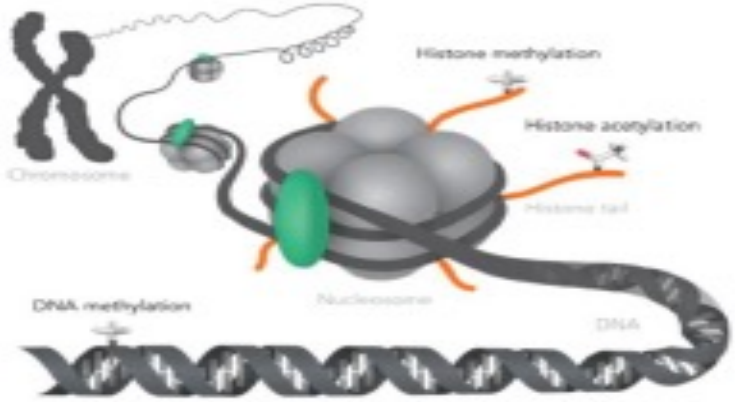
Epigenetics and cancer

National Cancer Institute

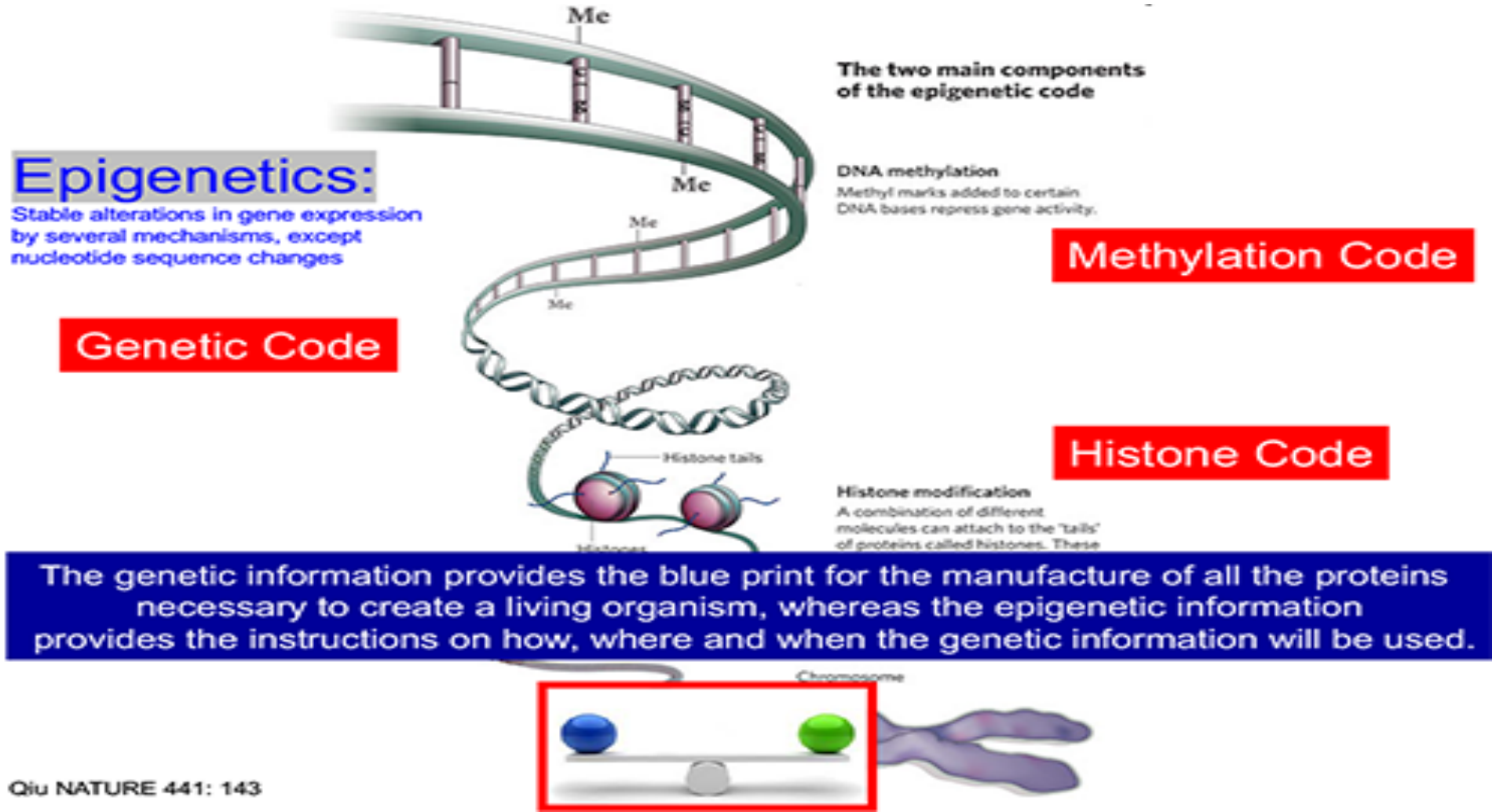
Epigenetics and Cancer



Mukesh Verma, Ph.D.
Chief, Methods and Technologies Branch
Program Director,
Epidemiology and Genomics Research Program
DCCPS, NCI, NIH

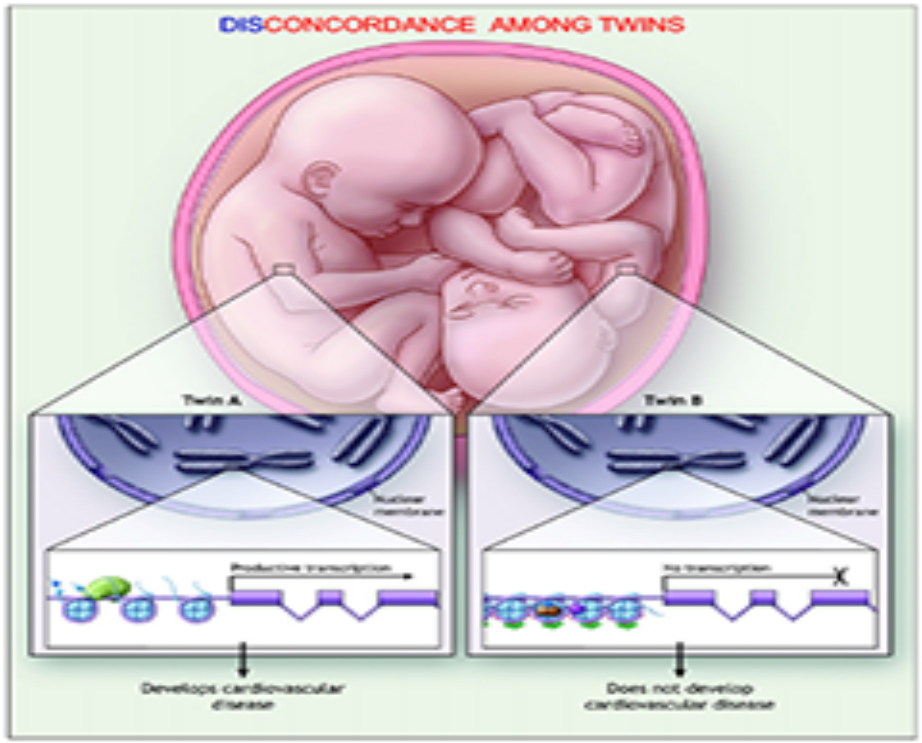
Fig. Credit: https://horizondiscovery.com/en/applications/cell-line/epigenetics

Epigenetics



DNA and destiny

The choices you make
can change your genes
-- and those of your kids.



Epigenetic predisposition to angiogenesneis? Individual? Populations?

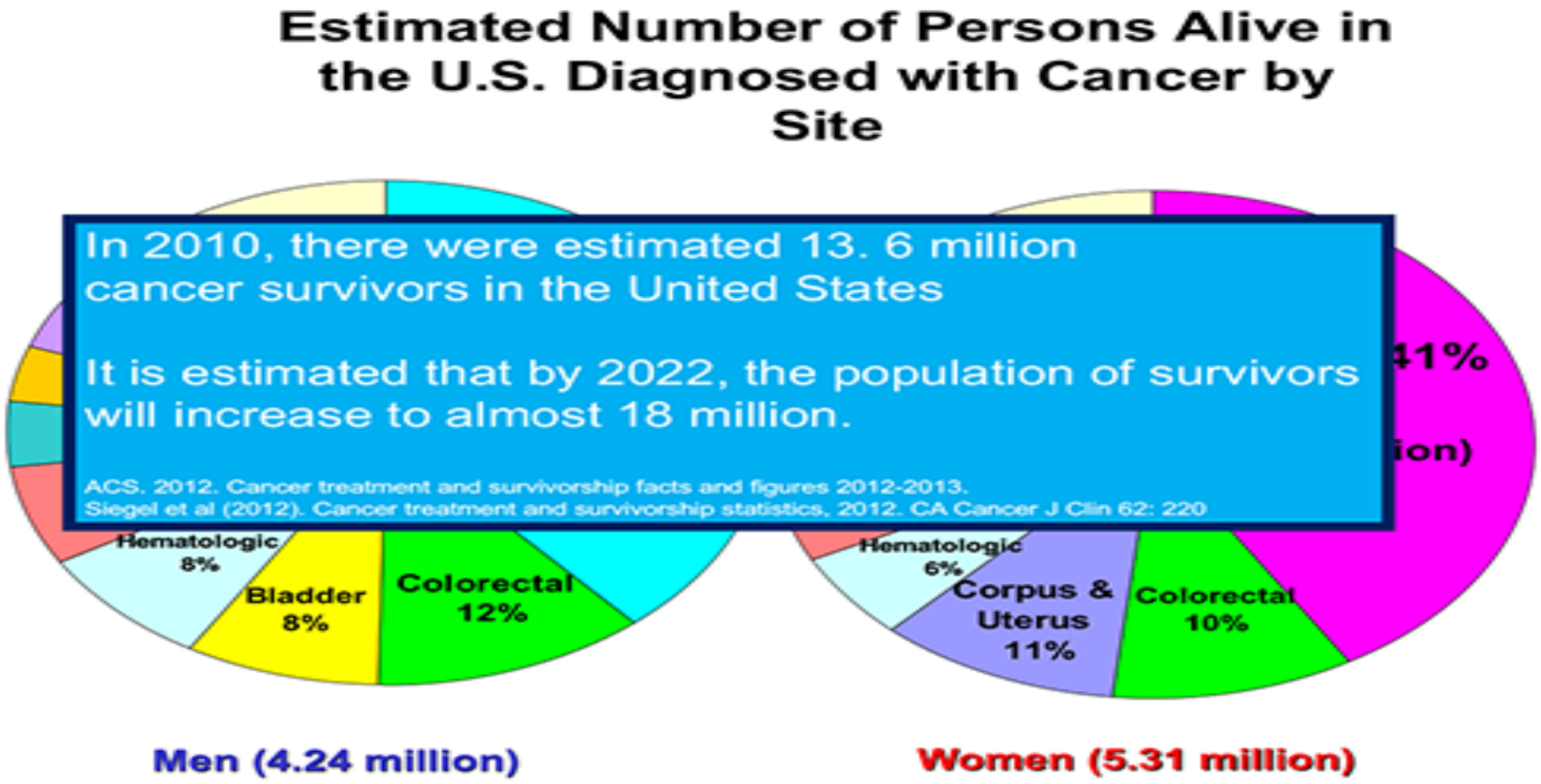
Pharmacogenomics and pharmacoepigenomics (personalized medicine)

Microenvironment, microbiome, and gene expression

GWAS and EWAS

Adapted from Matouk and Marsden Cir Res 102:873

Cancer Survivors



Cancer continuum

DCCPS covers cancer continuum

Prevention

Tobacco, physical activity, diet, sun, environment, HPV immunization

Early Detection

Breast, cervical, colorectal cancer screening

Diagnosis

Incidence, Stage at diagnosis

Treatment

Trends in cancer treatment

Life After Cancer

Financial burden of cancer care, Cancer survivorship

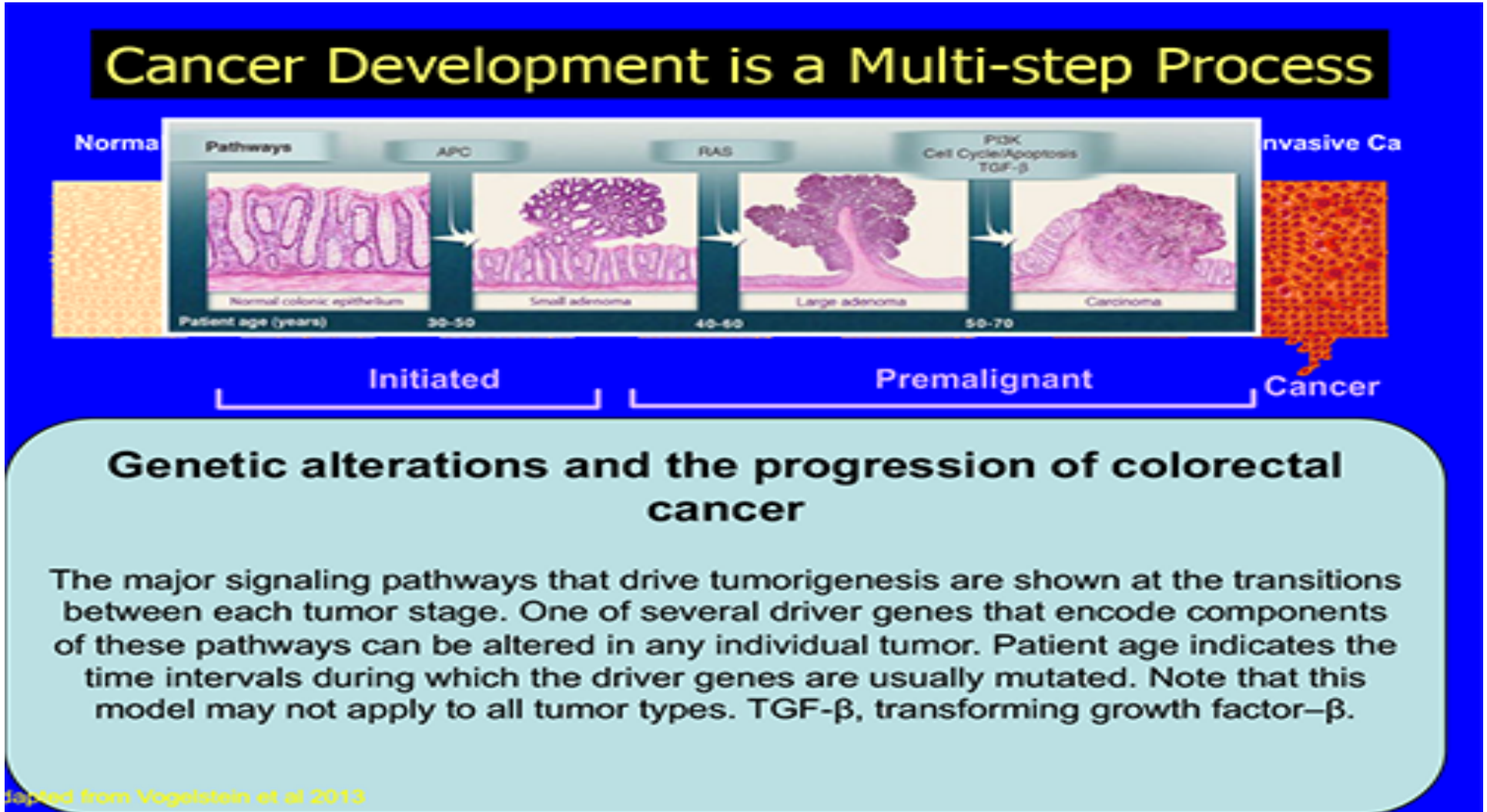
End of Life

Mortality, Person – years of life lost

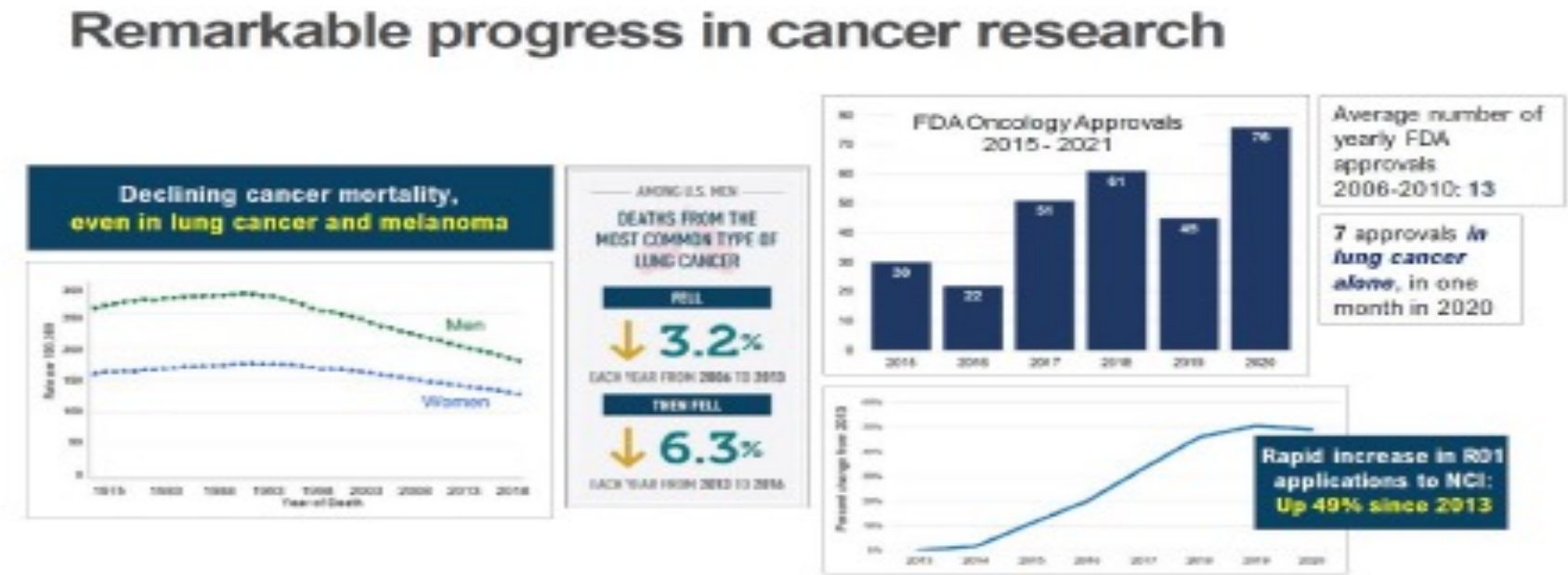
Prevention → Cancer recurrence, Secondary cancer

Prevention: restoring transcription, halting progression, or stopping metastasis

Cancer development

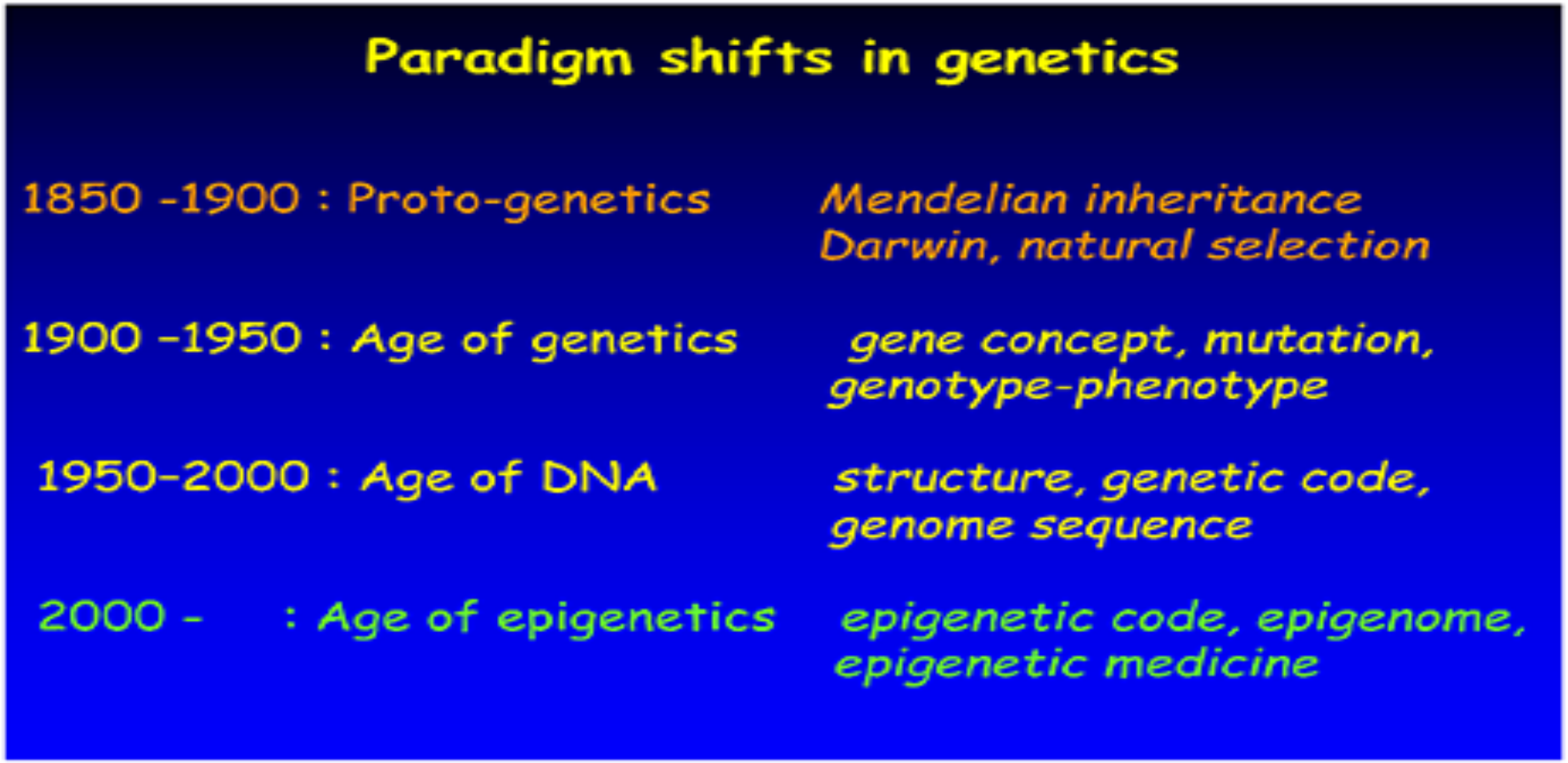


Cancer research progress

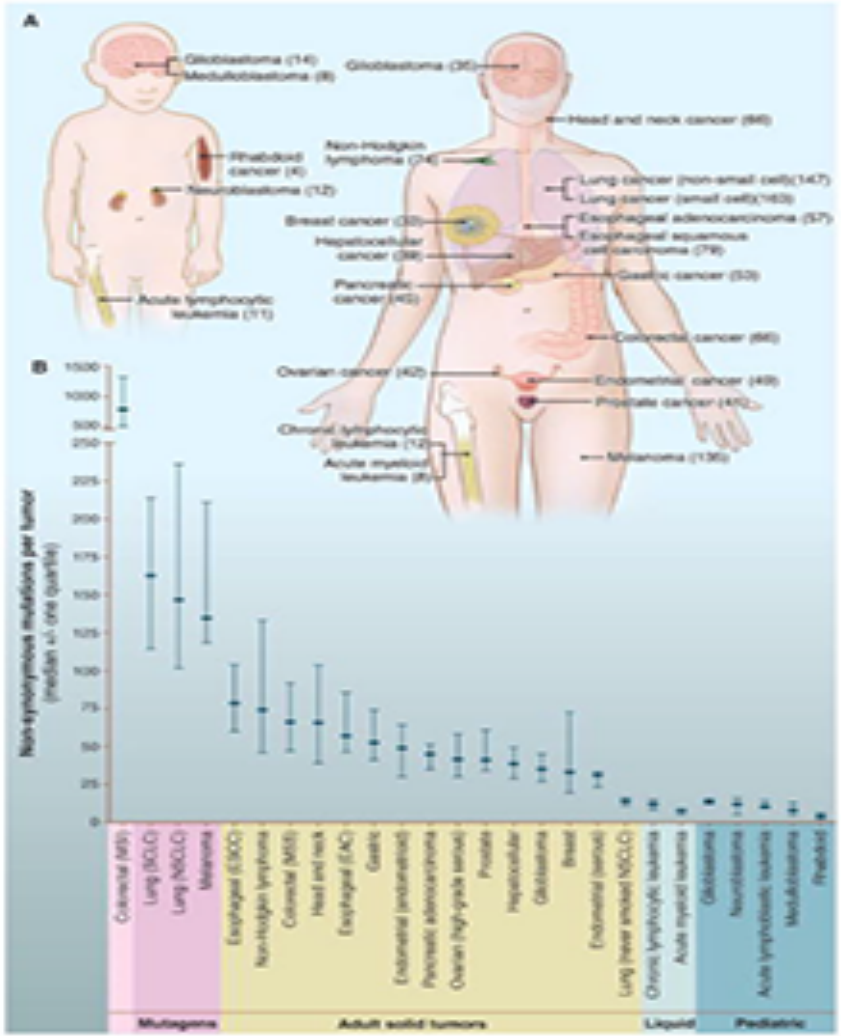


Cancer Letters 5 November 2021

Paradigm shift



Genome landscape

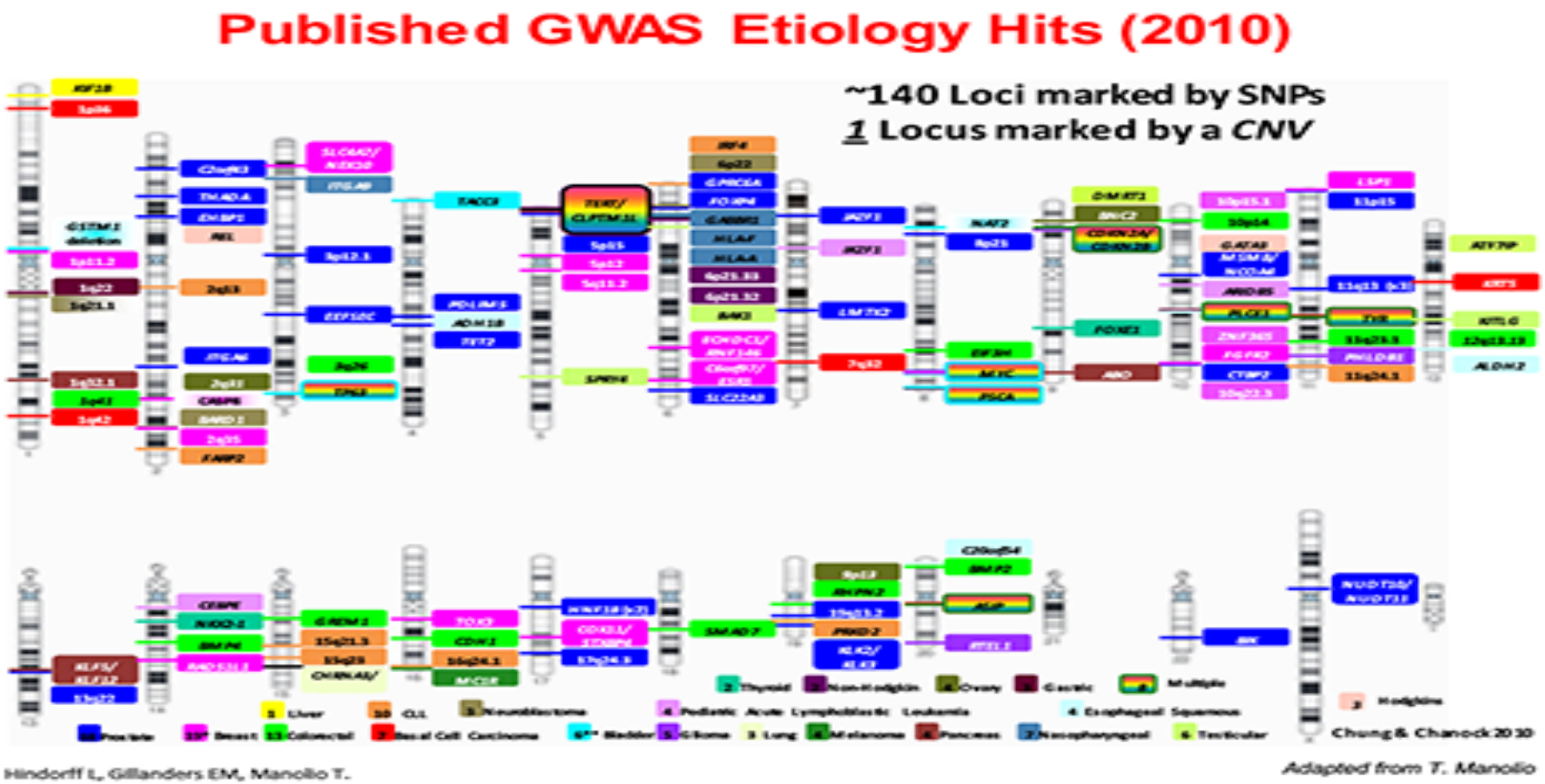


CANCER GENOME LANDSCAPE

Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

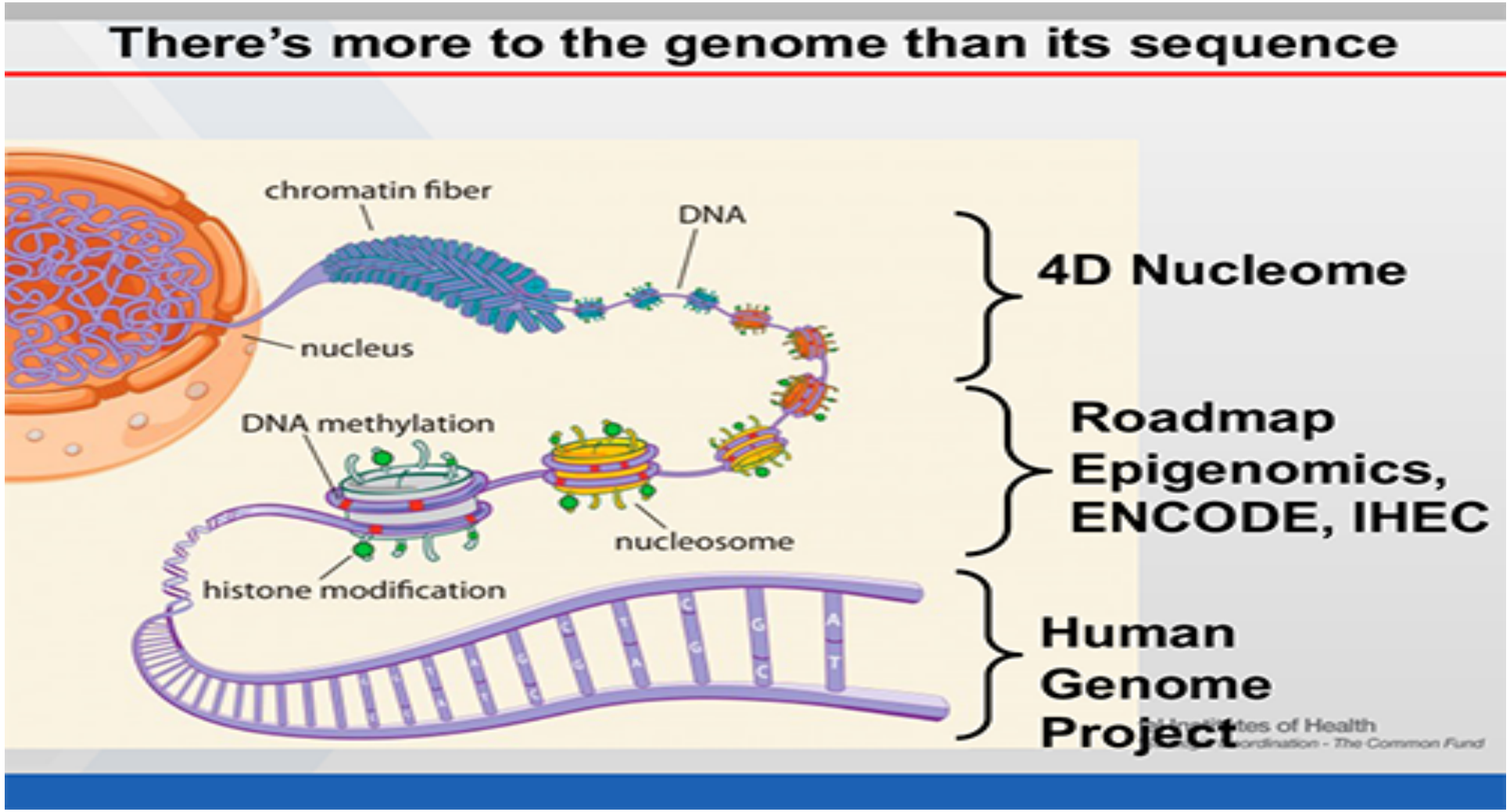
Adapted from Vogelstein and Kinzler (Science 2013)

GWAS hits


Published GWAS Etiology Hits (2010)
~140 Loci marked by SNPs
1 Locus marked by a CNV
Chung & Chanock 2010
Hindorff L, Gillanders EM, Manolio T.
Adapted from T. Manolio

Cancer genes

Genome sequence



Kornberg and nucleosome

Nucleosomes (Units of Chromatin)

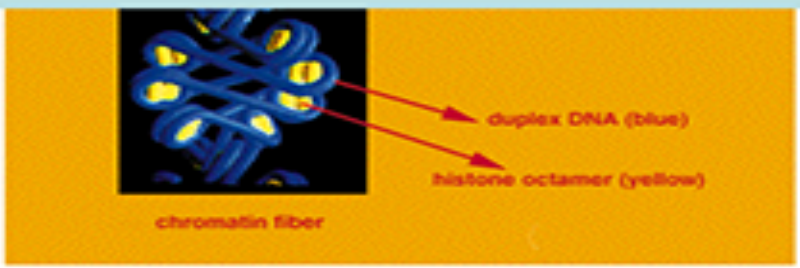
DNA
Histones H2a, H2b, H3, H4

To neutralize charge and provide stability

H1 is a linker histone which binds to the DNA linking two adjacent nucleosomal cores

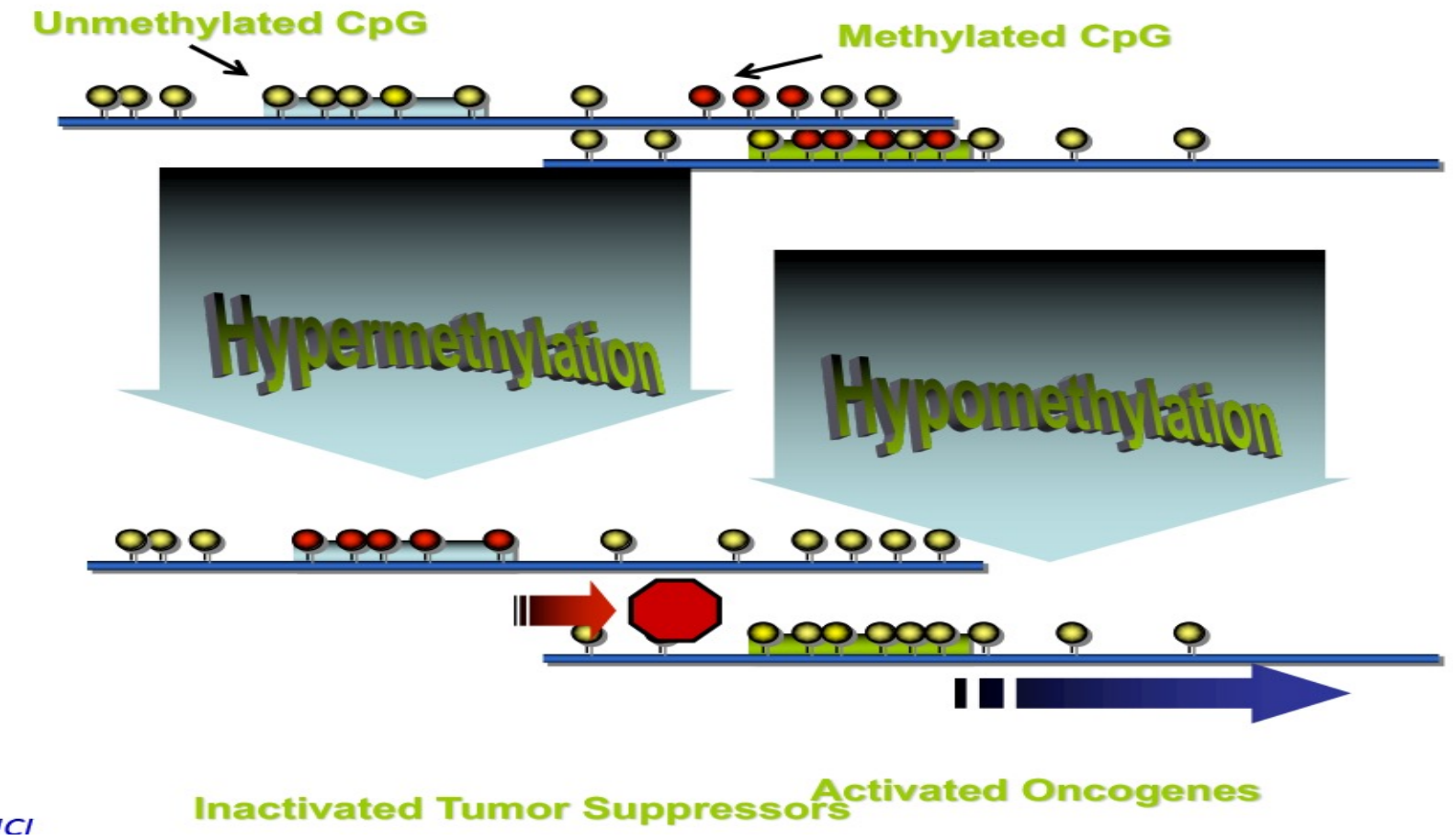
Nucleosome: two turns of DNA (146 base pairs) wrapped around an octomeric complex of two of each of histone types

1974: Roger Kornberg discovers nucleosome who won Nobel Prize in 2006.



