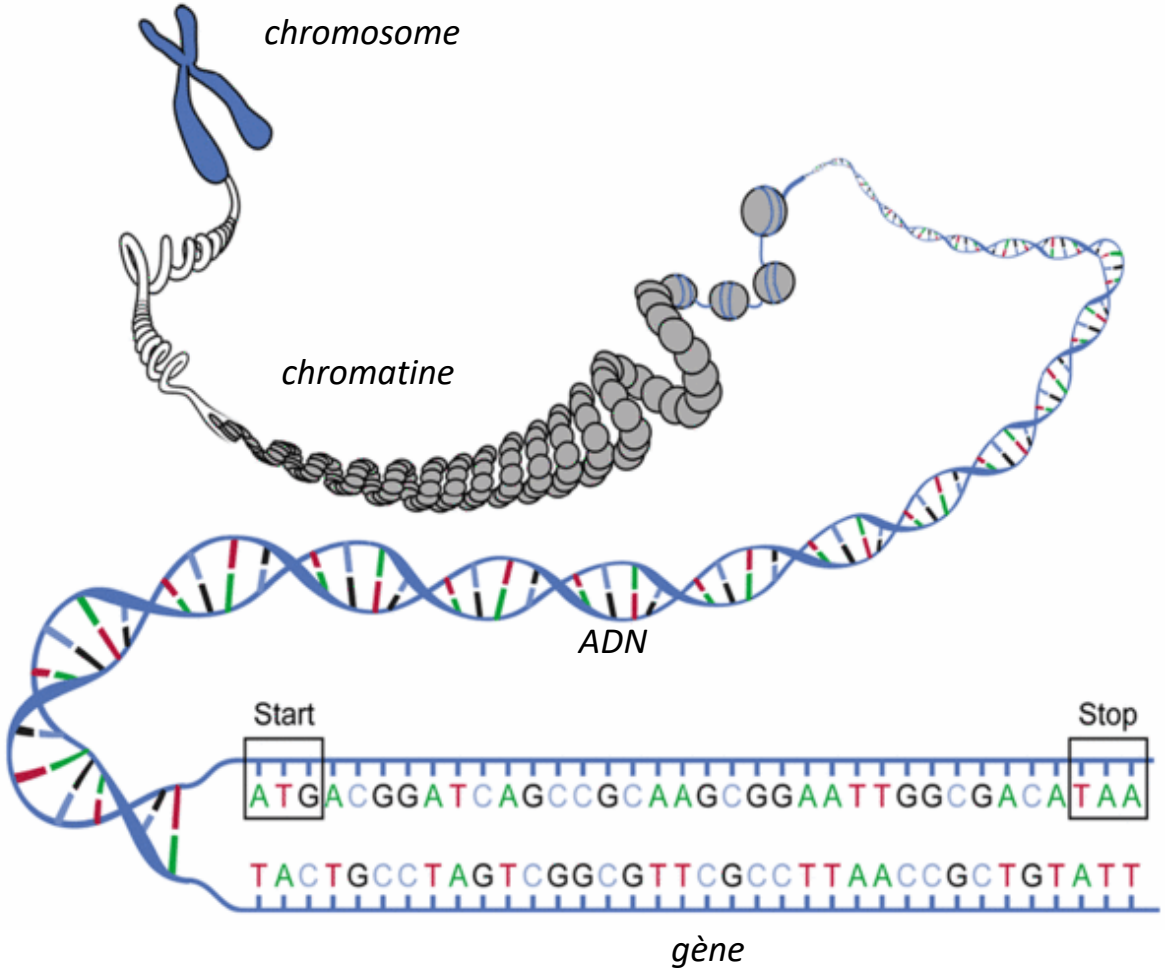
La génétique (du grec *« donner naissance »)* est la science qui étudie l'hérédité et les gènes.

1909 – notion de gène, une base d'hérédité
1953 – découverte du double hélice d'ADN
1977 – séquençage des fragments d'ADN
2003 – séquençage complet du génome humain

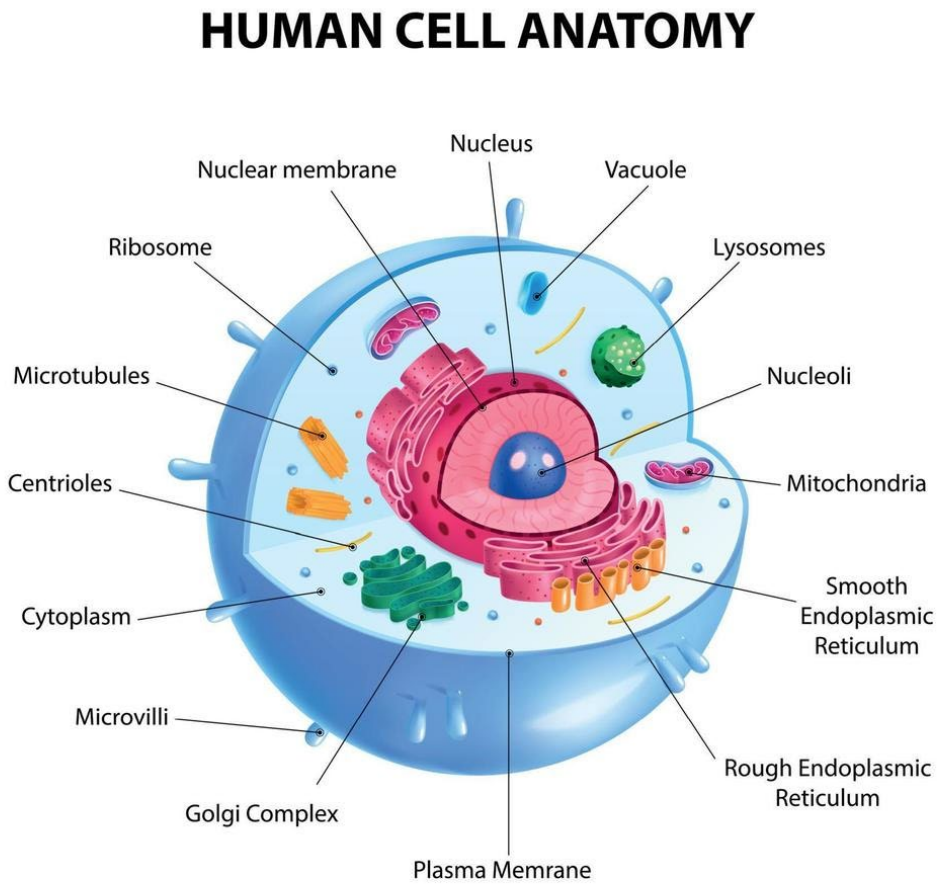
21-ème siècle – L'épigénétique

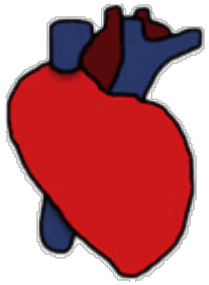
Épi : « *au dessus de* »

L'épigénétique étudie les mécanismes moléculaires qui modifient l'expression des gènes en fonction de l'environnement.

