

**ALTERAZIONI A CARICO DI ONCOGENI E
ONCOSOPPRESSORI**

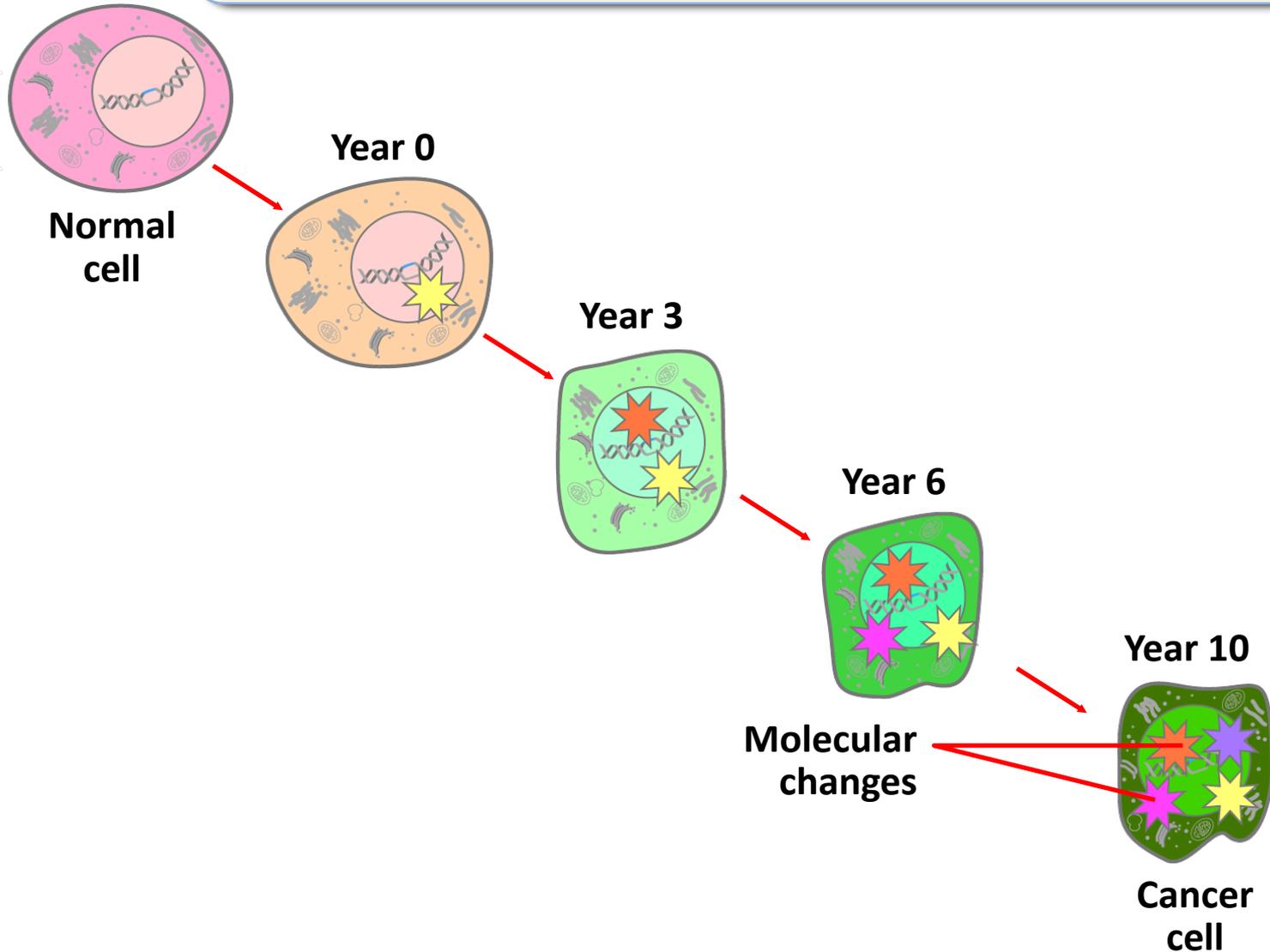
**IL RUOLO DELLE ALTERAZIONI
EPIGENETICHE NEL CANCRO**

**ALTERAZIONE DELL'ESPRESSIONE GENICA
NEL CANCRO**

ALTERAZIONI A CARICO DI ONCOGENI E ONCOSOPPRESSORI

La trasformazione e l'evoluzione tumorale dipendono dall'accumulo sequenziale di alterazioni in geni driver

Attribuita da Jeanne Kelly, © 2001.



Un semplice modello di evoluzione darwiniana (sequenziale)

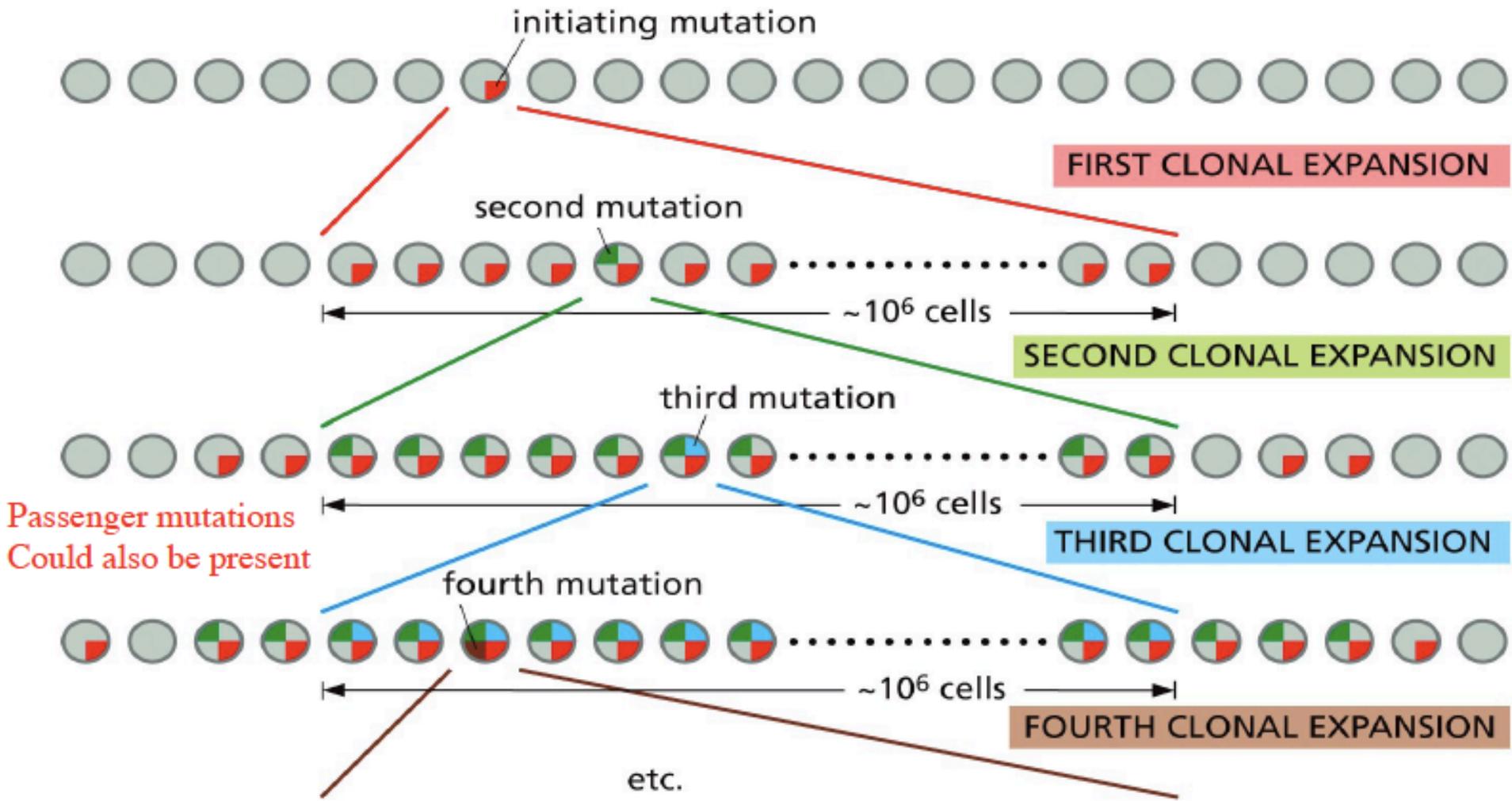
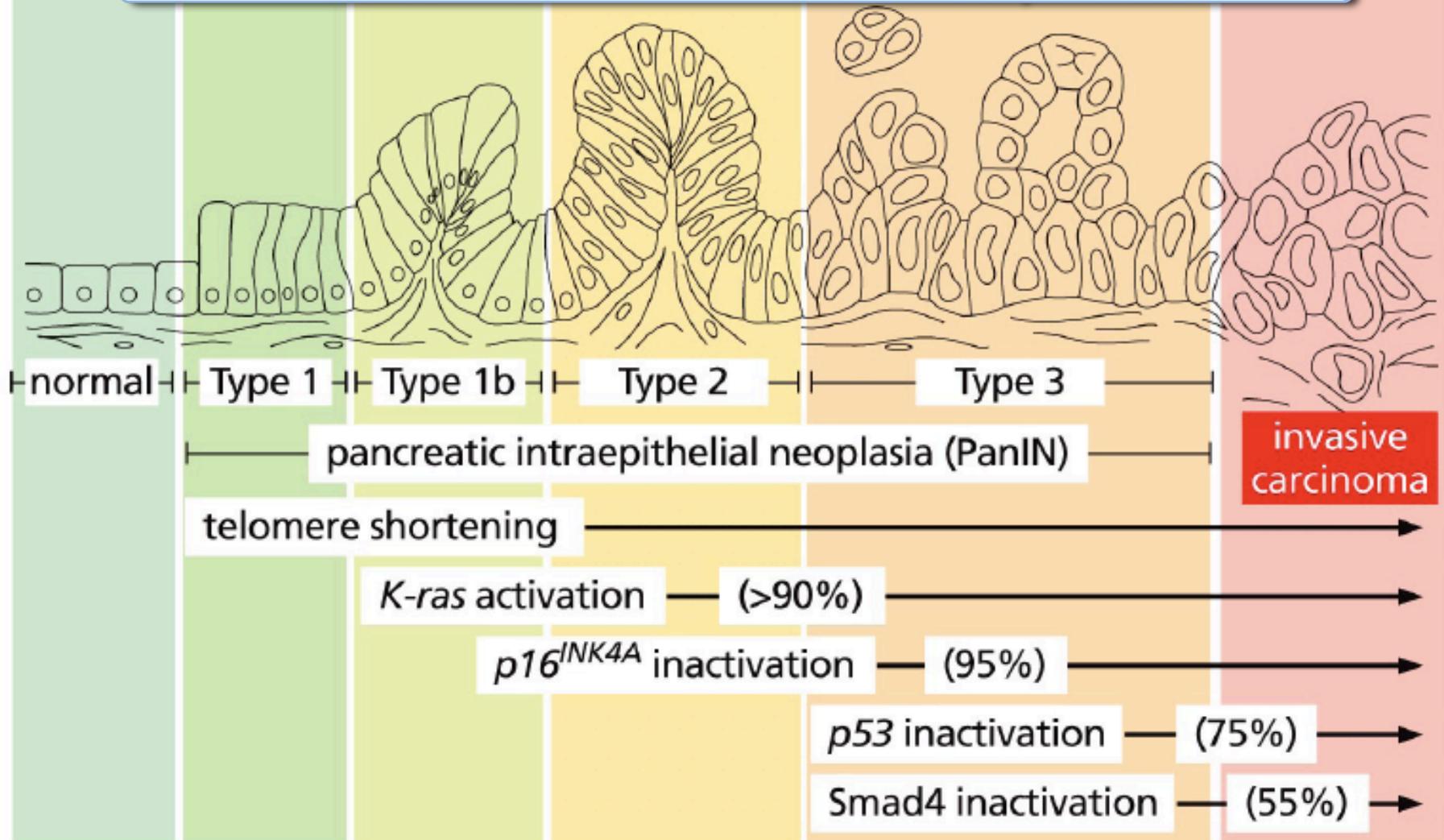


