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Genomic Medicine

Genomic Medicine in Spain.

The Oncology approach.

Joaquín Arribas, Scientific Director, ciberonc

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Genomic Medicine

Outline:

- Introduction. Genomic Oncology.
- Variability and selection.
- Liquid Biopsy.
- CIBERONC.

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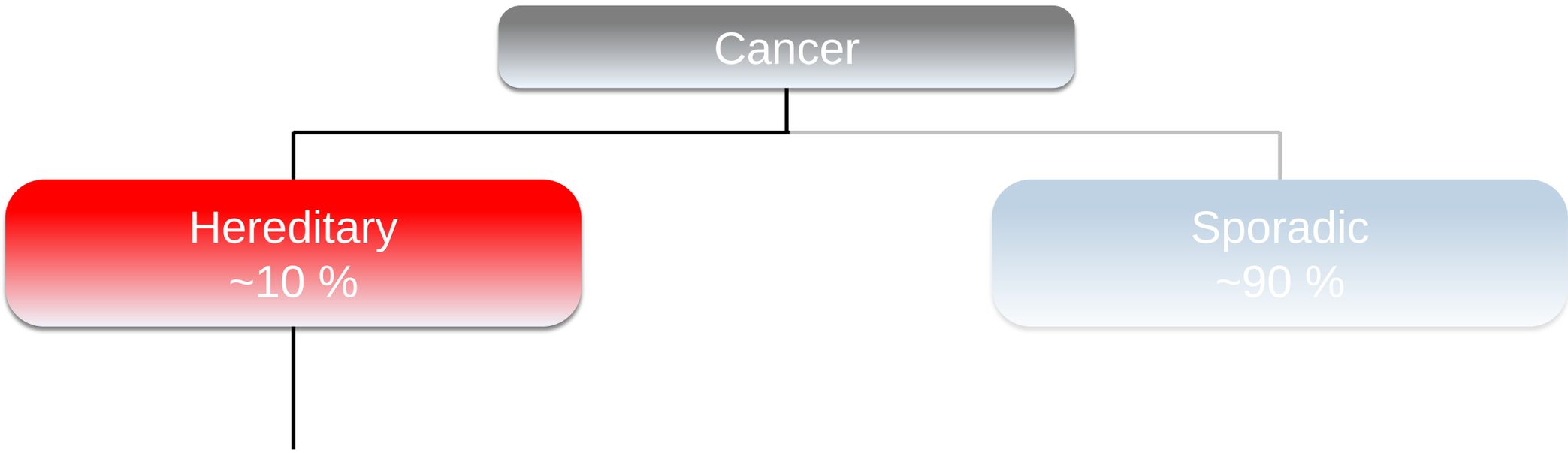
Hereditary tumors



Syndrome	Associated Gene
Familial retinoblastoma	RB1
Li-Fraumeni	TP53
Familial adenomatous polyposis	APC
Hereditary non –polyposis colorectal cancer	MLH1, MSH2, MSH6, PMS1, PMS2
Wilms' tumor	WT1
Framiliar breast and ovarian cancer	BRCA1, BRCA2
Von Hippel-Lindau	VHL
Cowden	PTEN

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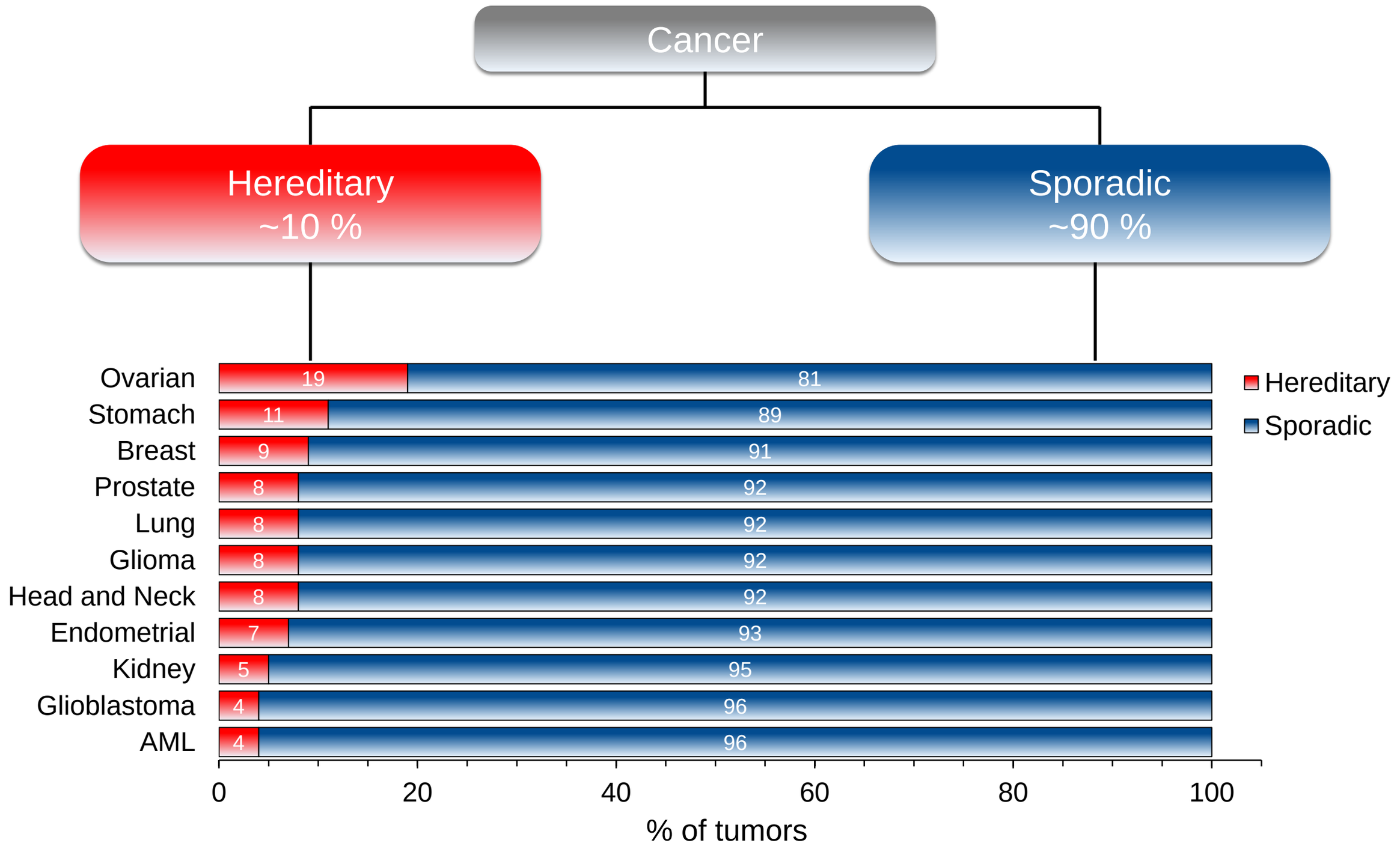
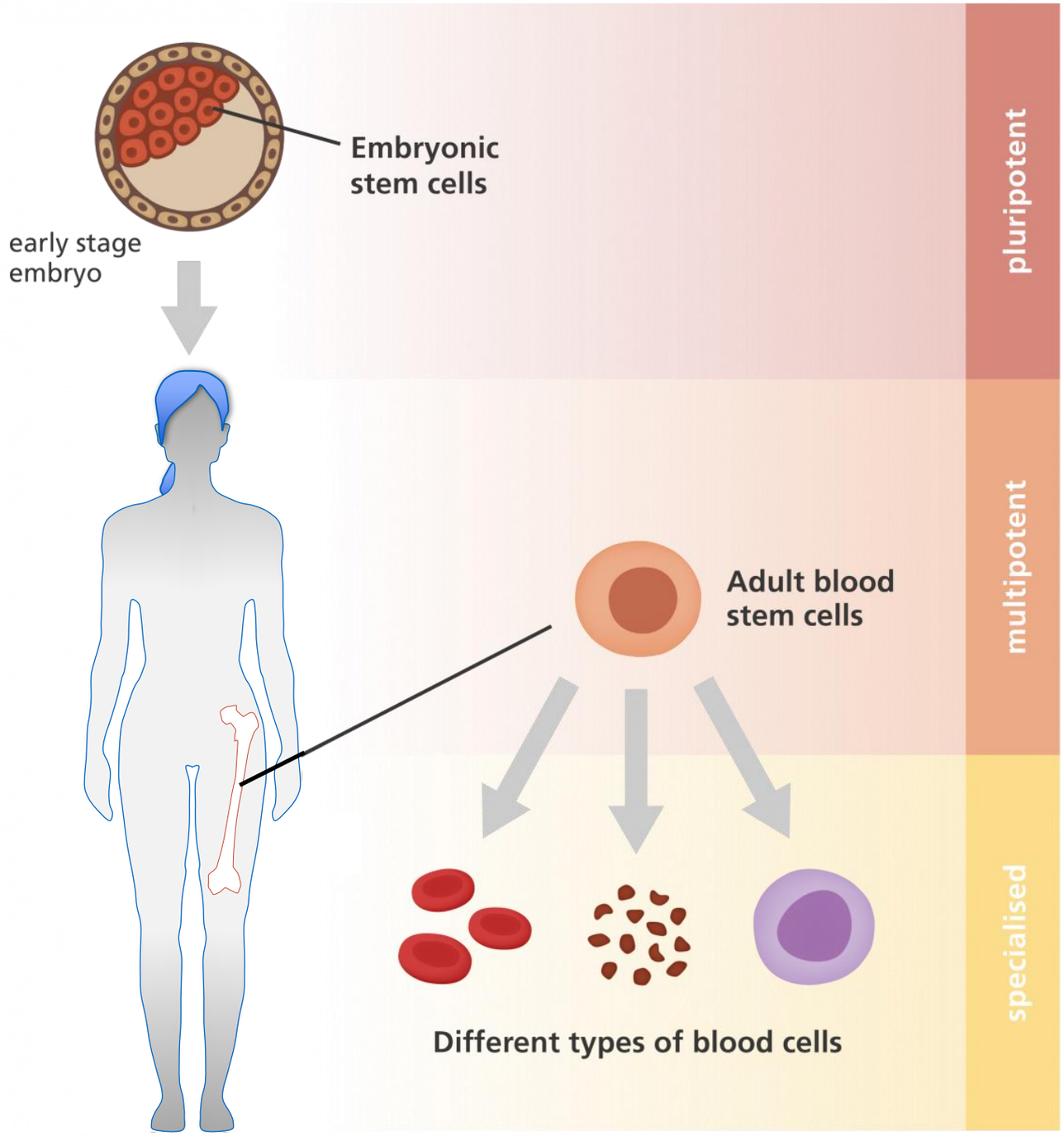
Cancer genomics



Cellular differentiation



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The Waddington hill -Differentiation

