



Epigenetic Biomarker and Therapy

May 10 2025

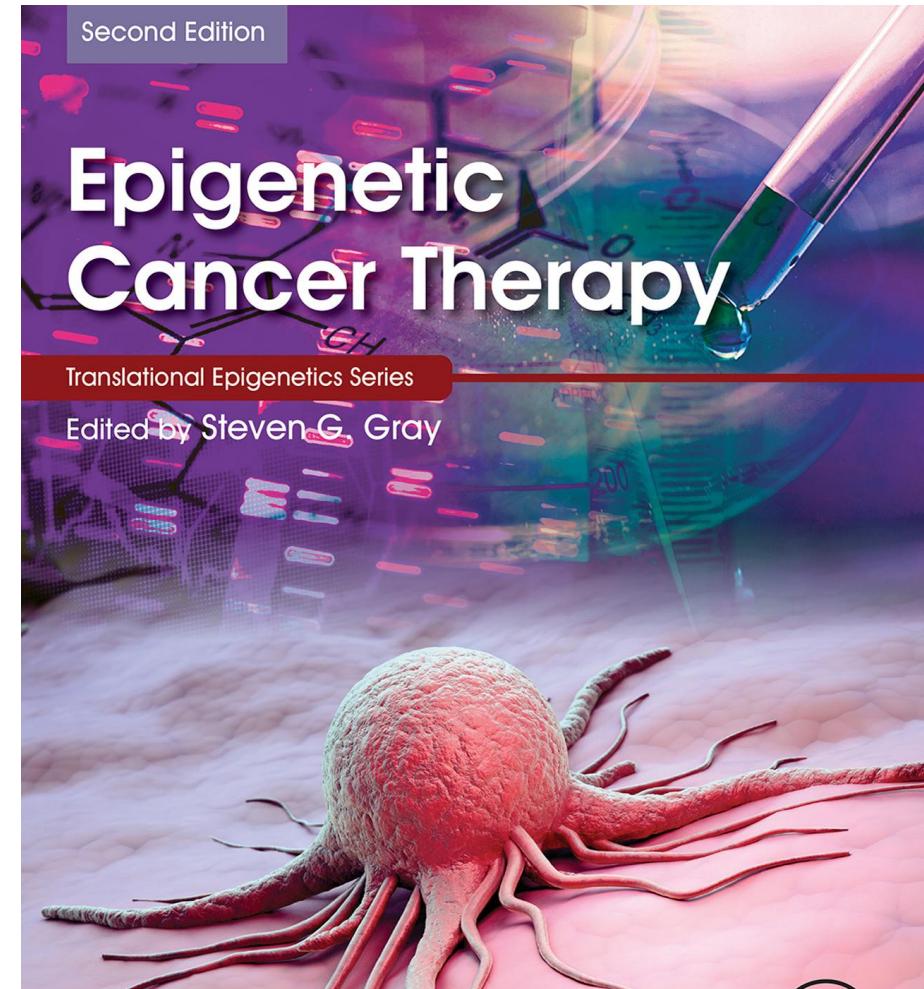
Phuc Loi Luu, PhD

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Zalo: 0901802182

Content

- Epigenetic Biomarker
 - Breast Cancer
 - Prostate Cancer
- Epigenetic Therapy
 - Epigenetic targeted therapies in hematological malignancies
 - Epigenetic therapy in lung cancer (Read Chapter 12 of The Book)





Epigenetics: DNA methylation and epigenetic control

Methylation-Based Breast Cancer Screening: primary tissue genomic DNA and circulating cell-free DNA (ccfDNA)

April 12 2025

Phuc Loi Luu, PhD

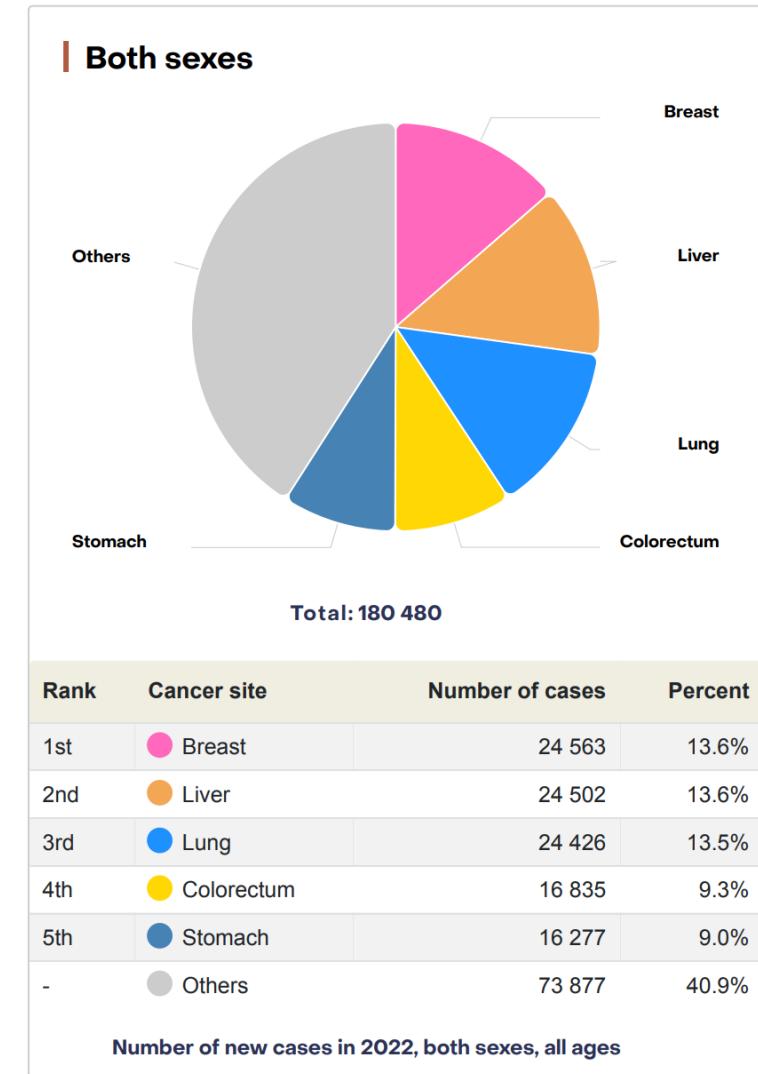
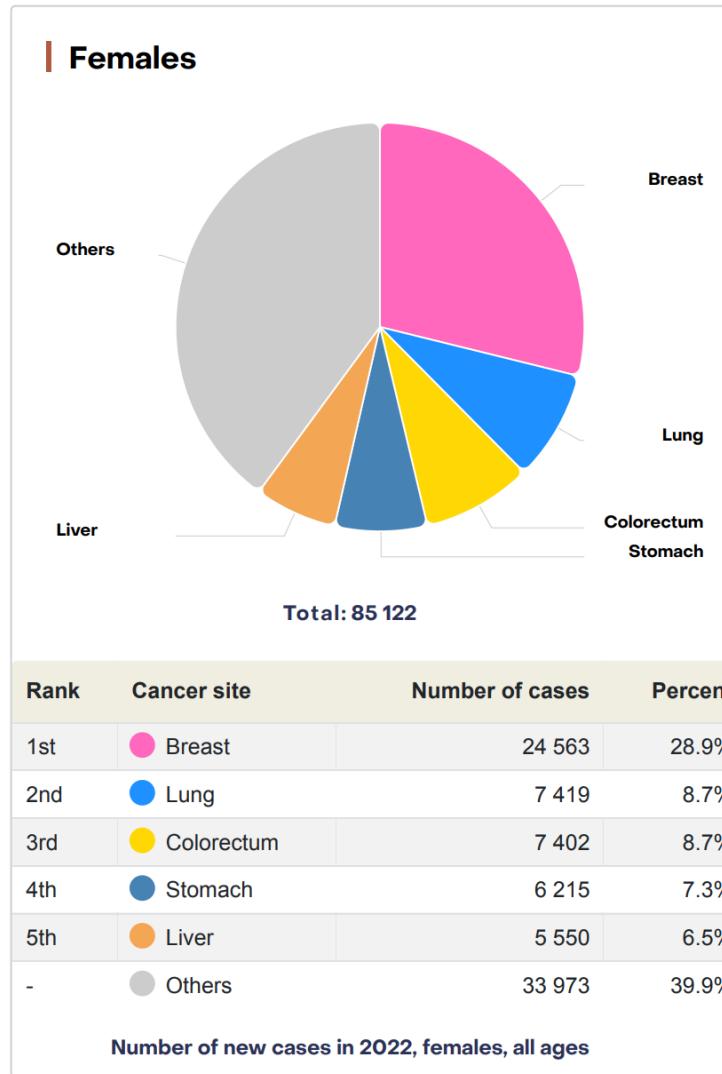
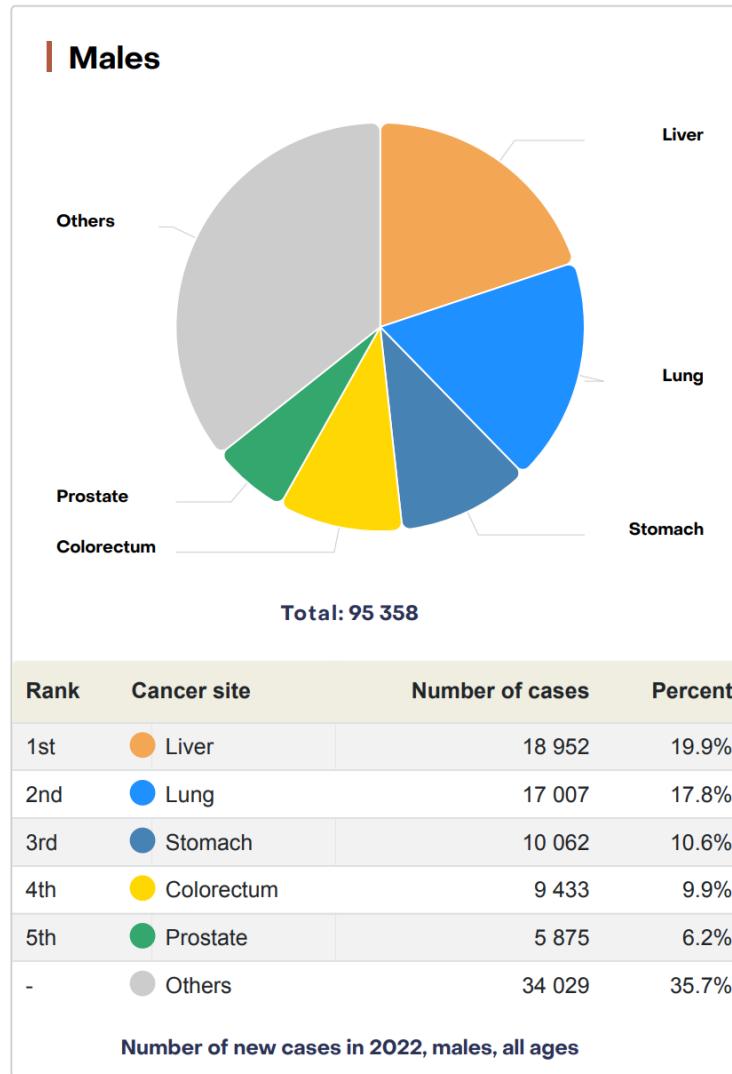
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Content

- Breast cancer in Vietnam
- Screening information for breast cancer
- Diagnosing breast cancer
- Epigenetics: DNA methylation and epigenetic control
- Breast Cancer DNA methylation signatures in circulating tumor DNA

Breast cancer is ranked the first top number of cases in Vietnam

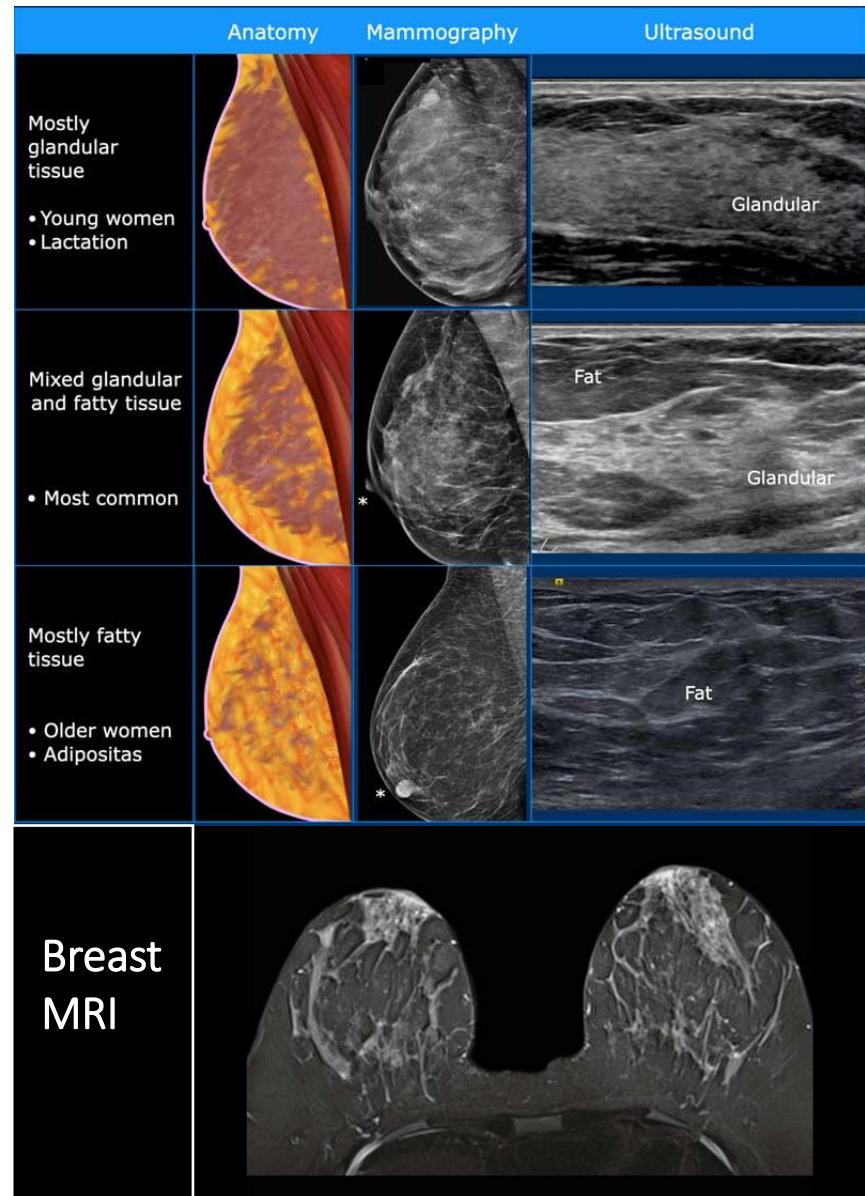
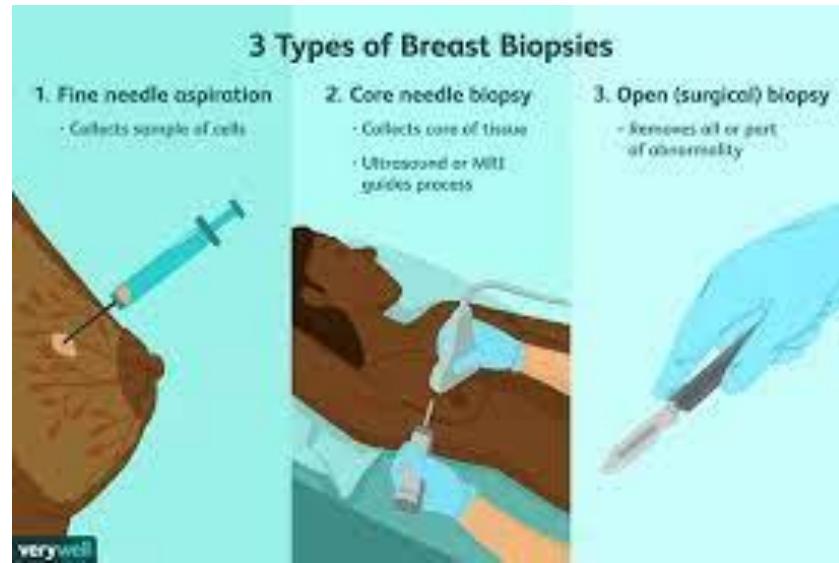


Screening information for breast cancer: goals

- Screening is used to look for cancer before you have any symptoms or signs.
- The overall goals of breast cancer screening are to:
 - Detect the cancer at an earlier stage of disease, which is when the cancer is **most curable**
 - Lower the number of people who die from the disease, or **eliminate deaths** from cancer altogether
 - Identify people with a **higher risk** of developing a specific type of cancer who may need screening more often or a different type of screening due to **genetic mutations** or diseases

Screening information for breast cancer

- Diagnostic mammogram: 10% to 15% of the time false-negative
- Breast ultrasound
- Breast magnetic resonance imaging (MRI)
- Biopsy (fine-needle aspiration, core biopsy, or open biopsy)