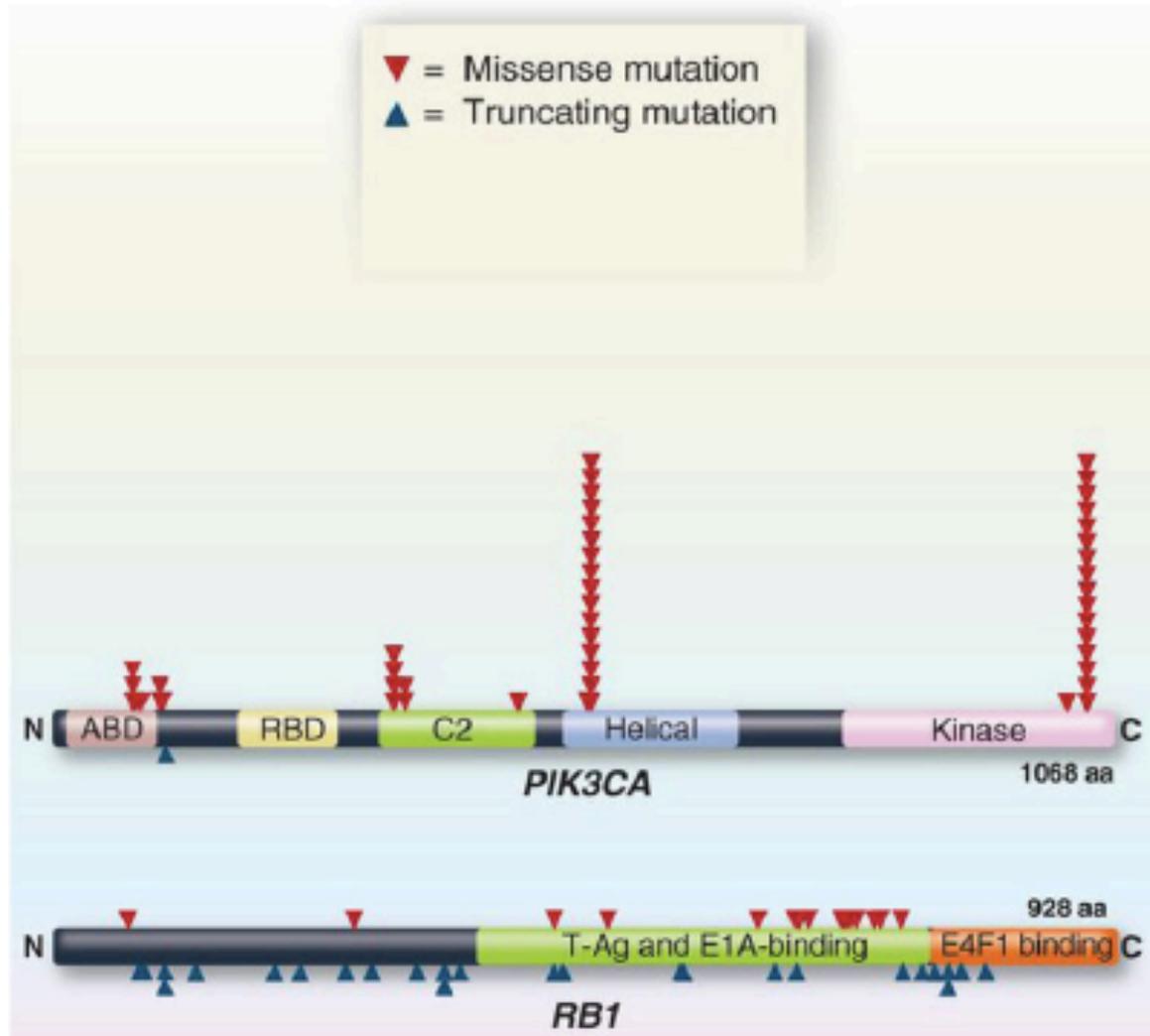
Figure 11.15 The Biology of Cancer (© Garland Science 2014)

Ciascun tumore presenta mutazioni a carico di oncogeni e oncosoppressori

Mutazioni nell'evoluzione del tumore al pancreas



Diverso pattern di mutazione in oncogeni e oncosoppressori



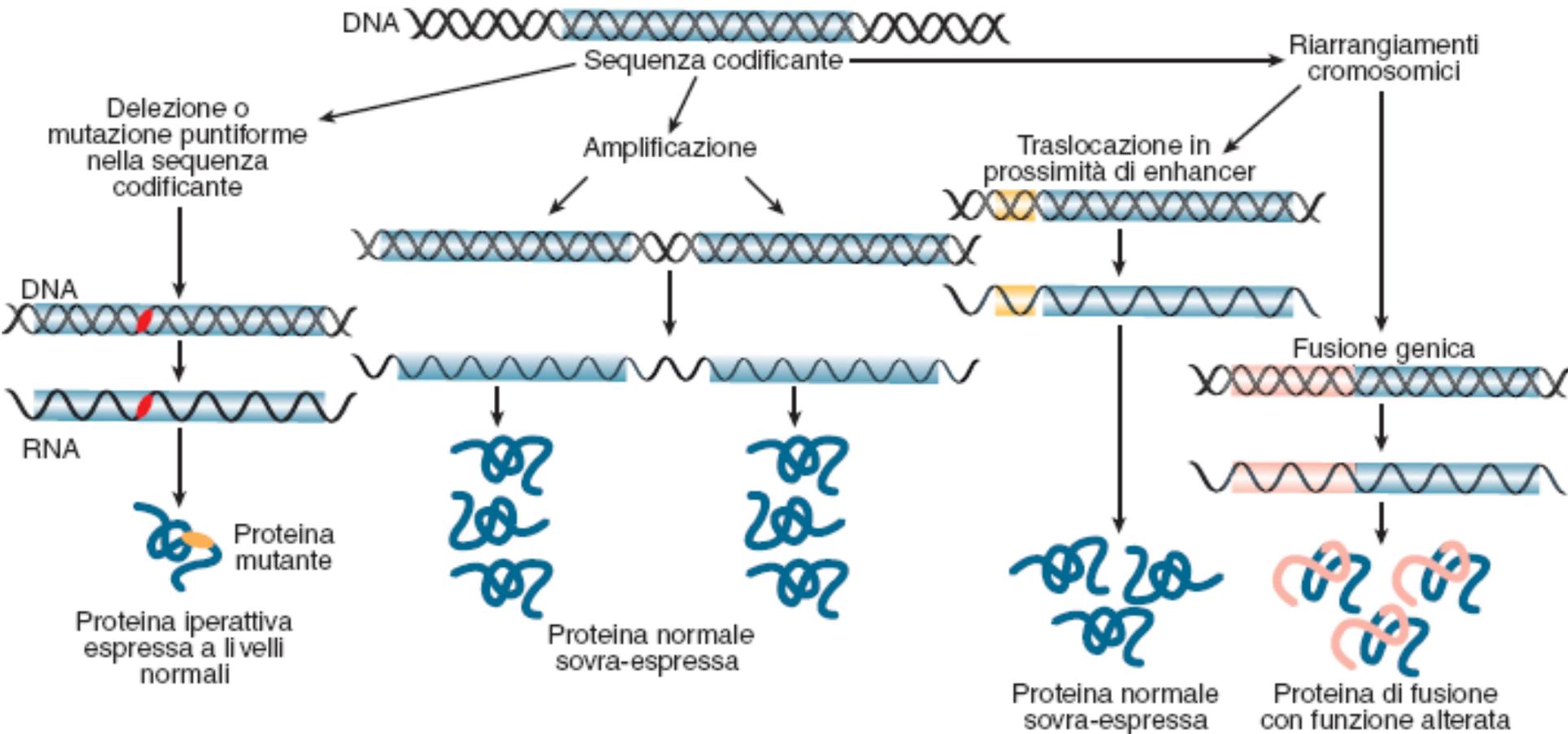
Pattern mutazionali dei geni del cancro

I pattern mutazionali osservati in oncogeni e oncosoppressori sono altamente caratteristici e non casuali.

