INTRODUCTION TO EPIGENOME-WIDE ASSOCIATION STUDIES (EWAS)

1. WELCOME AND INTRODUCTION TO THE COURSE

To introduce basic concepts and guidelines to conduct epigenome-wide association studies (EWAS) using DNA methylation data obtained from arrays.

Teachers:

- Juan R González (juanr.gonzalez@isglobal.org)

- Mariona Bustamante (mariona.bustamante@isglobal.org)

- Laura Balagué (laura.balague@isglobal.org)

- Sofía Aguilar (sofia.aguilar@isglobal.org)

- Felix P Chilunga (f.p.chilunga@amsterdamumc.nl)

SESSIONS

Five sessions of 2 hours:

- Day 1: Introduction to epigenetics and Bioconductor
- Day 2: Pre-processing of DNA methylation data
- Day 3: Epigenome-wide association studies (EWAS)
- Day 4: Meta-analysis of epigenome-wide association studies (meta-EWAS)
- Day 5: Biological interpretation

Each session:

- Theory (30 min)
- Practices
  - Introduction (all together – 15 min)
  - Practical session (in groups – 45 min)
  - Resolution (all together – 30 min)

MATERIAL

Material:
- Laptop or computer with >8Gb RAM
- Power points: https://github.com/isglobal-brge/course_methylation/tree/main/Slides
- Bookdown with all R code: https://isglobal-brge.github.io/course_methylation/
- Data: https://mega.nz/folder/Y3EDAD6Y#pQB_HeqEfAYTg6UixU-k5A

Recommended papers:
- **Recommendations for the design and analysis of epigenome-wide association studies**
https://clinicalepigeneticsjournal.biomedcentral.com/articles/10.1186/s13148-021-01200-8
- **Epigenetic Signatures of Cigarette Smoking**
https://www.ahajournals.org/doi/full/10.1161/CIRCGENETICS.116.001506
- **Meffil: efficient normalization and analysis of very large DNA methylation datasets (ADDED NOW)**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6247925/
- **Orchestrating high-throughput genomic analysis with Bioconductor**
https://www.nature.com/articles/nmeth.3252

INTRODUCTION TO EPIGENOME-WIDE ASSOCIATION STUDIES (EWAS)

## 1. INTRODUCTION TO EPIGENETICS

EPIGENOME

The sum of all modifications to DNA or to DNA-associated RNA and proteins, that permit interpretation of the genome to instruct cell identity and function.
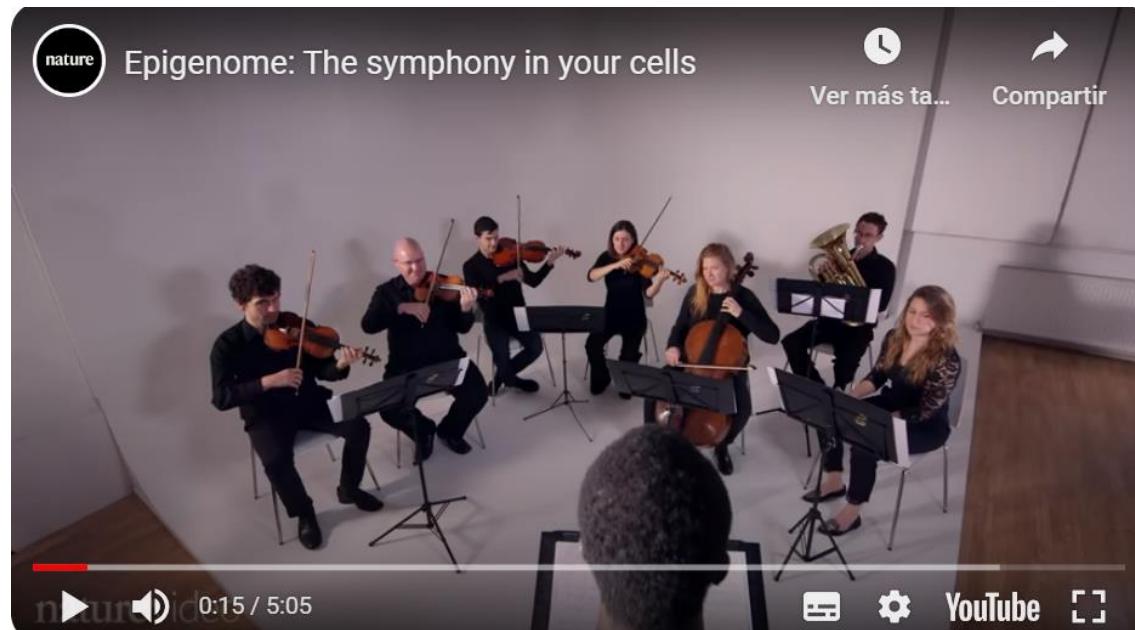

