N E W L A Y O U T

Health Hackathon
14 & 21.12.2023

With Prof Susan M Gasser and Prof Olivier Michielin

THE MAKING OF AN INNOVATIVE MEDICINE

Introductory workshops on translational biomedical research and drug discovery and development

BIO-698 resumes Thursday September 21. 2023
4:15 PM @ AAC 108

EPFL

Sciences de la Vie -SV

Prof Roger G. Clerc

The Making Of An Innovative Medicine – course schedule

Thursday's @ 4-6 PM except 14.12/21.12.23 @2-6 PM

Session 1: **Scope of the course _ general organization _ case study**
21.09.23 *Embracing a career at the heart of biomedical research !?*
AAC108

Session 2: **Historical perspective: the modern pharmacy**
28.09.23 *Advent of modern medicines - placebo controlled drug development*
AAC108

Session 3: **Introduction to translational research: crossing the bridge**
05.10.23 *A chasm has opened wide between biomedical research and patients in need*
AAC014

Session 4: **Therapeutic target identification I & II**
12-19.10.23 *"me too" vs a wealth of innovative targets _ small MW cpds vs biologicals*
AA014 AAC108 *Early front loading of biomarker identification for cohort stratification*

Session 5: **Structure based drug design _medicinal chemistry_low/high throughtput**
26.10.23 **screening assays_ multiple parallel parameters optimization MDO**
AAC108 *Setting up screening assays, the robotics, the million cpds librairies*

Session 6: **Therapeutic modalities peptides and biologicals: today's -**
02.11.23 **tomorrow's pharmacy NBEs**
AAC108 *Challengies (cost of goods - healthcare payers) and opportunities*

The Making Of An Innovative Medicine - course schedule

Thursday's @ 4-6 PM except 14.12/21.12.23 @2-6 PM

Session 7: **Personalized Healthcare PHC _ precision medicine**
09.11.23 *How PHC started: from a single case to a paradigm change*
AAC108

Session 8: **Pha[illegible]agenetic polymorphisms_Pharm[illegible]omics**
16.11.23 *Interindividual variability toxicity in response to medicines*
AAC014

Session 9: **In vivo pharmacology, investigative toxicology with Dr Nathalie Brandenberg PhD**
23.11.23 *Preclinical research ends up with IDB's, FDA guidelines for FIH*
AAC108

Session 10: **Clinical research_ phase 0, phase I, II, III, IV**
30.11.23 *The long and complex experimental procedures with human patients*
AAC108

Session 11: **Intellectual property_ integrity in research_my genome vs our genomes**
07.12.23 *Why are patents essential to new medicine/biotech development*
AAC108

Session 12: **Health Hackathon – Hacking medicine I with Dr Greg Michielin MD PhD**
14.12.23 *Pitches –building teams – hacking problem - 5Ws – brainstorm*
starts @ 2PM ! MED21522

Session 13: **Health Hackathon – Hacking medicine II with Prof O. Michielin MD - Prof SM Gasser PhD judges**
21.12.23 *Building up solutions – make it better - final presentations*
starts @ 2PM ! AAC231

WORKSHOP LISTING - THE MAKING OF AN INNOVATIVE MEDICINE BIO698			
! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !			
sessions	no	workshops	speaker/s
S02 (28-09-23) ! AAC108 !			
historical medicines	1	vaccine discovery : E. Jenner and smallpox	Danica M
with Nobel laureates while	2	penicilin: impact, whose invention ?	
hopping on giant shoulders	3	prozac at the core of psychiatry	
	4	lipitor/statins at last a blockbuster	
	5	artemisinin and malaria	Umair
	6	cyclosporin from soil sample to blockbuster	Umair
S03 (5-10-23) ! AAC014 !			
translational research	7	expanding the scope of targeted therapies	
an emerging field	8	chronotherapy	Pitt
S04 (12-10-23) ! AAC014 !			
therapeutic target identification	9	rare diseases repurposing medicines	Adrien
S04b (19-10-23) ! AAC108 !	10	nocosomial inf/MRSA/phage antibacterials	Georges
therapeutic target identification	11	Crispr/Cas9 gene editing huntington disease	Pitt
	12	AI in drug discovery	Simon
S05 (26-10-23) ! AAC108 !			
structure based drug design	13	macrocycles and non druggable targets	Masota
	14	chemoproteomics - NMEs	Nico G
		my therapeutic target	Roger
S06 (02-11-23) ! AAC108 !			
therapeutic modalities - NBEs	15	therapeutic peptides/incretins	Tim
	16	biologicals on the rise MABs medicines	Nico G
	16	RNA therapeutics, antisense medicines	
S07 (9-11-23) ! AAC108 !			
PHC personalized healthcare	17	BRCA1 preventive surgery/tumor board	Nikita
Human genomics	18	SOPHiA Genetics - GWAS	
	19	disease enabling biomarkers/micro RNAs	Isika
S08 (16-11-23) ! AAC014 !			
pharmacogenetic polymorphism	20	NextGenSequencing - precision medicine	Hien
	21	deCODE Inc pharmgenomic/iceland genealogy	
S09 (23-11-23) ! AAC108 !			
in vivo pharmacology	22	organoids come of age	Nathalie B
toxicology	23	thalidomide repurposing	Ekaterina
S10 (30-11-23) ! AAC108 !			
clinical research	24	AI medicine 2.0	Simon
	25	most common genetic defect : cystic fibrosis	
	26	sex bias in preclicnial and clinical research	Weilin
	27	placebo/nocibo effects	Tim
S11 (07-12-23) ! AAC108 !			
intellectual property/integrity	28	SMA gene therapy - pay for performance	Abtin
	29	biopatents - 23 and Me - my genome	khosiyat
S12 (14-12-23) starts @ 2PM		Hacking medicine	all + invitees
! MED21522!			
S13 (21-12-23) start @ 2 PM		Hacking medicine	all + invitees
! AAC231 !			

Workshops _ The Making Of An Innovative Medicine

(today's class)

Session 7 - PHC - 4P medicine

ComPaRe
LA COMMUNAUTÉ DE PATIENTS POUR LA RECHERCHE

participative

- Personalized healthcare – PHC *personalized*
- Precision medicine *precise*
- Disease enabling biomarkers *preventive -predictive*
- CTCs real time DIA

Personalized Healthcare (PHC) : a paradigm change into the future of medicine 2.0

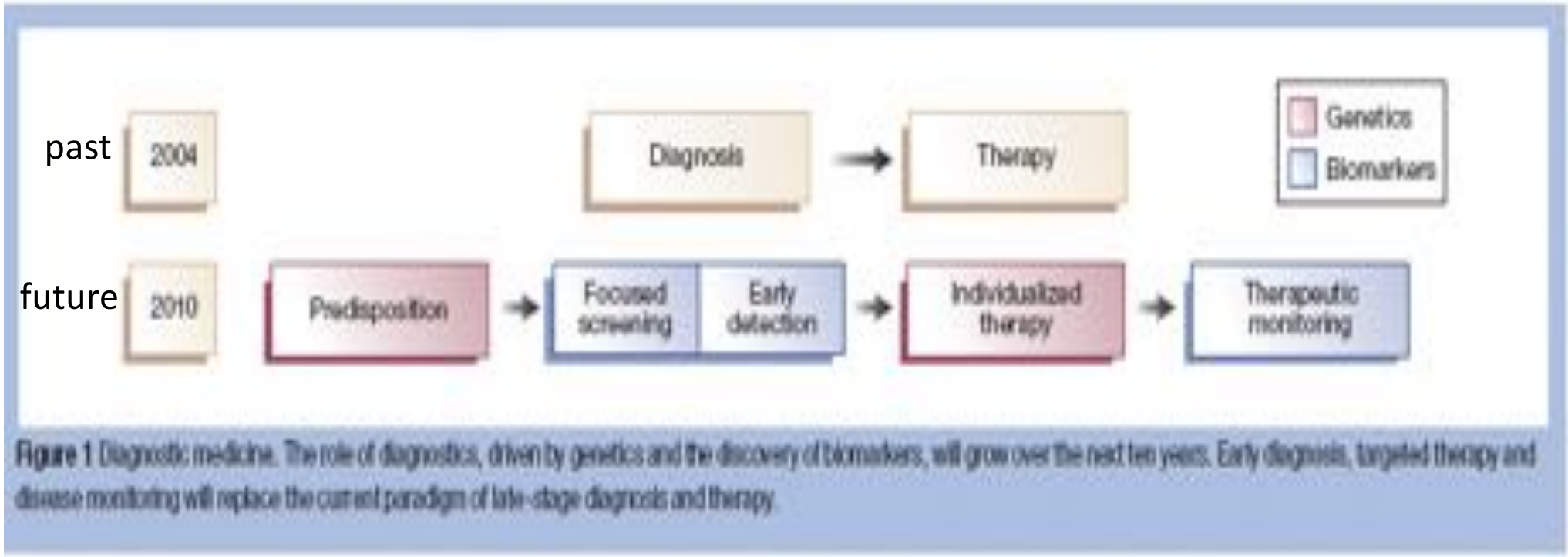


Figure 1 Diagnostic medicine. The role of diagnostics, driven by genetics and the discovery of biomarkers, will grow over the next ten years. Early diagnosis, targeted therapy and disease monitoring will replace the current paradigm of late-stage diagnosis and therapy.

- **GENOMIC SCIENCES AND THE MEDICINE OF TOMORROW**
- **BEYOND THE HUMAN GENOME PROJECT (e-health) PRECISON MEDICINE**
- **DISEASE ENABLING BIOMARKERS (prodromal phase, eg. AZ !)**
- **4P MEDICINE – PREVENTIVE, PERSONALIZED, PARTICIPATIVE, PRECISE**

Personalized Healthcare (PHC) : a paradigm change

- **GENOMIC SCIENCES AND THE 4P MEDICINE OF TOMORROW**
- **BEYOND THE HUMAN GENOME PROJECT – AI MEDICINE ON THE RISE**

"One pill fits all" concept non longer suitable in drug discovery and precision medicine !

EACH GROUP OF PATIENTS IS UNIQUE

SUCH AS… eg A GWAS STUDY ON HUMAN HEIGHT…

Annals of human genetics

Ann Hum Genet. 2010 Jan; 74(1): 11–16.

HMGA2 Is Confirmed To Be Associated with Human Adult Height

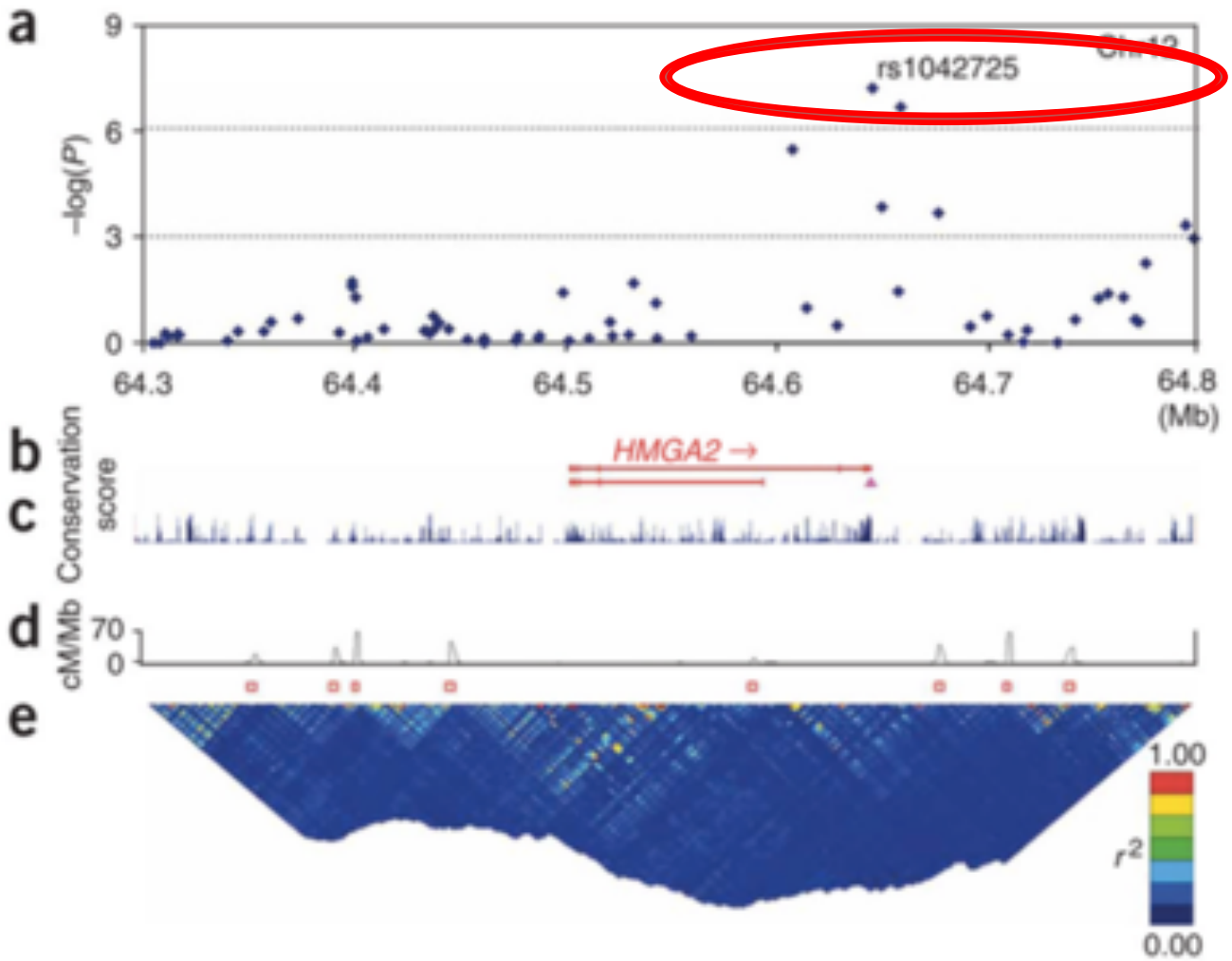
Tie-Lin Yang[1,2], Yan Guo[1,2], Li-Shu Zhang[2], Qing Tian[2], Han Yan[1], Yan-Fang Guo[1] and Hong-Wen Deng[1,2,3]*

[1]*Key Laboratory of Biomedical Information Engineering of Ministry of Education, and Institute of Molecular Genetics, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an 710049, P. R. China*
[2]*School of Medicine, University of Missouri – Kansas City, Kansas City, MO 64108, USA*
[3]*Center of System Biomedical Sciences, Shanghai University of Science and Technology, Shanghai 200093, P. R. China*

Summary

Recent genome-wide association studies have identified a novel polymorphism, rs1042725, in the *HMGA2* gene to

Linkage disequilibrium of the human height HMGA2 locus

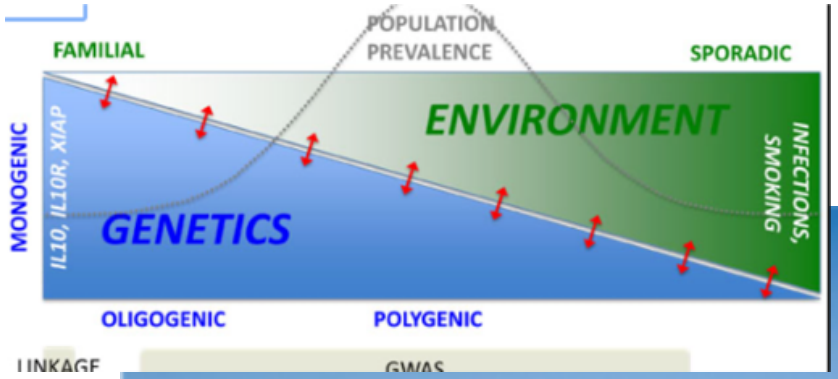


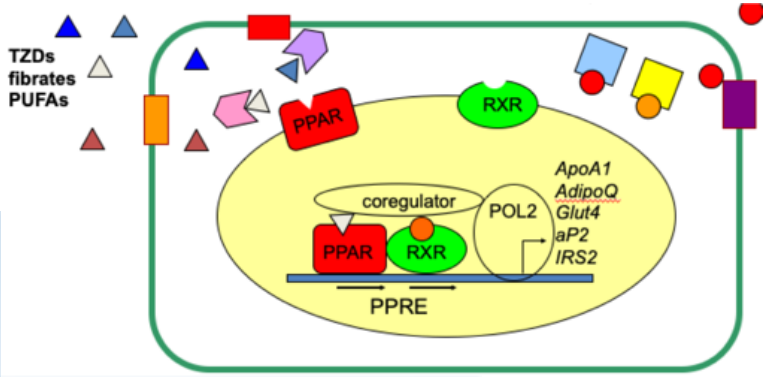
Loci are said to be in linkage desequilibrium when the frequency of association of their different alleles is higher or lower than what would be expected if the loci were independent and associated randomly.