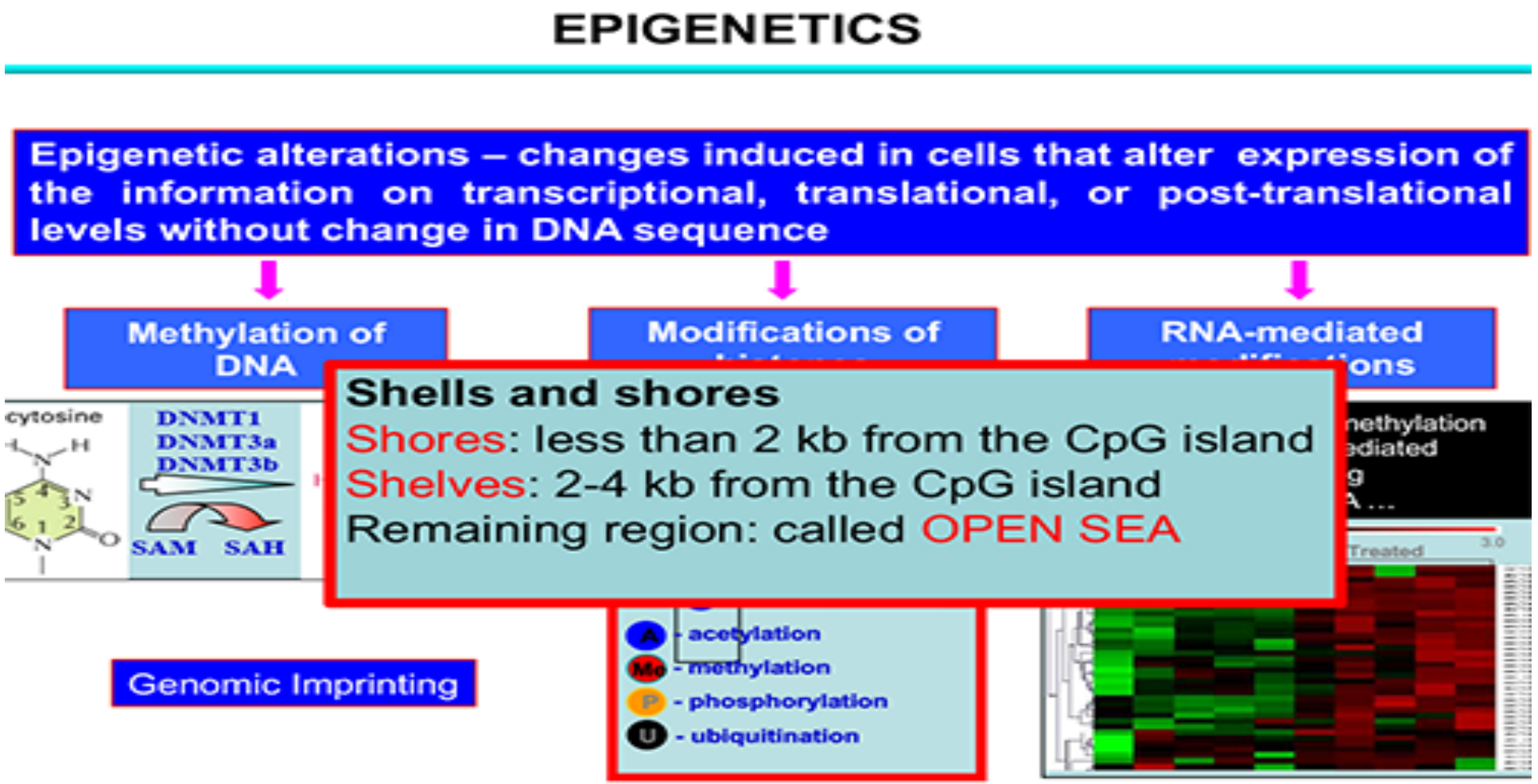
Shores are 0-2kb from islands
Shelves are 2-4 kb and enhancers are beyond shelves

DNA methylation

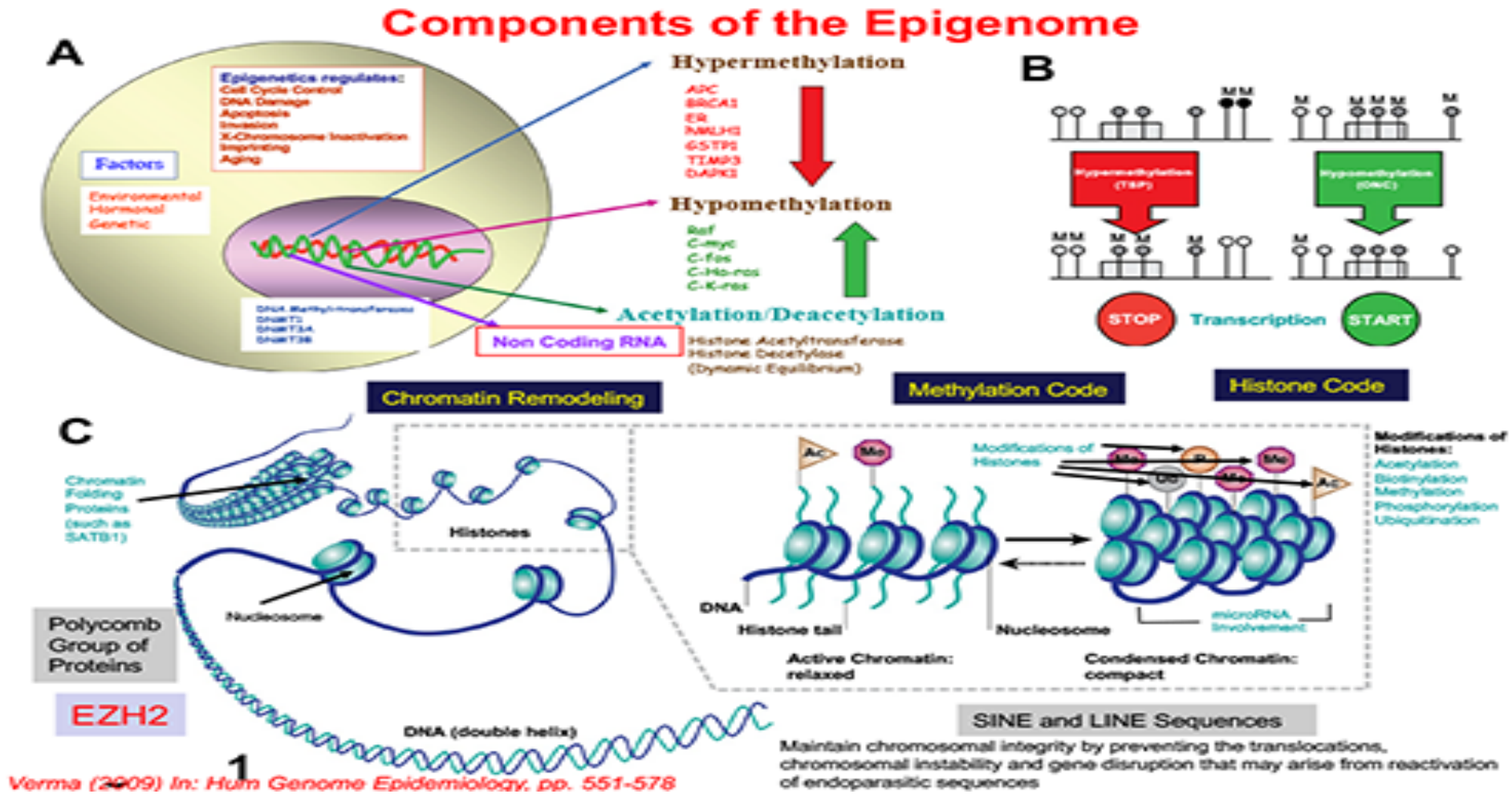


Asad Umar, NCI

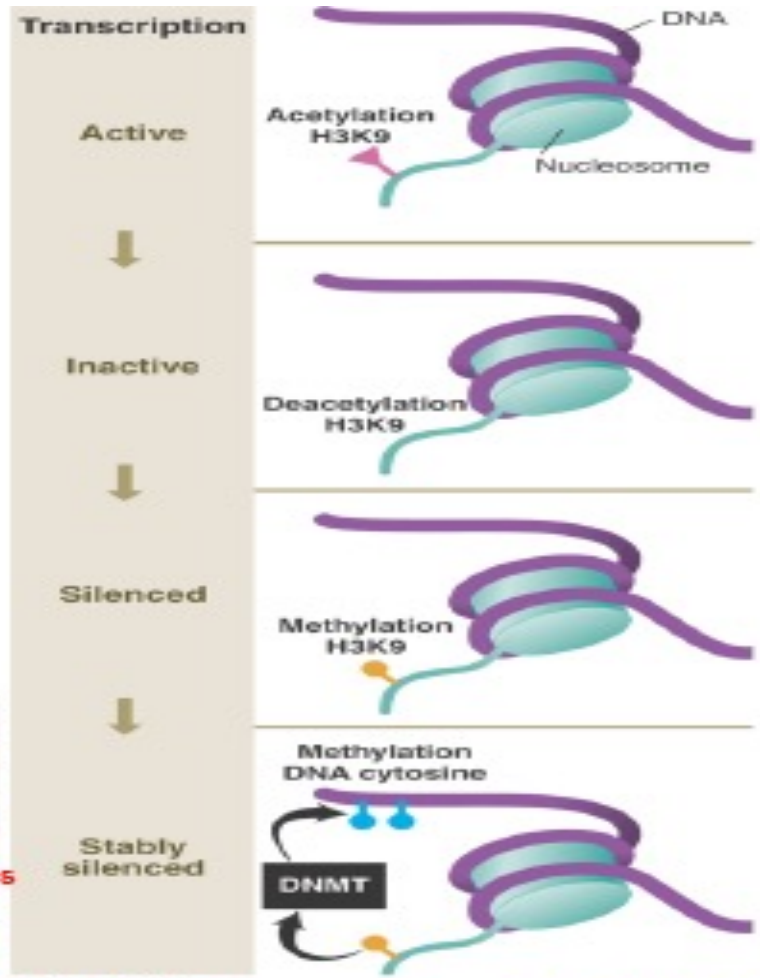
Epigenetics



Epigenome components

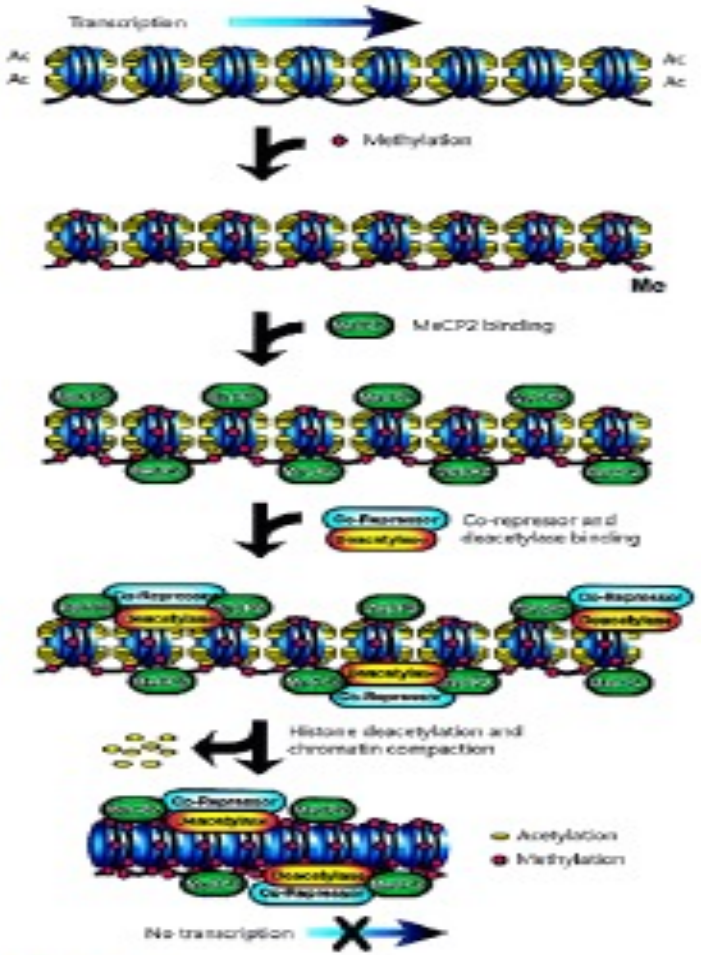


Methylation




Peter Jones


Andrew Feinberg

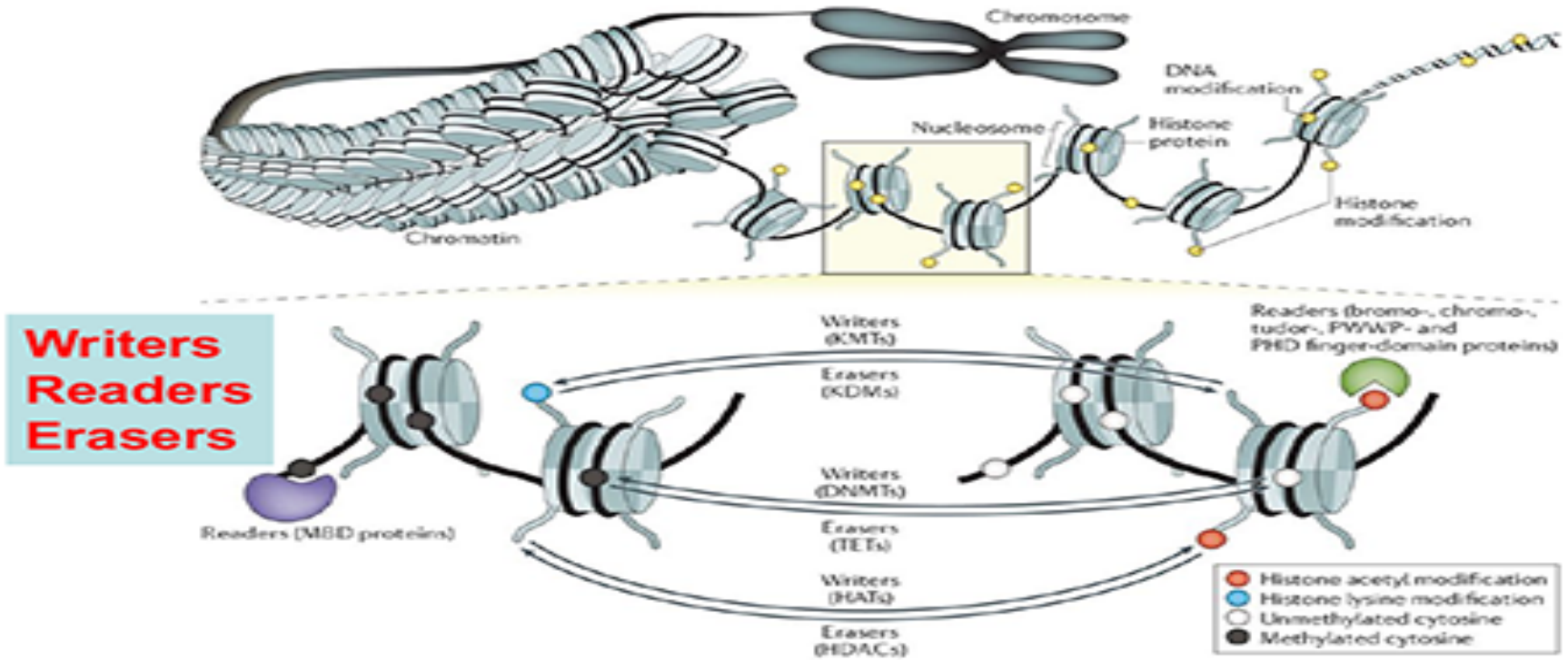


Jones and Laird. *Nat Rev Gen* 21: 163

Chromatin modifications

Figure 1 : Modulation of covalent modifications on chromatin.

From: Targeting the cancer epigenome for therapy



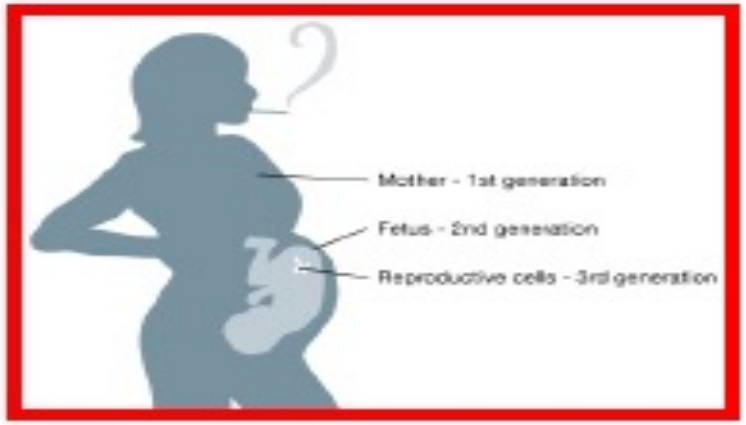
Ten-eleven translocation (TET) family of 5-methylcytosine oxidases.

Exercise


Exercise is important for everyone
portant?
changes
• Drug targeting
You only need to sequence your genome once, but you need to determine your epigenome multiple times...
https://www.youtube.com/watch?v=JMT6oRYgkTk

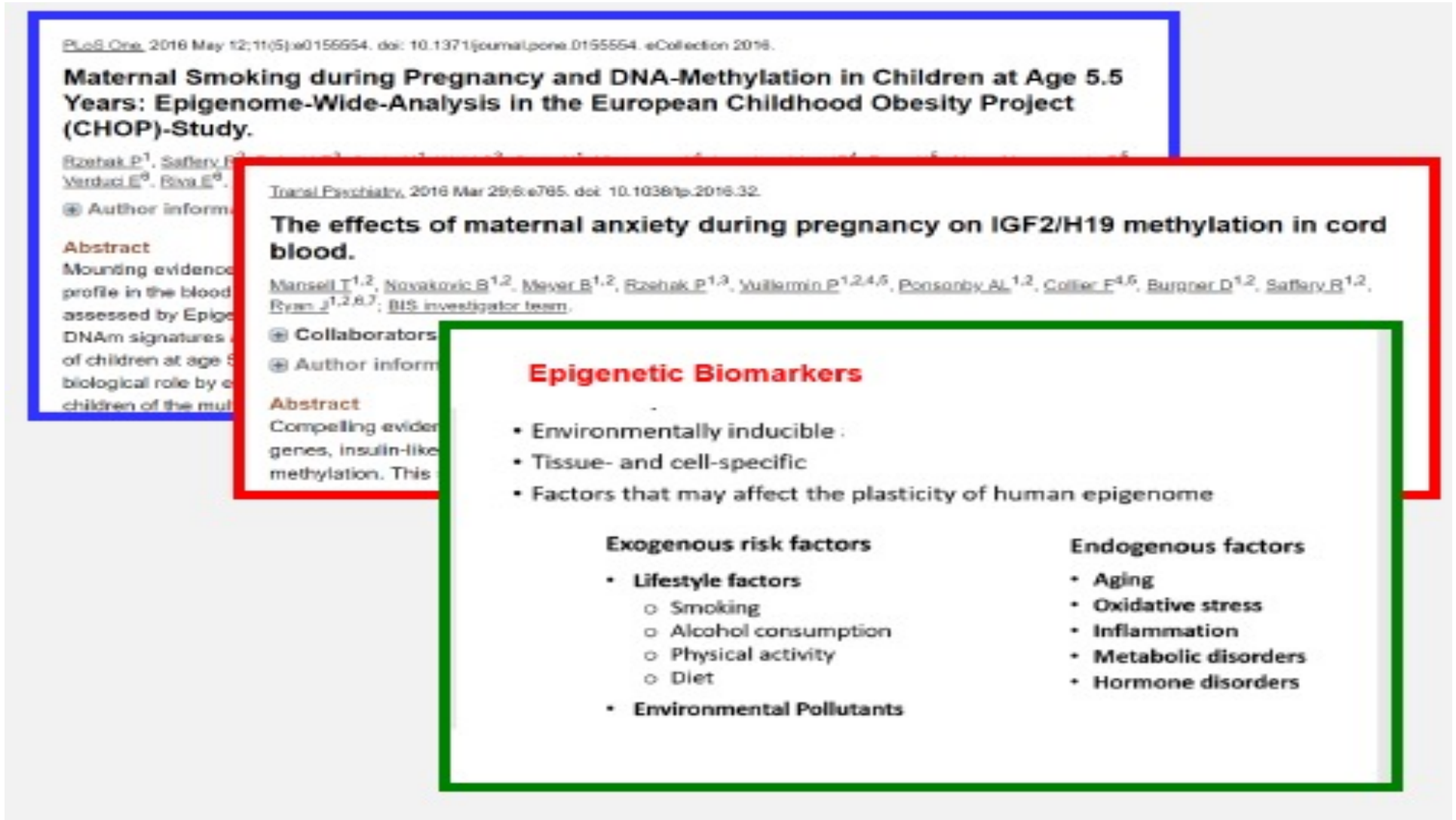
Environment and development

Histone phosphorylation



Aldehyde and nitric oxide, present in cigarette smoke induce phosphorylation of histones resulting in decreased histone deacetylase 2 activity

Endogenous factors



Cancer etiology

Understanding Cancer Etiology and Risk Assessment

Need healthy population (pathologically disease free) (cohort) with information about

- Exposure (Chemicals, Radiations, Infectious Agents, Toxic substance)
- Family History
- Diet and Life Style
- Medication

Need easily collected biospecimens (non-invasive technologies) and analytic tools

Need follow up (for longitudinal studies) for several years

Challenge: Expensive, data sharing

Advantage: Essential to identify risk factors for cancer

Special populations

Special Populations in EGRP

African-American men & women

South American women

Asian-American & Asian men & women

Latin-American/Hispanics

African men & women

Alaskan & Hawaiian Natives

Middle-Eastern populations

American-Indian, incl. Navajo

Rural South

Chinese

EGRP Studies Are Everywhere

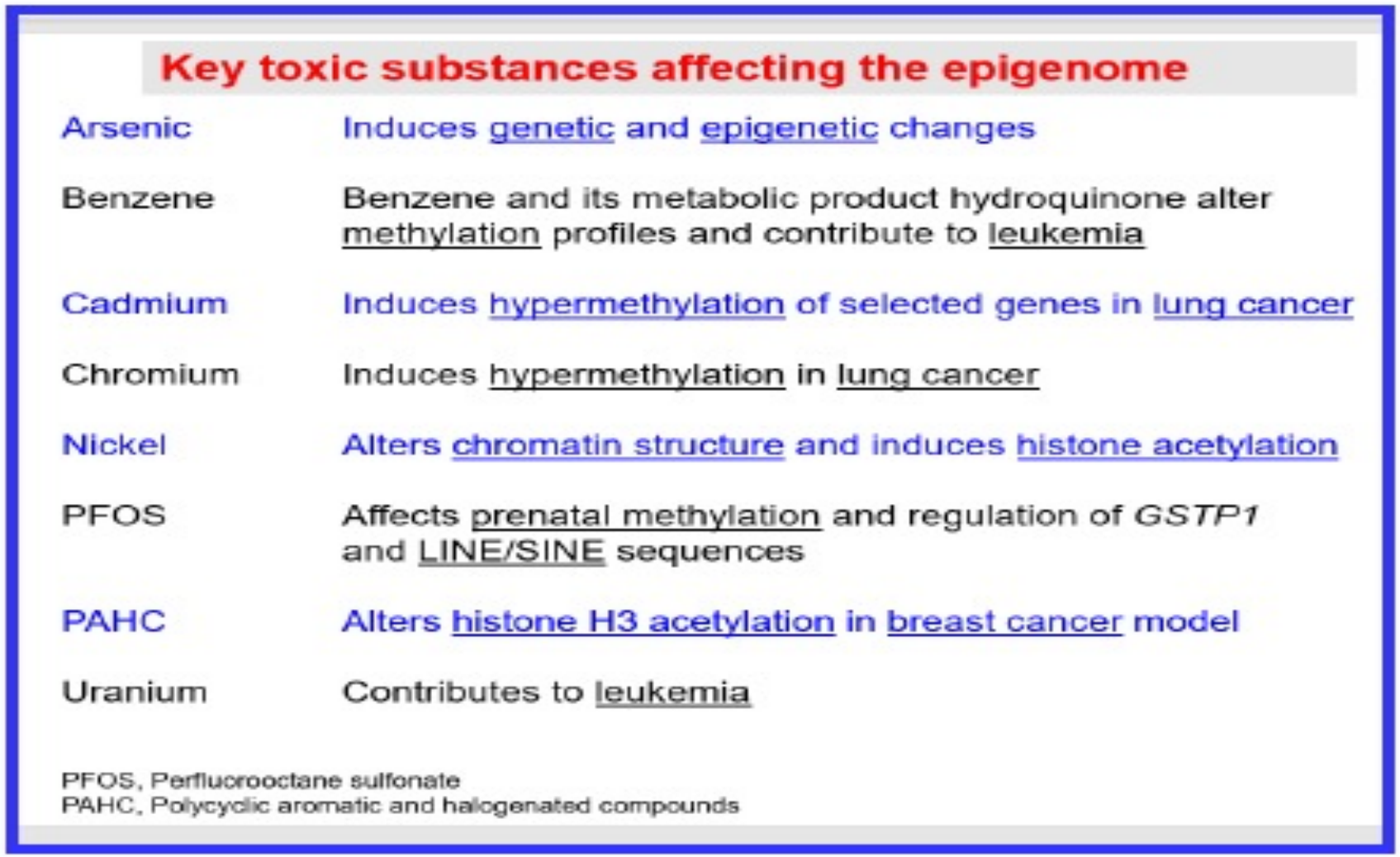
- Senegal
- Malawi
- The Zambia
- China
- Japan
- Egypt
- Israel
- Brazil
- Colombia
- England
- Canada
- Sweden
- Denmark
- France
- Costa Rica
- Singapore
- Poland
- Australia
- U.S., including Alaska & Hawaii

2.3 Million Subjects
Cohorts, CGN and Family Registries

Cohort consortium

- 62 cohorts, over 4 million individuals
- Membership: cohort studies worldwide with >10,000 subjects, blood samples and questionnaire data on important cancer risk factors
- The Cohort Consortium was formed by NCI to address the need for large-scale collaborations for
  - Rapid identification and confirmation of common polymorphisms and cancer susceptibility (GWAS)
  - Studies of GxG and GxE interactions in the etiology of cancer.

Toxic substances



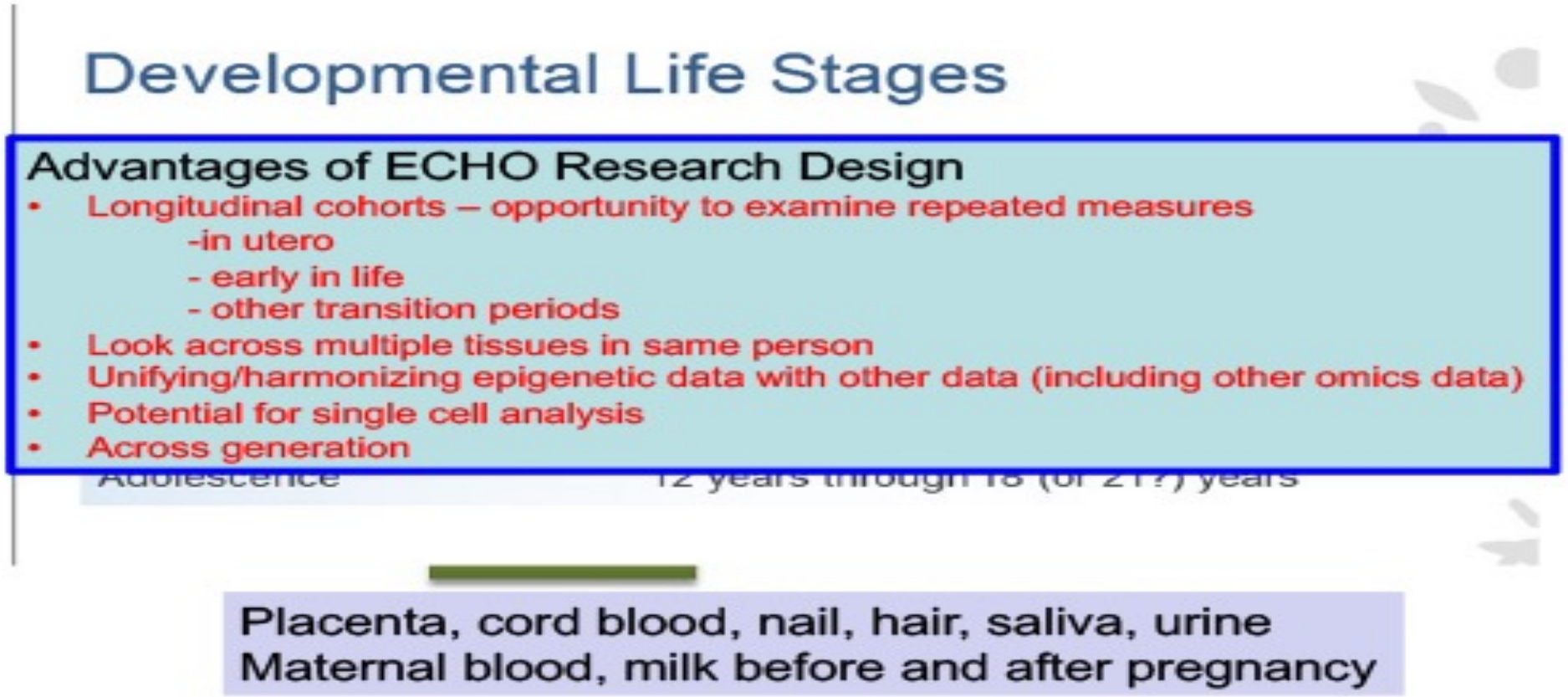
Environment and child health outcomes

Scientific goal

Developmental Life Stages

Placenta, cord blood, nail, hair, saliva, urine
Maternal blood, milk before and after pregnancy

ECHO advantages



Epigenetics and behavior

Epigenetics and behavior (including emotions)

Transl Psychiatry. 2016 Mar 29;6:e765. doi: 10.1038/tp.2016.32.

The effects of maternal anxiety during pregnancy on IGF2/H19 methylation in cord blood.

Mansell T[1,2], Novakovic B[1,2], Meyer B[1,2], Rzehak P[1,3], Vuillermin P[1,2,4,5], Ponsonby AL[1,2], Collier F[4,5], Burgner D[1,2], Saffery R[1,2], Ryan J[1,2,6,7]; BIS investigator team.