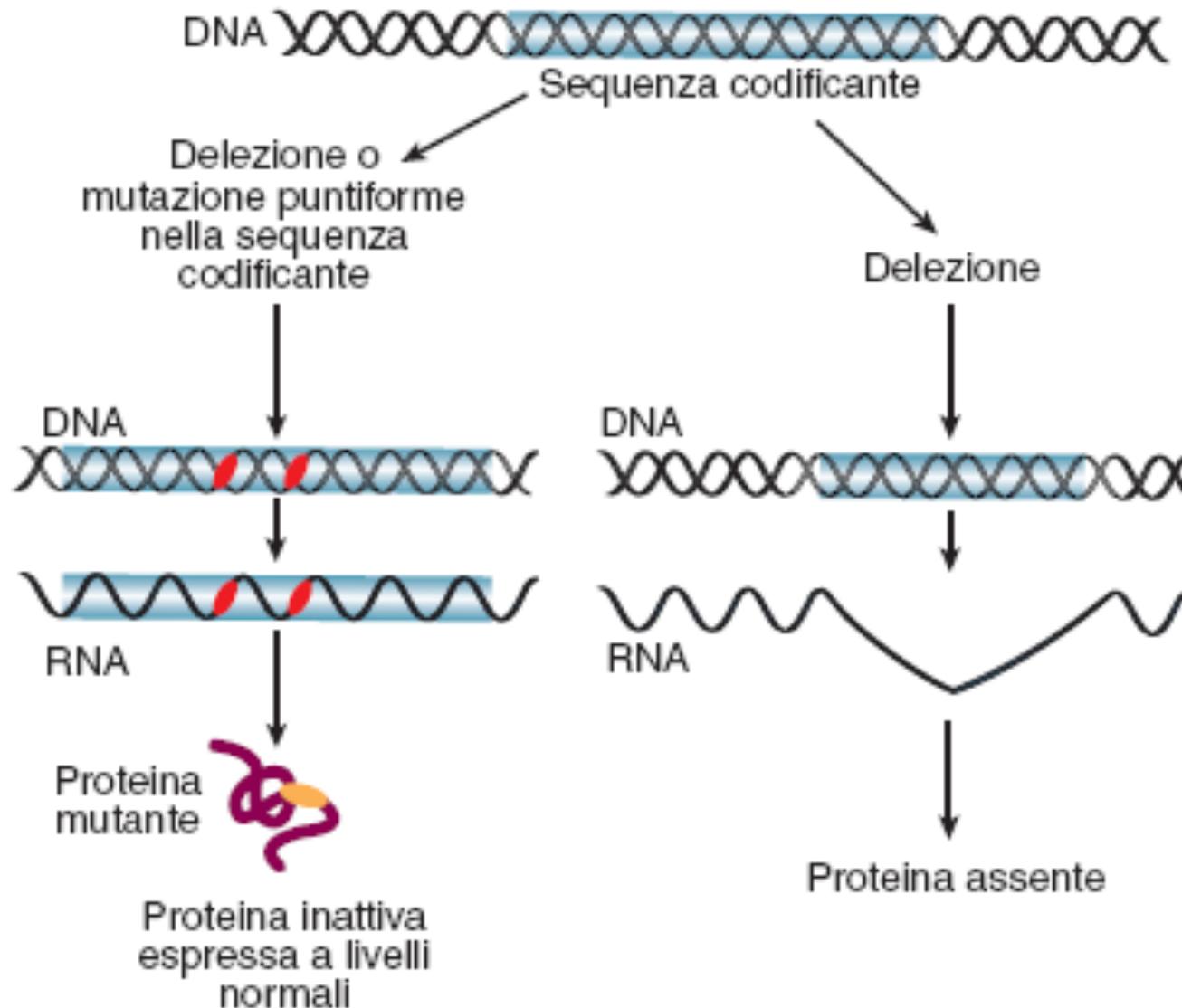
Gli **oncogeni** presentano tipicamente **mutazioni missenso** (che causano sostituzioni aminoacidiche) a specifici codoni, mentre gli **oncosoppressori** presentano pattern di mutazioni **inattivanti** (più frequentemente **frameshift** che causano delezioni) lungo l'intera sequenza.

Geni **Epi-driver** sono **espressi** in maniera aberrante che conferisce un vantaggio selettivo.

Alterazioni che causano attivazione di oncogeni

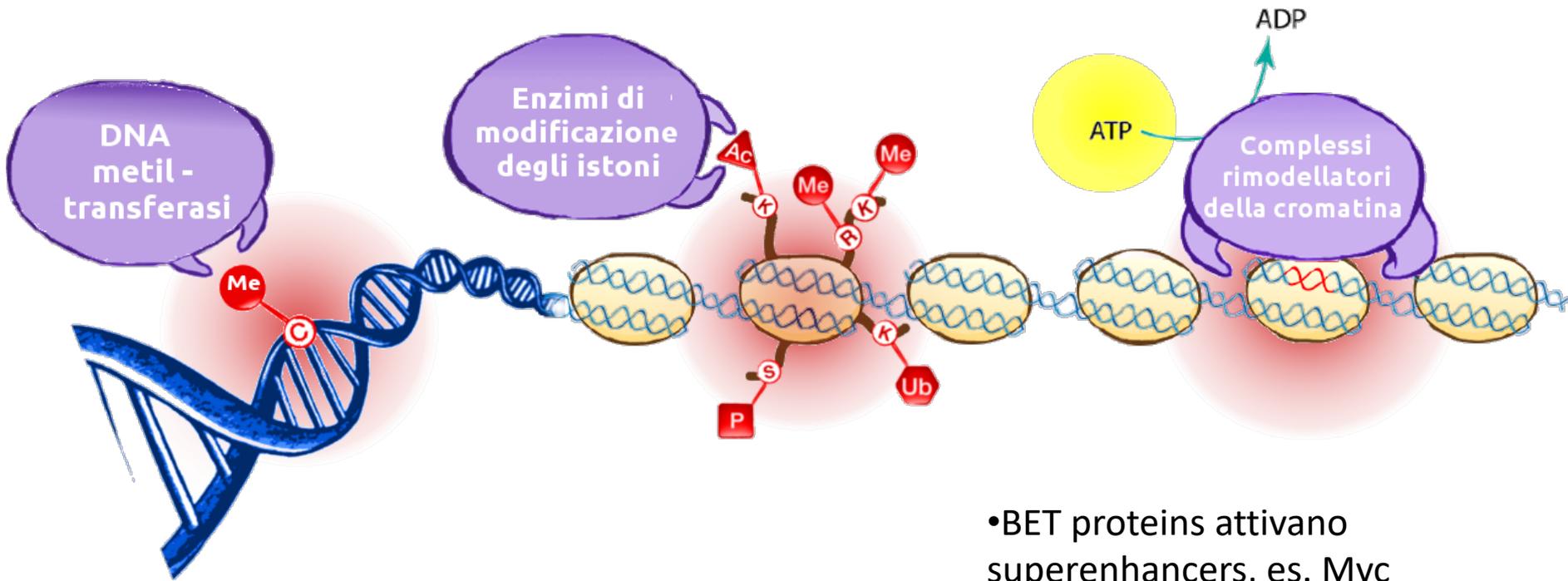


Alterazioni che causano inattivazione di oncosoppressori



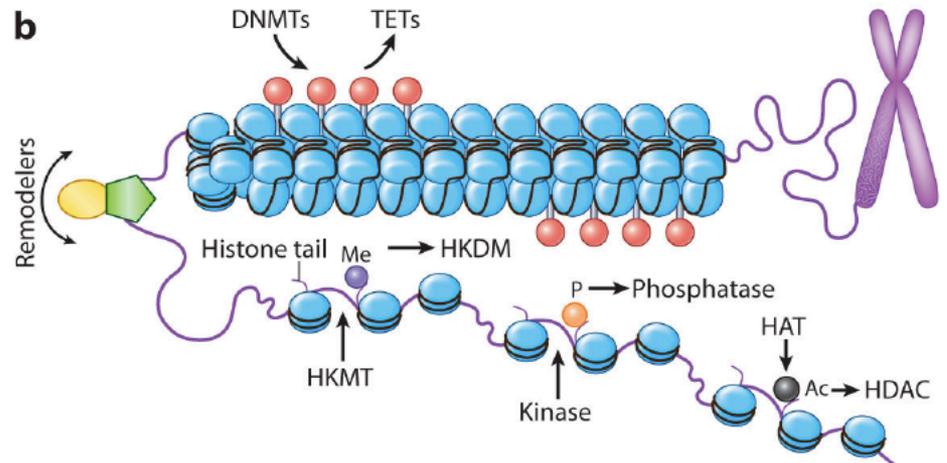
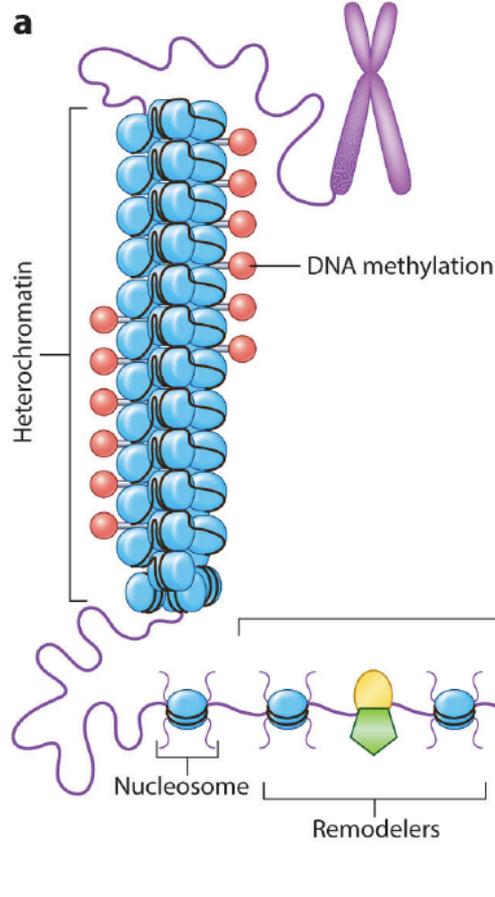
**GENI EPI-DRIVER
IL RUOLO DELLE ALTERAZIONI
EPIGENETICHE NEL CANCRO**