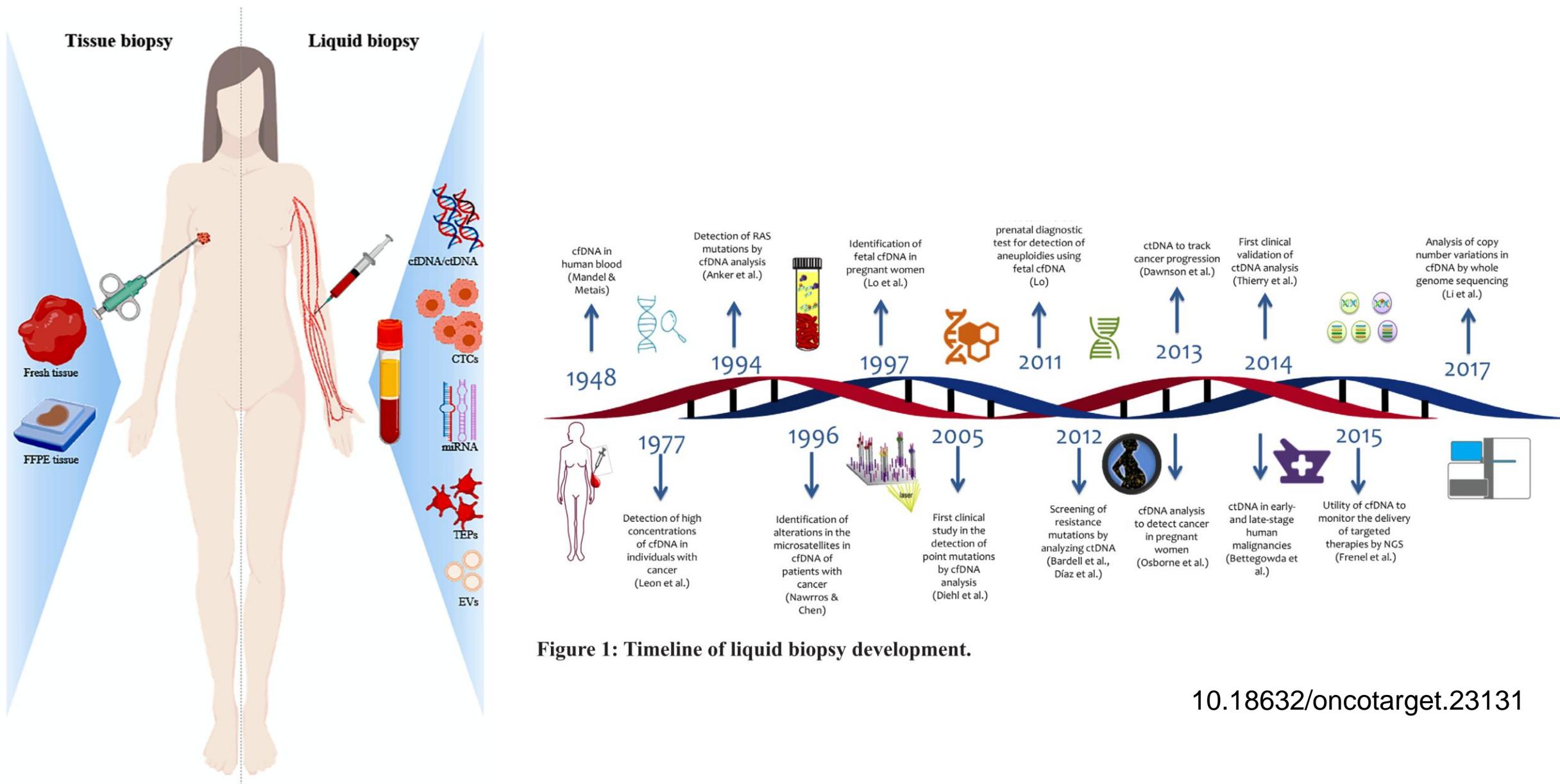
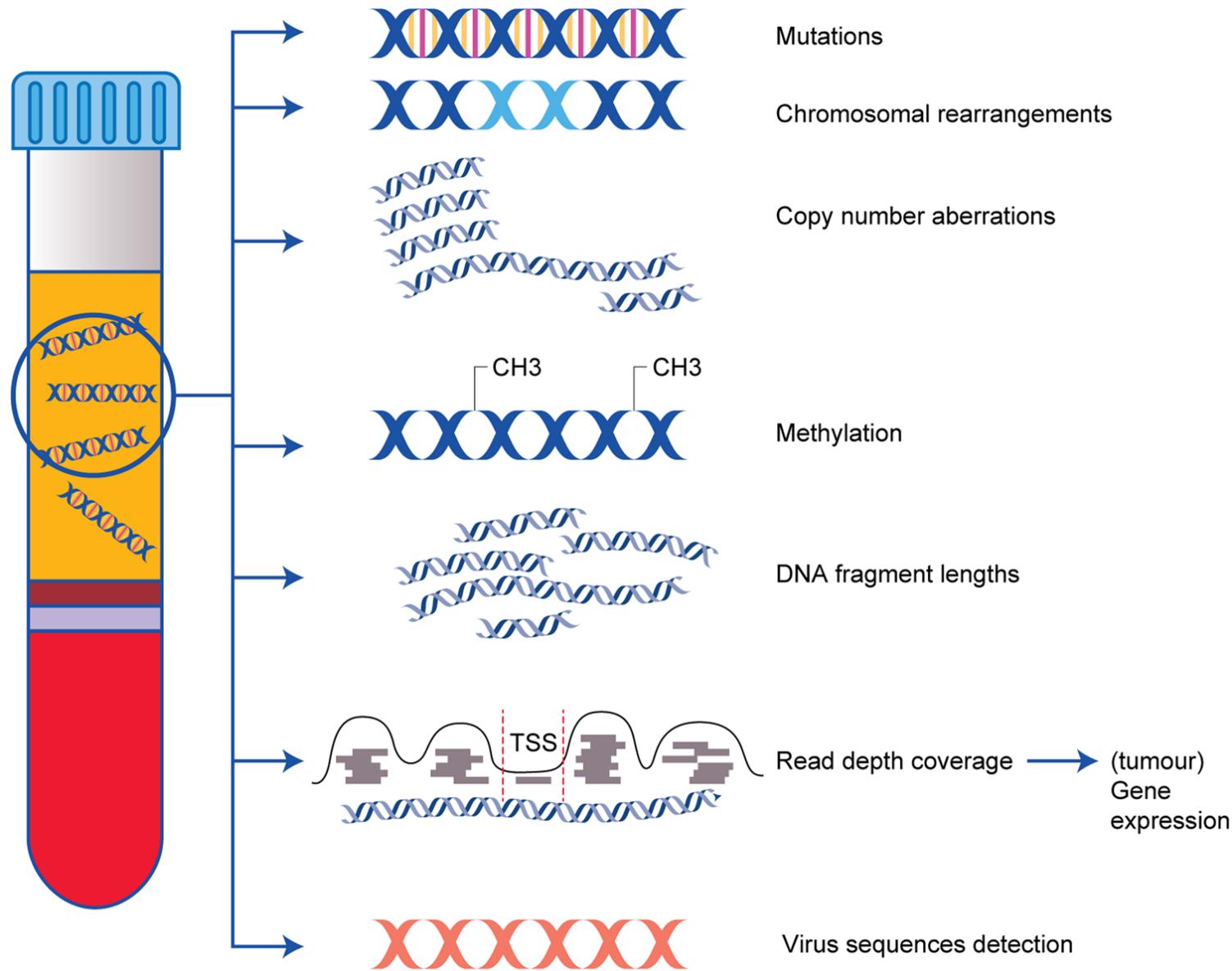


Figure 1: Timeline of liquid biopsy development.

10.18632/oncotarget.23131

Different features of ctDNA and potential clinical implications



The Human Genome

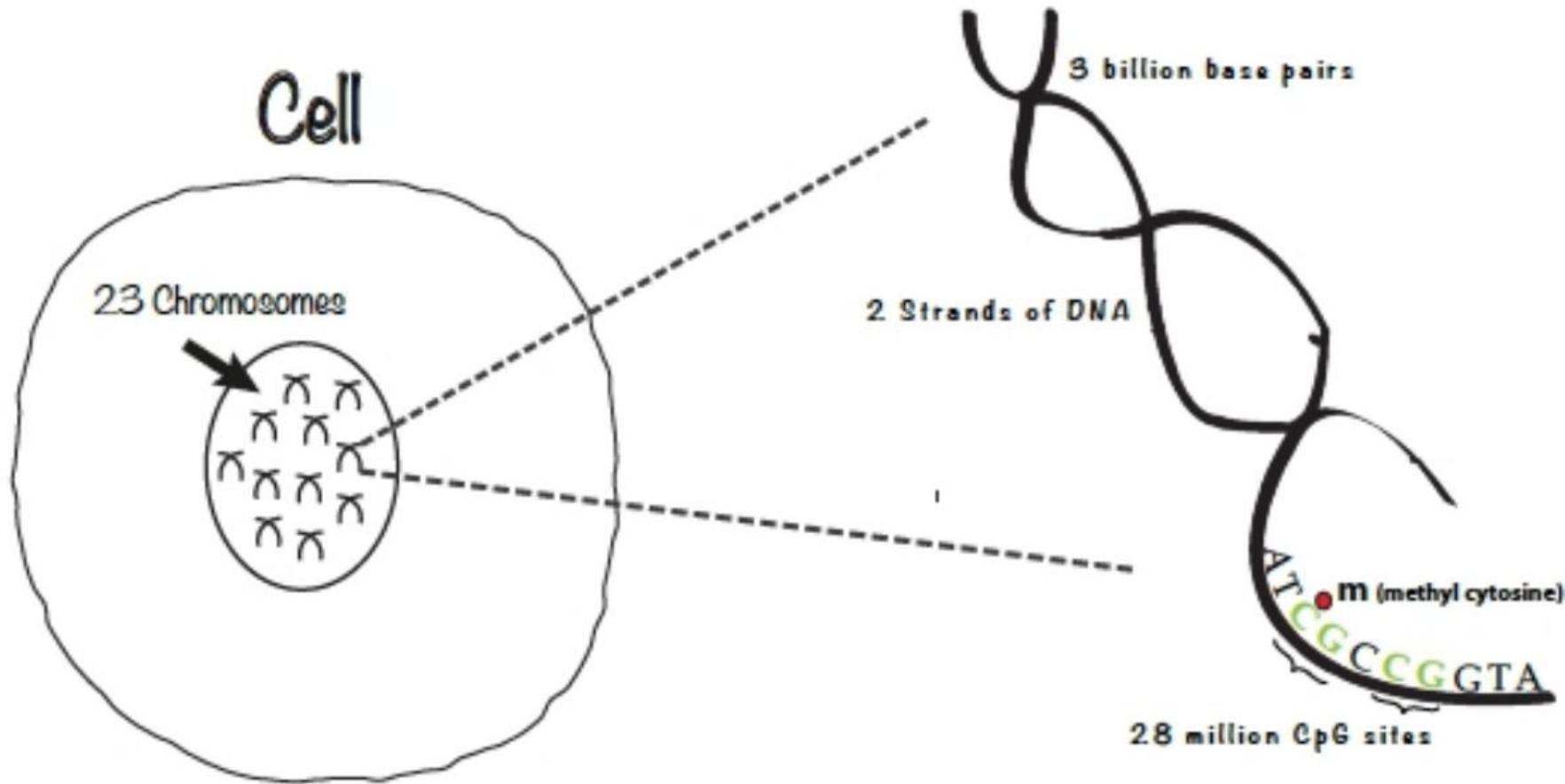
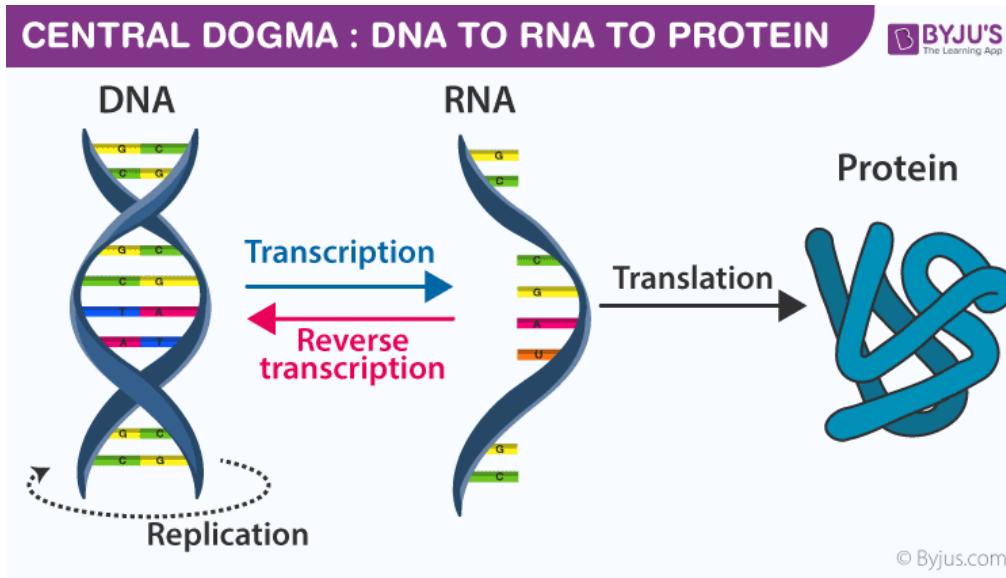


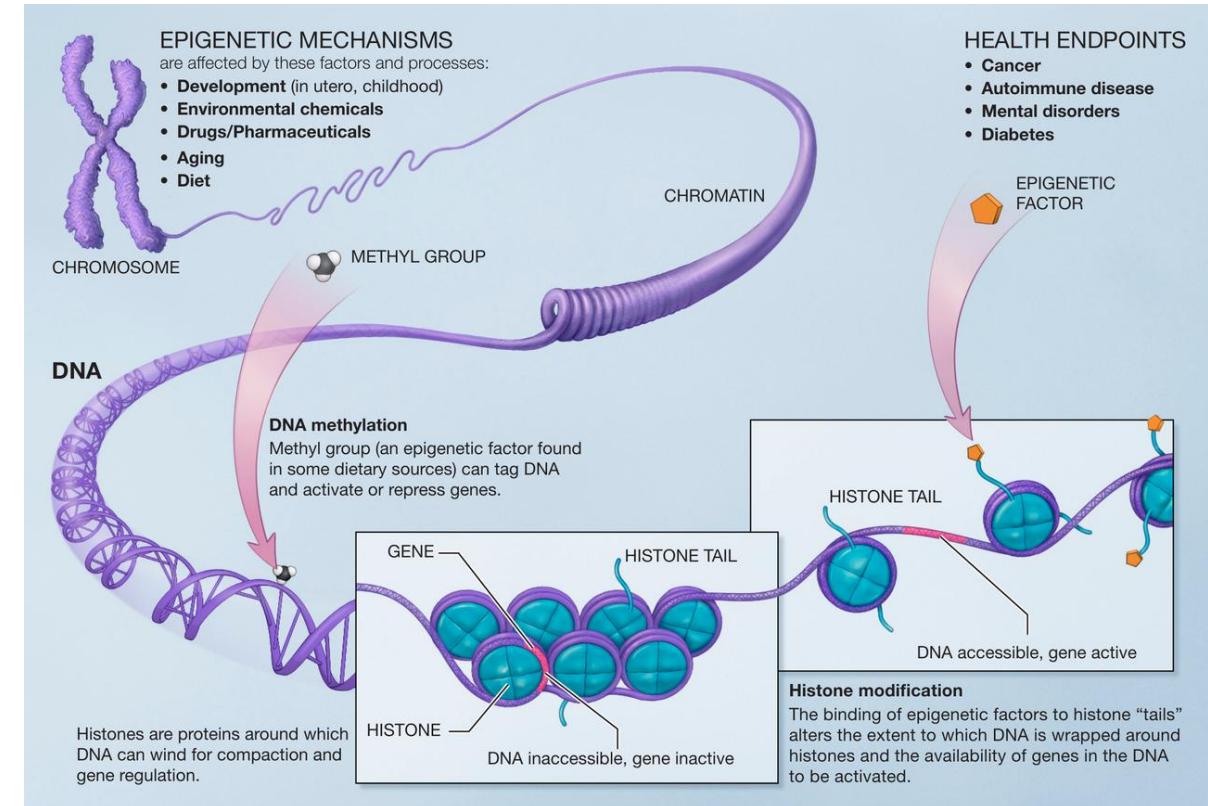
Figure 1. DNA is packaged inside cells in discrete units called chromosomes. Each cell contains 3 billion DNA base pairs, of which ~28 million are CpG sites that can be methylated.

What is Epigenetics?

Your genes play an important role in your health



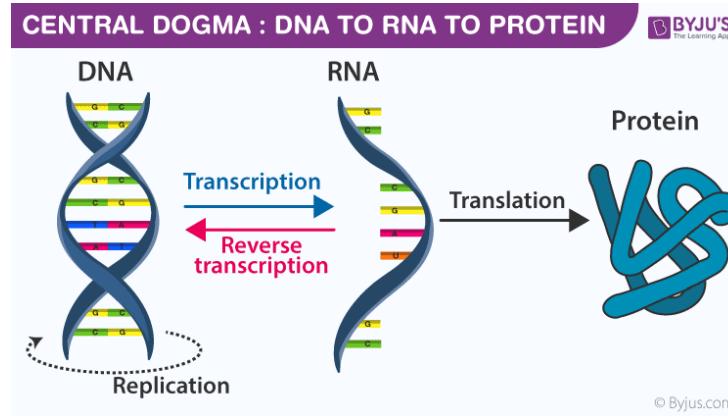
Your behaviors and environment can cause changes that affect the way your genes work



[Epigenetics - Wikipedia](#)

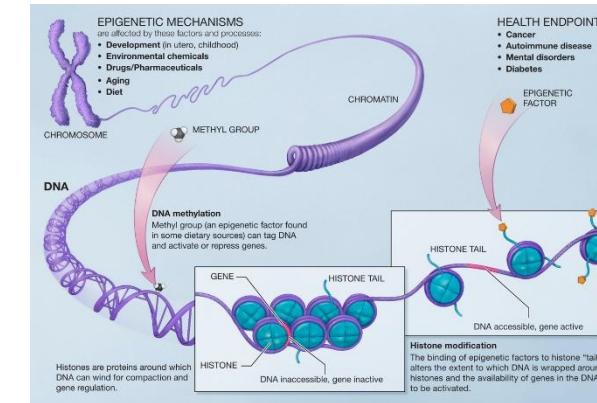
Genetics

Your genes play an important role in your health



Epigenetics

Your behaviors and environment can cause changes that affect the way your genes work



A woman without her man is nothing

A woman, without her man, is nothing
A woman: without her, man is nothing

Genetics

“Reading the book of life”

EPIGENETIC REGULATION OF NORMAL CELLULAR PROCESSES IS TYPICALLY DRIVEN IN A CELL TYPE DEPENDENT MANNER. THIS REQUIRES AN EXQUISITE LEVEL OF INTERPLAY BETWEEN EPIGENETIC LAYERS INCLUDING DNA METHYLATION, NUCLEOSOME POSITIONS AND HISTONE MODIFICATIONS AMONGST OTHERS. TOGETHER, THESE MECHANISMS ESTABLISH THE CORRECT GENE EXPRESSION PATTERNS AND HIGHER ORDER CHROMATIN STRUCTURES. THUS, THE IDENTITY OF EACH CELL IS DETERMINED BY THE PATTERN OF DNA METHYLATION.

Epigenetics

“Translating the book of life”

EPIGENETIC REGULATION OF NORMAL CELLULAR PROCESSES IS TYPICALLY DRIVEN IN A CELL TYPE DEPENDENT MANNER. THIS REQUIRES AN EXQUISITE LEVEL OF INTERPLAY BETWEEN EPIGENETIC LAYERS, INCLUDING DNA METHYLATION, NUCLEOSOME POSITIONS AND HISTONE MODIFICATIONS, AMONGST OTHERS.

TOGETHER, EPIGENETIC MECHANISMS ESTABLISH THE CORRECT GENE EXPRESSION PATTERNS AND HIGHER ORDER CHROMATIN STRUCTURES; THUS, THE IDENTITY OF EACH CELL. OF THESE, DNA METHYLATION IS THE BEST-STUDIED EPIGENETIC MODIFICATION. PRECISE DNA METHYLATION PATTERNS ARE ESTABLISHED DURING EMBRYONIC DEVELOPMENT AND ARE MITOTICALLY HERITABLE THROUGH MULTIPLE CELLULAR DIVISIONS.



Genetics



The structure of DNA was discovered in 1953

```
GTAAGGCAGTCGATATAGGTT  
CACCGGTCTTAGGCACGTTGAG  
CTGACCAGTGCTAACGTCCAA  
TGGCATTGCAGCTGGGGTACAC  
AGTCTTGTGTCACAGTCAGGTC  
TATCTGTACTAGTCTTACGTAGT  
CGGTACCCCATGACATCGACTT  
GTGTCGGATCGATCATC
```

DNA code was mapped in 2001 – 3 billion letters (GATC)

Genetics



How does each cell know what it is supposed to be?

```
GTAAGGCAGTCGATATAGGTT  
CACCGGTCTTAGGCACGTTGAG  
CTGACCAGTGCTAACGTCAA  
TGGCATTGCAGCTGGGGTACAC  
AGTCTTGTGTCACAGTCAGGTC  
TATCTGTACTAGTCTTACGTAGT  
CGGTACCCCATGACATCGACTT  
GTGTCGGATCGATCATC
```

DNA code was mapped in 2001
– 3 billion letters (GATC)

Genetics



How does each cell know what it is supposed to be?

COL1A1 gene expressed in hair cells, but not brain cells

Epigenetics



```
GTAAGGCAGTCGATATAGGTT  
TTGAG  
CTGACCAGTGCTAACGTCCAA  
TGGCATTGCAGCTGGGGTACAC  
AGTCTTGTGT  
  
CGGTACCCCATGACATCGACTT  
GTGTCGGATCGATCATC
```

Only parts of the genome are active at any one time

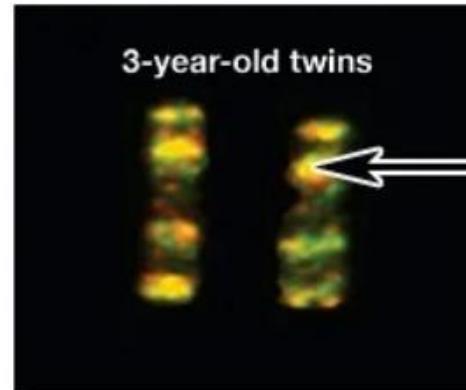
Example 1: Identical twins

Identical twins come from the same fertilized egg
→ share identical genetic profiles (genome)

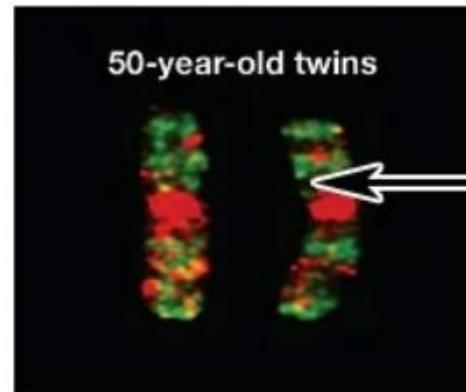


→ Your behaviors and environment can cause changes that affect the way your genes work

Chromosome 3 Pairs
3-year old twins vs. 50-year-old twins



Yellow shows where the twins have epigenetic tags in the same place.



Red and green show where the twins have epigenetic tags in different places.

Chromosome 3 pairs in each set of twins are digitally superimposed. One twin's epigenetic tags are dyed red and the other twin's tags are dyed green. When red and green overlap, that region shows up as yellow. The 50-year old twins have more epigenetic tags in different places than do 3-year-old twins.