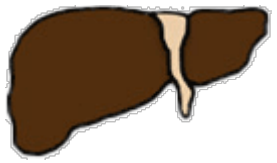


Epigenetic regulations

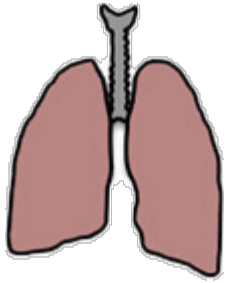




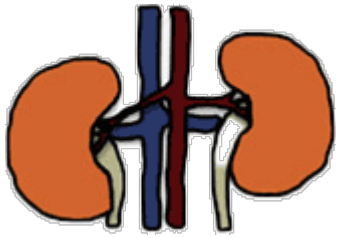
Heart



Liver

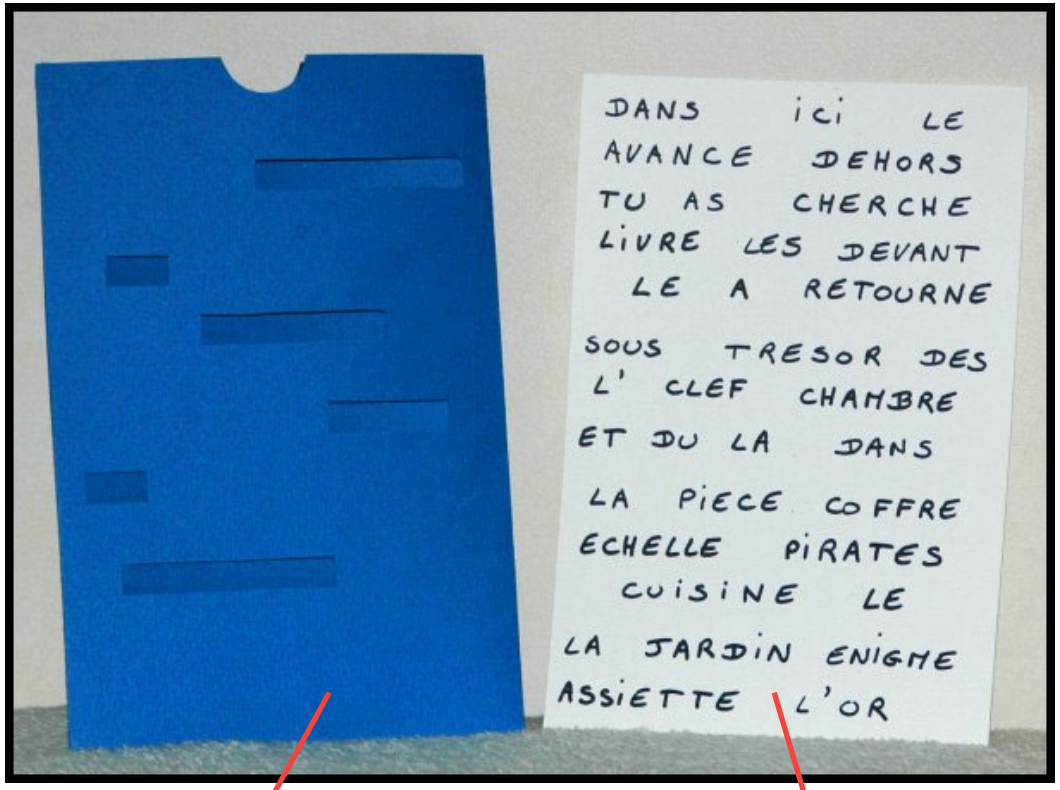


Lung



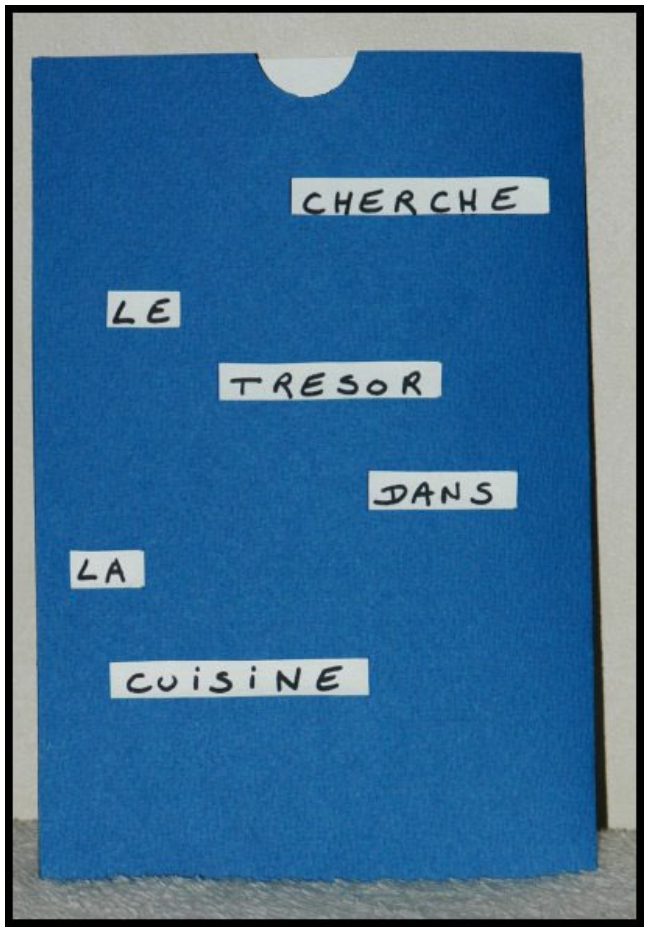
Kidney

Epigenetic regulations