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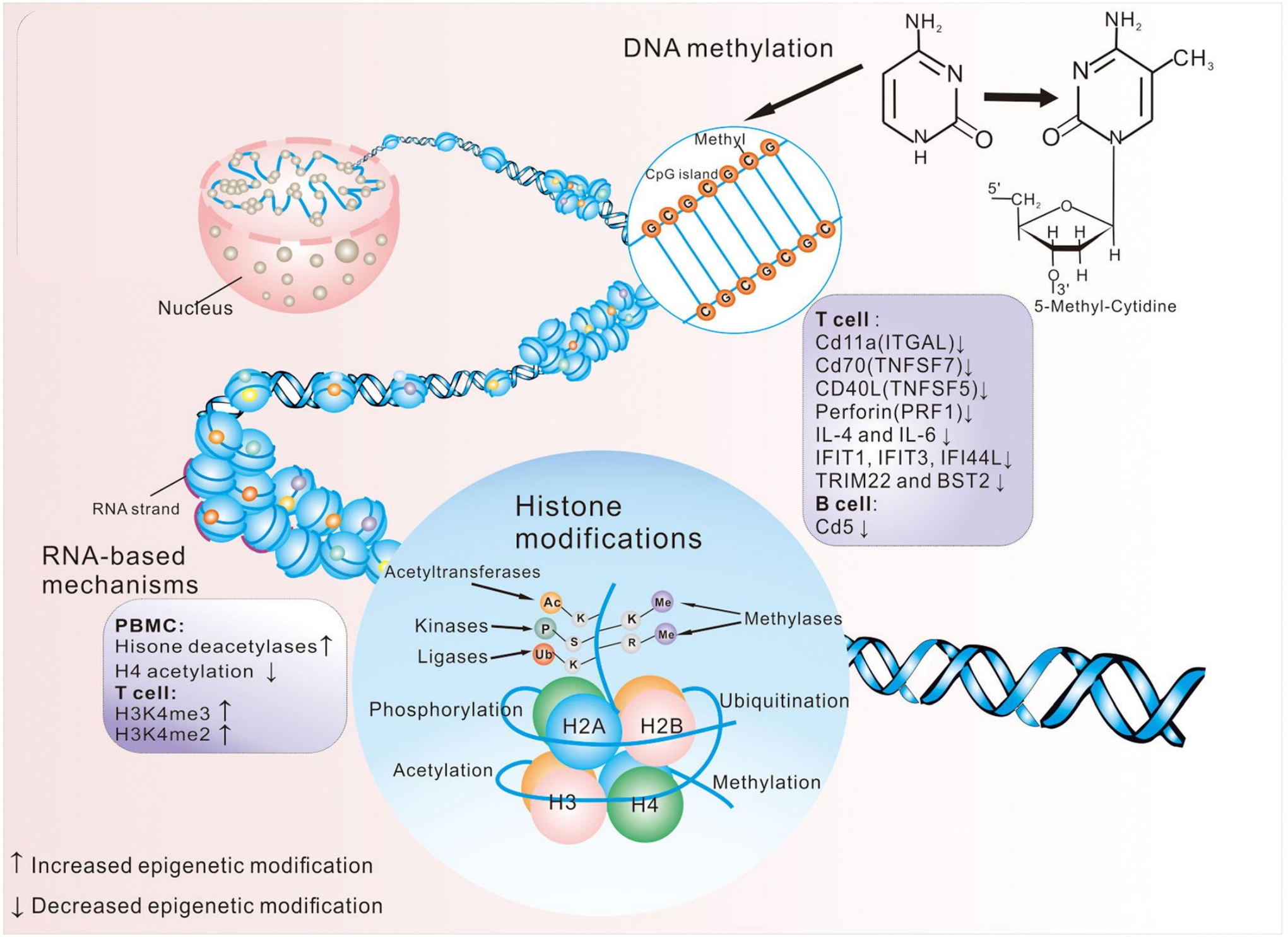
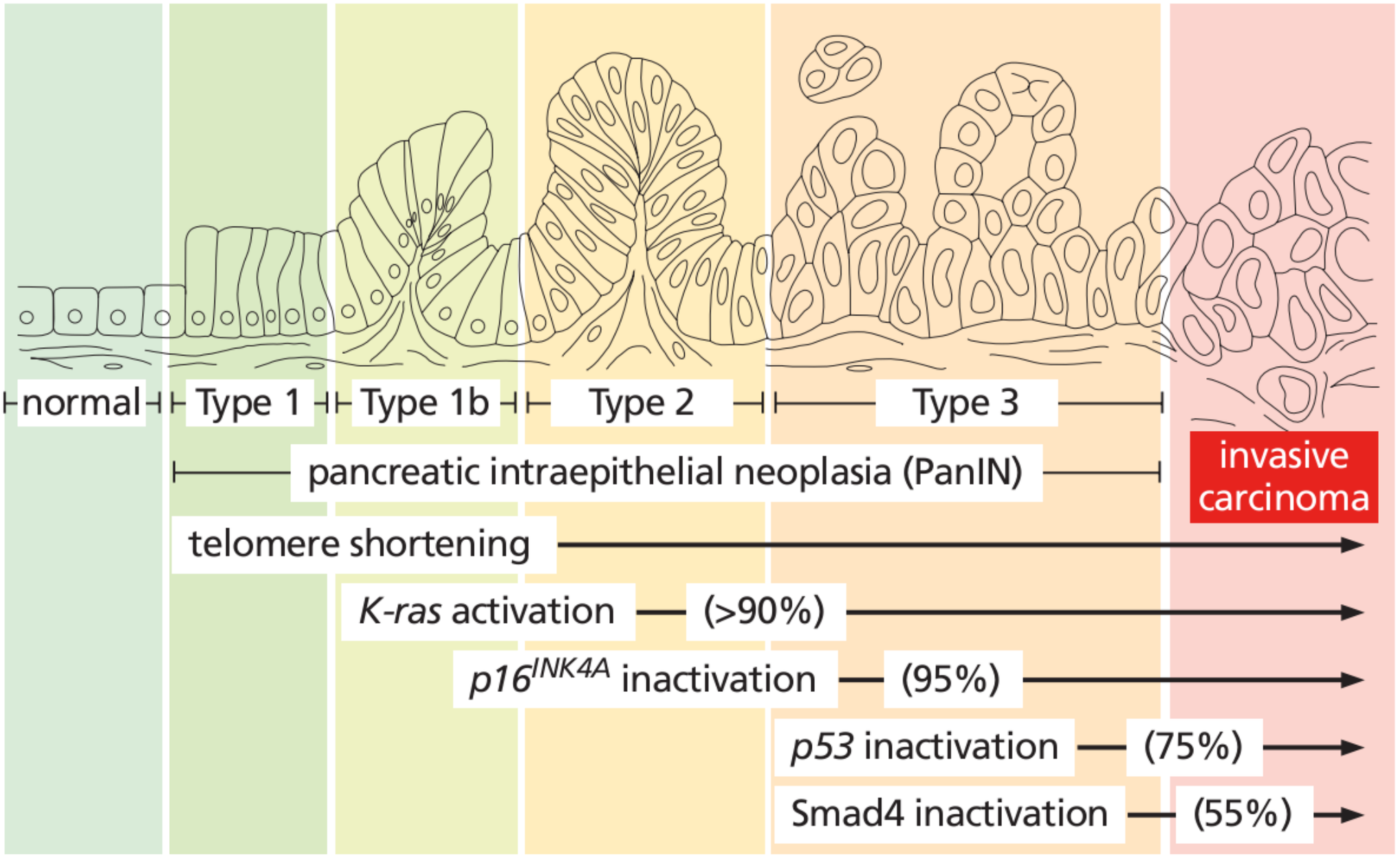
Differentiation. Epigenetics

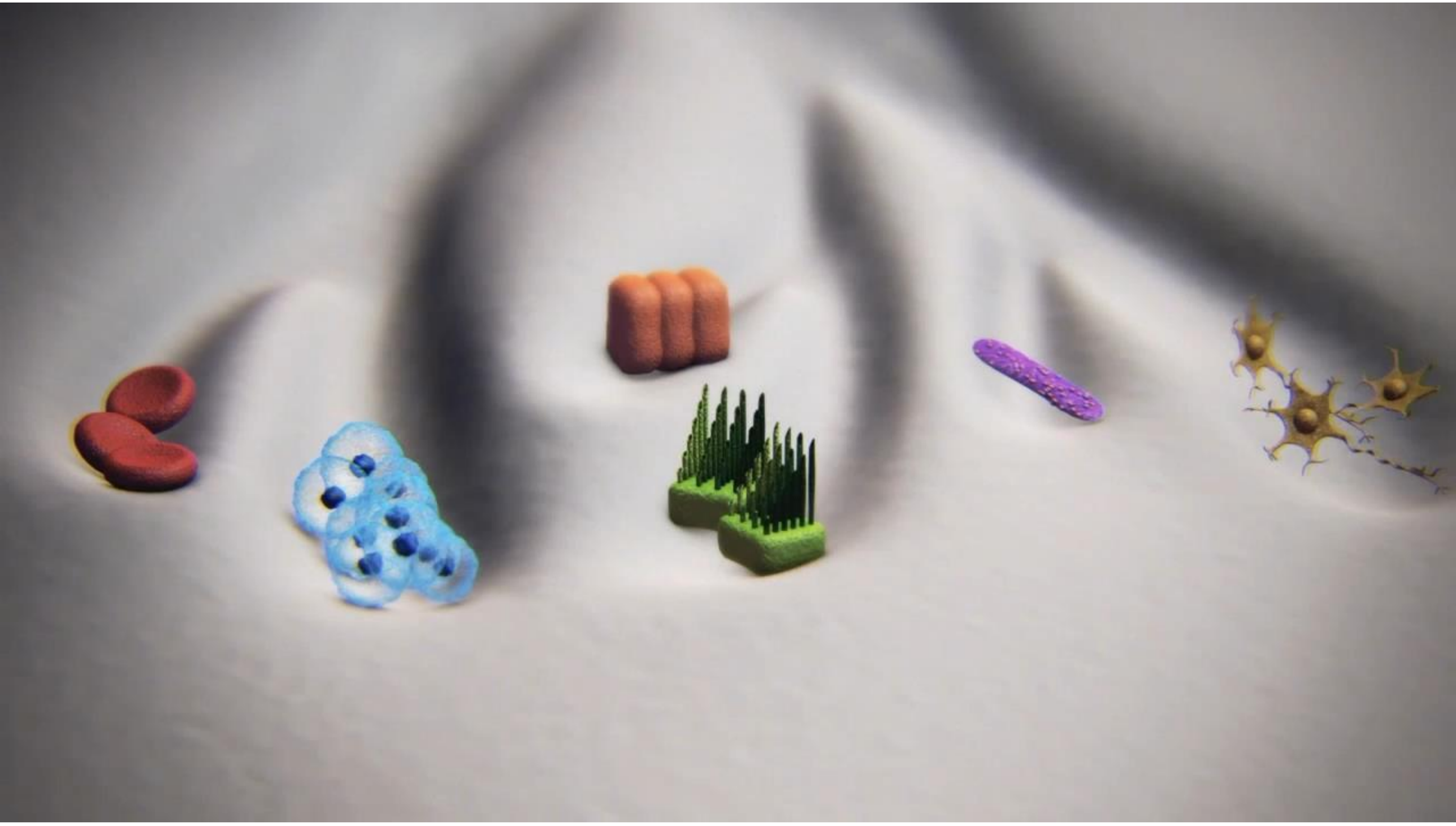


Pancreatic cancer: genetics



Weinberg RA (2014) **The Biology of Cancer** (2nd Ed)

Cancer reprograming



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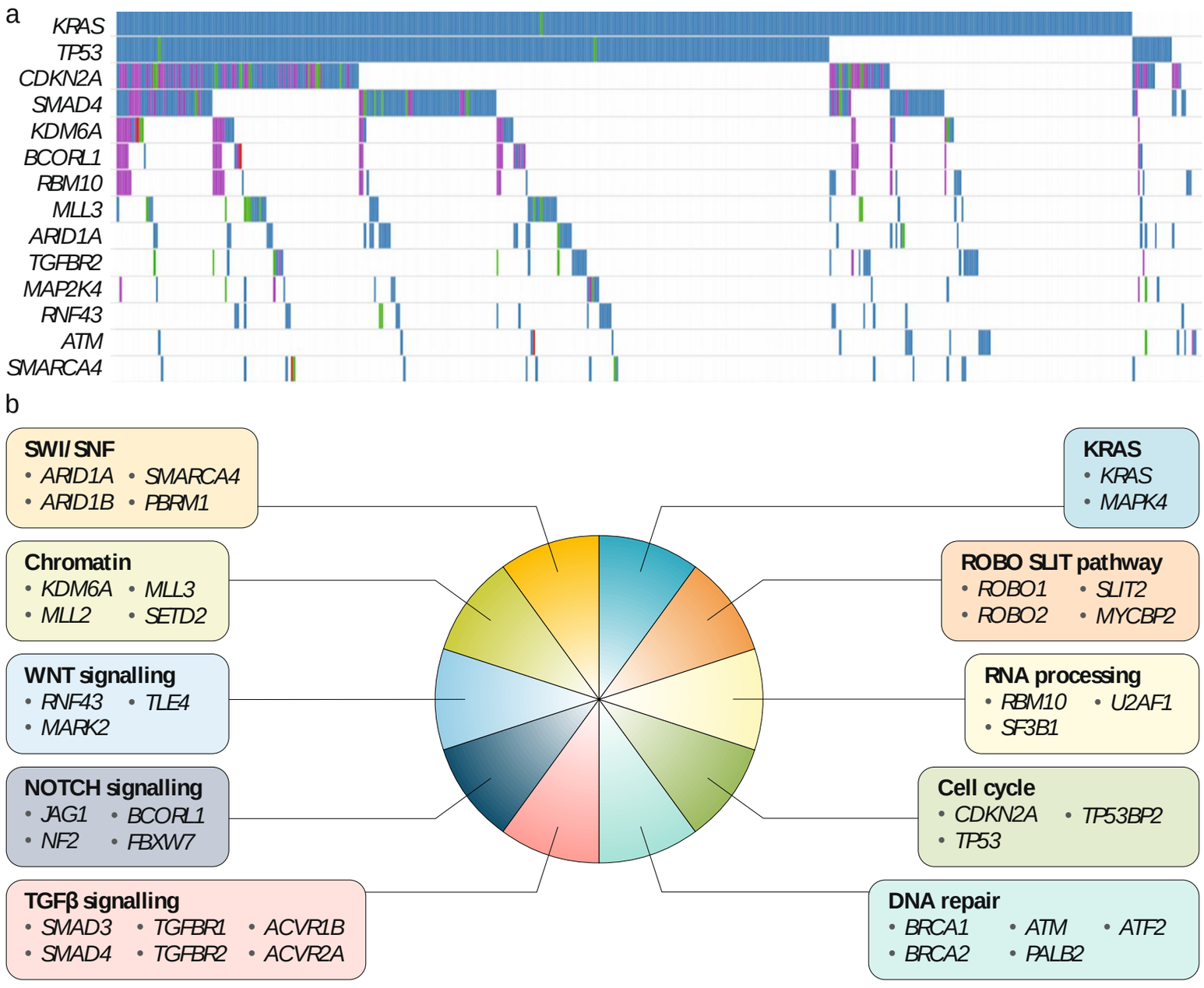
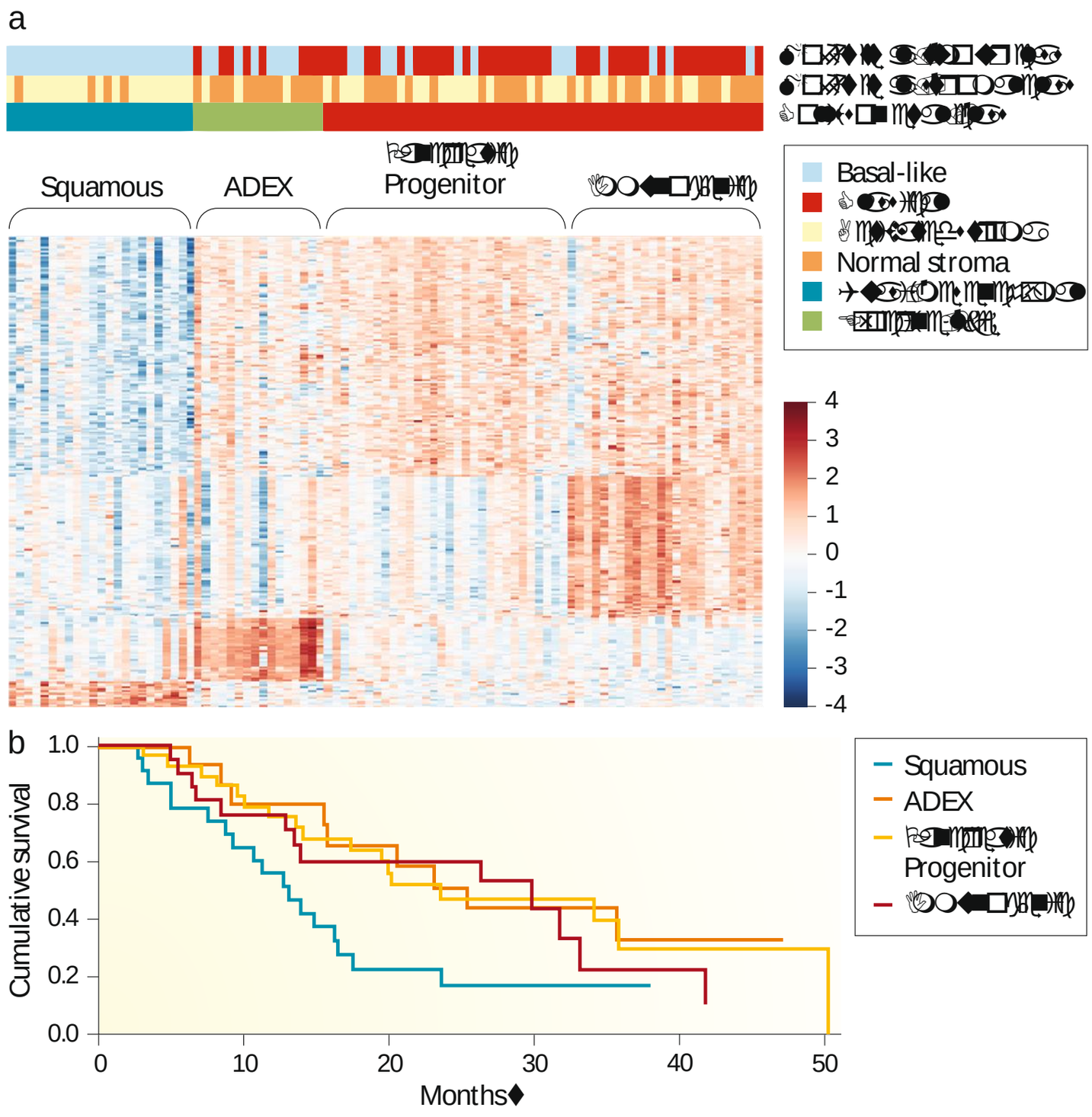
Heterogeneity: intertumoral