Ruolo delle alterazioni epigenetiche nel cancro

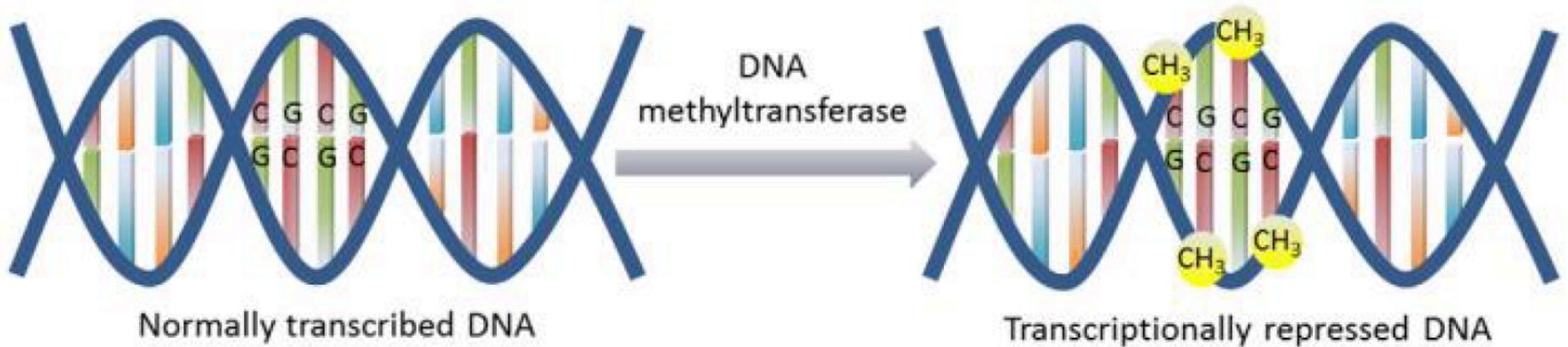


•BET proteins attivano superenhancers, es. Myc

Ruolo delle alterazioni epigenetiche nel cancro



Ipermetilazione di isole CpG nei promotori di geni oncosoppressori



Mutazioni DNMTs nei tumori

Silenziamento genico dovuto a Ipermetilazione di CpG

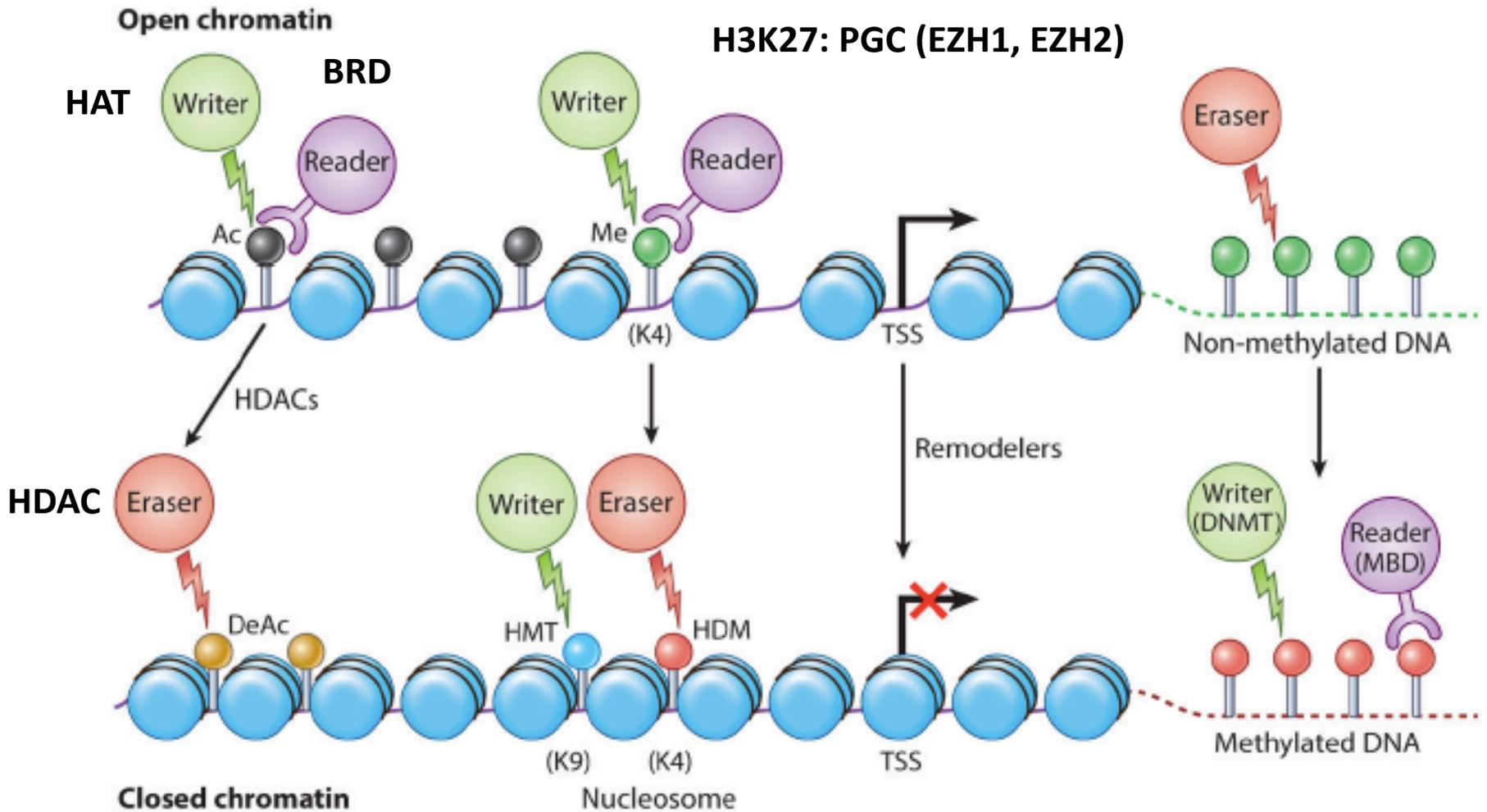
Es. ER in carcinoma ovarico

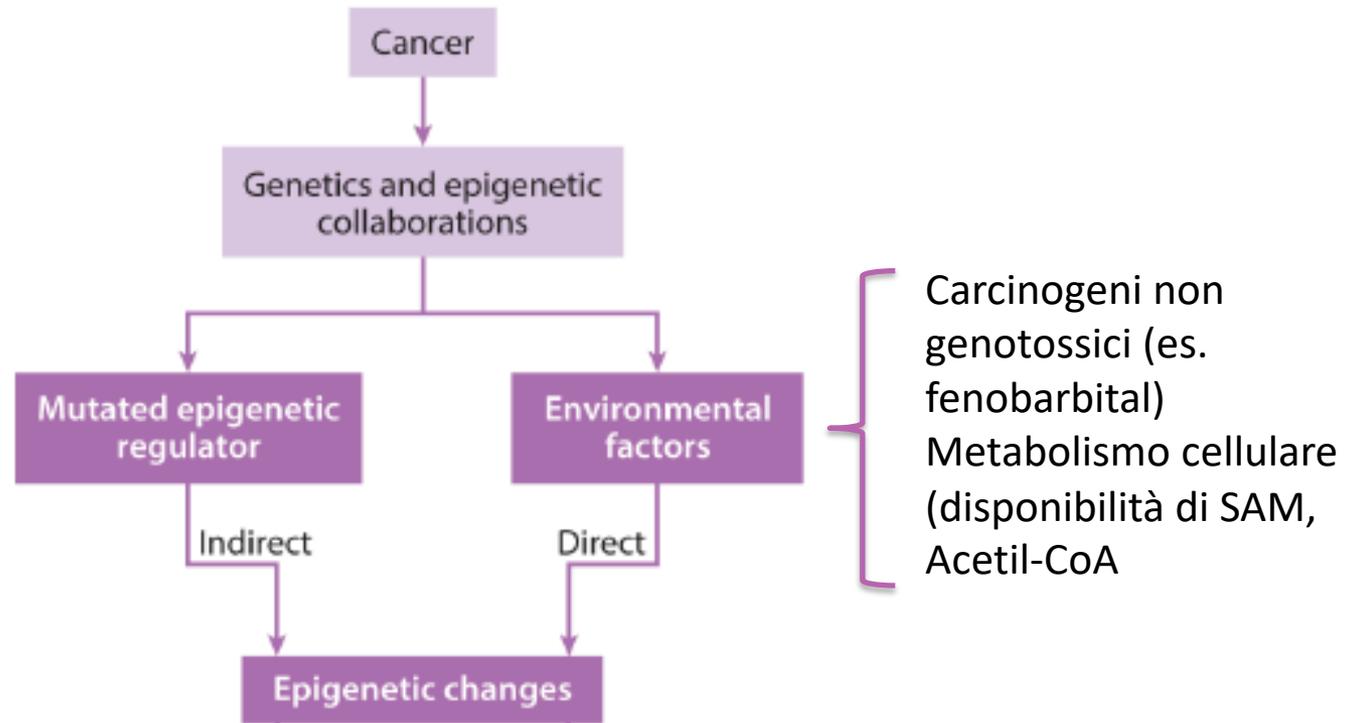
BRCA1 in tumore BC sporadico,

Rb in tumore polmone sporadico

p16

Alterata espressione/mutazioni di enzimi modificatori della cromatina

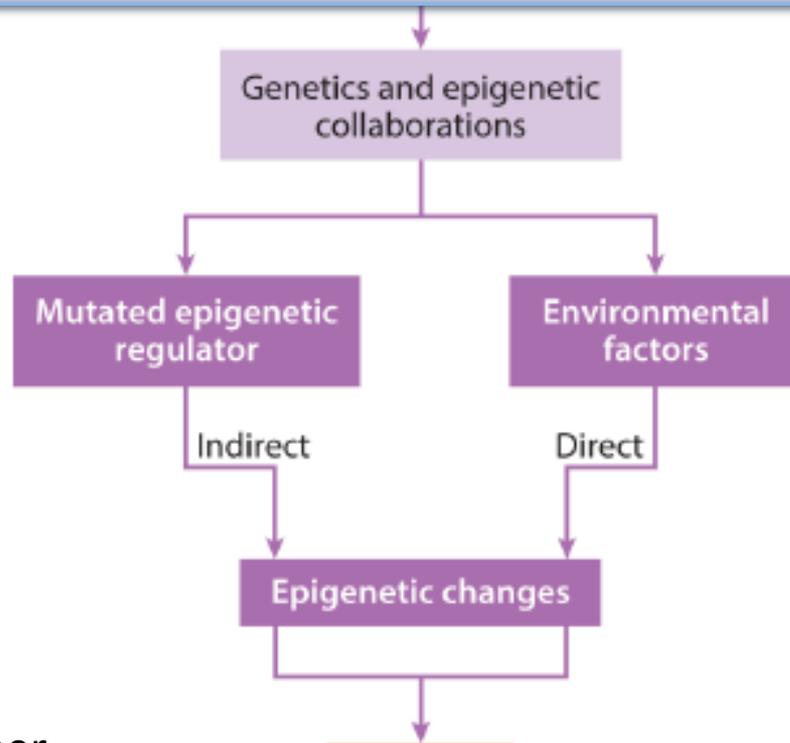




- Mutazioni DNMTs
- Espressione alterata di HAT e HDAC (leucemie, tumori epiteliali)