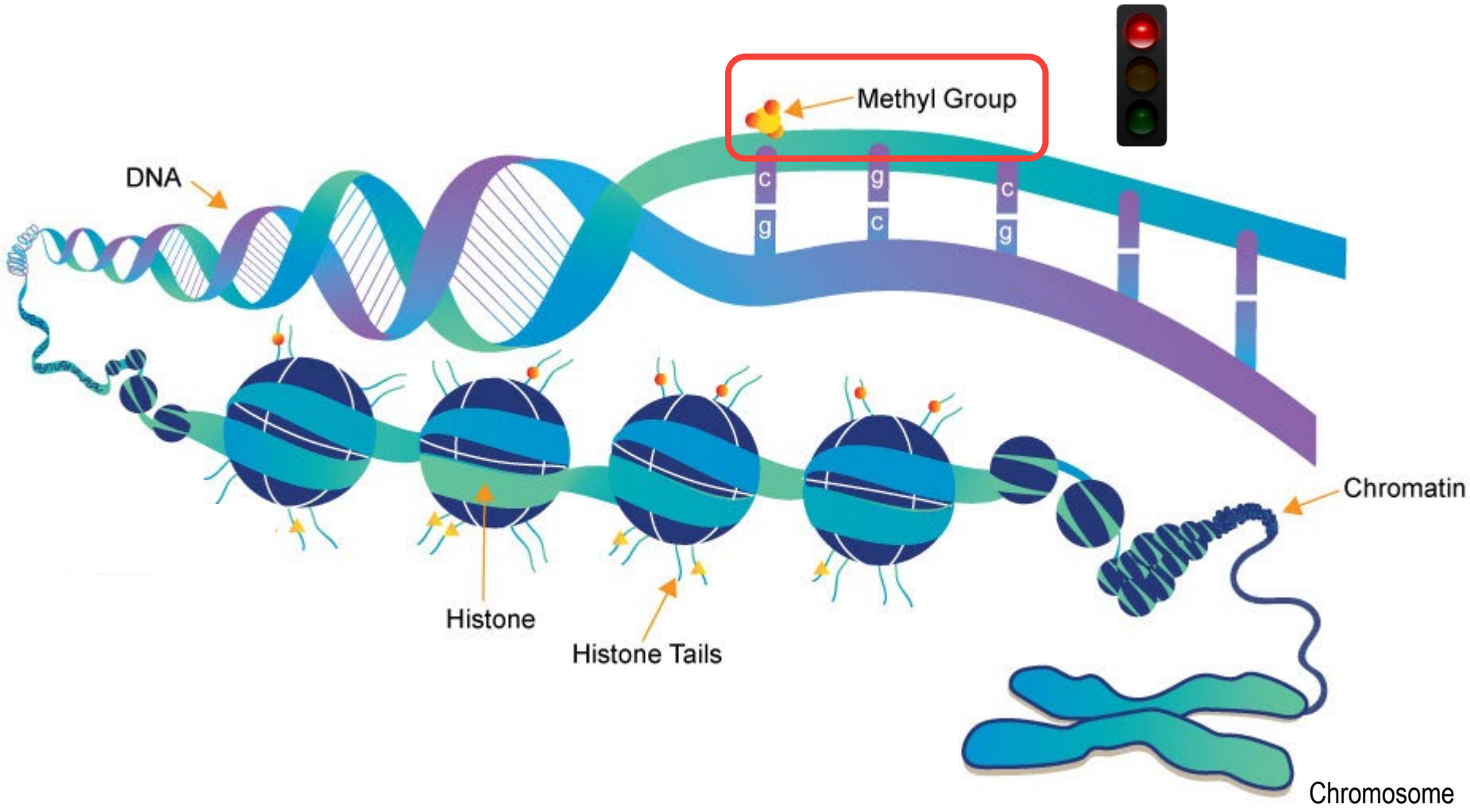


Epigenetic system

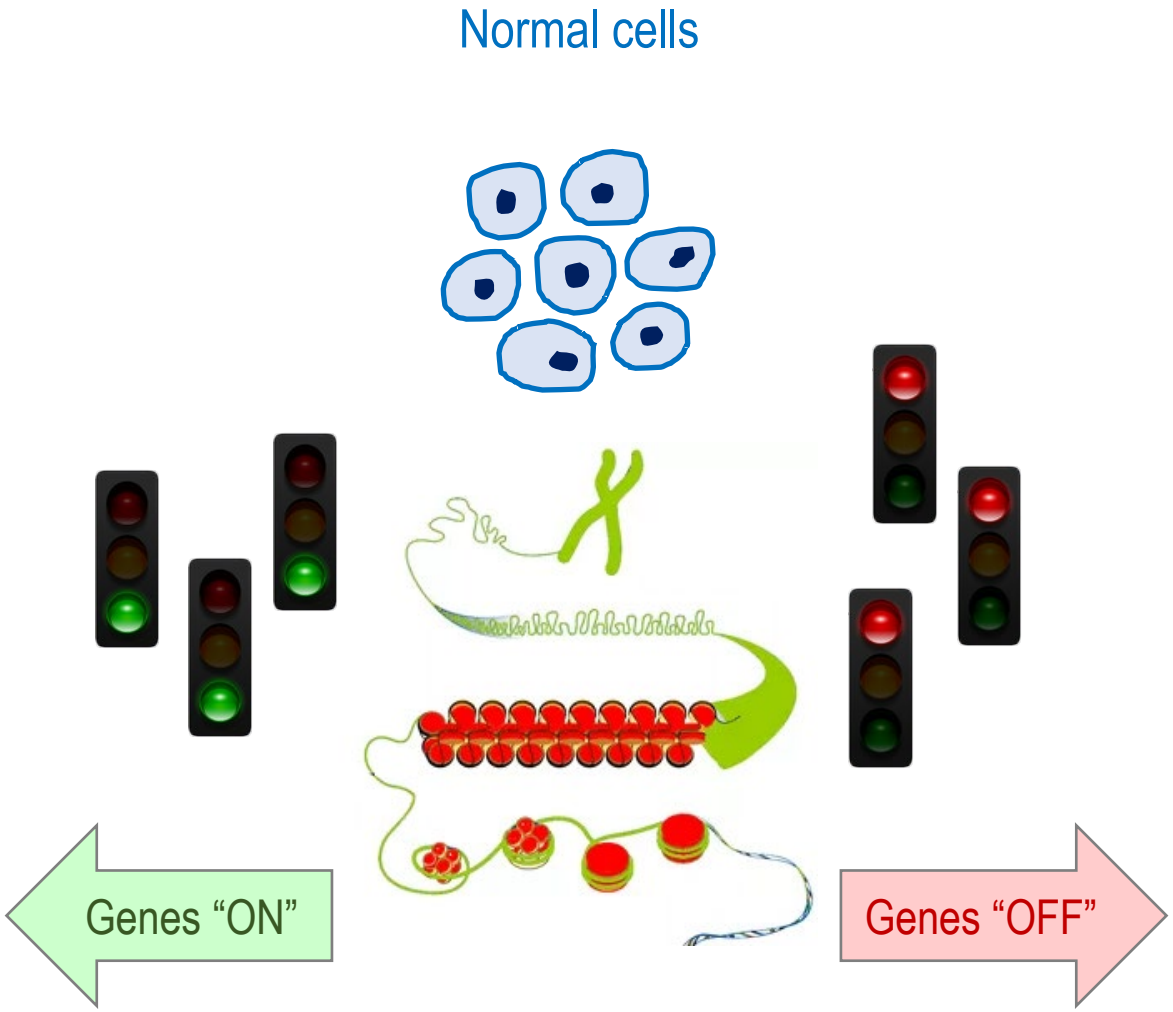
DNA



Epigenetic regulations

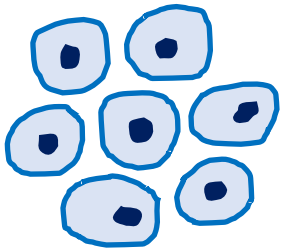


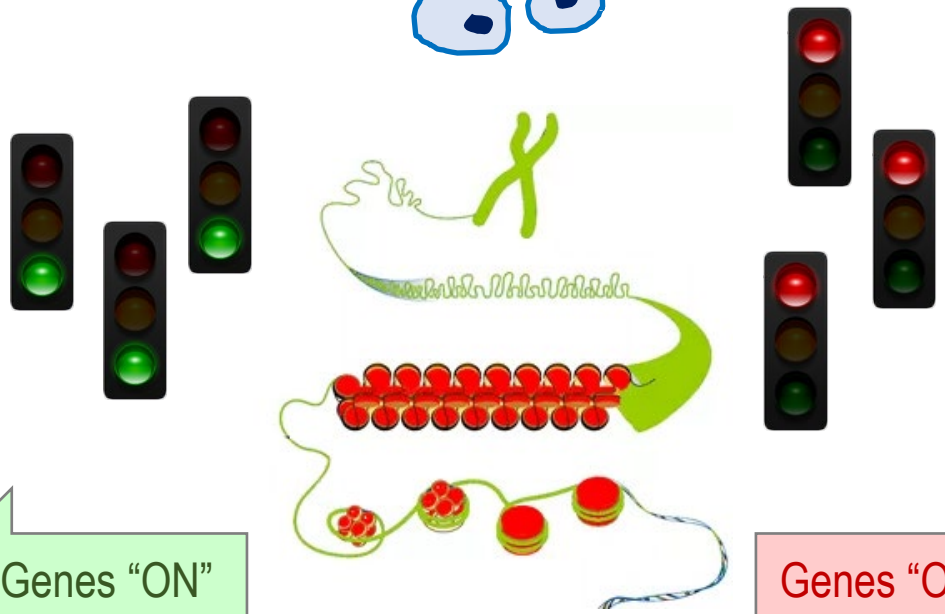
Aberrant (ectopic) activations of genes in cancers