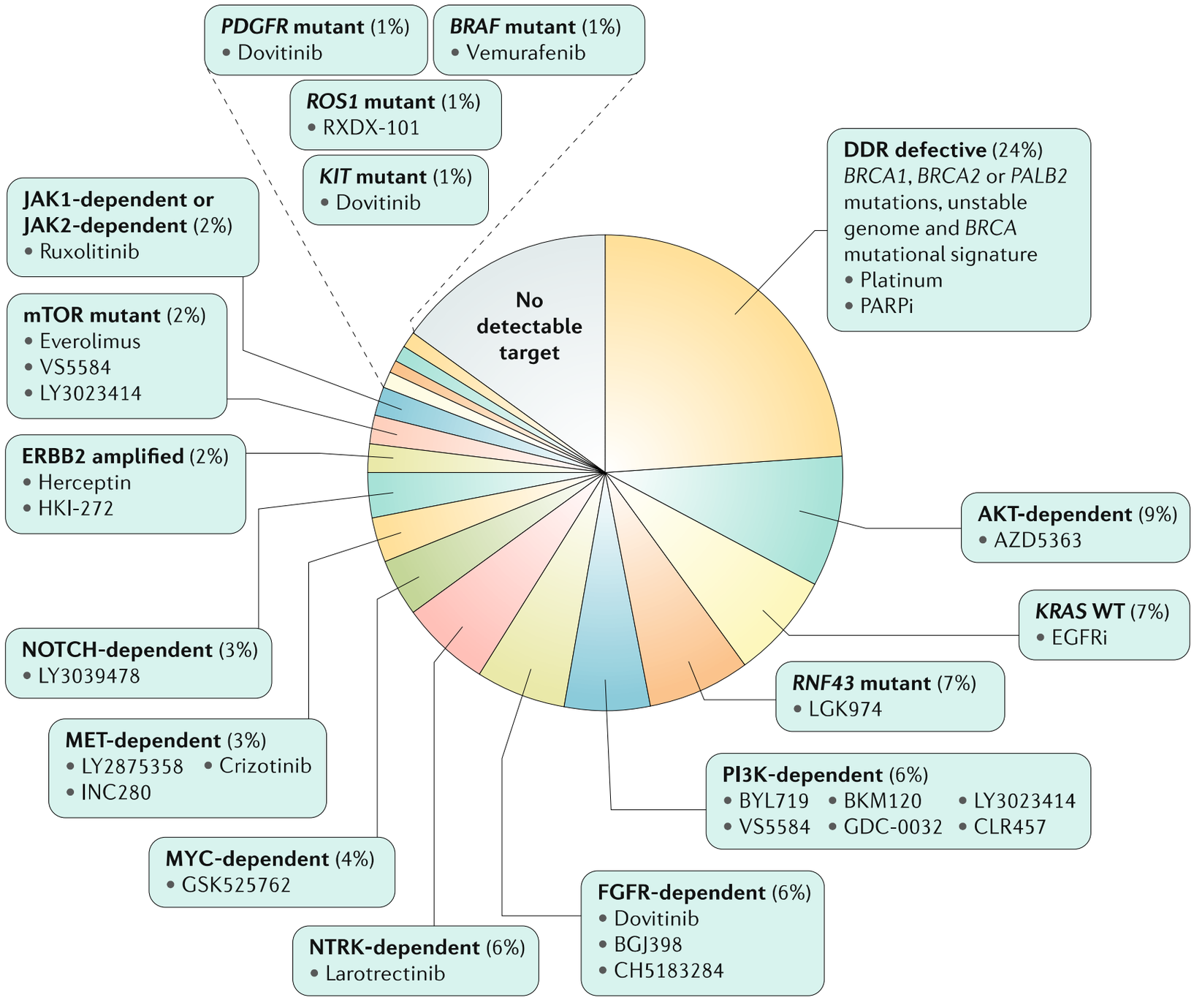
Collison EA (2019) **Nat Rev Gastroenterol & Hepathol**

Heterogeneity: intertumoral



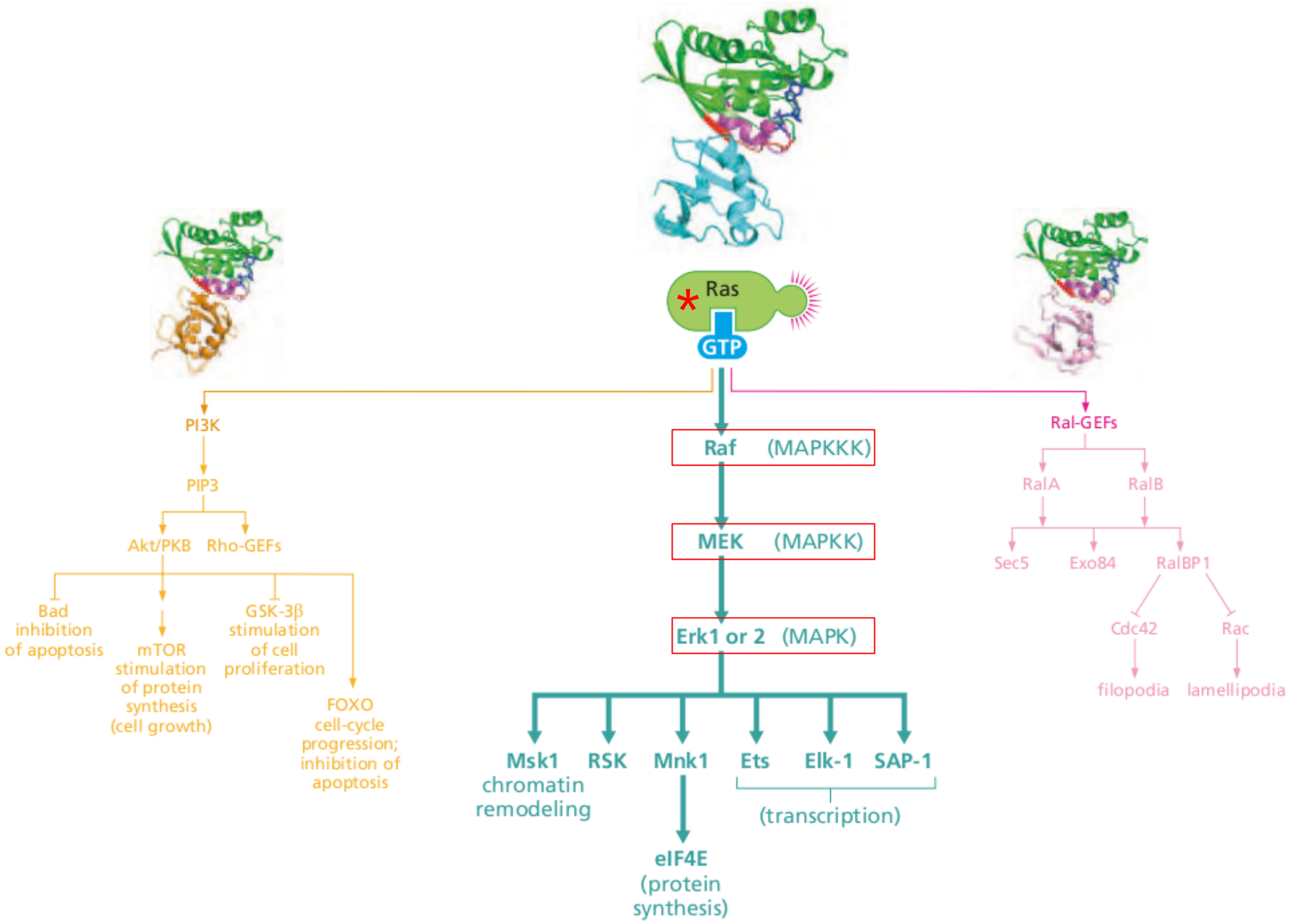
Collison EA (2019) **Nat Rev Gastroenterol & Hepathol**

Intertumoral heterogeneity. Actionable mutations



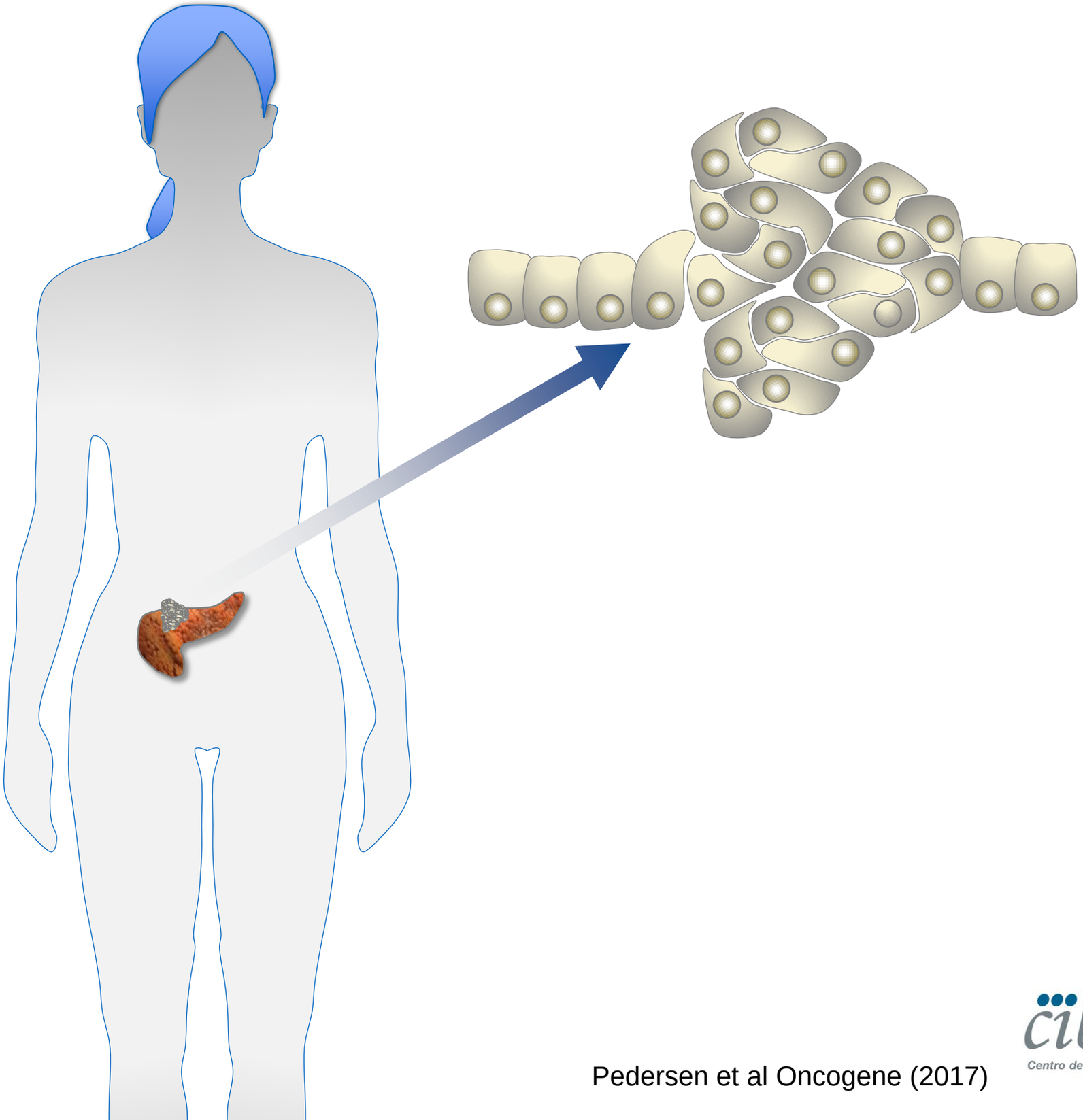
Collison EA (2019) **Nat Rev Gastroenterol & Hepathol**

Indirect therapeutic targets



Weinberg RA (2014) **The Biology of Cancer** (2nd Ed)

Heterogeneity: intratumoral



Pedersen et al Oncogene (2017)

