An integrated approach for development of epigenetic biomarkers of cancer risk in prospective studies

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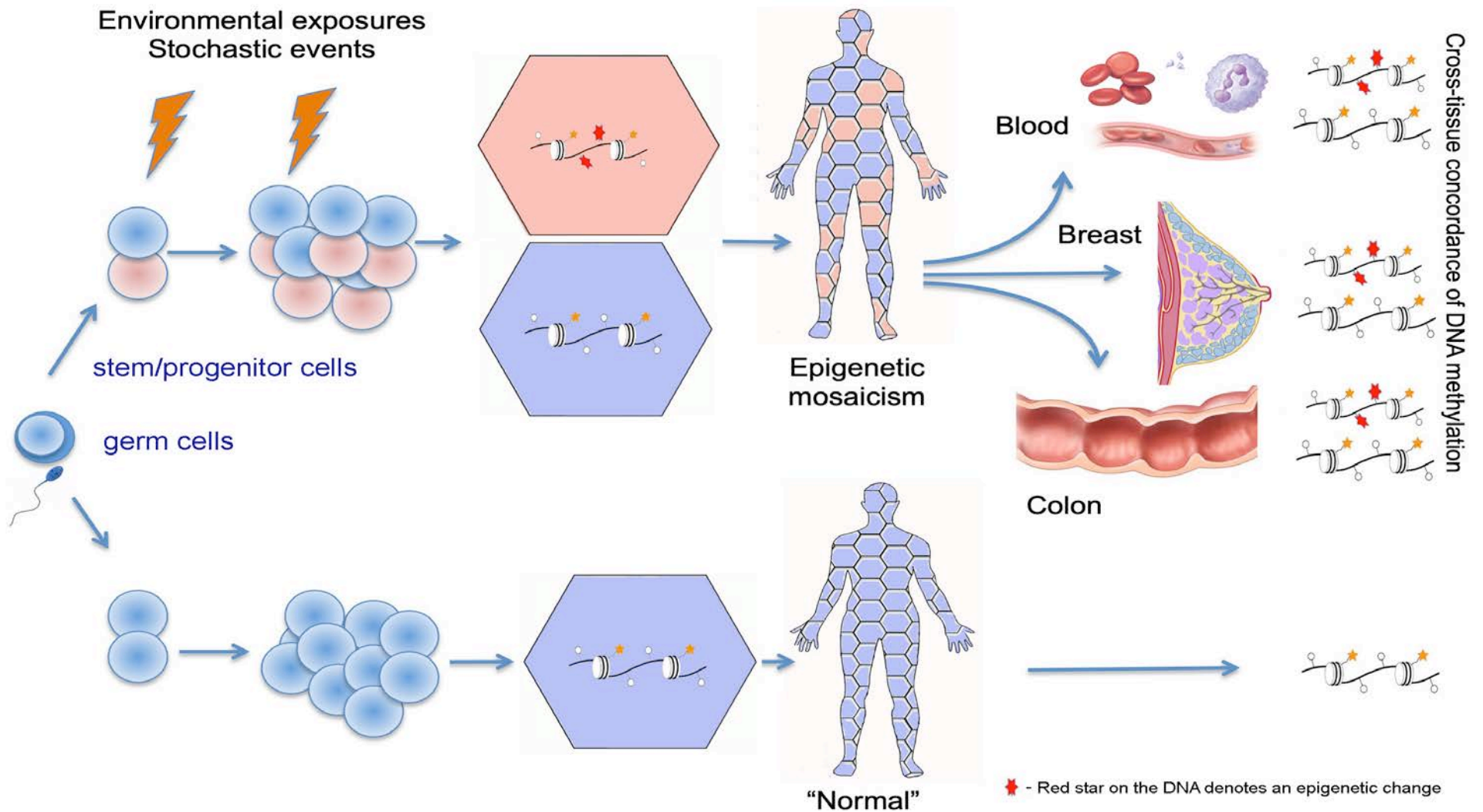International Agency for Research on Cancer/World Health Organization, Lyon, France