⊕ **Collaborators (11)**

⊕ Author information

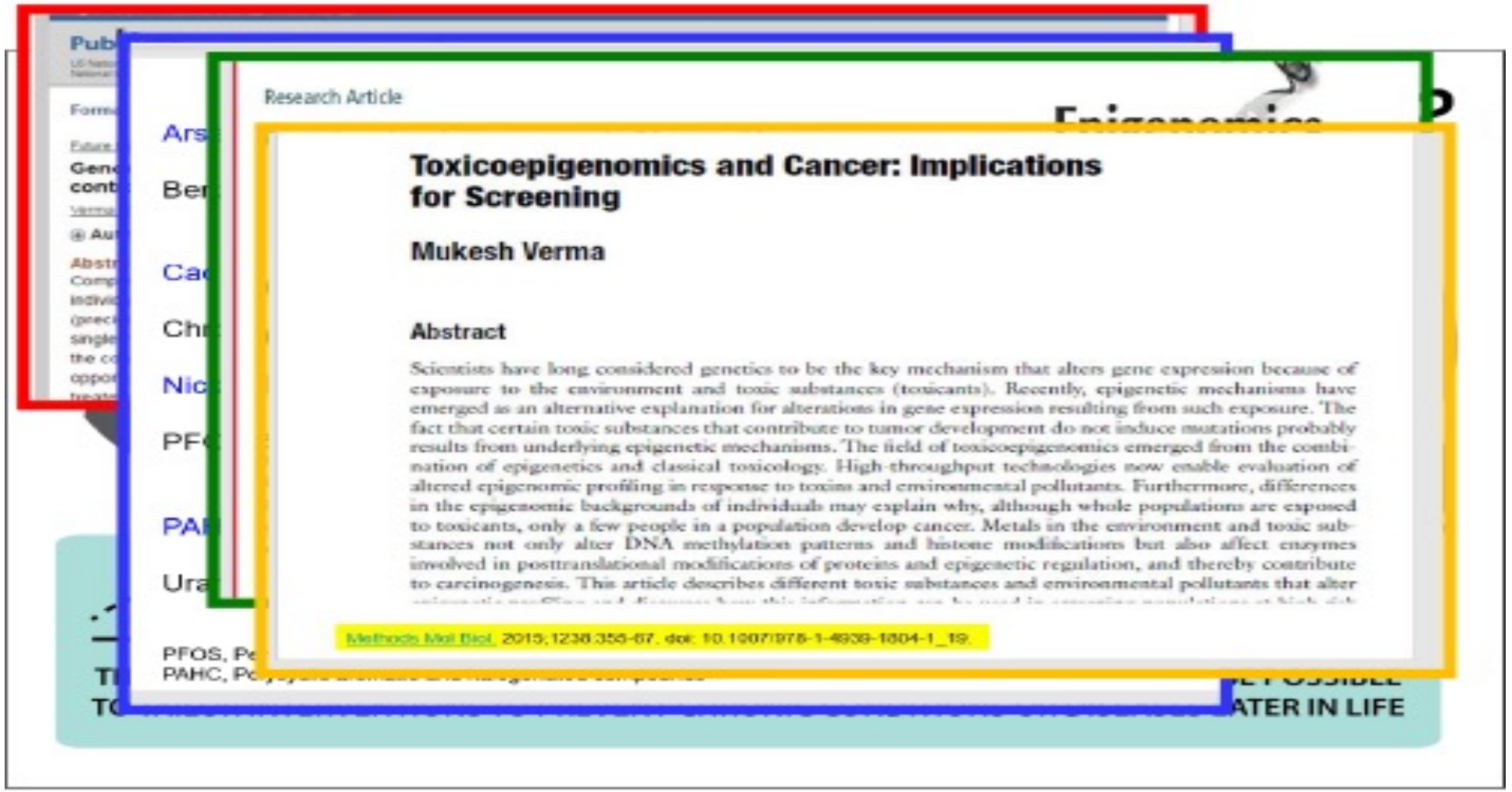
Open/close author information list

Abstract

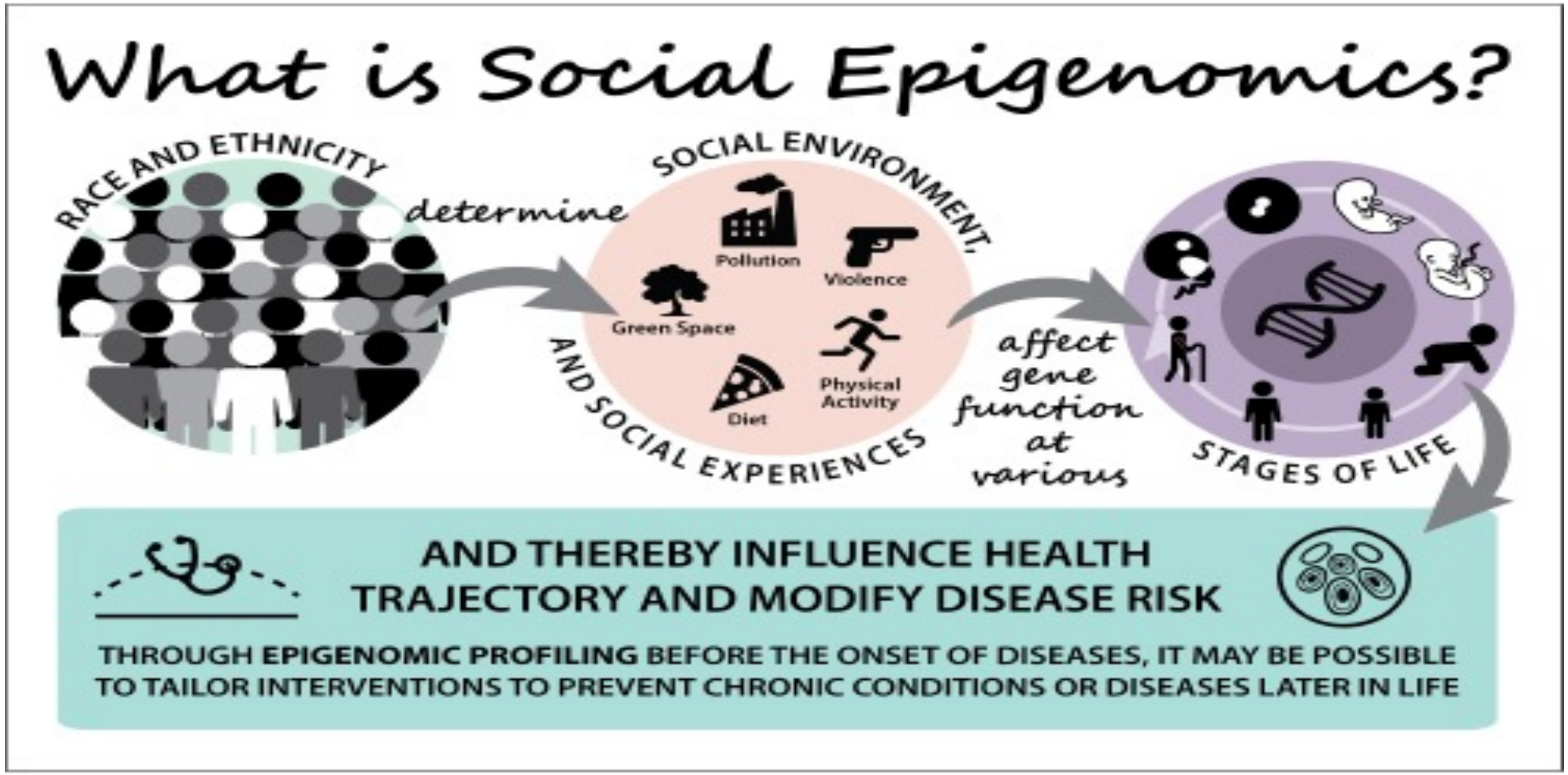
Compelling evidence suggests that maternal mental health in pregnancy can influence fetal development. The imprinted genes, insulin-like growth factor 2 (IGF2) and H19, are involved in fetal growth and each is regulated by DNA methylation. This study aimed to determine the association between maternal mental well-being during pregnancy and differentially methylated regions (DMRs) of IGF2 (DMR0) and the IGF2/H19 imprinting control region (ICR) in newborn offspring. Maternal depression, anxiety and perceived stress were assessed at 28 weeks of pregnancy in the Barwon Infant Study (n=576). DNA methylation was measured in purified cord blood mononuclear cells using the Sequenom

within your DNA that can be controlled by you, by your emotions, beliefs and behavioral choices."

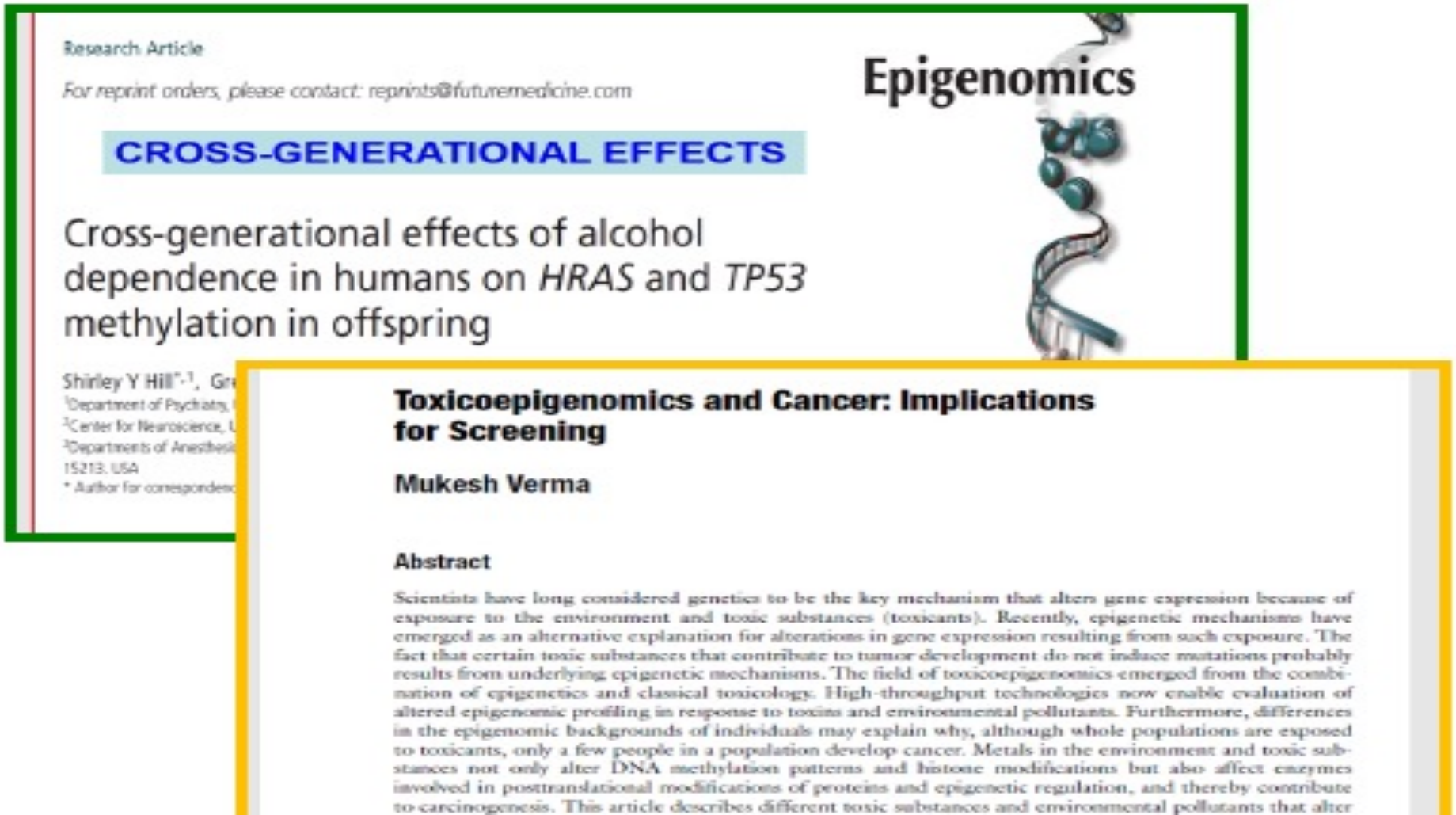
Toxico epigenomics



Social epigenomics



Epigenomics



Research Article

For reprint orders, please contact: reprints@futuremedicine.com

CROSS-GENERATIONAL EFFECTS

Cross-generational effects of alcohol dependence in humans on *HRAS* and *TP53* methylation in offspring

Epigenomics

Shirley Y Hill*,[1], Gr

[1]Department of Psychiatry,

[2]Center for Neuroscience, U

[3]Department of Anesthesi

15213, USA

* Author for correspondenc

Toxicoepigenomics and Cancer: Implications for Screening

Mukesh Verma

Abstract

Scientists have long considered genetics to be the key mechanism that alters gene expression because of exposure to the environment and toxic substances (toxicants). Recently, epigenetic mechanisms have emerged as an alternative explanation for alterations in gene expression resulting from such exposure. The fact that certain toxic substances that contribute to tumor development do not induce mutations probably results from underlying epigenetic mechanisms. The field of toxicoepigenomics emerged from the combination of epigenetics and classical toxicology. High-throughput technologies now enable evaluation of altered epigenomic profiling in response to toxins and environmental pollutants. Furthermore, differences in the epigenomic backgrounds of individuals may explain why, although whole populations are exposed to toxicants, only a few people in a population develop cancer. Metals in the environment and toxic substances not only alter DNA methylation patterns and histone modifications but also affect enzymes involved in posttranslational modifications of proteins and epigenetic regulation, and thereby contribute to carcinogenesis. This article describes different toxic substances and environmental pollutants that alter

Loss (or gain) of gene function in cancer

Loss (or Gain) of gene function in cancer

Most permanent → Most dynamic

Genetic

- Deletion
- Point mutations
- Amplification
- Chromosomal Translocation (Ig rearrangement)

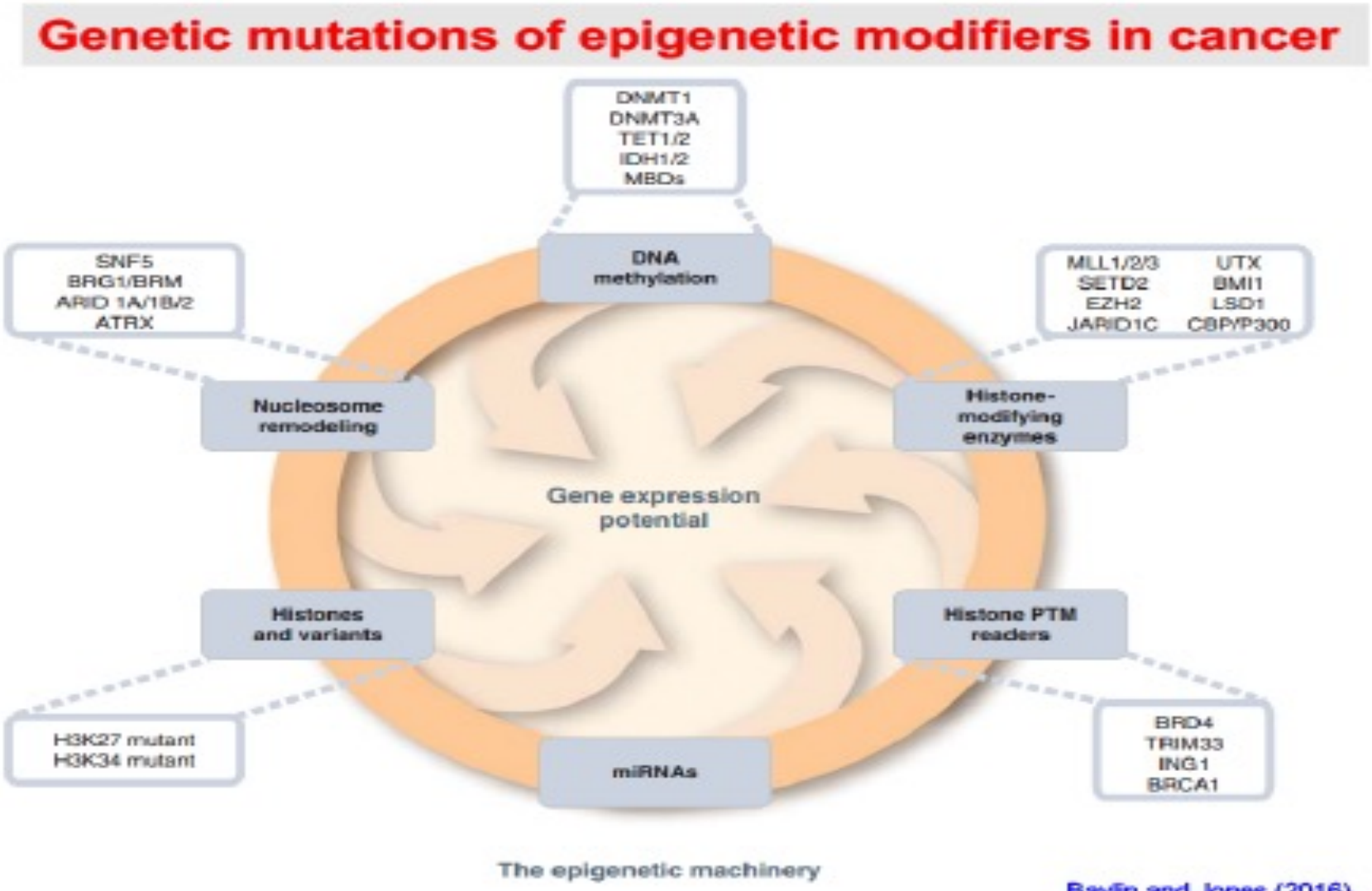
Epigenetic

- Chromatin Changes
- Promoter Methylation Silencing

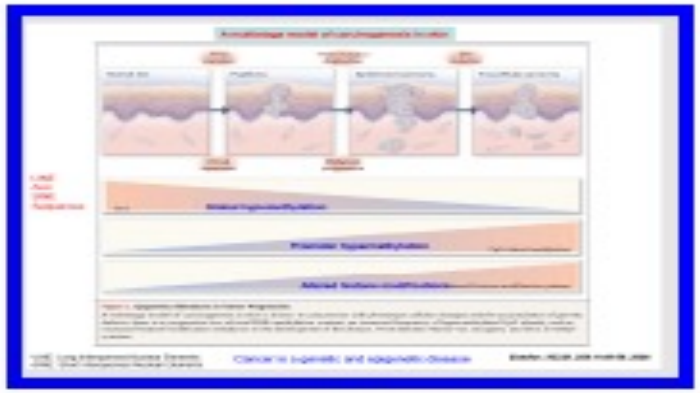
Transcription Factor Changes

Cell-cycle Regulated Changes

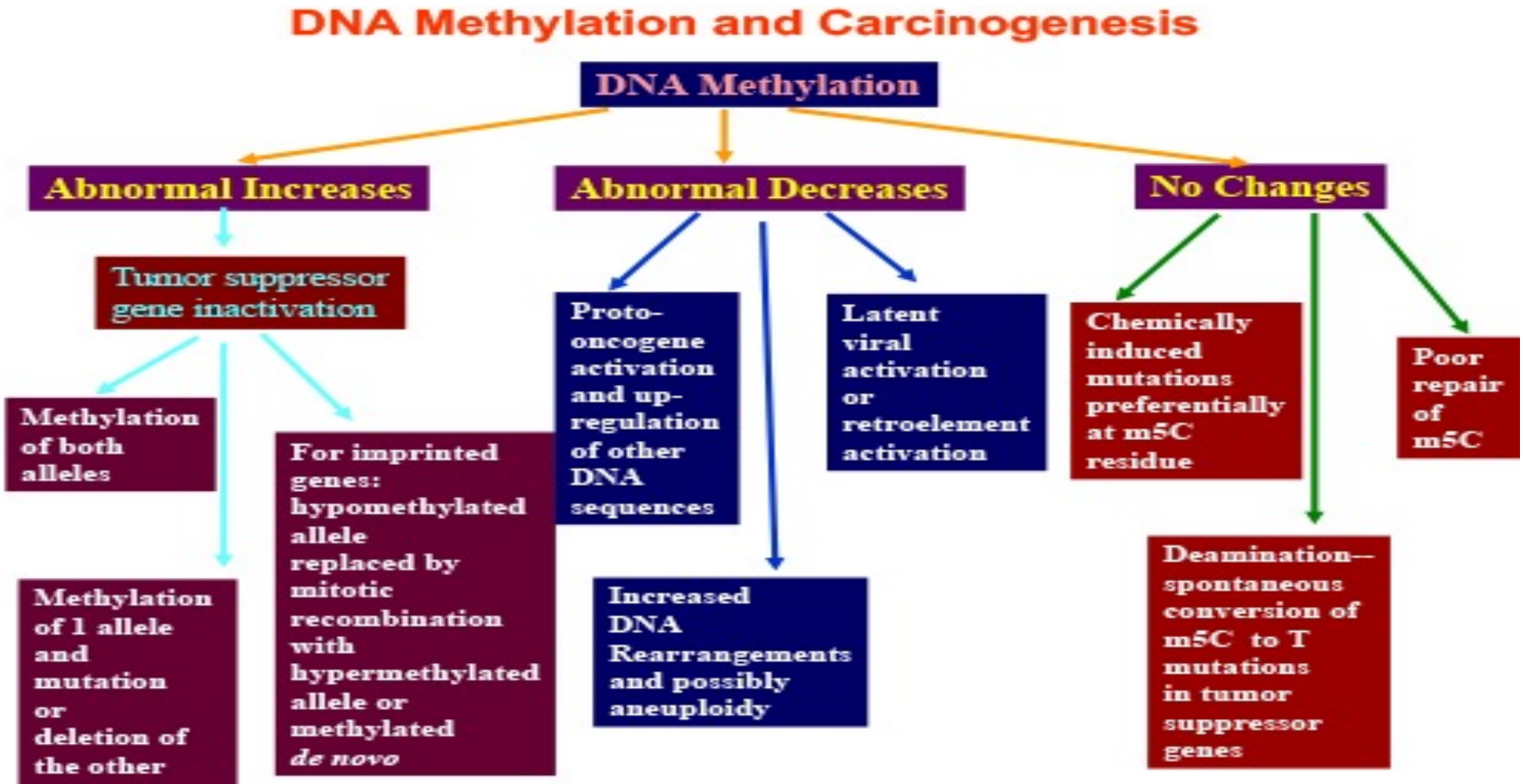
Genetic mutations



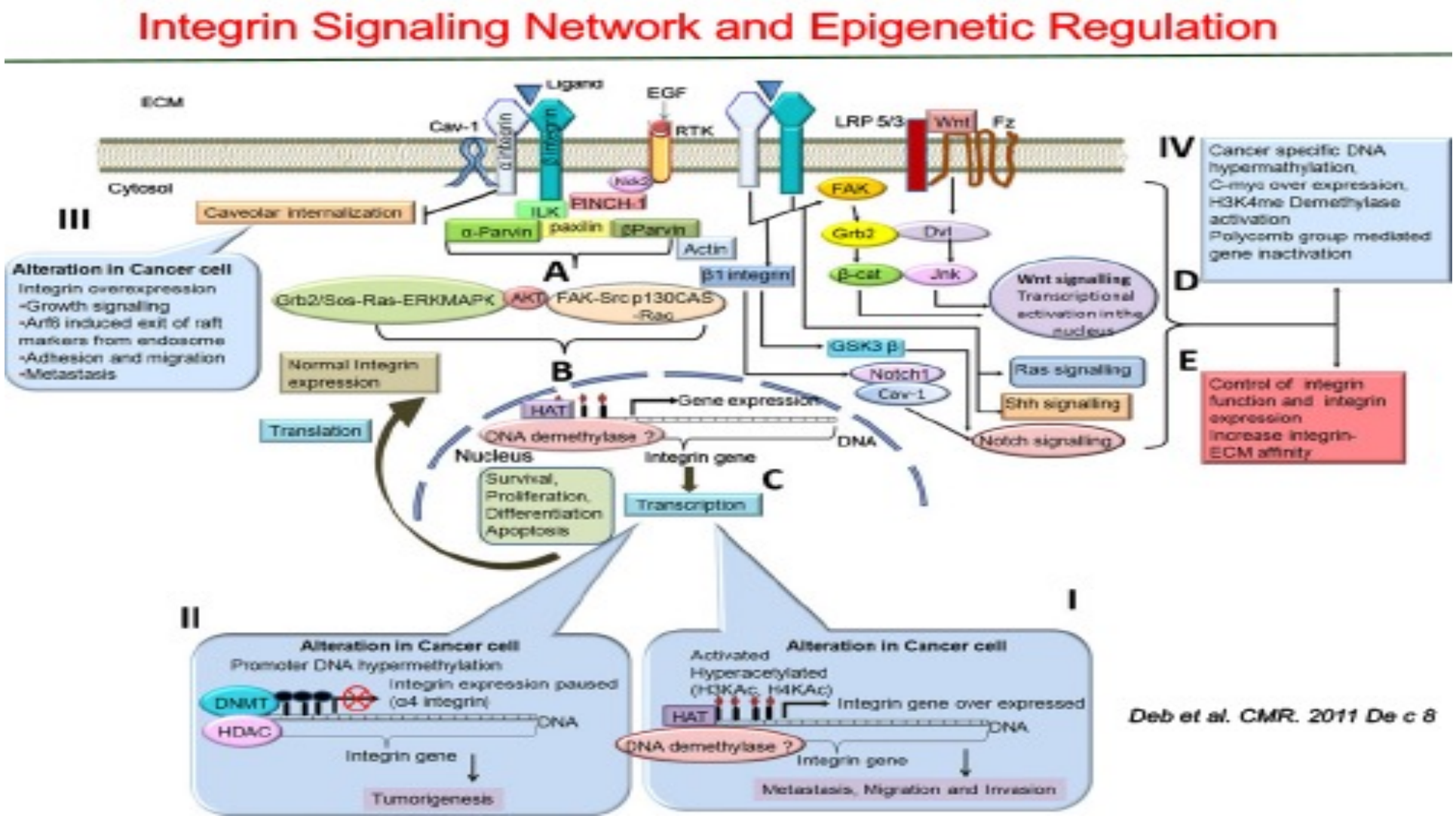
Hypomethylation



DNA methylation and carcinogenesis

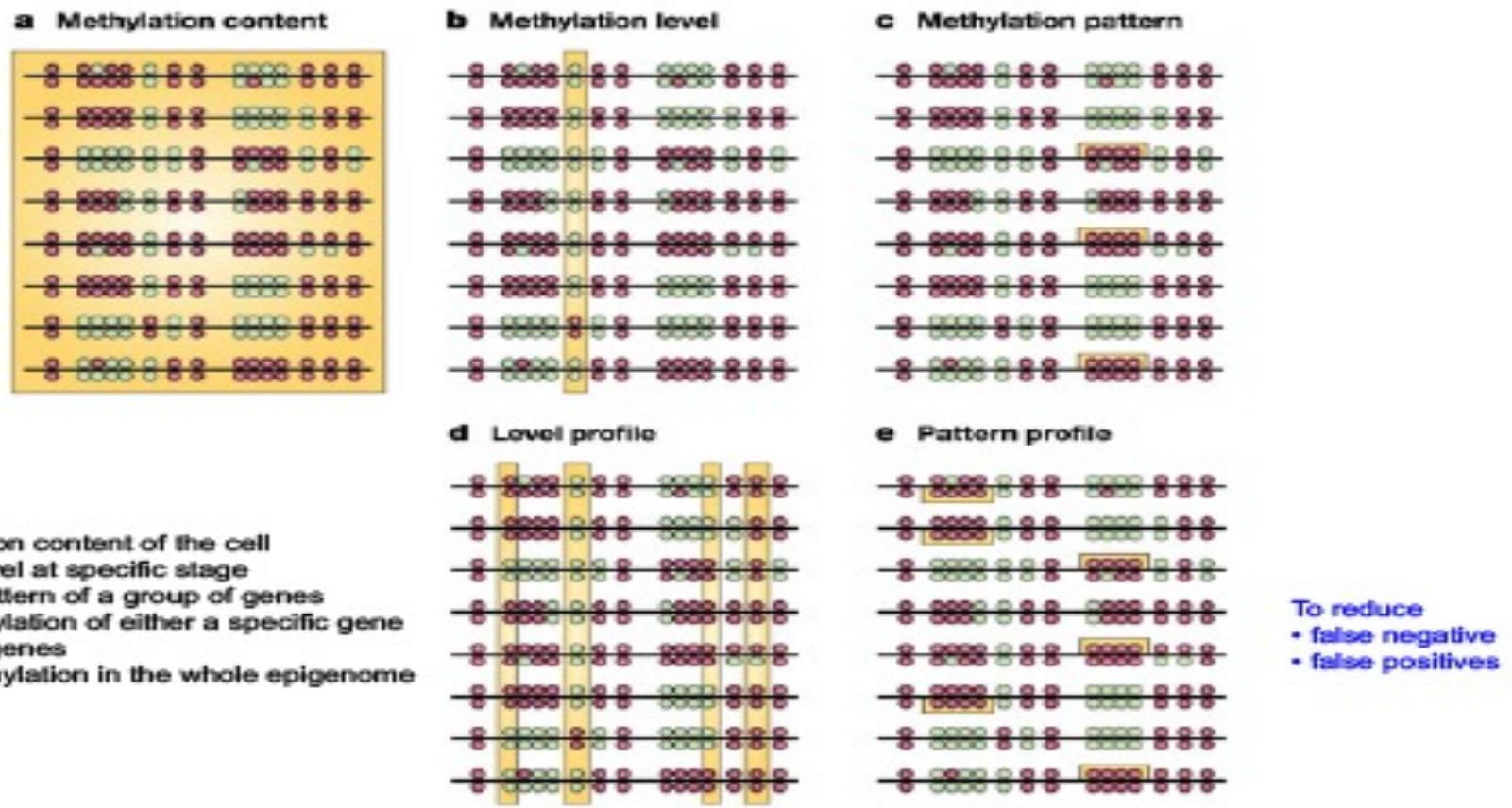


Integrin signaling



Deb et al. CMR. 2011 De c 8

Methylation

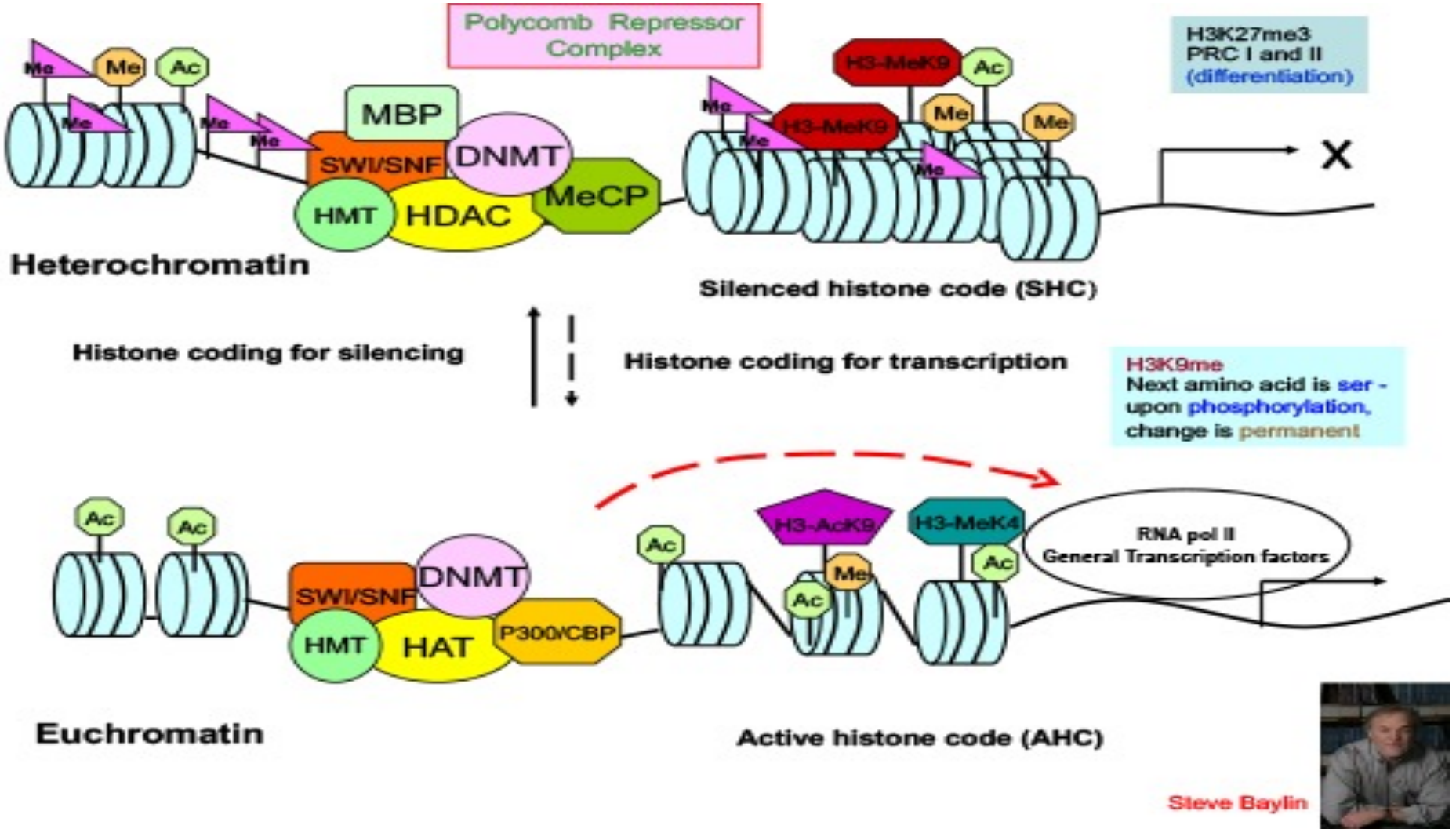


- Total methylation content of the cell
- methylation level at specific stage
- methylation pattern of a group of genes
- profile of methylation of either a specific gene or a number of genes
- pattern of methylation in the whole epigenome

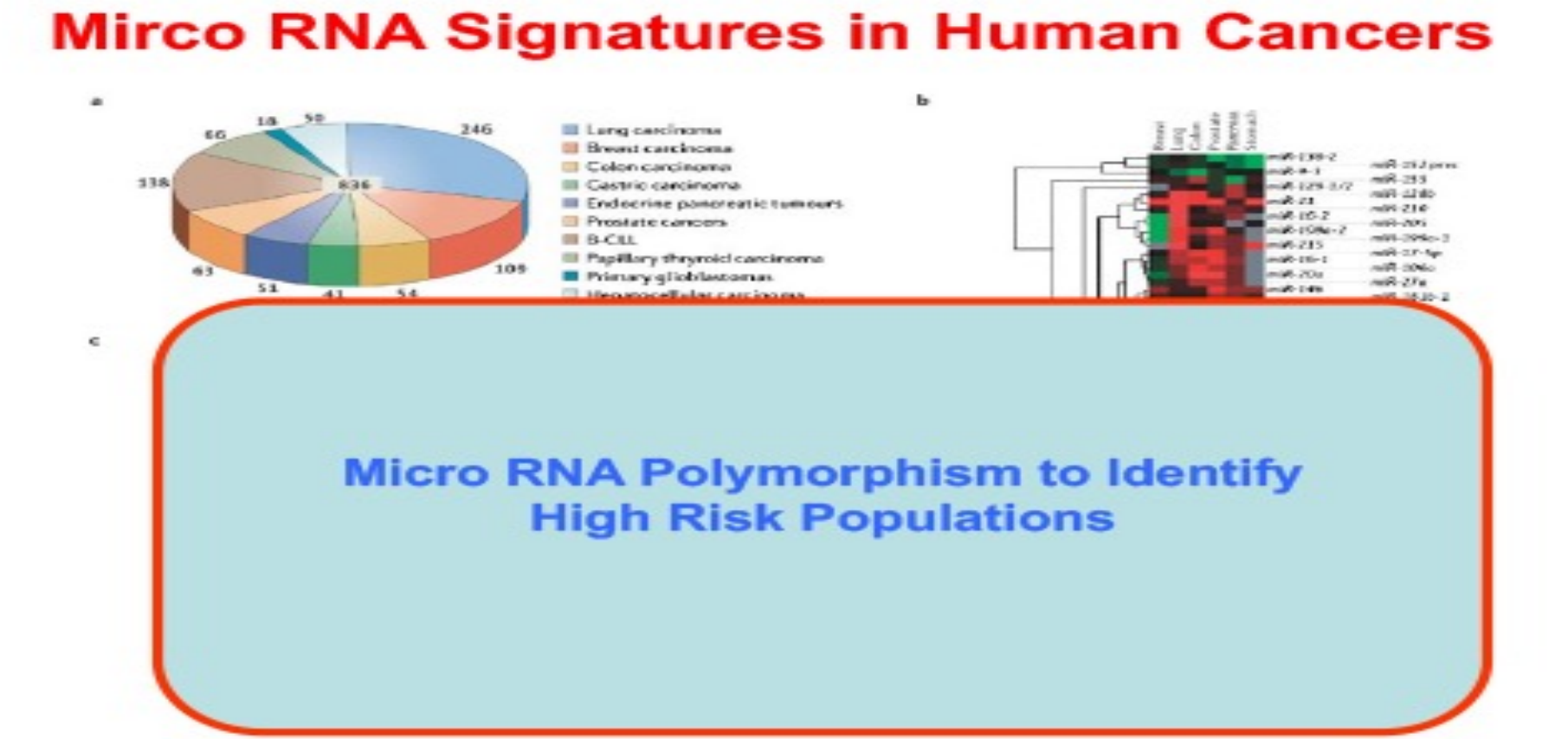
To reduce
- false negative
- false positives