Aberrant (ectopic) activations of genes in cancers

Normal cells

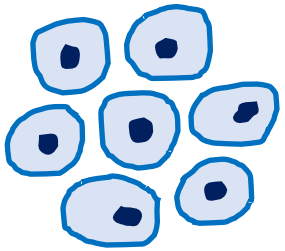




Cancer cells

Aberrant (ectopic) activations of genes in cancers

Normal cells



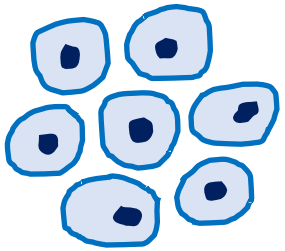
OFF

Cancer cells

ON

Aberrant (ectopic) activations of genes in cancers

Normal cells



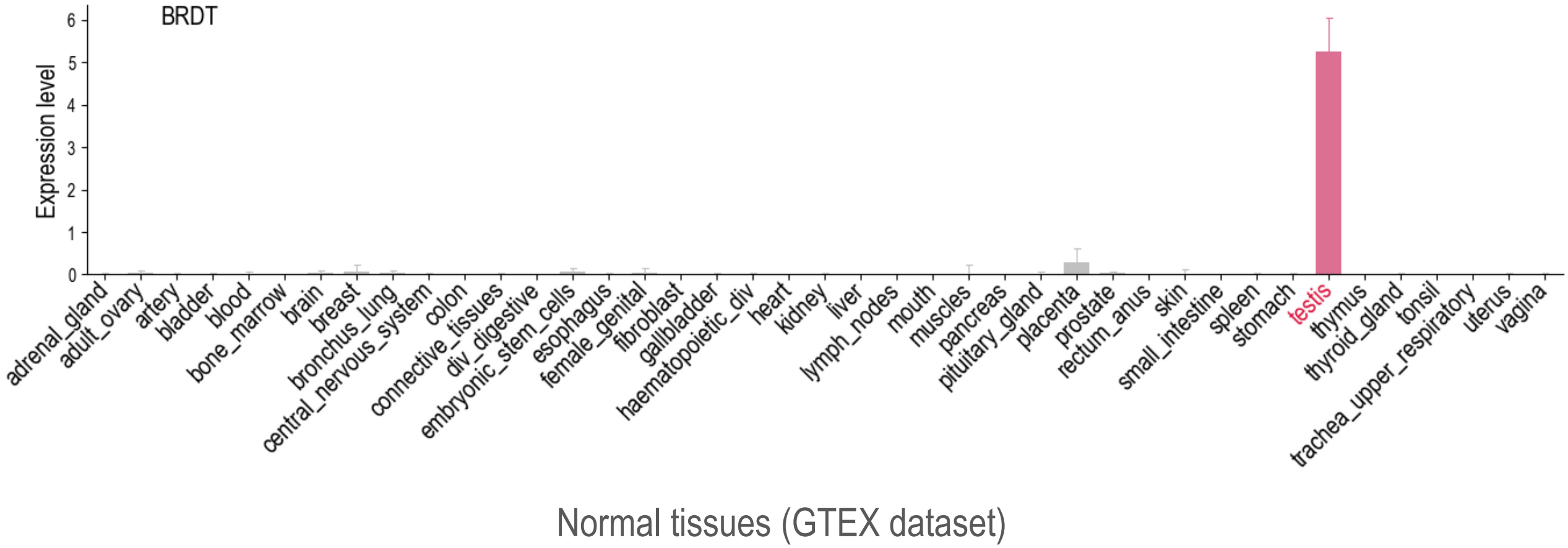
OFF

Tissue-specific genes

Cancer cells

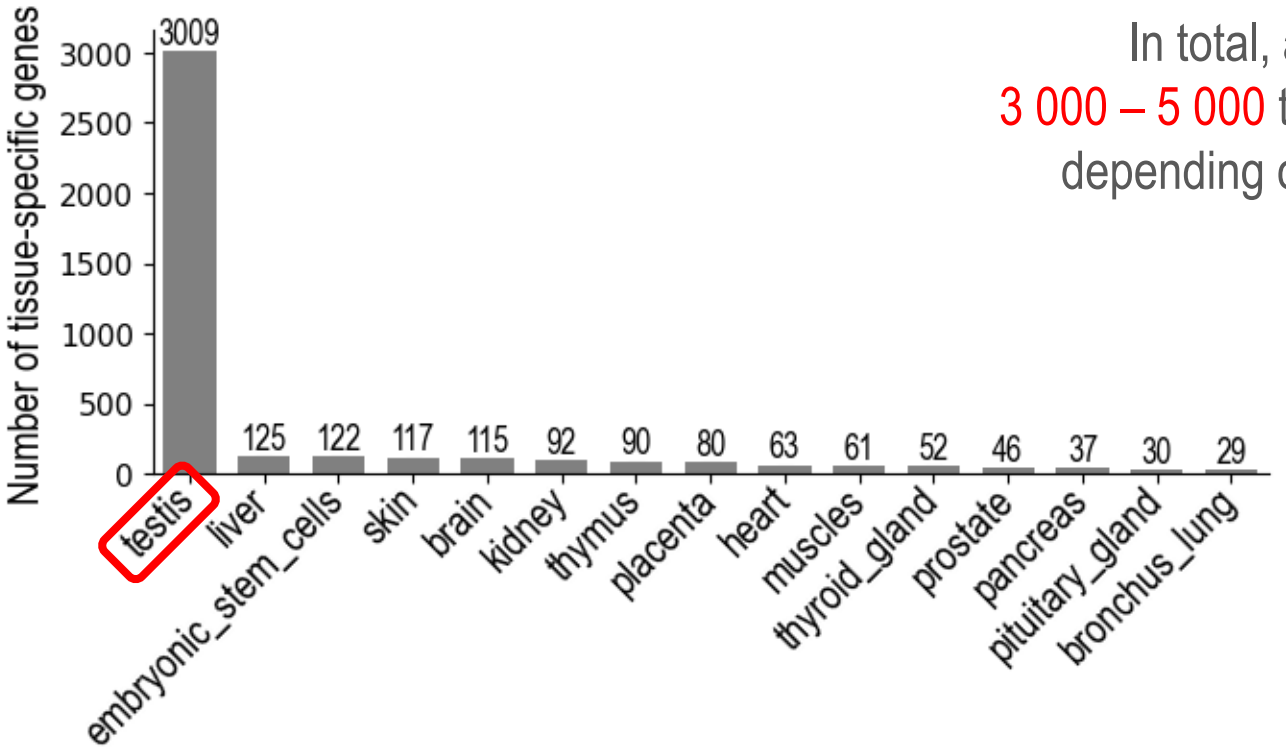
ON

Tissue-specific genes in human normal tissues



Normal tissues (GTEX dataset)

Tissue-specific genes in human normal tissues

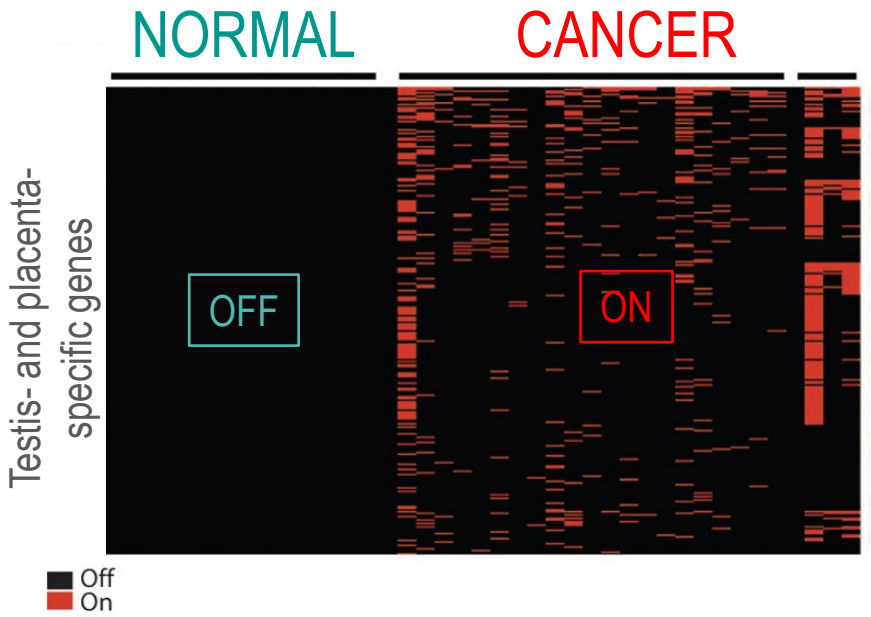


In total, approximately
3 000 – 5 000 tissue-specific genes
depending on applied criteria