- Iperespressione PRC (EZHe PRC2 e BMI1 PRC1) in tumori comuni (prostata, lung, BC)
- Frequenti mutazioni nei readers e nei componenti di complessi di rimodellamento della cromatina, sovraespressione di BET proteins

La promessa delle terapie epigenetiche



Carcinogeni non genotossici (es. fenobarbital)
 Metabolismo cellulare (disponibilità di SAM, Acetil-CoA)

Sono approvati da FDA per il trattamento delle leucemie

5-AZA-citidina
 5-aza-2'-deossicitidina

HDACi es. butirati,
 Acido valproico
 SAHA/Vorinostat

Generation 1
 DNMTs

Generation 2
 DNMTs
 + HDACs

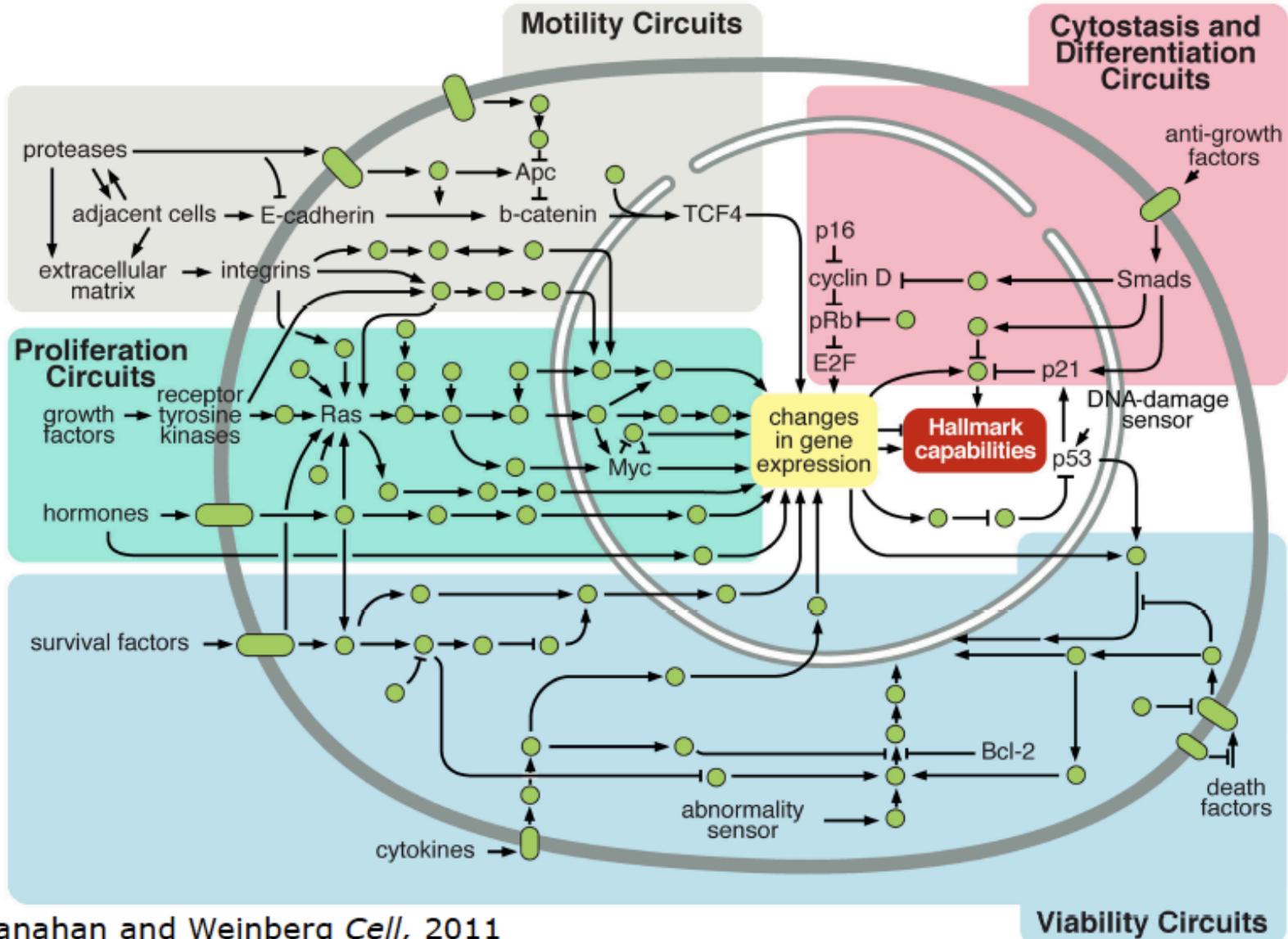
Generation 3
 DNMTs
 + immunotherapy
 + chemotherapy
 + targeted therapy

Generation 4
 Readers
 +writers
 + small molecules

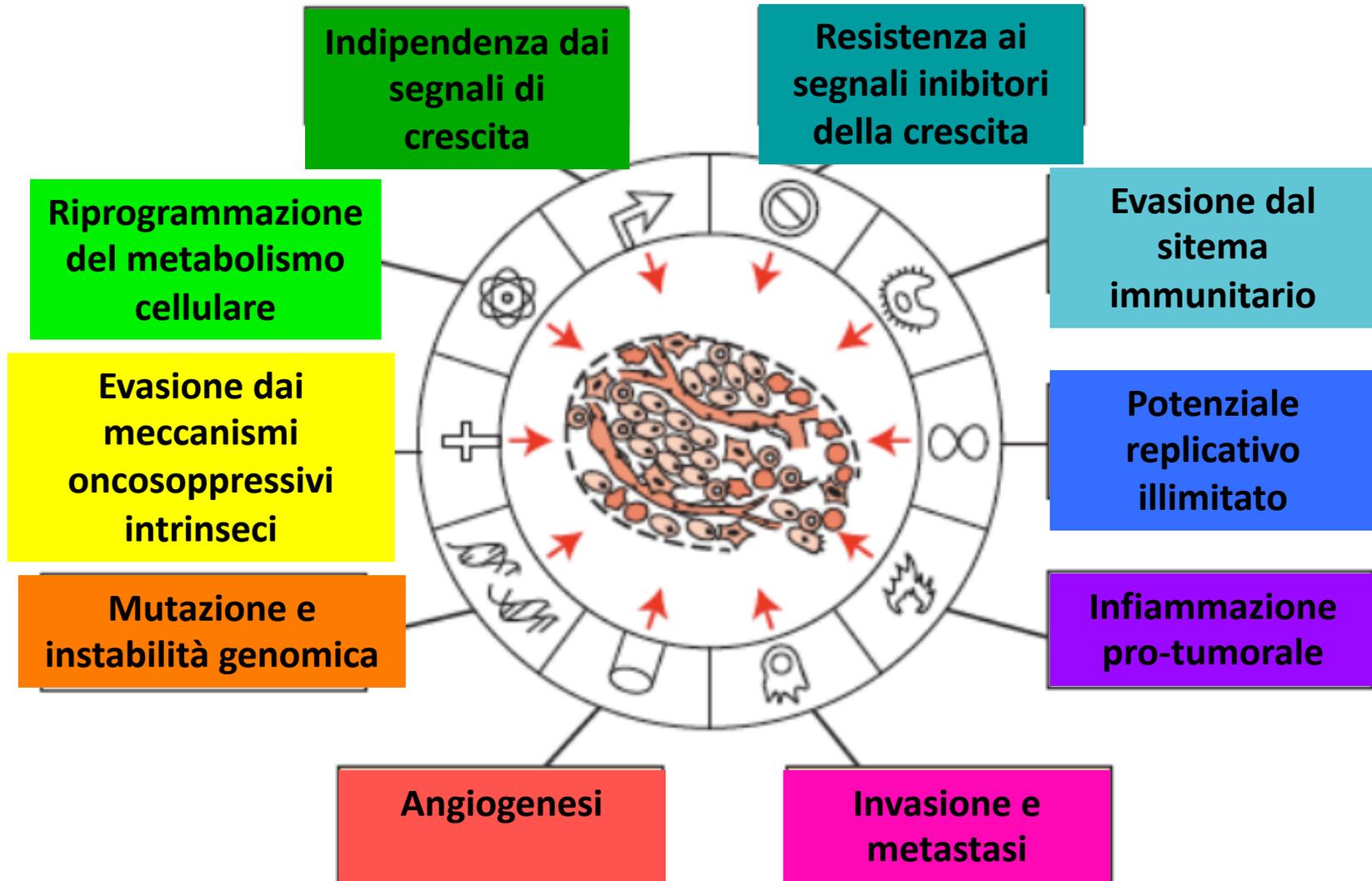
In trial: BETi es. JQ1 inibitore di BRD proteins
 BMI1 e EZH2 inhibitors
 Farmaci metabolici

Epigenetic engineering

La maggiorparte dei circuiti alterati nel cancro regola l'espressione genica

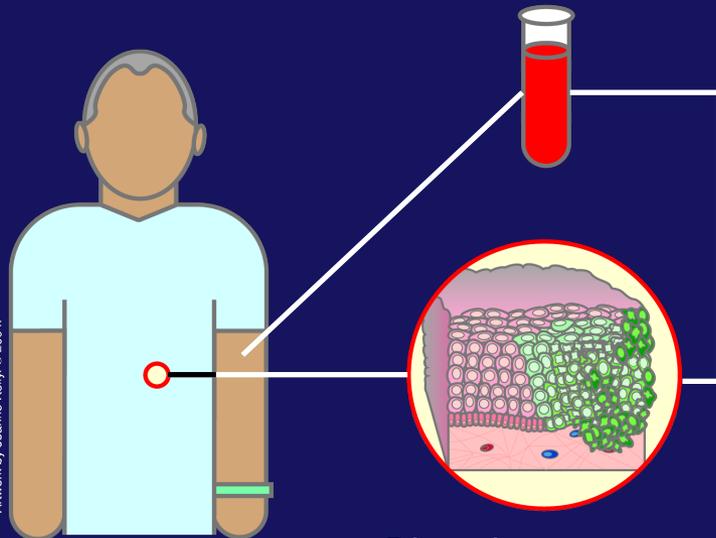


L'acquisizione degli hallmarks del cancro coinvolge cambiamenti dell'espressione genica



FIRME MOLECOLARI TUMORALI = PATTERN DI ESPRESSIONE GENICA

Artwork by Jeame Kelly. © 2004.