Example 2: Identical twins 2

Identical twins come from the same fertilized egg → share identical genetic profiles (genome)

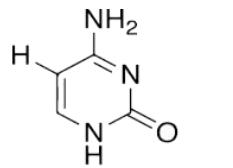


Leora Eisen

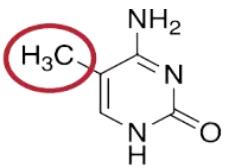
Linda Lewis
(leukemia)

→ Your behaviors and environment can cause changes that affect the way your genes work

What are DNA Methylation and genome-wide DNA methylation (Epigenome)?

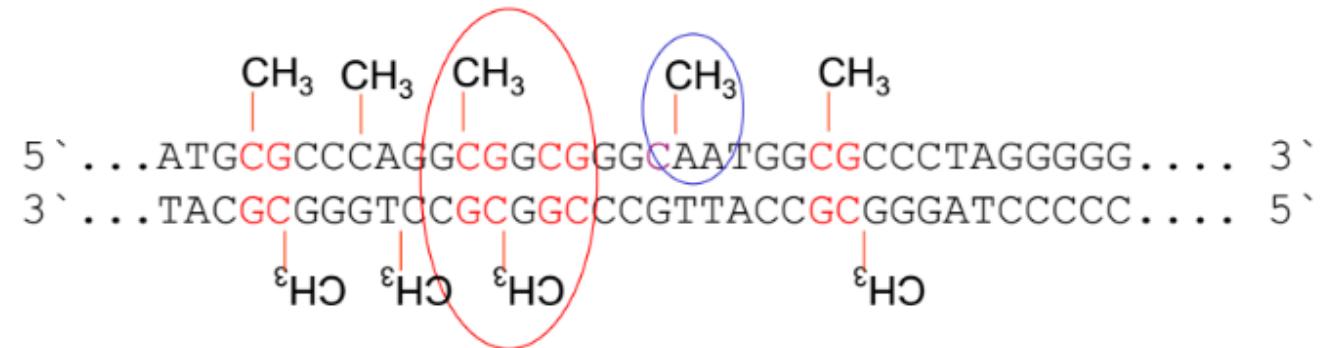
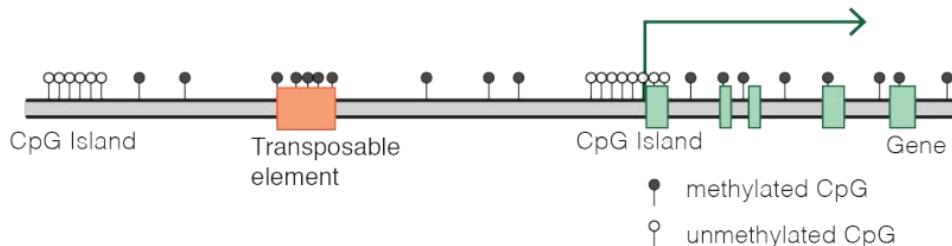


Cytosine

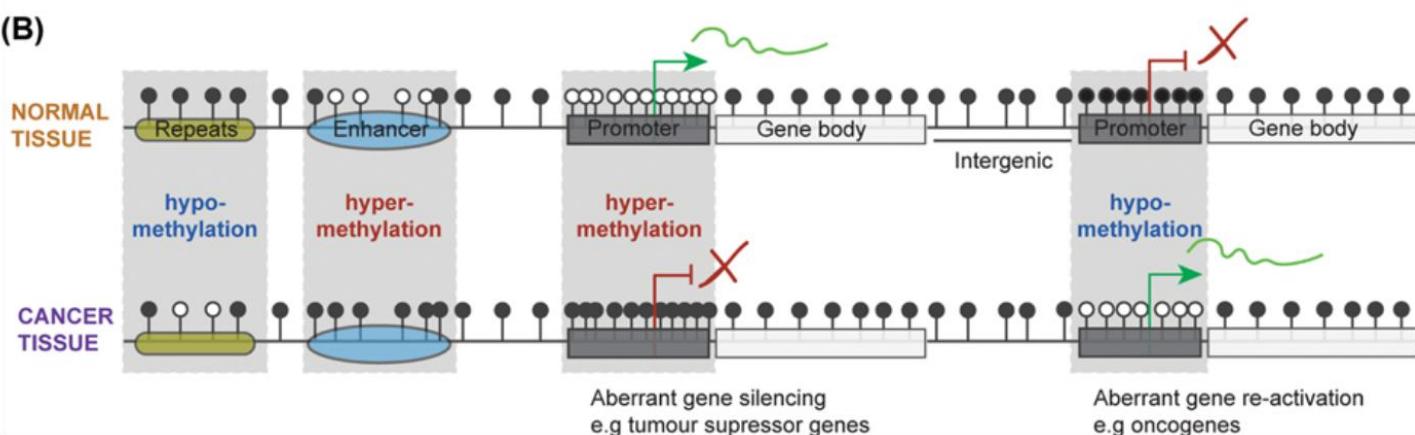


methylated Cytosine

Typical mammalian DNA methylation landscape



(B)



DNA methylation regulates gene expression

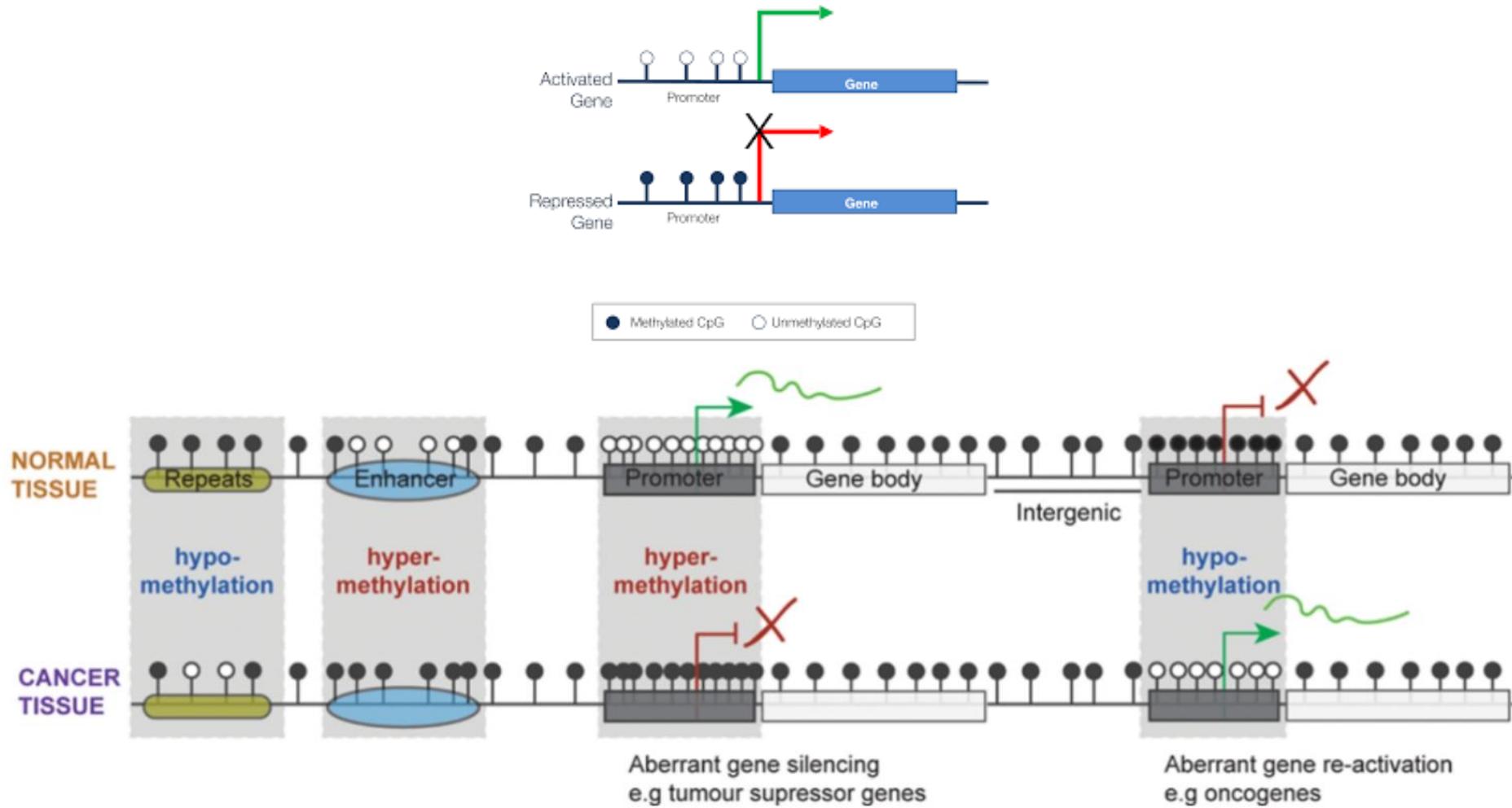
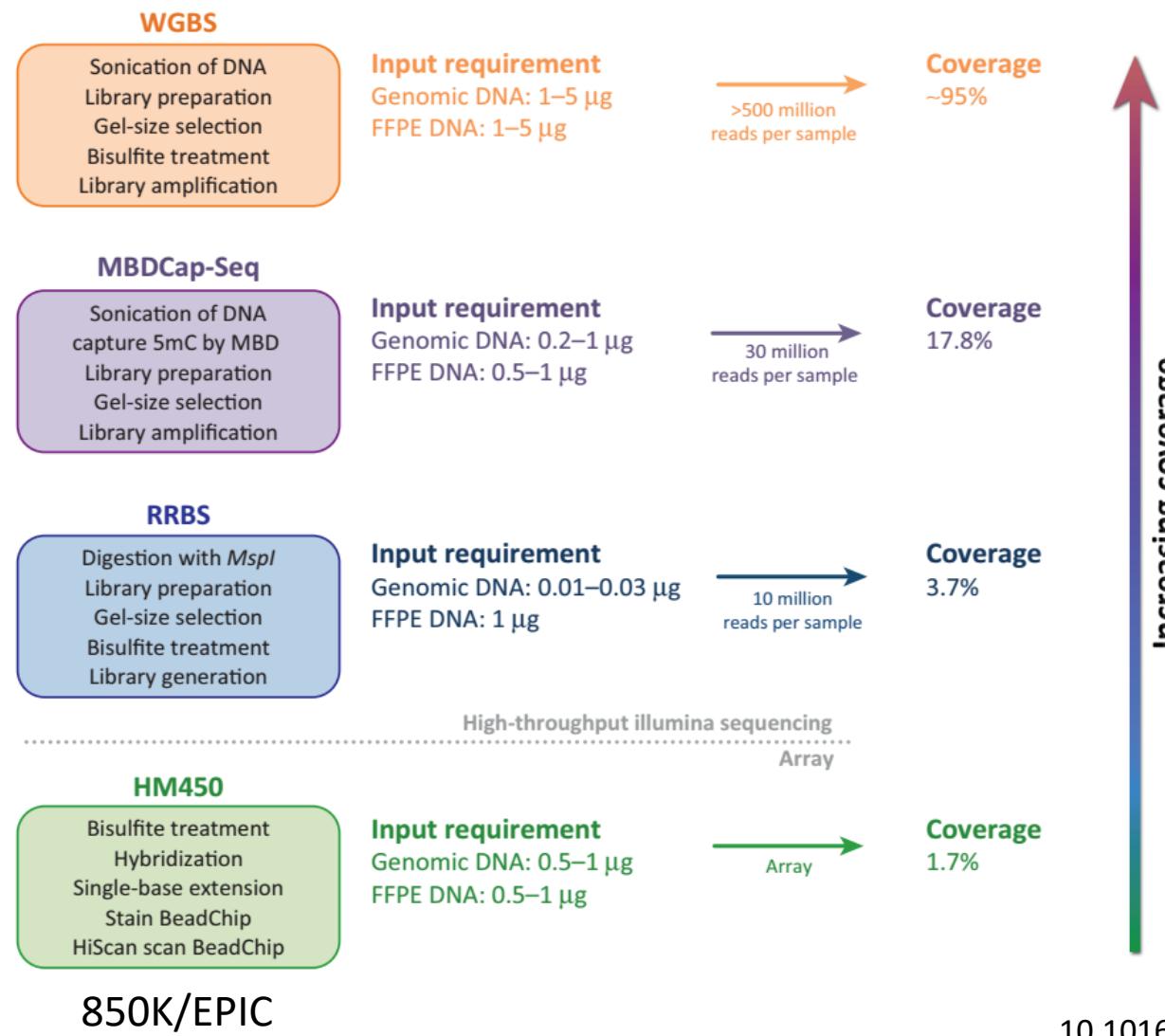


Figure 2. The aberrant gene silencing and re-activation in cancer tissue due to alteration of promoter DNA methylation. The green string is mRNA and the red cross is repression. The figure adapted from 10.1042/EBC20190037.

Methods to profile DNA methylation



Bisulphite Sequencing

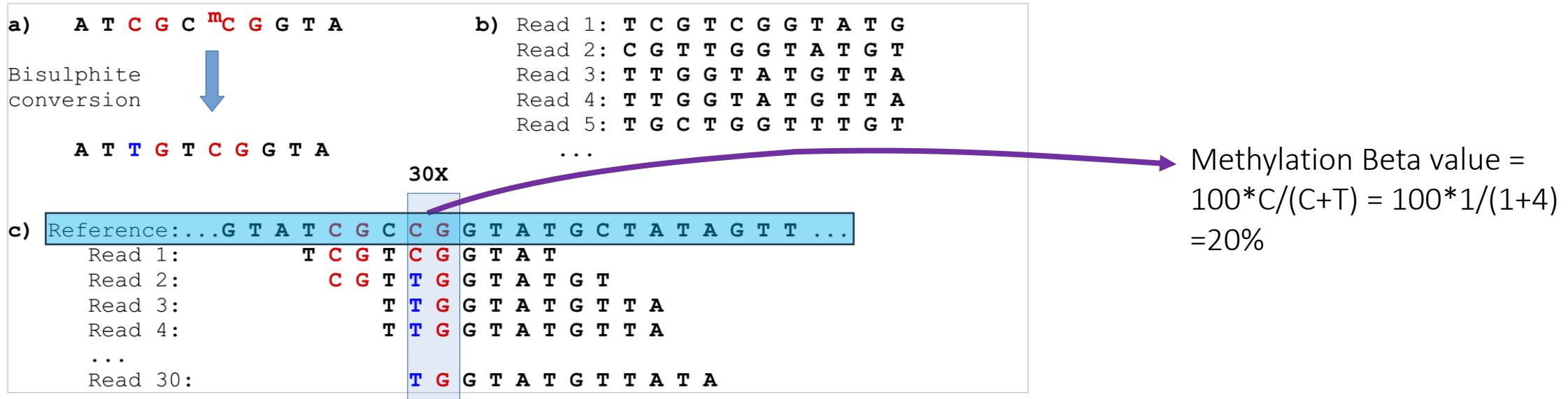


Figure 1. a) Sodium bisulphite converts unmethylated cytosines to thymines. b) The converted DNA is sequenced. c) Alignment and aggregation of these short sequence can be used to quantify the ratio of methylated (C) to unmethylated (converted T) cytosines from a population of cells at a single locus.

Total_cov_matrix_CpG.txt

	A	B	C	D
1	chr	pos	nmDNA1	nmDNA2
2	chr2	133031228	56	55
3	chr2	133031240	74	81
4	chr2	133031244	82	79
5	chr2	133031249	64	70
6	chr2	133031265	65	69
7	chr2	133031268	67	56

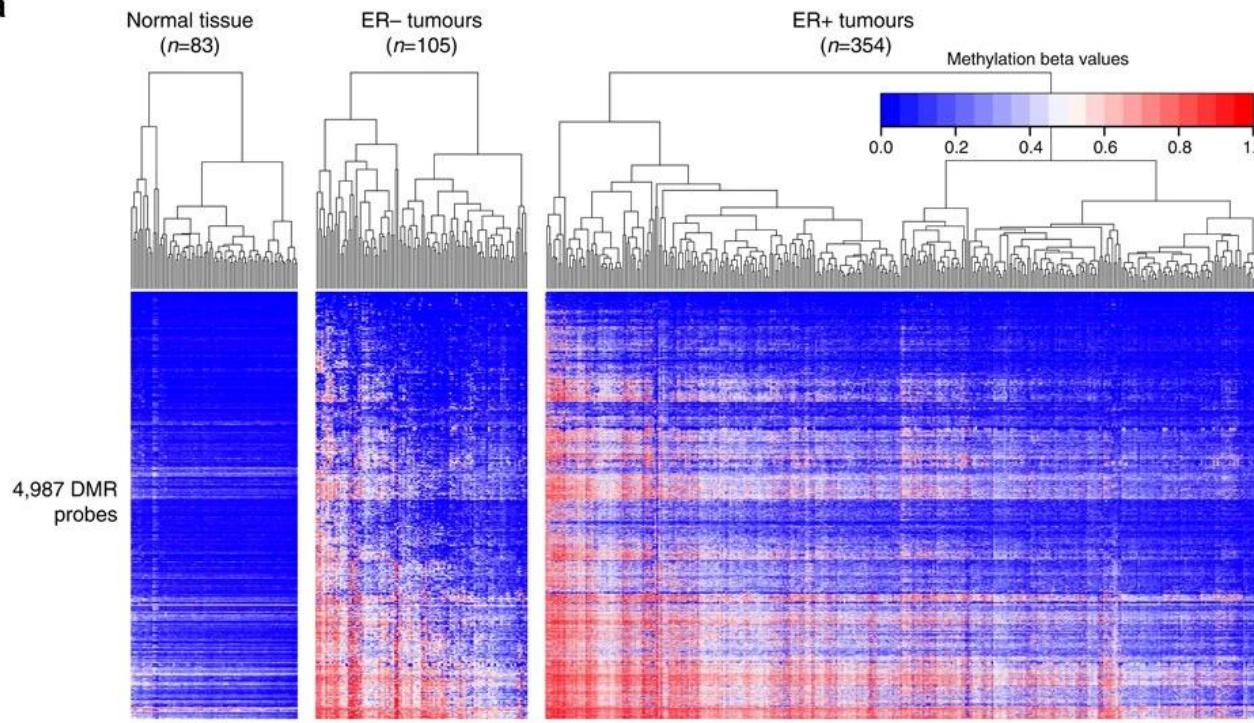
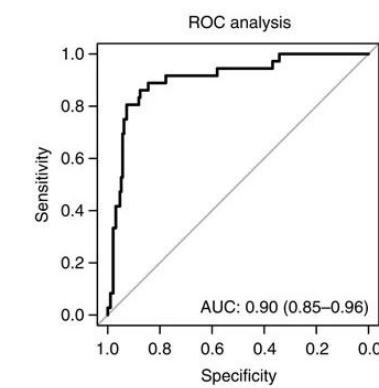
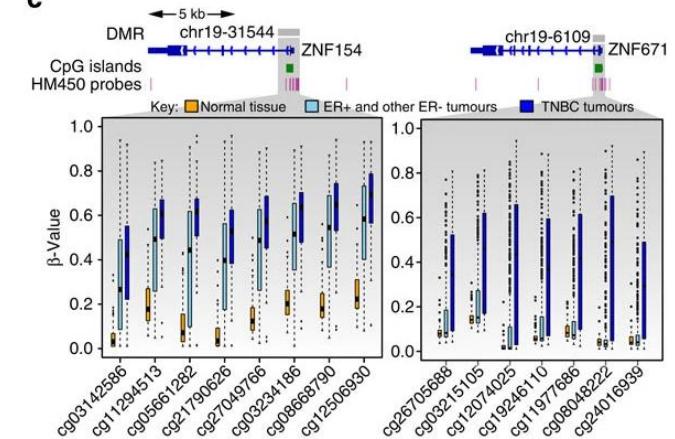
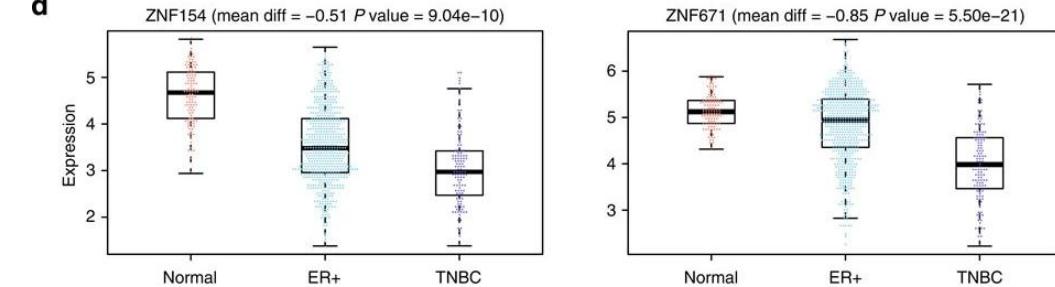
Meth_cov_matrix_CpG.txt