Tissue-specific genes in cancers

Rousseaux et al. 2013
Science Translational Medicine

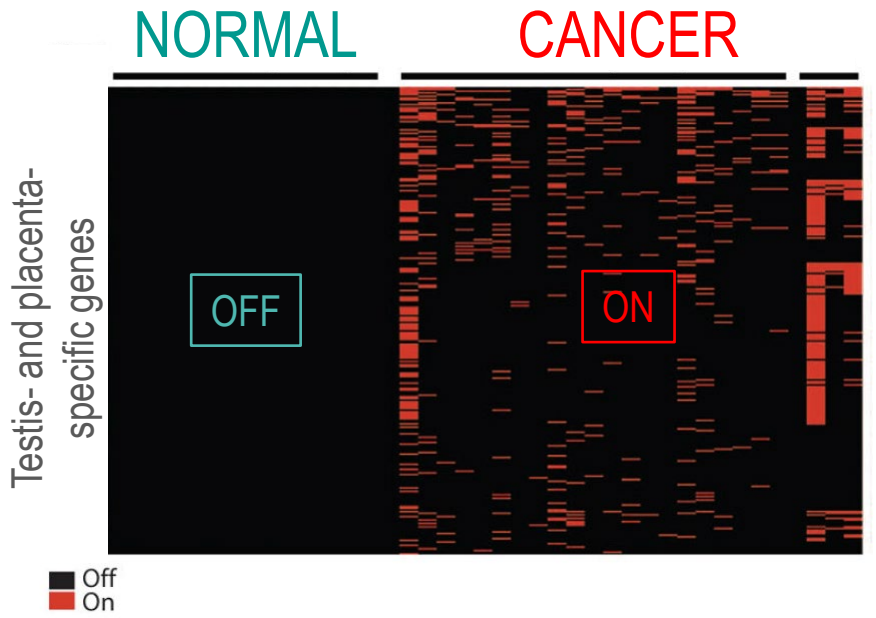
1. Massively activated



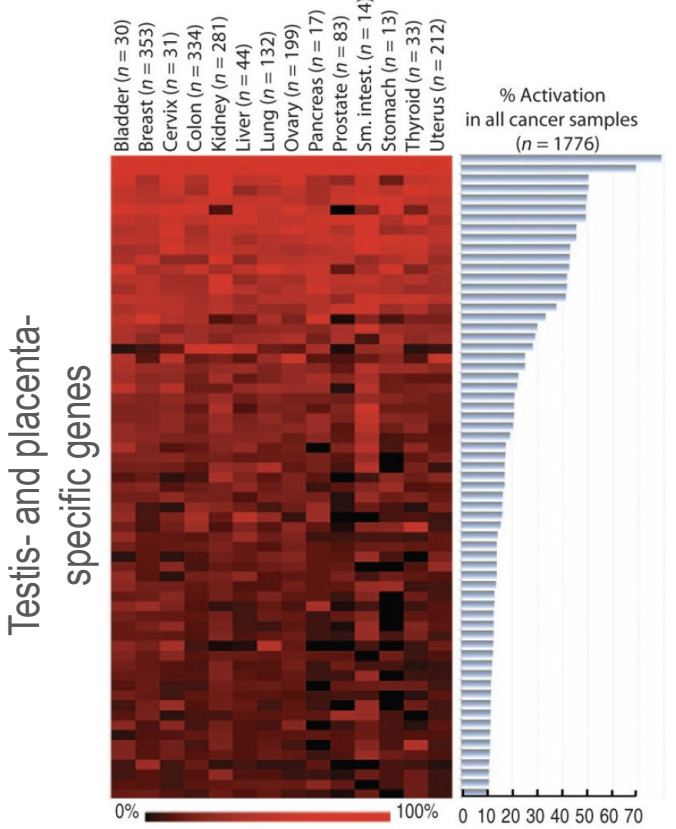
Tissue-specific genes in cancers

Rousseaux et al. 2013
Science Translational Medicine

1. Massively activated



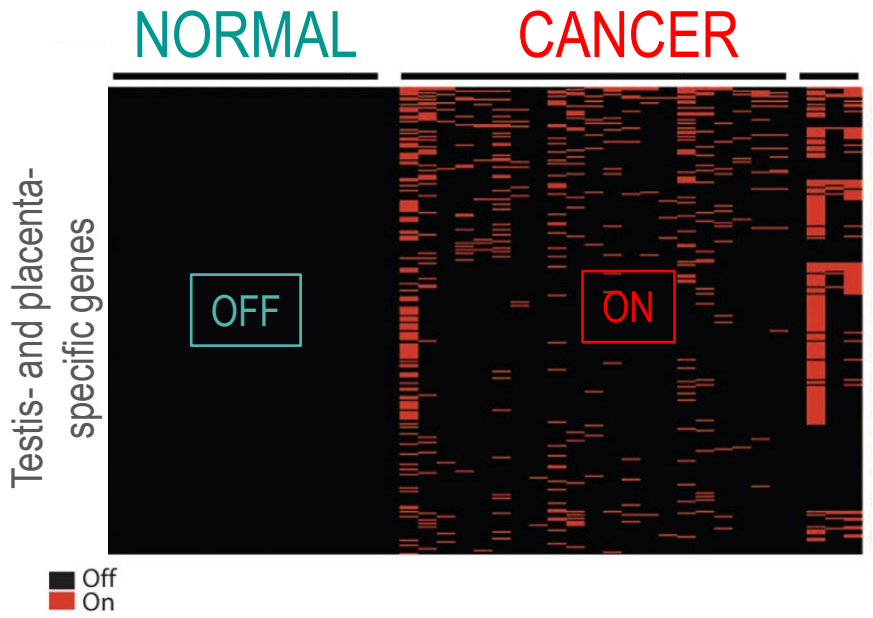
2. In all cancer types



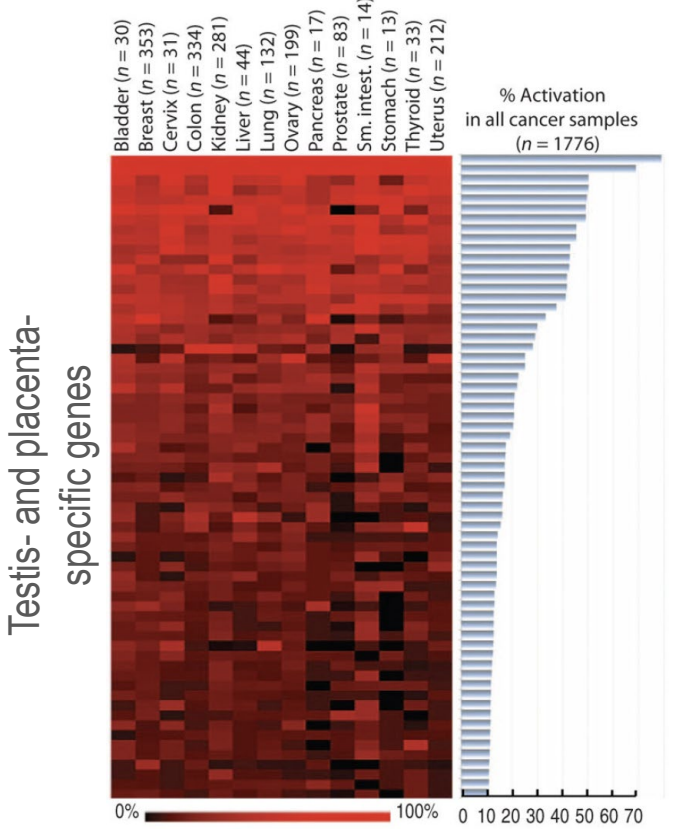
Tissue-specific genes in cancers

Rousseaux et al. 2013
Science Translational Medicine

1. Massively activated

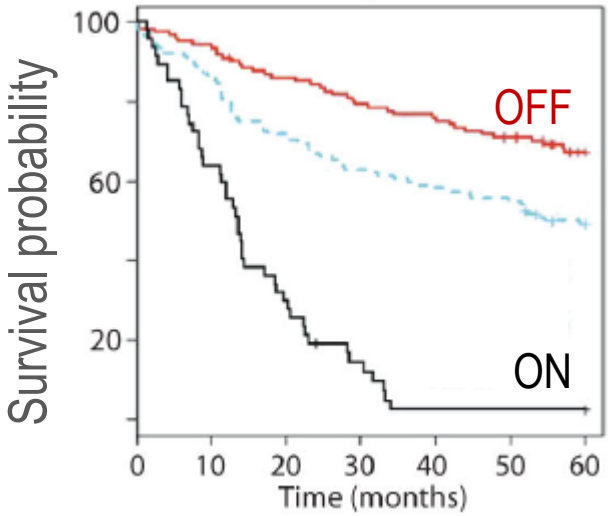


2. In all cancer types



3. Aggressive forms

"ON" status = poor prognosis



EpiMed

Novel source for discovery of prognosis biomarkers in cancers

Outline

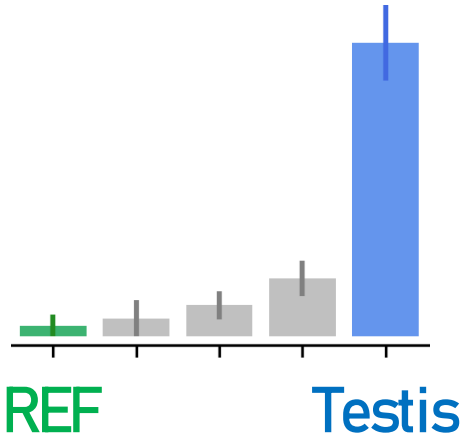
Biomarker discovery pipeline “ectopy”: Overview

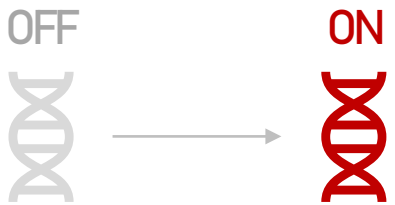
1 → 2 → 3

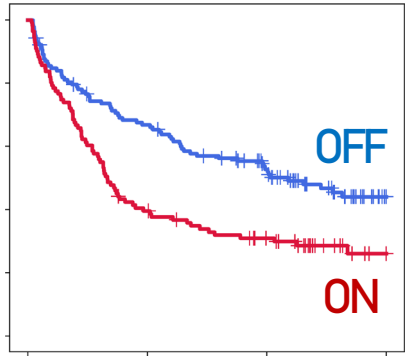
Tissue-specific genes, OFF in normal samples

Frequently activated in cancer

Activation is associated with a shorter survival







Biomarker discovery pipeline “ectopy”: Survival analysis

Training dataset

Validation datasets

Test datasets

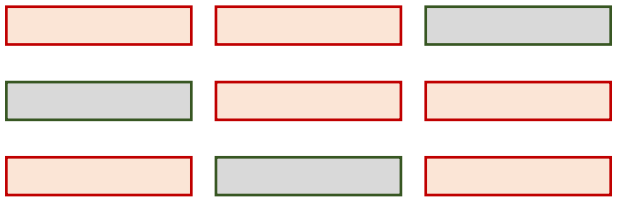
Biomarker discovery pipeline “ectopy”: Survival analysis