LOD stands for "logarithm of the odds." **LOD score** is a statistical estimate of whether two genes, or a gene and a disease are near each other and likely to be inherited together.

Weedon MN et al. 2007 Nature Genetics 39: 1245-1250

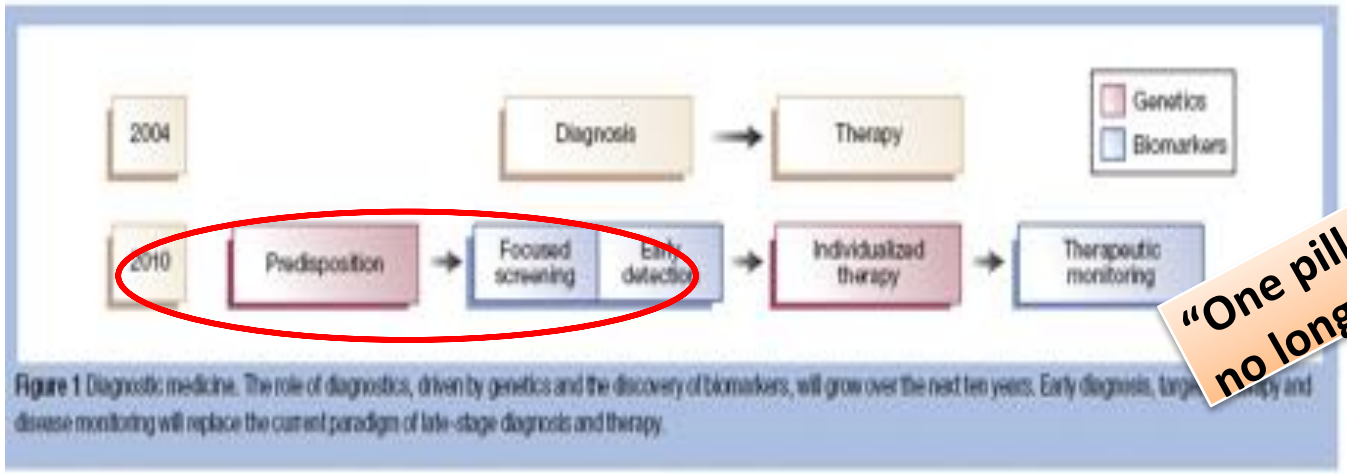
Personalized Healthcare : the obesity pandemia and the predictive medicine complexity of a multifactorial disease





- METABOLIC DISEASES - GENOMES AND ENVIRONMENTAL FACTORS
- THRIFTY GENE HYPOTHESIS-EPIGENETIC IMPACT-PATIENT DERIVED

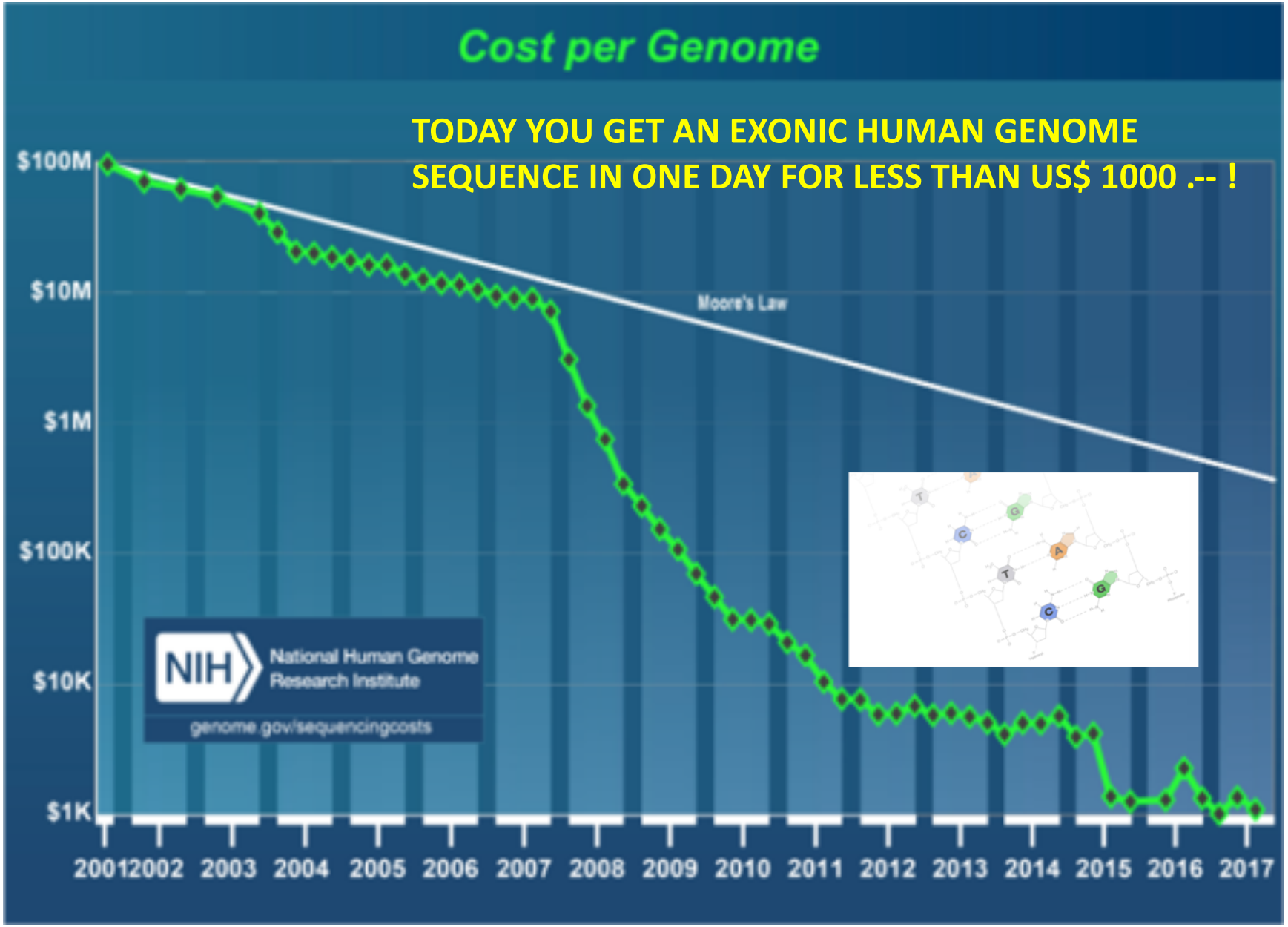
Personalized Healthcare (PHC) a paradigm change



- Diagnostic medicine focuses on genetic diversity of groups of individuals
- Predisposition to a particular pathology using predictive biomarkers (eg. any body fluid, genomic next gen sequencing polymorphisms, etc)
- Do I want to know ? Do I decide not to know ? Ownership of blueprint !?
- Personalized medecine shall focus on disease prevention, participative therapy and therapy monitoring ! Do we also need preventive hospitals ? preventive MDs as compared to today's curative hospitals, current therapeutic approaches ?

Next Gen DNA sequencing (NGS) : superseeded computer development technologies

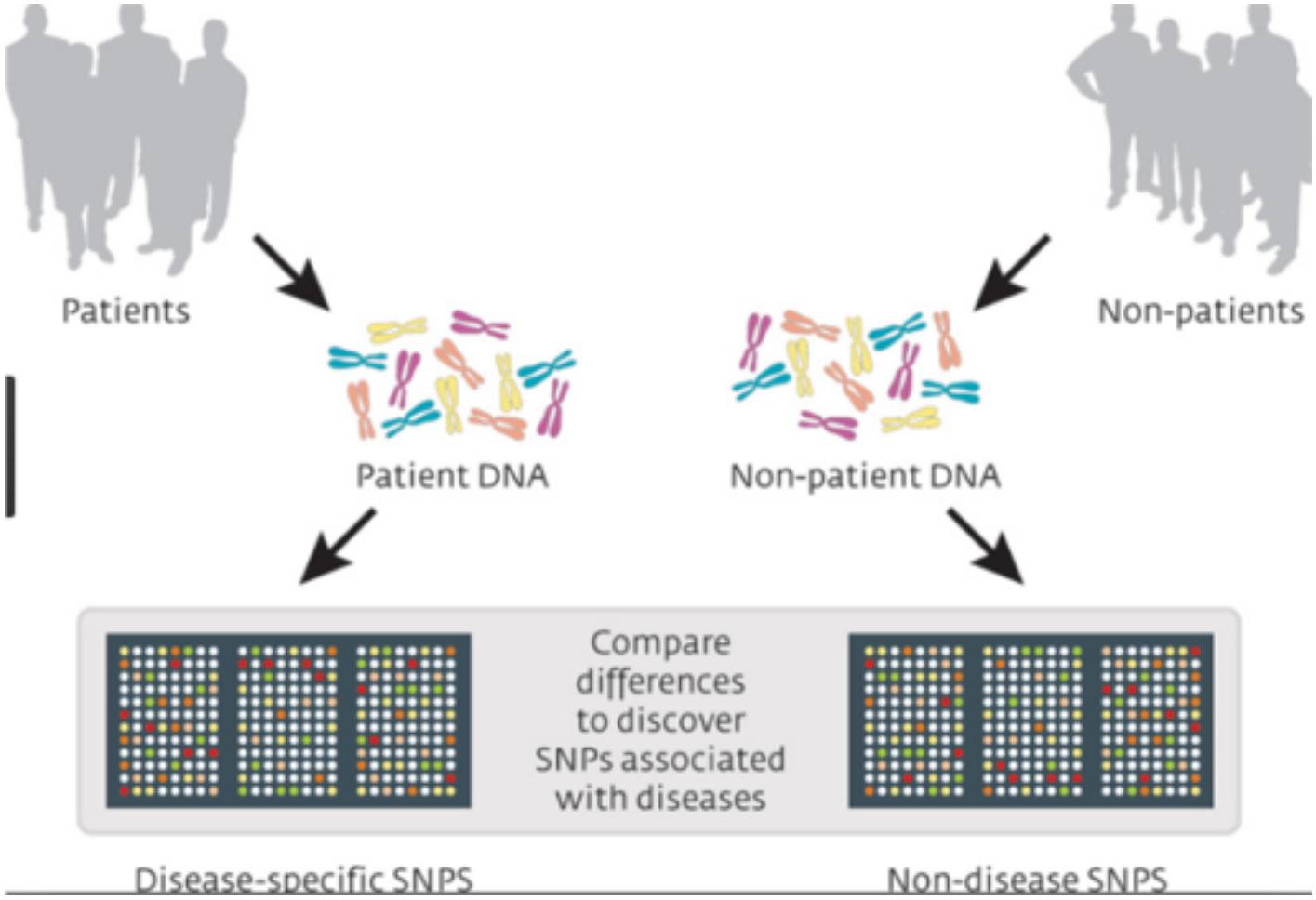
EXCEEDING MOOR'S LAW : EVERY TWO YEARS DOUBLING THE TRANSISTOR CAPACITY OF AN INTEGRATED CICUIT



Genetics and Genomics – Impact on Healthcare : my genome vs your genome

OPPORTUNITIES

- **G**enome **W**ide **A**ssociation **S**tudies (GWAS) looks for *associations* with **S**ingle **N**ucleotide **P**olymorphisms (SNPs) and genetic factors across the whole genome to correlate with particular traits (clinical symptoms, phenotypes) *eg. ApoE4 polymorphism and AZ*



Next Gen DNA sequencing (NGS) :
every group of patients is different

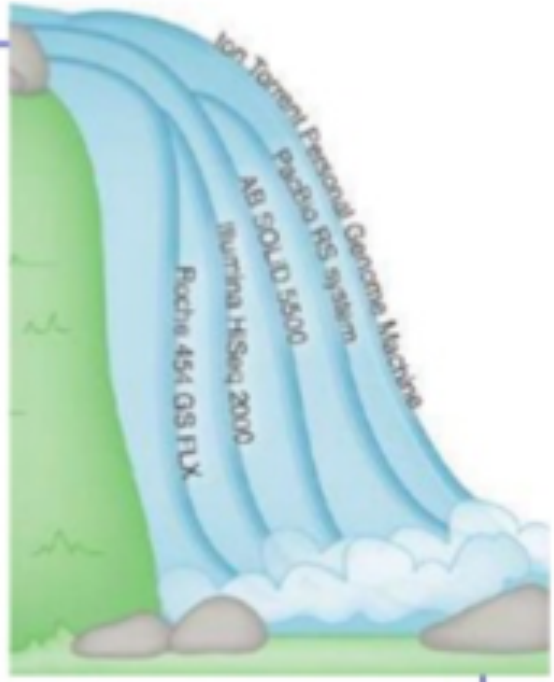
NGS - ULTIMATE REVOLUTION IN PERSONLIZED HEALTHCARE, CHANGES PATHOLOGY DIAGNOTICS PRACTICE - OFFERS PATIENTS A BETTER LIFE ? AT WHAT COSTS ?