Laird *Nat Rev Cancer* 3:253

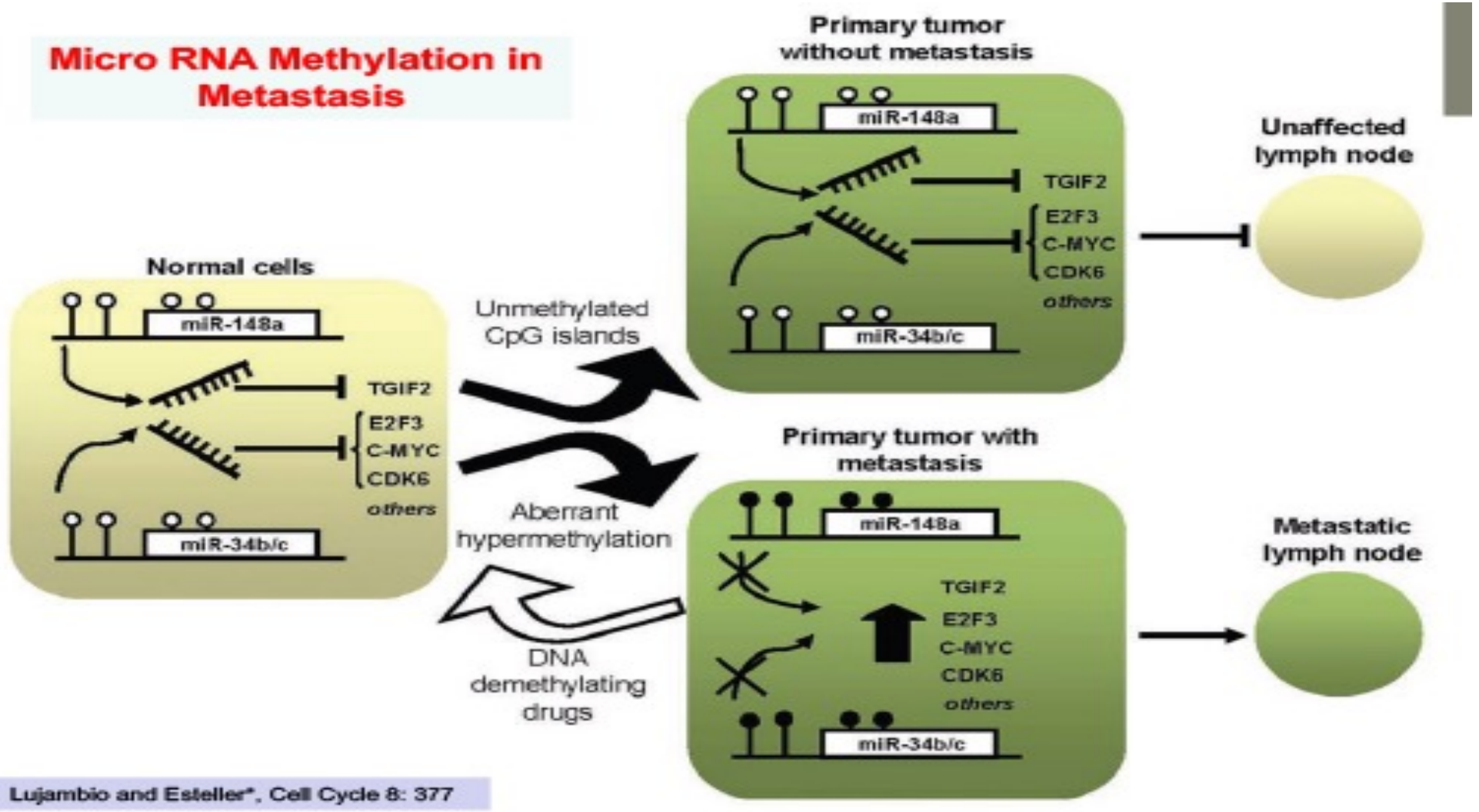
Histone acetylation



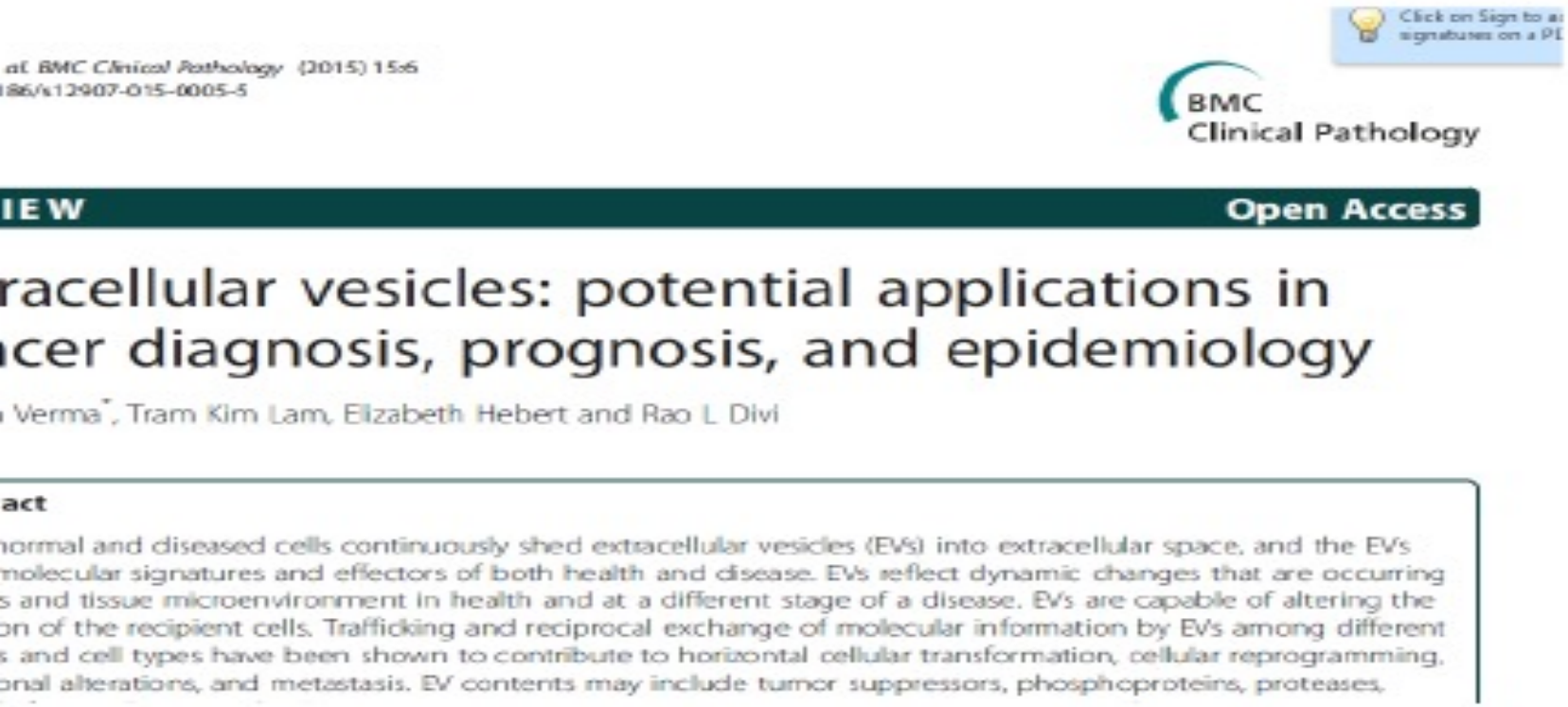
Micro RNA signatures



Micro RNA methylation



Extracellular vesicles



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signatures on a PI

al. BMC Clinical Pathology (2015) 15:6
186/s12907-015-0005-5

BMC
Clinical Pathology

IEW Open Access

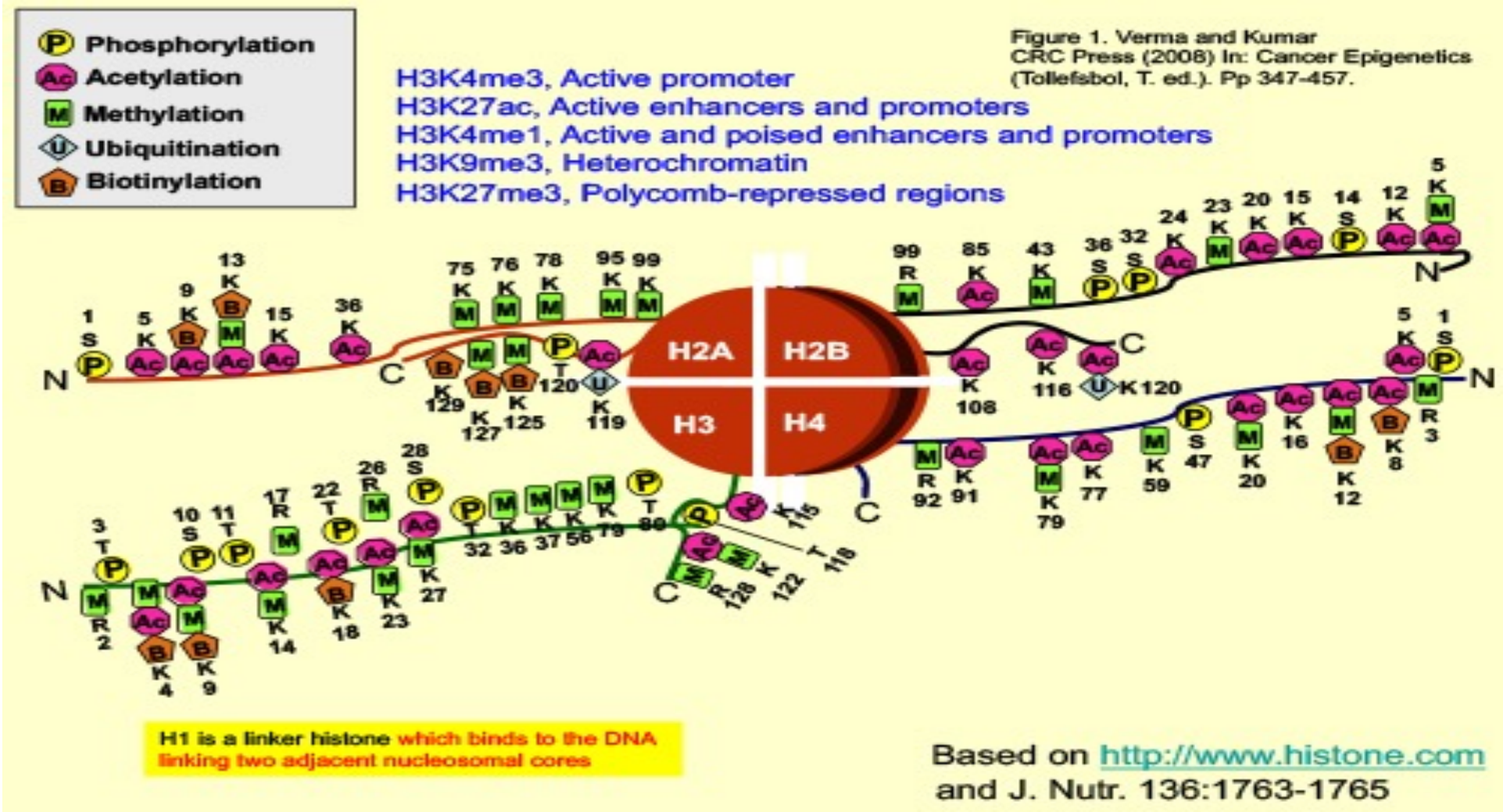
racellular vesicles: potential applications in
ncer diagnosis, prognosis, and epidemiology

Verma*, Tram Kim Lam, Elizabeth Hebert and Rao L Divi

act

normal and diseased cells continuously shed extracellular vesicles (EVs) into extracellular space, and the EVs
molecular signatures and effectors of both health and disease. EVs reflect dynamic changes that are occurring
s and tissue microenvironment in health and at a different stage of a disease. EVs are capable of altering the
on of the recipient cells. Trafficking and reciprocal exchange of molecular information by EVs among different
s and cell types have been shown to contribute to horizontal cellular transformation, cellular reprogramming,
onal alterations, and metastasis. EV contents may include tumor suppressors, phosphoproteins, proteases,

Histone modifications



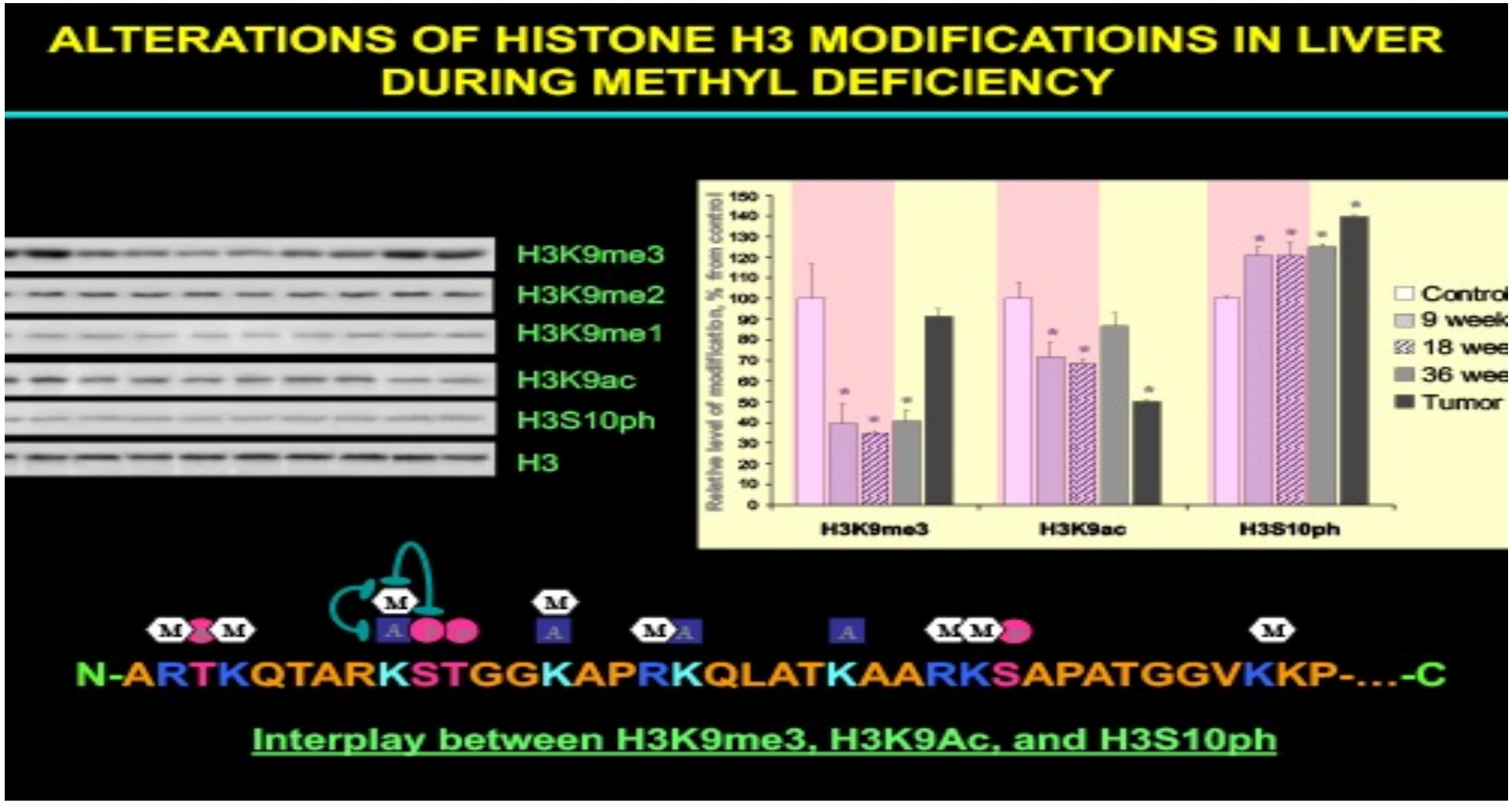
Histones

Clin Epigenetics. 2016; 8: 57

Activating: e.g. H3K4me3

Silencing: e.g. H3K9me3, H3K27me3

Histone H3 modifications



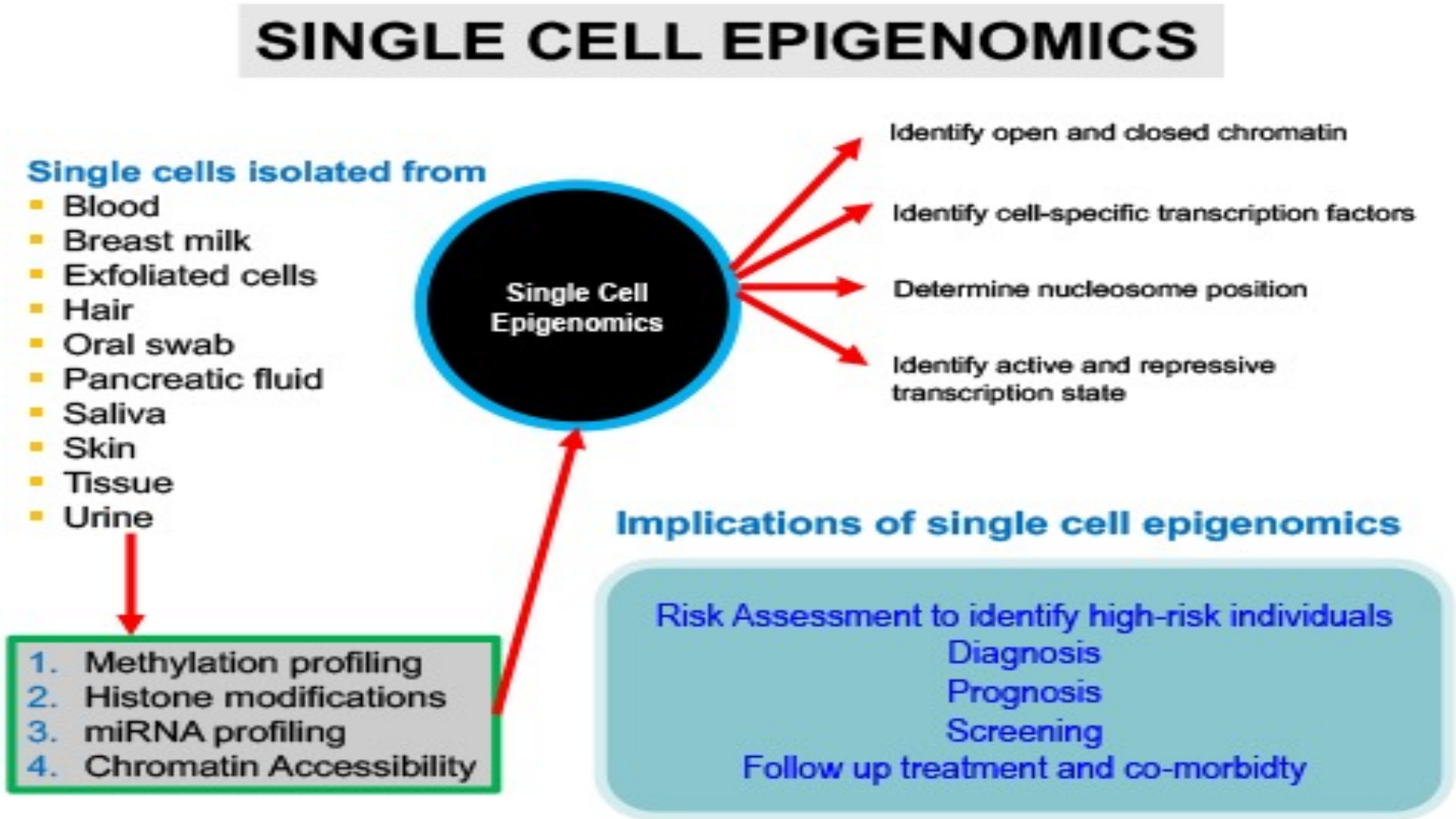
Epigenetic regulation

Epigenetic Gene Regulation:

Modification		Methylation			Acetylation
		Mono-methylation	Di-methylation	Tri-methylation	
DNA		Repression	--	--	--
Histone	H3K4	Activation	Activation	Activation	--
	H3K9	Activation	Repression	Repression	Activation
	H3K27	Activation	Repression	Repression	--
	H3K36	--	Repair	Activation	Activation
	H3K79	Activation	Activation	Activation Repression	--
	H3R17	--	Activation	--	--
	H4K5	--	--	--	Activation
	H4K8	--	--	--	Activation
	H4K12	--	--	--	Activation
	H4K16	--	--	--	Activation
	H4K20	Activation	Activation	Repression	--
	H4K16	--	--	--	Activation

Abnova

Single cell epigenomics



Histone modifications

20 Diagnosing Cancer Using Histone Modification Analysis

Mukesh Verma and Deepak Kumar

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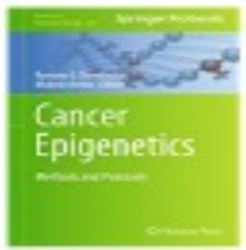
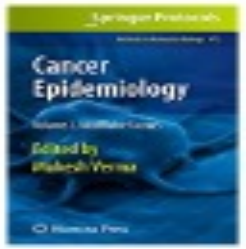
ISBN 9781420045796 - CAT# 45792

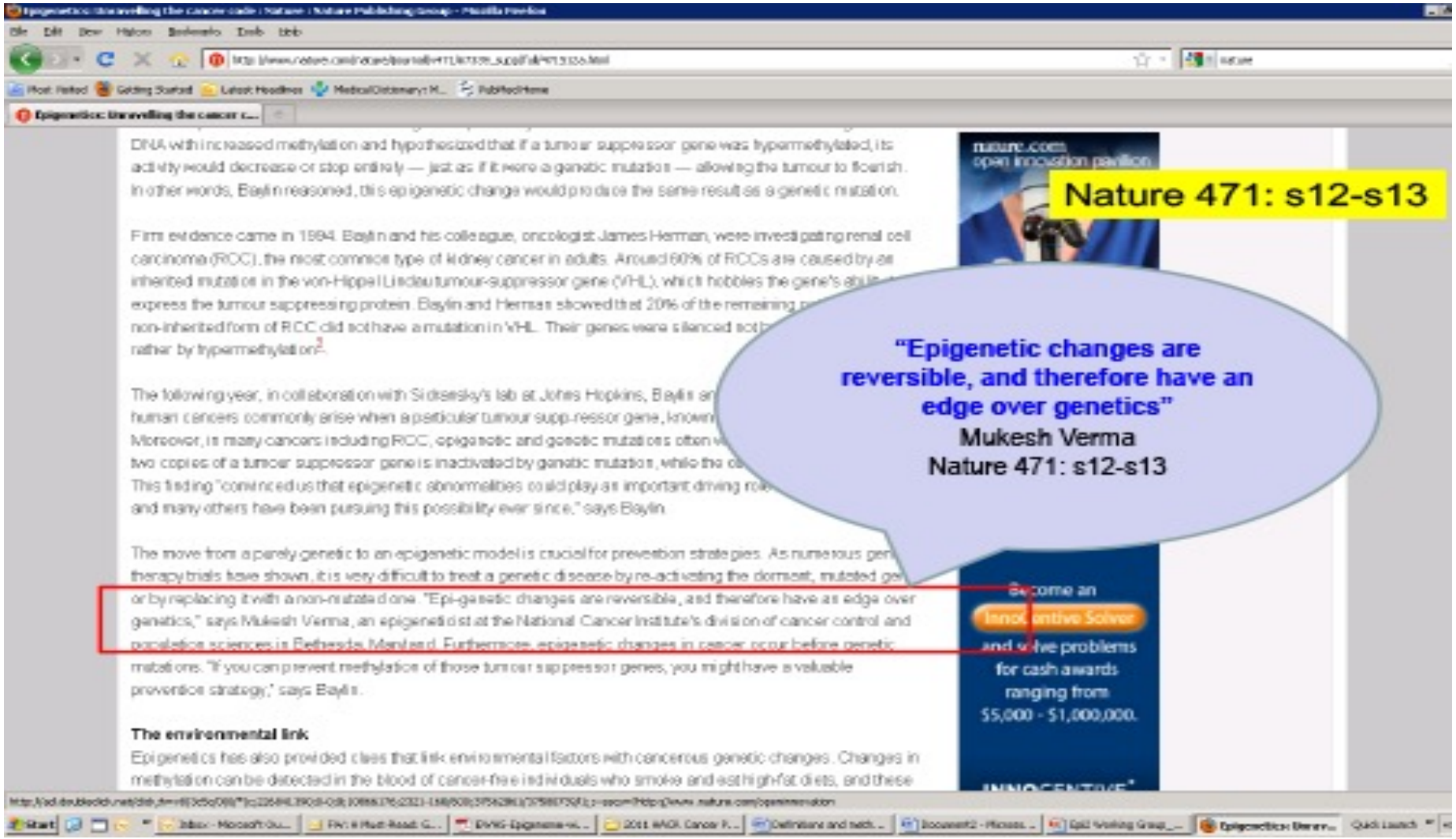
Books



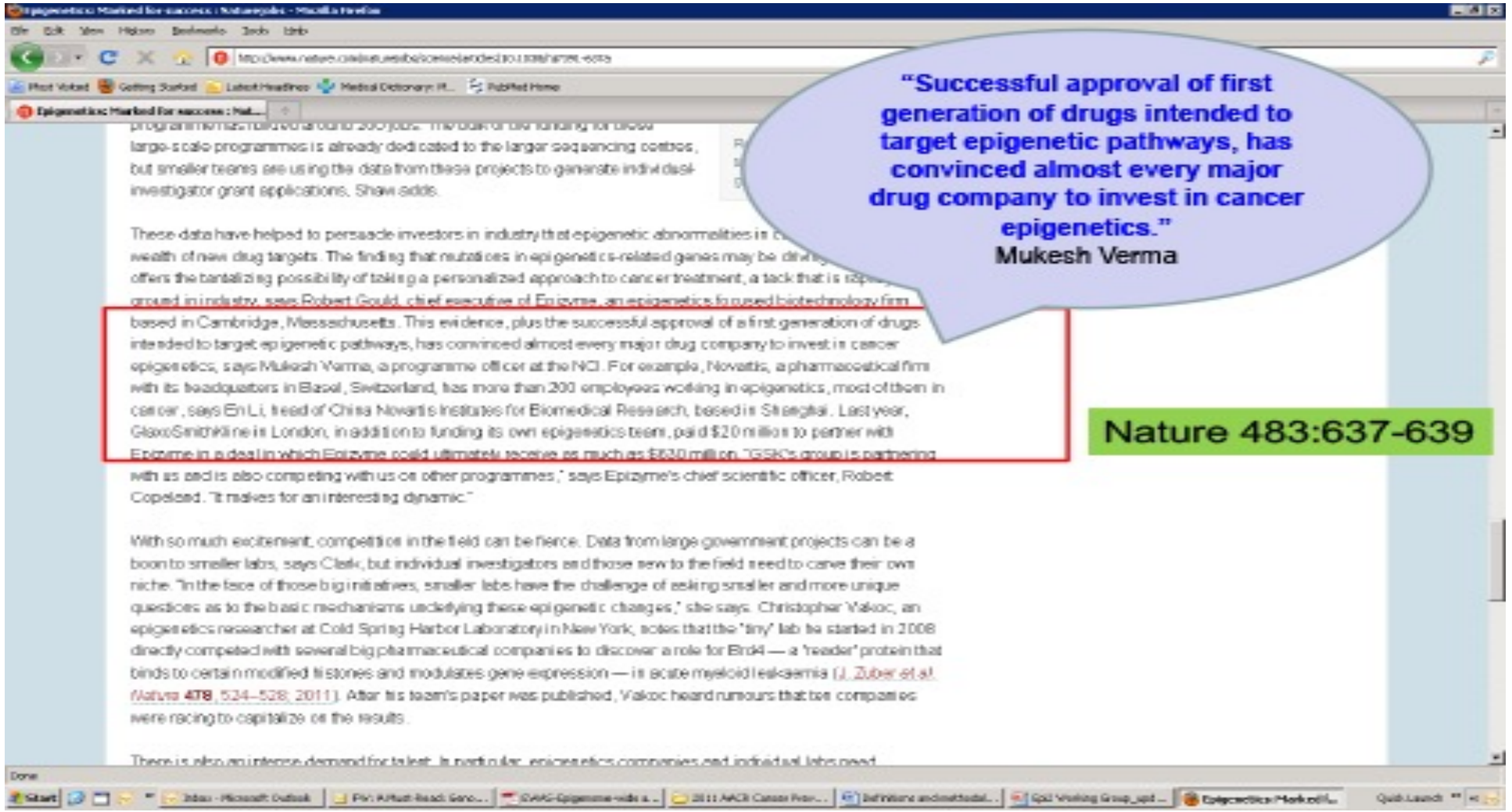


Books edited by Mukesh Verma

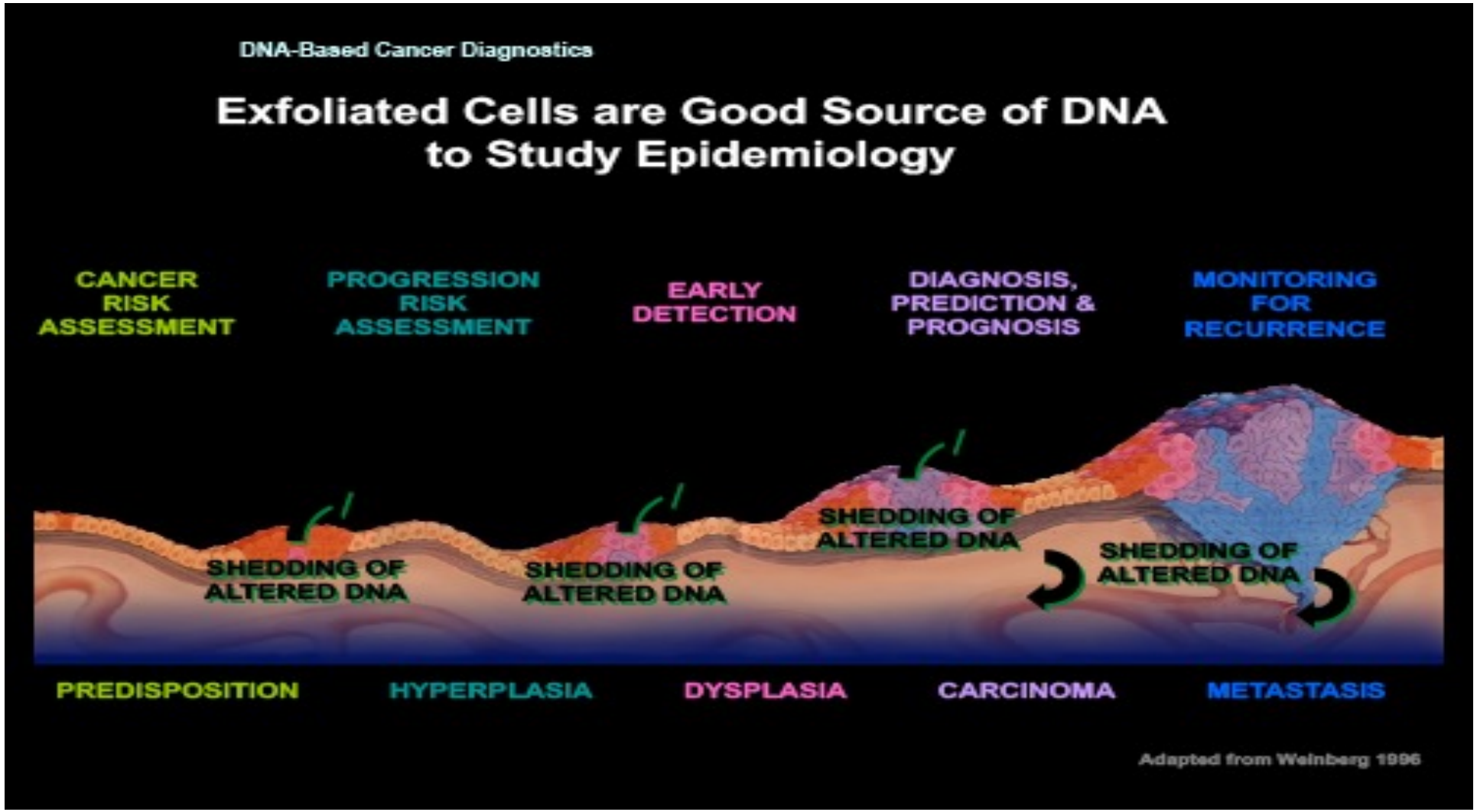
Epigenetic changes



Epigenetic drugs



Exfoliated cells



Tumors and epigenetics

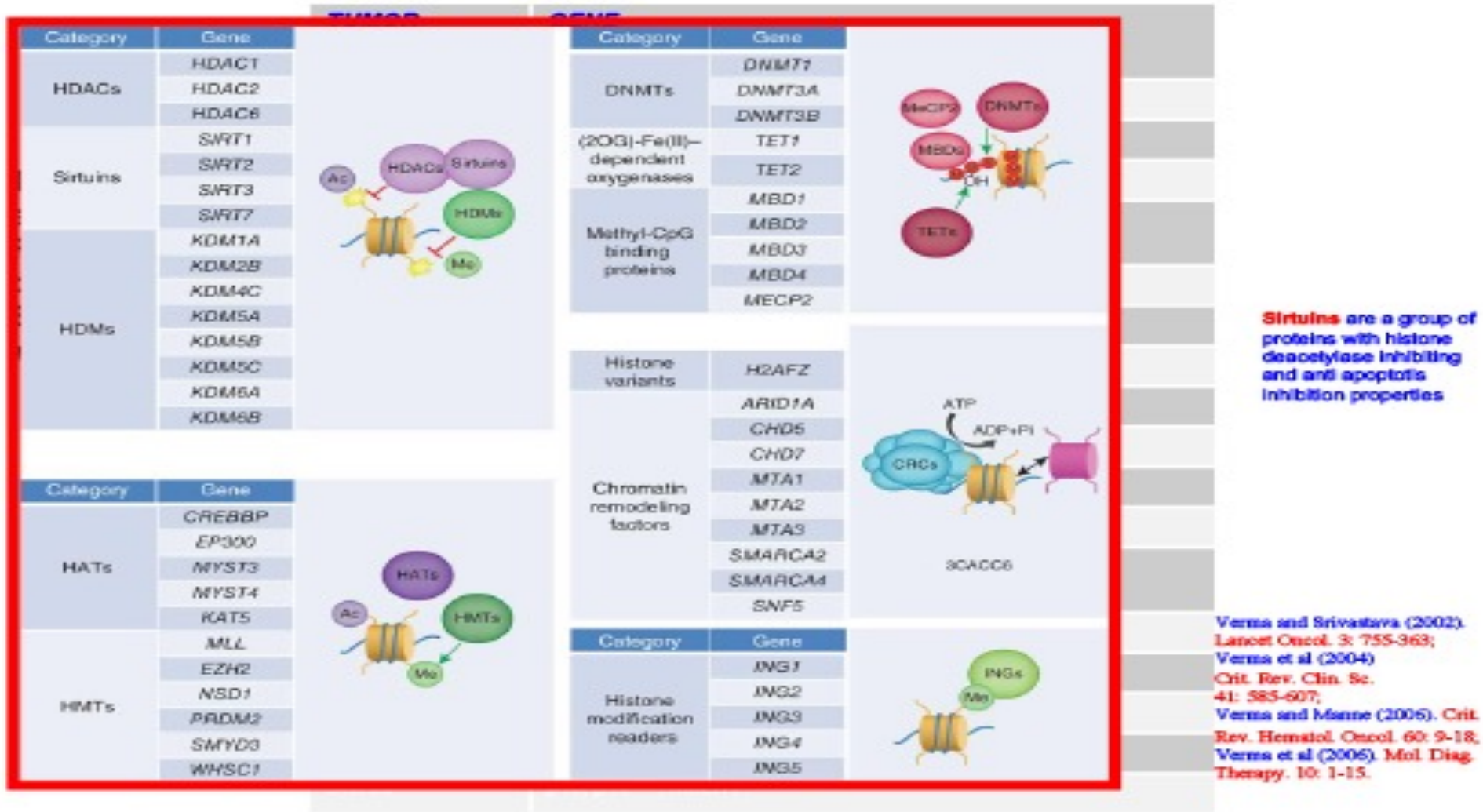
Tumor Types and Genes Regulated by Epigenetic Mechanism