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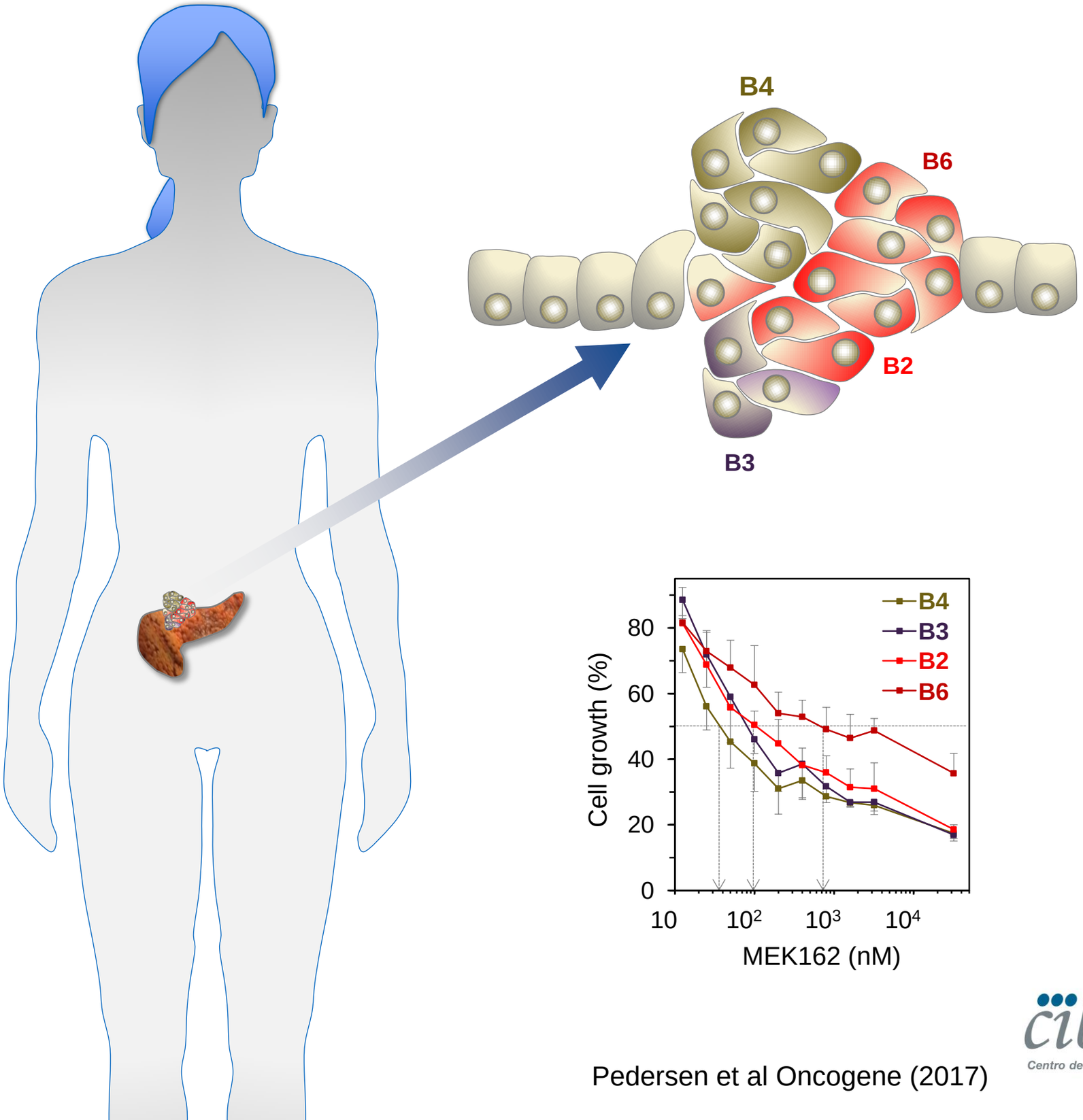
Heterogeneity: intratumoral, intralessional



	PC-PDX21.p4			
	B4	B3	B2	B6
KRAS G12V	41	49	42	39
KRAS G12D				
TP53 V272M	99	99	99	99
TP53 Y103*				
SMAD4 P246Q	15			
SMAD4 G247R		26		
STK11 A273T	4			
STK11 P324L	19			
CDKN2A G114C	10			
VHL W88C	6			

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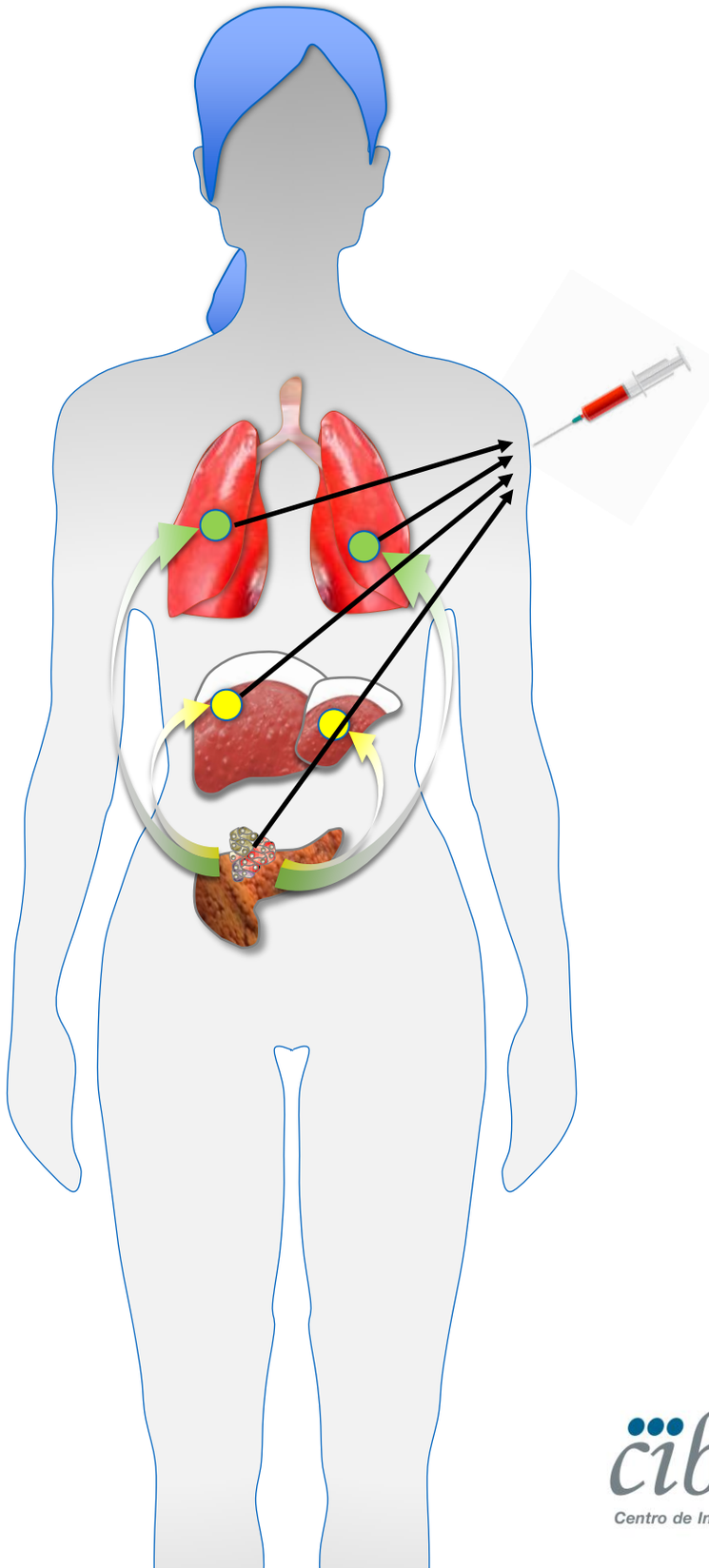
Heterogeneity: intratumoral, interlessional



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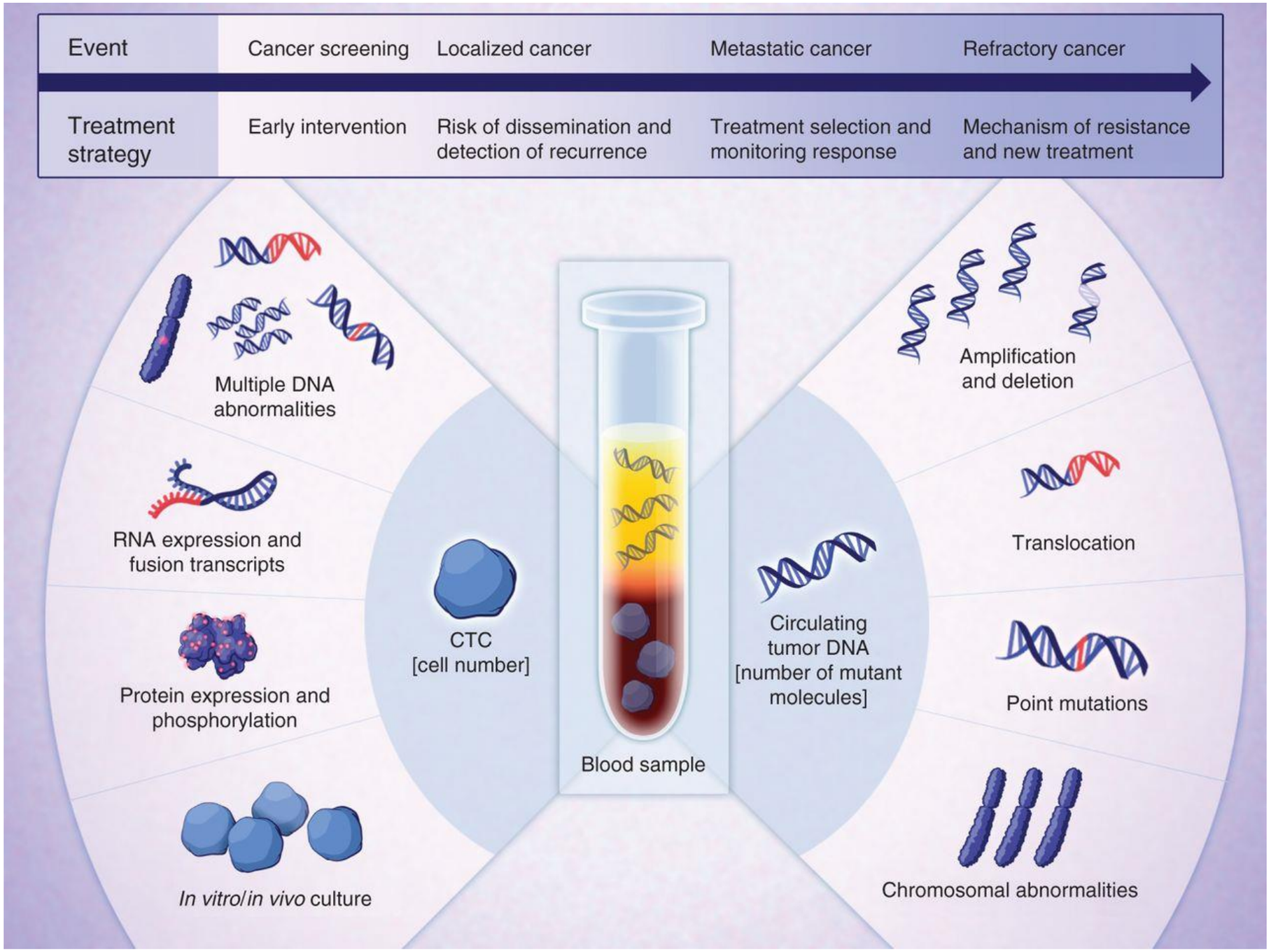
Liquid biopsy



Haber, D & Velculescu, VE (2014) Blood-Based Analyses of Cancer: Circulating Tumor Cells and Circulating Tumor DNA. **Cancer Discovery**

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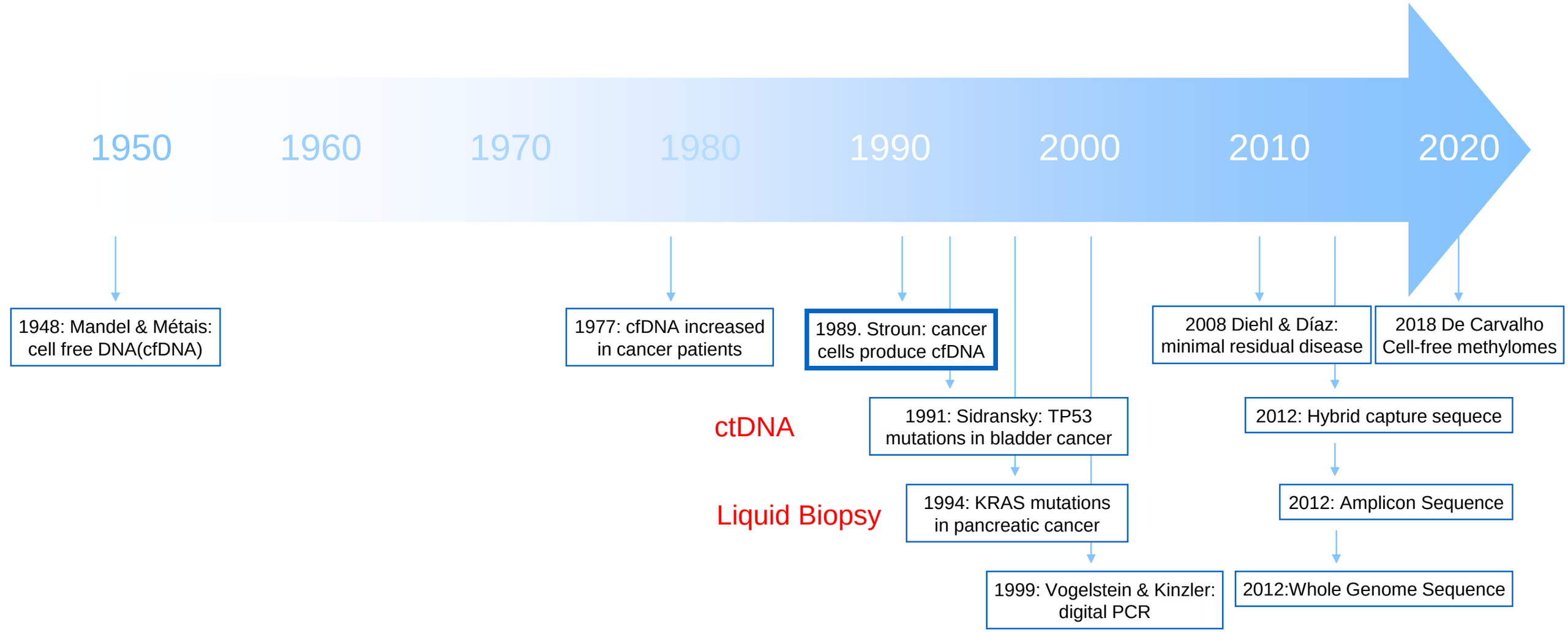
Liquid Biopsy Time-Line