Next Gen Sequencing [NGS]

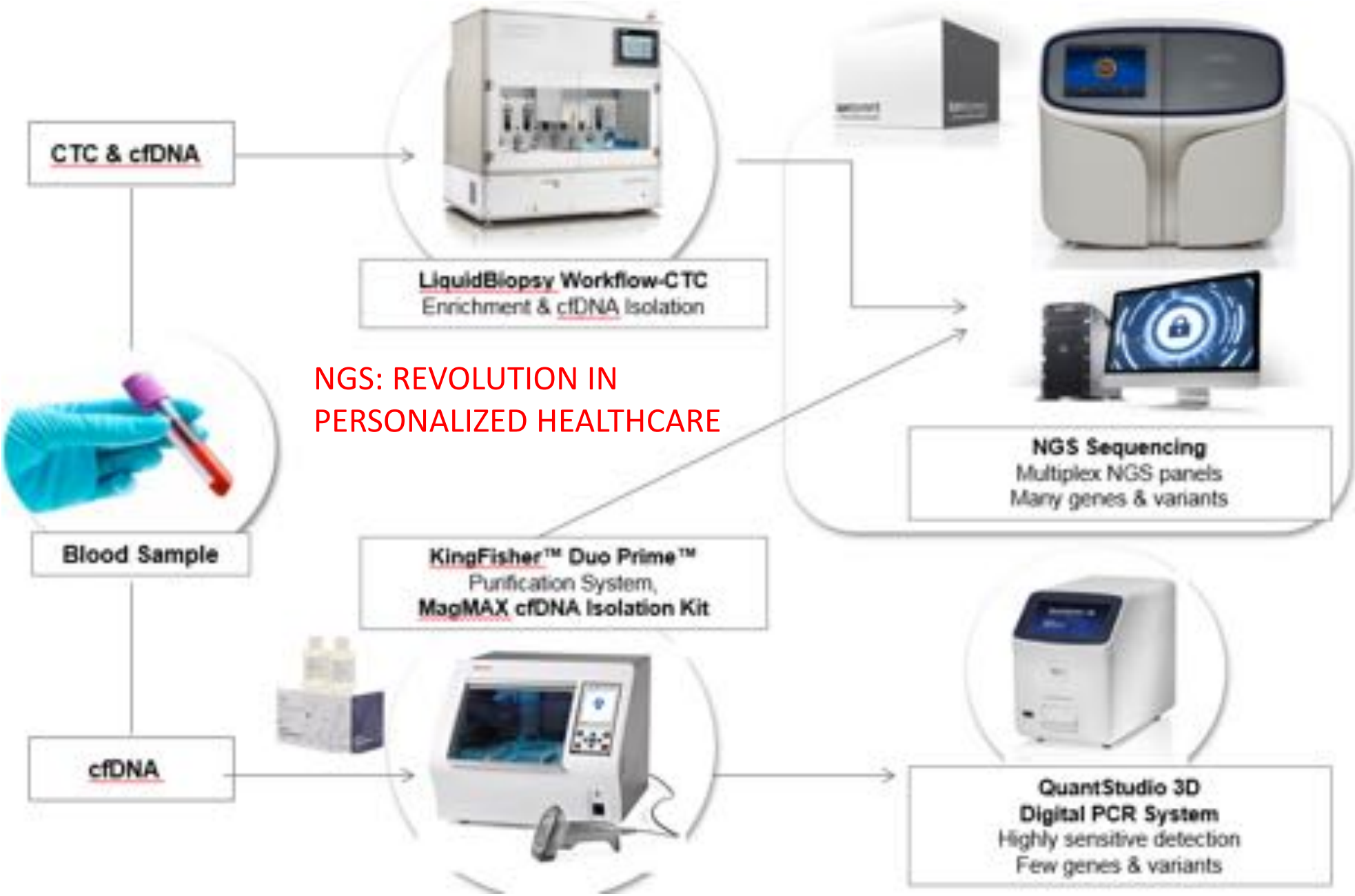
- History of DNA Sequencing
  - Maxam-Gilbert
  - Sanger
  - ABI

Human Genome: 1990-2000

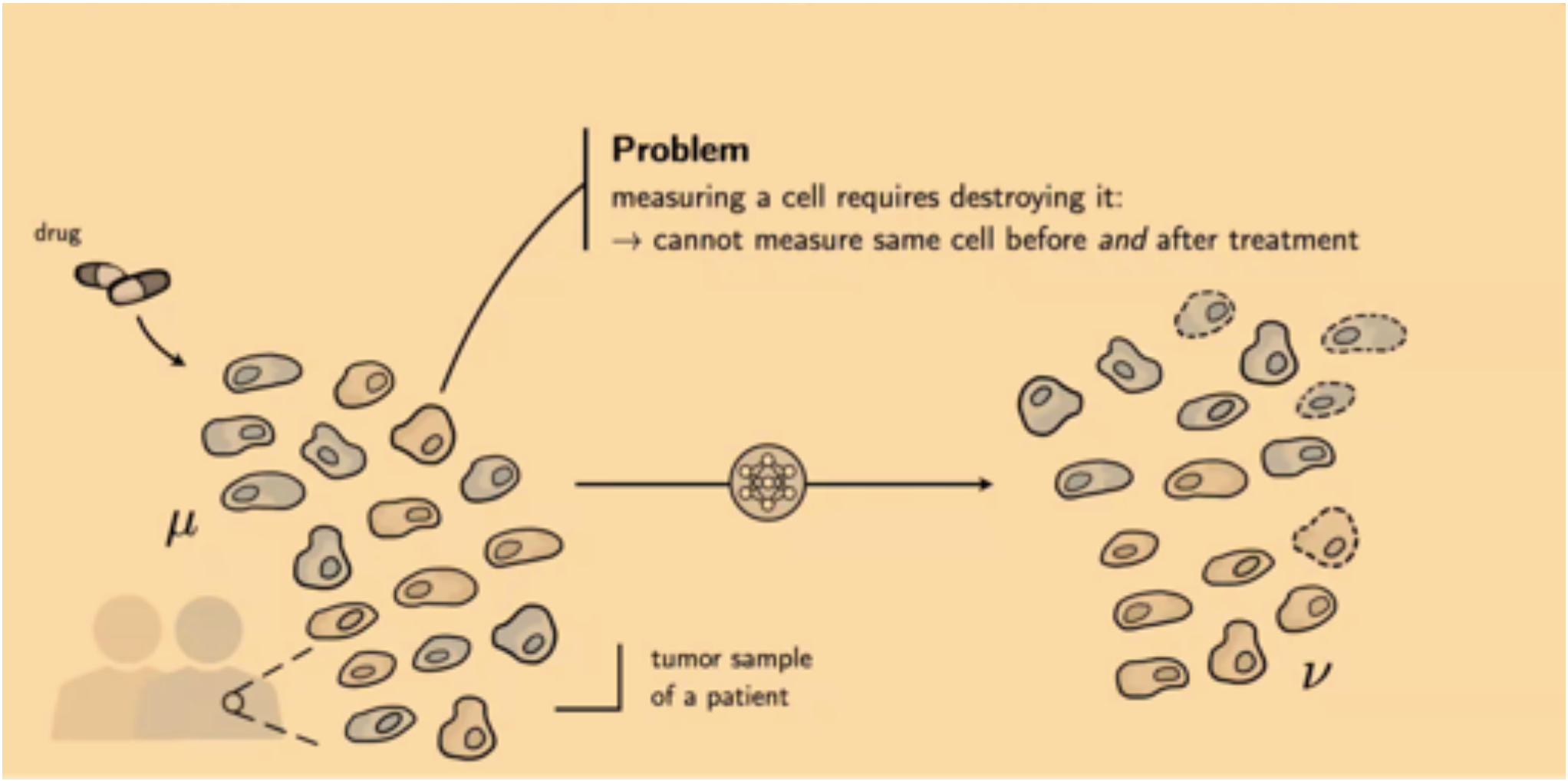
- NGS Technologies:
  - 454, Illumina, PacBio, ABI, Helicos,
  - Ion Torrent, Nanopores
- Applications:
  - Genomes, RNASeq, ChIPSeq, CGH, CancerGenome , Environmental



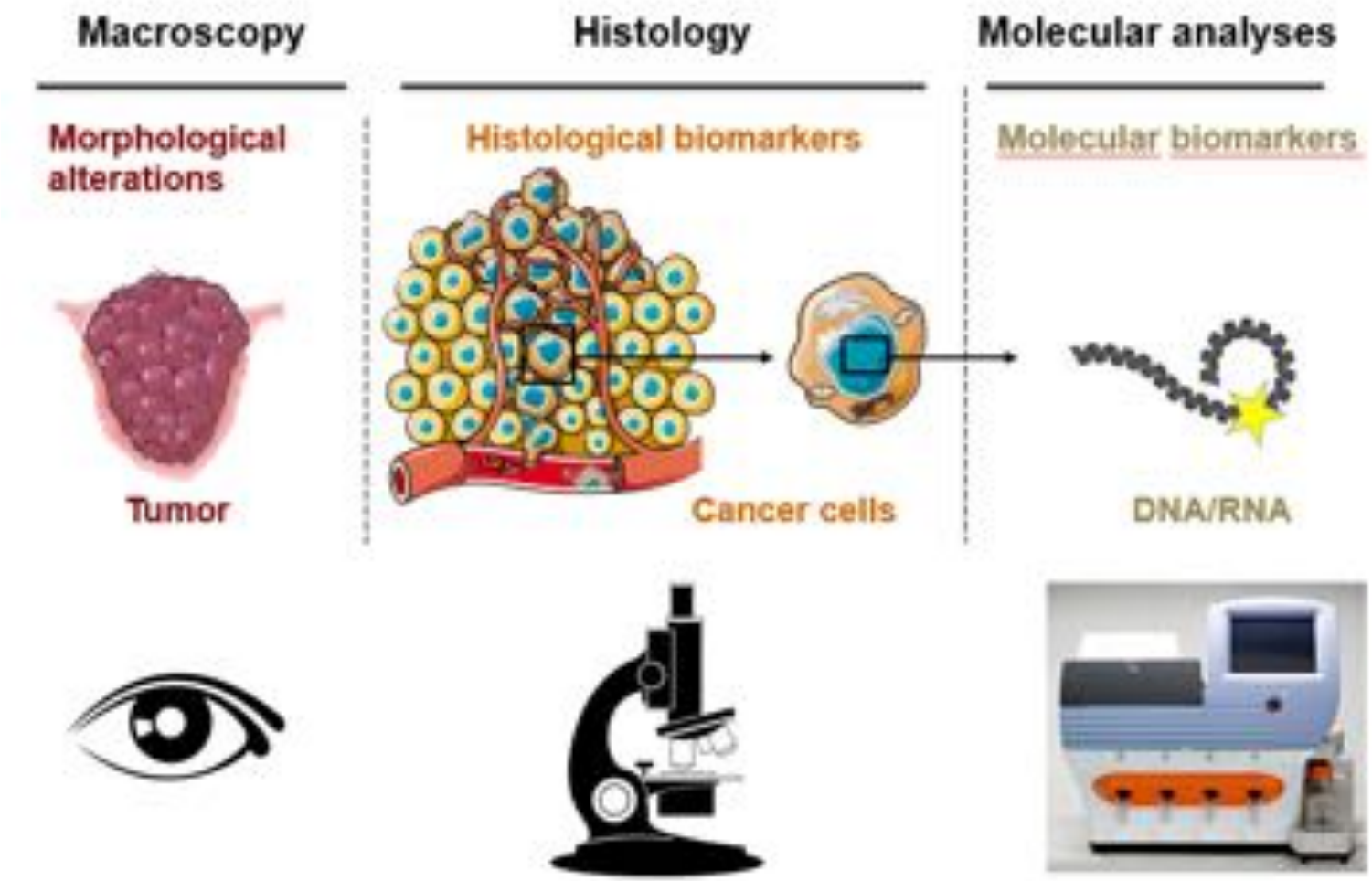
Liquid biopsies_Next Generation Sequencing NGS



Predicting treatment responses using generative modelling



PHC – front loading biomarker discovery



AI - ML POWERED IMAGING ALGORITHMS

NGS - REVOLUTION
AI – 4P MEDICINE

WHAT IS A BIOMARKER ? How to discover a biomarker ? What makes it a good biomarker ?

A biological marker of any particular healthy and disease state ! Any analytes from biofluids such as blood, urine, and stool tests, solid vs liquid biopsies, in situ hybridization etc.

MANY OPPORTUNITIES

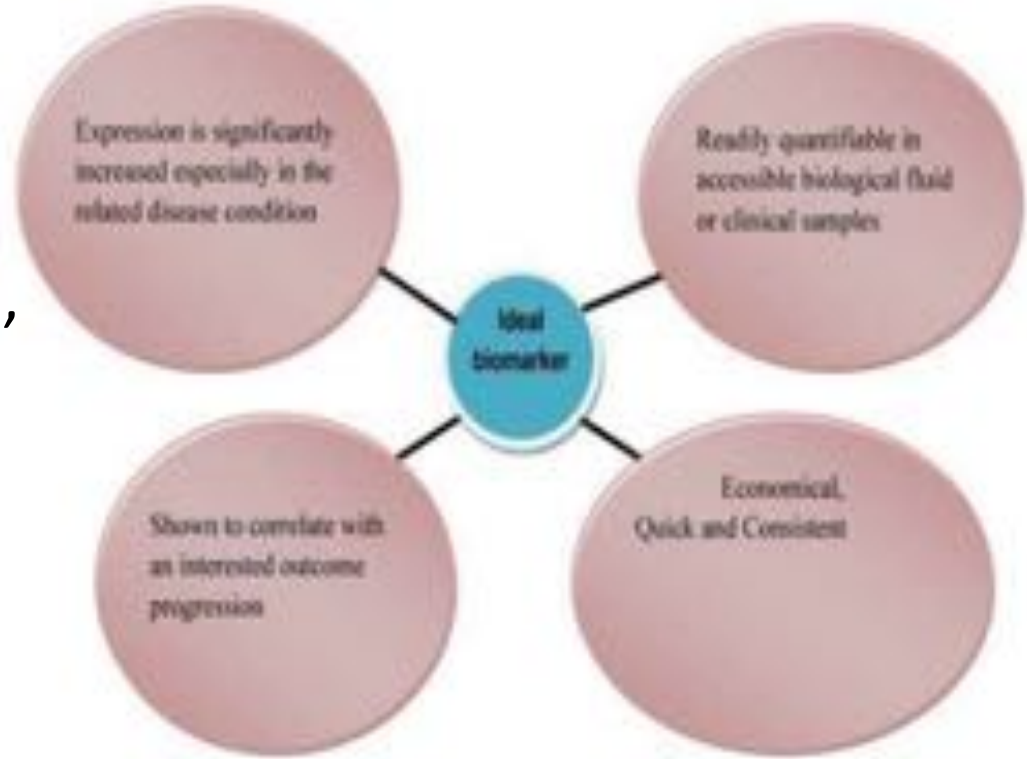
Genomics: GWAS,microarrays, PCR,RT-PCR,microRNAs

Proteomics: MALDI TOF, 2D gel , ELISA,phosphoproteomics

Imaging: biopsies, IVUS, IRM

Metabolomics: metabolites, metabolic pathways

Lipidomics: TG, FA contents, Cholesterol ester, HDL, LDL



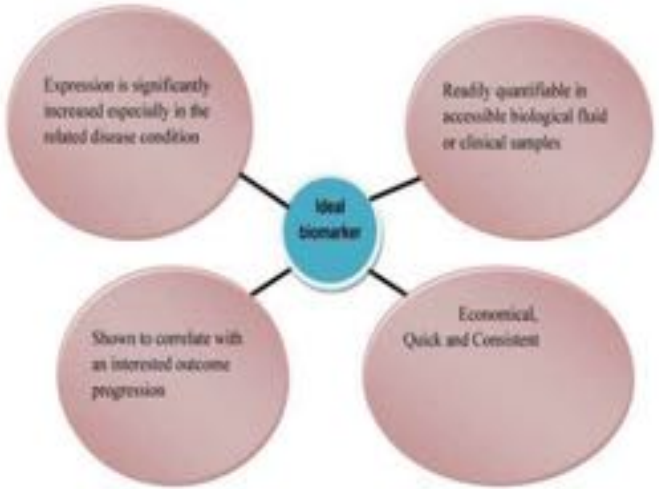
Personalized Healthcare _ front loading biomarker discovery

"Any substance, structure or process that can be measured in the body or its product and influence or predict the incidence of outcome or disease." WHO international programme on chemical safety 2001

	Sick	Non-sick	
Test +	A= True positive	B= False positive	PPV=A/(A+B)
Test-	C= False negative	D= True negative	NPV=D/(C+D)
	Sensitivity = A/(A+C)	Specificity = D/(B+D)	

→Disease enabling biomarkers = more complex! We have to take into account the prevalence of the disease, the pre-test probability, compute the post-test probability....