TUMOR LOCATION	*GENE*
Breast	p16, BRCA1, GSTP1, DAPK, CDH1, TIMP-3
Brain	p16, p14^{ARF}, MGMT, TIMP-3
Bladder	p16, DAPK, APC
Colon	p16, p14^{ARF}, CREBP1, MGMT, hMLH1, DAPK, TIMP-3, APC
Endometrium	hMLH1
Esophagus	p16, p14^{ARF}, GSTP1, CDH1, APC
Head and Neck	p16, MGMT, DAPK
Kidney	p16, p14^{ARF}, MGMT, GSTP1, TIMP-3, APC
Leukemia	p15, MGMT, DAPK1, CDH1, p73
Liver	p16, CREBP1, GSTP1, APC
Lymphoma	p16, p15, CREBP1, MGMT, DAPK, p73
Lung	p16, p14^{ARF}, CREBP1, MGMT, GSTP1, DAPK, FHIT, TIMP-3, RARbeta, RASSF1A
Ovary	p16, BRCA1, DAPK
Pancreas	p16, MGMT, APC
Prostate	GSTP1, p27(kip1)
Stomach	p14^{ARF}, P16, APC, hMLH1, MGMT
Uterus	p16, p14^{ARF}, hMLH1

Silencing of a group of promoters with histone deacetylase inhibitors and demethylating inhibitor properties

Verma and Srivastava (2002) Lancet Oncol 3: 755-763
Verma et al (2004) Curr Rev Clin Sci 41: 585-607
Verma and Manne (2006) Curr Rev Hematol Oncol 06:9-18,
Verma et al (2006) Mol Diag Therapy 10:1-15

Histone enzymes



Sirtuins are a group of proteins with histone deacetylase inhibiting and anti apoptotic inhibition properties

Verma and Srivastava (2002). Lancet Oncol. 3: 755-363;
Verma et al (2004) Crit. Rev. Clin. Sc. 41: 585-607;
Verma and Manne (2006). Crit. Rev. Hematol. Oncol. 60: 9-18,
Verma et al (2006). Mol. Diag. Therapy. 10: 1-15.

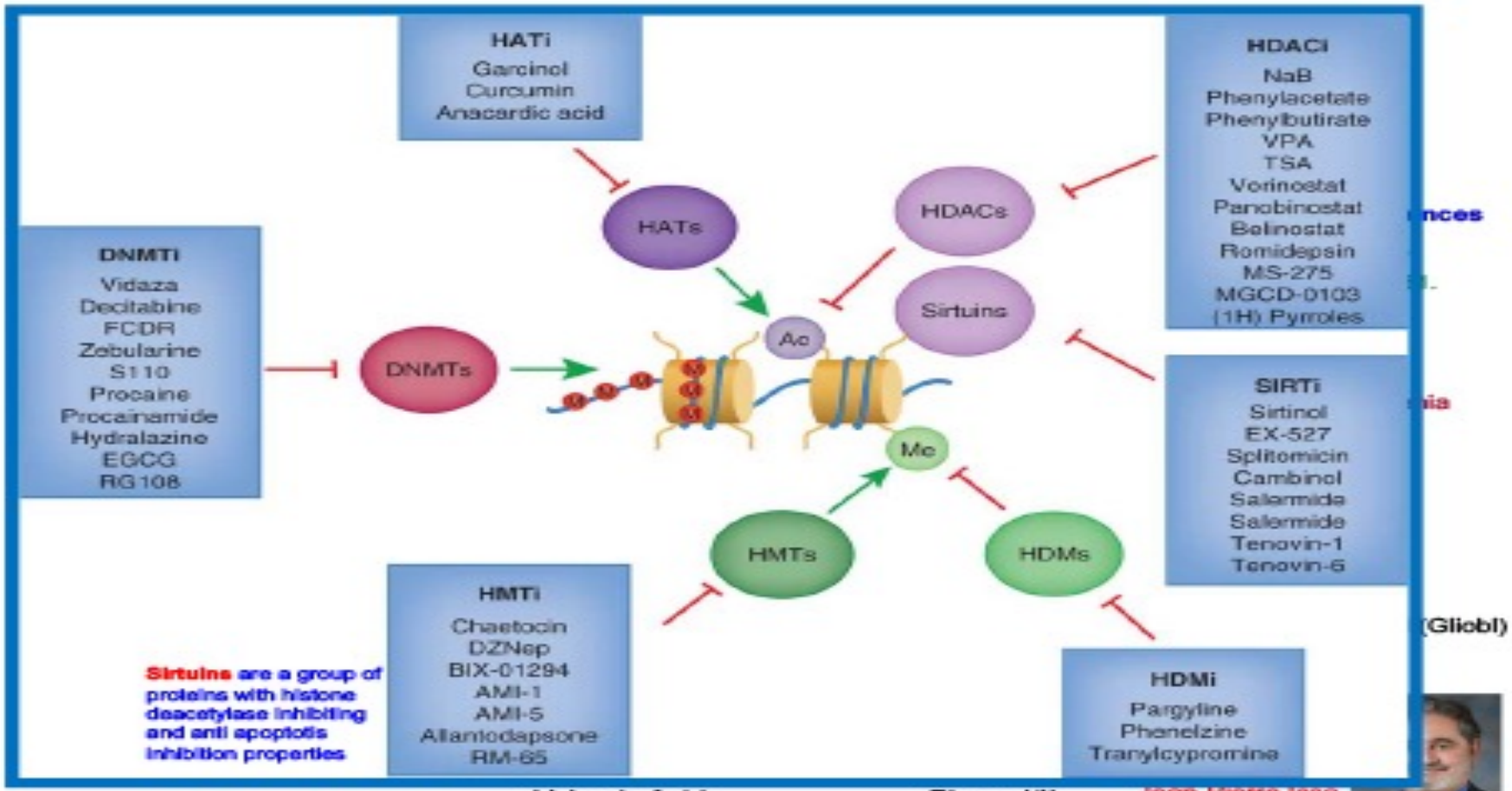
Epigenetic drugs

Target	Drug	Clinical Trial
DNA Methylation	5-Azacytidine	Phase I/II
	5-Aza-2'deoxycytidine	Phase I/II
	FCD R	
	Zebularine	
	Procainamide	
	EGCG	Phase I
	Psamaplin A	
	Antisense Oligomers	Phase I
Histone deacetylase	Phenylbutyric acid	Phase I/II
Sirtuins are a group of proteins with histone deacetylase inhibitor and other enzymatic inhibitor properties	SAHA (Suberoylanilide hydroxamic acid) or Vorinostat	Phase I/II
	Depsipeptide	Phase I/II
	Valproic Acid	Phase I/II

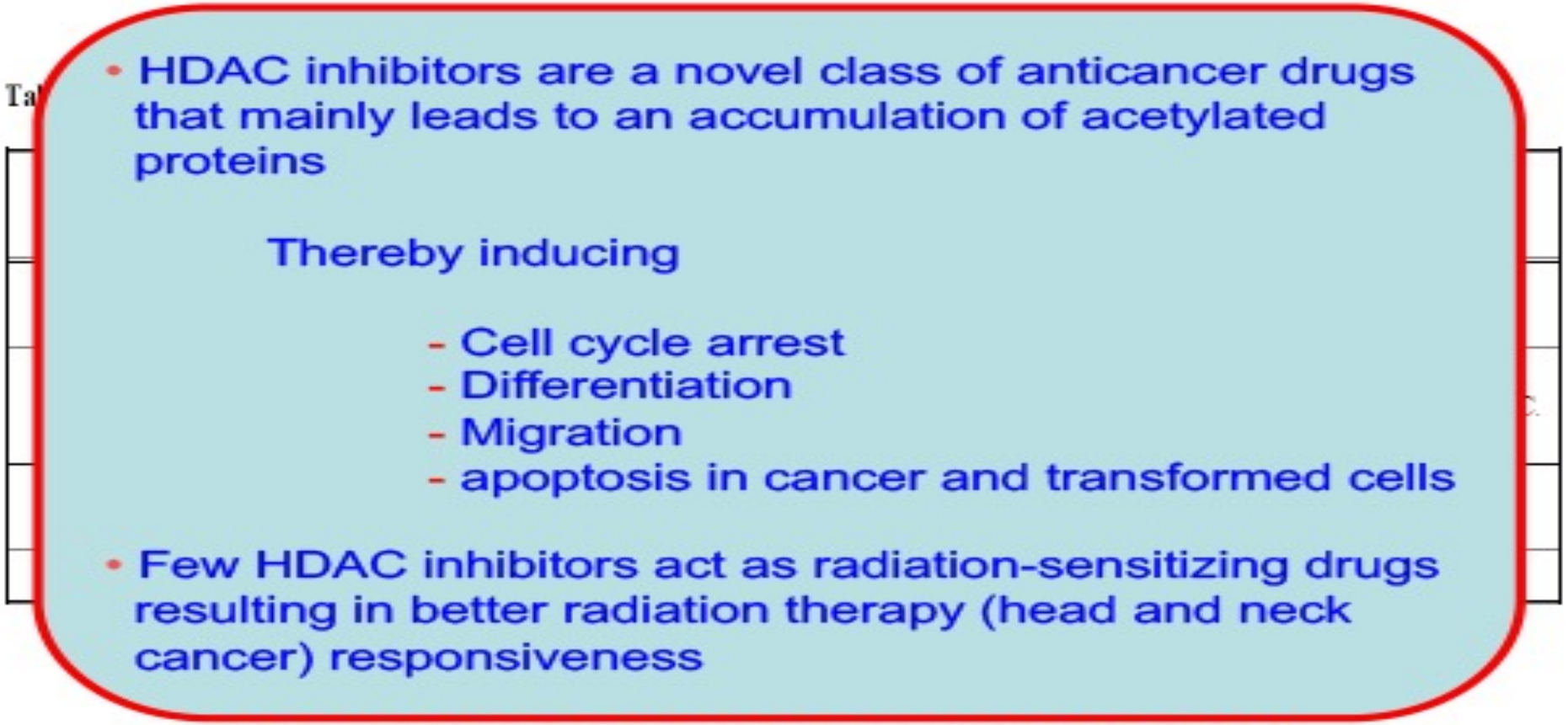
Adverse Experiences SAHA

- Dehydration
- Diarrhea
- Nausea
- Thrombocytopenia
- Vomiting

Methylation and acetylation enzymes

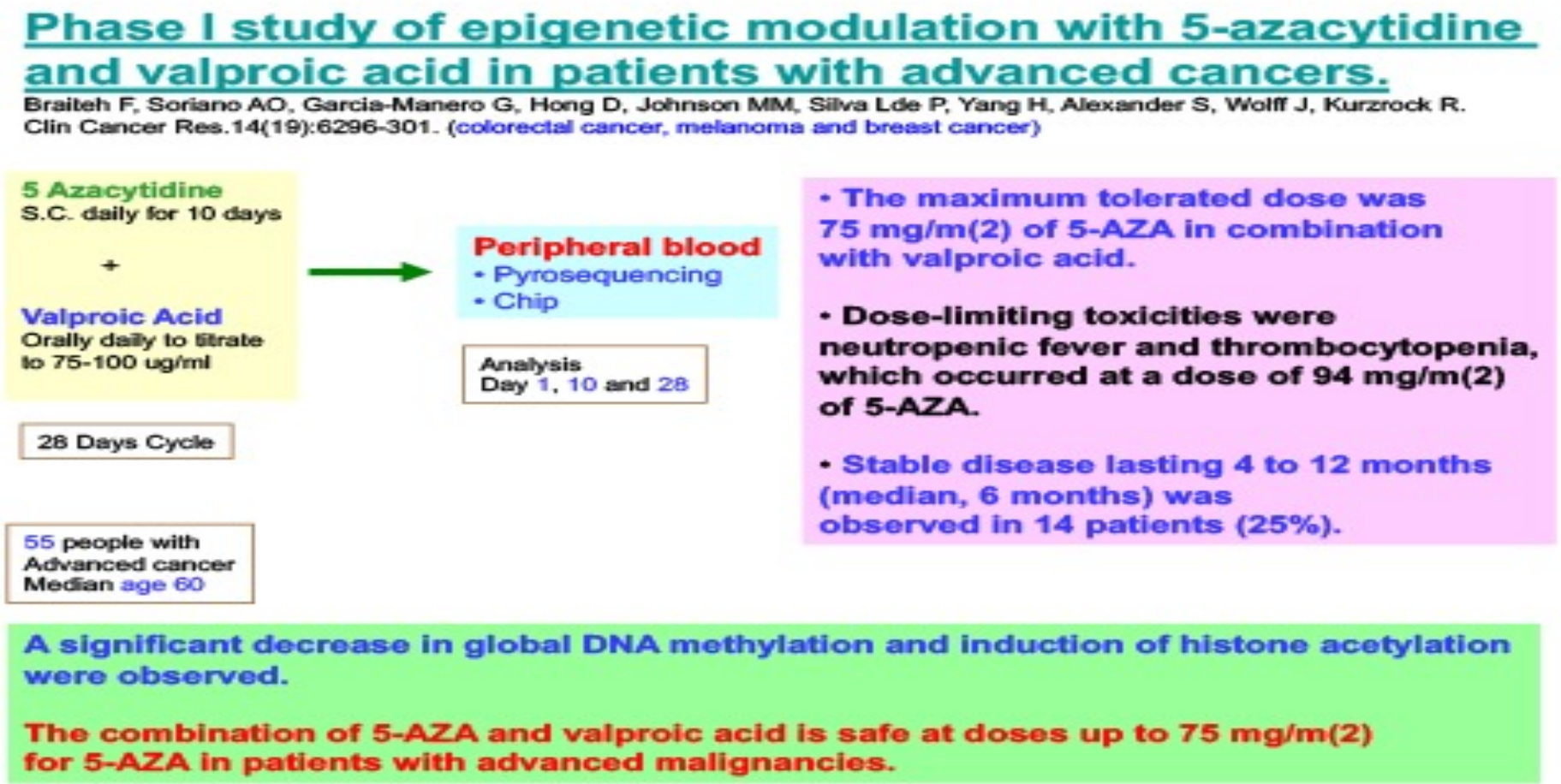


HDAC inhibitors



HDAC 1, 2, 3, 8, 11 have been characterized (Khan, I , 2007)

Phase I study



5-azacytidine, valproic acid and ATRA

Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome.

Soriano et al. Blood. 110(7):2302-8.

- **Combination of 5-azacitidine (5-AZA), valproic acid (VPA), and ATRA in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome.**
- **A total of 53 patients were treated.**
- **The overall response rate was 42%.**
- **A significant decrease in global DNA methylation and induction of histone acetylation were achieved.**
- **VPA blood levels were higher in responders.**
- **The combination studied is safe and has significant clinical activity.**

This clinical trial was registered at www.clinicaltrials.gov as no. NCT00326170.

Histone inhibitors

Histone Inhibitors in Clinical Trials (Clinicaltrials.gov)

STATUS	STUDY
Recruiting	Safety Study of the Histone Deacetylase Inhibitor, CHR-3996, in Patients With Advanced Solid Tumours
Recruiting	Phase II Study of Histone-Deacetylase Inhibitor ITF2357 in Refractory/Relapsed Lymphocytic Leukemia
Recruiting	phII Study of an HDAC Inhibitor in Very High-Risk Relapsed/Refractory Hodgkin's Lymphoma Patients
Recruiting	Phase IIA Study of the HDAC Inhibitor ITF2357 in Patients With JAK-2 V617F Positive Chronic Myeloproliferative Diseases
Recruiting	Phase II Trial of the Histone-Deacetylase Inhibitor ITF2357 Followed by Mechlorethamine in Relapsed/Refractory Hodgkin's Lymphoma Patients
Recruiting	HDAC Inhibitor Vorinostat (SAHA) With Capecitabine (Xeloda) Using a New Weekly Dose Regimen for Advanced Breast Cancer
Recruiting	Valproic Acid, Temozolomide, and Radiation Therapy in Treating Patients With Glioblastoma Multiforme
Recruiting	Study of Vorinostat (MK0683) an HDAC Inhibitor, or Placebo in Combination With Bortezomib in Patients With Multiple Myeloma
Recruiting	Study of Vorinostat (MK0683), an HDAC Inhibitor, in Combination With Bortezomib in Patients With Relapsed or Refractory Multiple Myeloma
Completed	A Phase II Study of Epigenetic Therapy to Overcome Chemotherapy Resistance in Refractory Solid Tumors
Recruiting	Sorafenib and LBH589 in Hepatocellular Carcinoma (HCC)
Recriting	Phase II Study of Valproic Acid With FEC100 for Patients With Locally Advanced Breast Cancer

Total : 84 studies

http://clinicaltrials.gov/ct2/results?term=histone+inhibitors&pg=4

Methylation inhibitors

Methylation Inhibitors in Clinical Trials (Clinicaltrials.gov)

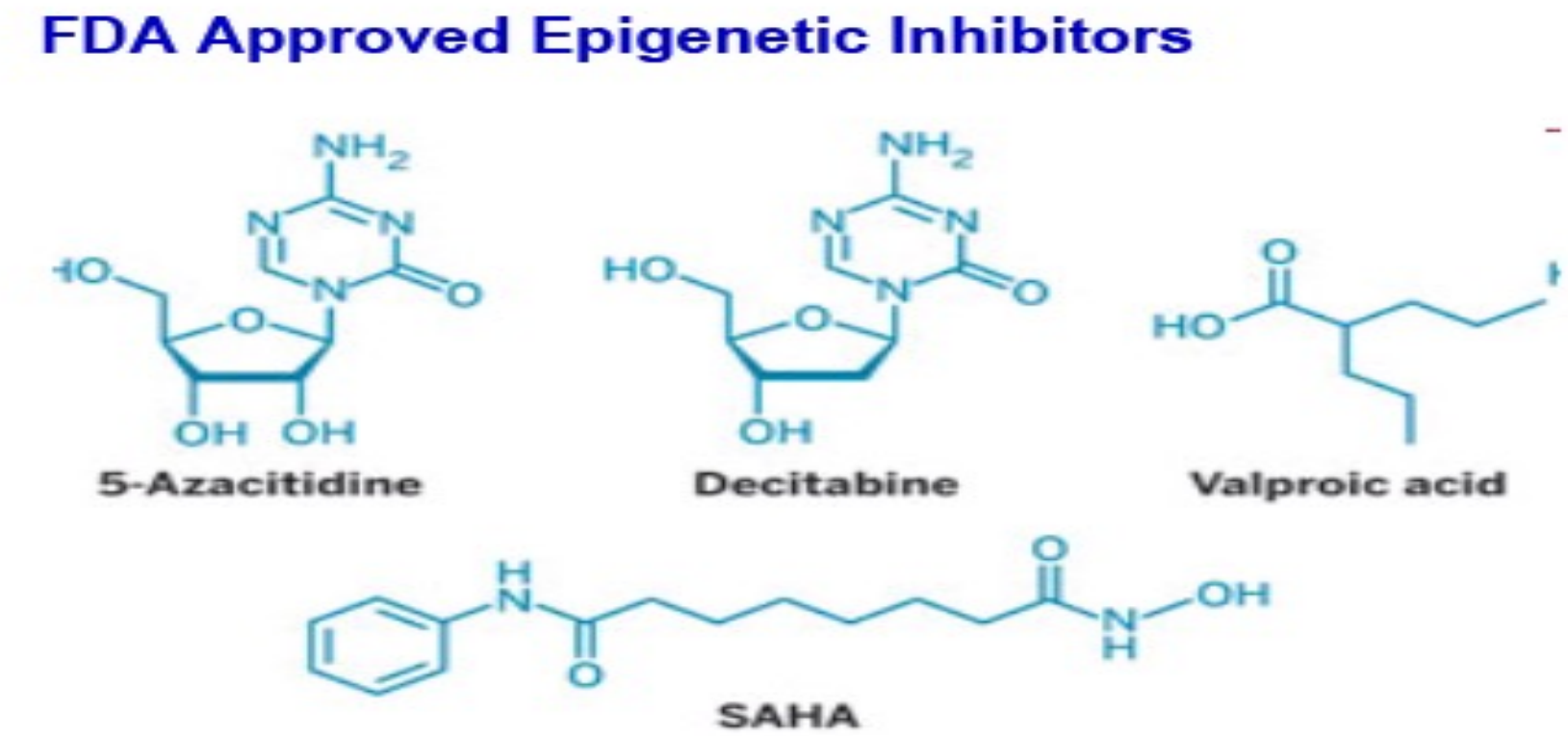
STATUS	STUDY
Completed	A Phase II Study of Epigenetic Therapy to Overcome Chemotherapy Resistance in Refractory Solid Tumors
Active Not Recruiting	Azacytidine and Valproic Acid in Patients With Advanced Cancers
Recruiting	Azacitidine With MS-275 in Treating Patients With Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia, or Acute Myeloid Leukemia
Active Not Recruiting	Phase I Azacytidine Plus Valproic Acid and Preventive Strain in Intermediate II and High Risk MDS
Recruiting	Decitabine With or Without Interferon Alfa-2b in Treating Patients With Unresectable or Metastatic Solid Tumors
Recruiting	Hydralazine Valproate for Cervical Cancer
Recruiting	Hydralazine Valproate for Ovarian Cancer
Recruiting	Decitabine in Treating Patients With Previously Untreated Acute Myeloid Leukemia
Recruiting	Chronic Hepatitis C Non-Responder Study With Ado Mot and Peginte
Recruiting	Azacitidine, Docetaxel, and Prednisone in Treating Patients With Metastatic Prostate Cancer That Did Not Respond to Hormone Therapy
Recruiting	Low Dose Decitabine + Interferon Alfa-2b in Advanced Renal Cell Carcinoma

Total : 51 studies

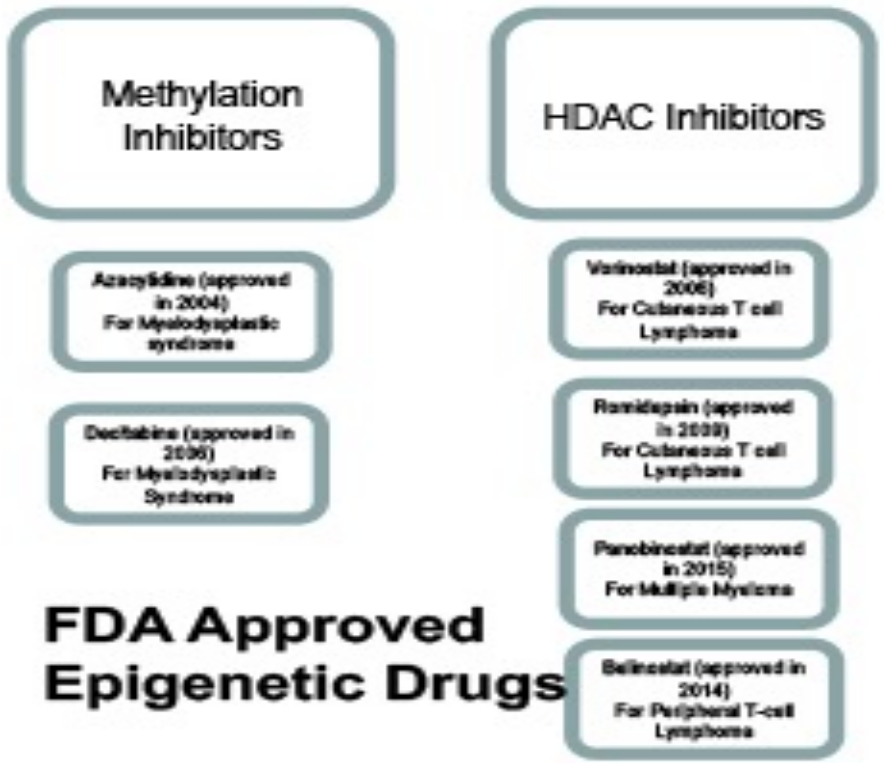
http://clinicaltrials.gov/ct2/results?term=methylation+inhibitors

Schering-Plough (Decitabine (5-aza-Deoxycytadine) Trial for melanoma) (8 hrs to inactivate DNMT1)
Bristol-Myers Squibb (other compounds)

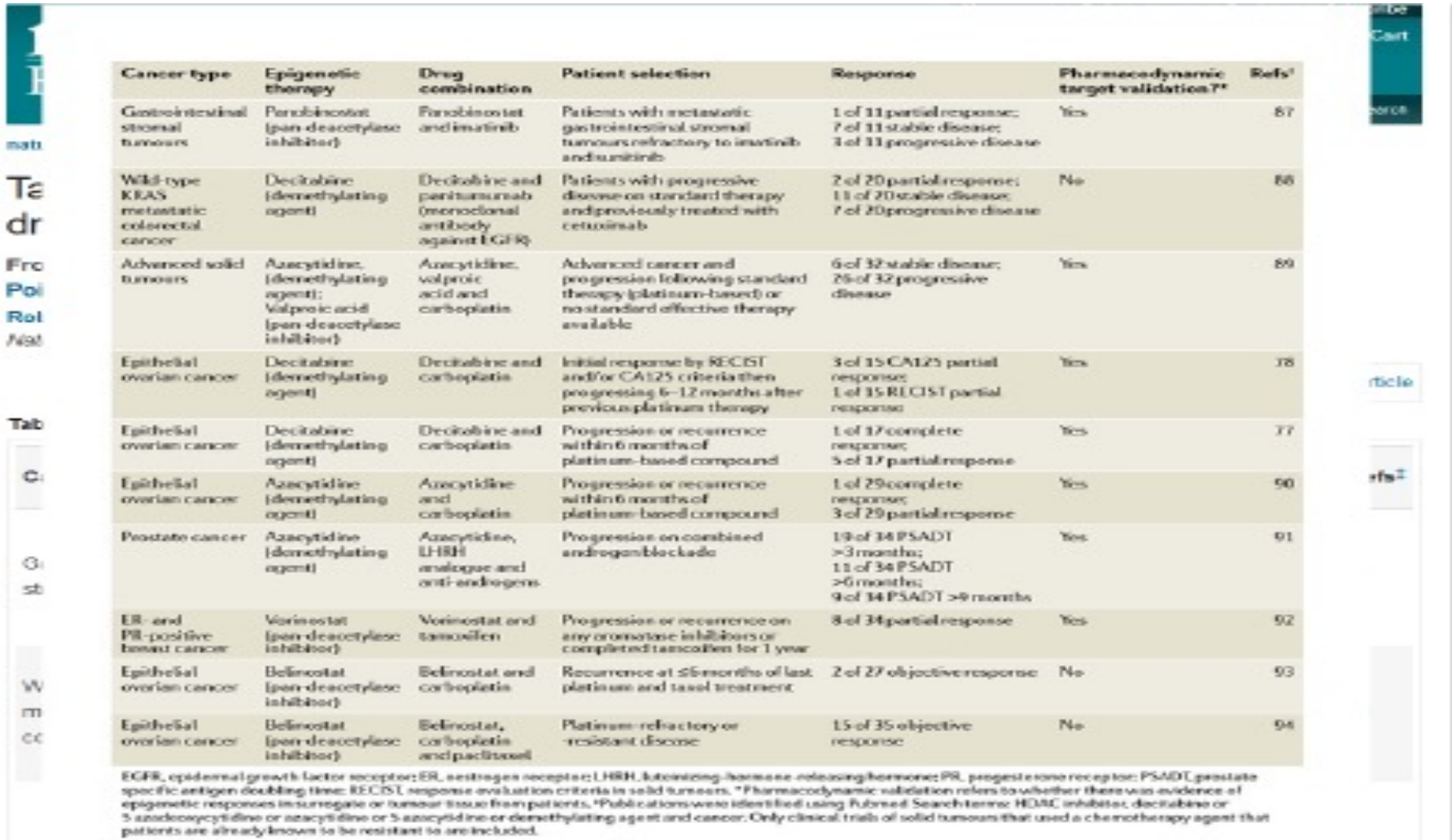
Epigenetic inhibitors



Approved epigenetic drugs



Epigenetic drugs



Cancer type	Epigenetic therapy	Drug combination	Patient selection	Response	Pharmacodynamic target validation?*	Refs‡
Gastrointestinal stromal tumours	Panobinostat (pan-deacetylase inhibitor)	Panobinostat and imatinib	Patients with metastatic gastrointestinal stromal tumours refractory to imatinib and sunitinib	1 of 11 partial response; 7 of 11 stable disease; 3 of 11 progressive disease	Yes	87
Wild-type KRAS metastatic colorectal cancer	Decitabine (demethylating agent)	Decitabine and panitumumab (monoclonal antibody against EGFR)	Patients with progressive disease on standard therapy and previously treated with cetuximab	2 of 20 partial response; 11 of 20 stable disease; 7 of 20 progressive disease	No	88
Advanced solid tumours	Azacytidine (demethylating agent); Valproic acid (pan-deacetylase inhibitor)	Azacytidine, valproic acid and carboplatin	Advanced cancer and progression following standard therapy (platinum-based) or no standard effective therapy available	6 of 32 stable disease; 26 of 32 progressive disease	Yes	89
Epithelial ovarian cancer	Decitabine (demethylating agent)	Decitabine and carboplatin	Initial response by RECIST and/or CA125 criteria then progressing 6–12 months after previous platinum therapy	3 of 15 CA125 partial response; 1 of 15 RECIST partial response	Yes	78
Epithelial ovarian cancer	Decitabine (demethylating agent)	Decitabine and carboplatin	Progression or recurrence within 6 months of platinum-based compound	1 of 17 complete response; 5 of 17 partial response	Yes	77
Epithelial ovarian cancer	Azacytidine (demethylating agent)	Azacytidine and carboplatin	Progression or recurrence within 6 months of platinum-based compound	1 of 29 complete response; 3 of 29 partial response	Yes	90
Prostate cancer	Azacytidine (demethylating agent)	Azacytidine, LHRH analogue and anti-androgens	Progression on combined androgen blockade	19 of 34 PSADT >3 months; 11 of 34 PSADT >6 months; 9 of 34 PSADT >9 months	Yes	91
ER- and PR-positive breast cancer	Vorinostat (pan-deacetylase inhibitor)	Vorinostat and tamoxifen	Progression or recurrence on any aromatase inhibitors or completed tamoxifen for 1 year	8 of 34 partial response	Yes	92
Epithelial ovarian cancer	Belinostat (pan-deacetylase inhibitor)	Belinostat and carboplatin	Recurrence at ≤6 months of last platinum and taxol treatment	2 of 27 objective response	No	93
Epithelial ovarian cancer	Belinostat (pan-deacetylase inhibitor)	Belinostat, carboplatin and paclitaxel	Platinum-refractory or -resistant disease	15 of 35 objective response	No	94

EGFR, epidermal growth factor receptor; ER, oestrogen receptor; LHRH, luteinizing-hormone-releasing hormone; PR, progesterone receptor; PSADT, prostate specific antigen doubling time; RECIST, response evaluation criteria in solid tumours. *Pharmacodynamic validation refers to whether there was evidence of epigenetic responses in surrogate or tumour tissue from patients. ‡Publications were identified using Pubmed Search terms: HDAC inhibitor, decitabine or 5 azadeoxycytidine or azacytidine or 5 azacytidine or demethylating agent and cancer. Only clinical trials of solid tumours that used a chemotherapy agent that patients are already known to be resistant to are included.