	A	B	C	D
1	chr	pos	nmDNA1	nmDNA2
2	chr2	133031228	41	28
3	chr2	133031240	29	19
4	chr2	133031244	47	47
5	chr2	133031249	35	24
6	chr2	133031265	19	21
7	chr2	133031268	24	16

Perc_cov_matrix_CpG.txt

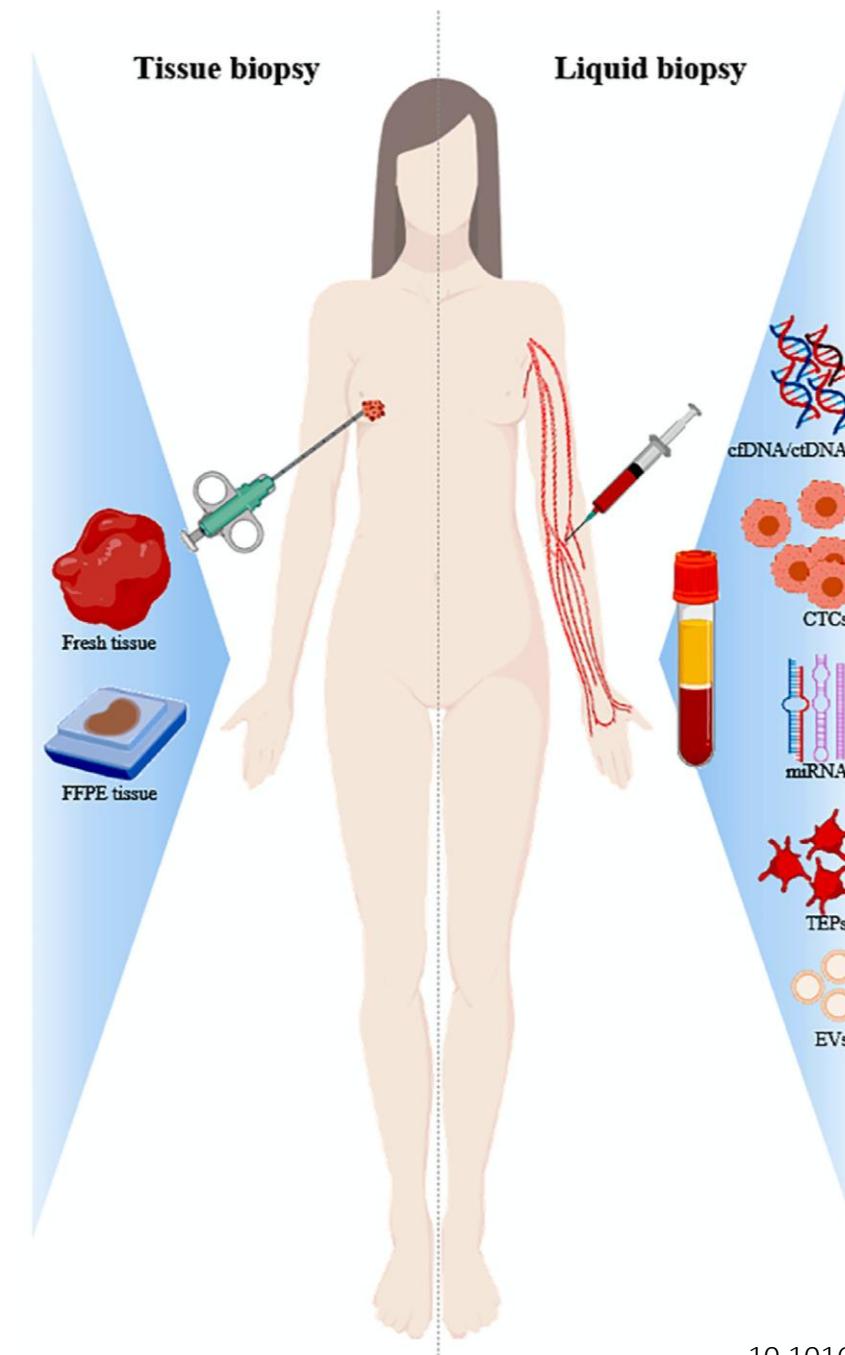
	A	B	C	D
1	chr	pos	nmDNA1	nmDNA2
2	chr2	133031228	73	51
3	chr2	133031240	39	23
4	chr2	133031244	57	59
5	chr2	133031249	55	34
6	chr2	133031265	29	30
7	chr2	133031268	36	29

DNA methylation are promising biomarkers for screening and early detection of breast cancer

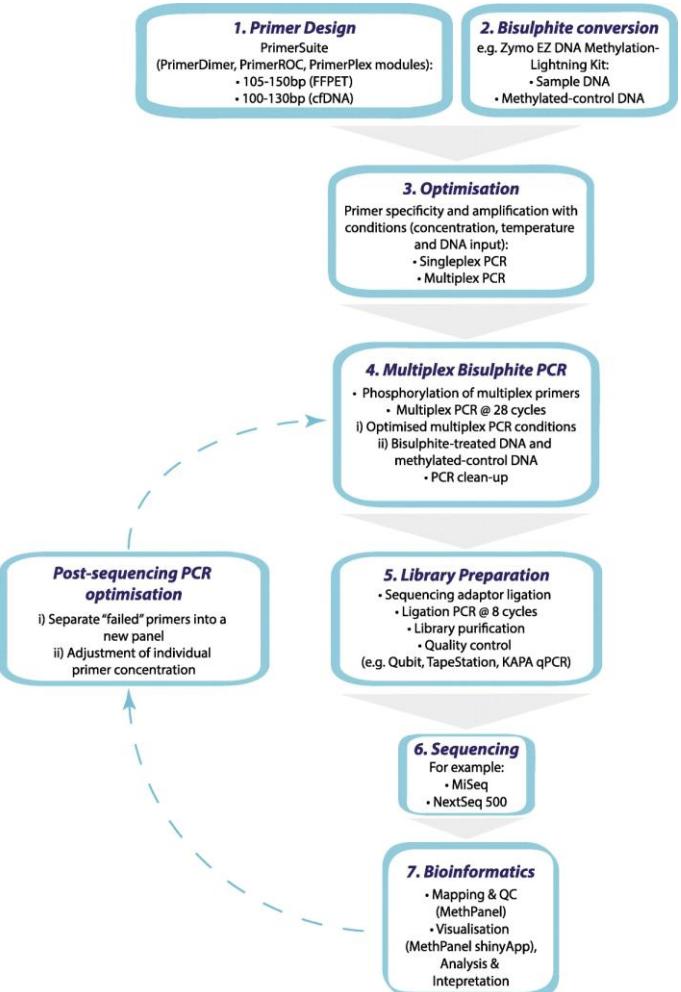
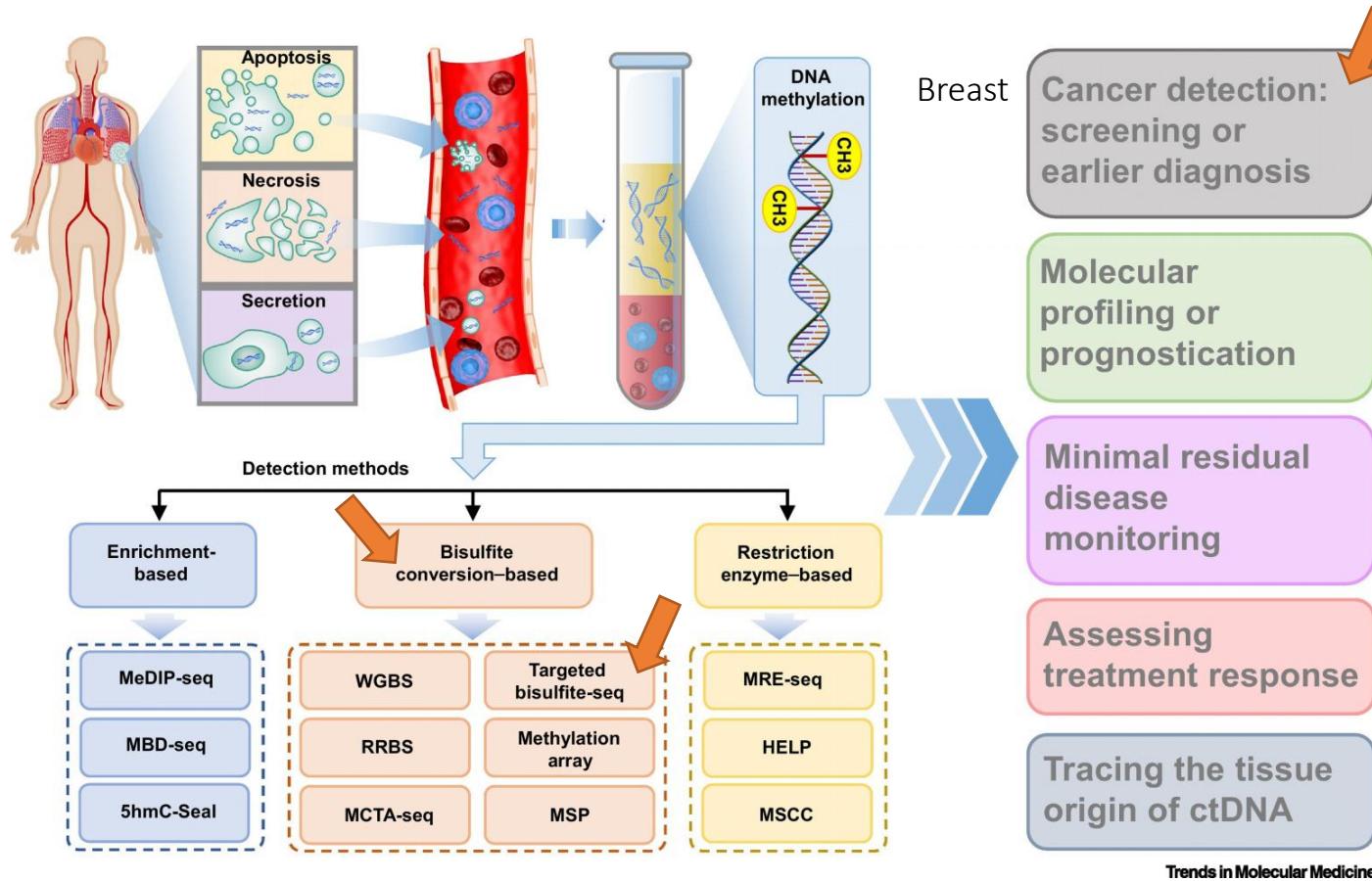
a**b****c****d**

Aims of the study

- Build up DNA methylation panel for early detection of breast cancer
- Validate the panel
 - Tissue biopsy of patients and healthy controls (**Tissue/FFPE**)
 - Liquid biopsy of patients and healthy controls (**cfDNA**)



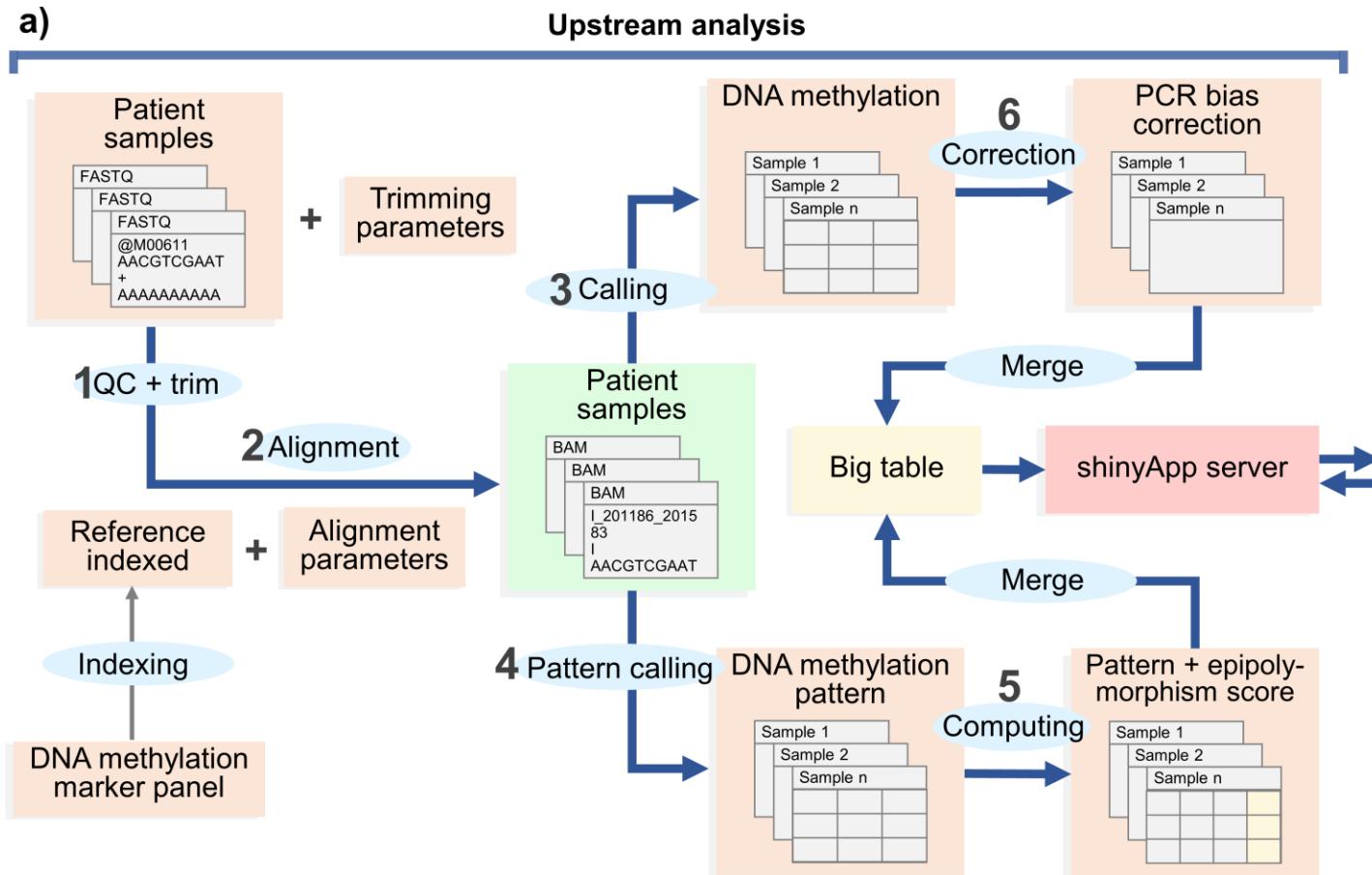
Targeted multiplex bisulphite PCR sequencing



Lam D*, Luu PL*, Song JZ, Qu W, Risbridger GP, Lawrence MG... SJ Clark, R Pidsley, Stirzaker C. Comprehensive evaluation of targeted multiplex bisulphite PCR sequencing for validation of DNA methylation biomarker panels. Clin Epigenetics. 2020;12(1):90. * Equal contribution authors

Luo H., Wei W., Ye Z., Zheng J., Xu R. Liquid biopsy of methylation biomarkers in cell-free DNA. Trends Mol. Med. 2021

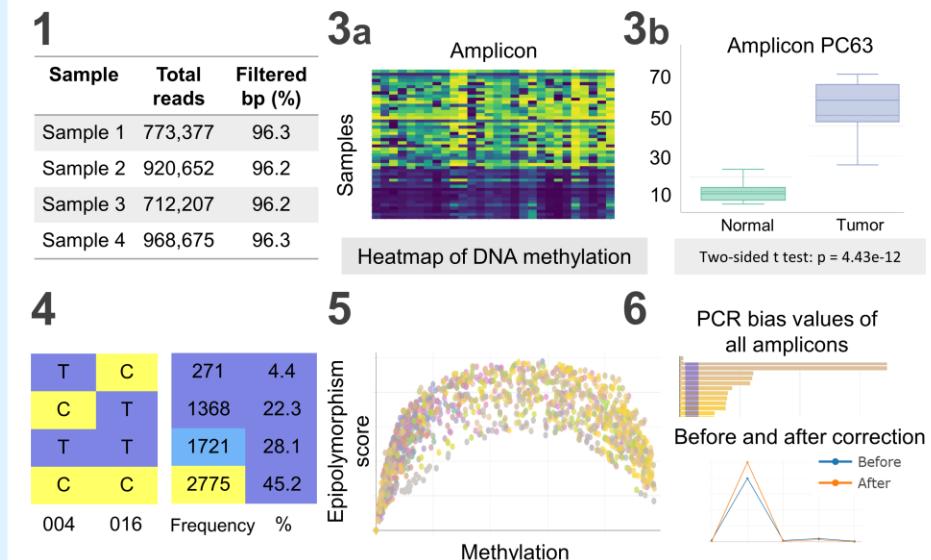
MethPanel: analysing and visualizing amplicon bisulphite sequencing data

a)**b)**

shinyApp client

MethPanel

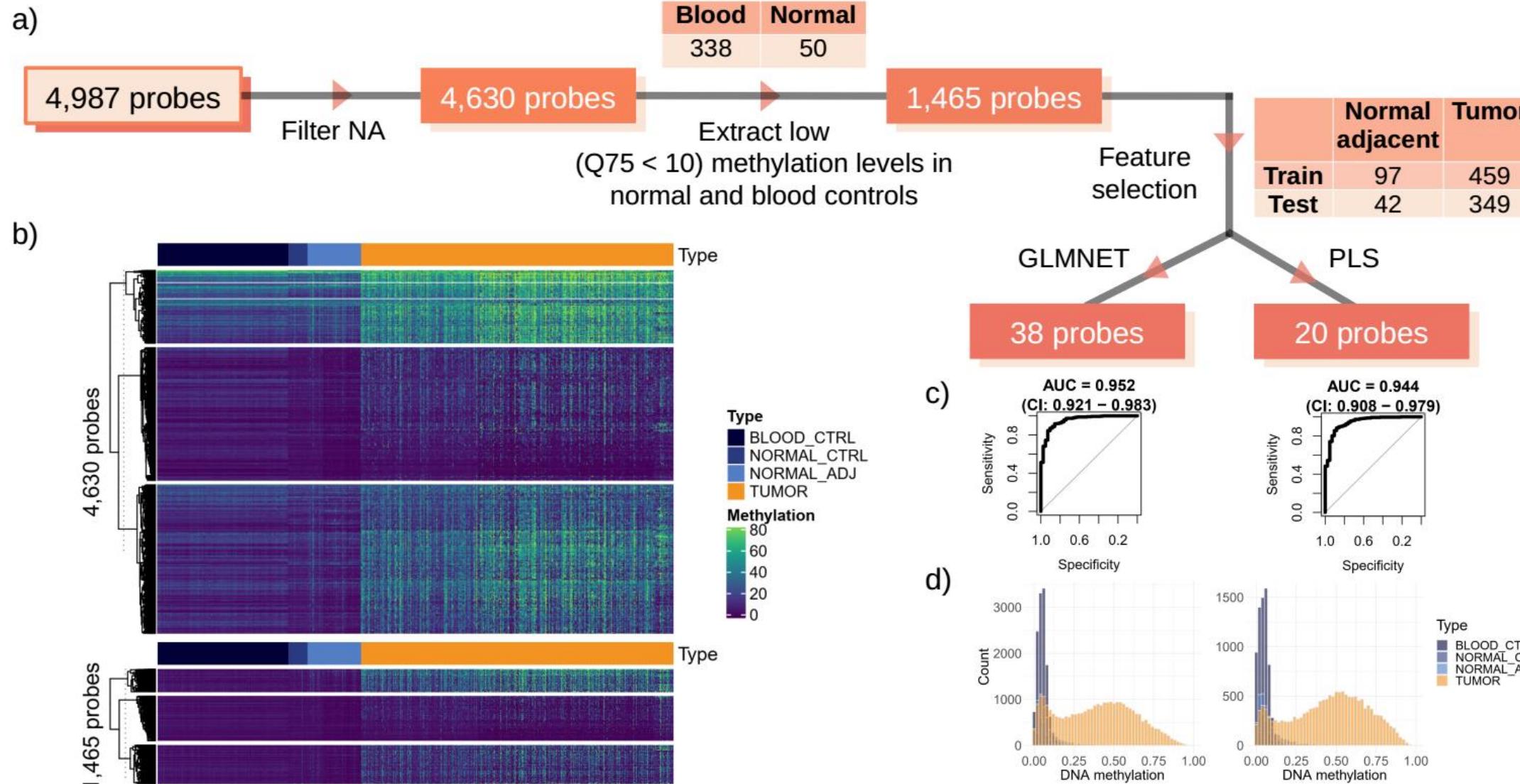
Login 1. Trimmed FASTQ QC 2. Alignment 3. DNA methylation 4. Pattern 5. Epipolymerism 6. PCR bias correction 7. DNA methylation after correction