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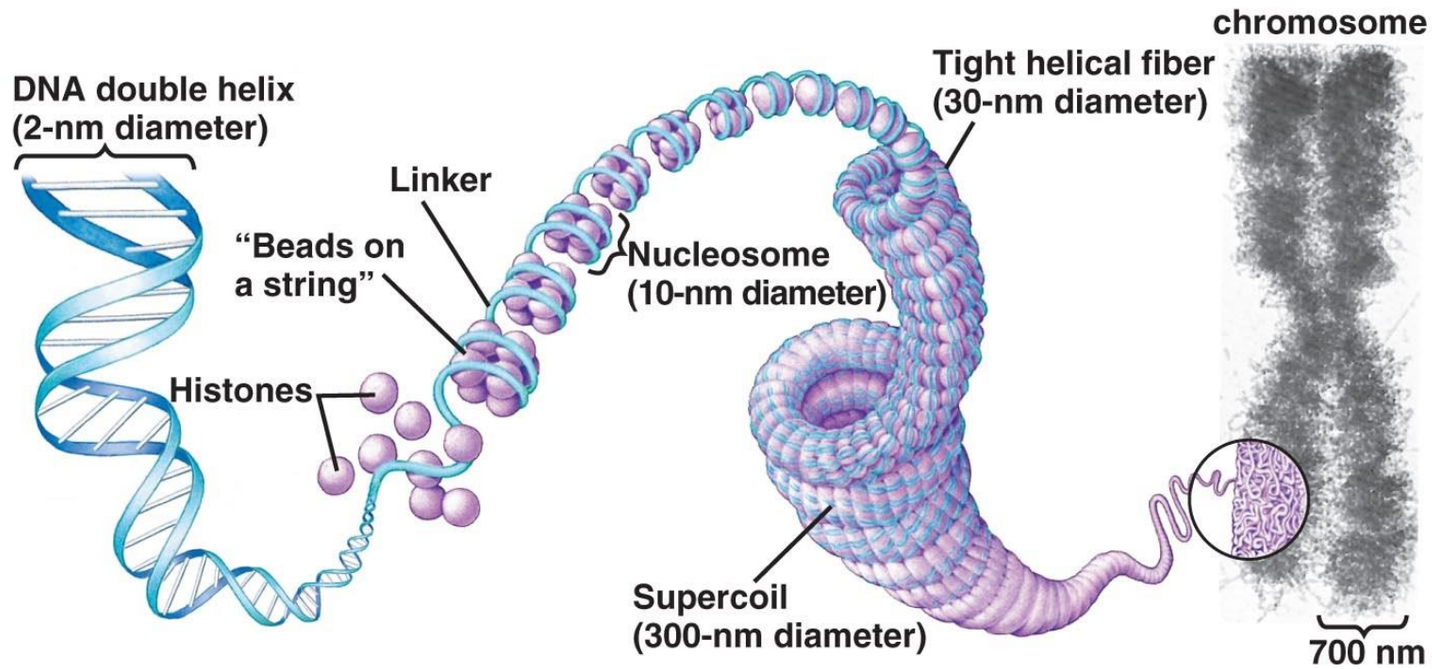
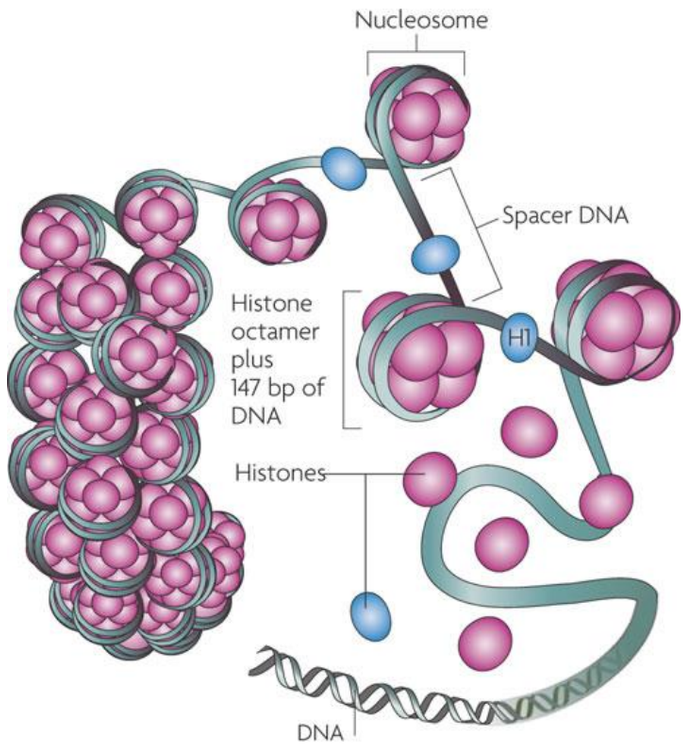
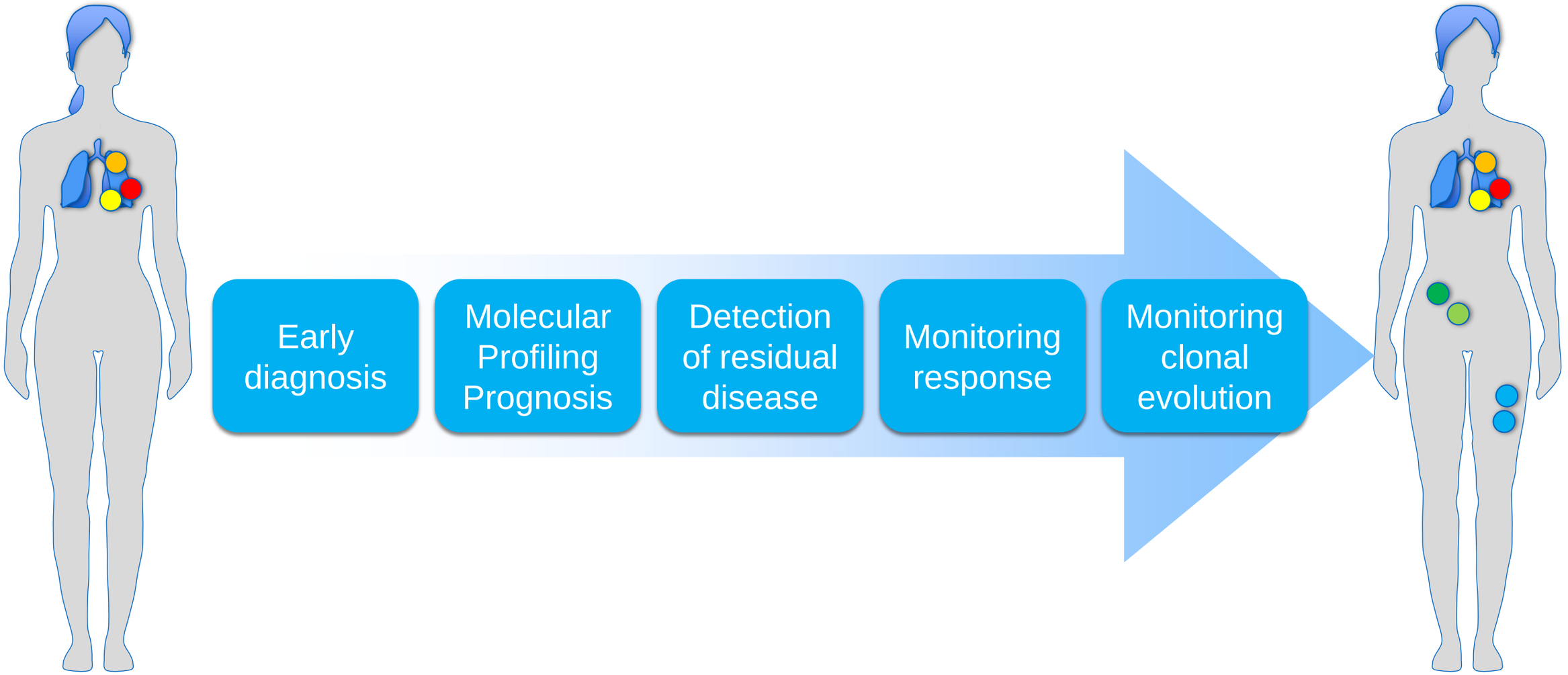
cfDNA: characteristics





- Concentration: 1-10 ng/ml
- Modal length: cfDNA166 nt
- Half-life: 15 min – 2.5 hours

Analysis of ctDNA during the course of disease



Wan J. C. M. et al (2017) **Nat Rev Cancer**

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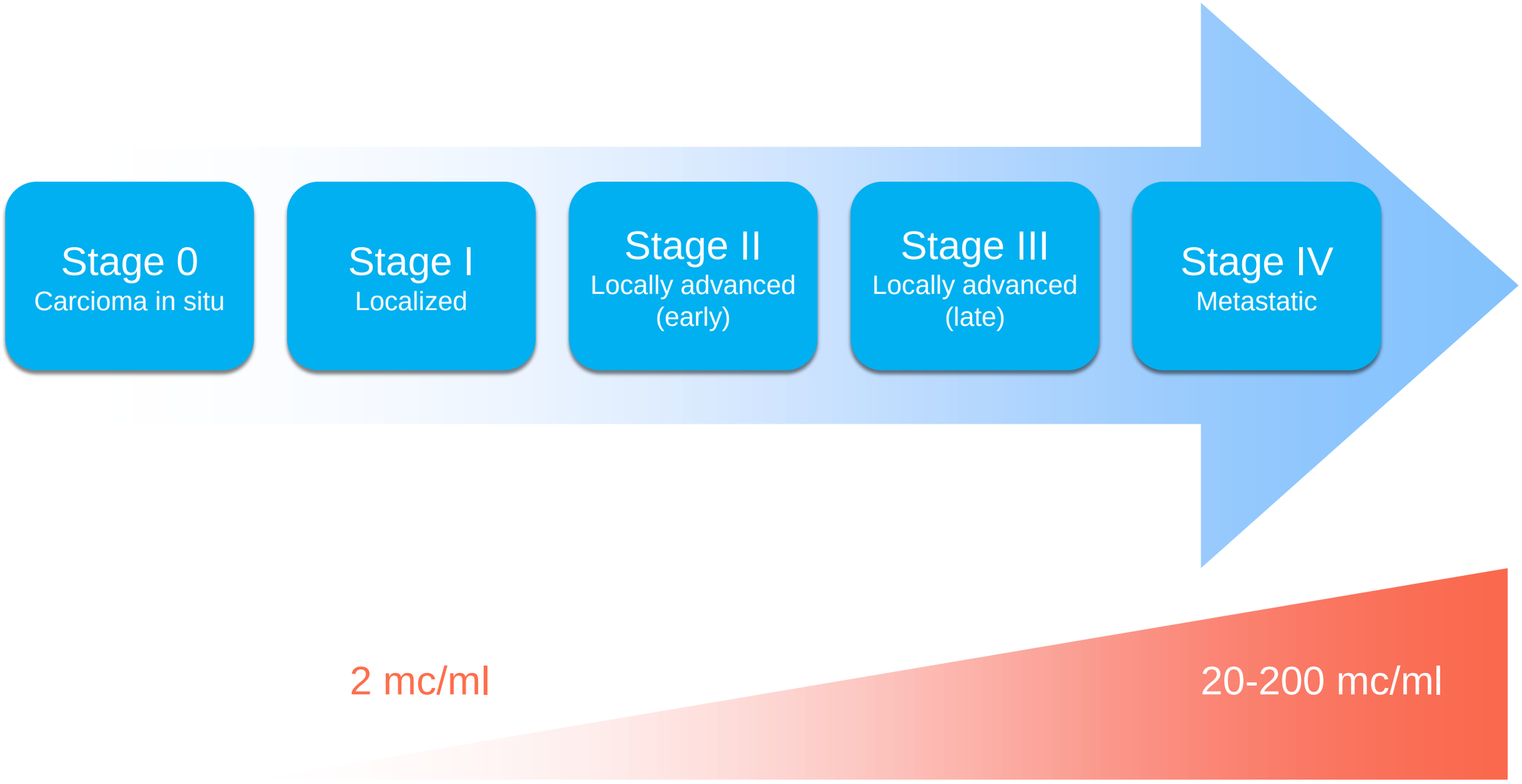
ctDNA across tumor stages



mc:mutant copy

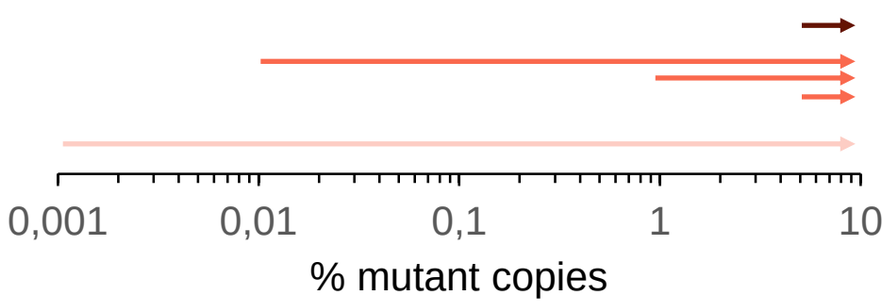
Bettegowda, C. et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. **Sci. Transl Med**. 6, 224ra24 (2014).