Combination therapy

AML subtypes and combination therapy

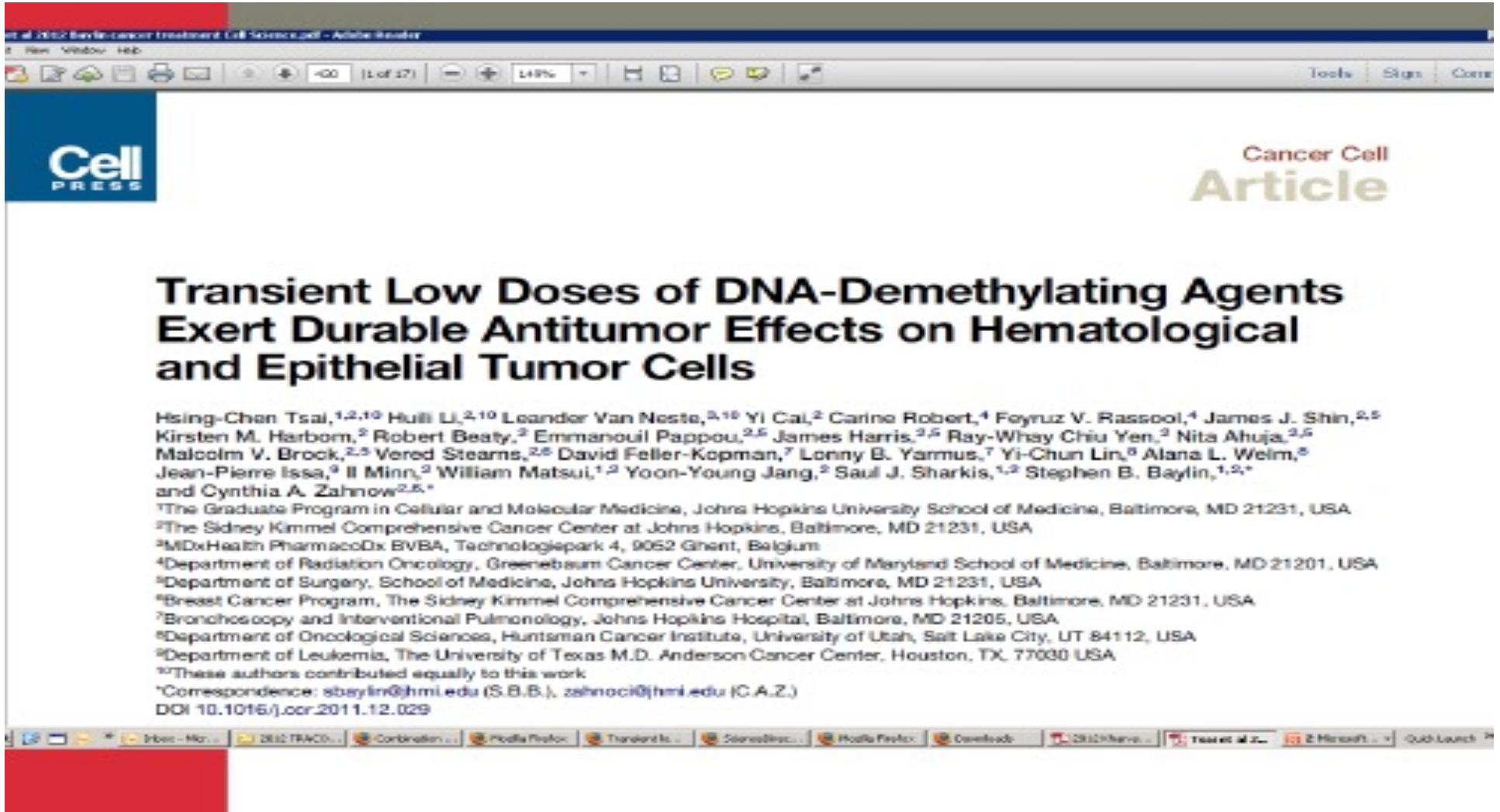
Pharmaceutical Participation

AML Subtype	Drug	Company
Tet2/WTI	CD33 + Aza	BI
IDH2 Mutation	Enasidenib	Celgene
MLL	Entospletinib (Syk inhibitor)	Gilead
CBF	Samalizumab (CD200 Ab) + induction	Alexion
P53 mutation	Entospletinib (Syk inhibitor) + Decitabine	Gilead
Complex Karotype	Entospletinib (Syk inhibitor) + Decitabine	Gilead
P53 mutation	Pevonedistat (Nedd8 inhibitor) + Aza	Takeda
Marker Negative	CD33 + Aza	BI
NPM1 w FLT3 WT	Entospletinib (Syk inhibitor)	Gilead
FLT3 mutation	Gilteritinib	Astellas
IDH1 Mutation	Ivosidenib + Aza	Agios

Source: Leukemia & Lymphoma Society

Cancer letters 17 July 2018

Low doses of DNA-demethylating agents



Cell PRESS

Cancer Cell
Article

Transient Low Doses of DNA-Demethylating Agents Exert Durable Antitumor Effects on Hematological and Epithelial Tumor Cells

Hsing-Chen Tsai,[1,2,10] Hui Li,[2,10] Leander Van Neste,[3,10] Yi Cai,[2] Carine Robert,[4] Feyruz V. Rassool,[4] James J. Shin,[2,5] Kirsten M. Harbom,[2] Robert Beaty,[2] Emmanouil Pappou,[2,5] James Harris,[2,5] Ray-Whay Chiu Yen,[2] Nita Ahuja,[2,5] Malcolm V. Brock,[2,5] Vered Stearns,[2,6] David Feller-Kopman,[7] Lonny B. Yarmus,[7] Yi-Chun Lin,[8] Alana L. Welm,[8] Jean-Pierre Issa,[9] Il Minn,[2] William Matsui,[1,2] Yoon-Young Jang,[2] Saul J. Sharkis,[1,2] Stephen B. Baylin,[1,2,*] and Cynthia A. Zahnow[2,5,*]

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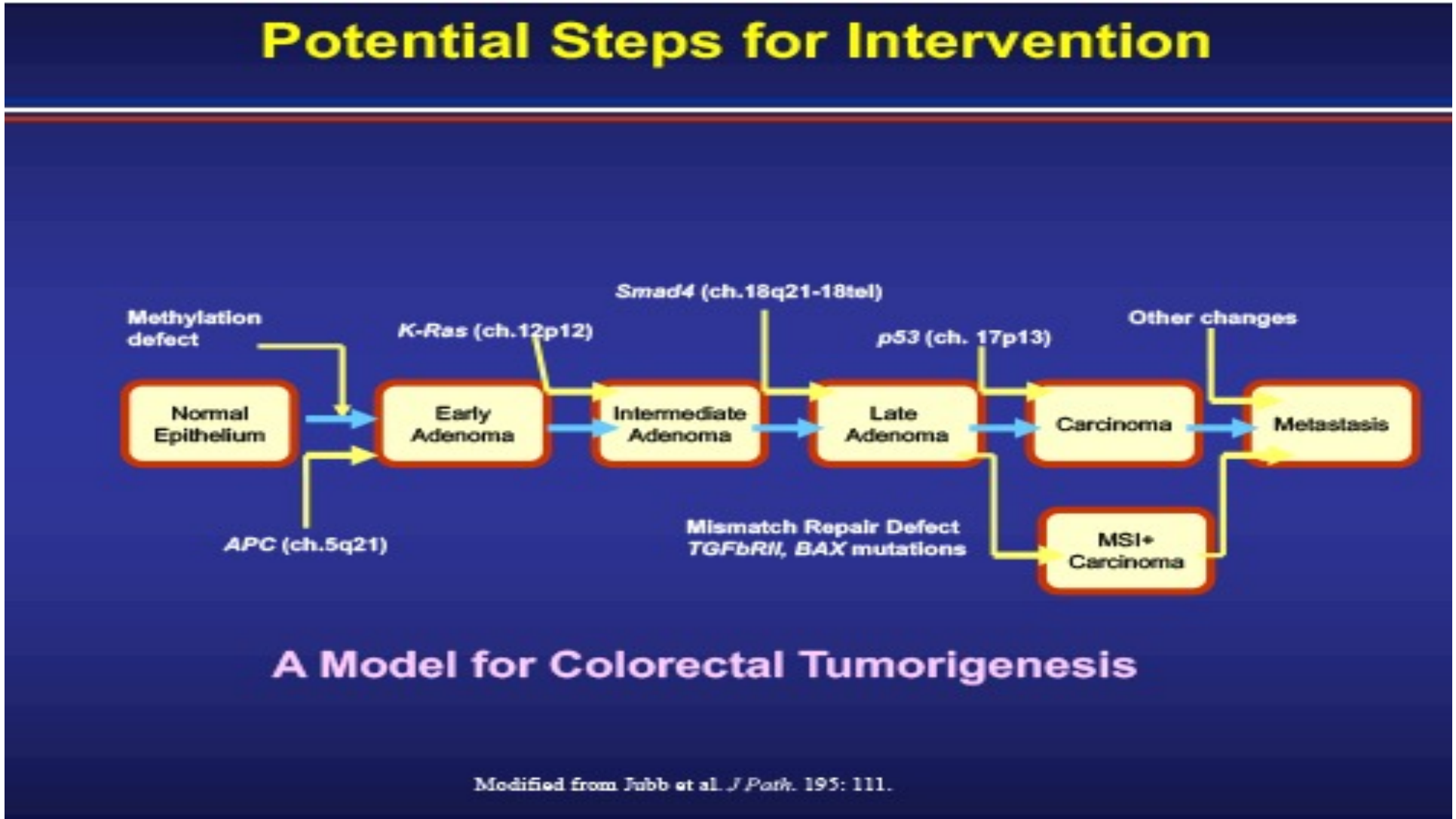
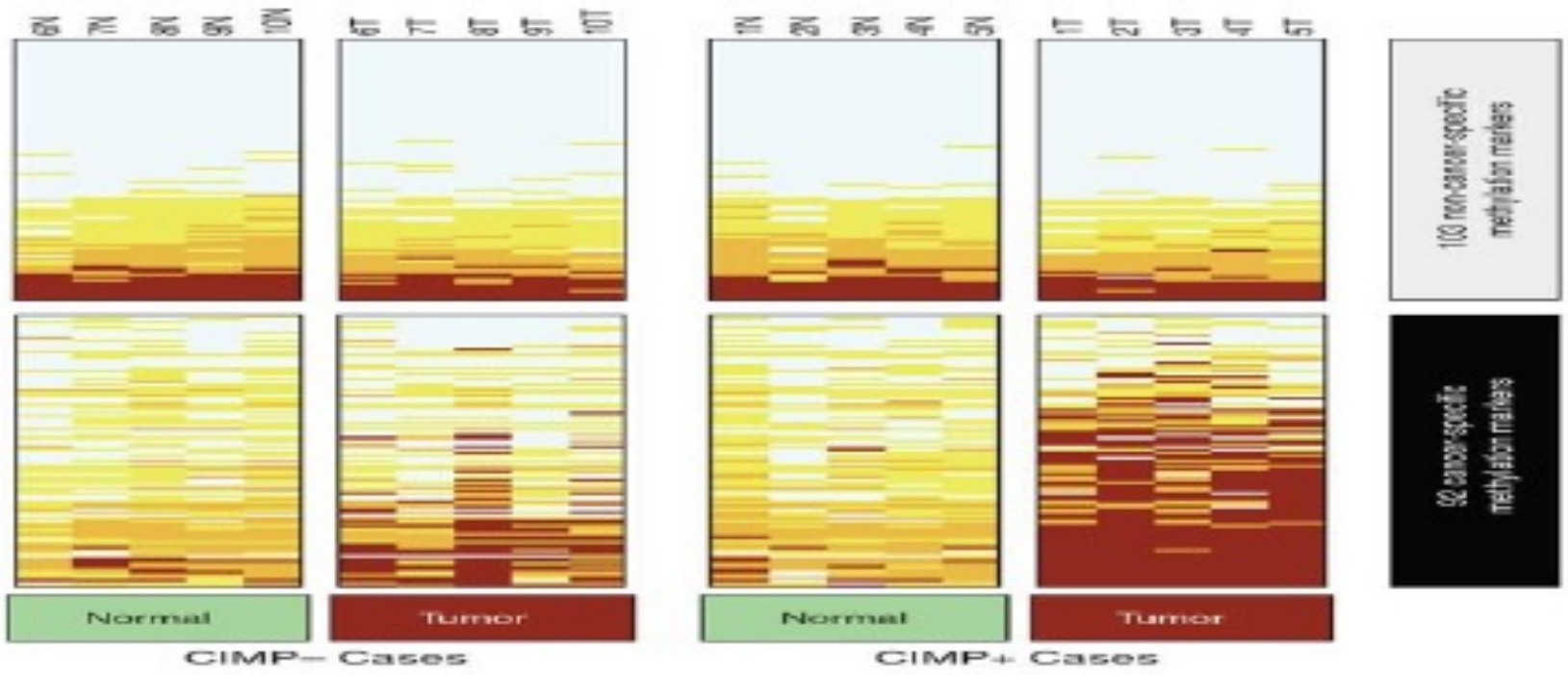
[5]Department of Surgery, School of Medicine, Johns Hopkins University, Baltimore, MD 21231, USA
[6]Breast Cancer Program, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA
[7]Bronchoscopy and Interventional Pulmonology, Johns Hopkins Hospital, Baltimore, MD 21205, USA
[8]Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, USA
[9]Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030 USA
[10]These authors contributed equally to this work
*Correspondence: sbaylin@jhmi.edu (S.B.B.), zahnoci@jhmi.edu (C.A.Z.)
DOI 10.1016/j.ccr.2011.12.029

Intervention



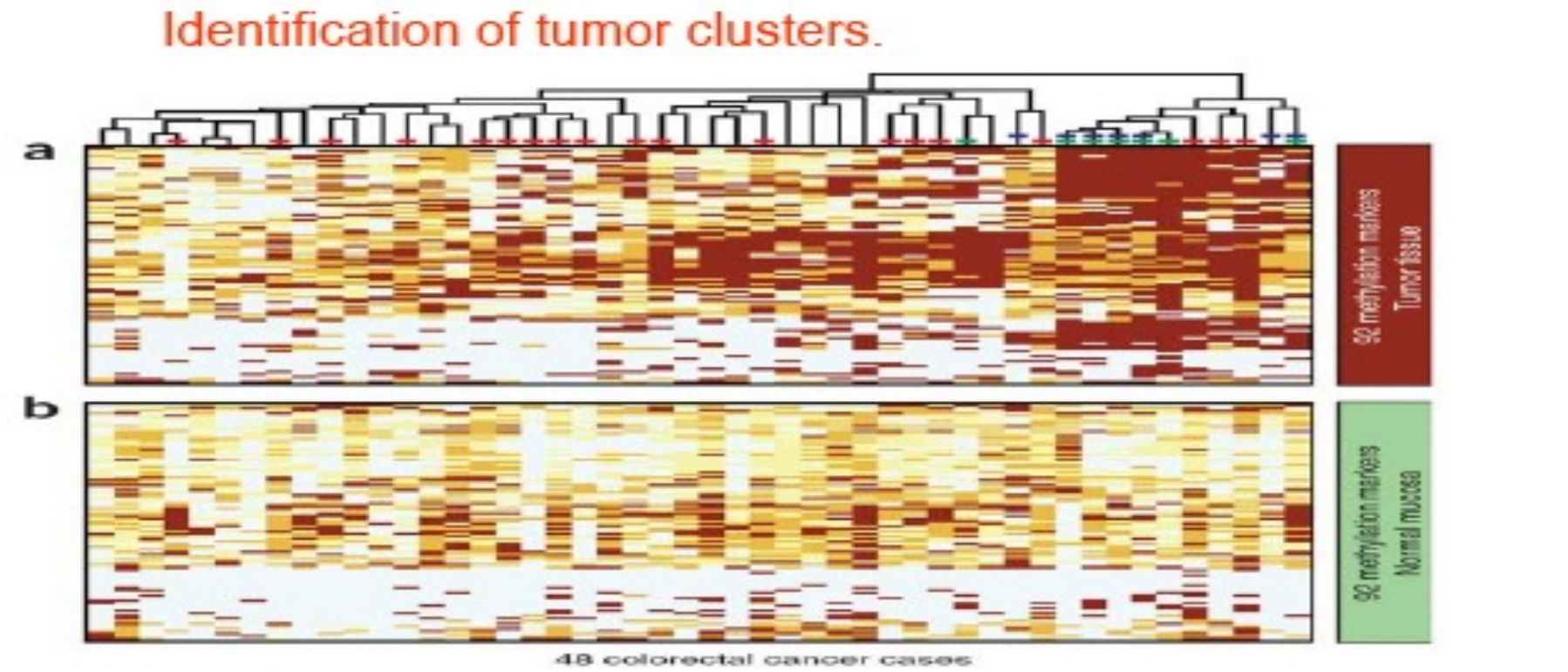
Microsatellite instability

CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer



Nature Genetics 38, 787 - 793

Tumor clusters

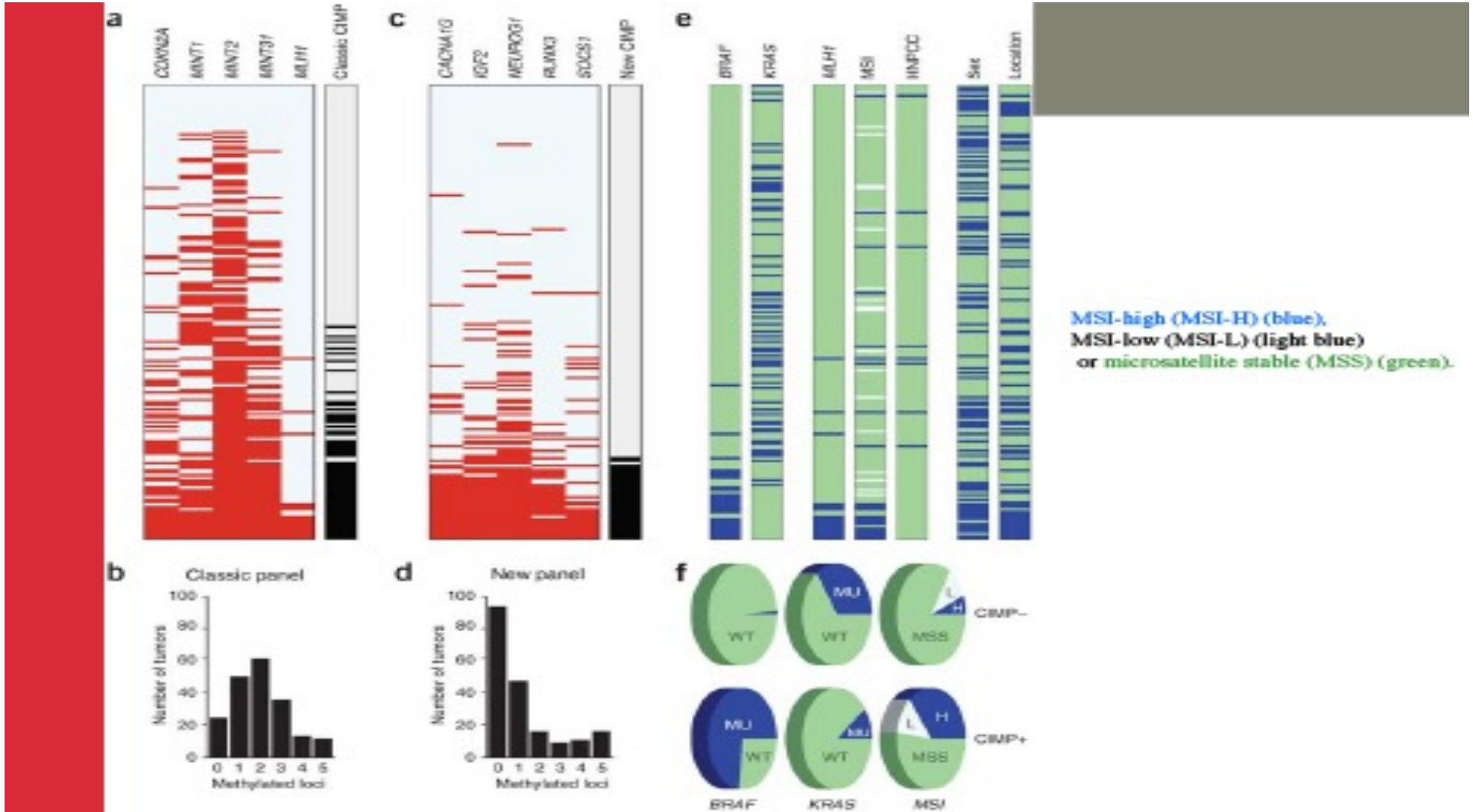


KRAS mutation indicated by a red rectangle overlaying the branch,
BRAF mutations indicated by a green rectangle
MSI-H cases designated with a blue rectangle.

48 Colorectal tumors

Nature Genetics **38**, 787 - 793

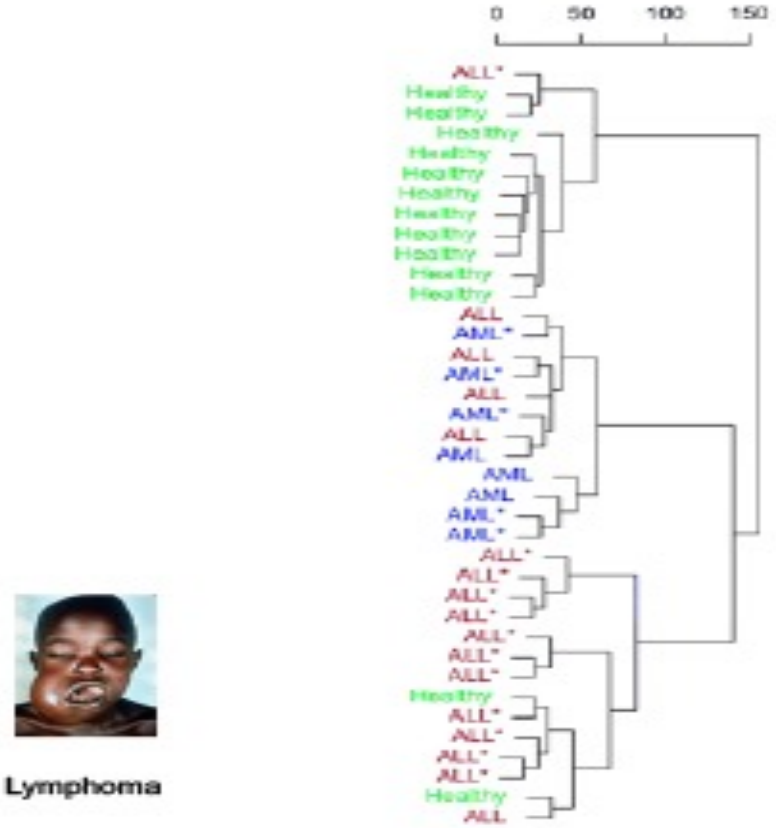
Genetic analysis



Methylation analysis

National Cancer Institute

Prediction of Tumor Class based on Methylation Analysis (AML and ALL)

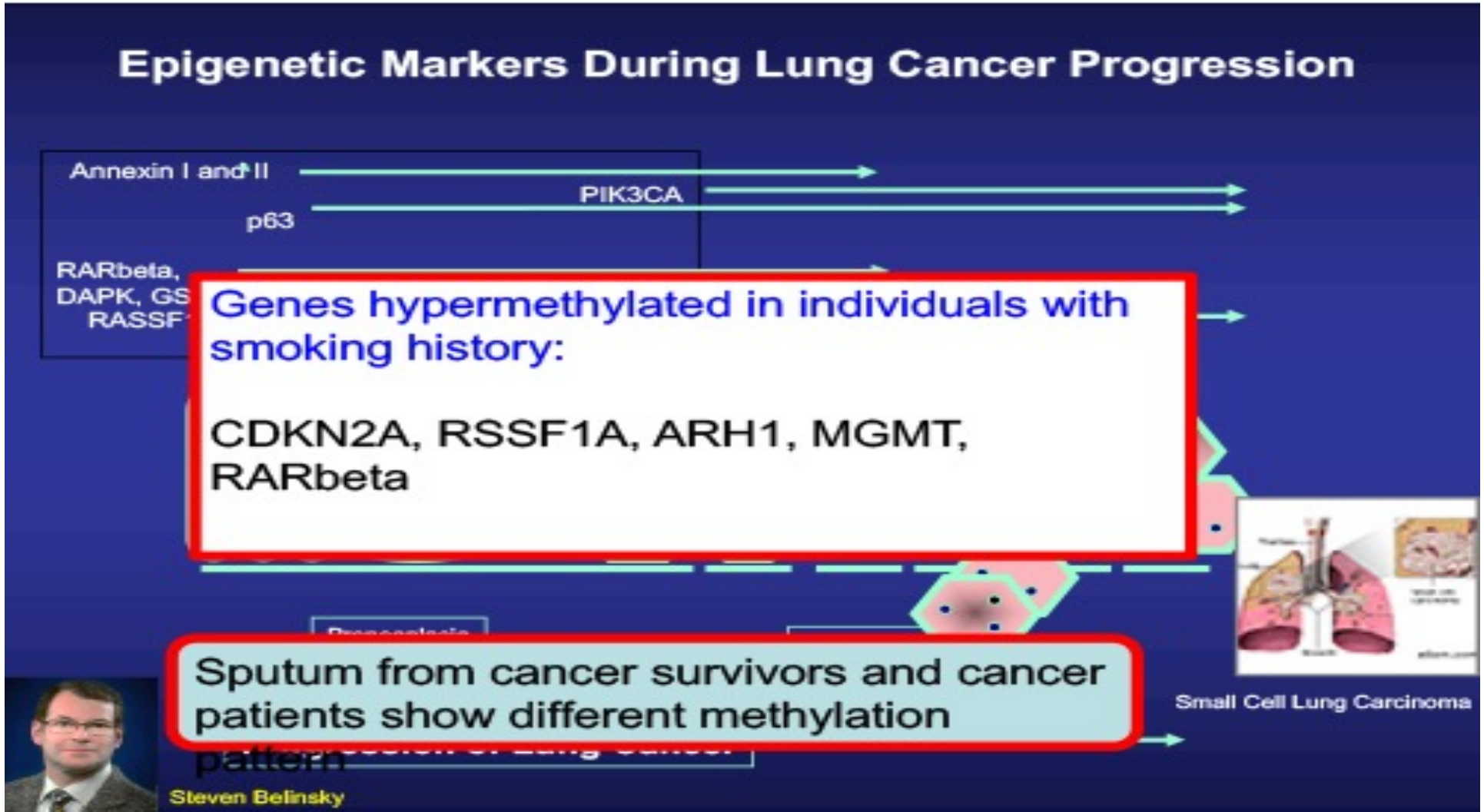


AML:Acute Myeloid Leukemia
ALL: Acute Lymphoblastic Leukemia

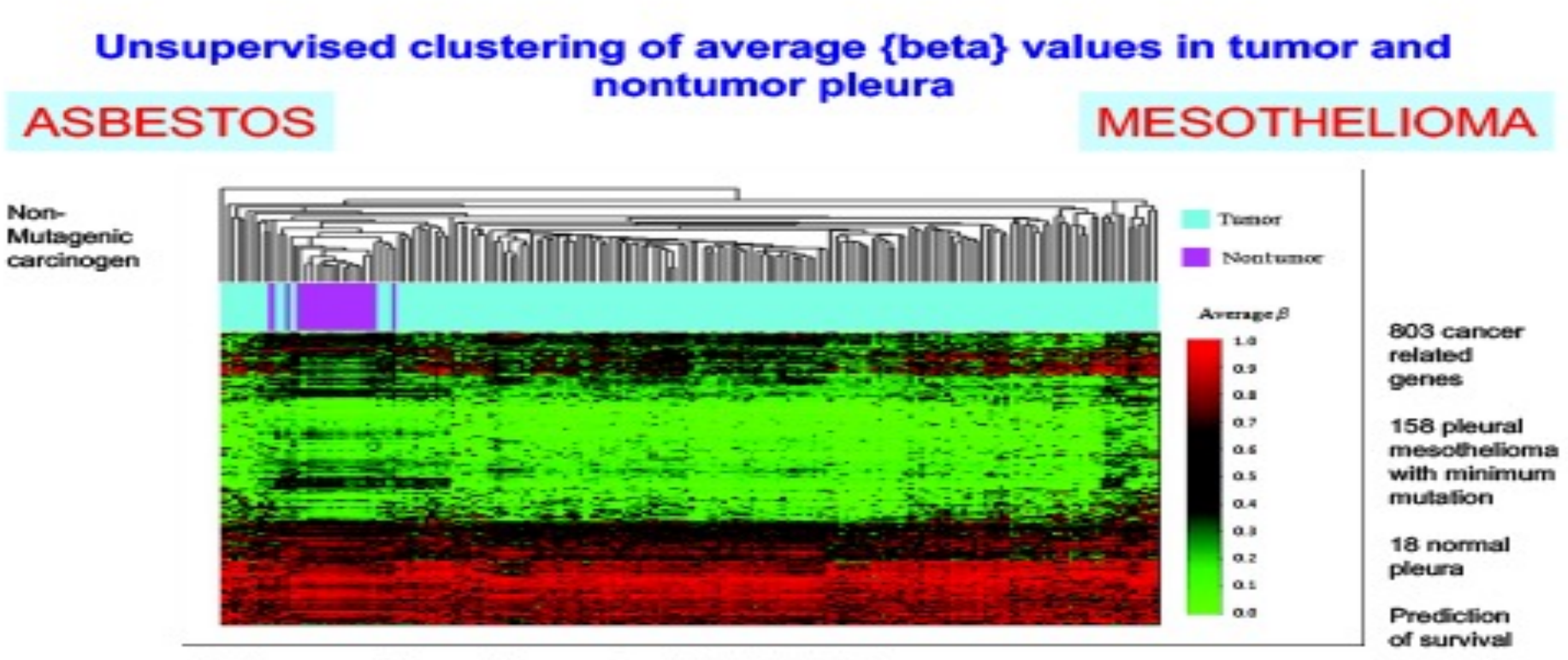
Lymphoma

Adorjan et al *Nuc Ac Res.* 30: e21

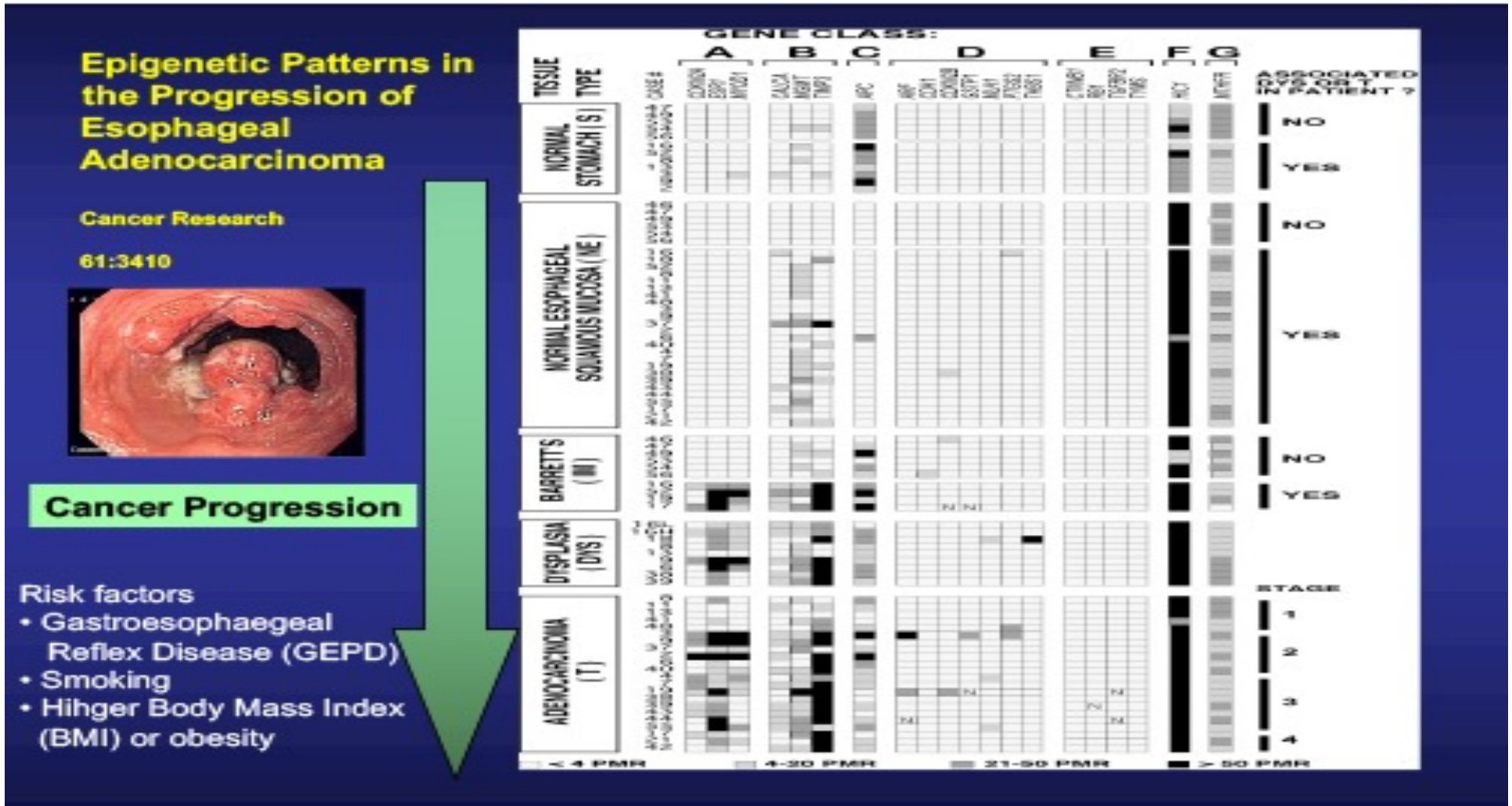
Epigenetic markers



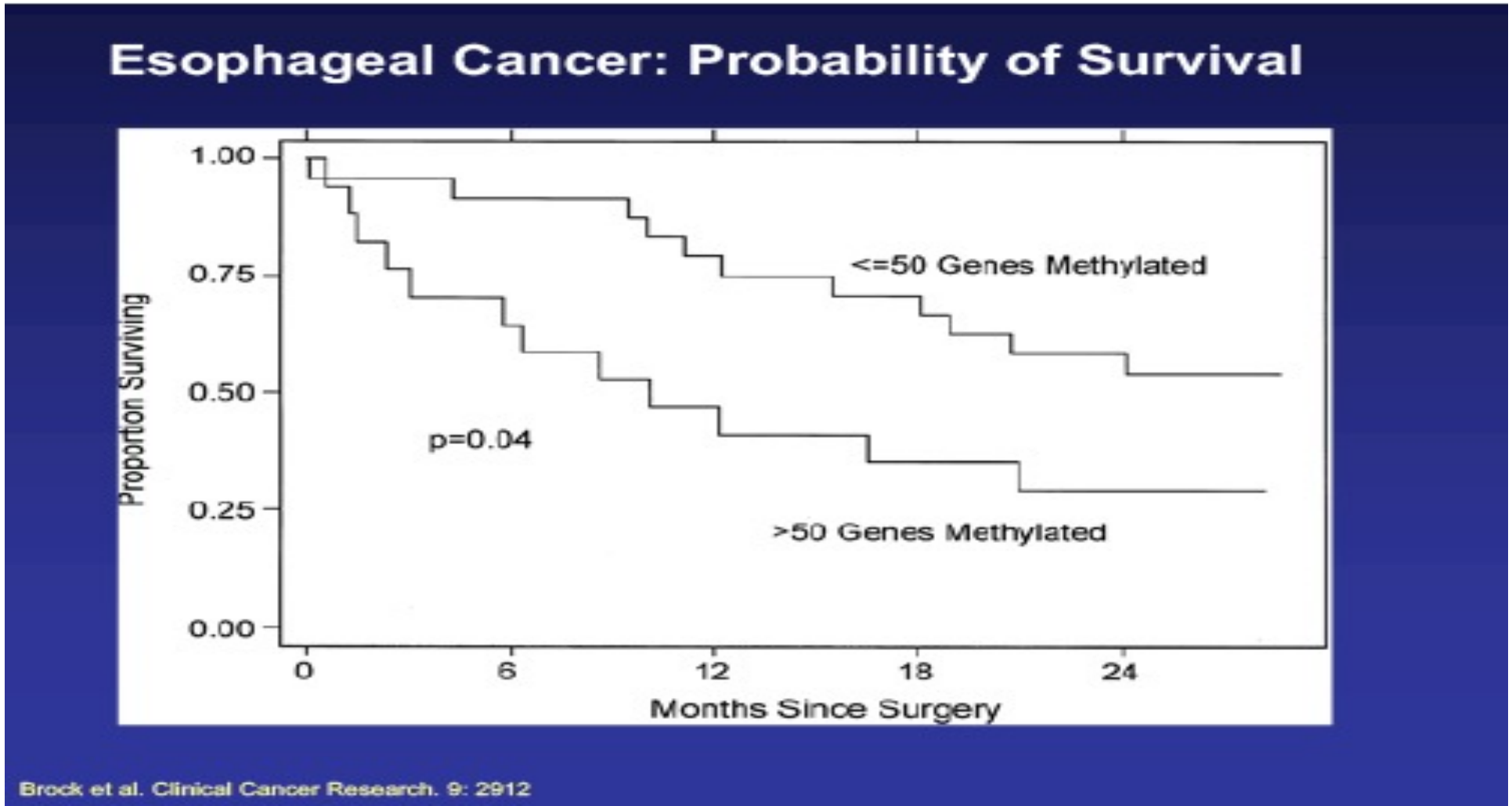
Mesothelioma



Epigenetic pattern



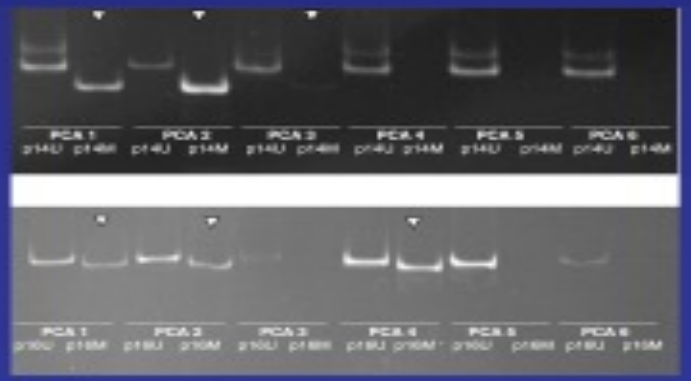
Esophageal cancer

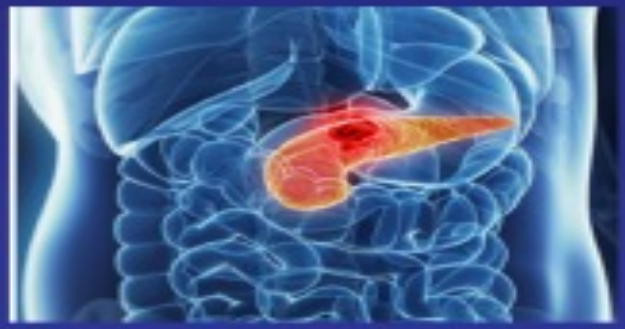


Pancreatic cancer

Pancreatic Cancer: Methylation of p14ARF and p16INK4a

Pancreatic Carcinoma (PCA) : 39	19/39	p16INK4a
Chronic Pancreatitis (CP) : 16	0/16	p16INK4a
Normal Pancreatogram (NAD) : 6	0/6	p16INK4a