Machine learning techniques

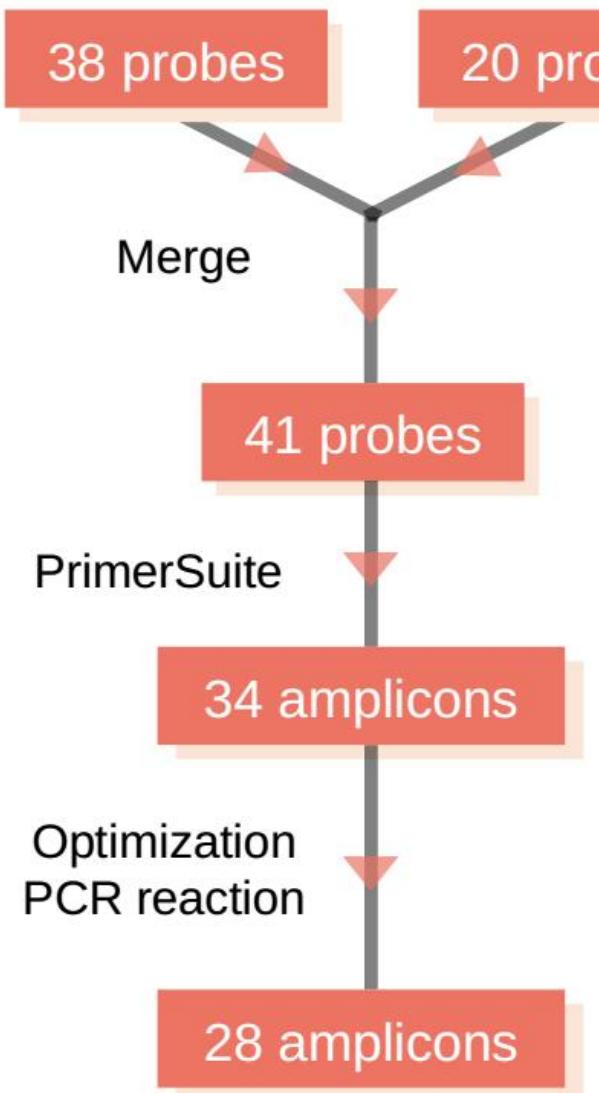
- Gmlnet, PLS and MVUR for feature selection
- Random Forest for classification
- Smote for up sampling in unbalance dataset of cfDNA

Build up DNA methylation breast cancer panel

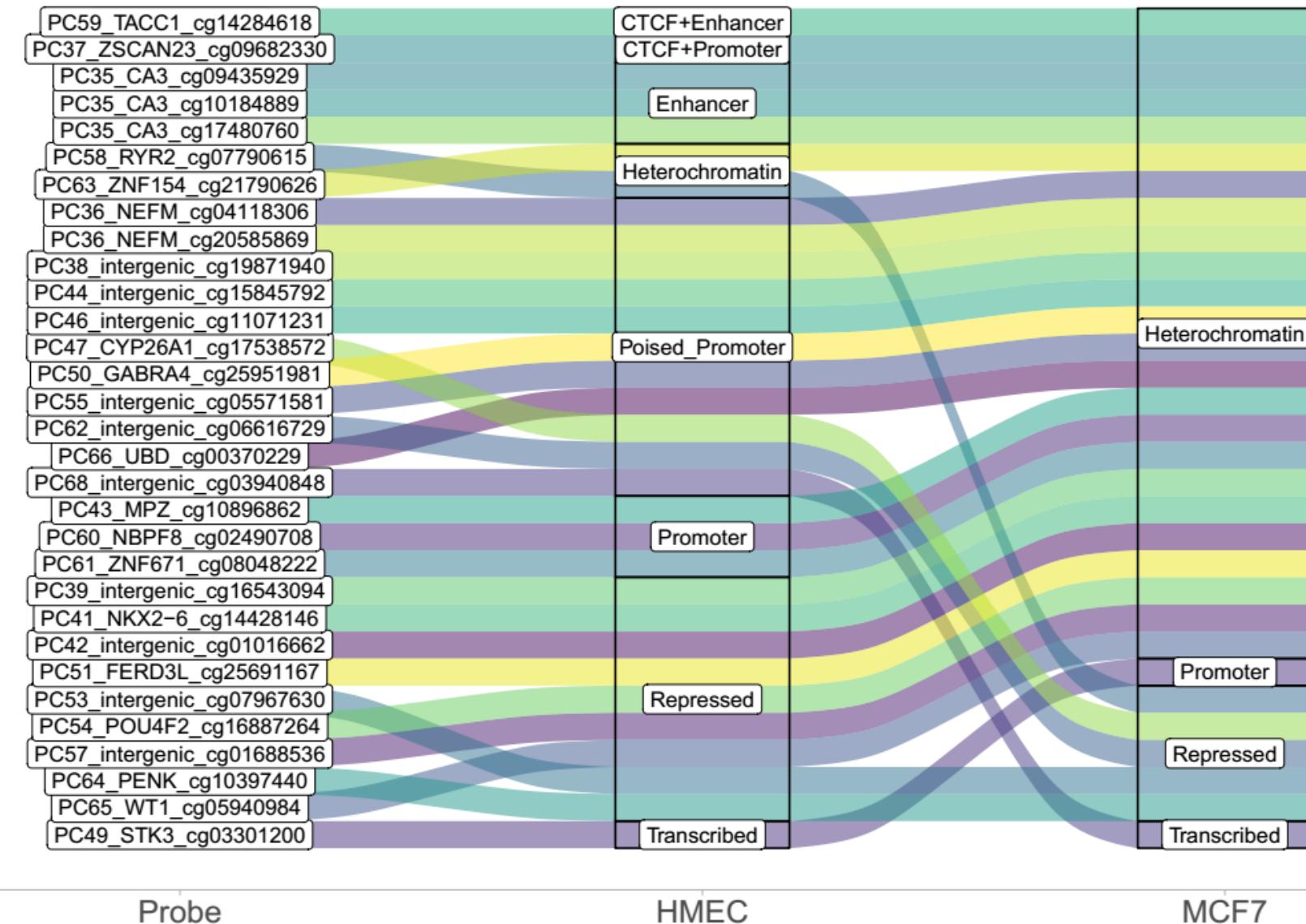


Characterization of DNA methylation breast cancer panel

a)

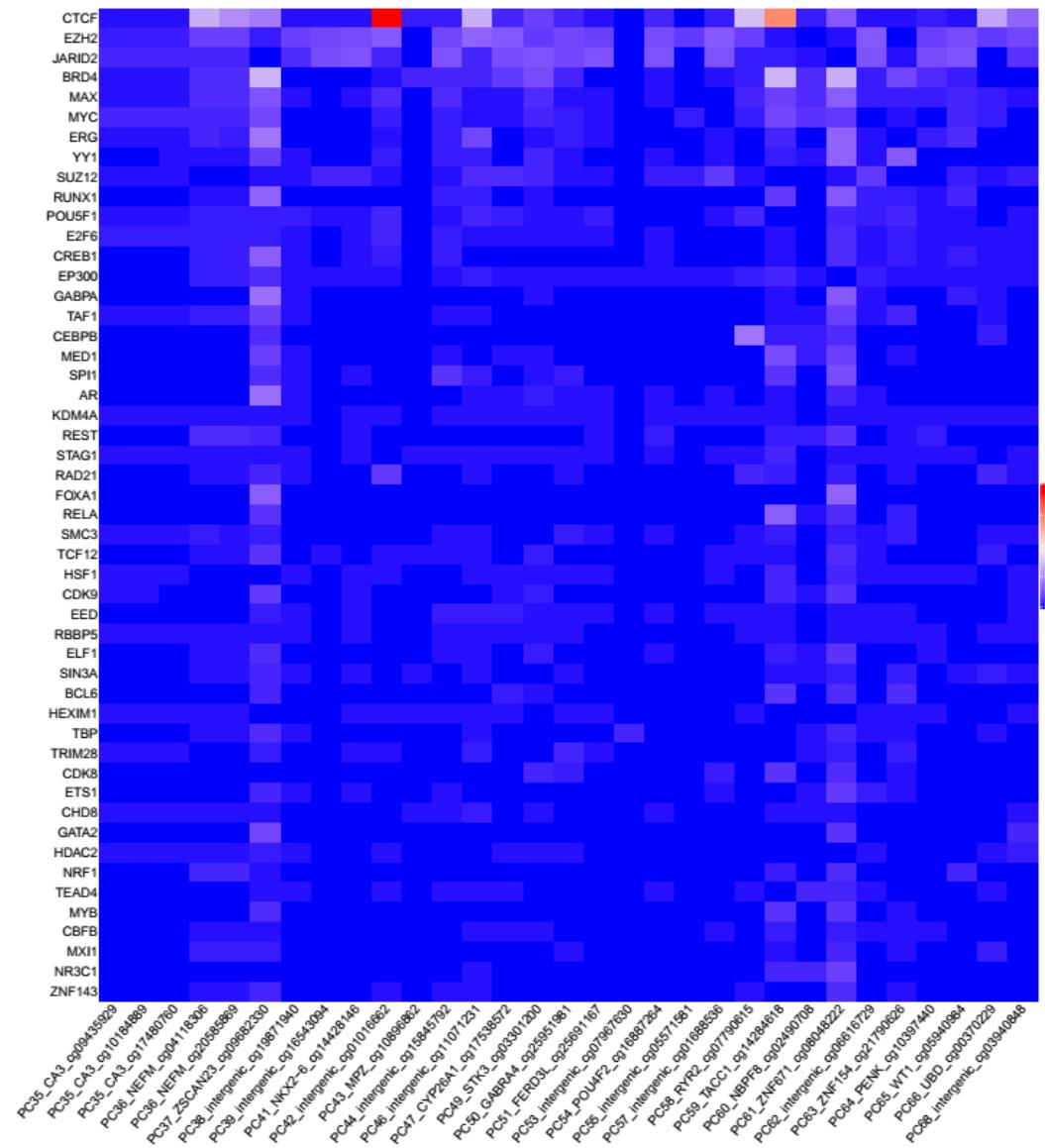


b) ChromHMM



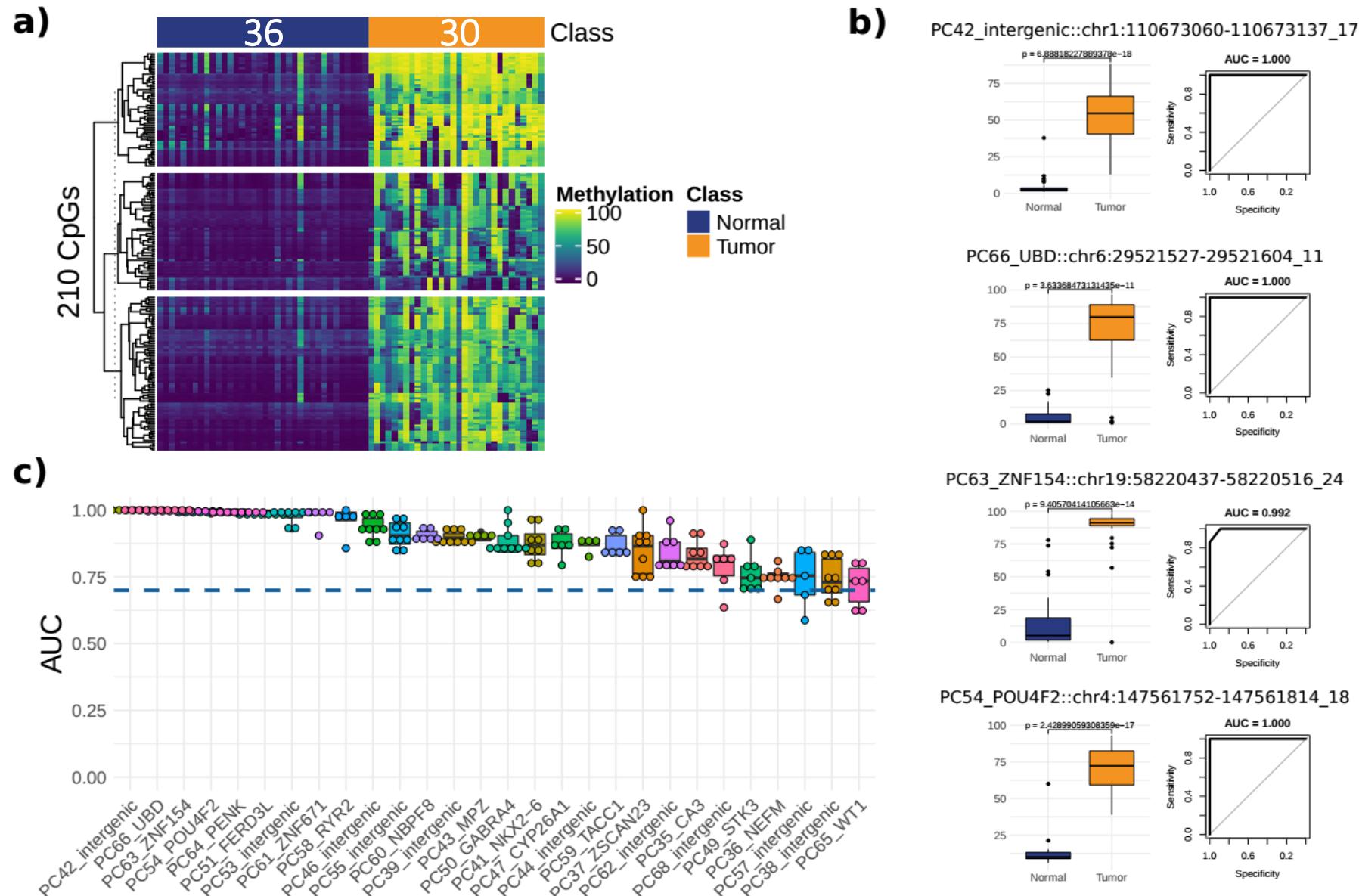
Characterization of DNA methylation breast cancer panel

c) TFBS



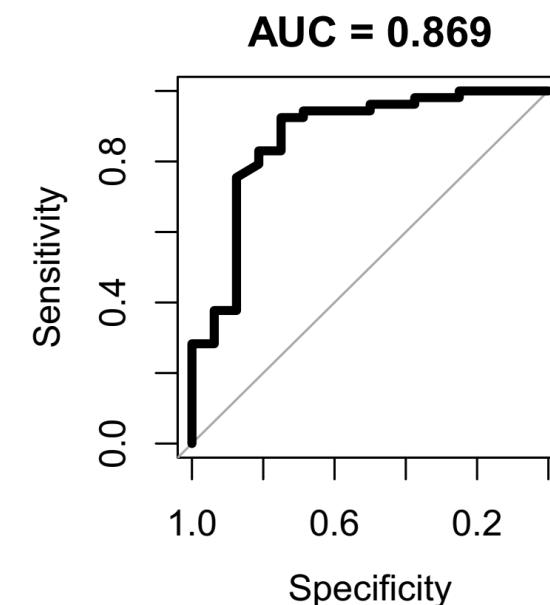
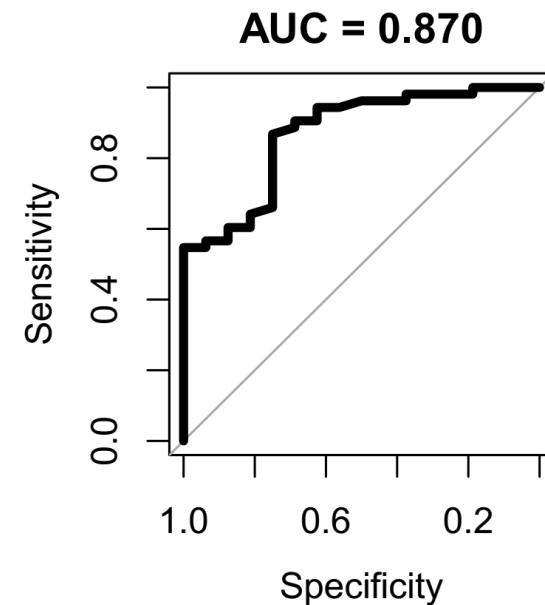
Validation of the breast cancer panel on Tissue/FFPE

Normal (36)		Tumor (30)
Blood	Normal	Tumor
20	16	30



Validation of the breast cancer panel cfDNA

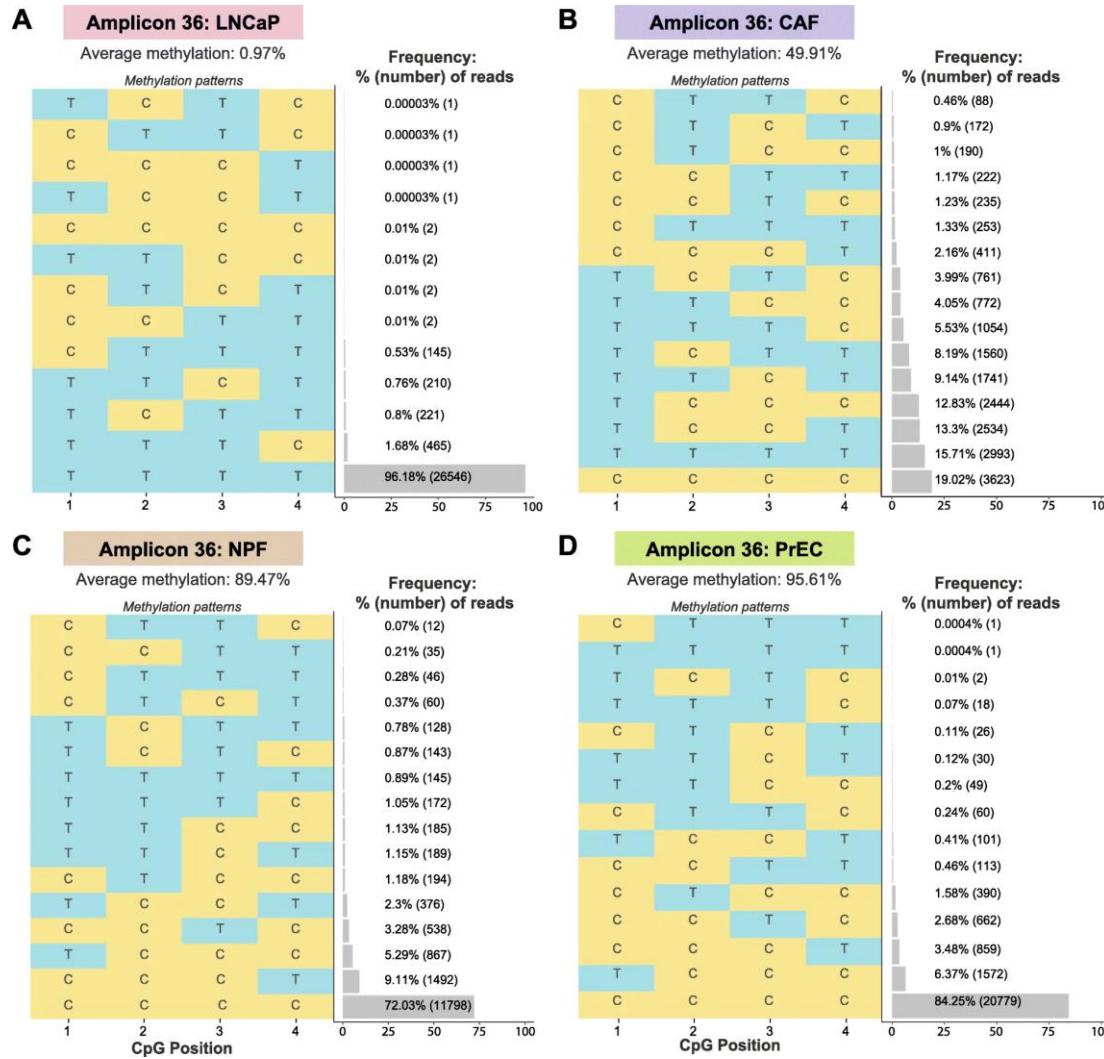
Liquid Biopsy (cfDNA)		
Normal (66)		Tumor (215)
Blood	Normal	Tumor
20	46	215