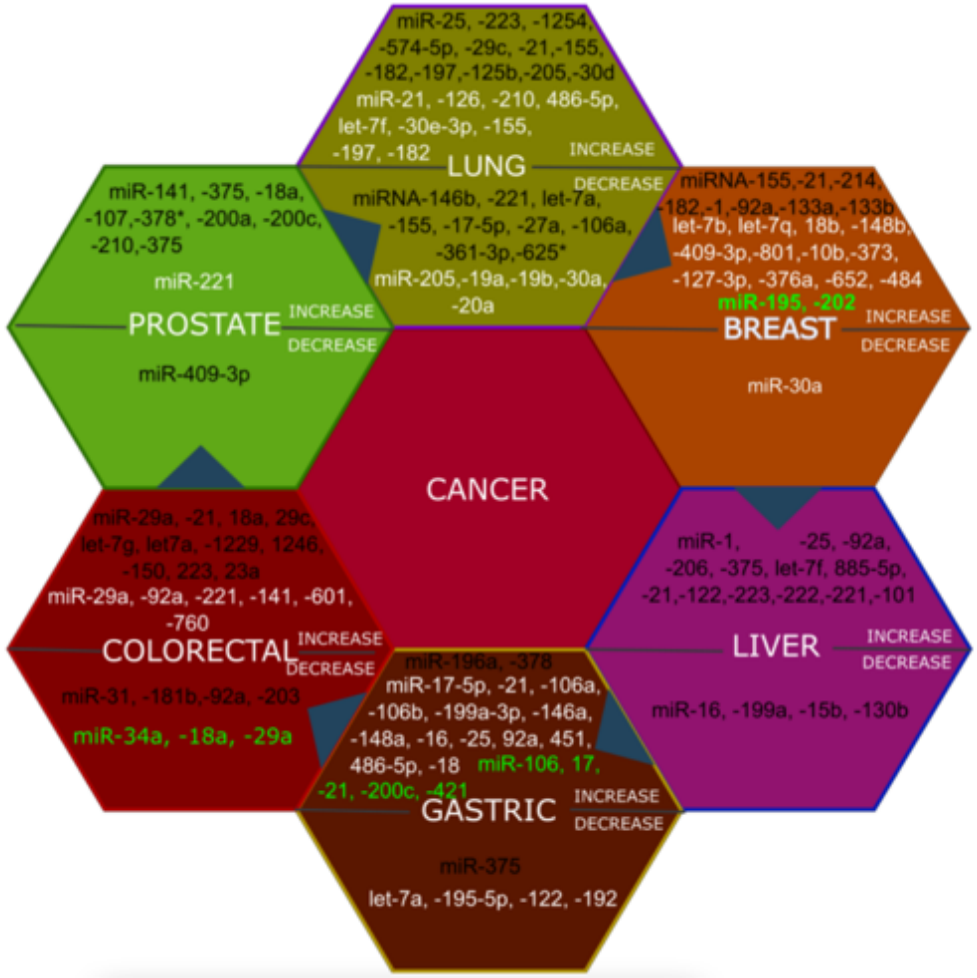
NEWLY DISCOVERED BIOMARKERS OF HUMAN DISEASE SHOULD REFLECT DISEASE PATHOGENESIS, CHANGE WITH INTERVENTION, AND OFFER DIAGNOSTIC OR PROGNOSTIC VALUE BEYOND CURRENT MEASURES.



Circulating miRs in diagnostics

TABLE 1 | Circulating microRNAs a potential biomarkers in human cancers.

Cancer type	miRNA	Source	Expression	Significance	Reference
Hematological cancer	miR-21				
	miR-150, miR-342				
	miR-155				
Lung cancer	miR-25, miR-223				
	miR-1254, miR-574-5p				
	miR-155, miR-197, miR-182				
Prostate	miR-375, miR-141				
	MiR-107, miR-574-3P				
	miR-205, miR-214				
Pancreatic	Index I (4 miRNAs) and Index II (10 miRNAs)				
Hepatocellular carcinoma	miR-16, miR-199a				
	MiR-15b, miR-130b, and miR-16				
	miR-625, miR-618, miR-532, miR-650, miR-516-5p				
Colorectal cancer	miR-29a, miR-92, miR-601, miR-760				
	miR-31, miR-181b, miR-92, miR-203 and miR-21, let-7g				
	miR-200c				
Gastric cancer	miR-18a	Plasma	Up	GC vs. healthy cor	
	miR-122, miR-192	Plasma	Differential	Diagnosis of distar	
Ovarian cancer	miR-205, miR-let-7f	Plasma	Differential	Epithelial ovarian c	



O. Faruq. 2015 Frontiers in Medicine Vol 2 Art 51

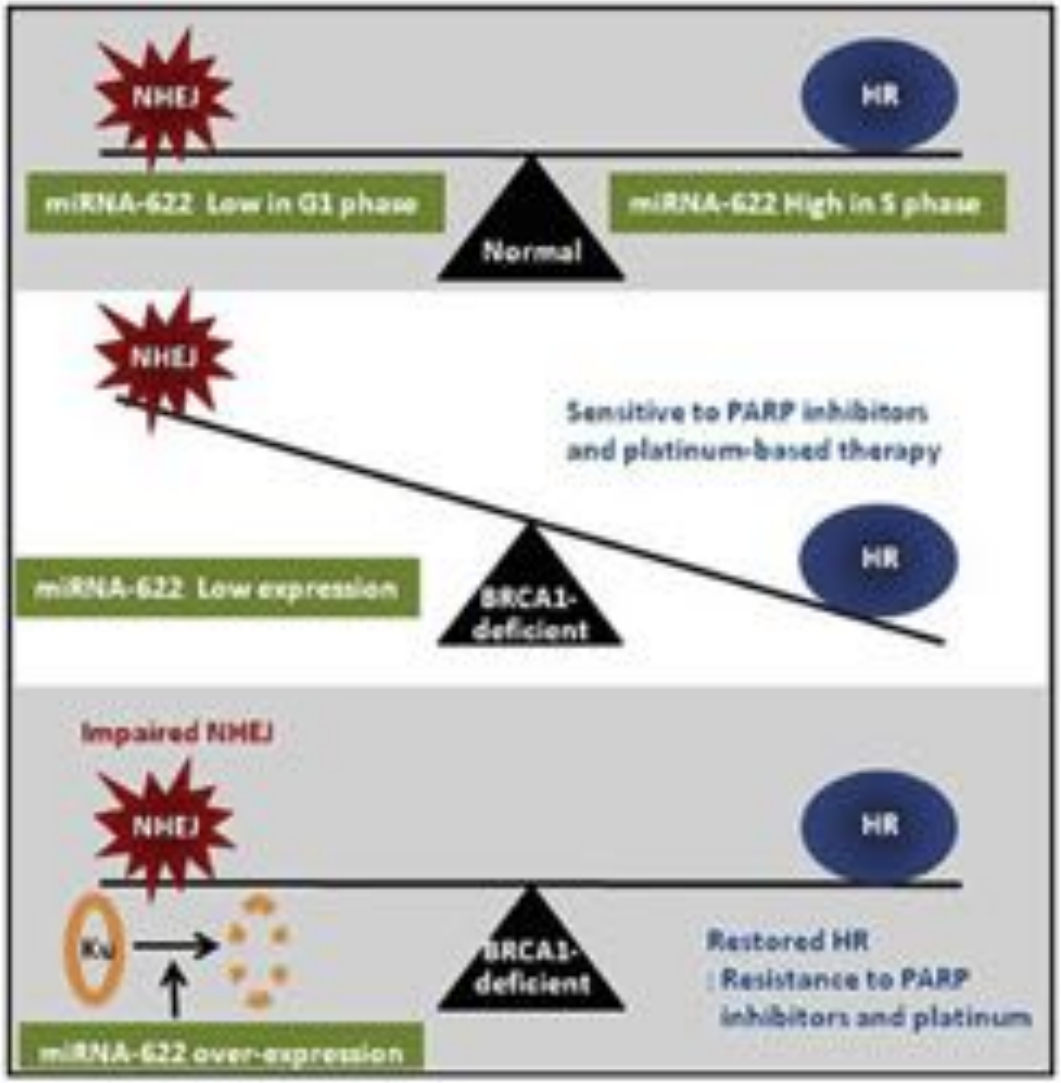
Cell Reports

Platinum and PARP Inhibitor Resistance Due to Overexpression of MicroRNA-622 in *BRCA1*-Mutant Ovarian Cancer

Choi YE et al. 2016 Cell R 14: 429-439

Expression of miR-622 in two cohorts of patients with BRCA1 inactivated human ovarian carcinomas correlates with reduced disease-free survival after platinum based therapies, suggesting a direct clinical relevance of miRs in cancer patients

Plasma circulating microRNAs signatures as biomarkers associated with human diseases : example relapsing resistant ovarian cancer

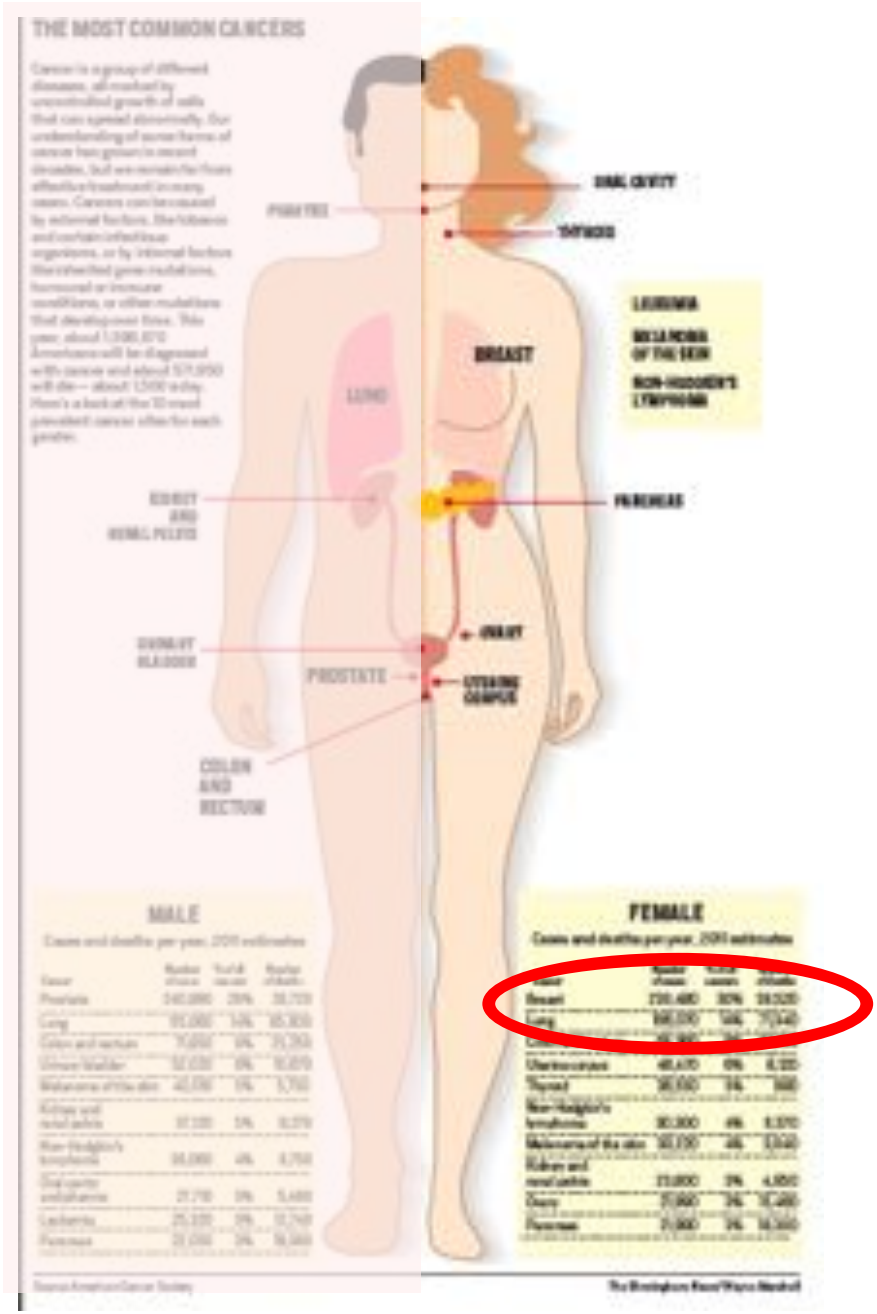


- Ovarian carcinoma with BRCA1/2 mutations exhibit sensitivity to DSB inducing agents (platinum/PARPis)
- Underlying molecular mechanism : defect in homologous recombination HR
- Resistance to platinum worses life prognostics to patients
- miR-622 induces resistance to PARPis and platinum in BRCA1 mutants
- Facilitation of HR mediated DSB repair
- High miR-622 correlates with worse outcome of ovarian cancer upon chemotherapy

Choi YE et al. 2016 Cell 14: 429-439

Disease enabling biomarker_driving innovation in PHC: from am examplary clinical practice of PHC