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International Agency
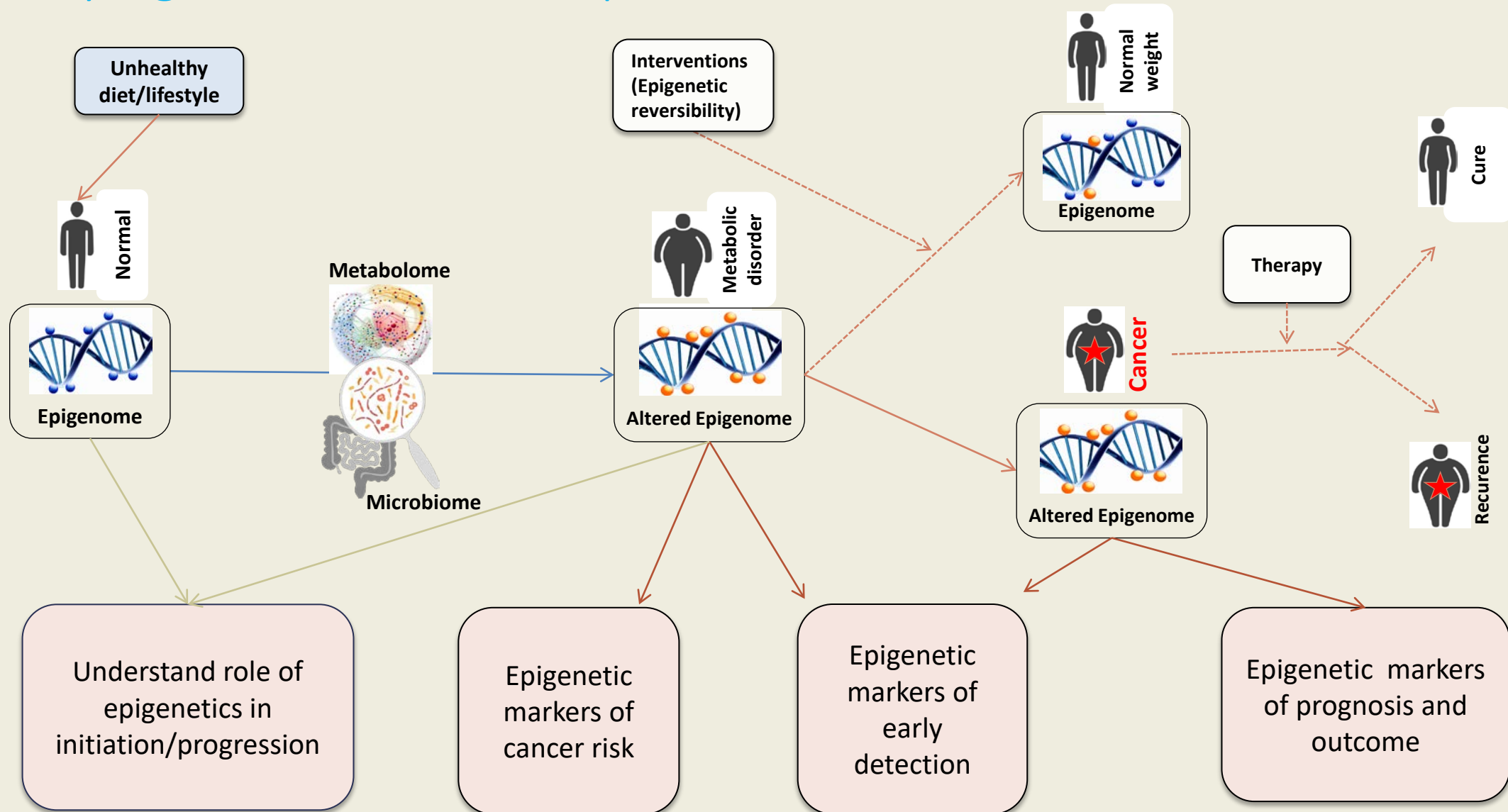for Research on Cancer