Symphony = Phenotype

Musicians = Epigenome

Partiture = Genome
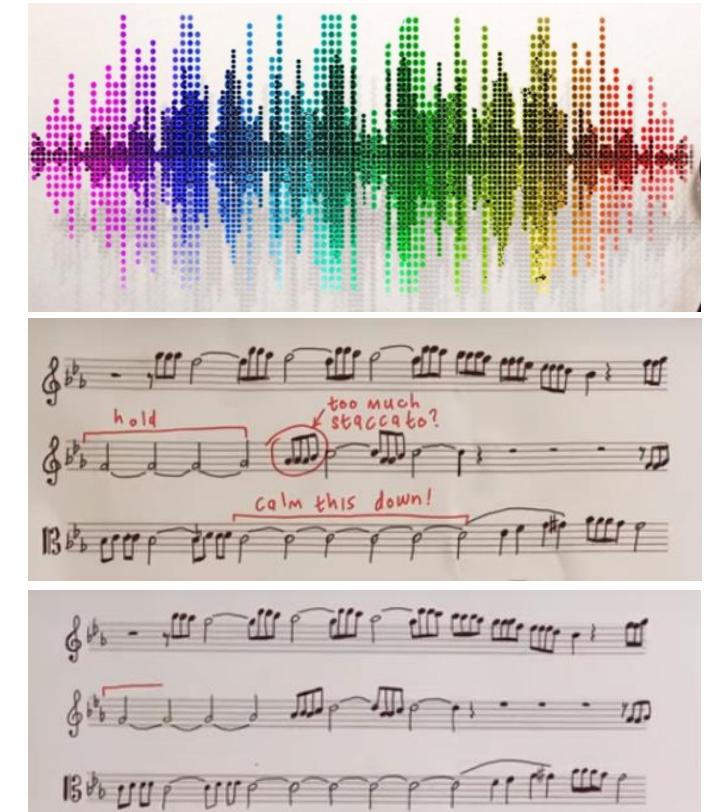
EPIGENETIC MARKS

- DNA methylation
- Histone modifications
- Non-coding RNAs
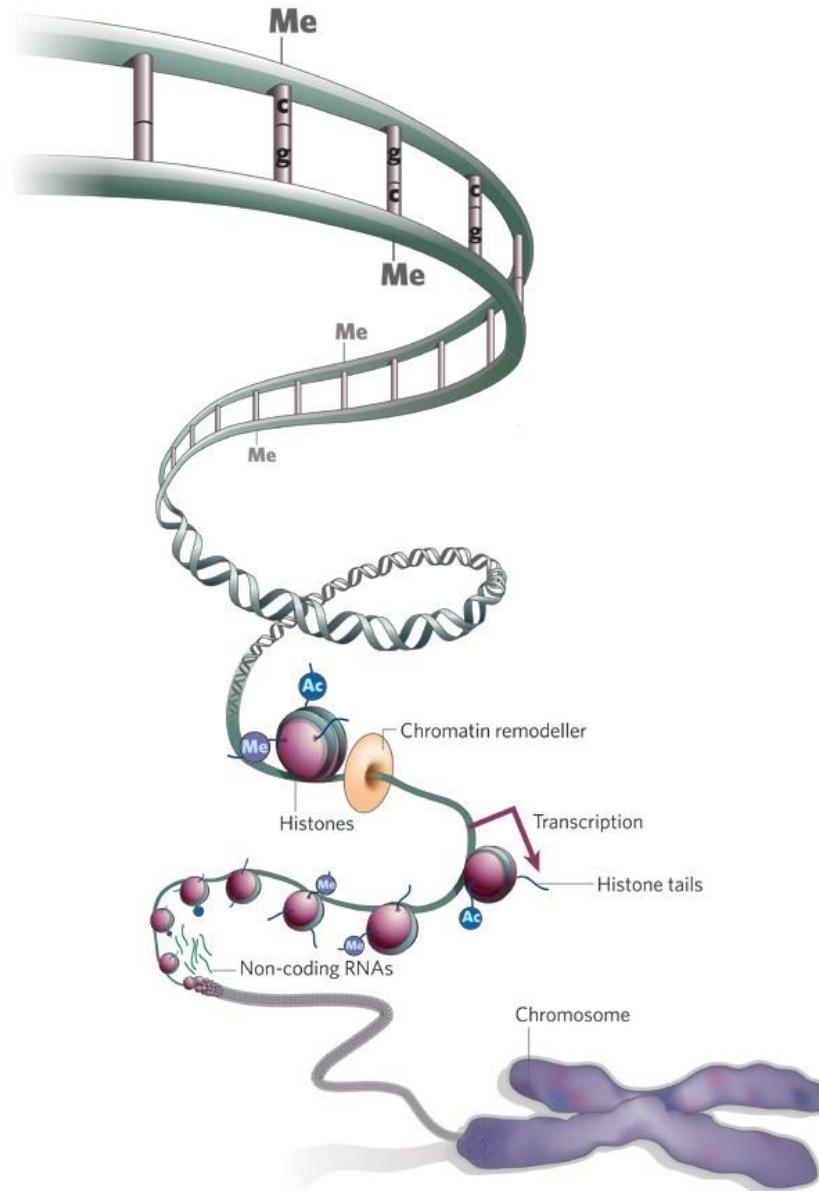
Histone modifications

Histones: proteins needed for DNA packaging

Kumar et al. Int. J. Mol. Sci. 2020
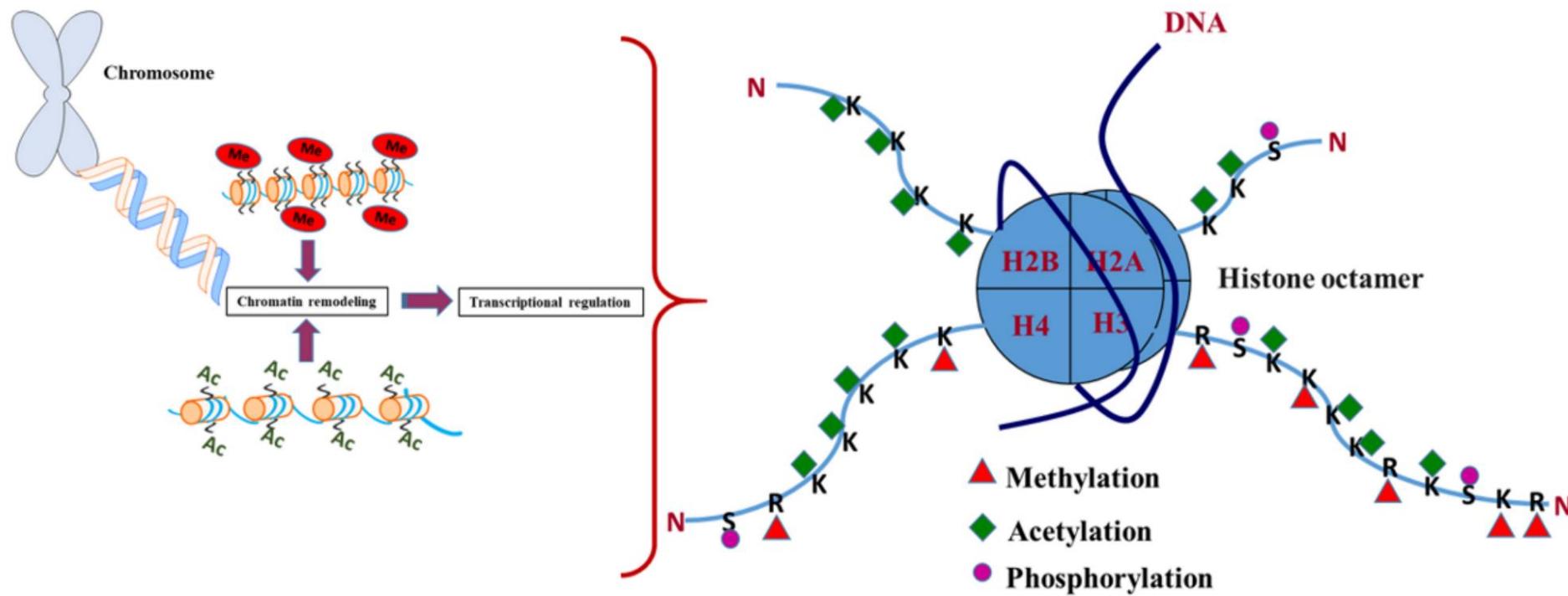
Non-coding RNAs

Types of non-coding RNAs
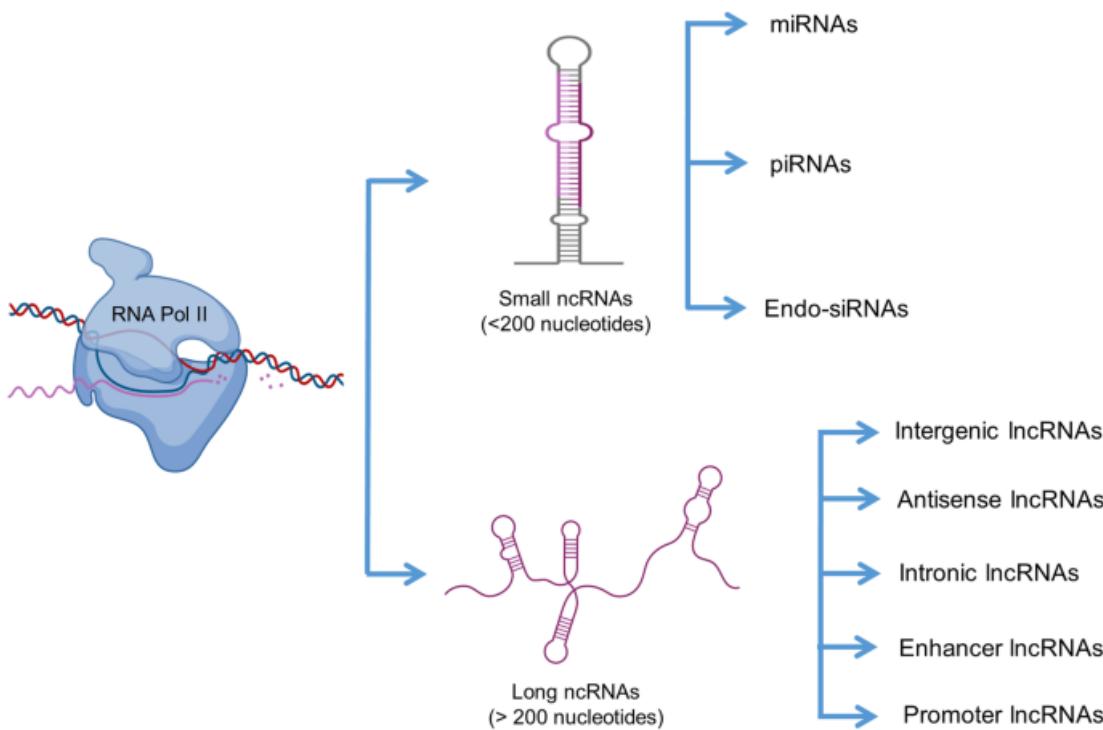
miRNA regulatory mechanism