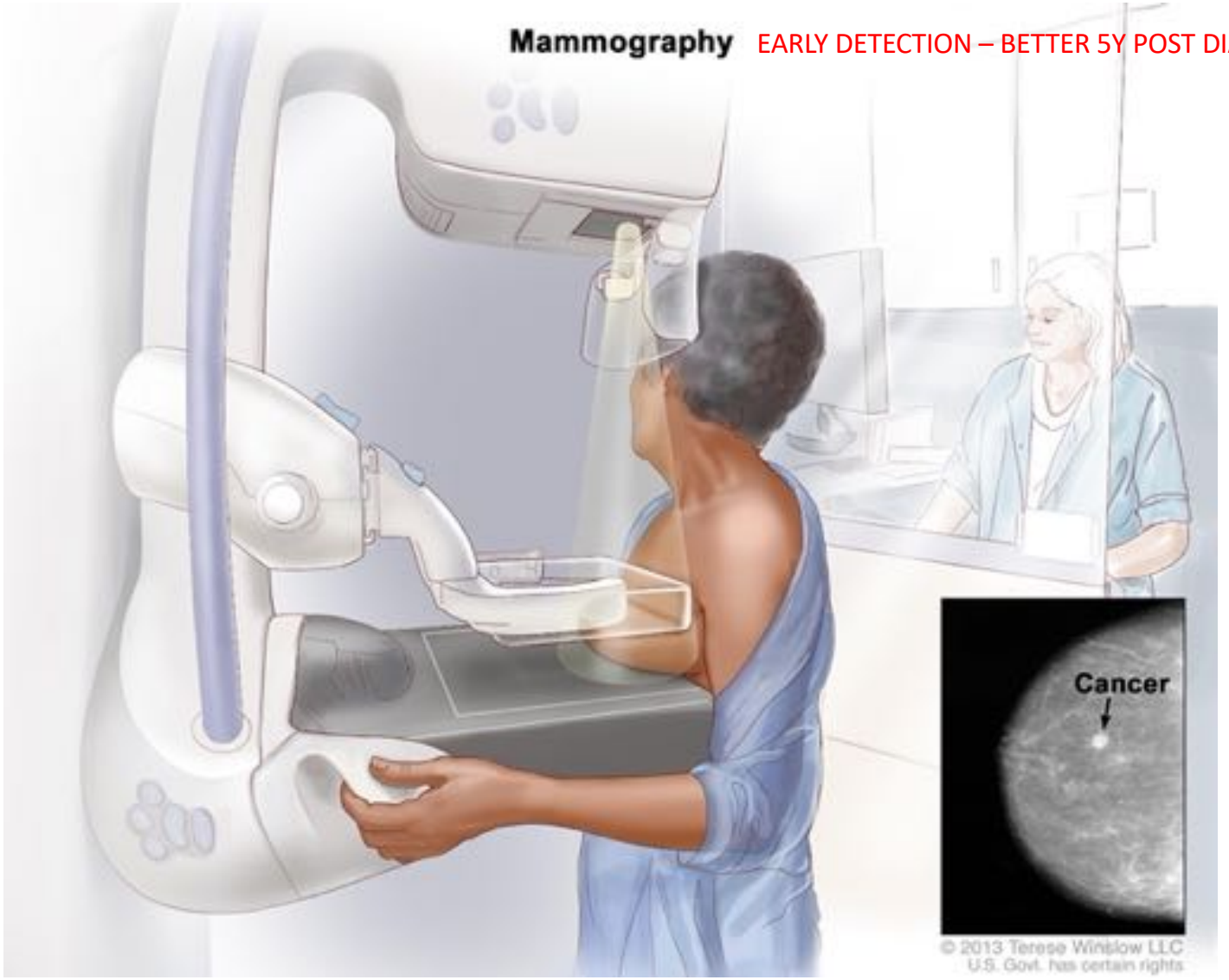
october



CANCER AT DIAGNOSTIC: WHAT IS THE STAGE OF THE DISEASE ?

CANCER DIAGNOSTIC REMAINS A MAJOR CHALLENGE !

The first PHC quantum leap with breast cancer



EARLY DETECTION – BETTER 5Y POST DIAGNOSIS SURVIVAL

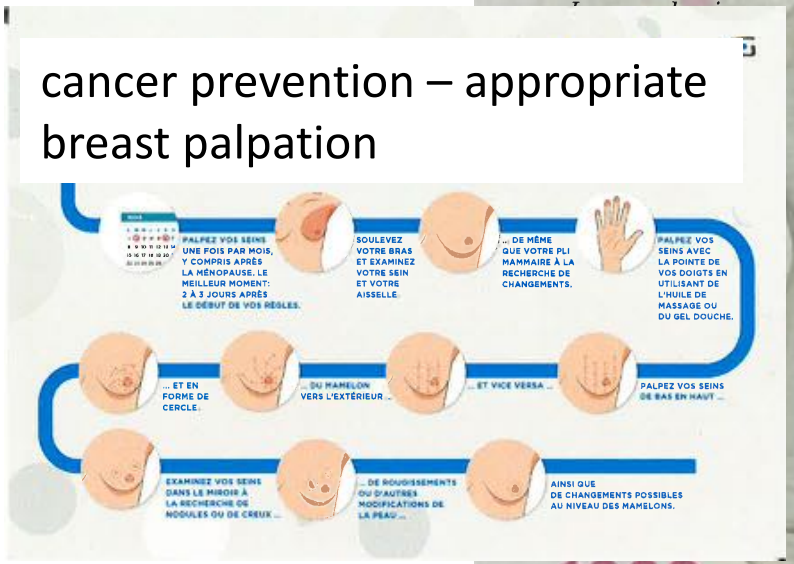
90% breast cancer are hormonal dependent (tamoxifen responsive)

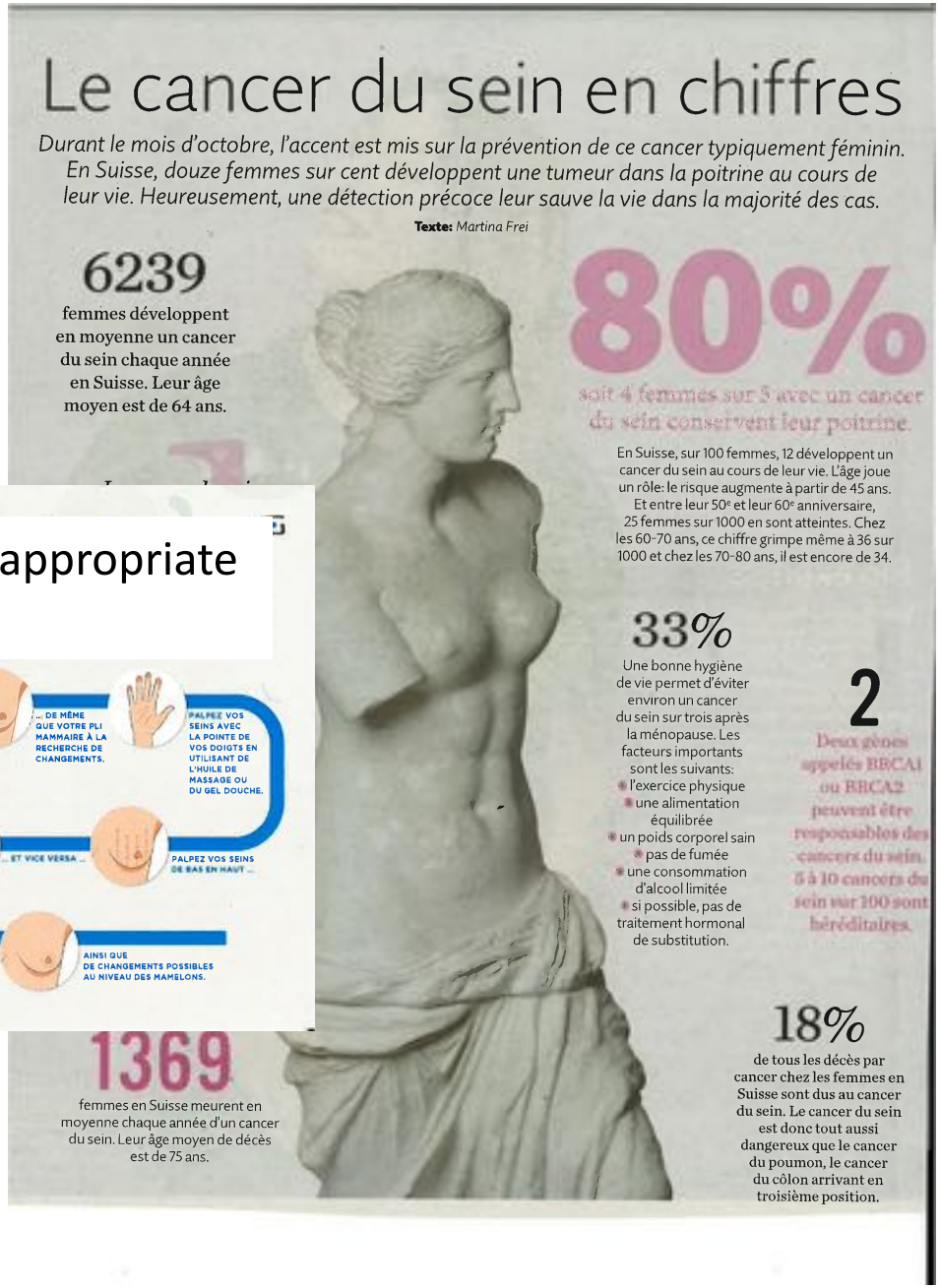
~10% breast cancers test HER2 positive !

disease diagnosis: algorithms assisted Screens of thousands of calcified breast regions

- **Cancer therapy was first "practicing" personalized healthcare (also called "precision medicine") with disease enabling biomarker HER2**

Disease enabling biomarker_breast cancer prevention - examplary clinical practice of PHC





CANCER AT DIAGNOSTIC: WHAT IS THE STAGE OF THE DISEASE ?

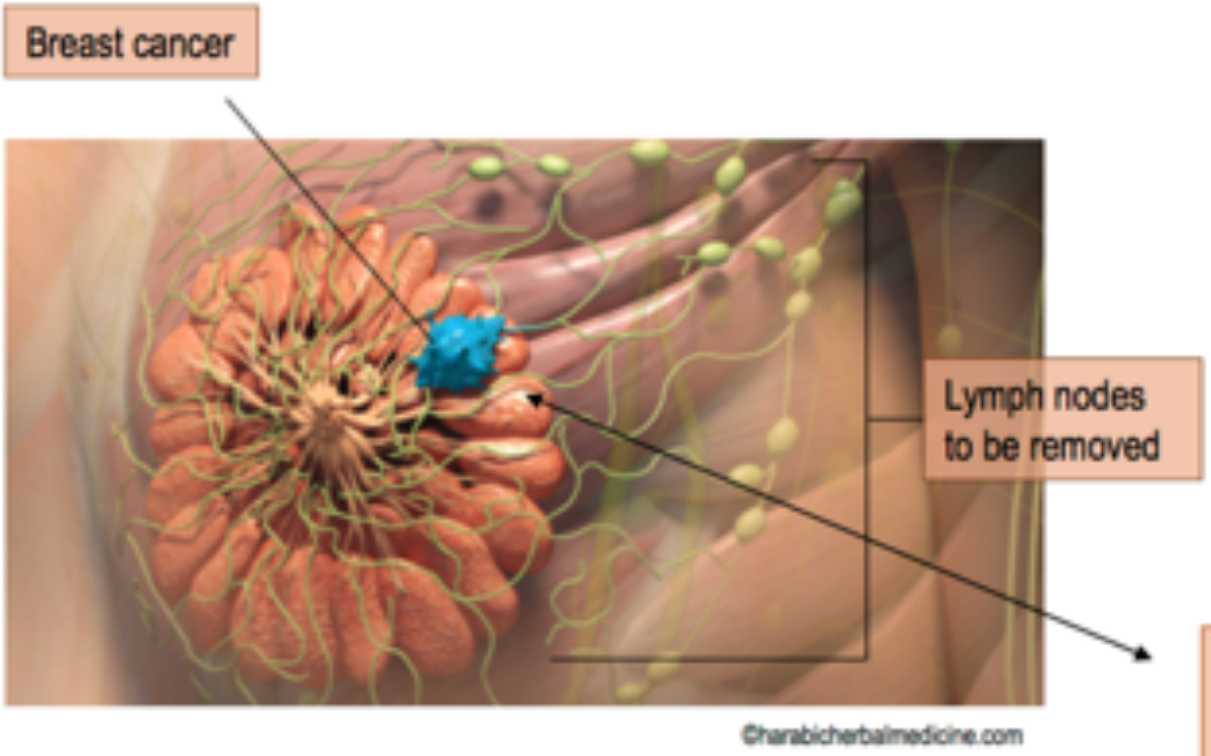
CANCER DIAGNOSTIC REMAINS A MAJOR CHALLENGE !

6239 new breast onco patient each year in Switzerland

1369 terminal patient

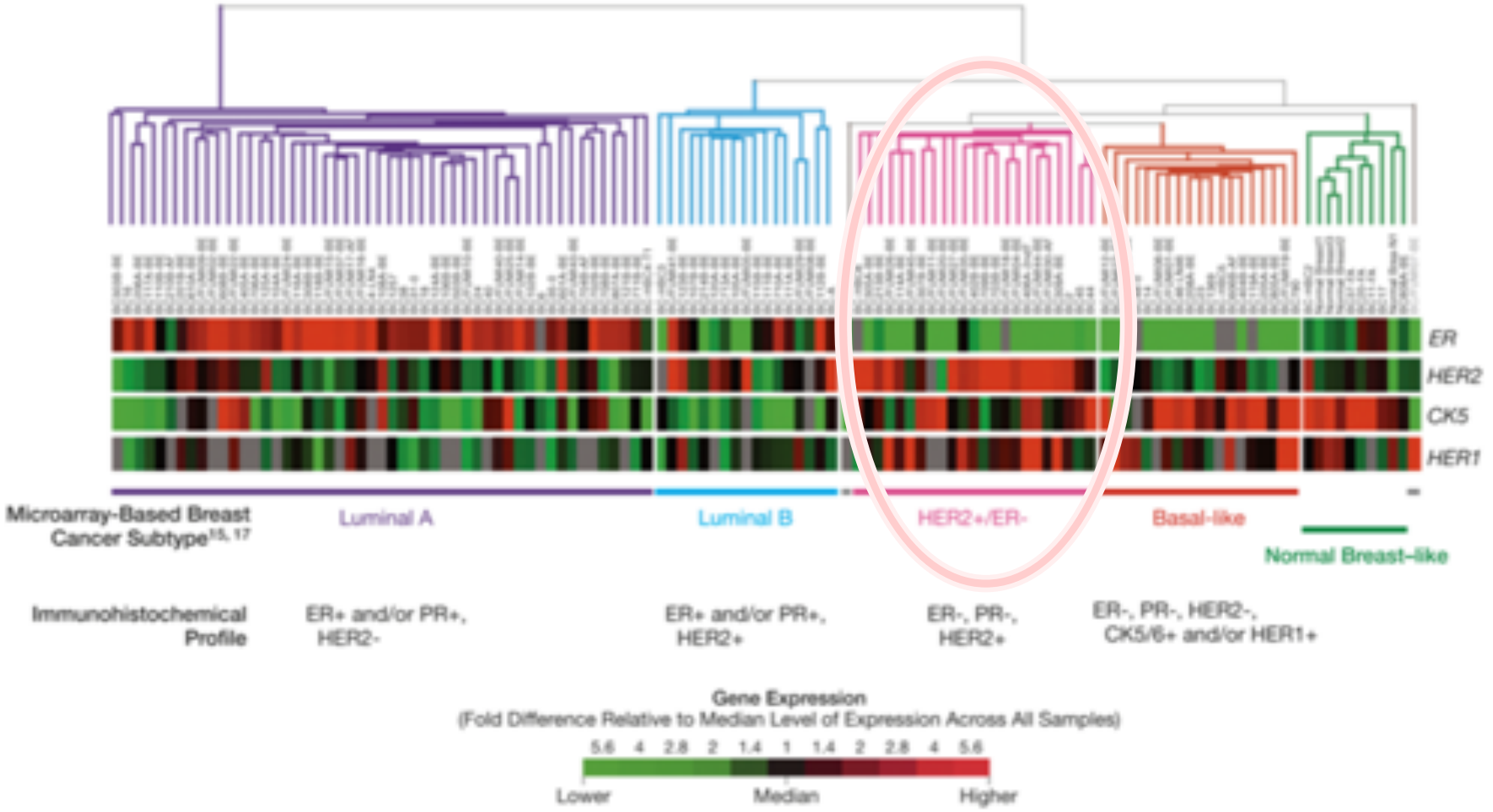
PHC : breast cancer

Targeted Cancer Therapy – Breast Cancer



The characterization of disease related factors has significantly changed treatment options…

Breast cancer subtypes – immuno-histo-morphological classification – impact of scRNAseq



TNBC : triple negative breast cancer all breast cancer biomarkers negative ER- PR- HER2-
(frequent among BRCA1 patients)

Carey LA, Perou CM, Livasy CA, et al. Race, Breast Cancer Subtypes, and Survival in the Carolina Breast Cancer Study. *JAMA*. 2006;295(21):2492–2502

Courtesy of Luisa Spisak

Biomarker: how to assess the risk of recurrence in breast cancer patients?