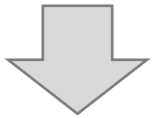
Training dataset

Validation datasets

Test datasets

Permutations and cross-validations





Robust candidates: A, B, C…

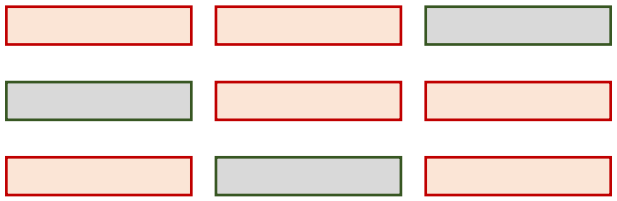
Biomarker discovery pipeline “ectopy”: Survival analysis

Training dataset

Validation datasets

Test datasets

Permutations and cross-validations



Select stable candidates

✗ A

✓ B

✓ C

Robust candidates: A, B, C…

Prognostic classifier (GEC)

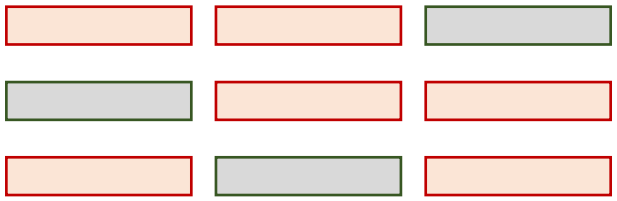
Biomarker discovery pipeline “ectopy”: Survival analysis

Training dataset

Validation datasets

Test datasets

Permutations and cross-validations



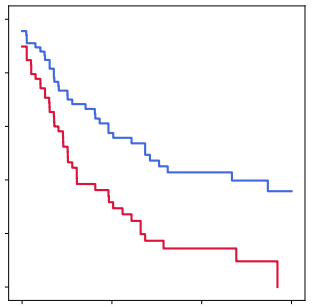
Select stable candidates

✗ A

✓ B

✓ C

Test GEC



Robust candidates: A, B, C…

Prognostic classifier (GEC)

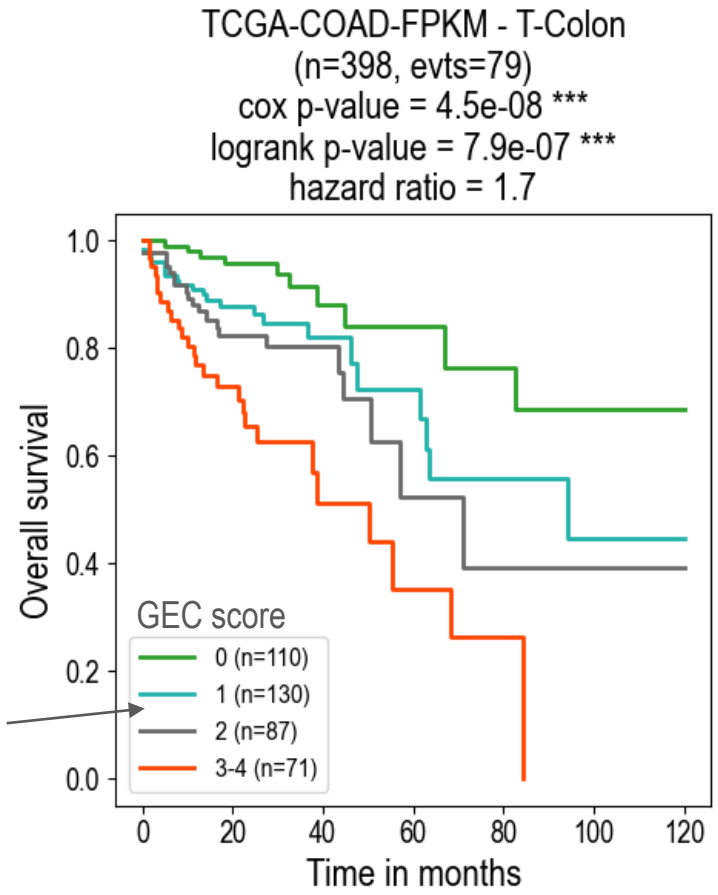
OK?