World Health
Organization
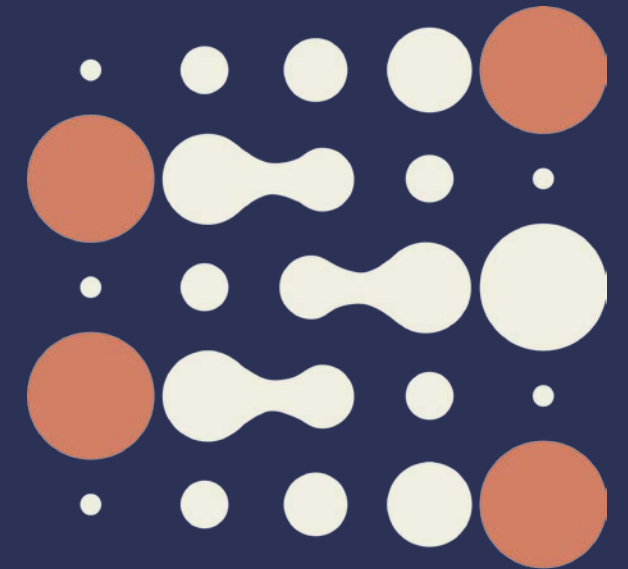
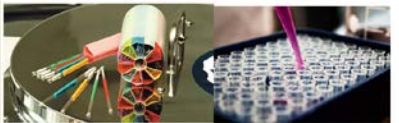# Epigenetic mosaicism as a mechanism of cancer causality & as targets for biomarker discovery

Profiling epigenetic changes to understand cancer mechanisms & identifying biomarkers of exposures and cancer risks

Resources

Wet-lab pipelines

Bioinformatics workflows

IARC biobanks

EPIC cohort

Cohorts

Cell models

DNA/RNA/chromatin

Methylome profiling

Chromatin analysis

Transcriptomics analysis

Genome-wide (discovery)