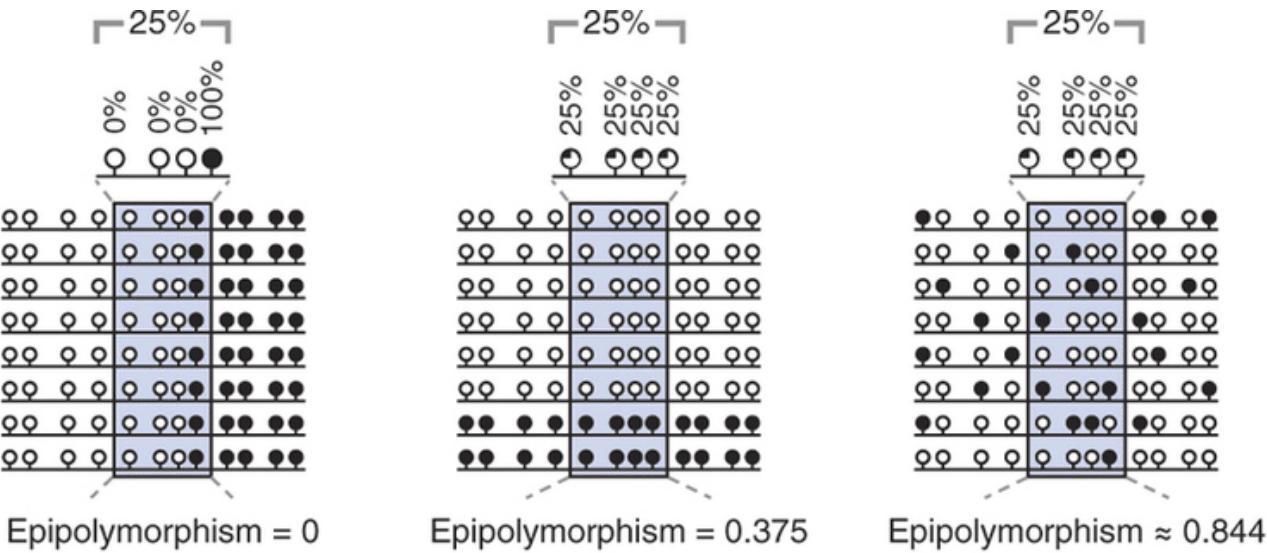
10 significant CpGs (T test, p value < 0.05)

6 important CpGs (from feature selection package MVUR)

DNA methylation pattern

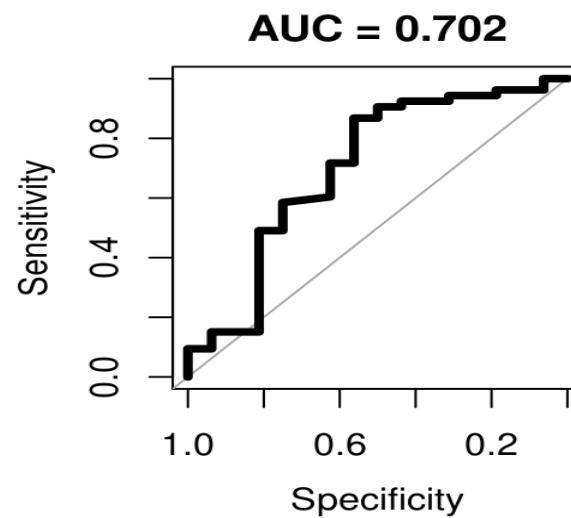


Epipolymorphism

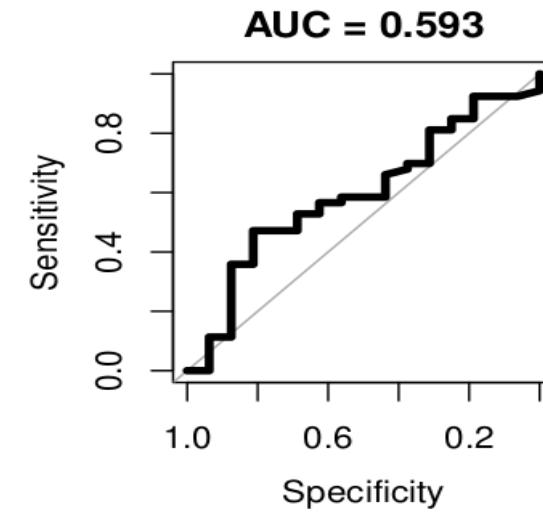


Pattern and EpiPolymorphism score on cfDNA

Liquid Biopsy (cfDNA)		
Normal (66)		Tumor (215)
Blood	Normal	Tumor
20	46	215



Pattern



EpiPolymorphism score

EpiClass

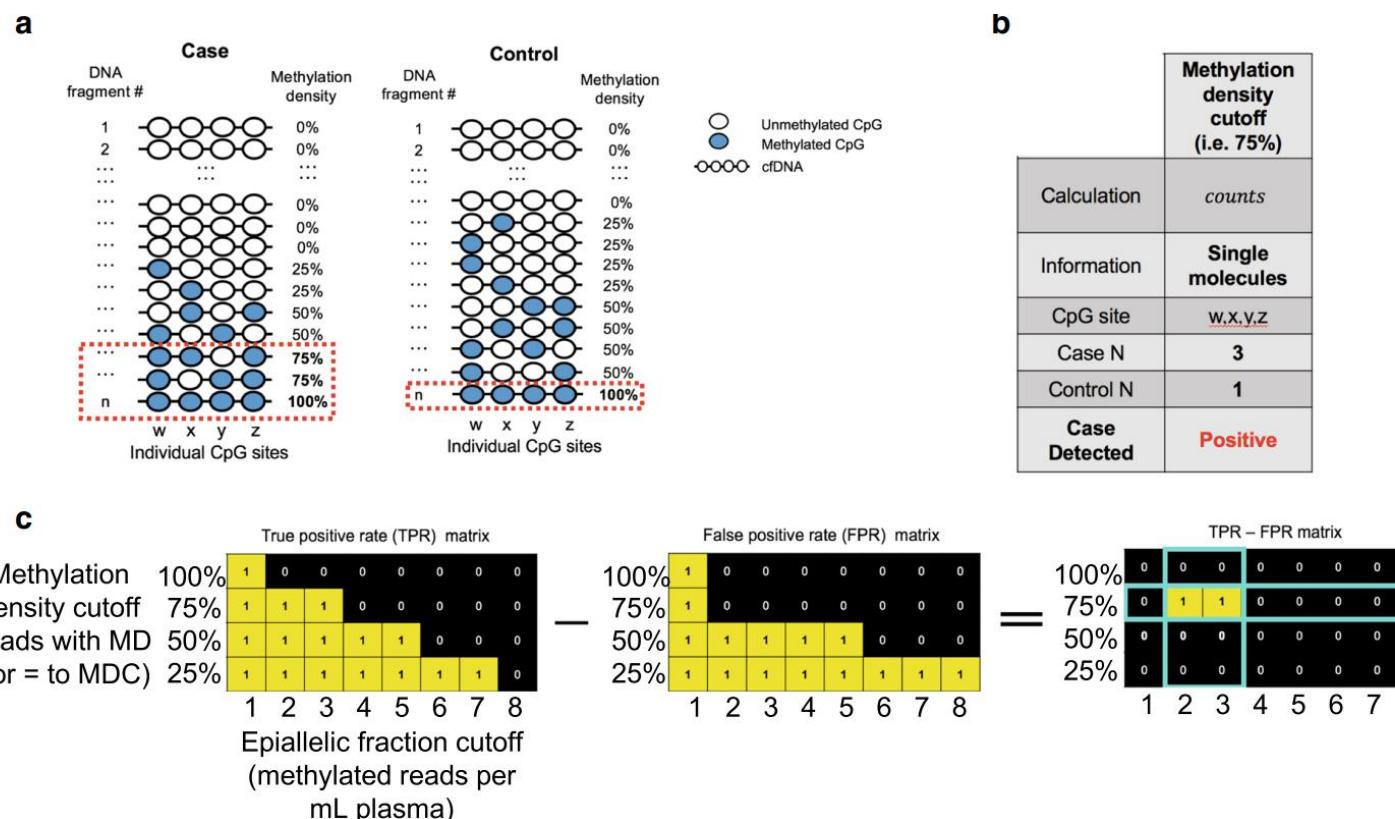
METHODOLOGY

Open Access

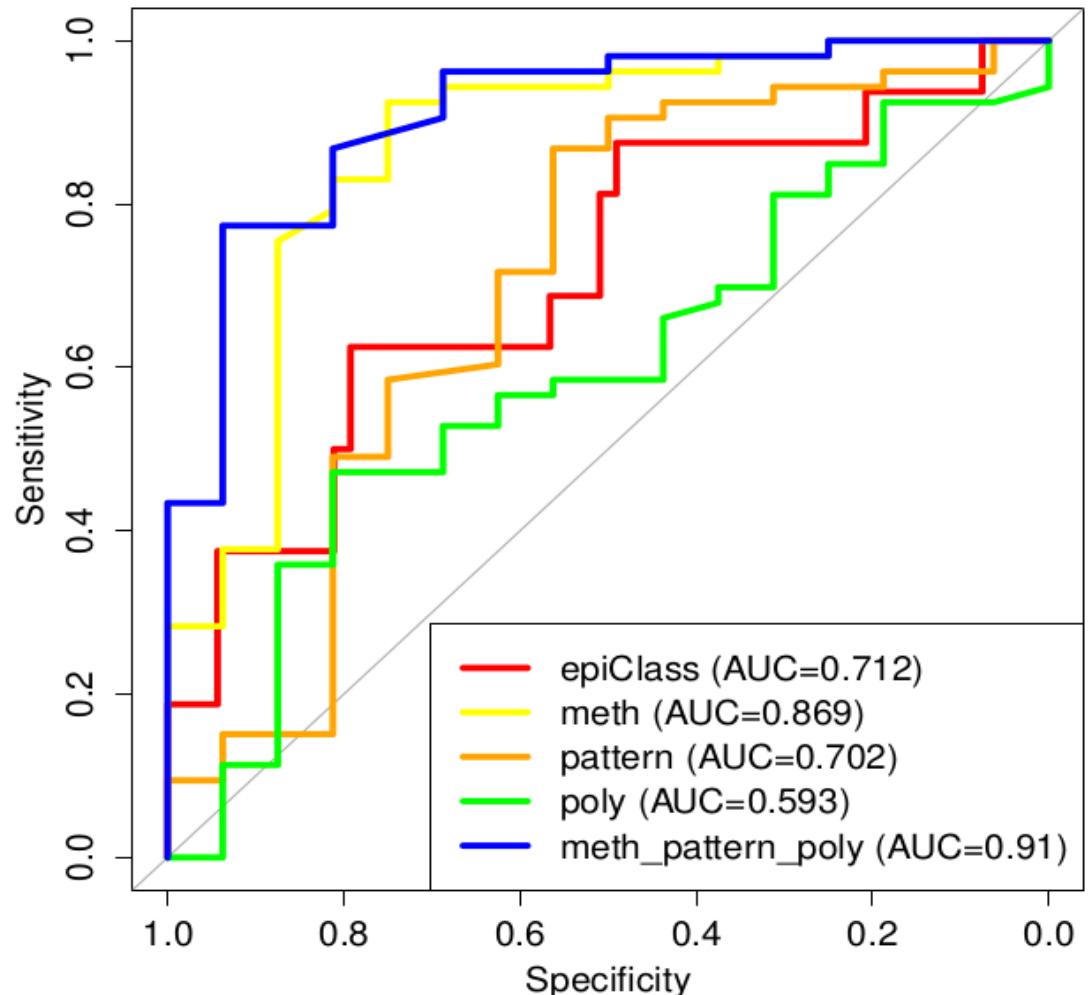


Leveraging locus-specific epigenetic heterogeneity to improve the performance of blood-based DNA methylation biomarkers

Brendan F. Miller¹, Thomas R. Pisani^{1,2*}, Gennady Margolin¹, Hanna M. Petrykowska¹, Pornpat Athamanolap⁵, Alexander Goncarenczo¹, Akosua Osei-Tutu³, Christina M. Annunziata³, Tza-Huei Wang^{2,4,5} and Laura Elnitski^{1*}

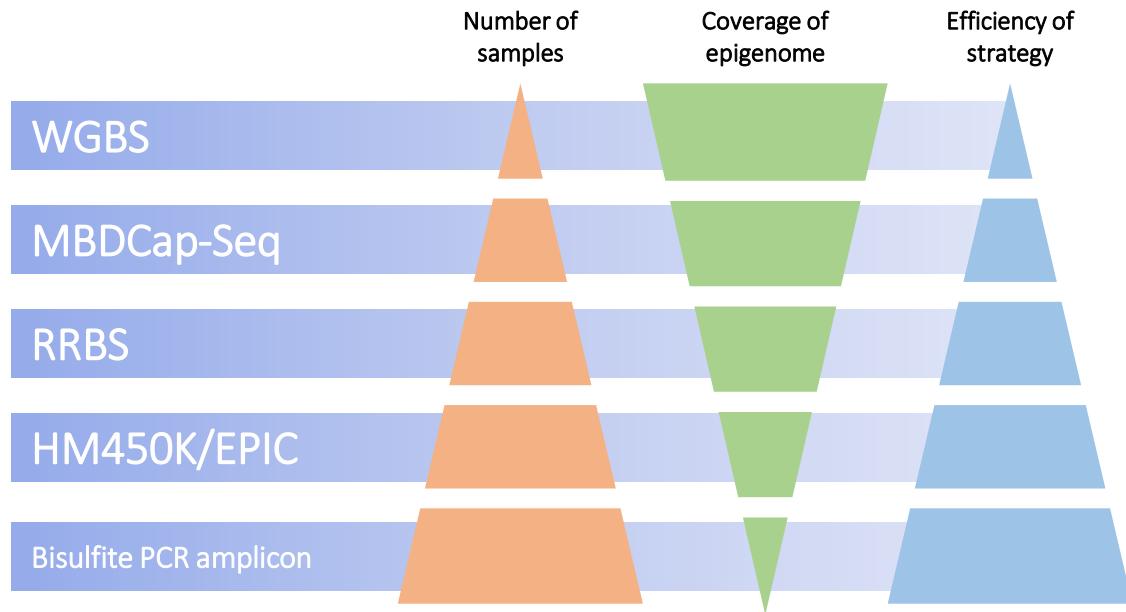


The power of combination of DNA methylation, Pattern and EpiPolymorphsim score for diagnosis of breast cancer using cfDNA (AUC=0.91)



Conclusion

- We succeed to build up the breast cancer DNA methylation panel.
- The breast cancer panel of DNA methylation biomarkers is feasible for diagnosis of both tissue and liquid biopsy.
- The combine DNA methylation status of different CpGs or with the other features such as methylated patterns and epi-polymorphism showed better performance ($AUC = 0.91$) than a single one.



Clinical Epigenomics, 1

mGSTM1 headloop PCR assay for monitoring for treatment
metastatic Castration-resistant prostate cancer with docetaxel

Serum Free Methylated Glutathione S-transferase 1 DNA Levels, Survival, and Response to Docetaxel in Metastatic, Castration-resistant Prostate Cancer: Post Hoc Analyses of Data from a Phase 3 Trial

Kate L. Mahon ^{a,b,c,e,†}, Wenjia Qu ^{b,†}, Hui-Ming Lin ^{b,c}, Calan Spielman ^b, Daniel Cain ^d, Cindy Jacobs ^d, Martin R. Stockler ^{a,e,f}, Celestia S. Higano ^g, Johann S. de Bono ^h, Kim N. Chi ⁱ, Susan J. Clark ^{b,c,†}, Lisa Glen Horvath ^{a,b,c,e,†,*}

^a Chris O'Brien Lifehouse, Sydney, Australia; ^b Garvan Institute of Medical Research, Sydney, Australia; ^c University of NSW, Sydney, Australia; ^d Oncogenex Pharmaceuticals Inc., Bothell, WA, USA; ^e University of Sydney, Sydney, Australia; ^f National Health and Medical Research Council Clinical Trials Centre, Sydney, Australia; ^g University of Washington, Fred Hutchinson Cancer Research Centre, Seattle, WA, USA; ^h Royal Marsden Hospital and Institute of Cancer Research, London, UK; ⁱ University of British Columbia, BC Cancer Agency, Vancouver Prostate Centre, Vancouver, BC, Canada

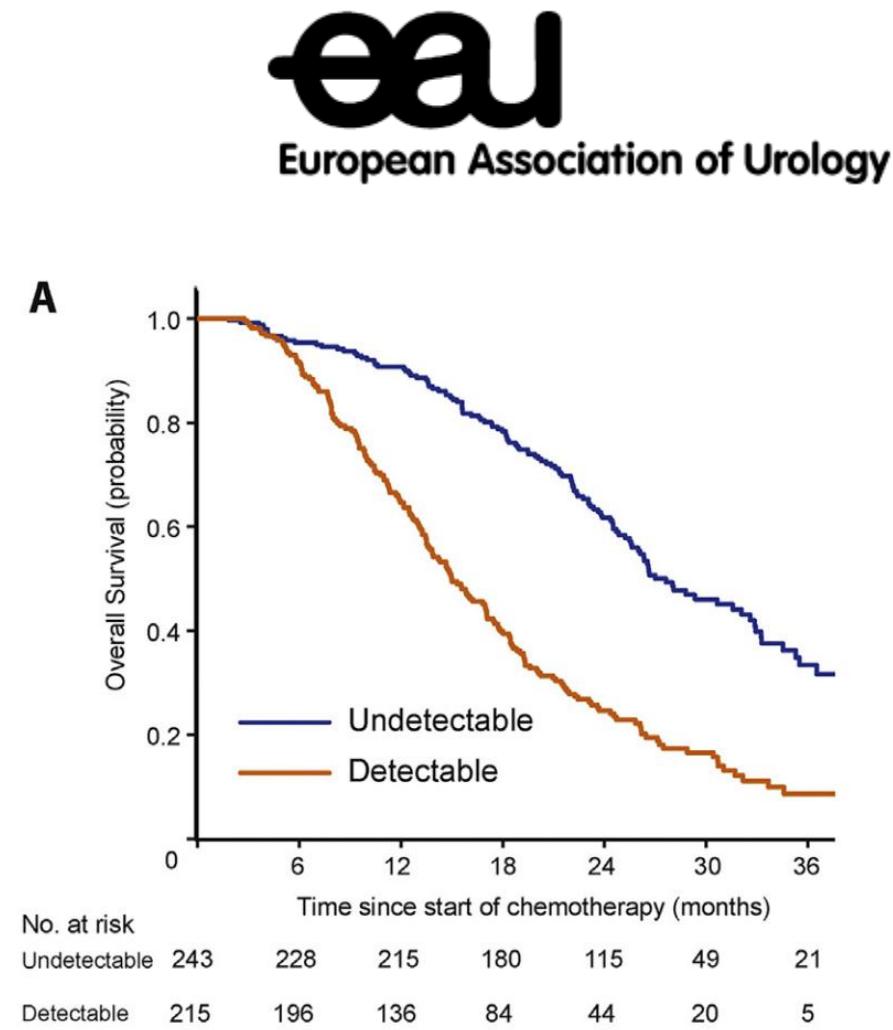
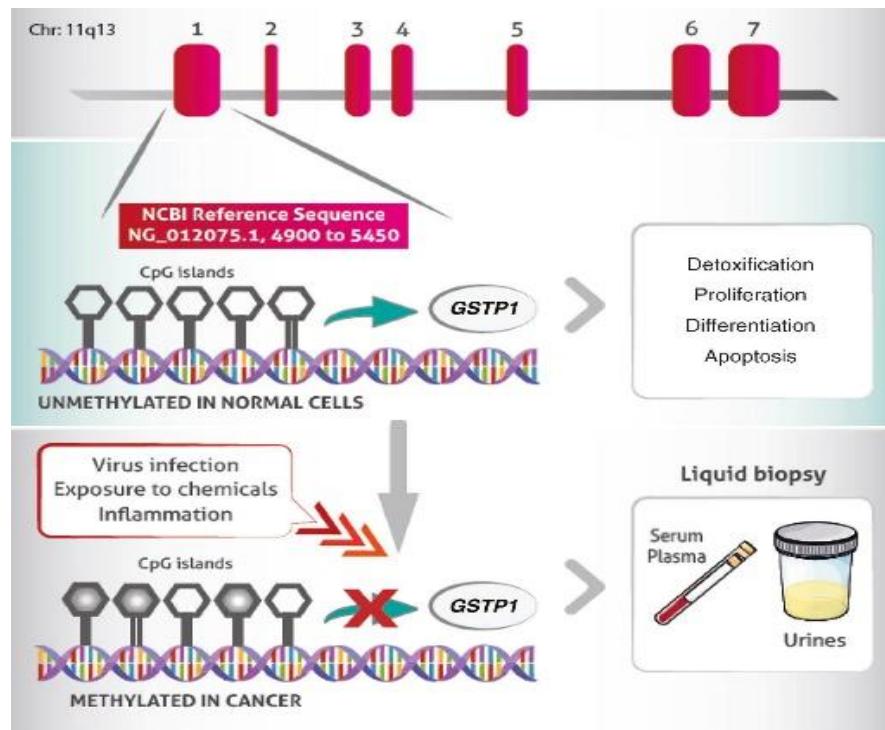


Fig. 3 – Kaplan-Meier estimates of survival in patients with a detectable mGSTP1 at baseline. (A) OS according to mGSTP1 detection after two cycles of docetaxel.