Joshi et al. Repr Biol Endocr 2020
Gurtam et al. Journal of Molecular Biology 2013

DNA methylation
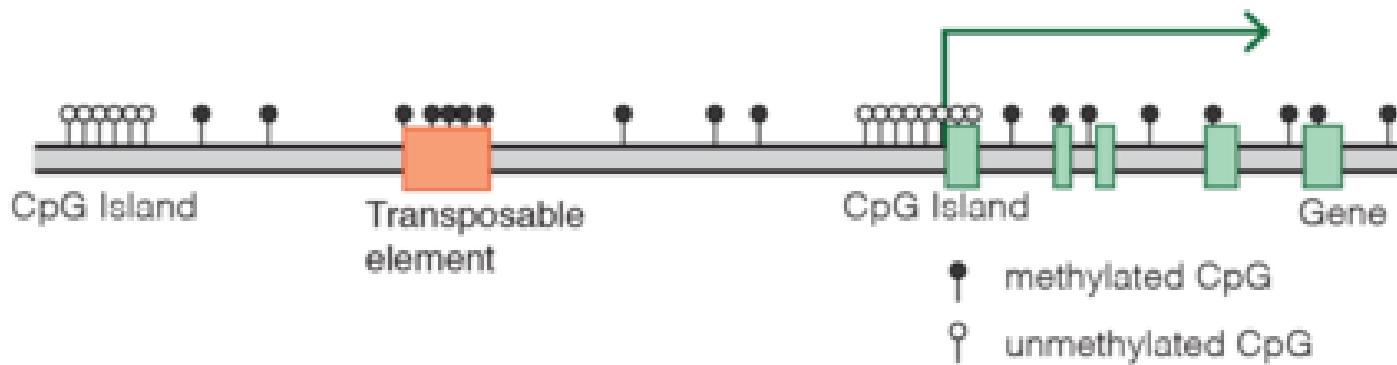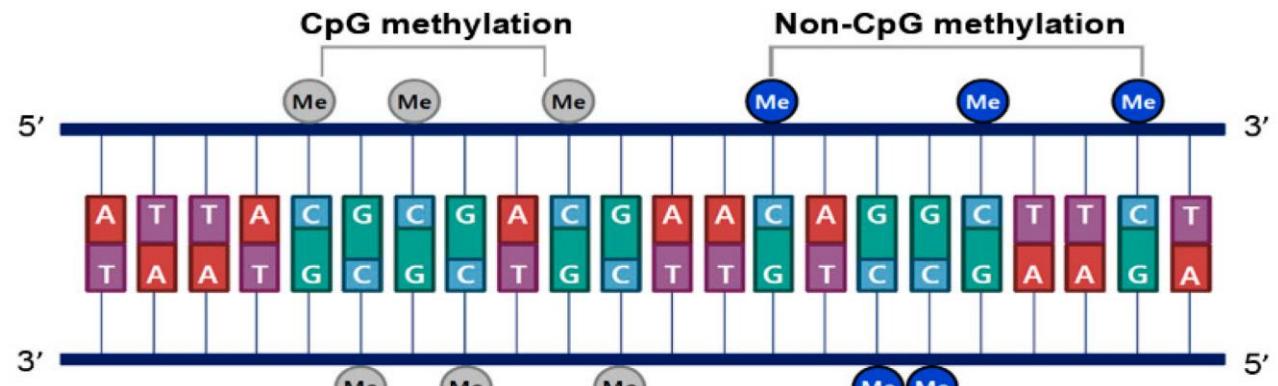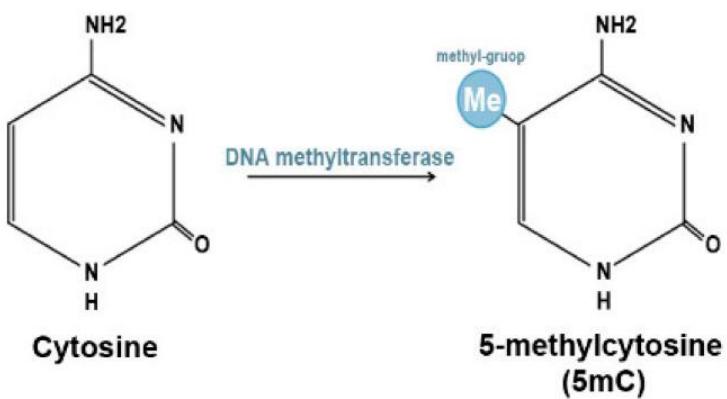
FUNCTIONS OF THE EPIGENOME

The epigenome regulates how genes are expressed (when, where, at what level…), thus it regulates:

- Embryo and fetal development
- Cellular differentiation
- Chromosome X inactivation
- Chromosome stability (ie. inhibition of DNA mobile elements)
- Response to environmental factors
- Involved in disease mechanisms