Automated preprocessing

TECAN robot

Illumina Beadchip

NextSeq/Outsourcing

Targeted (validation)

High-throughput preprocessing

Pyrosequencing

Bioruptor Pico

IP Star ChIP robot

NextSeq/Outsourcing

RNA-seq

NextSeq/Outsourcing

Methylation pipeline
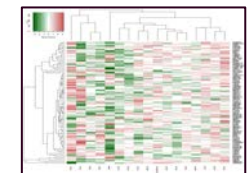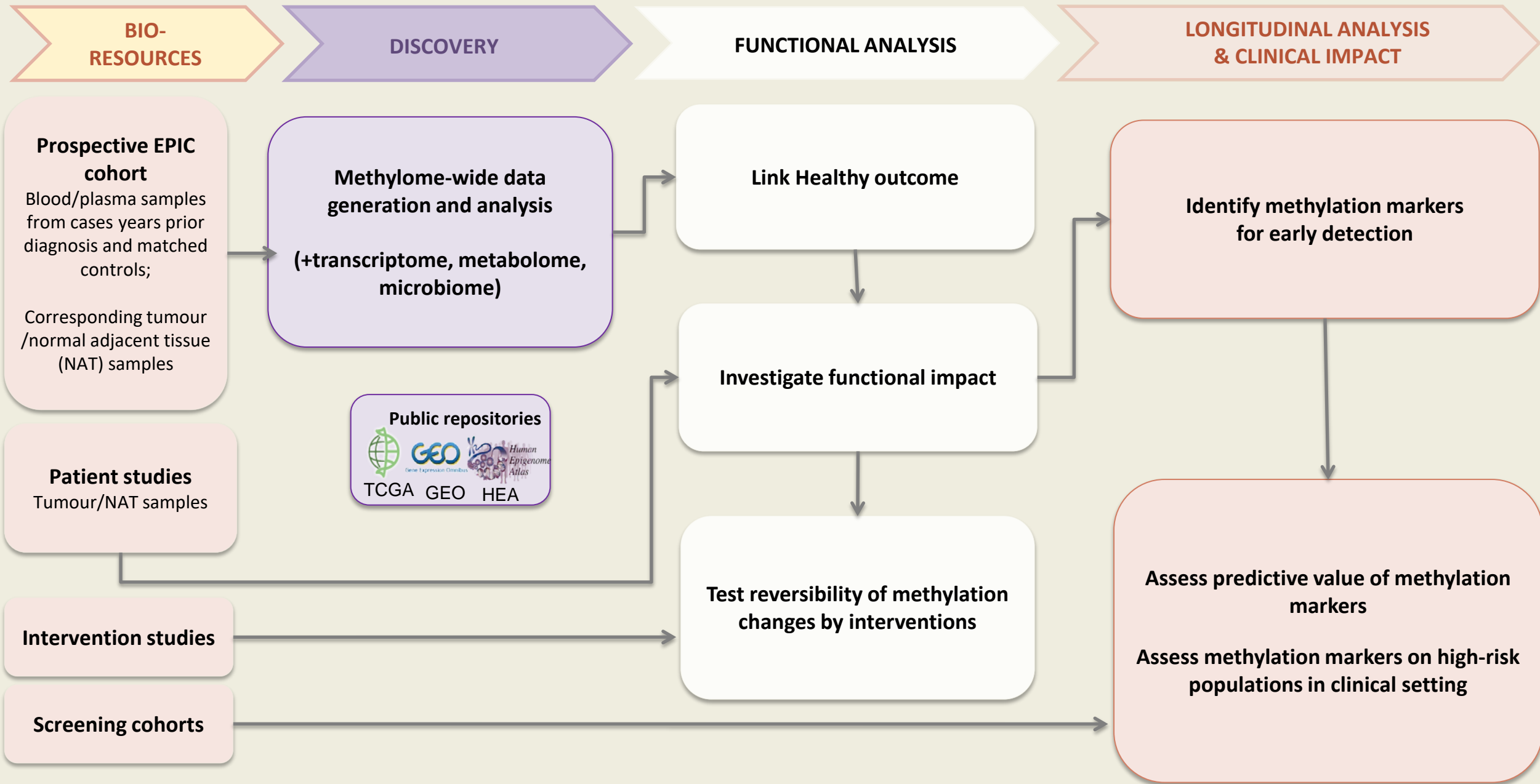(Arrays and base resolution)
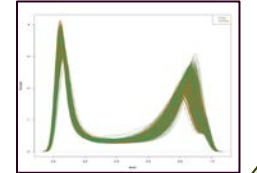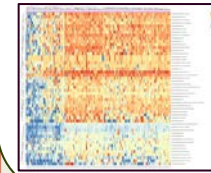
ChipSeq, ATAC-seq, cut&tag pipelines
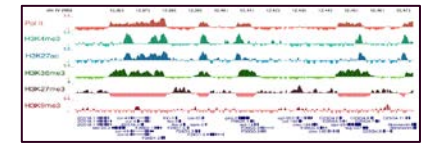
RNAseq pipeline
Transcriptomics