Methods

Table 1 | **Comparison and utility of technology platforms for circulating tumour DNA analysis**

Scale of analysis	Example technologies	Loci interrogated	Indicative limit of detection (mutant allele fraction or concentration)	Clinical utility
Single-locus or multiplexed assays	Microfluidic or allele-specific PCR: • Digital PCR[28,101,103,194] • BEAMing[29,30] • Intplex[3,122]	Microfluidic or allele-specific PCR: • 1–10 loci • Both ctDNA and cfDNA (Intplex)	Varies by method, optimal implementations can reach sensitivity of 0.001%–0.01% or individual mutant copies per millilitre[30,122,243,244]	• Detecting and quantifying recurrent hot-spot mutations • Monitoring for recurrent resistance mutations • Rapid turnaround time
	Enrichment for mutant alleles: • COLD-PCR[108] • SCODA[105,106] • NaME-PrO[107]	Enrichment for mutant alleles: 10–100 loci		
	Allele-specific or ARMS-PCR kits for companion diagnostics: • Cobas EGFR[99] • Therascreen EGFR[98]	• Cobas EGFR: 7 mutation assays covering multiple variants • Therascreen EGFR: 3 mutation assays covering multiple variants	Stated limit of detection (≥95% sensitivity): • Cobas EGFR: 25–100 copies per millilitre[99] • Therascreen EGFR: median 1.42% (range 0.05%–12.47% for different variants)[98]	Approved for *in vitro* diagnostic use: • Cobas EGFR: FDA approved • Therascreen EGFR: CE marked
Targeted sequencing approaches	Amplicon-based: • TAm-Seq[34] • Enhanced TAm-Seq[117] • Safe-SeqS[115]	10 kb to 50 Mb	• <0.01%–0.50% for purpose-built panels[34,111,114,115,117] • 1% for off-the-shelf multiplexed panels[45,112] • 5% for exome sequencing[39]	• Profiling gene panels • Monitoring for *de novo* resistance mutations • Monitoring clonal evolution in response to therapy • Sensitivity for disease burden can be increased by testing multiple loci in parallel (FIG. 4)
	Hybrid capture: • Exome sequencing[39] • CAPP-Seq[110,114] • Digital sequencing[111,118,185]			
Genome-wide	WGS: • Plasma-Seq[38] • PARE[197]	• 3.2 Gb (whole genome) • 21.6 kb unique to LINE-1 (REF. 184)	5%–10%[38]	• Identifying structural variants • Stratifying patient samples on the basis of disease burden • Detecting the presence of chromosomal aberrations
	Amplicon-based: • FAST-SeqS[184] • mFAST-SeqS[119]			

ARMS, amplification-refractory mutation system; BEAMing, beads, emulsion, amplification and magnetics; CAPP-Seq, cancer personalized profiling by deep sequencing; CE, *Conformité Européene* (European Conformity); cfDNA, cell-free DNA; ctDNA, circulating tumour DNA; COLD-PCR, co-amplification at lower denaturation temperature PCR; EGFR, epidermal growth factor receptor; FAST-SeqS, fast aneuploidy screening test-sequencing system; FDA, US Food and Drug Administration; LINE-1, long interspersed nucleotide element 1; mFAST-SeqS, modified FAST-SeqS; NaME-PrO, nuclease-assisted minor-allele enrichment with probe-overlap; PARE, personalized analysis of rearranged ends; Plasma-Seq, plasma sequencing; Safe-SeqS, safe sequencing system; SCODA, synchronous coefficient of drag alteration; TAm-Seq, tagged amplicon deep sequencing; WGS, whole-genome sequencing.



Known mutations

0.001%-0.01% mutant copies

1 mutant copy /ml

Panel of genes

0.01%-5% mutant copies

Whole genome

5%-10% mutant copies

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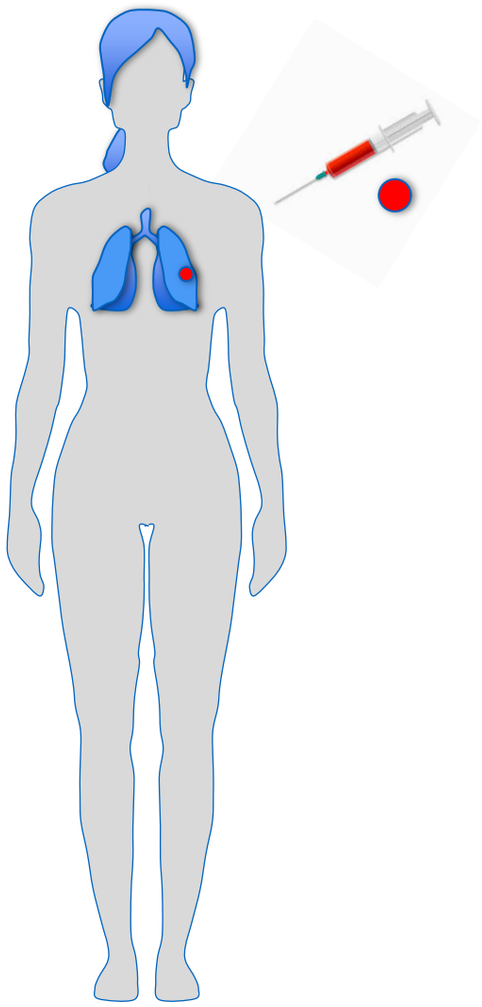
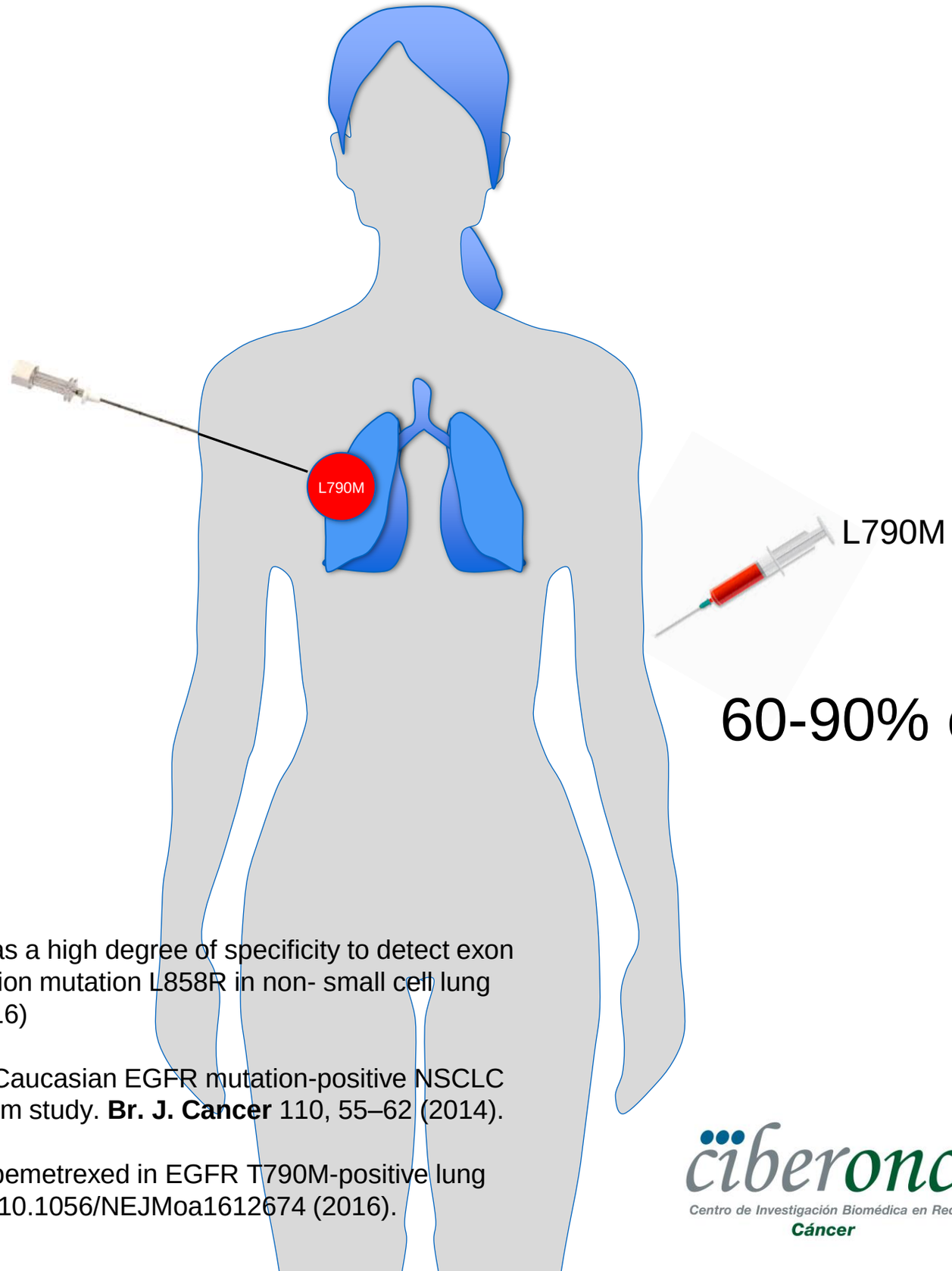
Early diagnosis



- Aiming for sensitivities > 1 mc/ml (0.001%) by improving:
  - Technology
  - Sources
- Biological relevance of TP53, KRAS or Notch mutations?

Martincorena, I. et al. High burden and pervasive positive selection of somatic mutations in normal human skin. **Science** 348, 880–886 (2015)

Molecular profiling: biopsy versus liquid biopsy



60-90% concordance

Qian, X. et al. Circulating cell-free DNA has a high degree of specificity to detect exon 19 deletions and the single-point substitution mutation L858R in non- small cell lung cancer. **Oncotarget** 7, 29154–29165 (2016)

Douillard, J.-Y. et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. **Br. J. Cancer** 110, 55–62 (2014).

Mok, T. S. et al. Osimertinib or platinum–pemetrexed in EGFR T790M-positive lung cancer**. N. Engl. J. Med**. http://dx.doi.org/10.1056/NEJMoa1612674 (2016).

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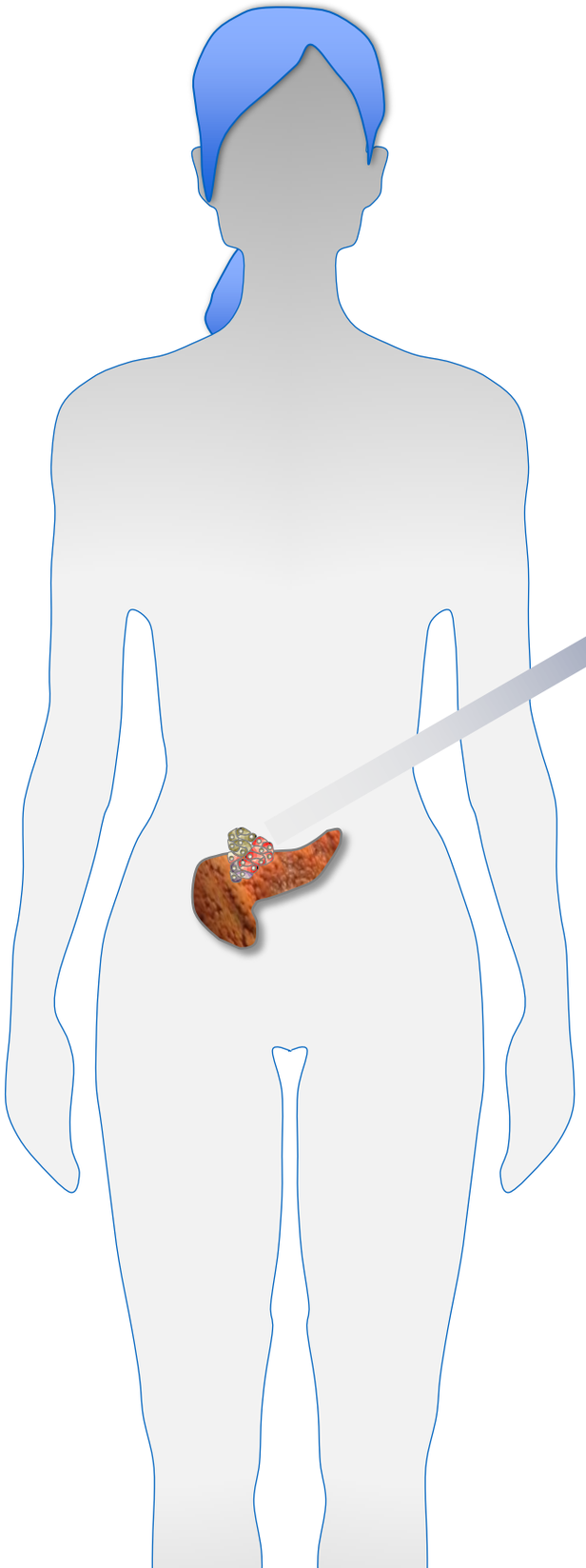
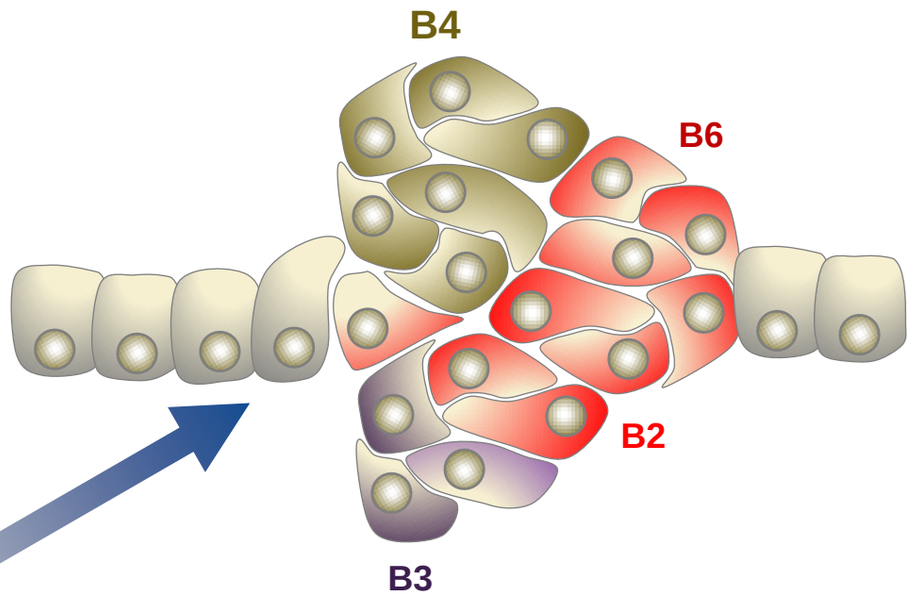
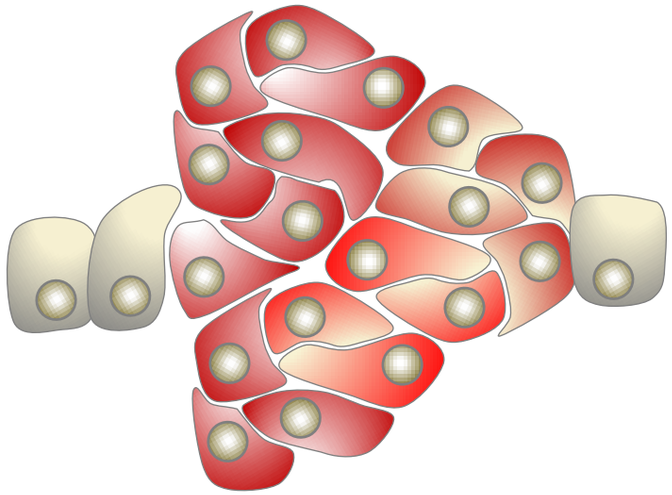
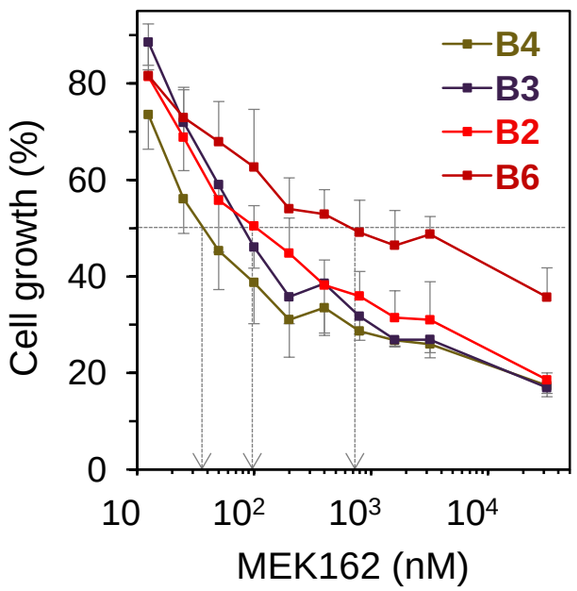
Selection by treatment