Tissue and cell specificity
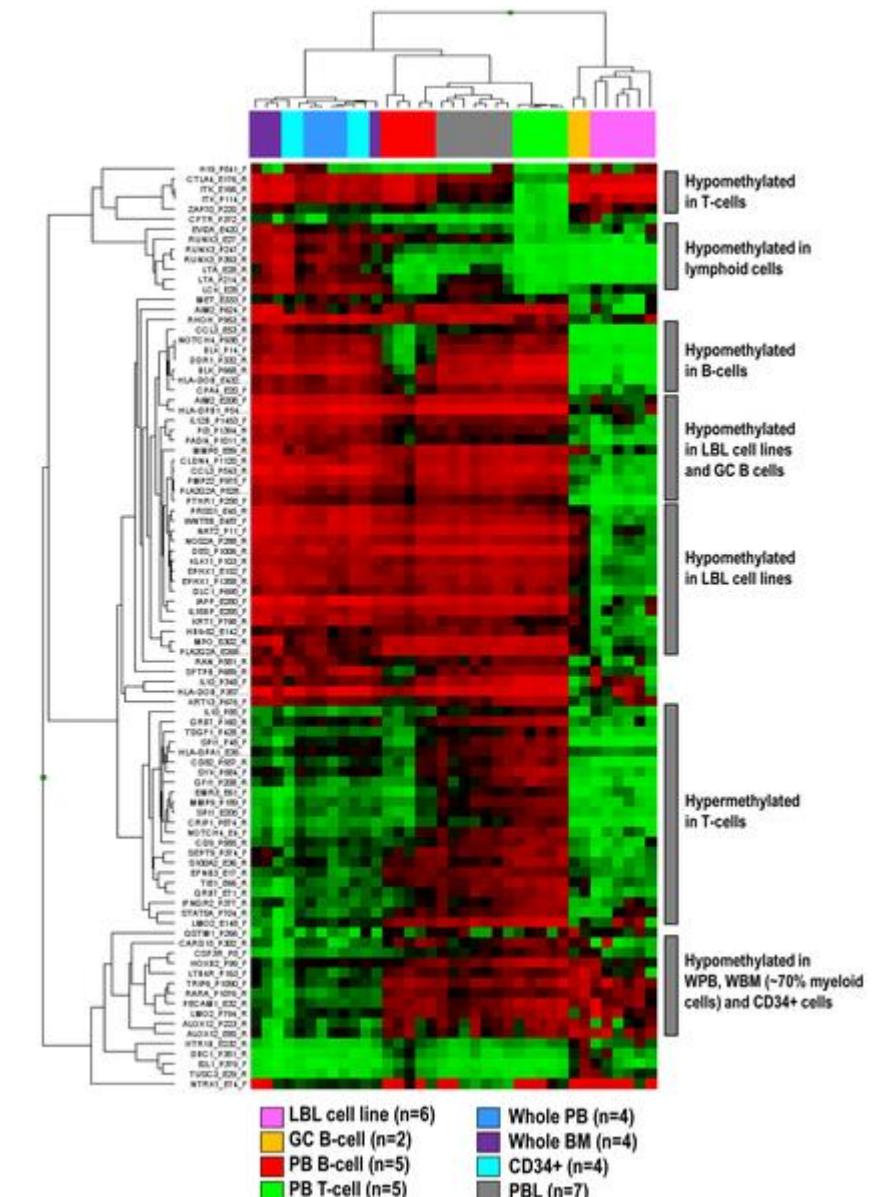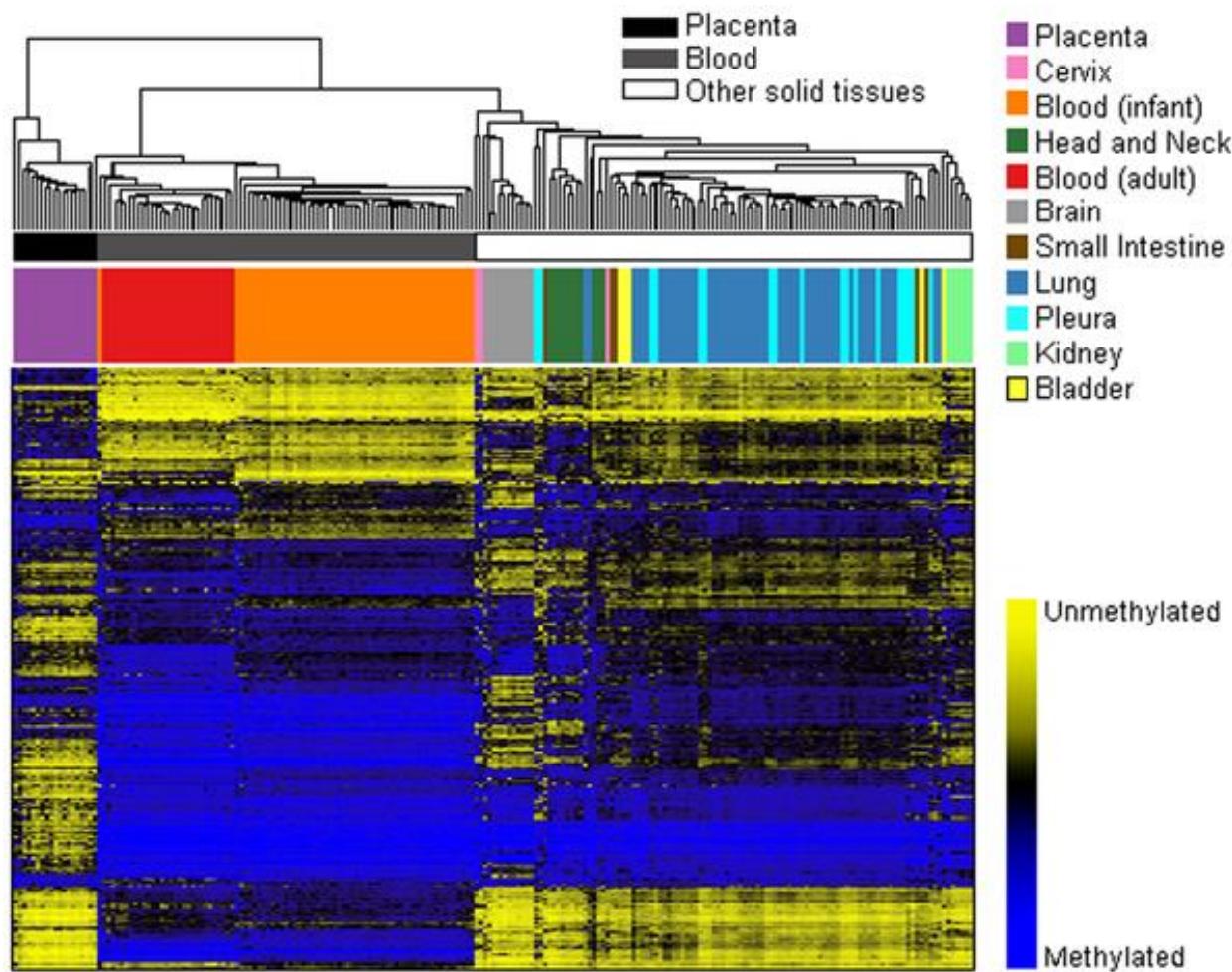
Fetal development
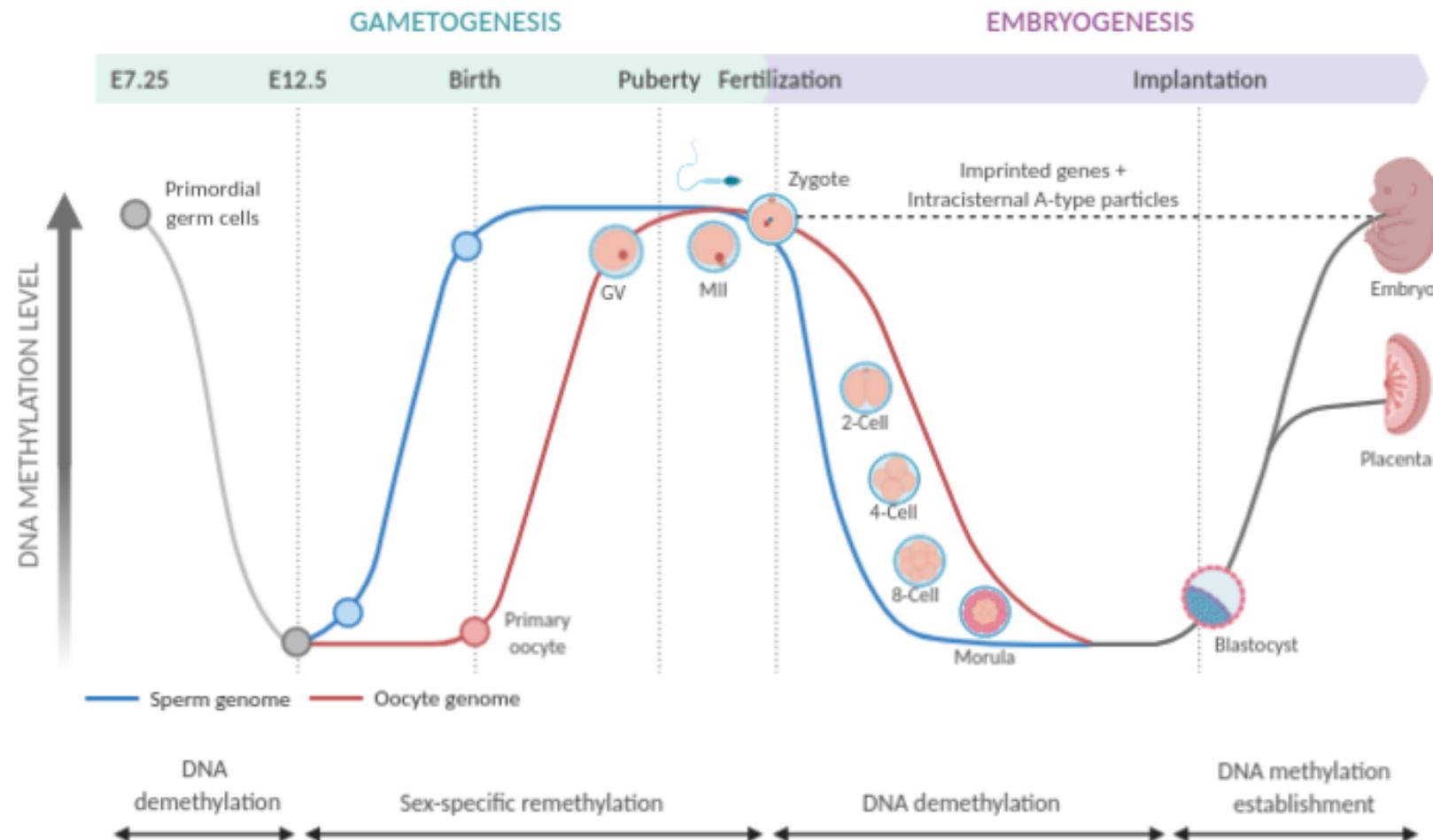
THE LINK BETWEEN EXPOSURES, GENETIC VARIATION AND TRAITS