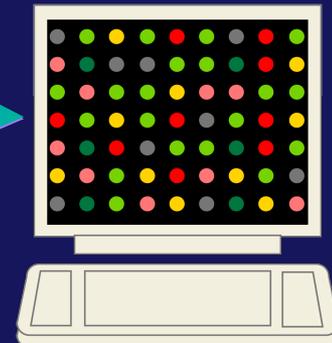


Biopsia
tumorale o
biopsia liquida



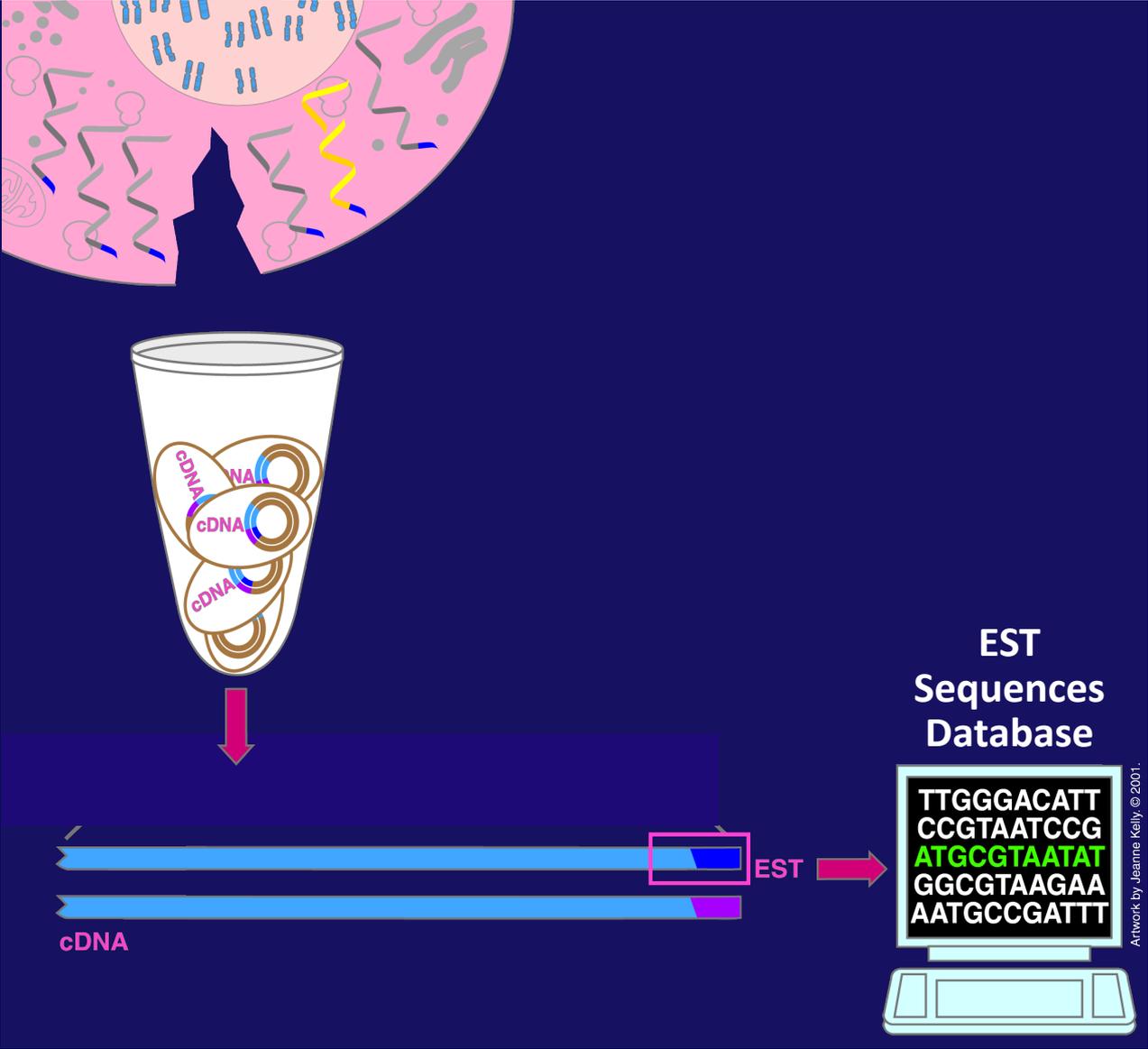
ANALISI DI
ESPRESIONE
GENICA

Expression pattern

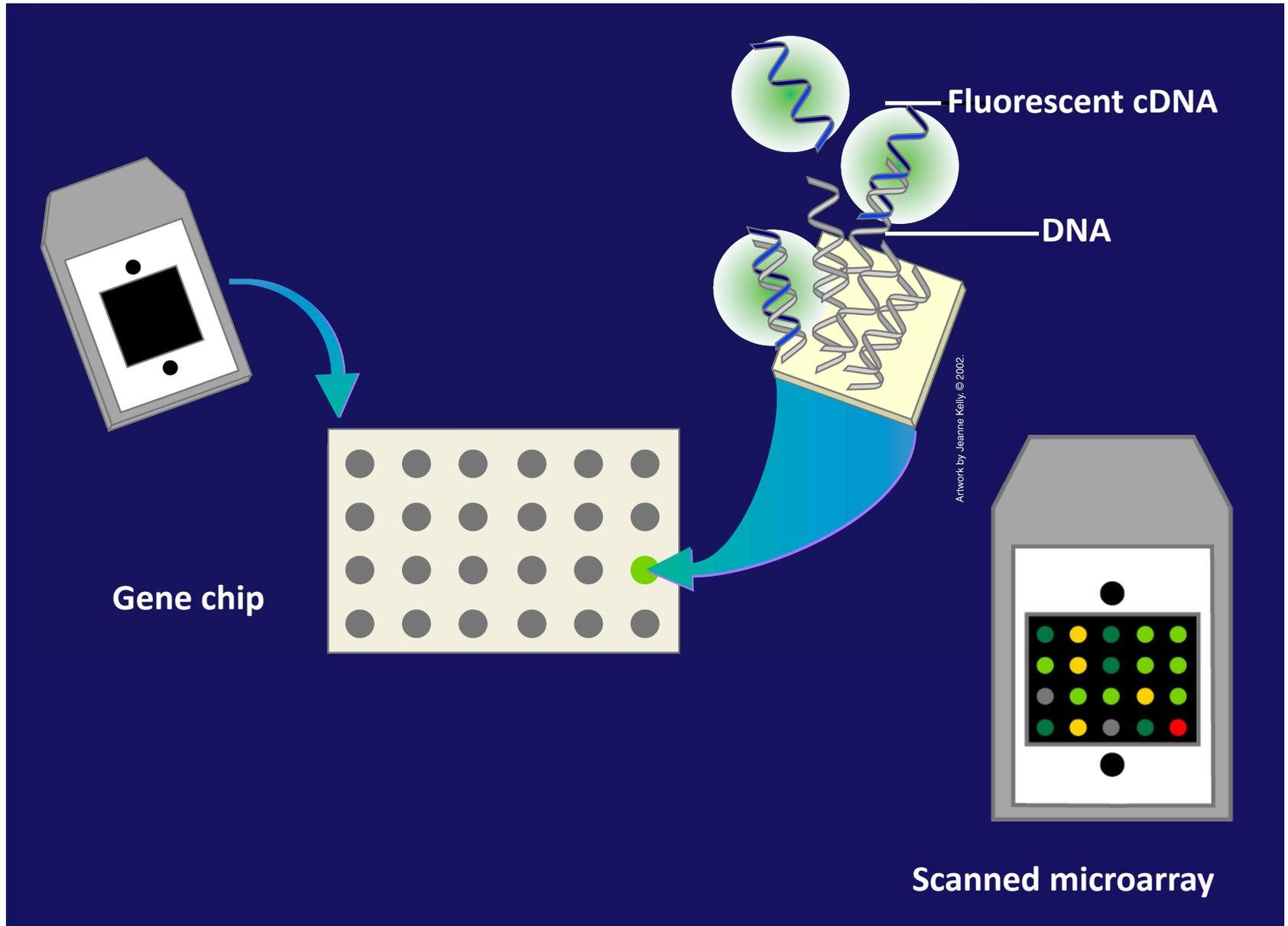


Artwork by Jeame Kelly. © 2002.

RNA sequencing



ANALISI DI ESPRESSIONE GENICA MEDIANTE MICROARRAY



The TCGA (The Cancer Genome Atlas) database

Home - The Cancer Genome Atlas - Cancer Genome - TCGA

← → + cancergenome.nih.gov Reader

PubMed Open University Dropbox Wikipedia WordReference GeneCards IPA Oncomine Venny Primer blast Banca osmer TS Amazon Synonyms CSI Google Maps

Home - The Cancer Genome Atlas - Cancer Genome - TCGA

 National Cancer Institute

National Human Genome Research Institute 

The Cancer Genome Atlas



Understanding genomics
to improve cancer care

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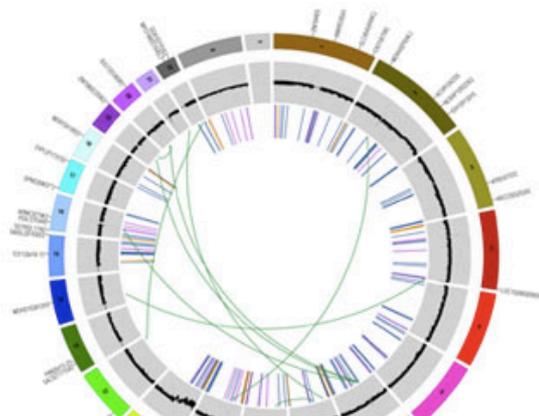
Cancers Selected for Study

Research Highlights

Publications

News and Events

About TCGA



Program Overview

Explore how The Cancer Genome Atlas works, the components of the TCGA Research Network and TCGA's place in the cancer genomics field in the Program Overview.