Outline

Colon cancer

Gene Expression Classifier (GEC): 4 biomarkers

HOXC6, ULBP2, ERFE, LAMP5

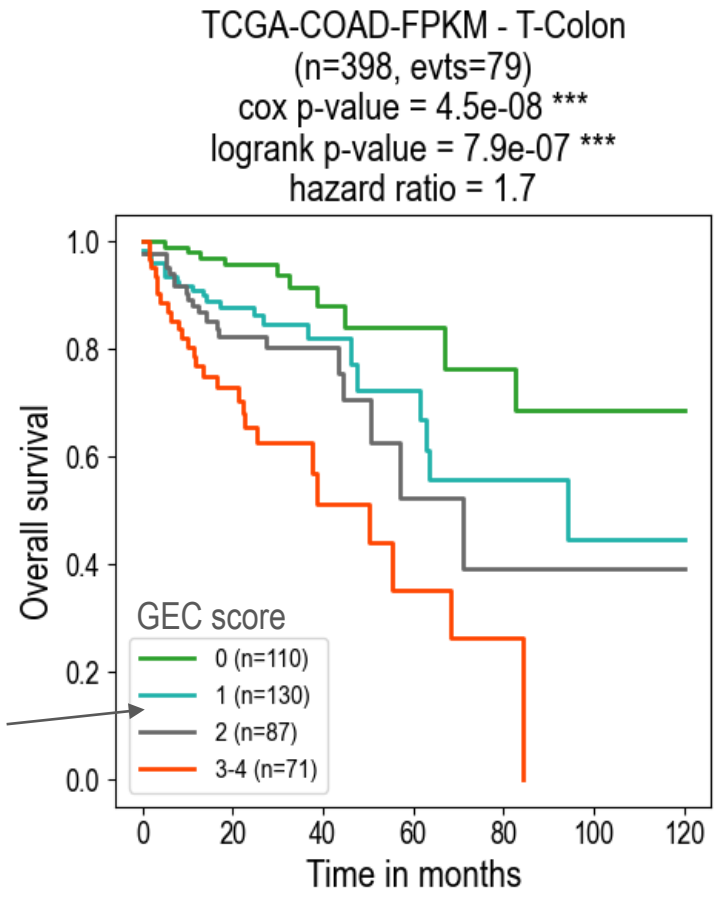


GEC score = number of activated biomarkers, from 0 to 4

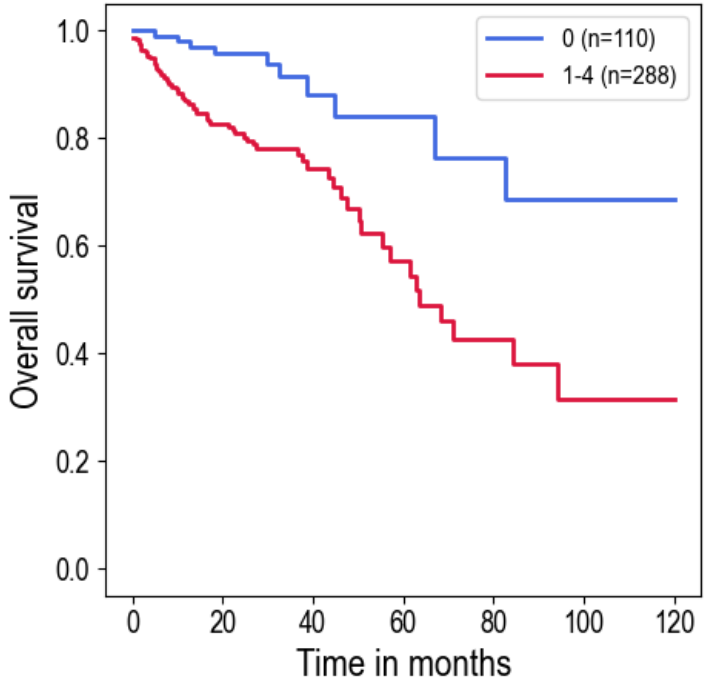
Colon cancer

Gene Expression Classifier (GEC): 4 biomarkers

HOXC6, ULBP2, ERFE, LAMP5



GEC score = number of activated biomarkers, from 0 to 4

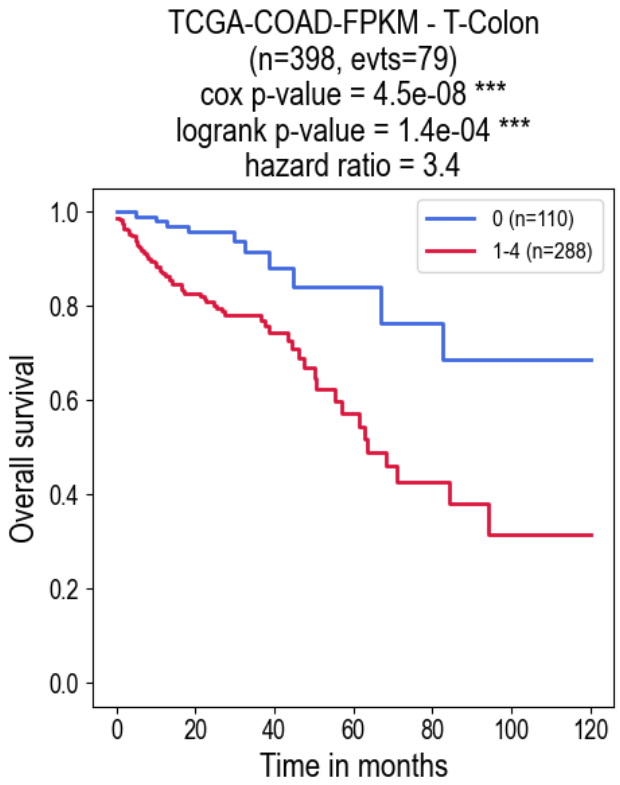


favourable prognosis (GEC-)

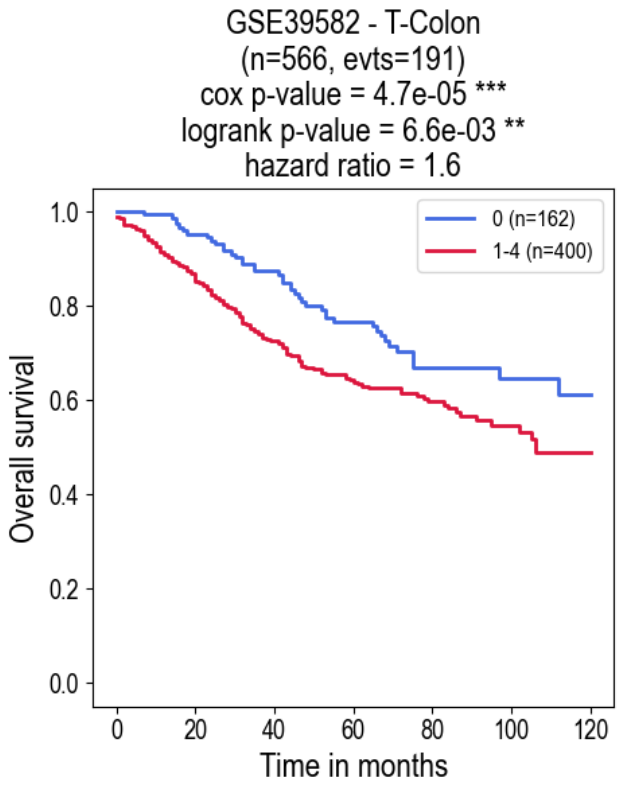
unfavourable prognosis (GEC+)