Metastatic Castration-resistant prostate cancer monitoring for treatment with docetaxel using mGASTP1 headloop PCR assay

Patient ID: 13268		MF	MF	MF	MF									
Block (Pre-2014)	Block No	Specimen ID	BS Plate	Tube No	Total DNA (ng)	GSTPiHL CT1	GSTPiHL CT2	GSTPiHL CT3	Ave Total Methylated GSTPi (ng)	Control CT1	Control CT2	Control CT3	Ave Total BS DNA(ng)	
	1	1453895	A1	1	85.2	44.64	36.10	43.39	1.48	16.12	16.24	16.40	33.38	
	2	1453896	B1	2	38	43.34	36.78	43.84	1.01	17.77	17.64	17.63	12.71	
	3	1453897	C1	3	18	42.37	41.57	49.93	0.10	18.38	18.39	18.47	7.73	
	4	1453898	D1	4	10	55.13	52.74	Undetermined	#VALUE!	20.04	20.11	19.89	2.62	
	5	1453899	E1	5	46.4	51.91	49.85	49.47	0.00	17.78	17.81	17.85	11.59	
	6	1453900	F1	6	64	39.88	41.87	40.89	0.30	16.81	17.02	16.91	21.36	
	7	1453901	G1	7	37.4	56.68	49.99	49.55	0.00	17.65	17.59	17.74	12.84	
	8	1453902	H1	8	58.4	37.09	36.36	36.77	3.04	17.42	17.52	17.63	14.11	
	9	1453903	A2	9	46.4	45.17	40.05	38.89	0.44	17.31	17.26	17.40	16.17	
	10	1453904	B2	10	136	40.66	40.25	36.54	1.35	15.91	15.92	15.82	42.81	
	11	1453905	C2	11	188	36.59	36.62	36.13	3.59	16.25	16.14	16.18	34.79	
	12	1453906	D2	12	65.2	44.77	39.06	37.14	1.06	17.21	17.14	17.12	18.04	
	13	1453907	E2	13	26.2	49.91	45.66	49.04	0.01	17.93	17.91	18.00	10.58	
	14	1453908	F2	14	28.2	50.18	49.83	46.54	0.00	17.73	17.76	17.97	11.54	
	15	1453909	G2	15	59.6	50.64	46.70	38.32	0.40	16.98	17.09	17.27	18.63	
	16	1453910	H2	16	52.8	37.82	49.00	49.32	0.53	17.81	17.94	17.92	11.01	
	17	1453911	A3	17	18.2	Undetermined	52.76	59.25	#VALUE!	18.86	18.76	18.85	5.85	
	18	1453912	B3	18	2.8	51.65	53.99	Undetermined	#VALUE!	21.35	21.35	21.40	1.04	
Block (Post-2019)	1	1453914	C3	21	354	36.33	35.58	34.63	6.65	13.20	13.37	13.36	244.49	
	2	1453915	D3	22	74.4	45.29	47.05	45.84	0.01	14.00	14.03	13.98	152.53	
	3	1453916	E3	23	182.4	35.70	36.23	35.07	5.81	12.81	12.98	12.93	321.46	
	4A	1453917	F3	24	440	35.91	36.65	35.85	4.35	13.01	13.09	13.02	293.19	
	4B	1453928	G3	25	146.8	37.93	35.81	37.74	2.77	12.93	13.01	13.11	298.63	
	5	1453918	H3	26	131.6	39.14	42.97	40.77	0.37	13.17	13.02	13.15	278.59	
	6	1453919	A4	27	82.4	37.63	40.19	40.64	0.83	13.40	13.38	13.46	227.71	
	7	1453920	B4	28	61.2	46.81	45.75	46.99	0.01	13.97	14.13	14.16	144.63	
	8	1453921	C4	29	9.2	49.48	47.88	48.59	0.00	15.91	15.86	15.92	42.32	
	9	1453922	D4	30	35.6	44.96	38.49	47.37	0.37	15.19	15.16	15.23	68.22	
	10	1453923	E4	31	191.6	37.30	36.28	36.91	2.93	13.01	13.06	13.11	289.79	
	11	1453924	F4	32	424	34.52	33.58	34.50	13.65	13.46	13.49	13.52	216.46	
	12	1453925	G4	33	133.2	32.83	33.40	32.68	27.40	13.13	13.13	13.29	266.47	

Prognostic epigenetic biomarkers for prostate cancer mortality

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RESEARCH ARTICLE

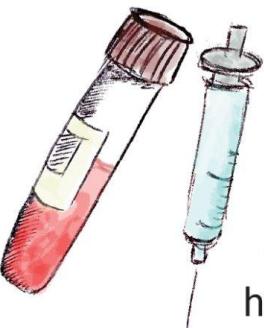


WILEY

Comprehensive methylome sequencing reveals prognostic epigenetic biomarkers for prostate cancer mortality

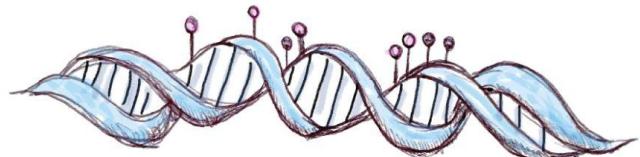
Ruth Pidsley^{1,2} | Dilys Lam¹ | Wenjia Qu¹ | Timothy J. Peters^{1,2} |
Phuc-Loi Luu^{1,2} | Darren Korbie³ | Clare Stirzaker^{1,2} | Roger J. Daly⁴ |
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Prostate cancer
is the second most
common cancer
diagnosed in men

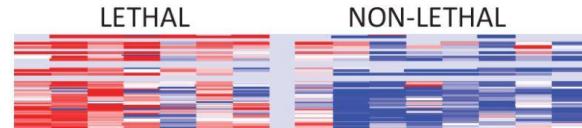


There is a critical need
for more biomarkers to
help guide management

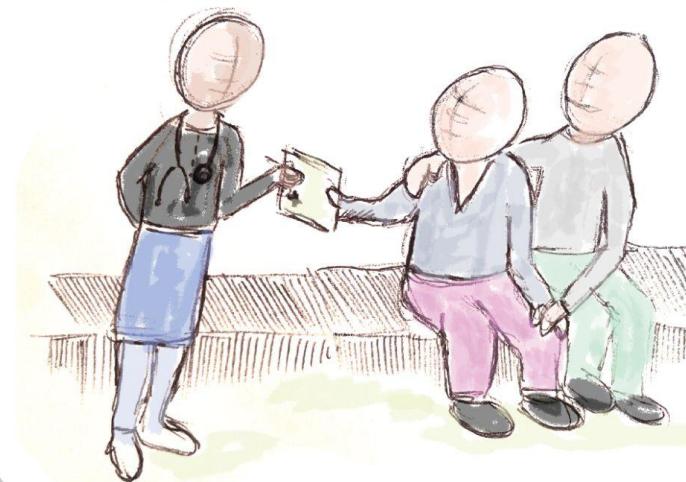
We know that **methylation markers**
on DNA are altered in prostate cancer



We compared lethal and non-lethal
prostate cancers and found prognostic
methylation markers on DNA

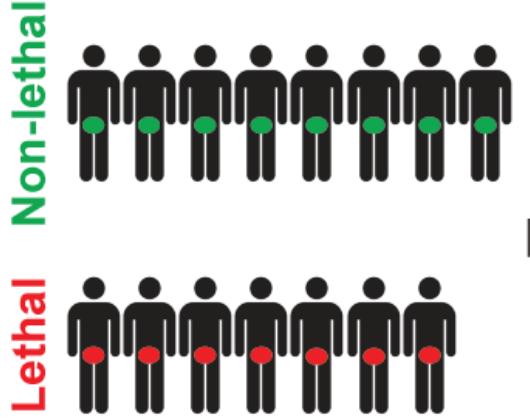


This **prognostic information** could
guide clinical decisions following a
diagnosis of prostate cancer

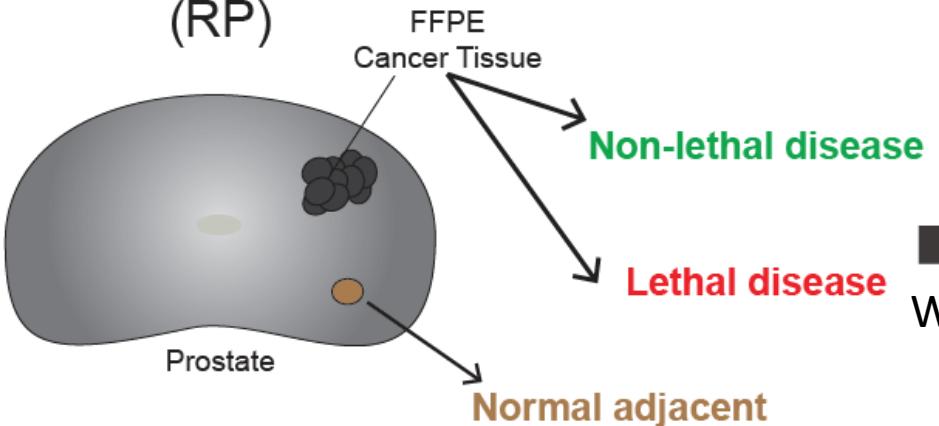


Credit to Dr Kate

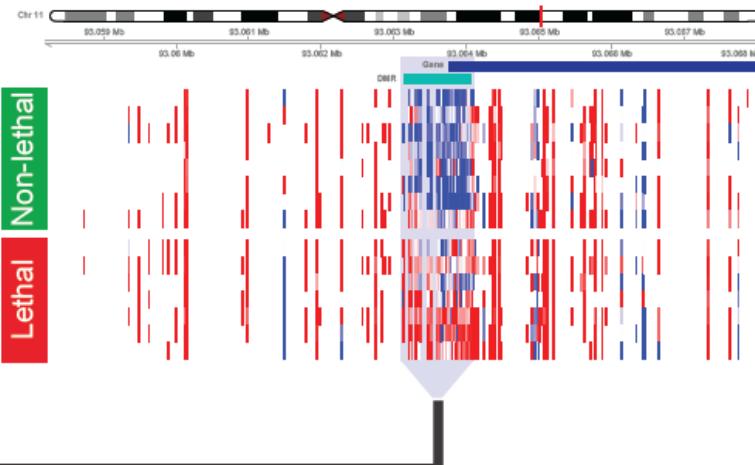
Discovery Cohort



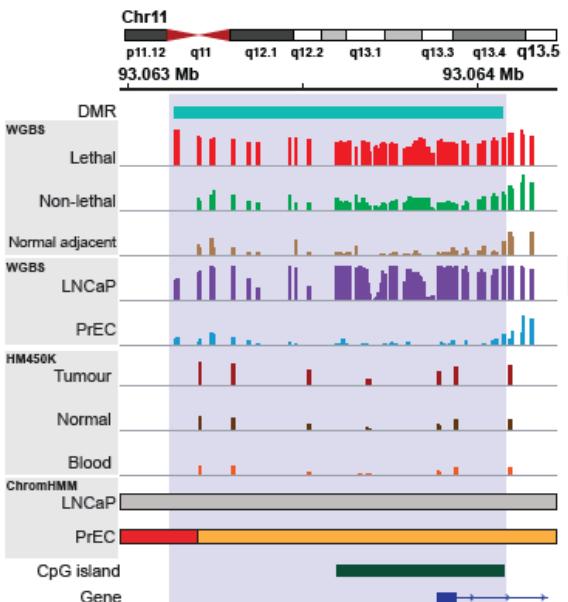
Radical prostatectomy (RP)



Genome-wide screen of methylation: DMR Identification

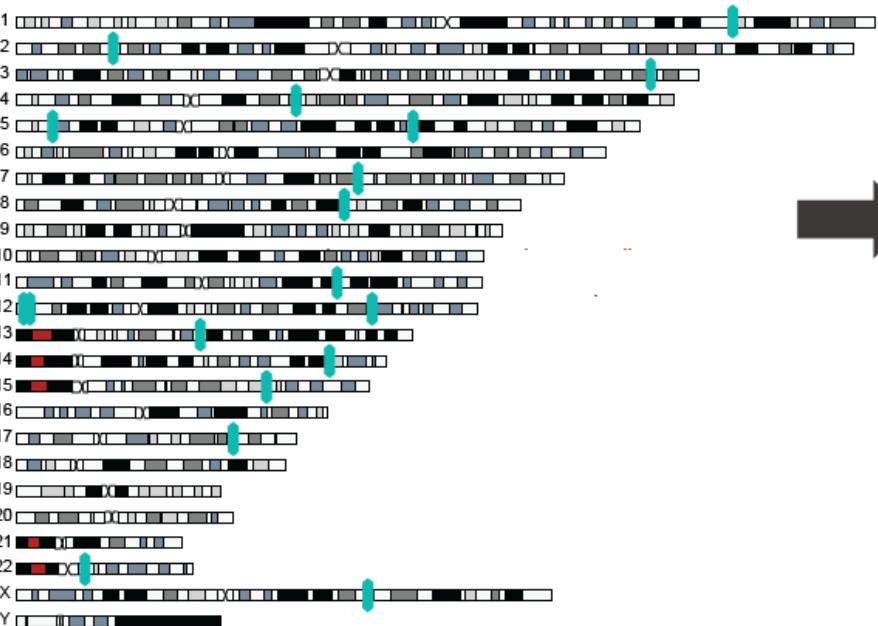


Biomarker selection



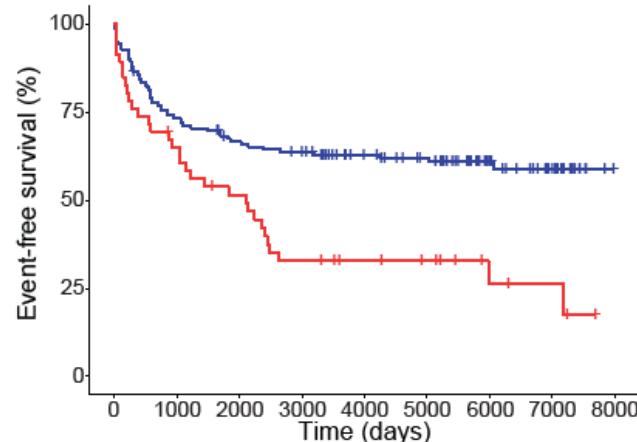
Comparison with in-house and public datasets

Targeted multiplex panel: 18 regions



Independent Validation RP Cohort (n = 185):

Long follow-up (median = 15 years)



Survival analysis

- Biochemical Recurrence
- Metastatic Relapse
- Prostate Cancer Death

- Epigenetic Therapy
 - Epigenetic targeted therapies in hematological malignancies
 - Epigenetic therapy in lung cancer (Read Book)

Differentiation stages in normal hematopoiesis and the origins of commonly observed hematological malignancies

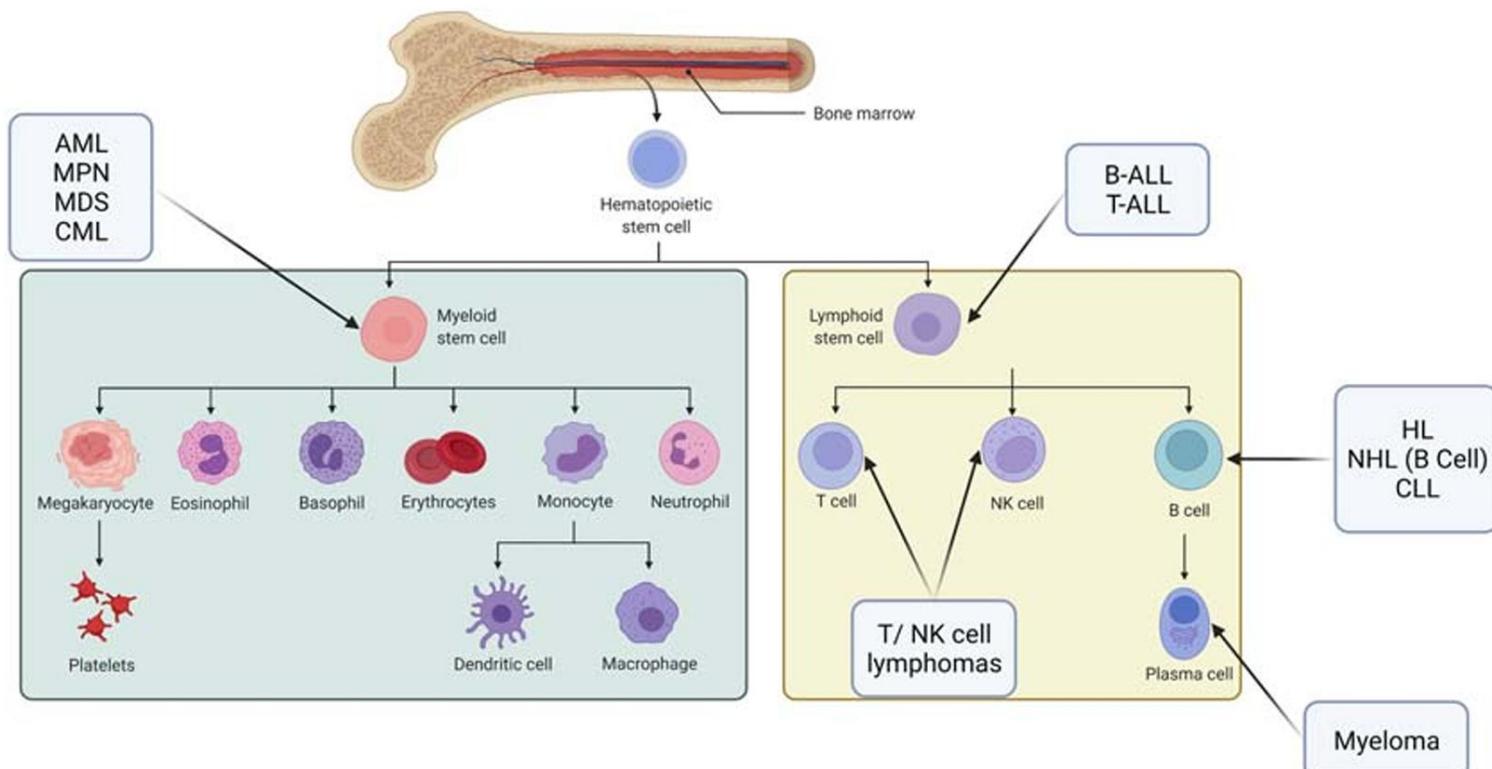
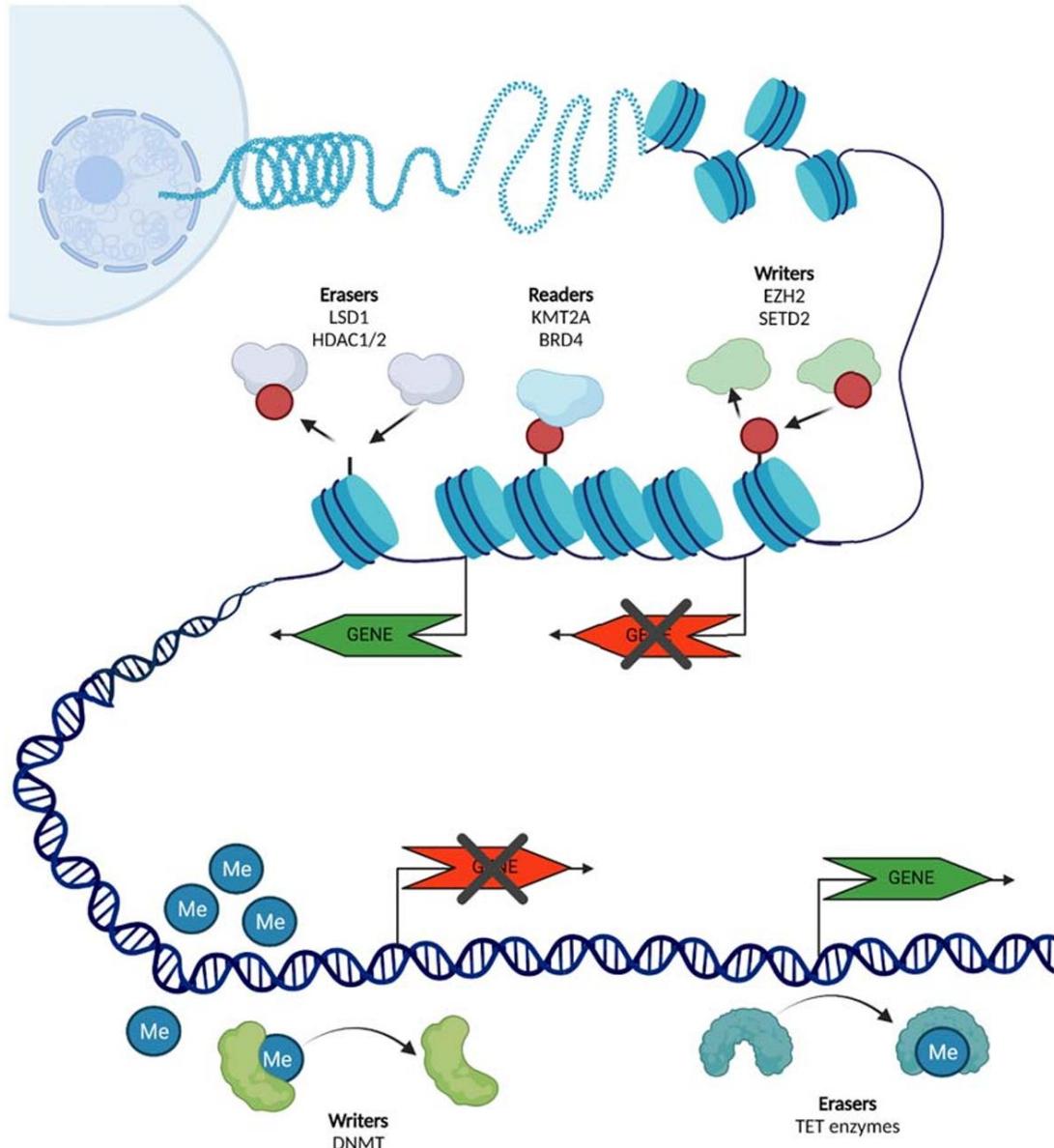