[Learn More](#)

[Launch Data Portal](#)

The Cancer Genome Atlas (TCGA) Data Portal provides a platform for researchers to search, download, and analyze data sets generated by TCGA.

Questions About Cancer

Visit www.cancer.gov

Call 1-800-4-CANCER

Use [LiveHelp Online Chat](#)



GBM News Release



Pan-Cancer News Release



Cancers Selected for Study



About TCGA

News Releases and Announcements 

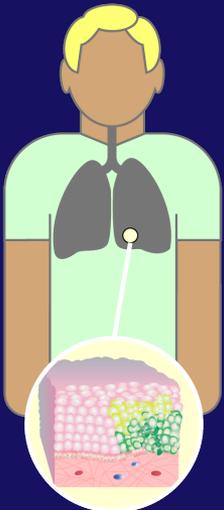
Research Briefs 

Multimedia Library

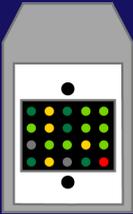
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 Videos and Animations

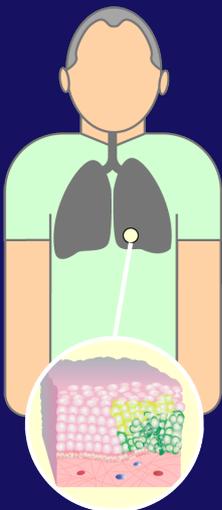
IDENTIFICAZIONE DI SOTTOTIPI TUMORALI IN BASE AI PROFILI MOLECOLARI



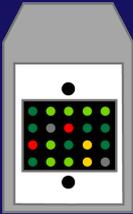
Cancer biopsy



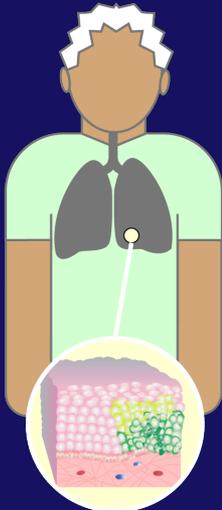
Small cell
lung carcinoma



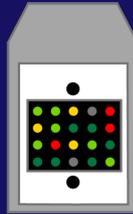
Cancer biopsy



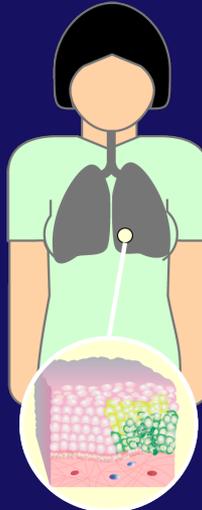
Adenocarcinoma



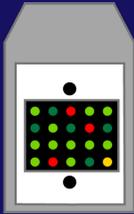
Cancer biopsy



Non-small cell lung carcinoma:
Pulmonary carcinoid



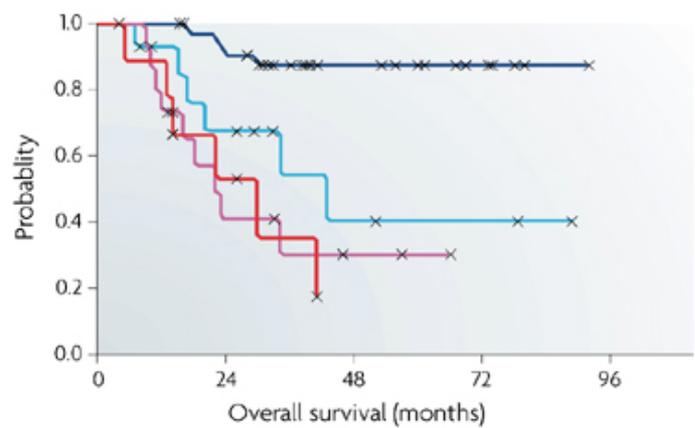
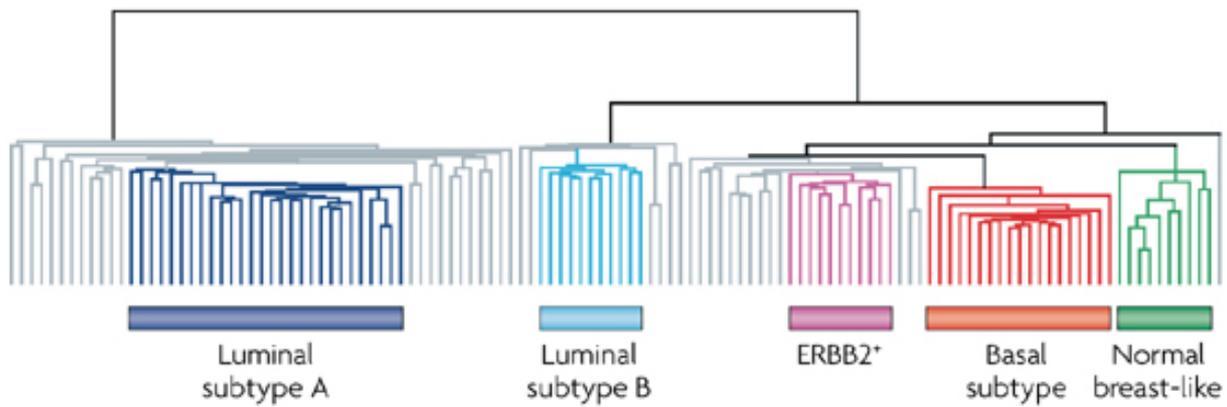
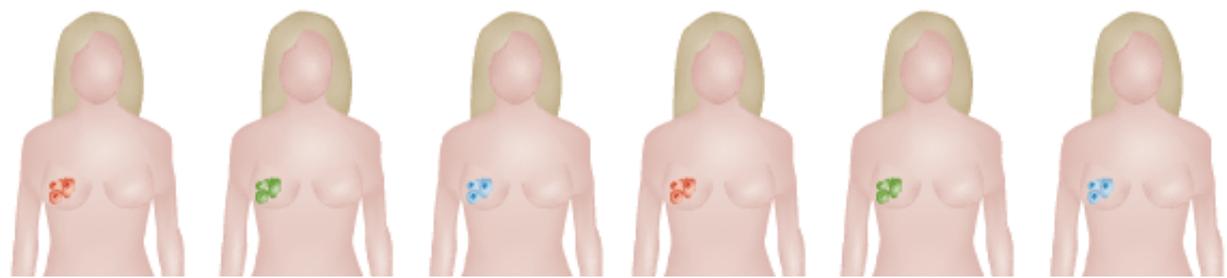
Cancer biopsy



Large cell carcinoma

Artwork by Jeanne Kelly, © 2002.

L'ETEROGENEITA' TUMORALE NEL BC (qualche anno fa)

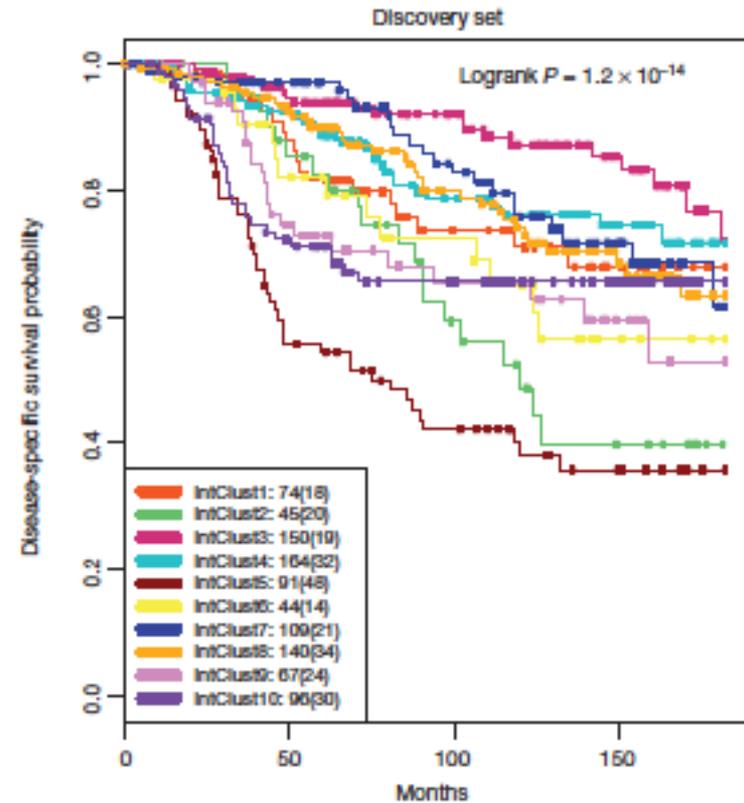


L'ETEROGENEITA' TUMORALE NEL BC OGGI

The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

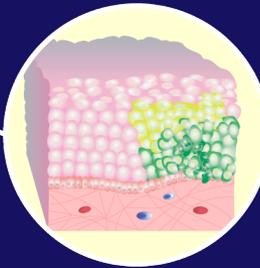
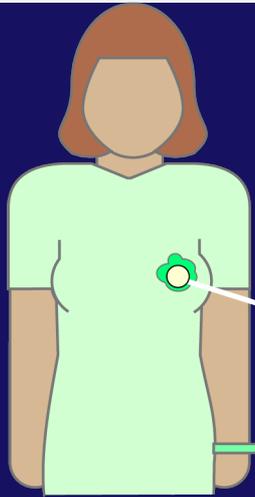
Christina Curtis^{1,2+*}, Sohrab P. Shah^{3,4*}, Suet-Feung Chin^{1,2*}, Gulisa Turashvili^{3,4*}, Oscar M. Rueda^{1,2}, Mark J. Dunning², Doug Speed^{2,5†}, Andy G. Lynch^{1,2}, Shamith Samarajiwa^{1,2}, Yinyin Yuan^{1,2}, Stefan Gräßl^{1,2}, Gavin Ha³, Gholamreza Haffari³, Ali Bashashati³, Roslin Russell², Steven McKinney^{3,4}, METABRIC Group†, Anita Langerød⁶, Andrew Green⁷, Elena Provenzano⁸, Gordon Wishart⁸, Sarah Pinder⁹, Peter Watson^{3,4,10}, Florian Markowetz^{1,2}, Leigh Murphy¹⁰, Jan Ellis⁷, Arnie Poxushoam^{9,11}, Anne-Lise Berresen-Dale^{6,12}, James D. Brenton^{2,13}, Simon Tavaré^{1,2,5,14}, Carlos Caldas^{1,2,8,15} & Samuel Aparicio^{3,7}