AGENDIA Inc (ROTTERDAM) RECEIVES US FDA CLEARANCE FOR THE "MammaPrint" BASED ON 70 RELEVANT GENE EXPRESSION SIGNATURES/PROFILES FROM OLIGONUCLEOTIDE MICROARRAYS

The New England Journal of Medicine

VOLUME 347 DECEMBER 19, 2002 NUMBER 25

A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

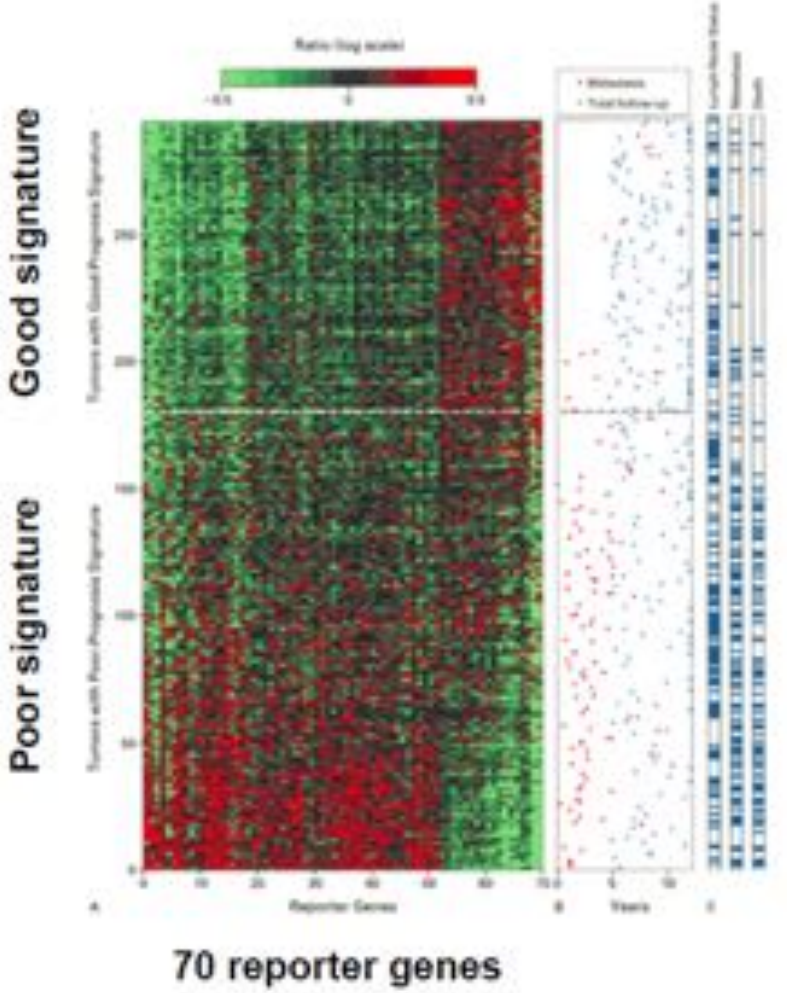
MARC J. VAN DE VIJVER, M.D., PH.D., YUDONG D. HE, PH.D., LAURA J. VAN 'T VEER, PH.D., HONGYUE DAI, PH.D., AUGUSTINUS A.M. HART, M.SC., DORIEN W. VOSKUIL, PH.D., GEORGE J. SCHREIBER, M.SC., JOHANNES L. PETERSE, M.D., CHRIS ROBERTS, PH.D., MATTHEW J. MARTON, PH.D., MARK PARRISH, DOUWE ATSMA, ANKE WITTEVEEN, ANNUSKA GLAS, PH.D., LEONIE DELAHAYE, TONY VAN DER VELDE, HARRY BARTELINK, M.D., PH.D., SJOERD RODENHUIS, M.D., PH.D., EMIEL T. RUTGERS, M.D., PH.D., STEPHEN H. FRIEND, M.D., PH.D., AND RENÉ BERNARDS, PH.D.

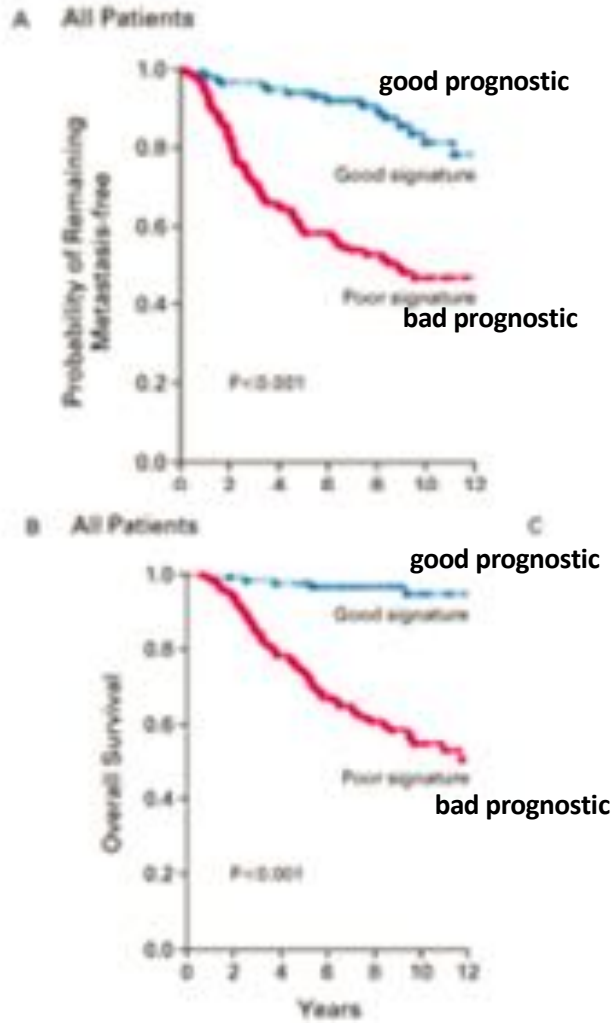
http://www.agendia.com/

Biomarker: how to assess the risk of recurrence in breast cancer patients?

Gene Expression "Signature" as a Predictor of Survival

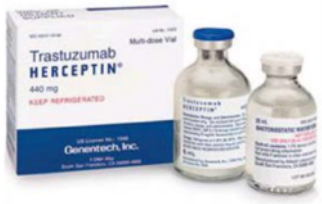
Adviser for treatment modalities





PHC_ the first quantum leap with breast cancer

1998-2023



Wednesday, Sep 2, 1998

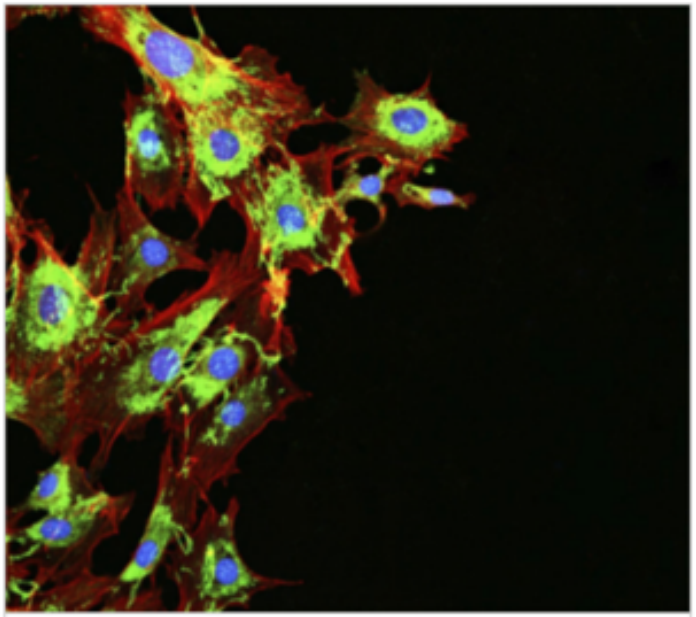
FDA Advisory Committee Recommends Approval of First Monoclonal Antibody for Metastatic Breast Cancer

New Biologic Approach May Help Women with HER2 Protein Overexpression Associated with Aggressive Disease

South San Francisco, Calif. -- September 2, 1998 --

Genentech, Inc. (NYSE: DNA) today announced that Herceptin® (Trastuzumab), a humanized monoclonal antibody, was recommended unanimously (11 to 0) for approval as a single agent in

Herceptin (anti-HER2) receives FDA approval for metastatic breast cancer



Work in the 1980s demonstrated that the growth factor HER2 is often amplified in breast cancer, which suggested that it might be suitable for targeting with monoclonal antibodies. Subsequently, Michael Shepard, Dennis Slamon and colleagues initiated work that ultimately resulted in the humanized monoclonal antibody trastuzumab (Herceptin), which blocks HER2. Herceptin receives approval from the US Food and Drug Administration in 1998, and in a sizable fraction of HER2-positive patients, Herceptin lowers the risk of relapse, extends survival and potentiates the efficacy of chemo- and immunotherapy.

ÉDITORIAL

La belle histoire de HER2

The great story of HER2

- **Cancer therapy was first “practicing” personalized healthcare (a new era in oncology called “precision medicine”)**

PHC_ the first quantum leap with breast cancer

Genentech
IN BUSINESS FOR LIFE

UCLA Research & Creative Activities

Format: Abstract ▾ Send to ▾

Science. 1987 Jan 9;235(4785):177-82.

Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene.

Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL.

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Science

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Similar articles
HER-2/neu amplification and overexpression in primary human breast can [Anticancer Res. 1992]
The association of HER-2/neu amplification with

Abstract

The HER-2/neu oncogene is a member of the erbB-like oncogene family, and is related to, but distinct from, the epidermal growth factor receptor. This gene has been shown to be amplified in human breast cancer cell lines. In the current study, alterations of the gene in 189 primary human breast cancers were investigated. HER-2/neu was found to be amplified from 2- to greater than 20-fold in 30% of the tumors. Correlation of gene amplification with several disease parameters was evaluated. Amplification of the HER-2/neu gene was a significant predictor of both overall survival and time to relapse in patients with breast cancer. It retained its significance even when adjustments were made for other known prognostic factors. Moreover, HER-2/neu amplification had greater prognostic value than most currently used pro
may play a role in

PMID: 3798106

[Indexed for MEDLINE]

Publication types

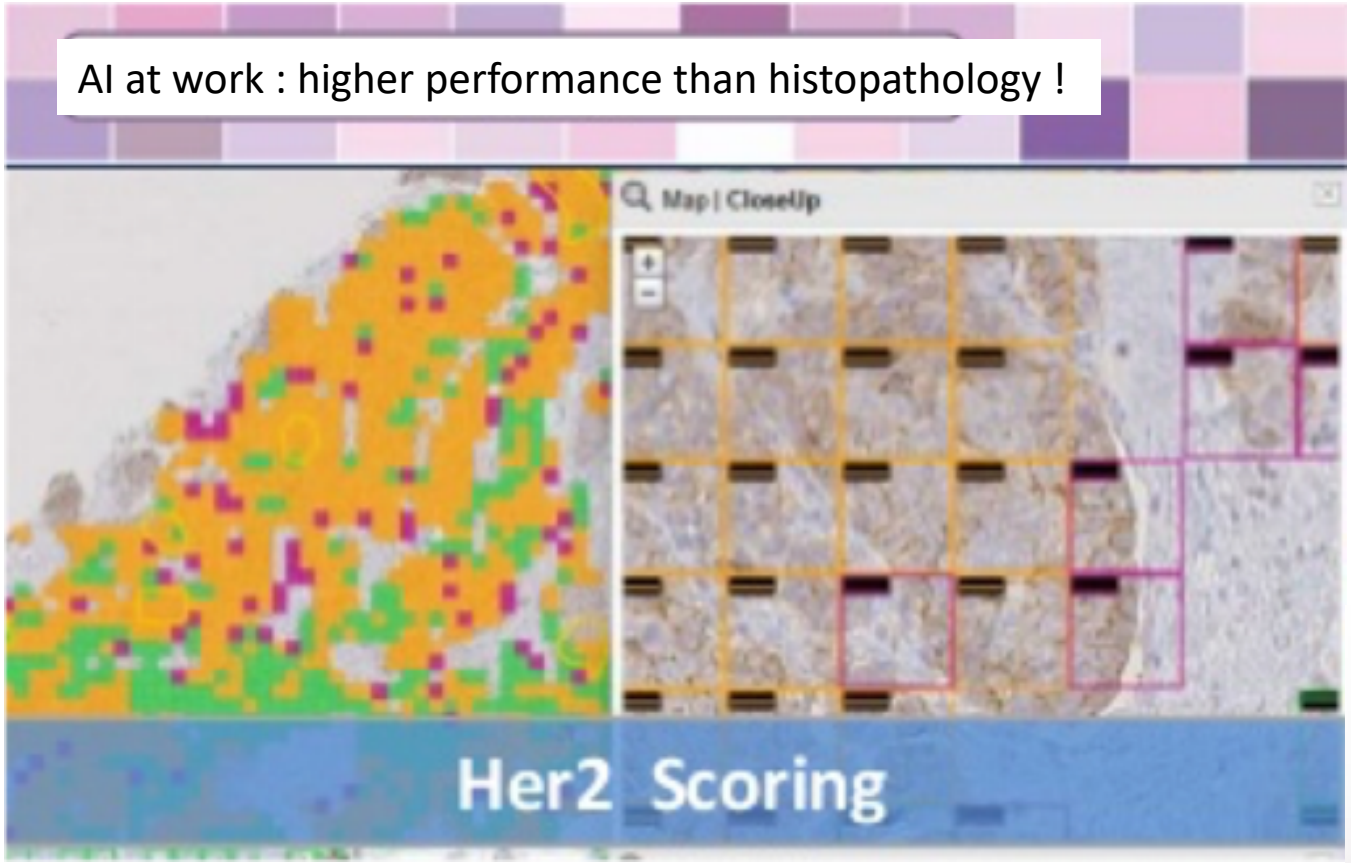
[CANCER RESEARCH 48, 1238–1243, March 1, 1988]

Correlation of c-*erbB*-2 Gene Amplification and Protein Expression in Human Breast Carcinoma with Nodal Status and Nuclear Grading

Mark S. Berger,[1] Gottfried W. Locher, Susanne Saurer, William J. Gullick, Michael D. Waterfield, Bernd Groner, and Nancy E. Hynes[2]

Ludwig Institute for Cancer Research, Inselspital, 3010 Bern, Switzerland [S. S., B. G., N. E. H.]; Ludwig Institute for Cancer Research, Middlesex Hospital/University College Branch, 91 Riding House Street, London W1P 8BT, England [M. S. B., M. D. W.]; University Women's Hospital, Schanzeneckstrasse 1, 3012 Bern, Switzerland [G. W. L.]; and Institute of Cancer Research, Chester Beatty Laboratories, Fulham Road, London SW3 6JB, England [W. J. G.]