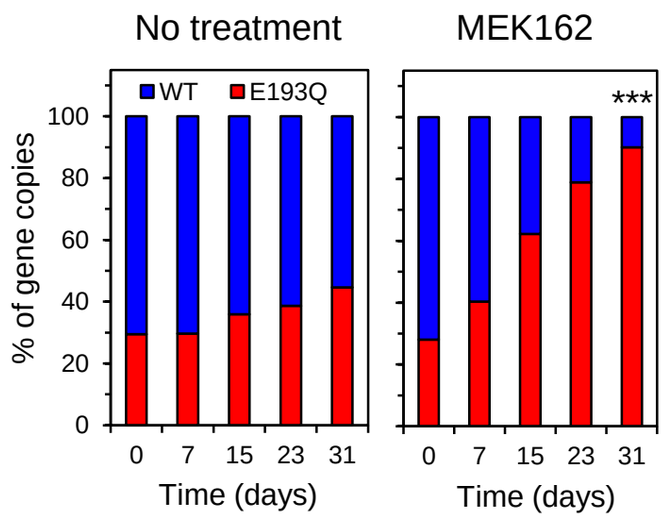






PC-PDX21
B4 vs B6





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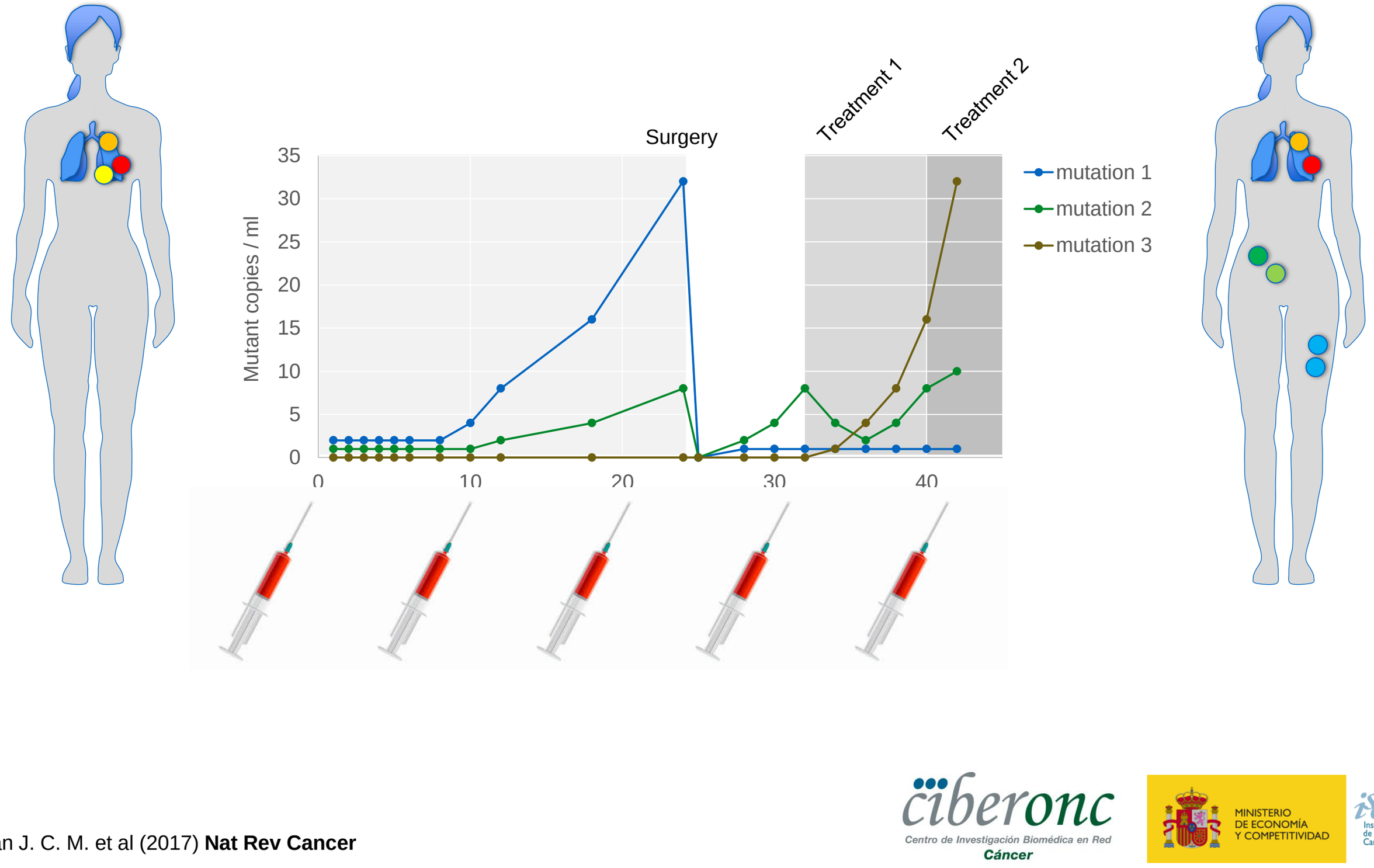
ctDNA to monitor response, clonal evolution and resistance



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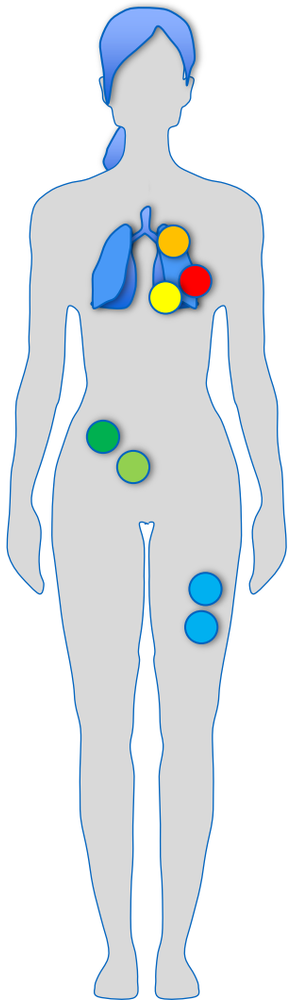
Future directions



- Mechanisms of ctDNA generation. Do all clones produce the same levels of DNA?
- DNA-binding proteins
- Integration with other circulating NA (miRNAs)
- Gene expression patterns
- Epigenetics

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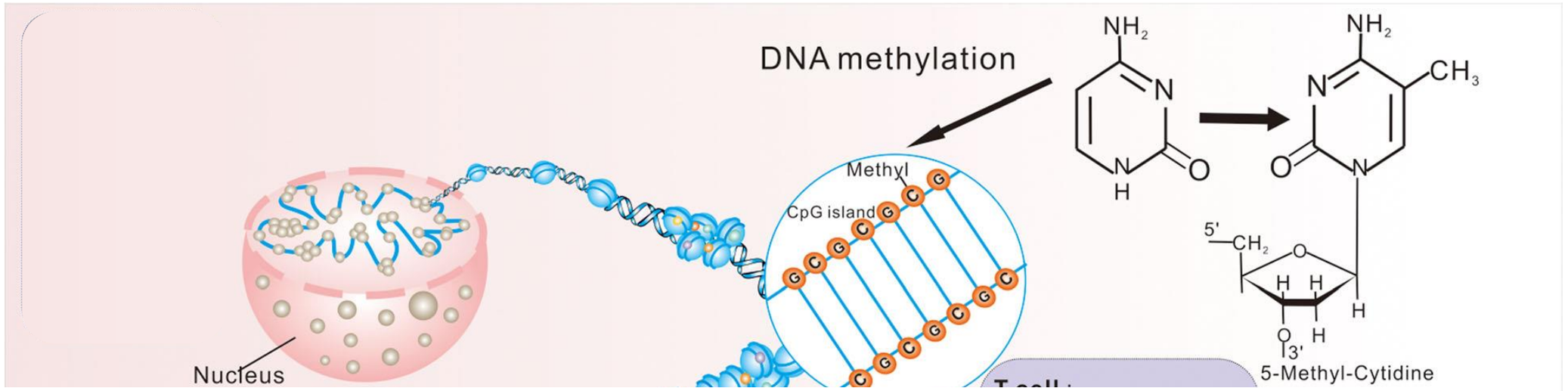
Epigenetics in liquid biopsy

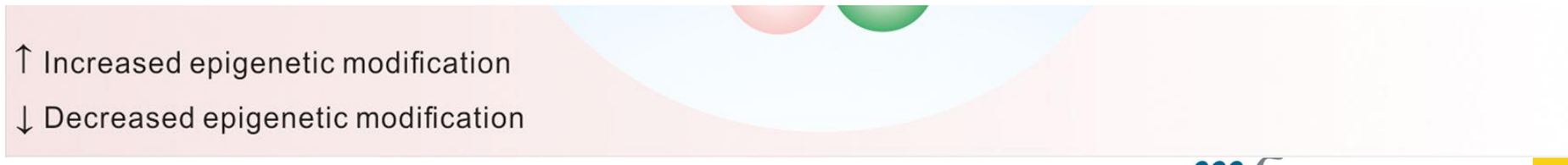


LETTER

https://doi.org/10.1038/s41586-018-0703-0

Sensitive tumour detection and classification using plasma cell-free DNA methylomes

Shu Yi Shen[1,12], Rajat Singhania[1,12], Gordon Fehringer[2,12], Ankur Chakravarthy[1,12], Michael H. A. Roehrl[1,3,4], Dianne Chadwick[1], Philip C. Zuzarte[5], Ayelet Borgida[2], Ting Ting Wang[1,4], Tiantian Li[1], Olena Kis[1], Zhen Zhao[1], Anna Spreafico[1], Tiago da Silva Medina[1], Yadon Wang[1], David Roulois[1,6], Ilias Ettayebi[1,4], Zhuo Chen[1], Signy Chow[1], Tracy Murphy[1], Andrea Arruda[1], Grainne M. O'Kane[1], Jessica Liu[4], Mark Mansour[4], John D. McPherson[7], Catherine O'Brien[1], Natasha Leighl[1], Philippe L. Bedard[1], Neil Fleshner[1], Geoffrey Liu[1,4,8], Mark D. Minden[1], Steven Gallinger[9,10], Anna Goldenberg[11], Trevor J. Pugh[1,4], Michael M. Hoffman[1,4,11], Scott V. Bratman[1,4], Rayjean J. Hung[2,8]* & Daniel D. De Carvalho[1,4]*



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Carlos III

CIBERONC. Centers

50 Groups

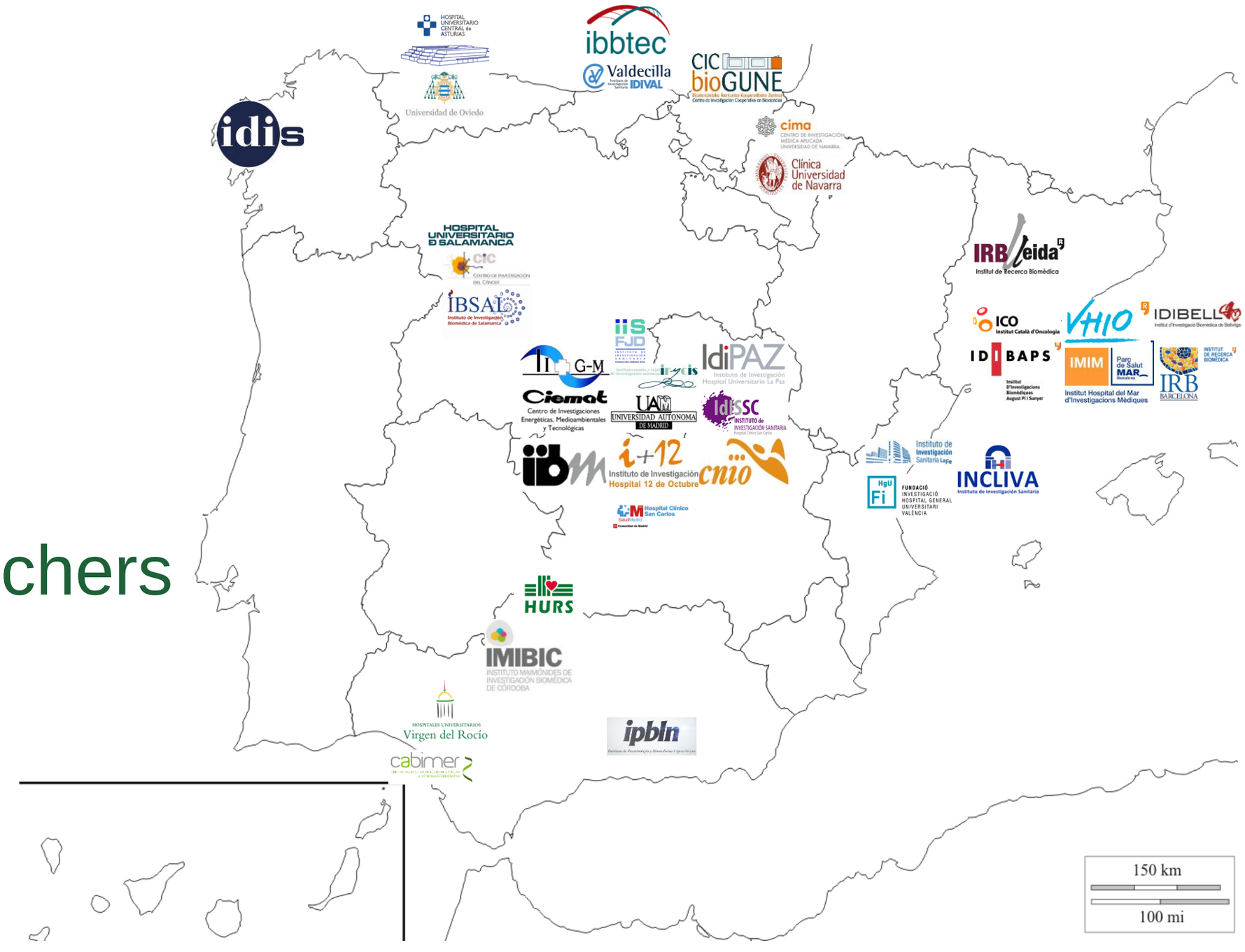
38 Centers

533 Members

34 Collaborators

81 Staff

701 Researchers



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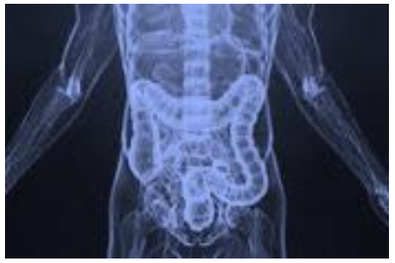
CIBERONC. Scientific Structure