Design

BIO-RESOURCES → DISCOVERY → FUNCTIONAL ANALYSIS → LONGITUDINAL ANALYSIS & CLINICAL IMPACT

Prospective EPIC cohort
Blood/plasma samples from cases years prior diagnosis and matched controls;

Corresponding tumour /normal adjacent tissue (NAT) samples

Methylome-wide data generation and analysis

(+transcriptome, metabolome, microbiome)

Public repositories
TCGA   GEO   HEA

Patient studies
Tumour/NAT samples

Intervention studies

Screening cohorts

Link Healthy outcome

Investigate functional impact

Test reversibility of methylation changes by interventions

Identify methylation markers for early detection

Assess predictive value of methylation markers

Assess methylation markers on high-risk populations in clinical setting
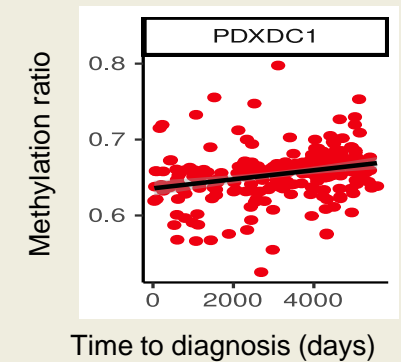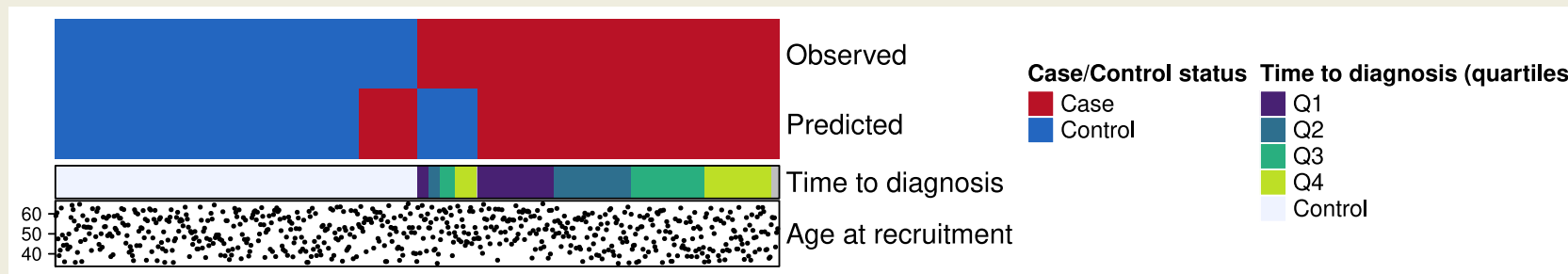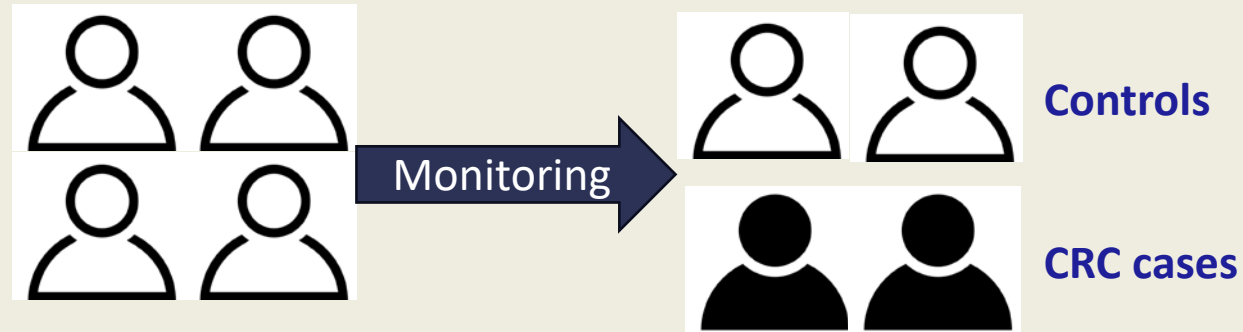
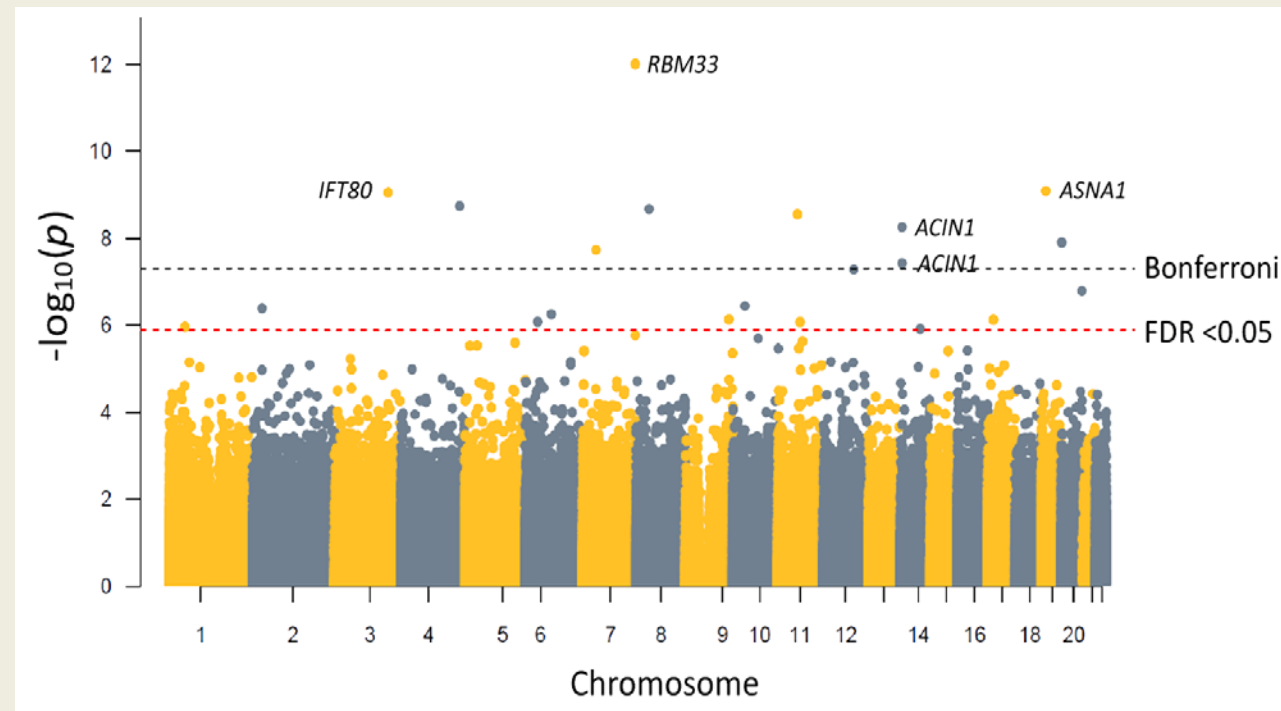# Results: Identifying predictive biomarkers of breast cancer risk
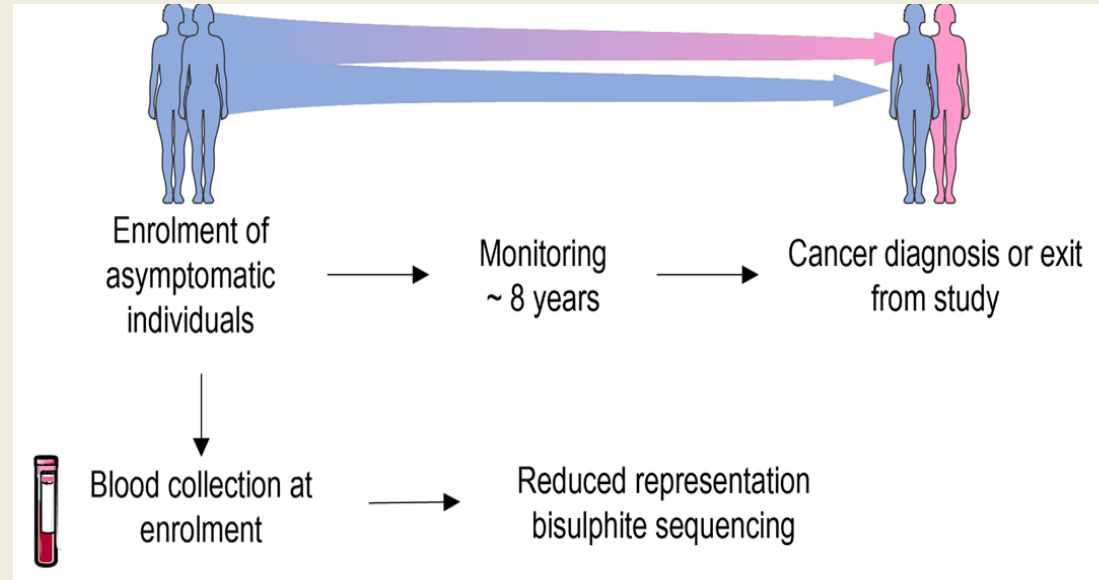
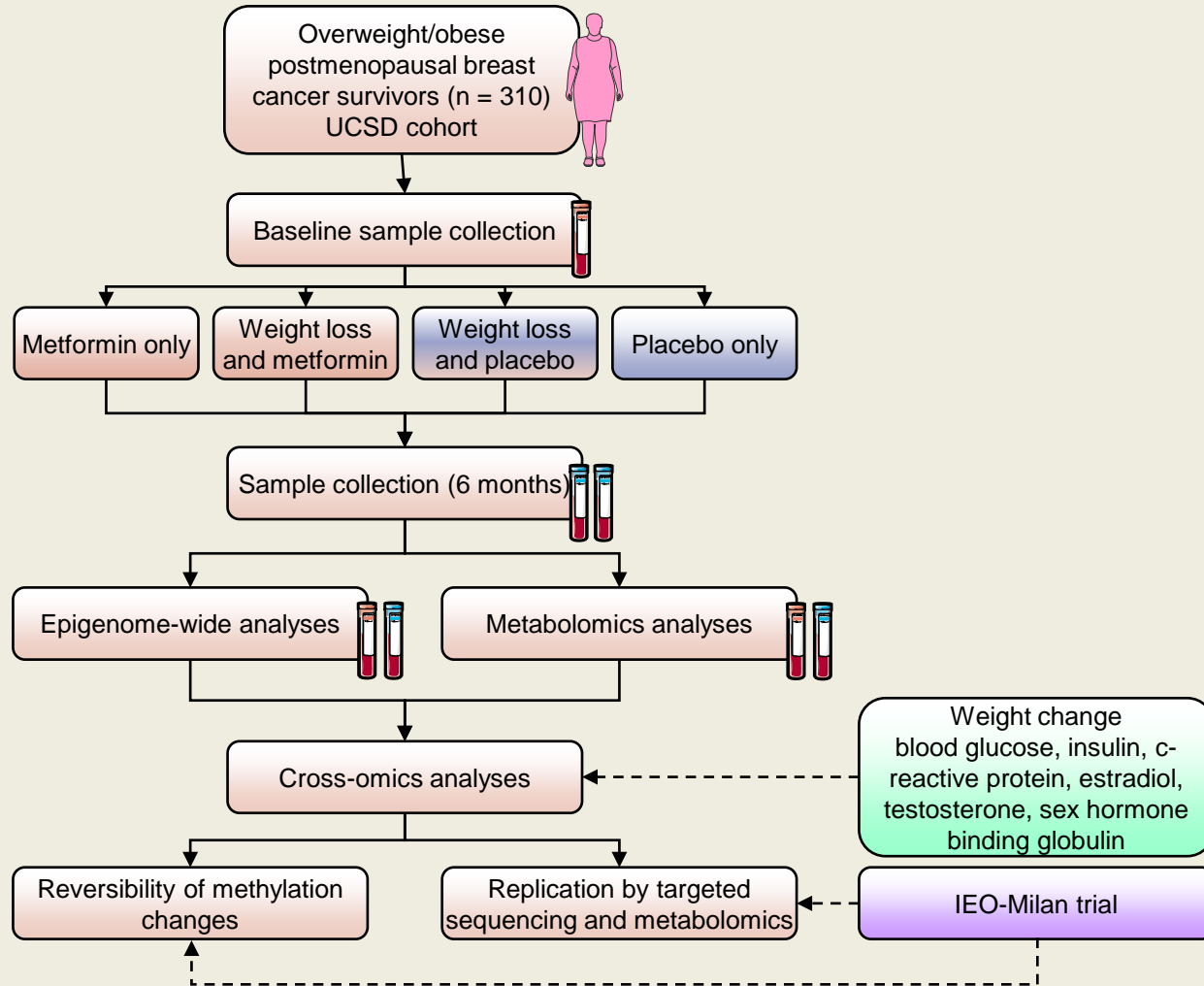NGS-based methylome (RRBS) obtained from 700 EPIC samples and machine learning approach