Colon cancer

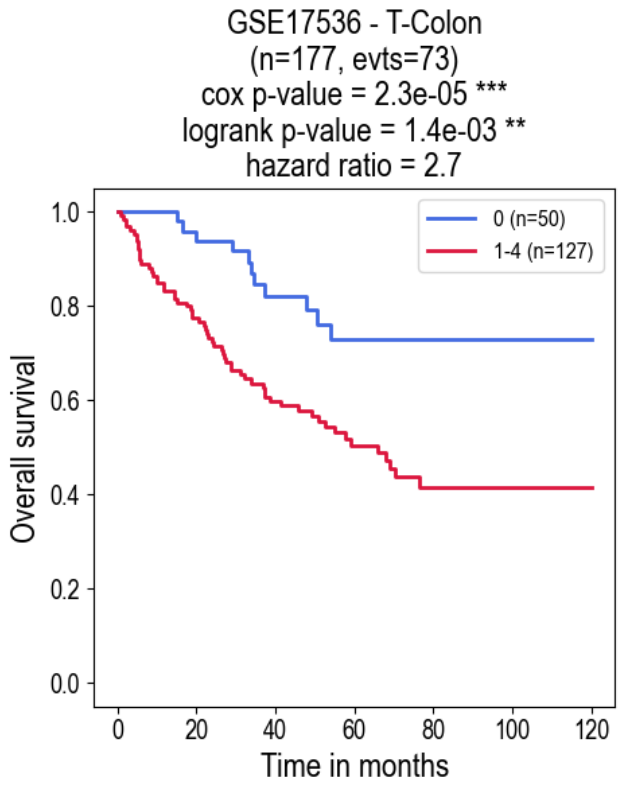
Training dataset



Validation dataset

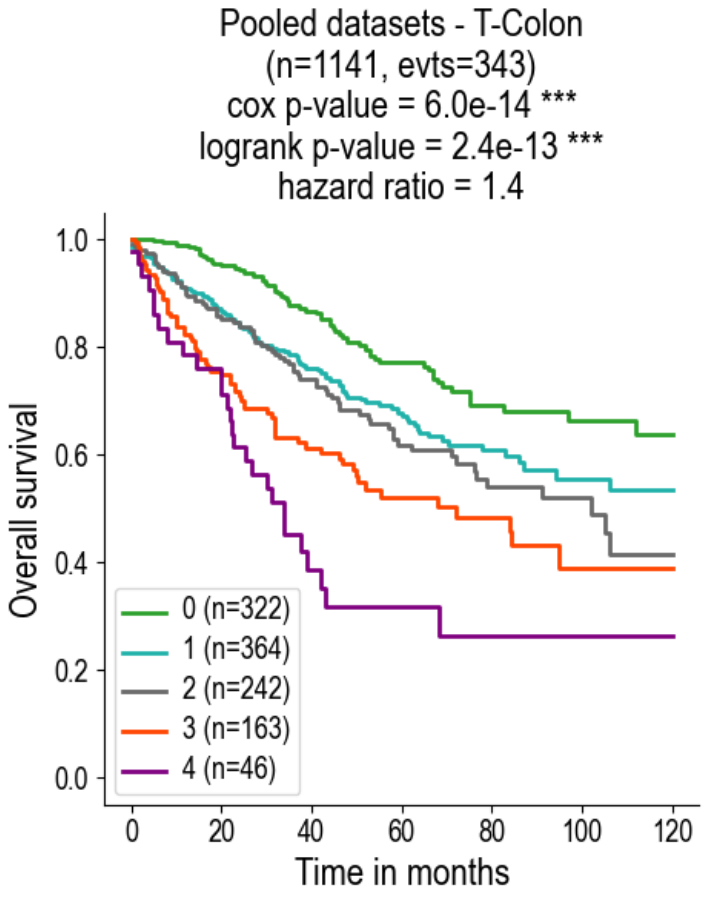


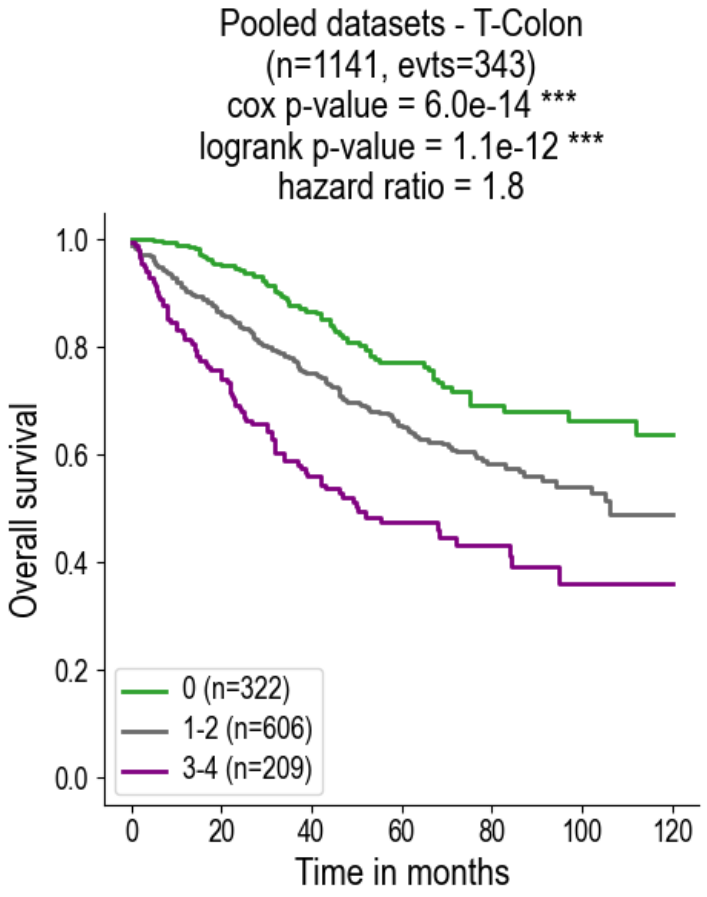
Test dataset

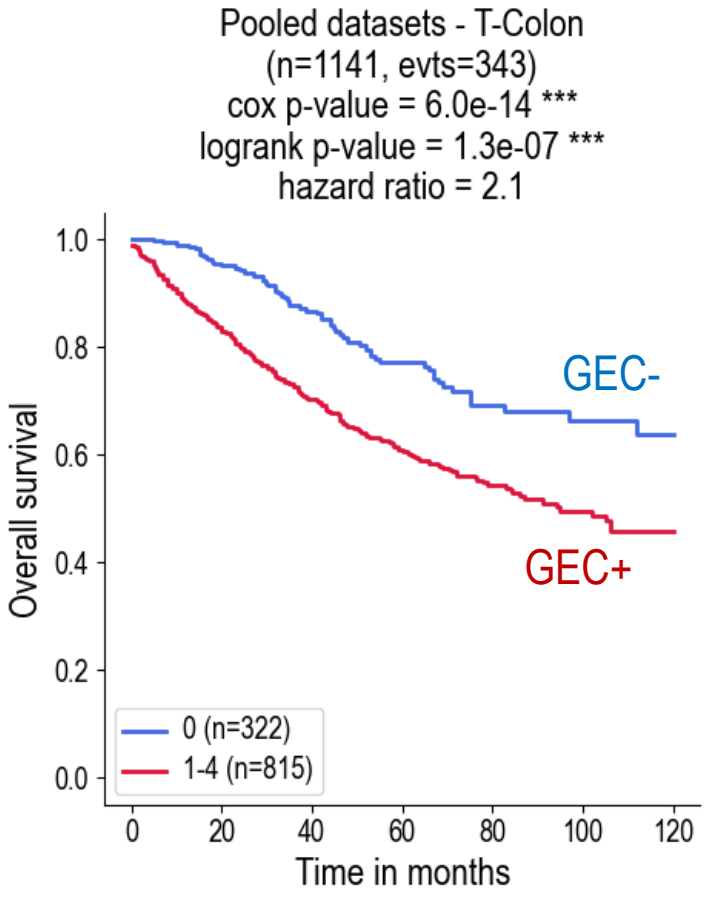


Colon cancer

Pooled datasets







Outline

Main objectives

Supposing that the prognostic GEC score has been already calculated for each patient in 3 colon cancer public datasets:

Identify subtypes of colon cancer in the TCGA-COAD dataset

These subtypes are not directly available in clinical annotations. They should be defined from an analysis of multi-omics data (mutation, methylation, copy number alteration and expression) available in the TCGA-COAD dataset

Predict the subtypes in two other datasets of colon cancer for which only transcriptomic data are available: GSE39582 and GSE17536

Several approaches are possible: machine learning, differential analysis, GSEA analysis using published molecular signatures in the MSigDB database

Analyze the GEC score in different subtypes of colon cancer

Main subtypes of interest: Microsatellite instability (MSI), KRAS mutations, …

[Optional objectives] Analysis of correlation between ectopic activations and epigenetic deregulations in colon cancer

Microsatellite instability

Microsatellite instability in colorectal cancer—the stable evidence

Eduardo Vilar & Stephen B. Gruber

Nature Reviews Clinical Oncology **7**, 153–162 (2010) | Cite this article

Abstract

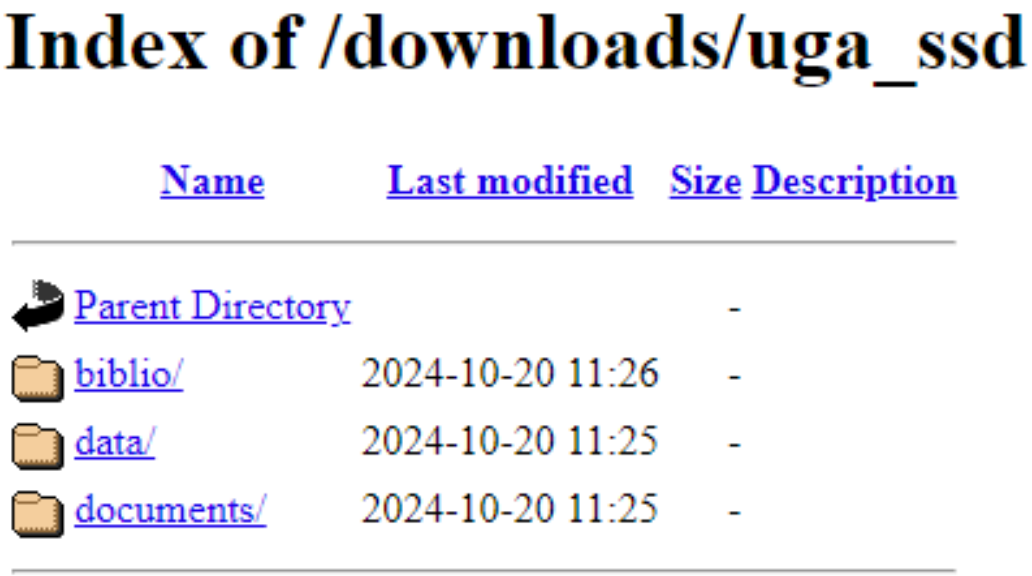
Microsatellite instability (MSI) is the molecular fingerprint of a deficient mismatch repair system. Approximately 15% of colorectal cancers (CRC) display MSI owing either to epigenetic silencing of *MLH1* or a germline mutation in one of the mismatch repair genes *MLH1*, *MSH2*, *MSH6* or *PMS2*. Methods to detect MSI are well established and routinely incorporated into clinical practice. A clinical and molecular profile of MSI tumors has been described, leading to the concept of an MSI phenotype in CRC. Studies have confirmed that MSI tumors have a better prognosis than microsatellite stable CRC, but MSI cancers do not necessarily have the same response to the chemotherapeutic strategies used to treat microsatellite stable tumors. Specifically, stage II MSI tumors might not benefit from 5-fluorouracil-based adjuvant chemotherapy regimens. New data suggest possible advantages of irinotecan-based regimens, but these findings require further clarification. Characterization of the molecular basis of MSI in CRC is underway and initial results show that mutations in genes encoding kinases and candidate genes with microsatellite tracts are over-represented in MSI tumors. Transcriptome expression profiles of MSI tumors and systems biology approaches are providing the opportunity to develop targeted therapeutics for MSI CRC.

Key Points

- Microsatellite instability (MSI) is present in approximately 15% of colorectal cancers (CRC), which are mostly nonfamilial (sporadic) and caused by hypermethylation of the *MLH1* promoter
- Approximately 2–3% of all CRC are caused by germline mutations in one of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*)
- The MSI phenotype is characterized by right-sided location, low pathological stage, mucinous presentation, tumor-infiltrating lymphocytes, absence of necrotic cellular debris and the presence of a Crohn-like nodular infiltrate
- MSI tumors have a good prognosis and reduced likelihood of metastasis compared with microsatellite stable tumors, which highlights the value of MSI as a prognostic marker in CRC
- Although 5-fluorouracil-based chemotherapy is the gold standard for CRC, this drug offers little benefit in early MSI CRC—irinotecan-based regimens and other drugs may hold promise, and are being studied in MSI CRC
- Transcriptome expression studies that characterize MSI tumors and cell lines have identified unique attributes of MSI cancers, and systems biology tools and other approaches enable investigation of targeted therapies

Access to data and documents

http://epimed.univ-grenoble-alpes.fr/downloads/uga_ssd/



Index of /downloads/uga_ssd

Name	Last modified	Size	Description
Parent Directory		-	
biblio/	2024-10-20 11:26	-	
data/	2024-10-20 11:25	-	
documents/	2024-10-20 11:25	-	