Genetic variation

SNP

GCAACGT

GCAGCG
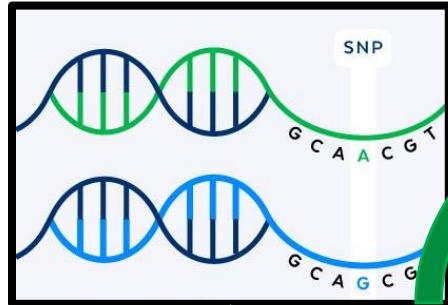
GxE
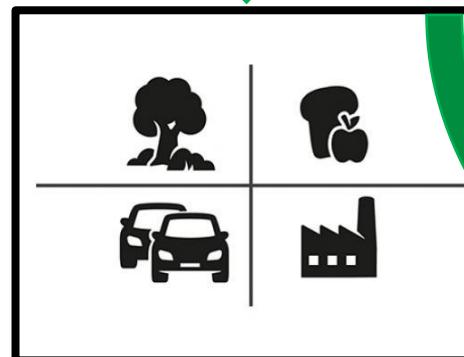
Environmental factors

Epigenome

Transcriptome

Proteome

Metabolome

Phenotype

UNDERWEIGHT < 18.5

NORMAL 18.5 - 22.9

RISK TO OVERWEIGHT 23-24.9

OVERWEIGHT 25-29.9

OBESE >30
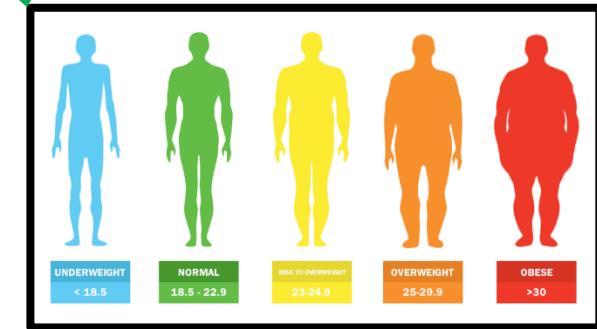
APLICATIONS OF EPIGENETICS

Main applications of epigenetics

- Understand biological mechanisms from environment to disease
- Stratify disease in subtypes for diagnosis
- Predict disease risk, treatment response…
- Predict past exposures