The elucidation of breast cancer subgroups and their molecular drivers requires integrated views of the genome and transcriptome from representative numbers of patients. We present an integrated analysis of copy number and gene expression in a discovery and validation set of 997 and 995 primary breast tumours, respectively, with long-term clinical

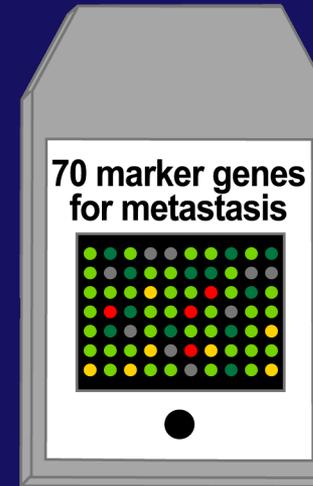


FIRME MOLECOLARI CON VALORE PROGNOSTICO

Cancer patient A



Cancer biopsy

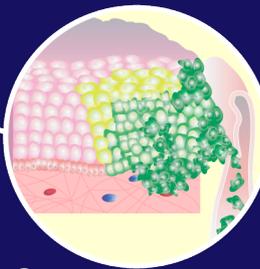
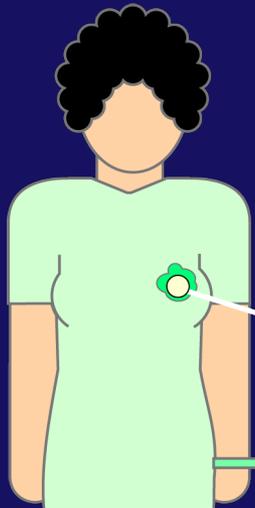


70 marker genes
for metastasis

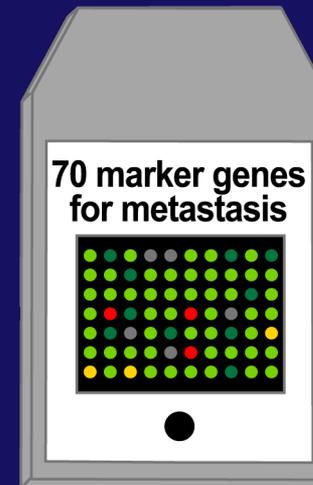
No metastatic
potential;
conservative
therapy possible

MAMMAPRINT

Cancer patient B



Cancer biopsy

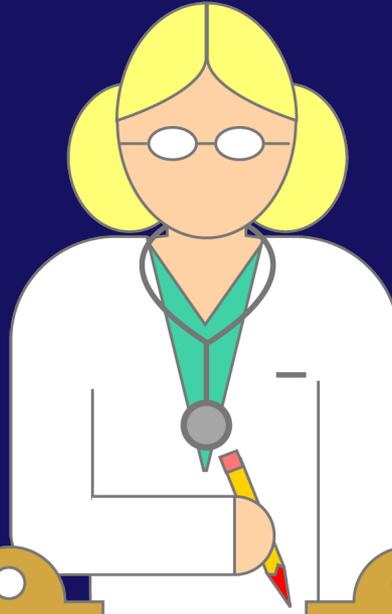


70 marker genes
for metastasis

Metastatic
potential;
aggressive
therapy needed

PROFILI MOLECOLARI PER GUIDARE LE SCELTE TERAPEUTICHE

Differentiating Between Cancers with Similar Clinical Symptoms



Patient A

History:
Has Lymphoma

Expression Profile
Completed ✓
Subtype A

Instructions:
Give Standard
Treatment

Patient B

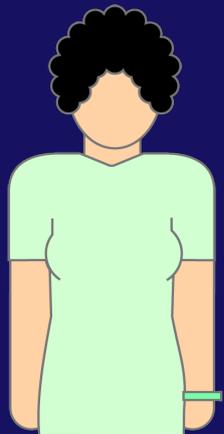
History:
Has Lymphoma

Expression Profile
Completed ✓
Subtype B

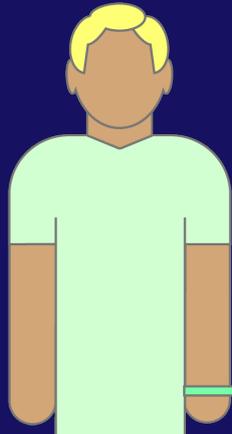
Instructions:
**Develop New
Treatment Strategies
to Improve Response**

PROFILI MOLECOLARI PER GUIDARE LE SCELTE TERAPEUTICHE

Patient A



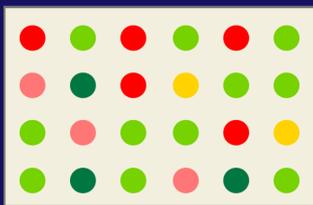
Patient B



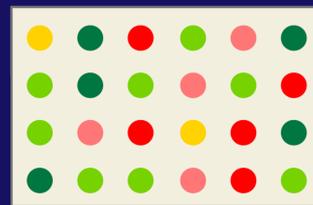
Same
Cancer

Gene expression
profile of tumors

Artwork by Jeanne Kelly © 2002.



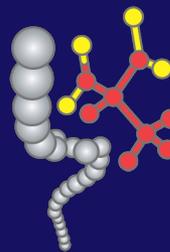
Gene expression
profile of tumors



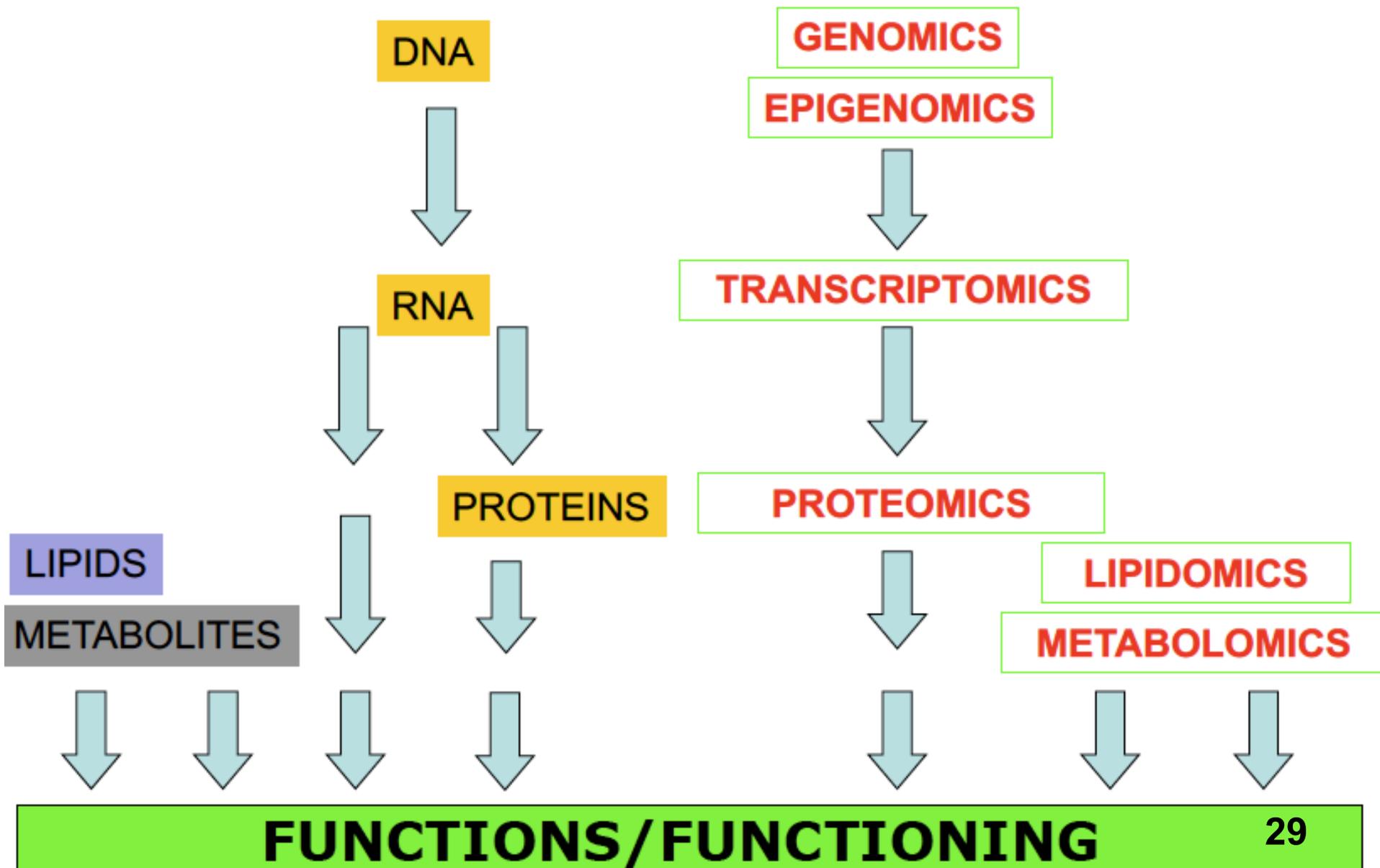
Anticancer
Drug A
EFFECTIVE



Drug A alone is
useless, combine
with drug B



DIVERSI TIPI DI ANALISI OMICHE NELLA RICERCA SUL CANCRO



FUNCTIONS/FUNCTIONING