Results: Identifying predictive biomarkers of colorectal cancer risk

Methylome analysis of 384 EPIC samples

Talukdar *et al.,* in prep

Results: Weight loss and Metformin intervention in breast cancer postmenopausal survivors


**Intervention impacted methylation of genes in metabolic, diabetes and cancer-associated pathways**

Pathways associated with differentially methylated regions	
Insulin secretion	0.0181
Diabetes pathways	0.0011
Bile salt and organic anion SLC transporters	0.0082
Ras activation upon calcium influx through NMDA receptor	0.020
Toll receptor cascades	0.038
Notch signaling pathway	0.0049
Canonical NF-kappaB pathway	0.03
HIF-1-alpha transcription factor network	0.041
AMPK-signaling pathway	0.16
Cancer, cell death and survival, organismal injury and abnormalities	2.39E-08
Cancer,Endocrine System Disorders,Organismal Injury and Abnormalities	6.7E-08

Chung *et al.,* in prep

Results: Bariatric surgery-induced weight loss and associated genome-wide DNA-methylation changes in obese individuals
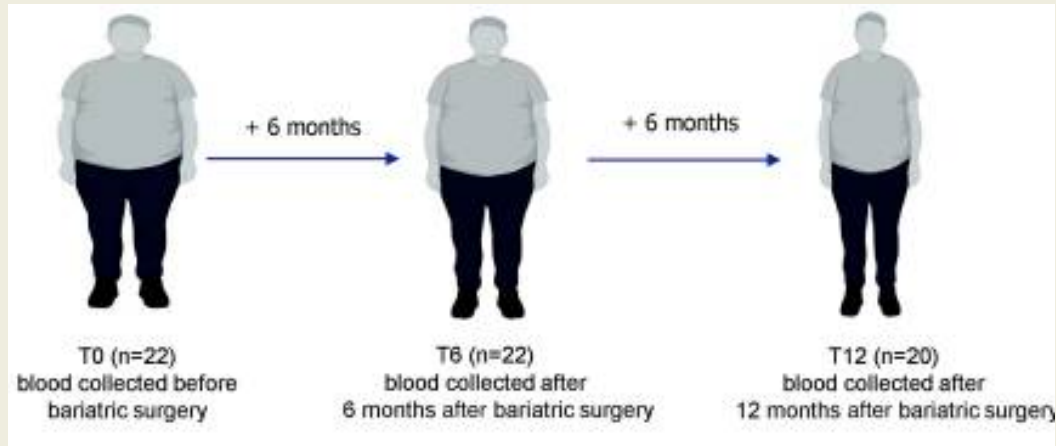
Enrichment of weight loss-associated DMPs in immune and inflammatory signaling pathways

Talukdar et al, *Clinical Epigenetics, 2022*
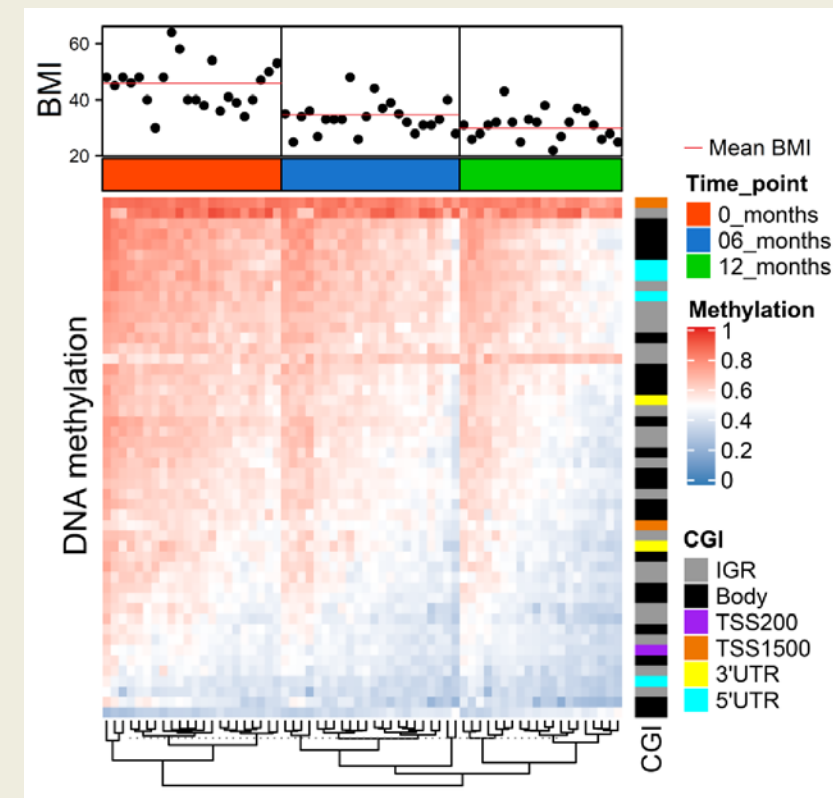
Discussion and Conclusions

- Identification of biomarkers associated with breast and colorectal cancer risks in prospective samples before disease onset.

- Revealing robust markers for interventions aimed at reducing cancer risk and potential targets for future preventative strategies.

Key take-home messages

1 This multidisciplinary study should improve our understanding on the role of epigenetic alterations in initiation and progression of cancer associated with unhealthy lifestyle habits. It should also result in the discovery of epigenetics-based biomarkers for risk stratification, early detection and prognosis.

2 Examining the influence of the interventions on epigenetics has relevance for prevention of cancer risk (i.e. obesity) and prevention of cancer recurrence.