UNDERSTAND BIOLOGICAL MECHANISMS

**Maternal tobacco smoking – placental methylation – birth weight**
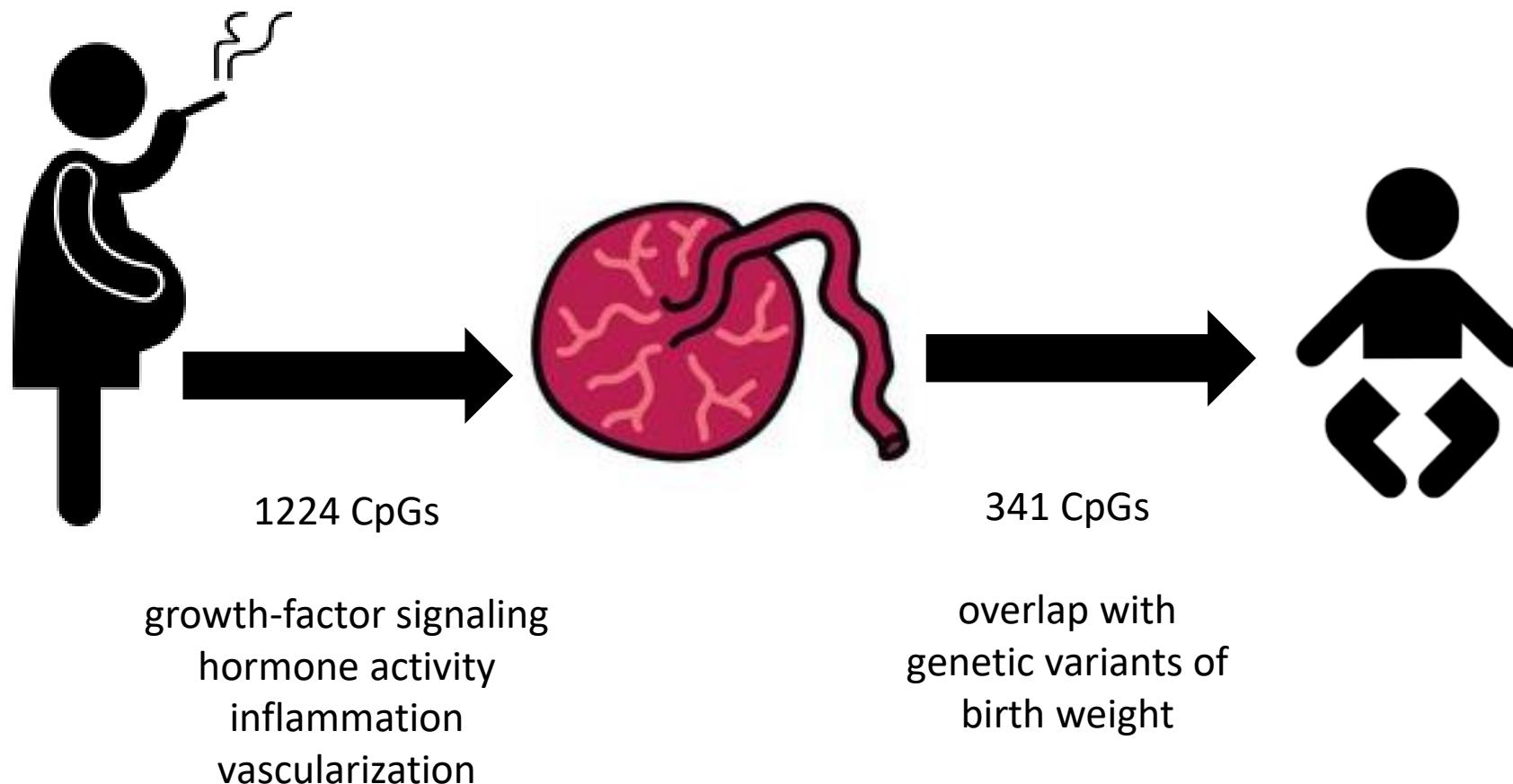
1224 CpGs

growth-factor signaling
hormone activity
inflammation
vascularization

341 CpGs

overlap with
genetic variants of
birth weight

Everson et al. Nat Comm 2021

Prediction of health risk factors and exposures


Yousefi et al Nat Rev Genet 2022
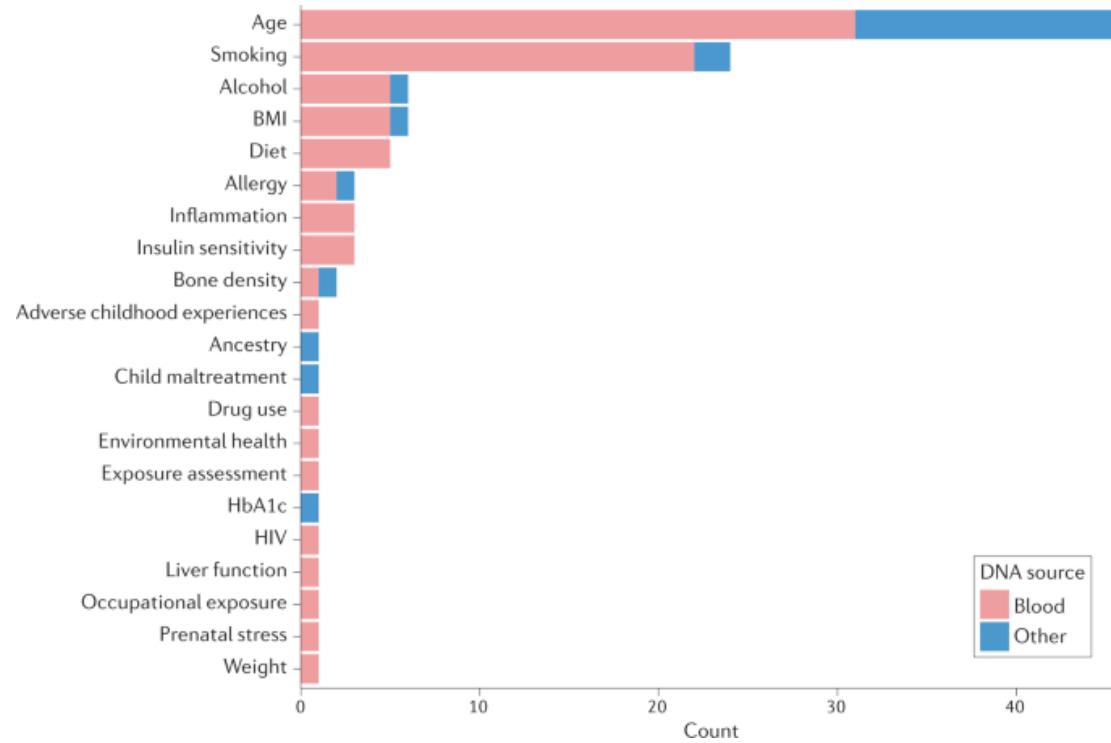
Prediction of health risk factors and exposures
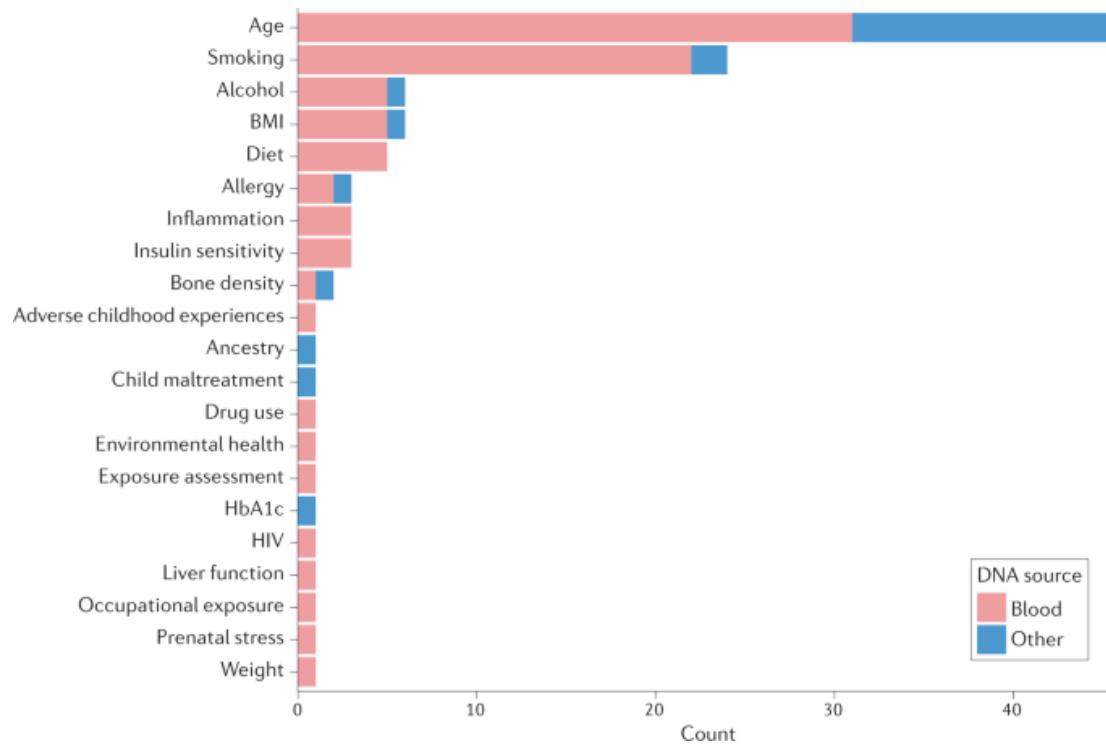
Prediction of smoking status