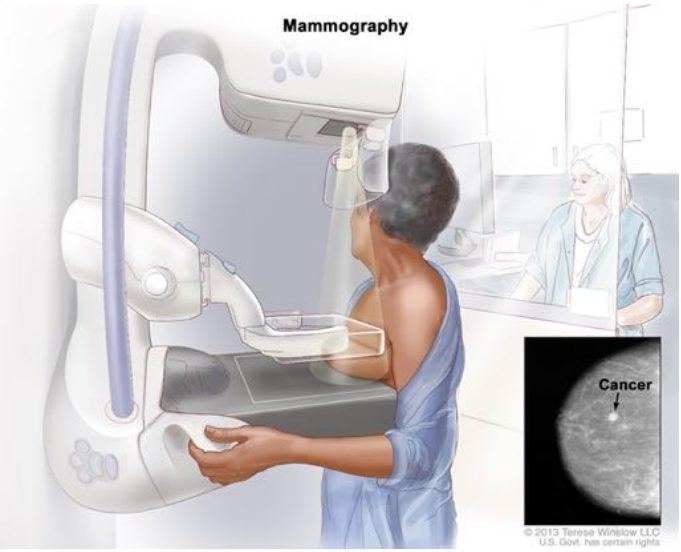
Case study : PHC_ the first quantum leap with breast cancer : HER2



~10-15% breast cancers test HER2 positive !

90% breast cancer are hormonal dependent (tamoxifen responsive)

disease diagnosis: machine learning assisted screens may search through thousands of calcified breast regions

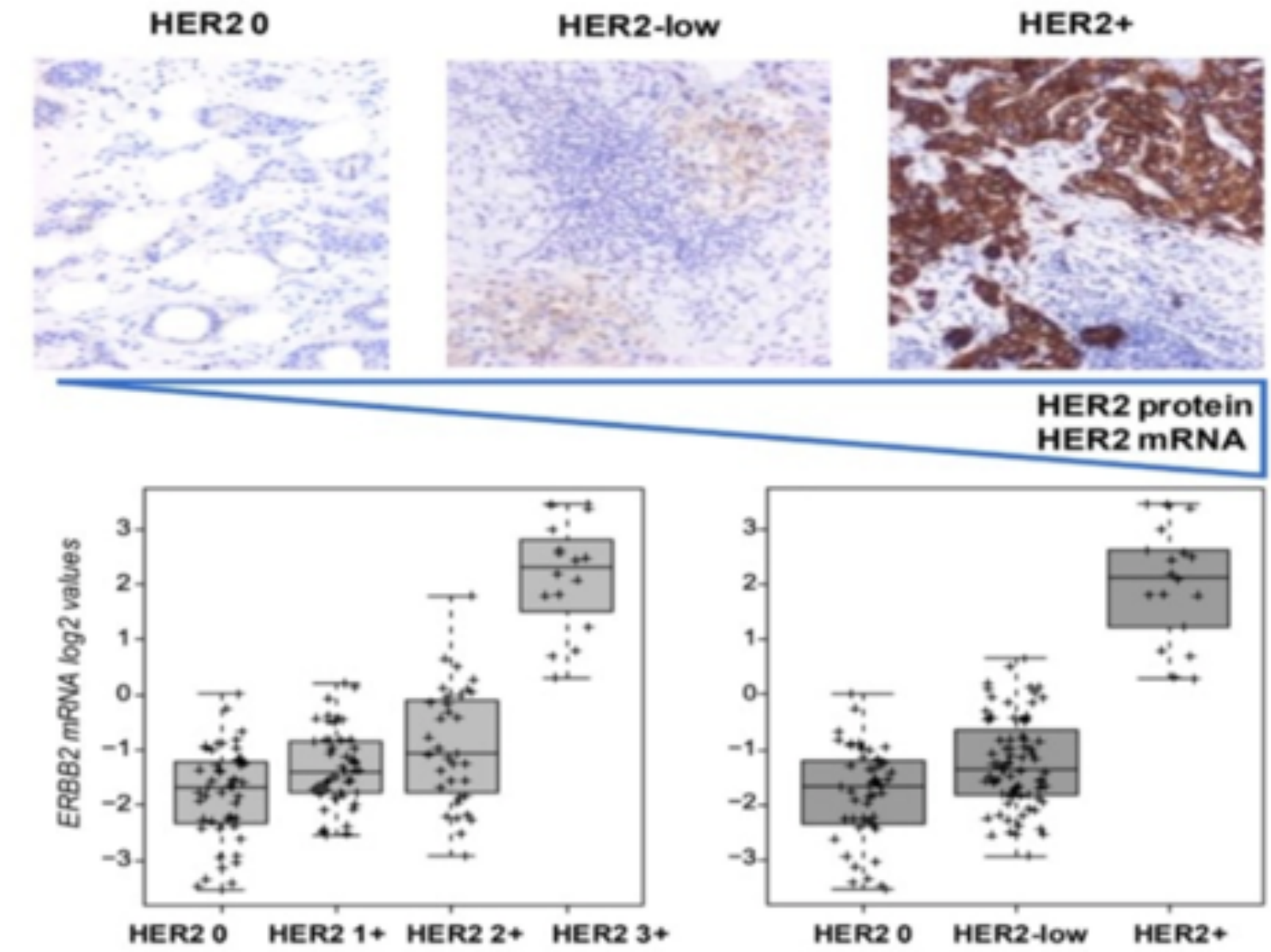


A healthy cell may hold as many as **20,000 HER2** proteins whereas a highly overexpressing cell as much as **2 <10^6 receptors**, hence HER2 grading scores.

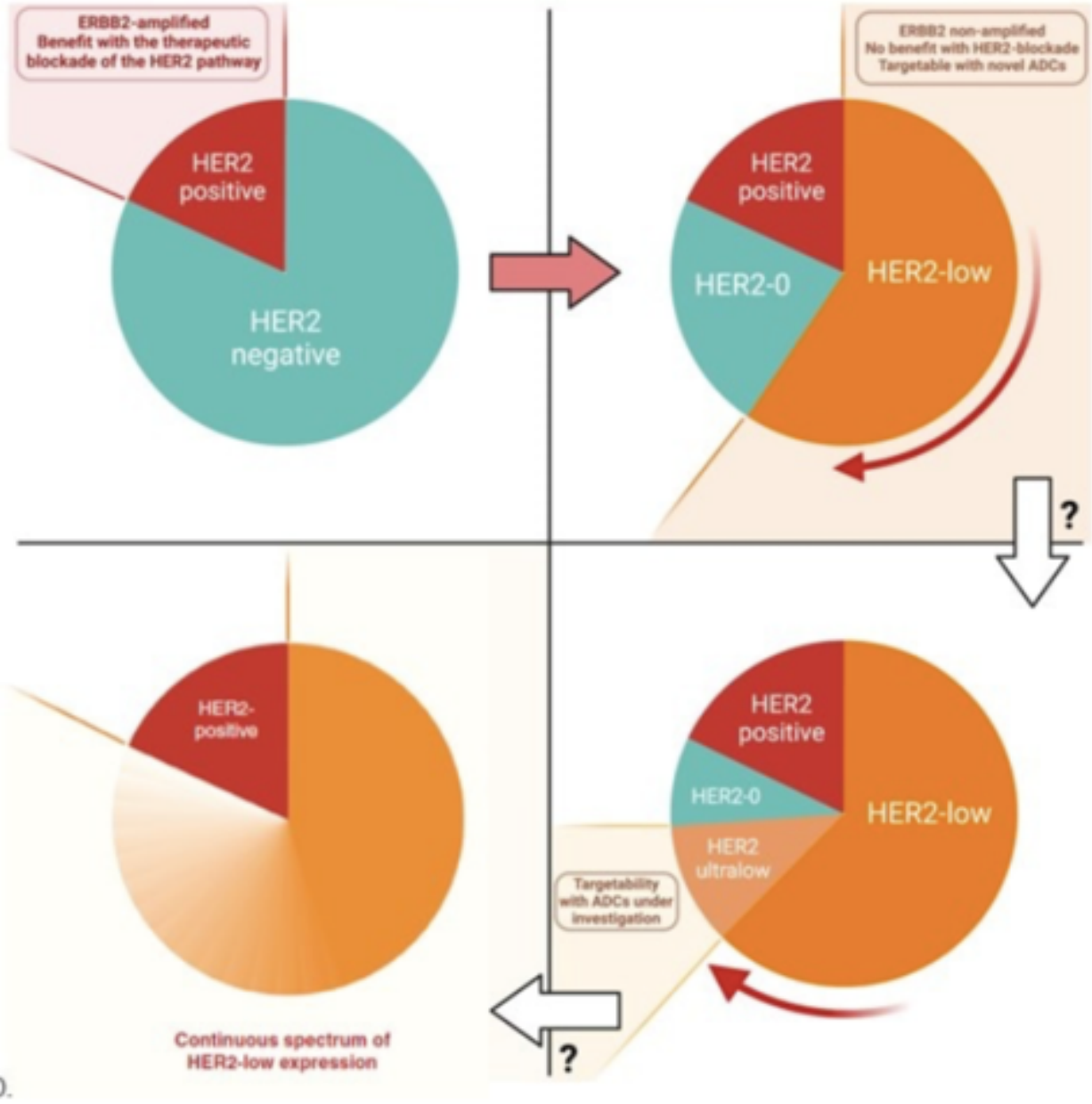
Currently clinical trials ongoing on low and very low HER2+ scoring patients

- **Cancer therapy was first "practicing" personalized healthcare (also called "precision medicine") Tomorrow deep/machine learning will aid histopathology diagnosis**

PHC_ Two decades of HER2 targeting:
he unfinished revolution in breast cancer



PHC_ the evolution of the HER2 pie chart : from selecting responders to excluding few non-responders



HER2 - human epic[illegible] e 2)

PHC_ HER2 biomarker_pioneer driver of personalized oncology

Three IHC scores = breast cancer !

Pour l'IHC, on note les résultats sur une échelle de 0 à 3+.

Échelle	Signification
0 ou 1+	Le taux de HER2 est normal. La tumeur est HER2 négative.
2+	La HER2 est légèrement surexprimée. On fera une FISH pour confirmer le statut HER2.
3+	Le taux de HER2 est plus élevé que la normale. La tumeur est HER2 positive.

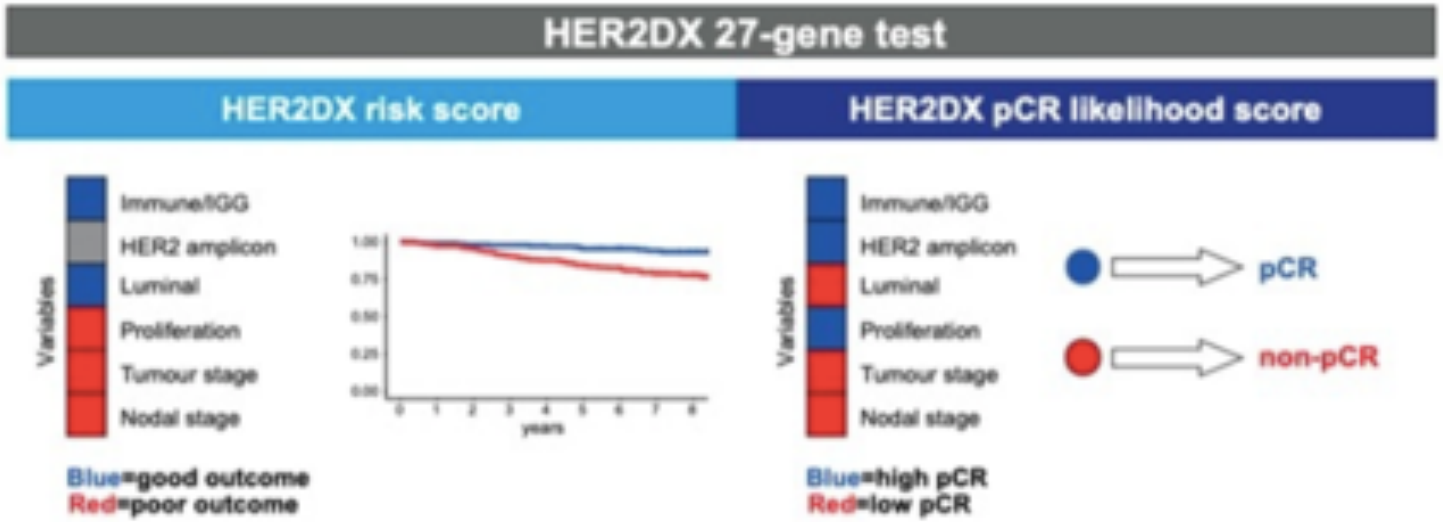
Les résultats de la FISH sont classés négatifs ou positifs.

- **Stratification of clinical cohorts trials based on biopses ! biomarker is key !**
- **Frontloading biomarker search is now common practice in translational research!**

PHC_ a supervised learning algorithm for HER2 assessment

HER2DX* is a tool incorporating tumor size, nodal staging, and 4 gene expression signatures tracking immune infiltration, tumor cell proliferation, luminal differentiation, and the expression of the HER2 amplicon into a single score.

The score was shown in retrospective analyses to be strongly prognostic both in the early and advanced setting (T-DM1)



*It is the policy of Medscape Education to avoid the mention of brand names or specific manufacturers in accredited educational activities; however, proprietary names related to diagnostic algorithms are provided in this activity in an effort to promote clarity for the learner.

Prat A, et al. EBioMedicine. 2022;75:103801.

Pioneering personalized Healthcare _ Herceptin and Perjeta

NB :Katrin S. is not a simulated patient !