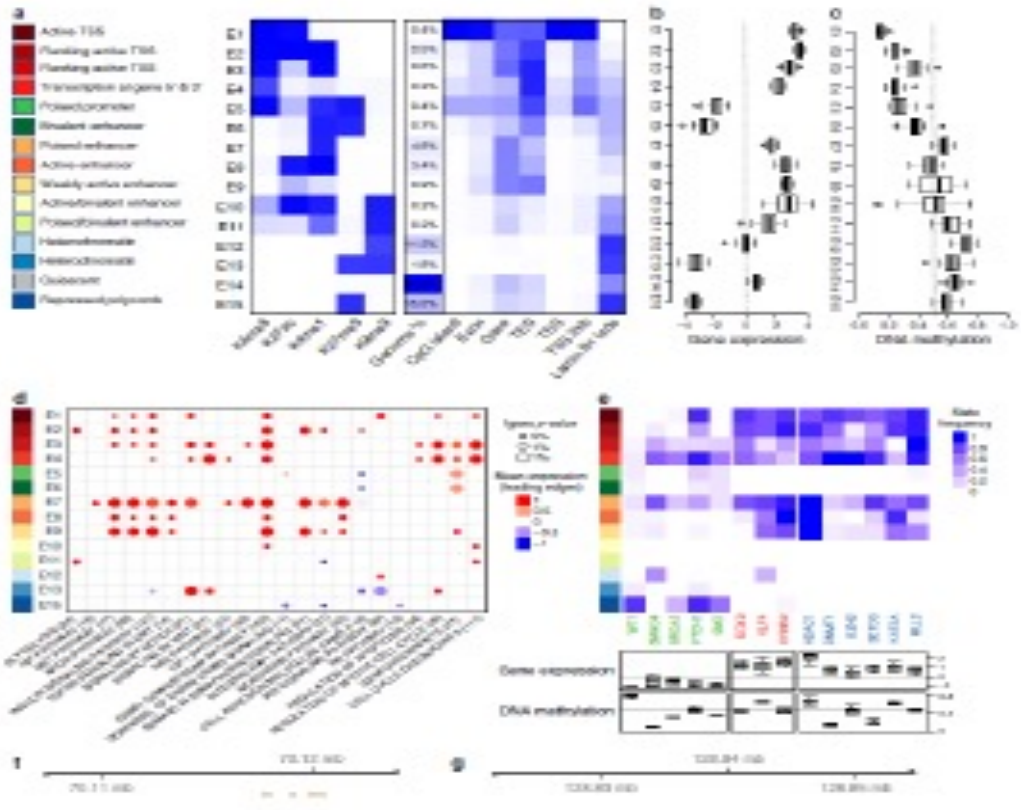


Sample: Pancreatic Fluid

(Klump et al. *Mol Cell Path* 88: 217)

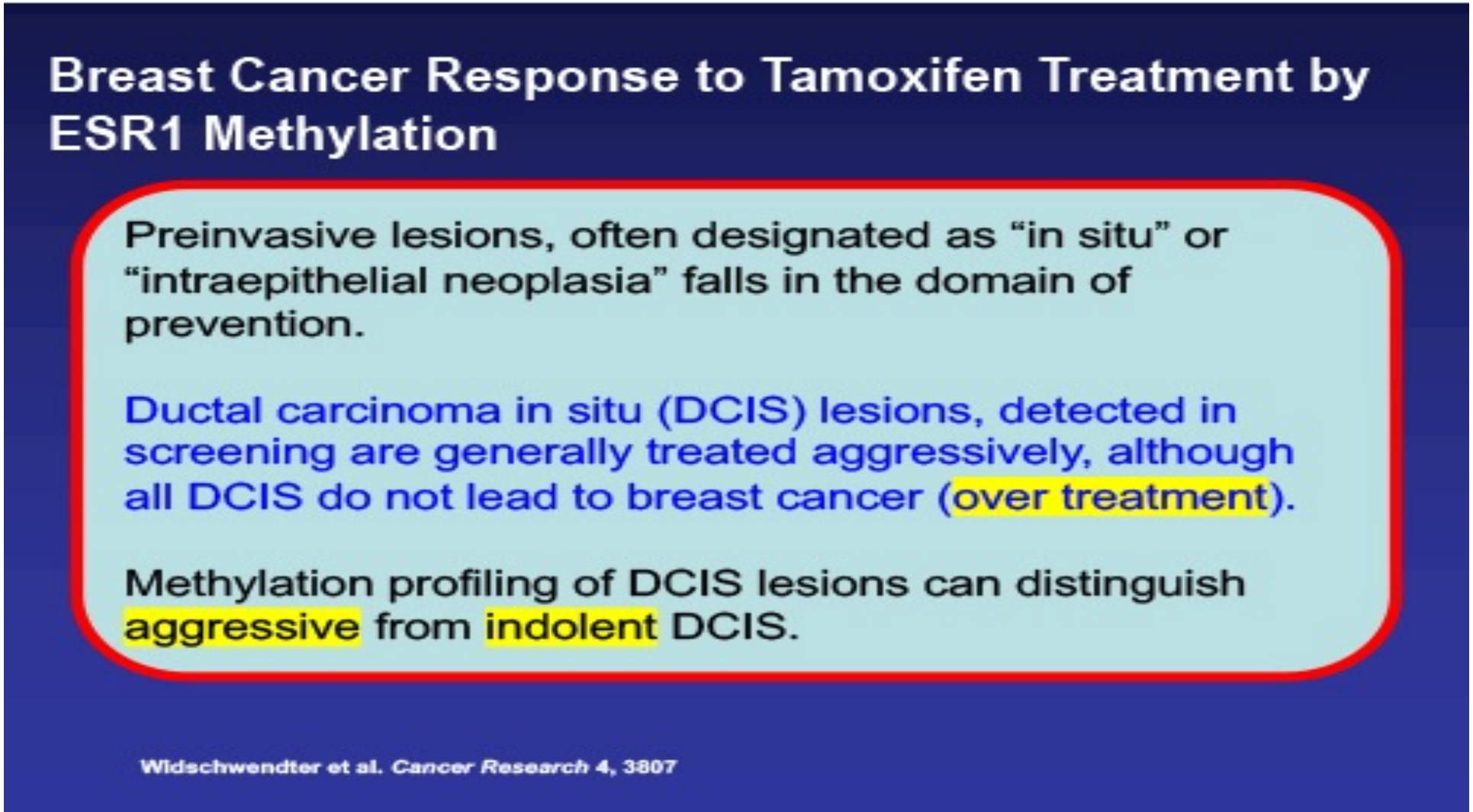
Chromatin states

Distinct chromatin states of human PDAC

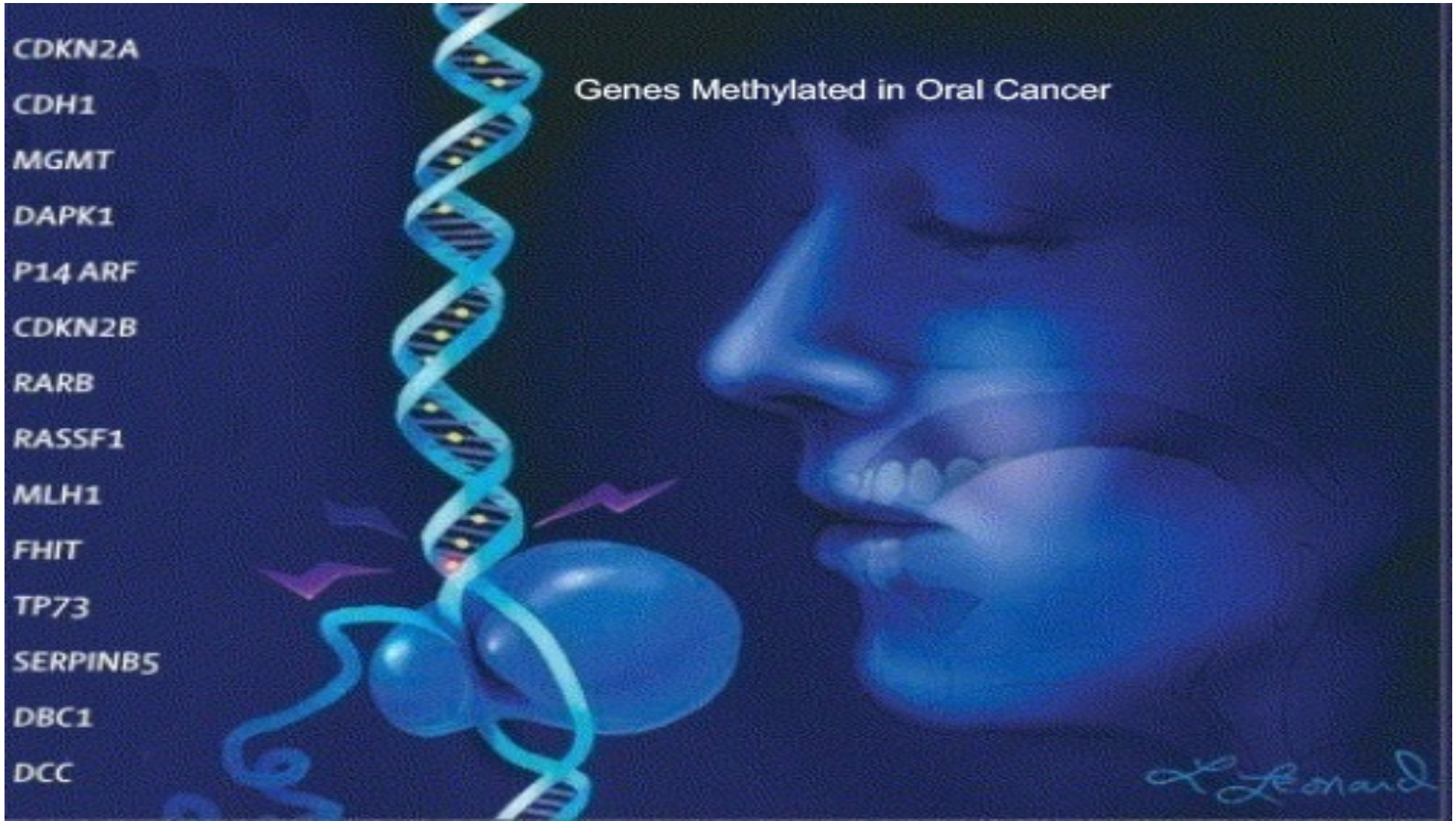


NATURE COMMUNICATIONS | (2018) 9:1978

Breast cancer



Methylated genes



Immune system and epigenetics

Immune System and Epigenetics

Shin HJ et al.
Links STAT4 expression in human T cells is regulated by DNA methylation but not by promoter polymorphism.
J Immunol.175(11):7143-50.

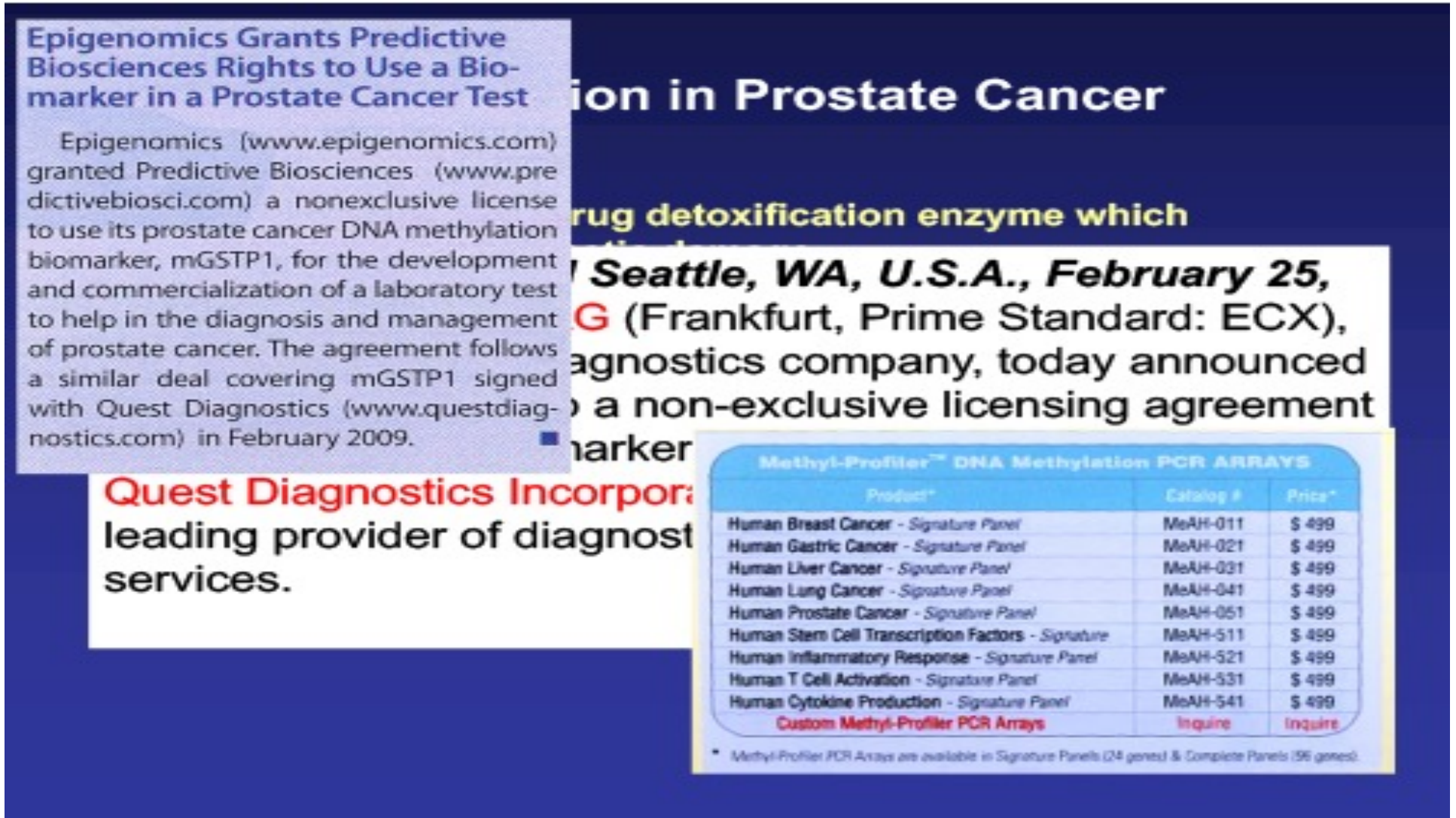
Espinoza CR, Feeney AJ.
The extent of histone acetylation correlates with the differential rearrangement frequency of individual VH genes in pro-B cells.
J Immunol. 175(10):6668-75.

Gasche JA, Hoffmann J, Boland CR, Goel A.
Interleukin-6 promotes tumorigenesis by altering DNA **methylation** in oral **cancer** cells.
Int J **Cancer**. 2011 Sep 1;129(5):1053-63.

Fujisawa T, Joshi BH, Puri RK.
Histone modification enhances the effectiveness of IL-13 receptor targeted immunotoxin in murine models of human pancreatic **cancer**.
J Transl Med. 2011 Apr 8;9:37.

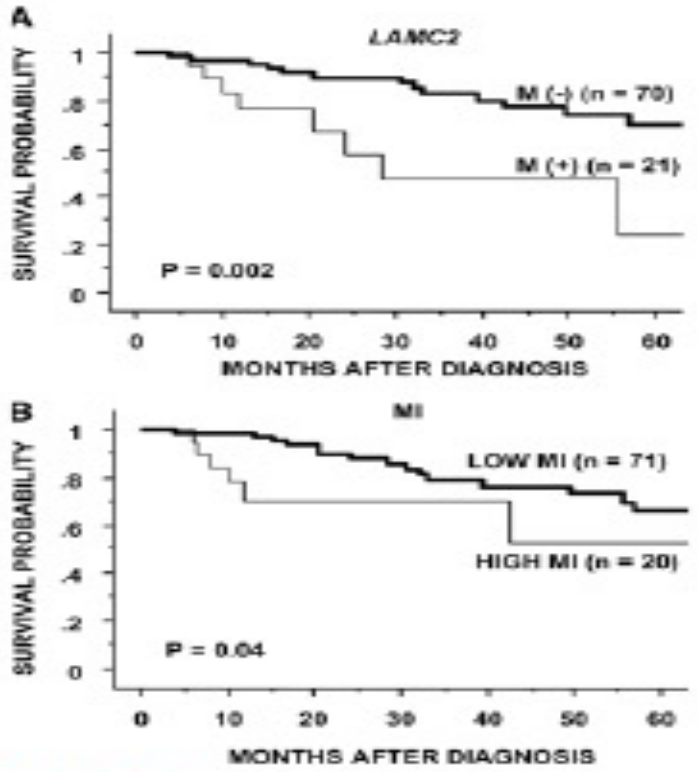
Tahara T et al.
Association between IL-17A, -17F and MIF polymorphisms predispose to CpG island hyper-**methylation** in gastric **cancer**.
Int J Mol Med. 2010 Mar;25(3):471-7.

Biomarkers


Epigenomics Grants Predictive Biosciences Rights to Use a Bio-marker in a Prostate Cancer Test
Epigenomics (www.epigenomics.com) granted Predictive Biosciences (www.predictivebiosci.com) a nonexclusive license to use its prostate cancer DNA methylation biomarker, mGSTP1, for the development and commercialization of a laboratory test to help in the diagnosis and management of prostate cancer. The agreement follows a similar deal covering mGSTP1 signed with Quest Diagnostics (www.questdiagnostics.com) in February 2009.
ion in Prostate Cancer
rug detoxification enzyme which
Seattle, WA, U.S.A., February 25,
G (Frankfurt, Prime Standard: ECX),
agnostics company, today announced
a non-exclusive licensing agreement
arker
Quest Diagnostics Incorpora
leading provider of diagnost
services.
Methyl-Profiler™ DNA Methylation PCR ARRAYS
Product* Catalog # Price*
Human Breast Cancer - Signature Panel MeAH-011 $ 499
Human Gastric Cancer - Signature Panel MeAH-021 $ 499
Human Liver Cancer - Signature Panel MeAH-031 $ 499
Human Lung Cancer - Signature Panel MeAH-041 $ 499
Human Prostate Cancer - Signature Panel MeAH-051 $ 499
Human Stem Cell Transcription Factors - Signature MeAH-511 $ 499
Human Inflammatory Response - Signature Panel MeAH-521 $ 499
Human T Cell Activation - Signature Panel MeAH-531 $ 499
Human Cytokine Production - Signature Panel MeAH-541 $ 499
Custom Methyl-Profiler PCR Arrays Inquire Inquire
* Methyl-Profiler PCR Arrays are available in Signature Panels (24 genes) & Complete Panels (96 genes).

Bladder cancer methylation

Bladder Cancer
Methylation of LAMC2 in Exfoliated Cells Isolated from Urine

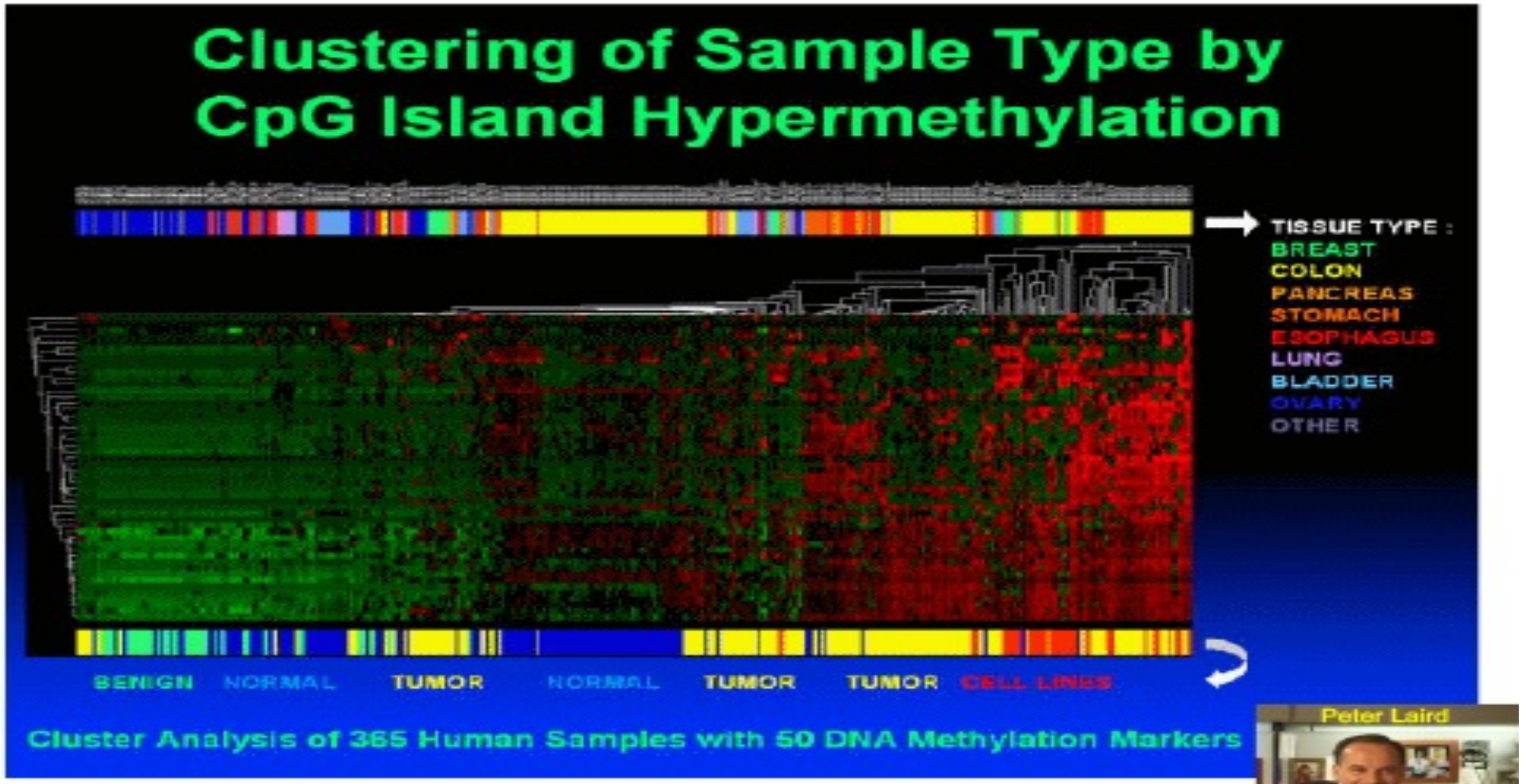


Another Study:
Schistosomes and Bladder Cancer

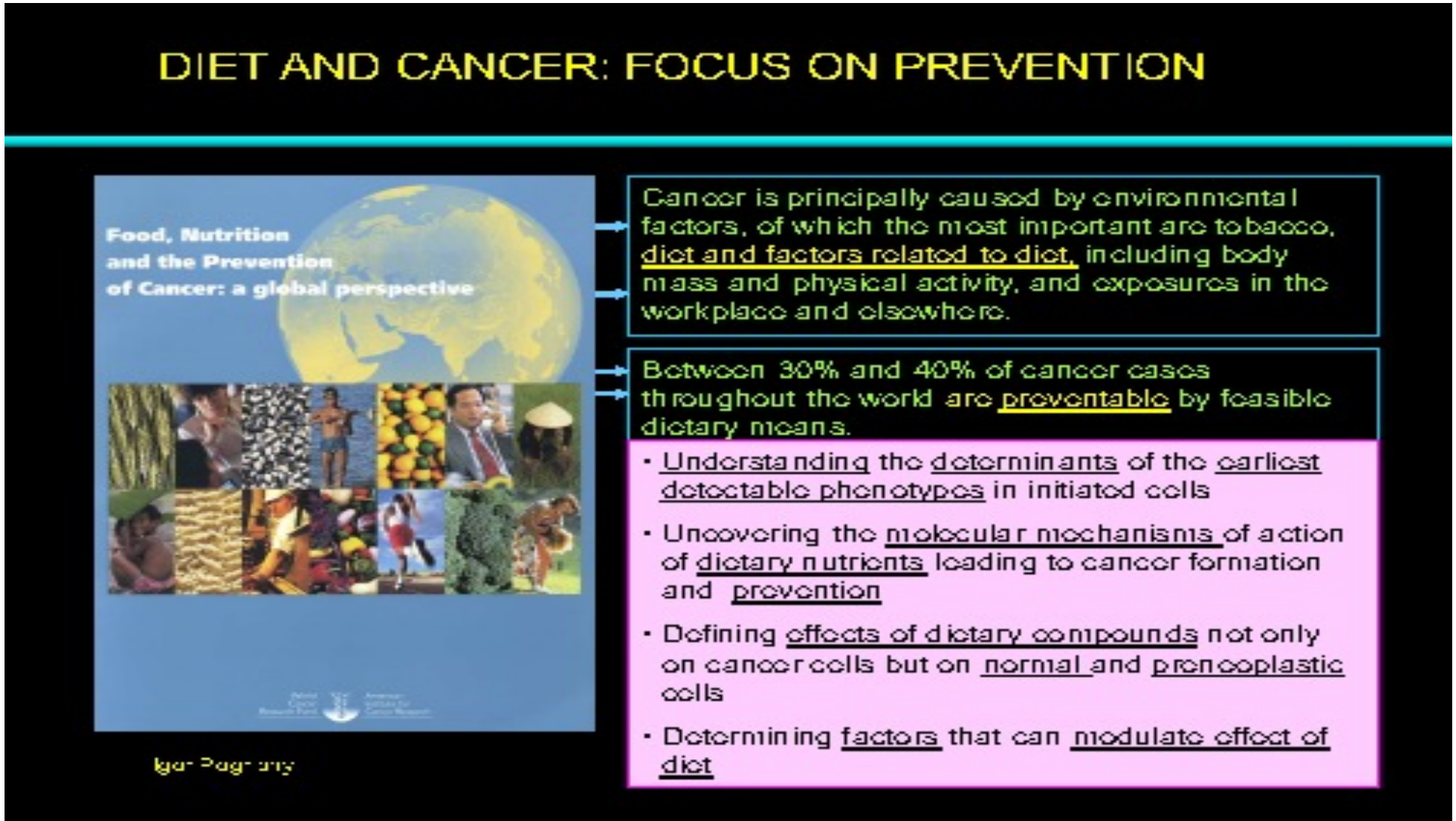
MI, Methylation Index

(Sathyanarayana et al. *Can Res* 64: 1425)

CpG island hypermethylation

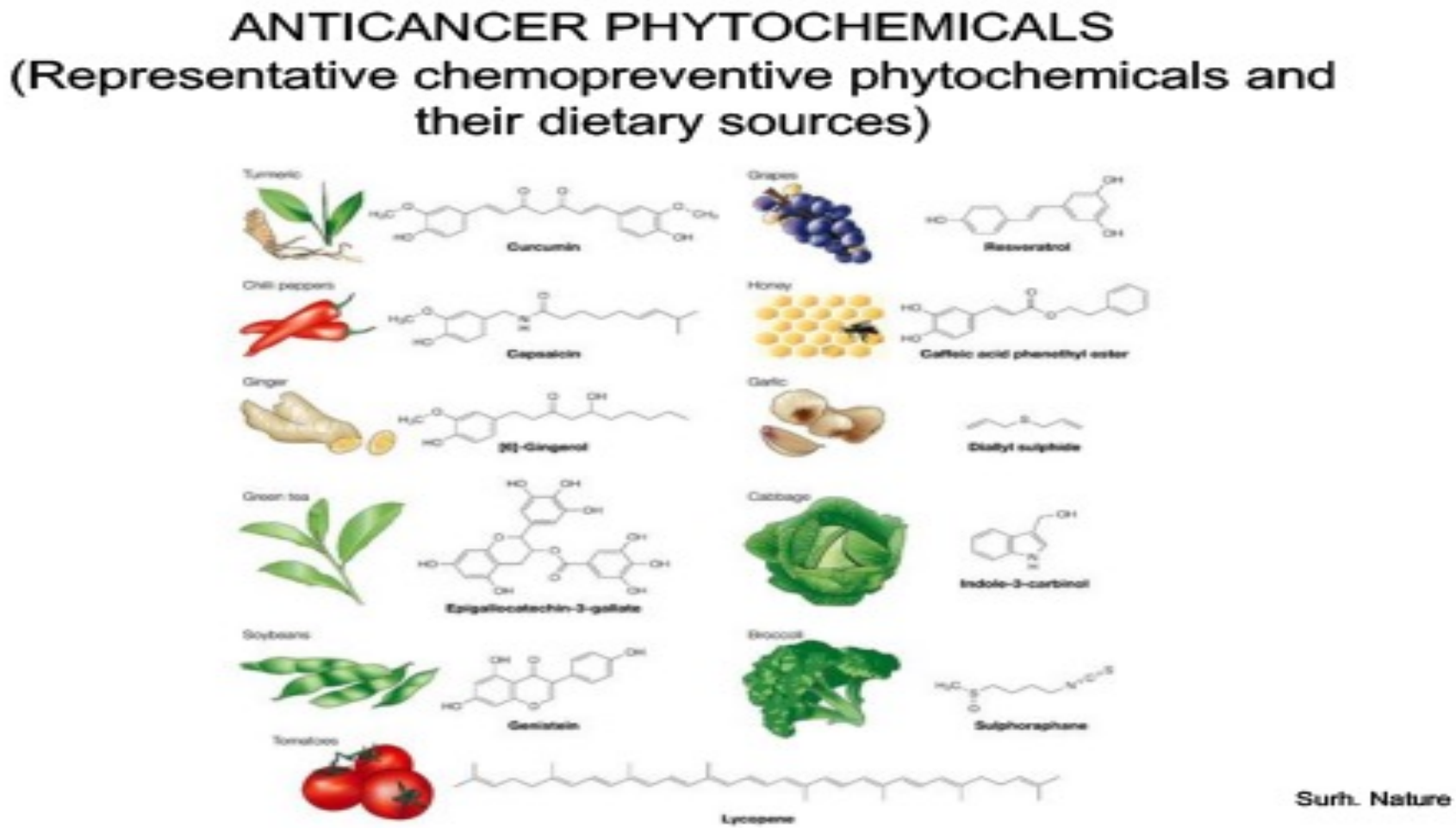


Diet and cancer

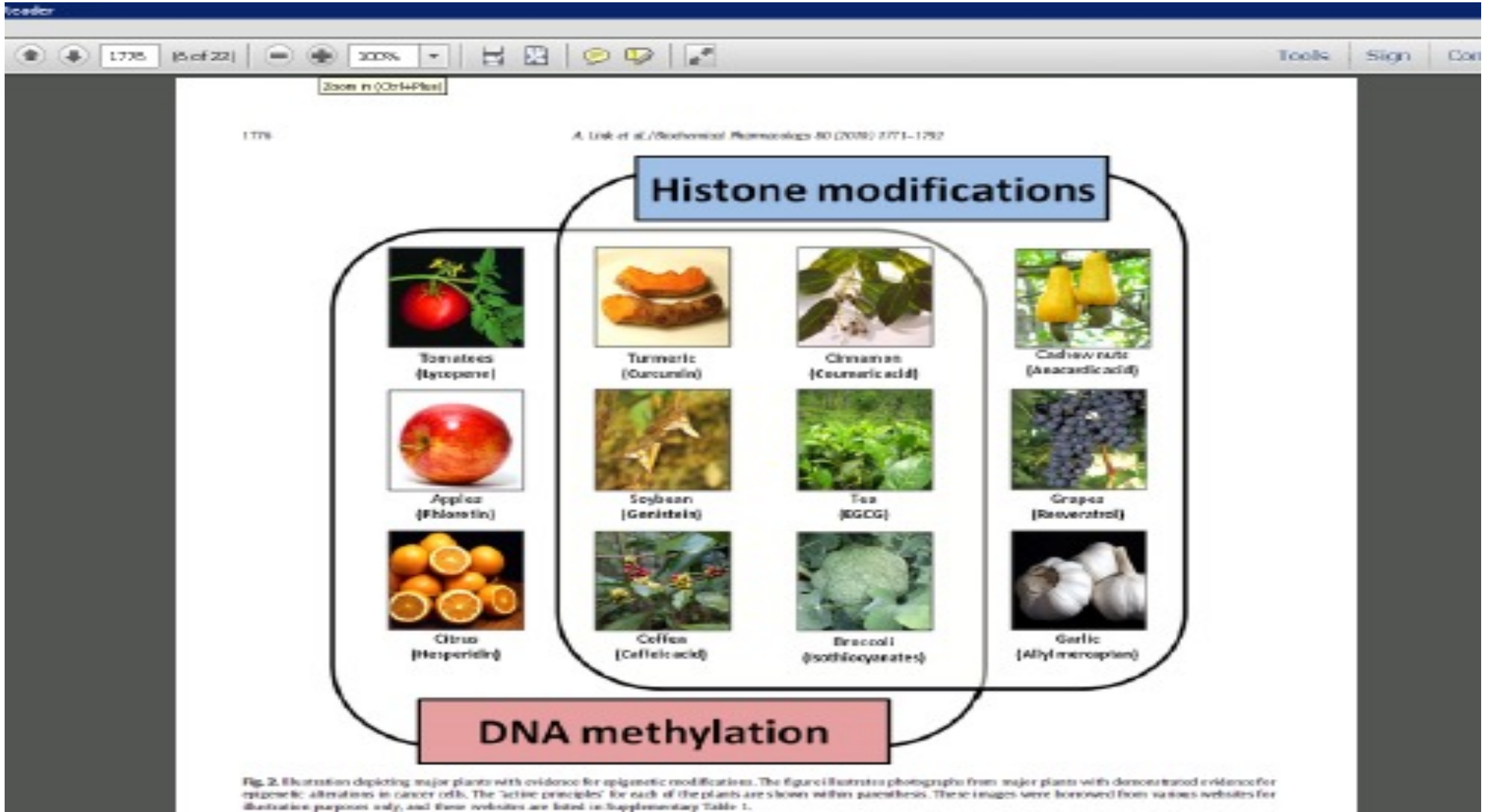


Methyl deficiency

Anticancer phytochemicals



Epigenetic foods



Research opportunities

National Cancer Institute

Research Opportunities and Challenges

Will inclusion of epigenetic markers help in identification of new risk factors (modifiable factors and host factors) in different races and ethnic groups?