EpiSmokEr R package – blood methylation data
C: Current, F: Former, N: Never and O: other two categories
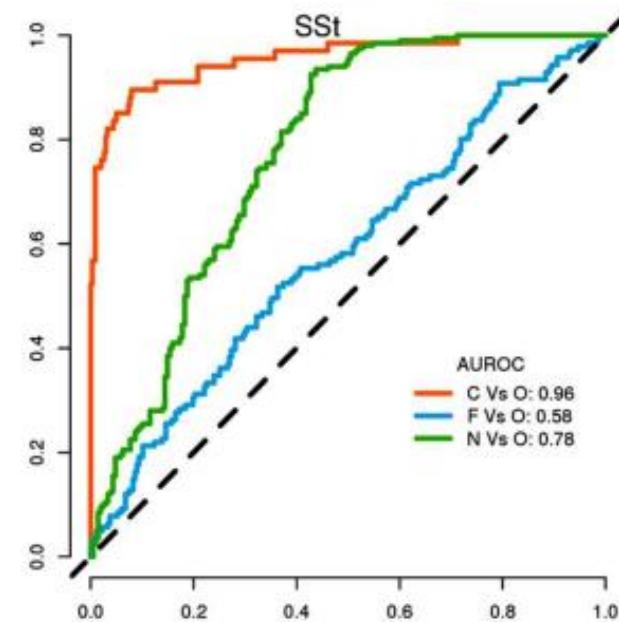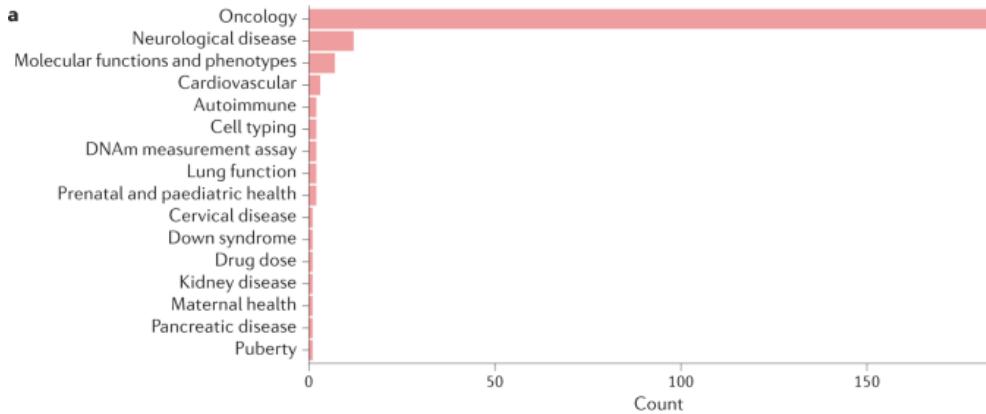
Yousefi et al Nat Rev Genet 2022

Bollepalli, bioarxiv 2022

Prediction of health outcomes

Yousefi et al Nat Rev Genet 2022

Prediction of health outcomes

Oncology

Prediction of health outcomes

Oncology

Yousefi et al Nat Rev Genet 2022
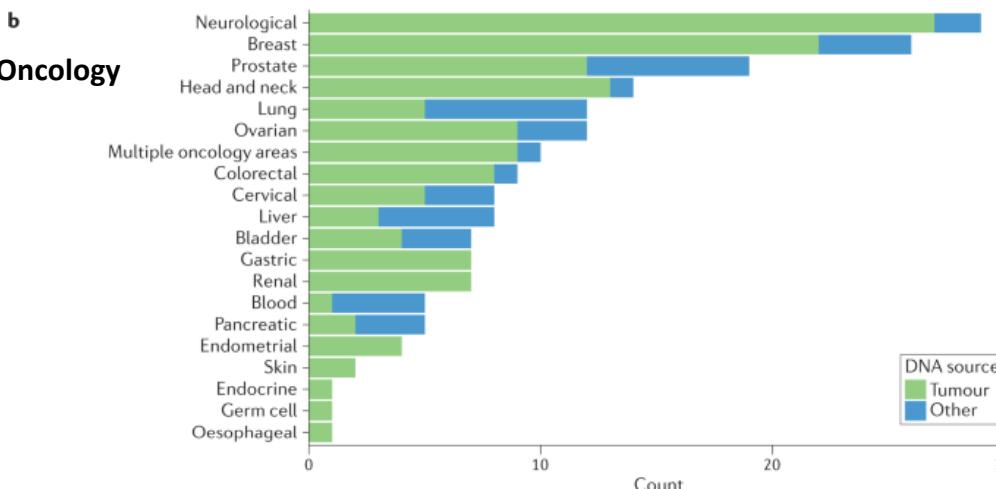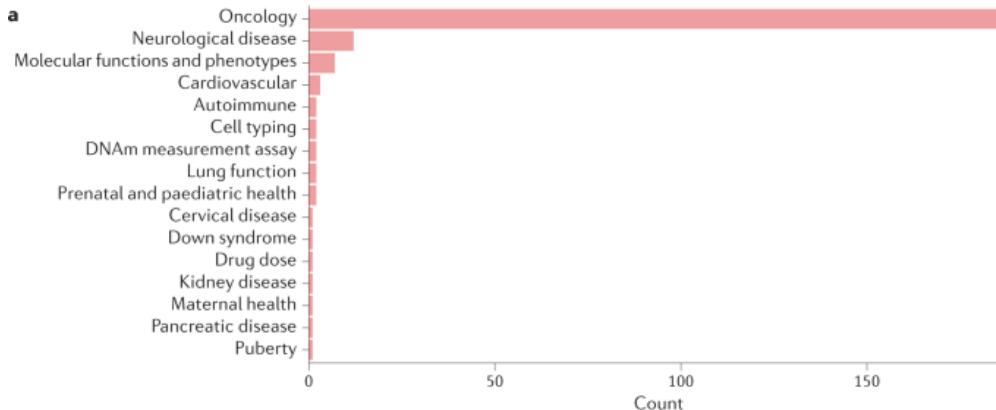
Prediction of health outcomes