FIGURE 11.1

The process of hematopoiesis and originating sites of various blood disorders. Hematopoiesis is where blood cellular components are formed beginning primarily in the bone marrow before differentiating down either myeloid or lymphoid lineages before circulating around the body. Also highlighted are the primary sites where hematopoietic disorders are formed. AML: acute myeloid leukemia, MPN: myeloproliferative neoplasms, MDS: myelodysplastic syndromes, CML: chronic myeloid leukemia, B-ALL: B-cell acute lymphoblastic leukemia, T-ALL: T-cell acute lymphoblastic leukemia, HL: Hodgkin's lymphoma, NHL: non-Hodgkin's lymphoma, CLL: chronic lymphocytic leukemia, T/NK cell lymphoma: T/natural killer cell lymphoma.

The impact of epigenetic readers, writers and erasers on both histones and DNA within the hematopoietic context



- Epigenetic writers catalyze the addition of chemical modifications to specific amino acids on histone tails and methylation of CpG islands on DNA therefore preventing gene transcription at both the histone and DNA levels.
- Epigenetic erasers remove these modifications thus allowing gene transcription to occur; while epigenetic readers recognize them and recruit larger chromatin remodeling complexes to further impact the alterations and dictate gene expression changes.
- Included are also examples of some well documented hematopoietic readers, writers, and erasers at the histone and DNA levels, however, not highlighted is the capability for some proteins to act in a dual function as writers and readers or erasers and readers.

Potential for pathogenicity when DNA methylation is perturbed along the hematopoietic tree

Table 11.1 The Approximate Percentages of Patients with Mutations in Key DNA Methylation Genes

Gene	AML (%)	MDS (%)	MPN (%)	MDS/MPN Overlap (%)
<i>DNMT3A</i>	21	13	5	9
<i>TET2</i>	12	33	13	45
<i>IDH1</i>	8	3	1	—
<i>IDH2</i>	12	4	1	2

AML percentages from [14], MDS percentages from [15], MPN percentages from [16], and MDS/MPN from [17].

Table 11.2 The Approved Indications for Hypomethylating Agents as Single Agents or Combination Therapies

Condition	Treatment Formulation	Single Agent Approvals	Combination Approvals
MDS	Azacitidine SC	<ul style="list-style-type: none"> – FDA approved for FAB myelodysplastic syndrome subtypes; RA, RARS, RAEB, RAEB-T – EMA approved for intermediate-2/high risk MDS in patients who cannot have HSCT 	
	Decitabine IV	FDA approved for all treated and previously treated <i>de novo</i> and secondary MDS of all FAB subtypes and intermediate-1, intermediate-2 and high risk.	
	Decitabine PO		FDA approved In combination with cedazuridine for all treated and previously treated <i>de novo</i> and secondary MDS with FAB subtypes (RA, RARS, RAEB) and intermediate-1, intermediate-2 and high risk.
	Azacitidine SC	EMA approved for patients who cannot have stem cell transplant and AML developed from MDS and bone marrow consists of 20%–30% blasts or AML where bone marrow has more than 30% blasts	<ul style="list-style-type: none"> – FDA approved in combination with venetoclax for newly diagnosed AML in patients 75 years or older or who have co-morbidities that preclude use of intensive induction therapy – EMA approved in combination with venetoclax in adults who cannot have intensive chemotherapy – FDA approved in combination with Ivosidenib for newly diagnosed with <i>IDH1</i> mutation in adults >75 years or who have co-morbidities precluding intensive induction chemotherapy

Table 11.2 The Approved Indications for Hypomethylating Agents as Single Agents or Combination Therapies *Continued*

Condition	Treatment Formulation	Single Agent Approvals	Combination Approvals
CMML	Azacitidine SC	<ul style="list-style-type: none"> – FDA approved for adult patients with CMML – EMA approved for CMML with 10%–29% marrow blasts without myeloproliferative disorder 	
	Decitabine IV	FDA approved in intermediate 1/intermediate 2 AND high risk IPSS	
	Decitabine PO		In combination with cedazuridine for intermediate 1/intermediate 2 AND high risk IPSS

FDA: US Food and Drug Administration, EMA: European Medicines agency, SC: subcutaneous, IV: intravenous, PO: oral, MDS: myelodysplasia, AML: acute myeloid leukemia, CMML: chronic myelomonocytic leukemia, JMML: juvenile myelomonocytic leukemia, FAB: French American British, RA: refractory anemia, RARS: refractory anemia with ringed sideroblasts, RAEB: refractory anemia with excess blasts, RAEB-T: refractory anemia with excess blasts in transformation, IPSS: International Prognostic Scoring System, HSCT: hematopoietic stem cell transplant.

Compounds targeting epigenetic readers, writers and erasers on both histones and DNA within hematological disorder

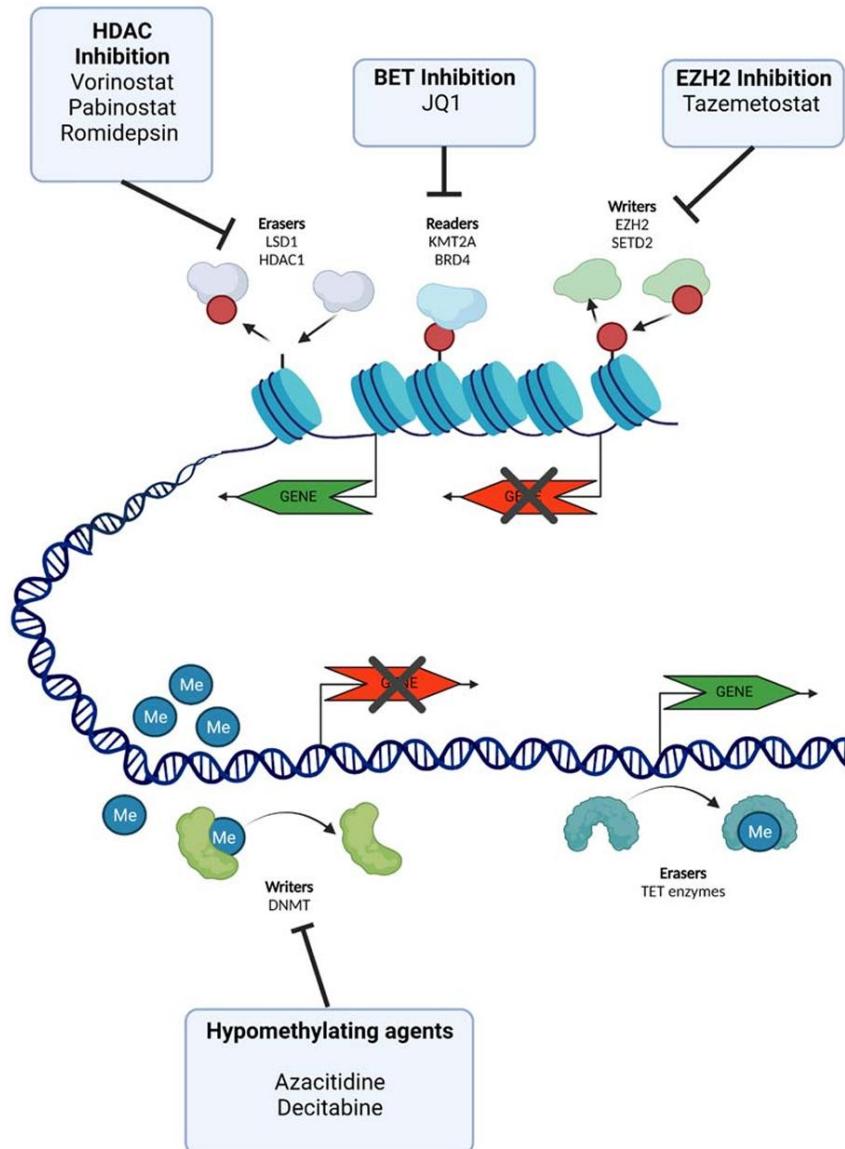
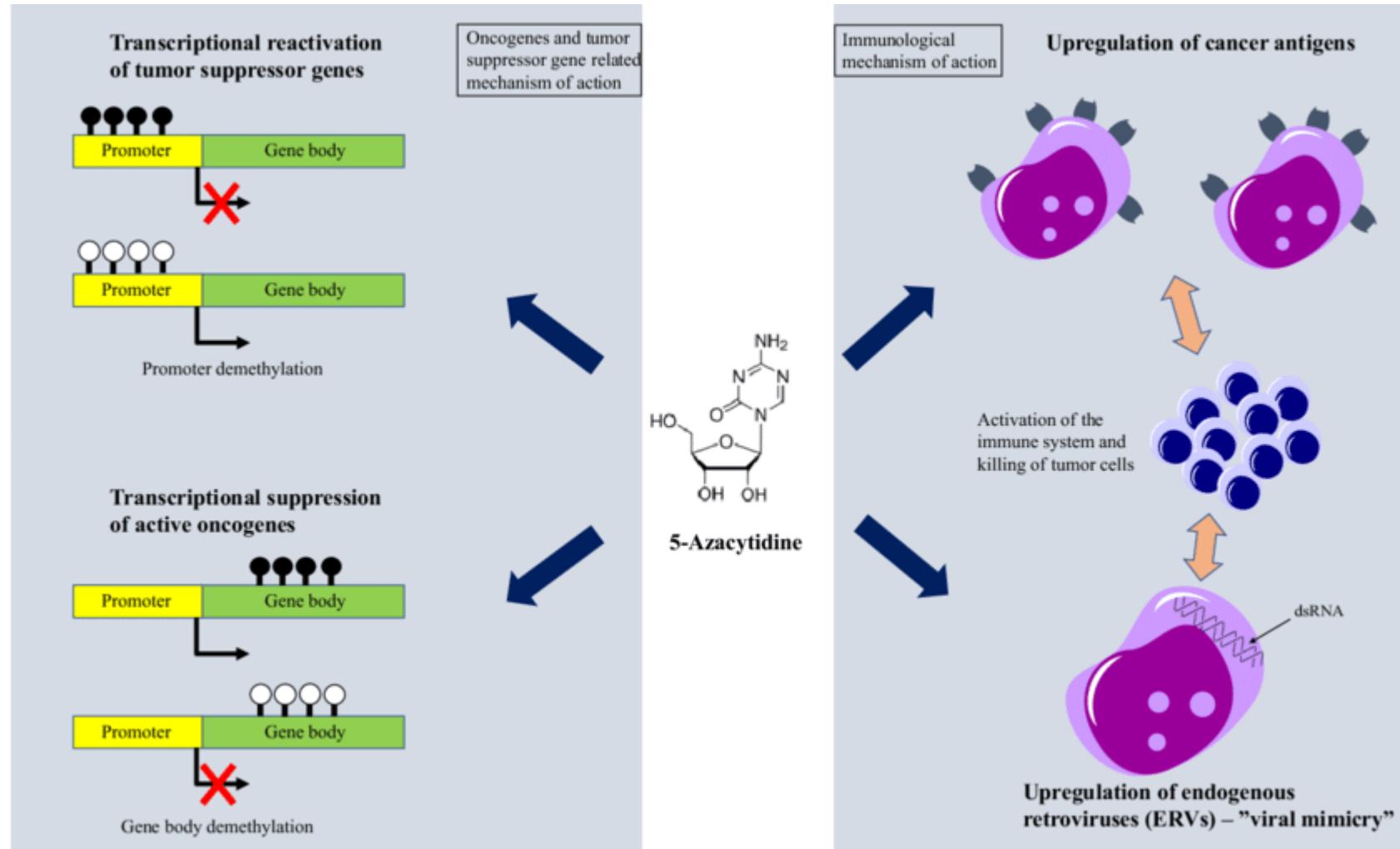


Figure adapted from Figure two with the inclusion of drug compounds commonly used to target the highlighted epigenetic readers, writers and erasers within hematological malignancies.

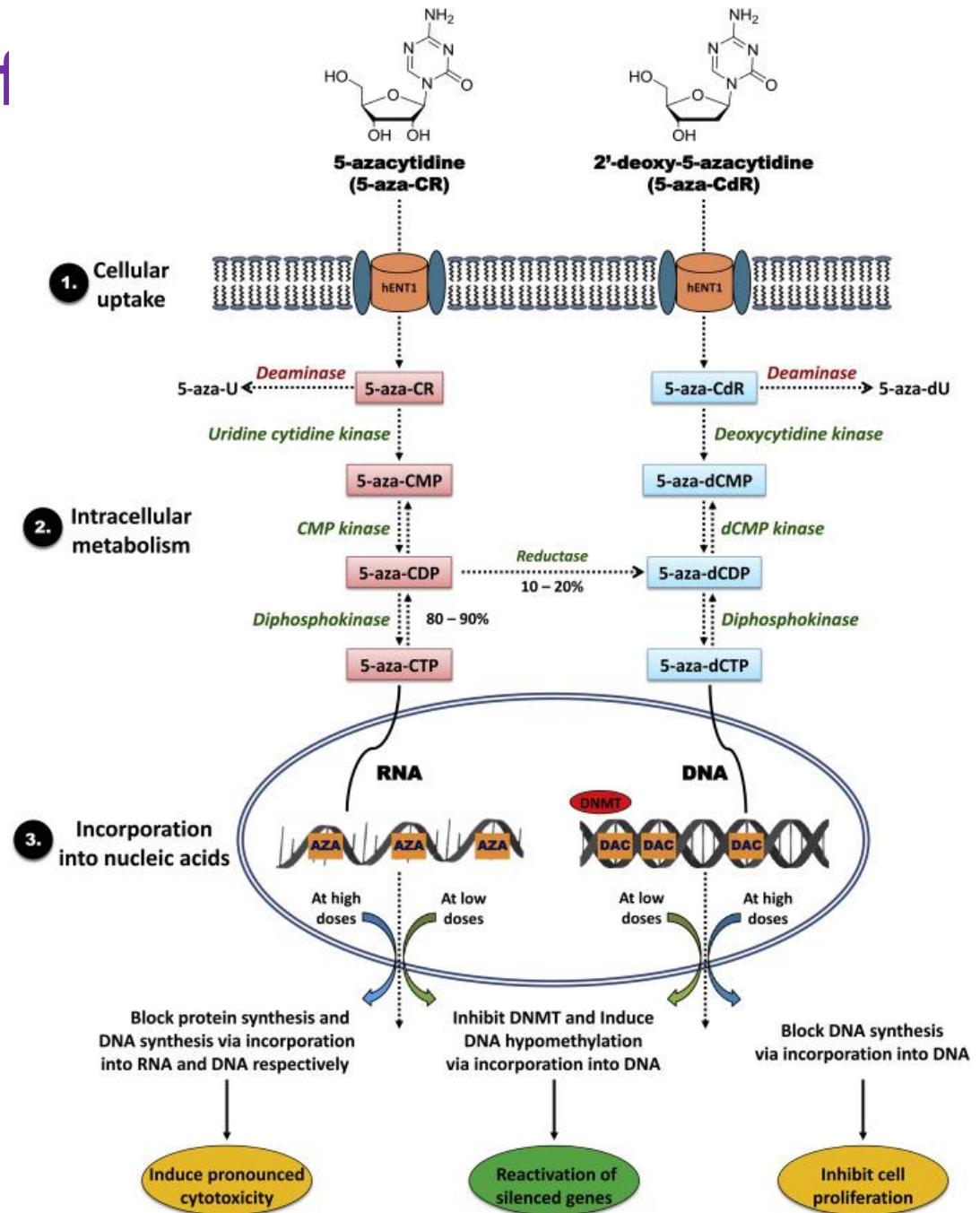
The different mechanisms of actions of 5-azacytidine



Treatment with 5-azacytidine can reactivate silenced tumor suppressor genes by demethylating their promoter area and/or reducing the expression of oncogenes by demethylating their gene bodies. In addition, 5-azacytidine has some immunomodulatory effects and activates the immune system either by overexpression of silenced cancer antigens or by activation of endogenous retroviruses (ERVs) in the cancer cells.

Mechanism of molecular action of azanucleosides Azacytidine and decitabine

After their cellular uptake, these AZN are metabolically converted into their active triphosphate forms, 5-aza-2'-cytidine-triphosphate (5-aza-CTP) and 2'-deoxy-5-azacytidine-triphosphate (5-aza-dCTP) respectively, through phosphorylation by the different kinase. During replication, decitabine-derived 5-aza-dCTP is incorporated into newly synthesized DNA, whereas, 80–90% of azacytidine is incorporated into RNA as 5-aza-CTP, and only 10–20% is incorporated into DNA after multistep conversion by the enzyme ribonucleotide reductase to 5-aza-dCTP.

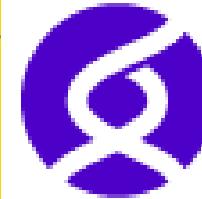


Acknowledgement

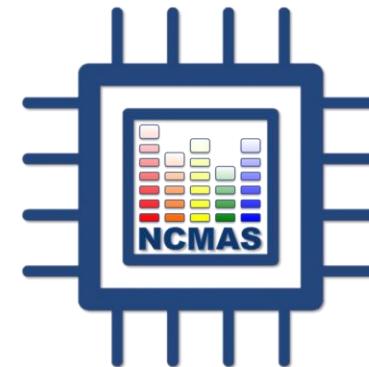
- Prof. Susan Clark
- Dr Clare
- Dr Hanh
- Dr Hiep
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- Dr Ngu
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- Dr Phuong
- Dr Ruth
- Jenny
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