TUMORS OF THE DIGESTIVE TRACT



GABRIEL CAPELLA MUNAR

JOSE M. TABERNERO CATURLA

ALFREDO CARRATO MENA
ANDRES CERVANTES RUIPEREZ
EDUARD BATLLE GOMEZ
EDUARDO DIAZ-RUBIO GARCIA
ENRIQUE ARANDA AGUILAR
FRANCISCO XAVIER REAL ARRIBAS
JAIME FELIU BATLLE
MANEL ESTELLER BADOSA
NURIA MALATS RIERA

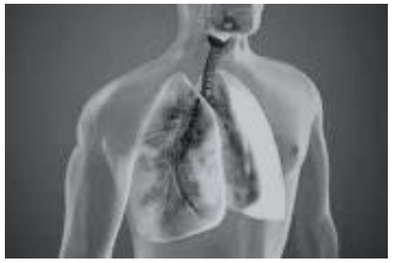
BREAST CANCER

JOAN ALBANELL MESTRES

FEDERICO ROJO TODO

ATANASIO PANDIELLA ALONSO
AMPARO CANO GARCIA
ANA LLUCH HERNANDEZ
JOAQUIN ARRIBAS LOPEZ
JOSE PALACIOS CALVO
MIGUEL MARTIN JIMENEZ

TUMORS OF THE RESPIRATORY TRACT



LUIS MONTUENGA BADIA

LUIS PAZ-ARES RODRIGUEZ

AMANCIO CARNERO MOYA
CARLOS CAMPS HERRERO
JUAN PABLO RODRIGO TAPIA

HEMATOLOGICAL TUMORS

DOLORS COLOMER PUJOL

MARCOS GONZALEZ DIAZ

ELIAS CAMPO GUERRI
JESUS F. SAN MIGUEL IZQUIERDO
JOSE ALBERTO ORFAO DE MATOS
FELIPE PROSPER CARDOSO
MIGUEL ANGEL SANZ ALONSO
MIGUEL ANGEL PIRIS PINILLA
JOSE ANTONIO PEREZ SIMON
MANEL ESTELLER BADOSA

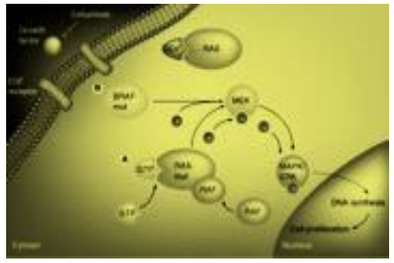
LOW PREVALENCE TUMORS

ENRIQUE DE ALAVA CASADO

IGNACIO MELERO BERMEJO

FRANCESC XAVIER BOSCH JOSE
FRANCISCO J. MATIAS-GUIU GUIA
RAFAEL LOPEZ LOPEZ
ROSA NOGUERA SALVA
SANTIAGO RAMON Y CAJAL

MECHANISMS OF TUMOR PROGRESSION



XOSE RAMON GARCIA BUSTELO

ANNA BIGAS SALVANS

ALBERTO MUÑOZ TEROL
ARKAITZ CARRACEDO PEREZ
CARLOS LOPEZ OTIN
EUGENIO SANTOS DE DIOS
FRANCISCO JAVIER OLIVER POZO
JESUS MARIA PARAMIO GONZALEZ
JOAN SEOANE SUAREZ
MARIA DEL P. SANTISTEBAN SANZ
PIERO CRESPO BARAJA

TRAINING AND MOBILITY

AMPARO CANO GARCIA

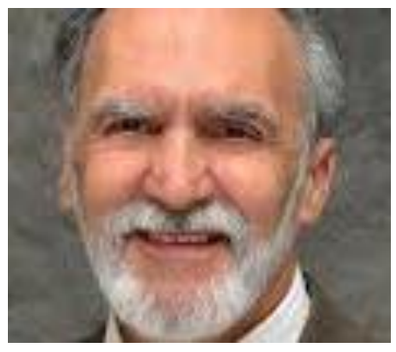
ANNA BIGAS SALVANS

Dirk Arnold

Giampaolo Bianchini

Giorgio Scagliotti

Catherine Thieblemont

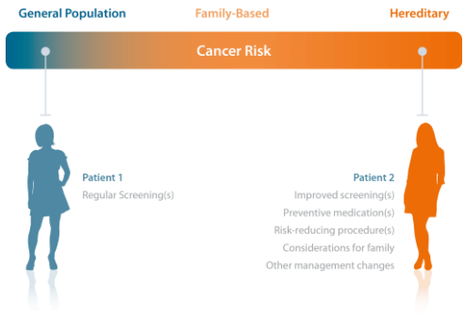


José Costa

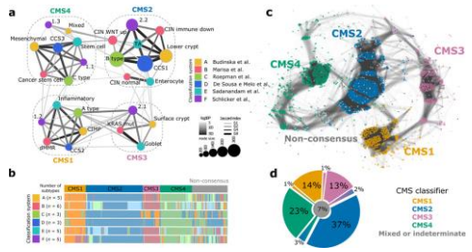
Ángel Alonso

CIBERONC - Aims

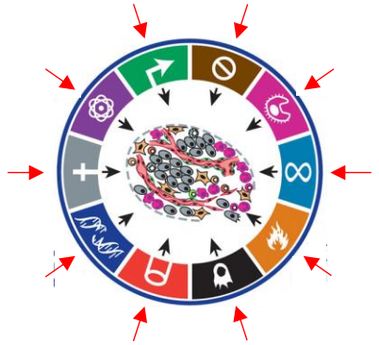
Epidemiology



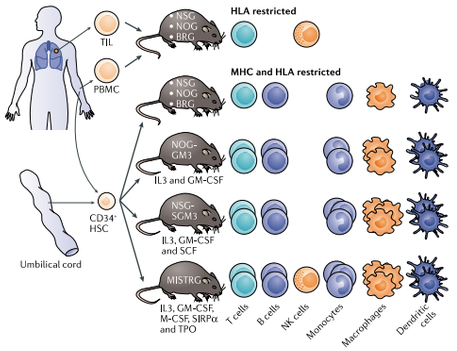
Classification / Biomarkers



Novel Drivers

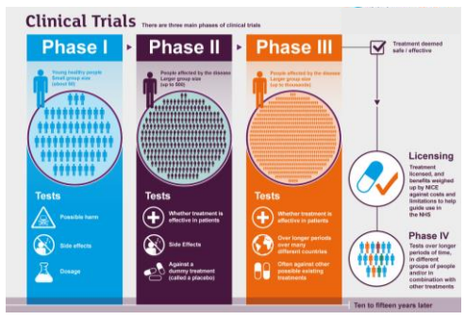


Models

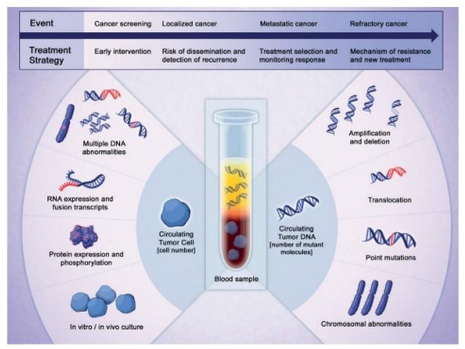


TUMORS OF THE DIGESTIVE TRACT
BREAST CANCER
TUMORS OF THE RESPIRATORY TR…
HEMATOLOGICAL TUMORS
TISSUE BIOMARKERS ONCOIMM …
MECHANISMS OF TUMOR PROGR…

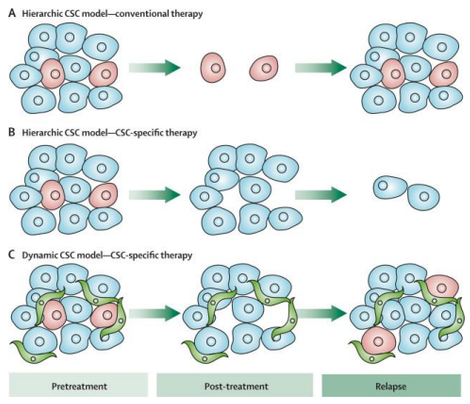
Clinical trials



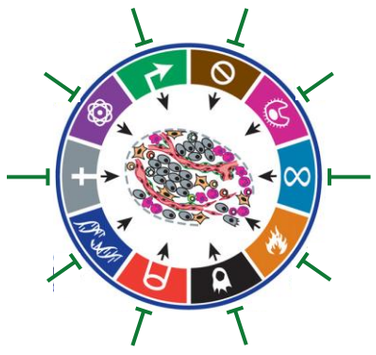
Liquid Biopsy



Resistance



Novel Therapies



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CIBERONC – Work modules

Liquid Biopsy & Biomarkers

Rodrigo Toledo

Vall d'Hebron Instituto de Oncología

Cancer Bioinformatics & Omics

Víctor Quesada

Universidad de Oviedo

Drug Resistance & New Therapies

Alberto Ocaña

Universidad de Castilla La Mancha

Immuno-Oncology

Pedro Berraondo

Centro de Investigación de Medicina Aplicada

Experimental Models

Patricia Pérez-Galán

Instituto de Investigaciones Biomédicas August Pi i Sunyer

Prediction of response to immunotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

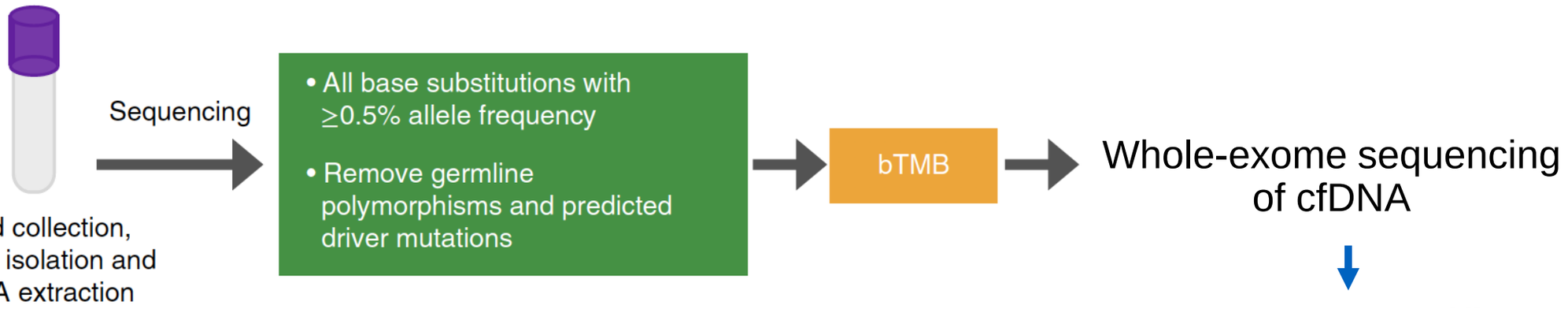
Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson, C. Audigier-Valette, E. Minenza, H. Linardou, S. Burgers, P. Salman, H. Borghaei, S.S. Ramalingam, J. Brahmer, M. Reck, K.J. O'Byrne, W.J. Geese, G. Green, H. Chang, J. Szustakowski, P. Bhagavatheeswaran, D. Healey, Y. Fu, F. Nathan, and L. Paz-Ares

- **AIMS:**

To develop a customized blood-based tumor mutation burden assay to predict the response to Immunotherapy.

Our ultimate goal is to develop a specific bTMB assay for different tumour types.



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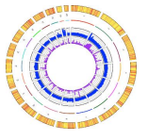
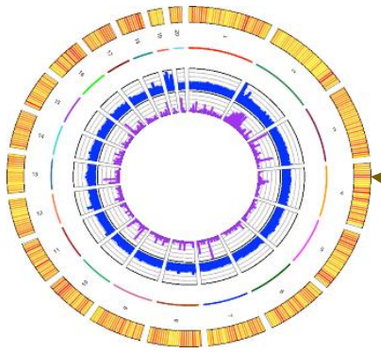
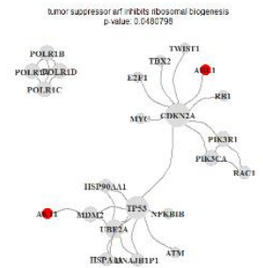
Cloud-based collaboration platform







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Genomic medicine at CIBERONC

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