Primary neuroblastoma

Oncology

Yousefi et al Nat Rev Genet 2022

H. Lalchungnunga British Journal of Cancer 2022
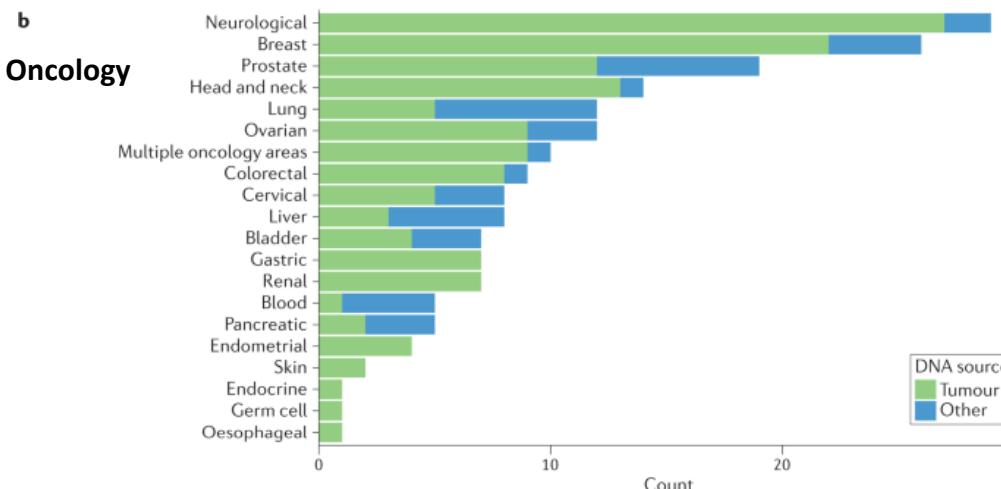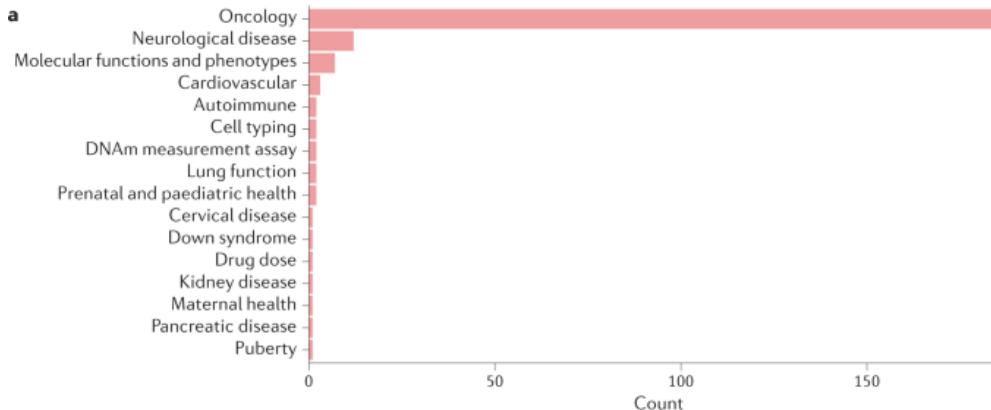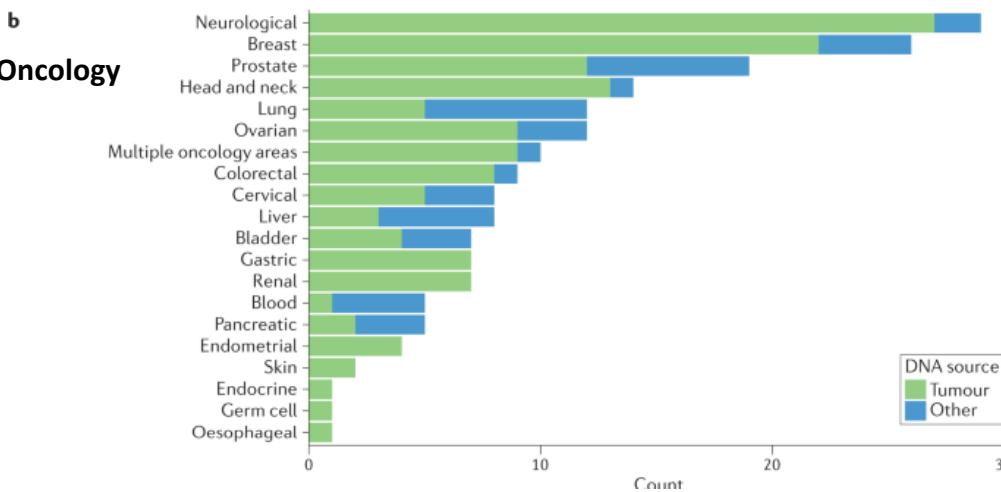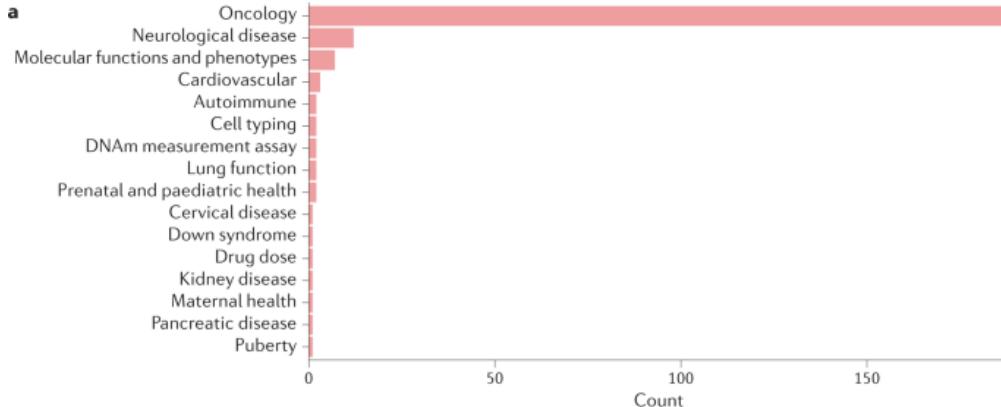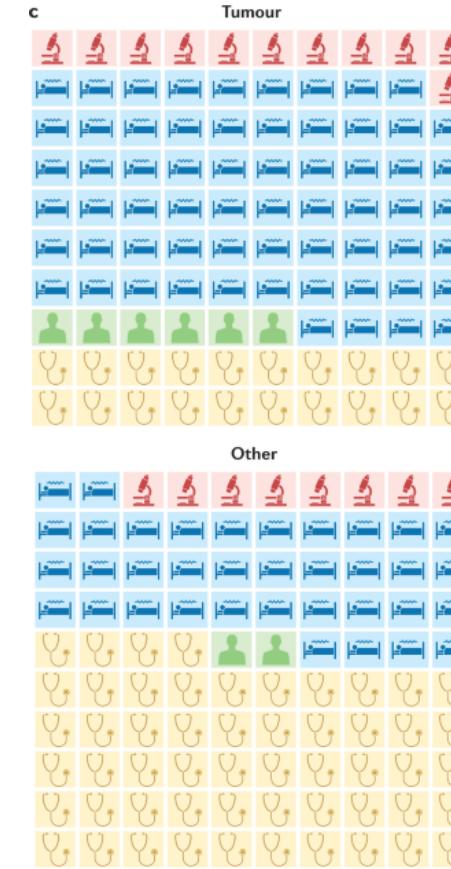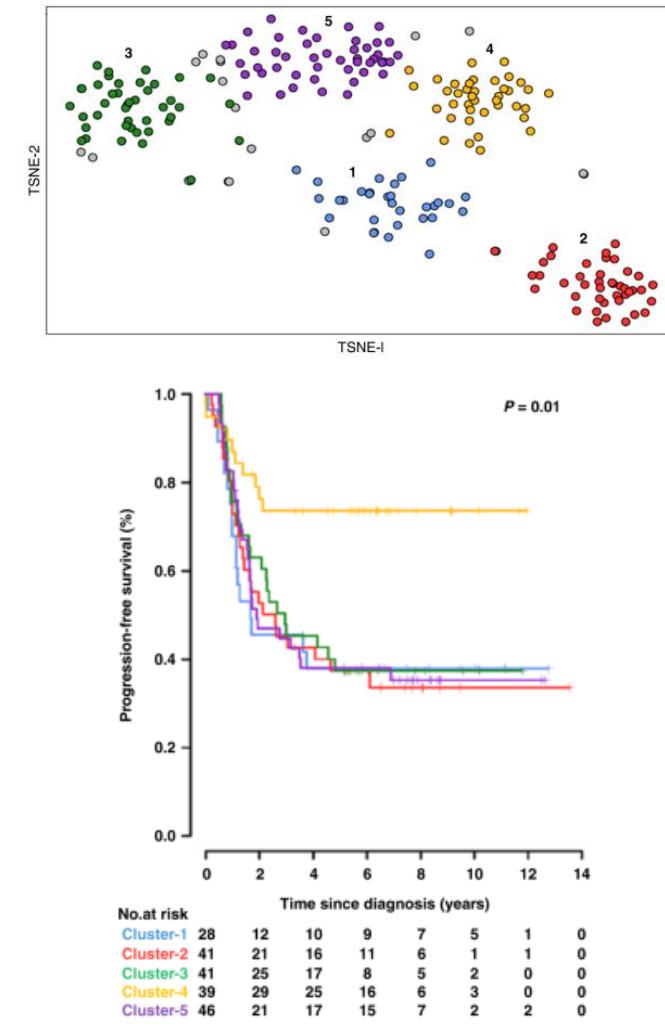
INTRODUCTION TO EPIGENOME-WIDE ASSOCIATION STUDIES (EWAS)

1. EPIGENETICS AMONG TRANSITIONING AFRICAN POPULATIONS

(Felix P Chilunga)

INTRODUCTION TO EPIGENOME-WIDE ASSOCIATION STUDIES (EWAS)

1. RESOURCES AND TOOLS FOR EPIGENETICS

Go to: https://isglobal-brge.github.io/course_methylation/resources-and-tools-for-epigenetics-in-bioconductor.html