Will epigenetic markers in cohort and case-control studies improve sensitivity and specificity of markers and help in identifying high-risk populations?

Are genetic and epigenetic events correlated during cancer development?

Are there race/ethnicity specific miRNAs and noncoding RNAs?

How can we use this information for better define cancer subcategories?

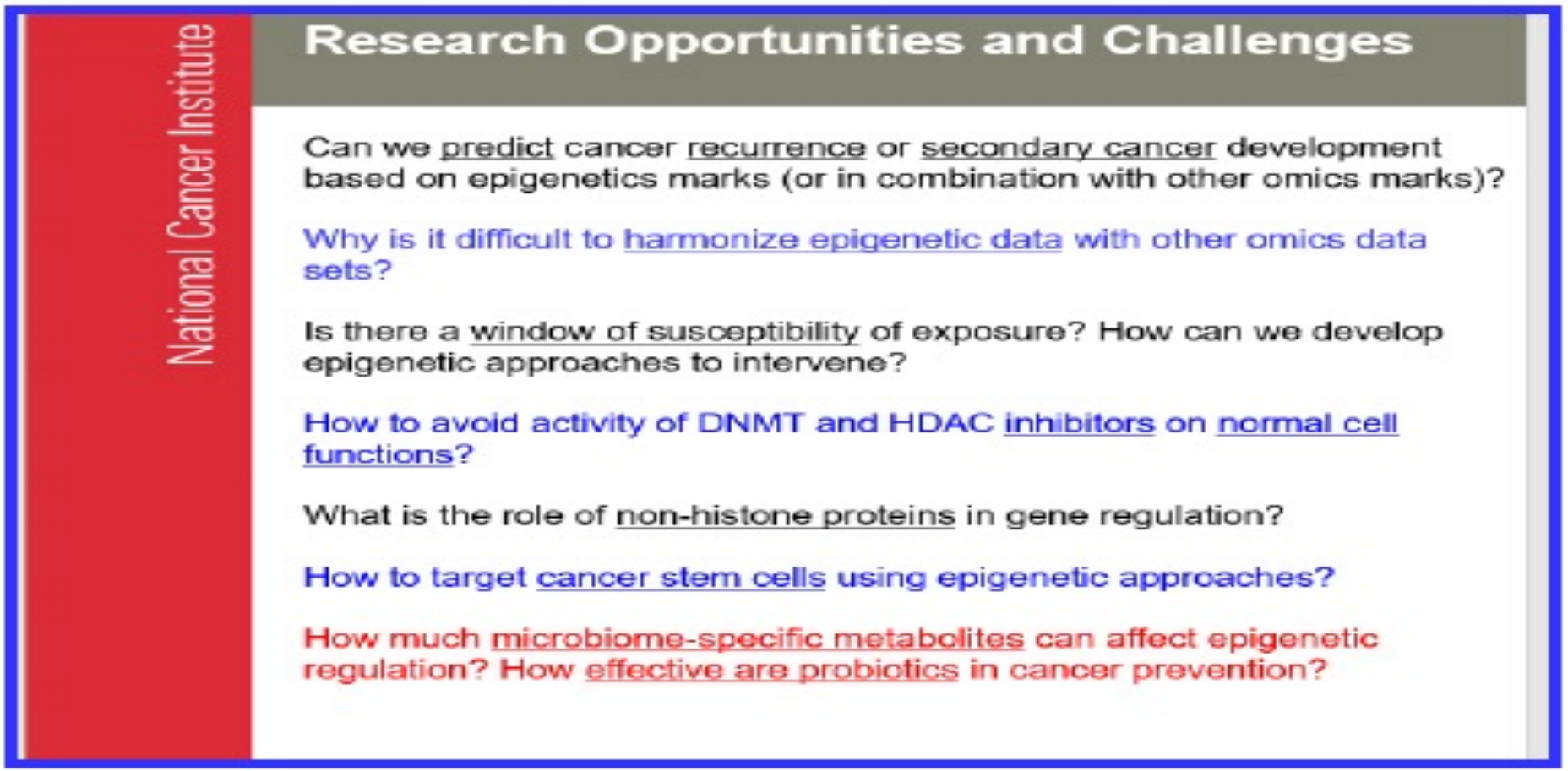
How can we overcome EWAS technical challenges?

Christopher Plass (Heidelberg)

Nancy Kiviat (Seattle)

Christine Ambrosone (Roswell Park, Buffalo)

Research challenges



How to address challenges

National Cancer Institute

How are we addressing these challenges?

NIH common fund

Personalized medicine

Cancer Epidemiology, Biomarkers & Prevention

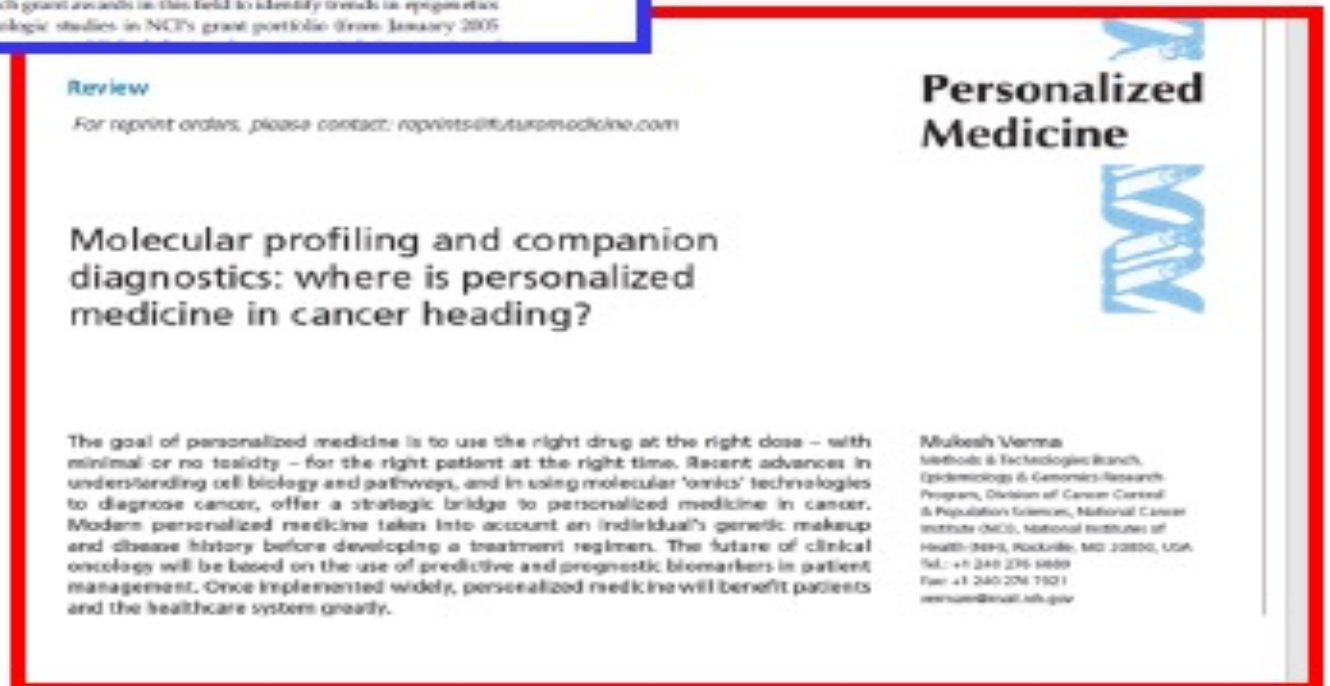
Minireview

Epigenetic Research in Cancer Epidemiology: Trends, Opportunities, and Challenges

Mukesh Verma[1], Scott Rogers[1], Rao L. Divi[1], Sheri D. Schully[1], Stefanie Nelson[1], L. Joseph Su[1], Sharon A. Ross[2], Susan Pitch[3], Deborah M. Winn[1], and Muin J. Khoury[1,4]

Abstract

Epigenetics is emerging as an important field in cancer epidemiology that promises to provide insights into gene regulation and facilitate cancer control throughout the cancer care continuum. Increasingly, investigators are incorporating epigenetic analysis into the study of etiology and outcomes. To understand current progress and trends in the inclusion of epigenetics in cancer epidemiology, we evaluated the published literature and the National Cancer Institute (NCI)–supported research grant awards in this field to identify trends in epigenetics research. We present a summary of the epidemiologic studies in NCI's grant portfolio (from January 2005



Review

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Personalized Medicine

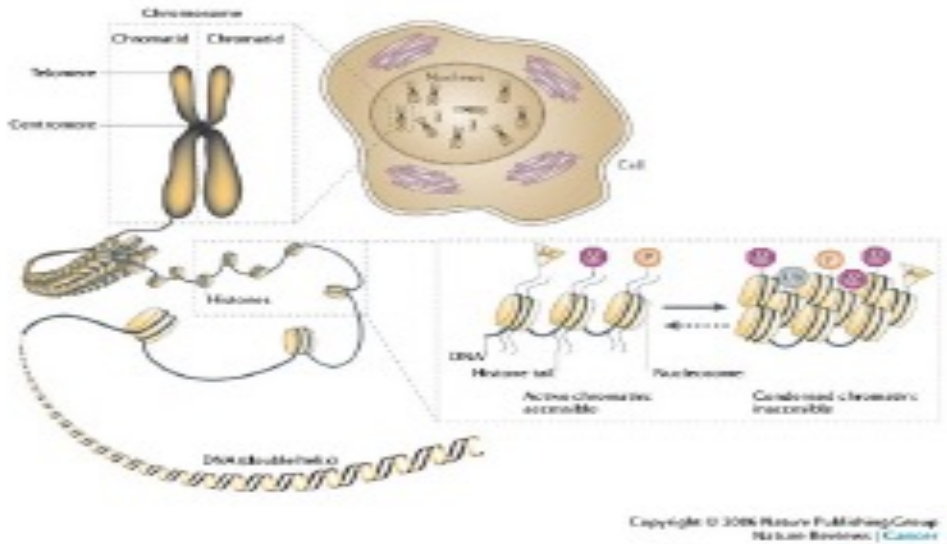
Molecular profiling and companion diagnostics: where is personalized medicine in cancer heading?

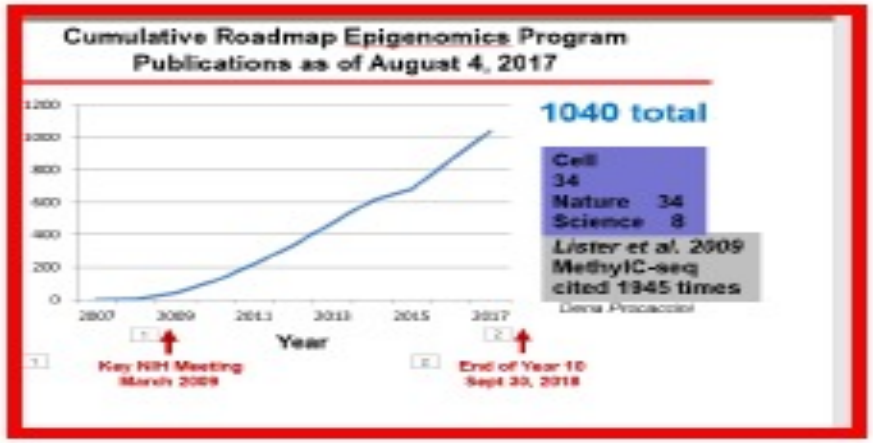
The goal of personalized medicine is to use the right drug at the right dose – with minimal or no toxicity – for the right patient at the right time. Recent advances in understanding cell biology and pathways, and in using molecular 'omics' technologies to diagnose cancer, offer a strategic bridge to personalized medicine in cancer. Modern personalized medicine takes into account an individual's genetic makeup and disease history before developing a treatment regimen. The future of clinical oncology will be based on the use of predictive and prognostic biomarkers in patient management. Once implemented widely, personalized medicine will benefit patients and the healthcare system greatly.

Mukesh Verma
Methods & Technologies Branch, Epidemiology & Genomics Research Program, Division of Cancer Control & Population Sciences, National Cancer Institute (NCI), National Institutes of Health (NIH), Rockville, MD 20850, USA
Tel.: +1 240 276 6609
Fax: +1 240 276 7821
vermuse@mail.nih.gov

Epigenetics roadmap

Epigenetics Roadmap



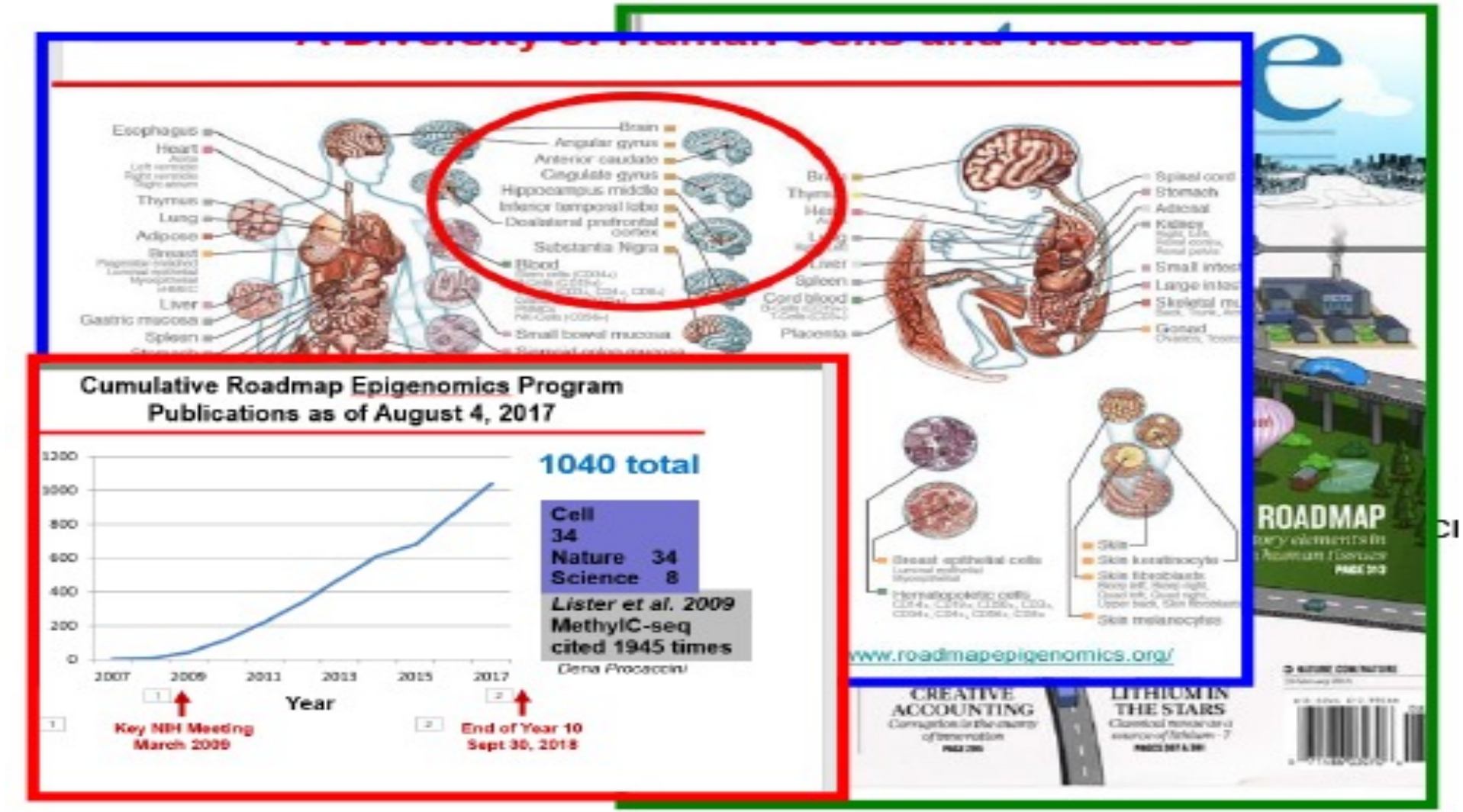


Epigenetically Regulated Diseases:
Several cancers, autoimmune disorders, reproductive disorders, and neurobehavioral and cognitive dysfunctions

The NIH Roadmap Epigenomics Mapping Consortium was launched with the goal of producing a public resource of human epigenomic data to catalyze basic biology and disease-oriented research.

http://nihroadmap.nih.gov/epigenomics/

Roadmap


Cumulative Roadmap Epigenomics Program
Publications as of August 4, 2017
1040 total
Cell 34
Nature 34
Science 8
Lister et al. 2009
MethylC-seq
cited 1945 times
Dena Procaccini
Year
Key NIH Meeting
March 2009
End of Year 10
Sept 30, 2018
www.roadmapepigenomics.org/
ROADMAP
CREATIVE ACCOUNTING
LITHIUM IN THE STARS

IHEC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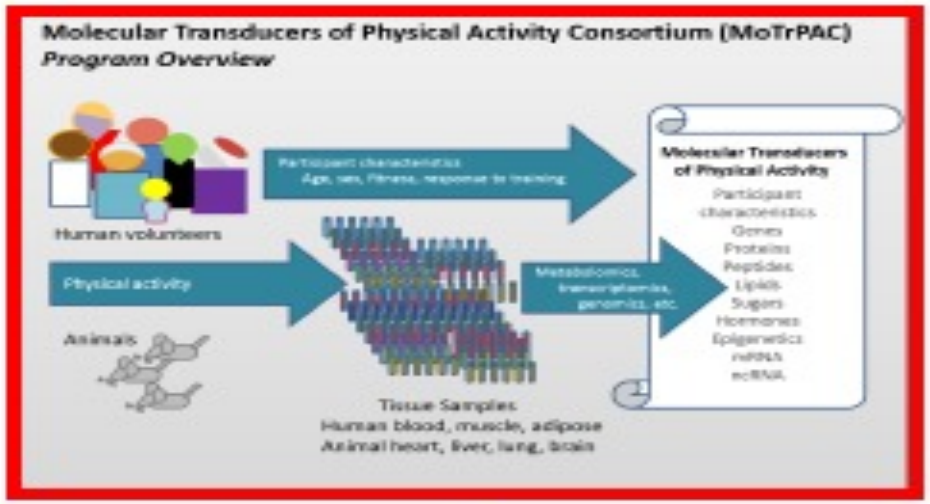
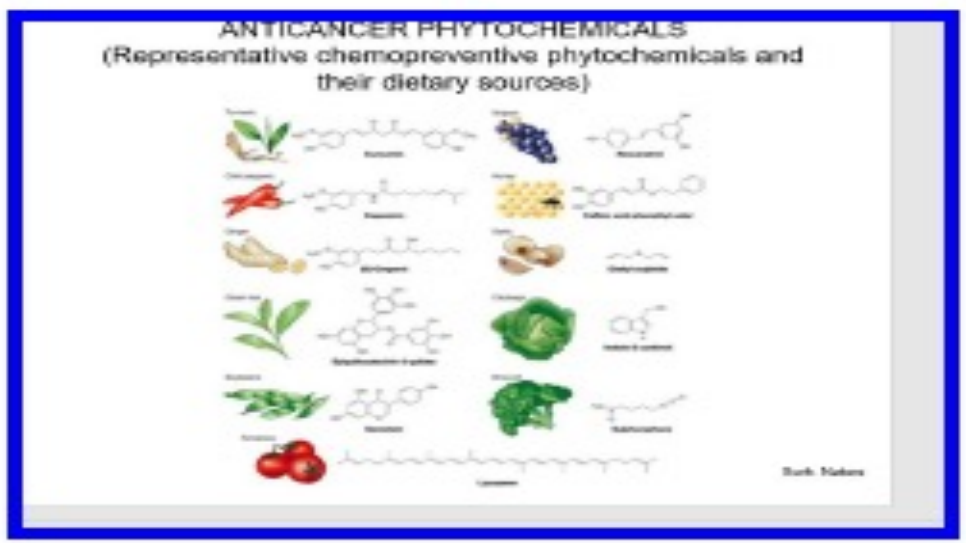
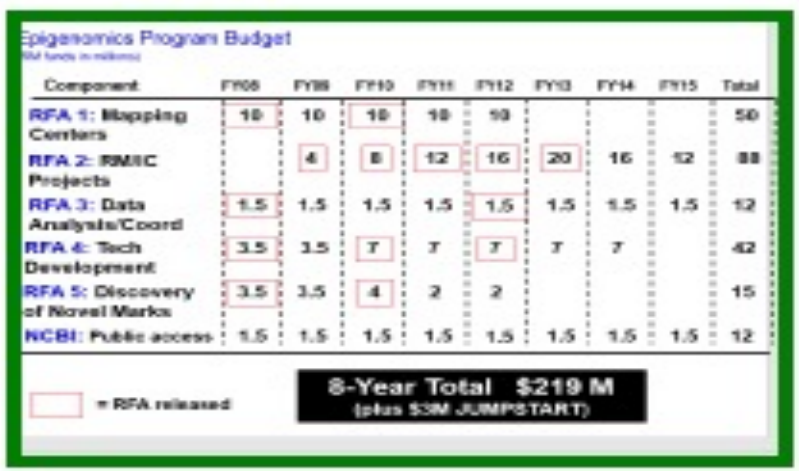
The International Human Epigenome Consortium (IHEC) unites scientists from all over the world working together to achieve one common goal:
Welcome to IHEC
Lectures
Research

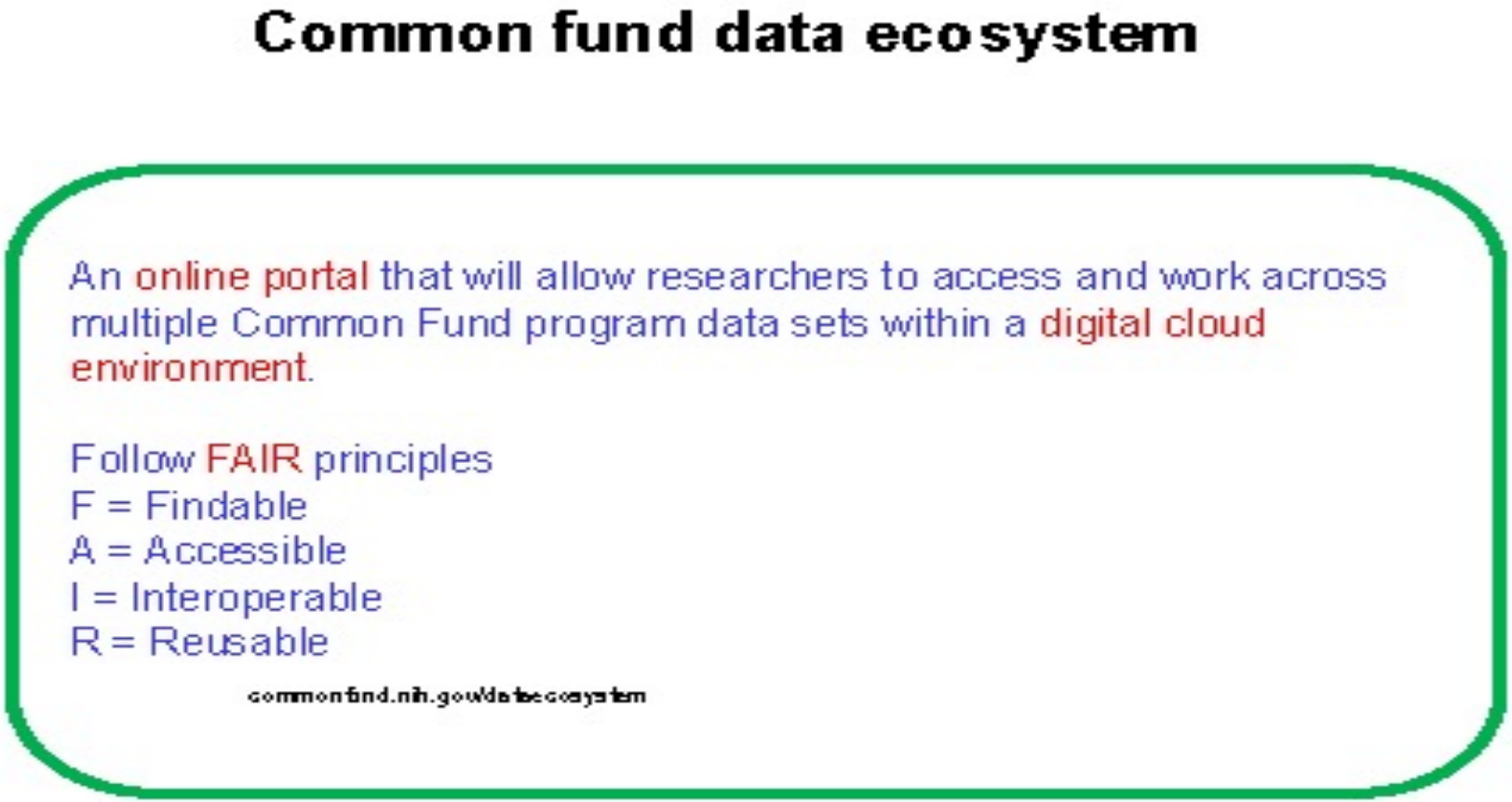
Miscellaneous



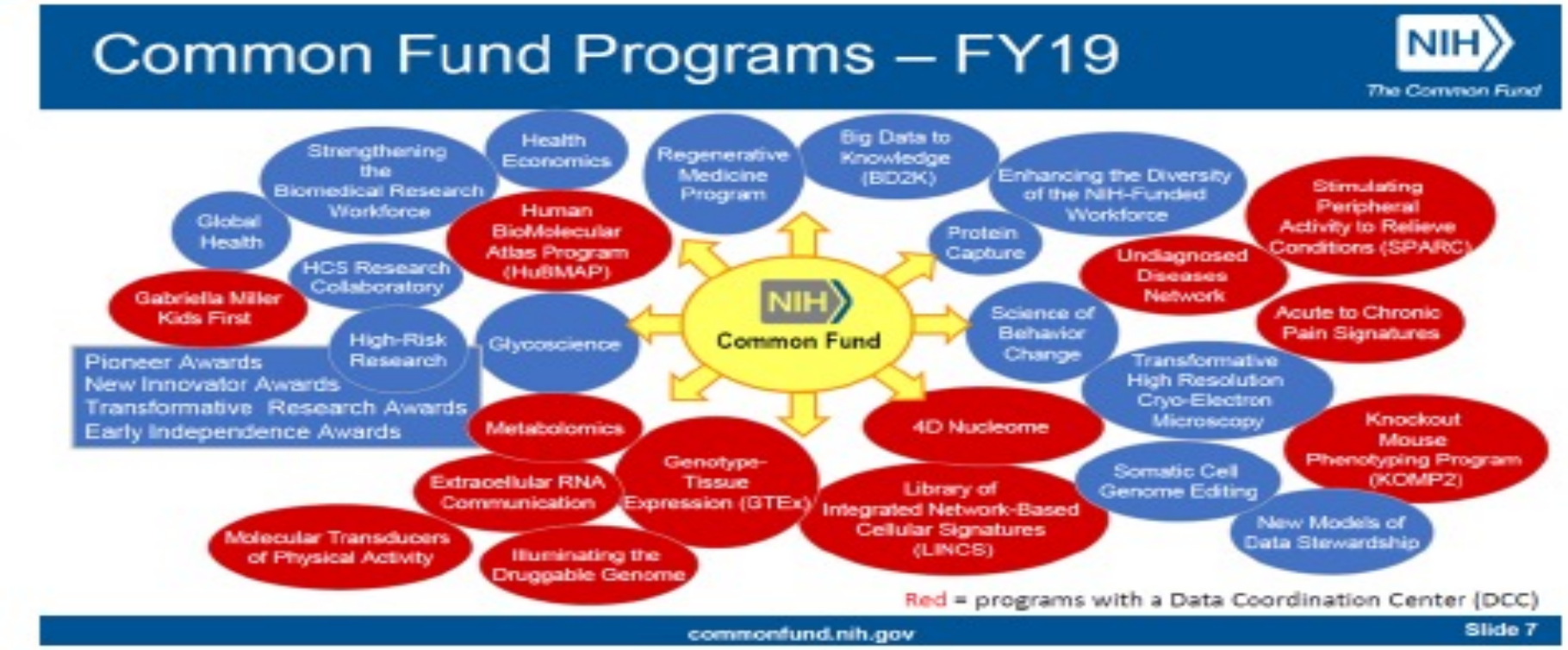




Common fund


Common fund data ecosystem
An online portal that will allow researchers to access and work across multiple Common Fund program data sets within a digital cloud environment.
Follow FAIR principles
F = Findable
A = Accessible
I = Interoperable
R = Reusable
commonfund.nih.gov/datecosystem

Common fund programs



CFDE projects

Status of CFDE Project activities

NIH The Common Fund

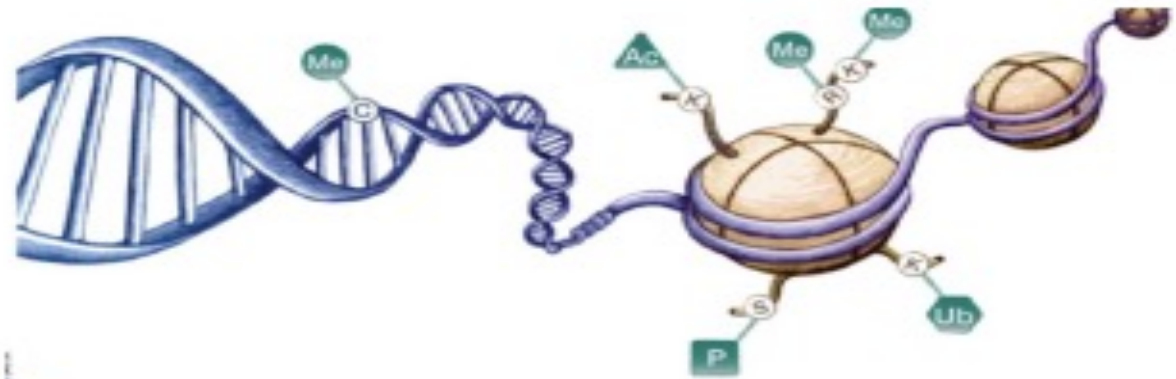
- Funded the CFDE Coordinating Center (Owen White, PI)
- The CFDE Coordinating Center had "Deep Dive" in-person visits to 8 Common Fund DCCs.
  - Kids First
  - GTEx
  - HMP
  - LINCS
  - SPARC
  - MoTrPAC
  - HuBMAP
  - 4D Nucleome
  - Metabolomics (Nov)
- Plan to evaluate "success" of the CFDE both impact on CF Programs and project process.
- Fund the next set of CFDE activities, such as addressing data storage and single-sign on.

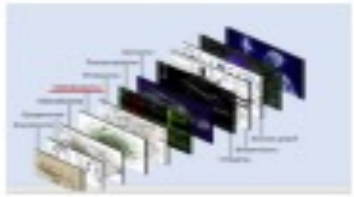
NIH


NIH...
Mukesh Verma, PhD
vermam@mail.nih.gov
Turning Discovery Into Health
98

Epigenetic approaches

EPIGENETIC APPROACHES IN CANCER CONTROL AND TREATMENT





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Program Director,
Epidemiology and Genomics Research Program
DCCPS, NCI, NIH