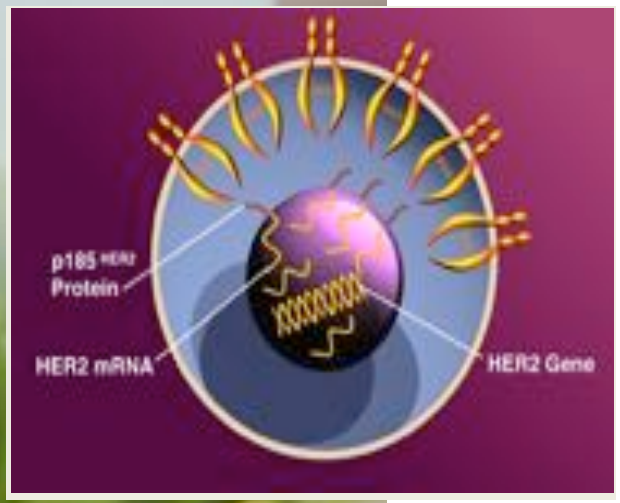
Breast cancer

700,000 newly diagnosed patients in Europe and USA -- 200,000 death cases

1 women over 10 has suffered a breastcancer during her lifetime

2/3 of all patients : survival is about 7 years

1/3 of all patients: 3 years life extension



Katrin S. enrolment

(1) Biopsy: + → (2) HerCep-Test: + → **Herceptin® regimen**

Pioneering PHC_HER2 receptor biomarker_Herceptin and Perjeta

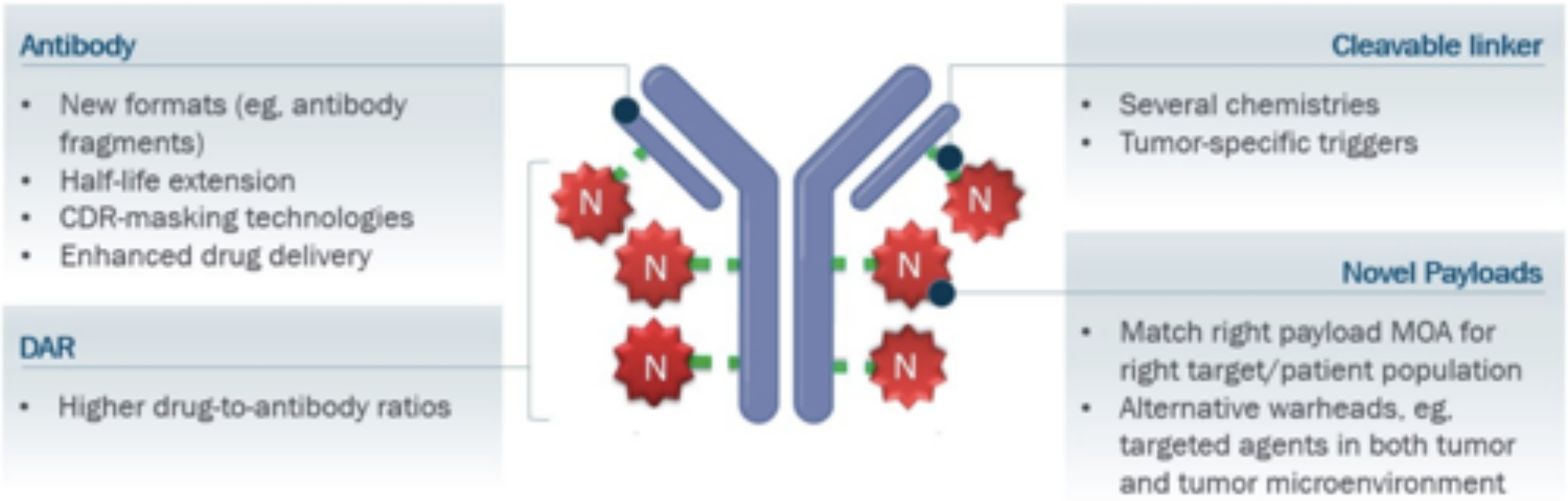
Kathrin S. was diagnosed an HER2 positive breast cancer in 1997 (3+ IHC score)

Life prognostic was no more than 3 years of life

Here at her 55th birthday…

on January 12, 2006, almost 10 years later

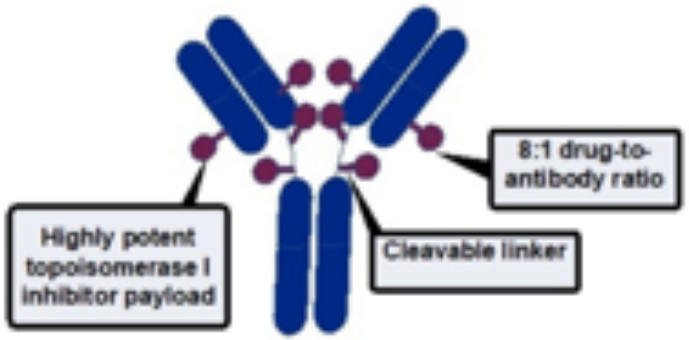
PHC_ very low - low HER2+ patients
ADC trastuzumab deruxtecan (T-DXd)



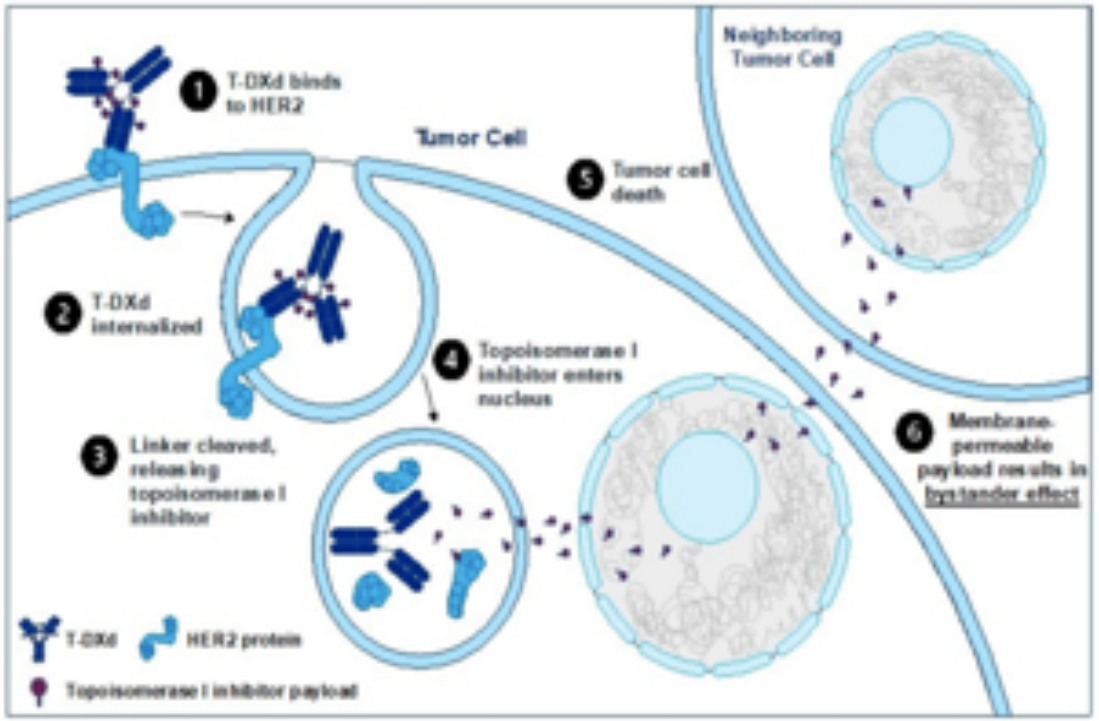
HER2 - human epidermal growth factor receptor 2, also called ERB-B2 (Erb-B2 receptor tyrosine kinase 2)

PHC_ very low - low HER2+ patients

Trastuzumab deruxtecan (T-DXd)

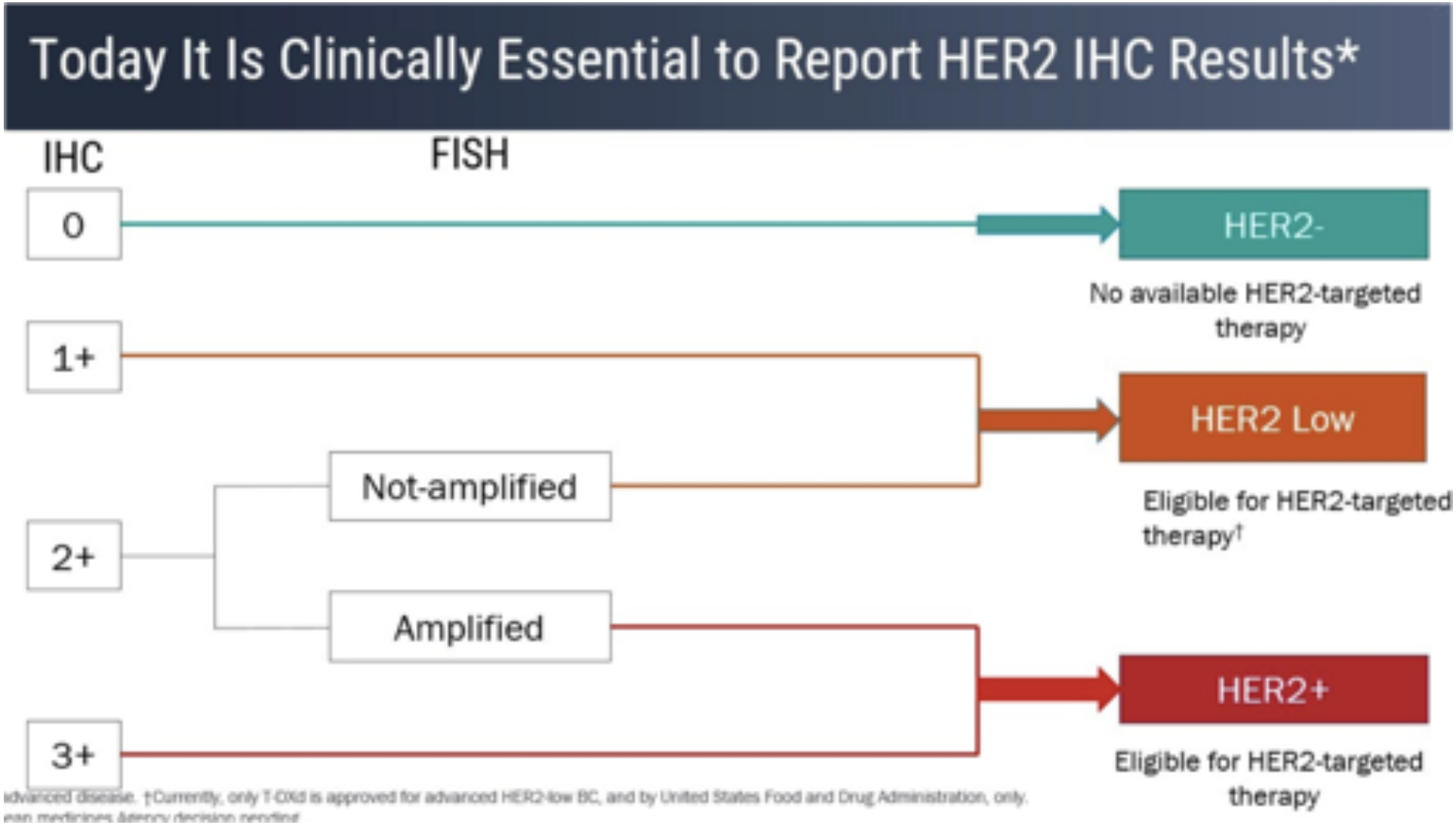


Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect



HER2 - human epidermal growth factor receptor 2, also called ERB-B2 (Erb-B2 receptor tyrosine kinase 2)

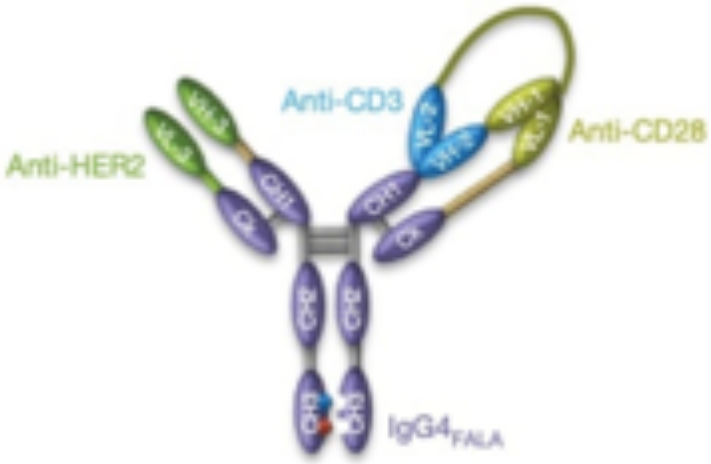
PHC_ very low - low HER2+ patients

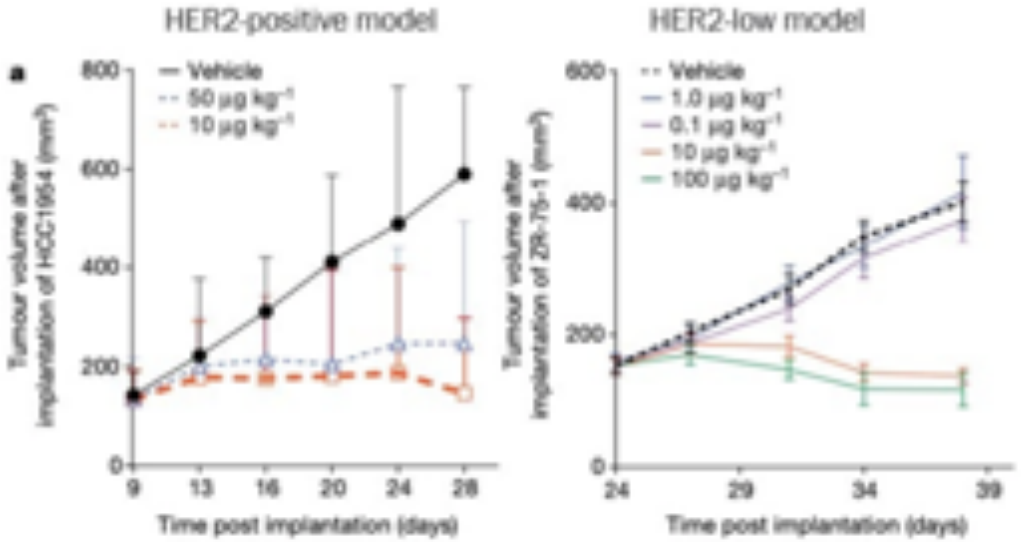


HER2 - human epidermal growth factor receptor 2, also called ERB-B2 (Erb-B2 receptor tyrosine kinase 2)

PHC_ very low - low HER2+ patients
Trispecific ADCs come of age

A trispecific antibody targeting HER2 and T cells (CD3xCD28) stimulates regression of HER2-positive and HER2-low breast cancers in a humanized mouse model through a CD4-dependent mechanism





Seung E, et al. Nature. 2022;603(7900):328-334.

HER2 - human epidermal growth factor receptor 2, also called ERB-B2 (Erb-B2 receptor tyrosine kinase 2)

PHC_ very low - low HER2+ patients
Into the future - weaponized biologicals

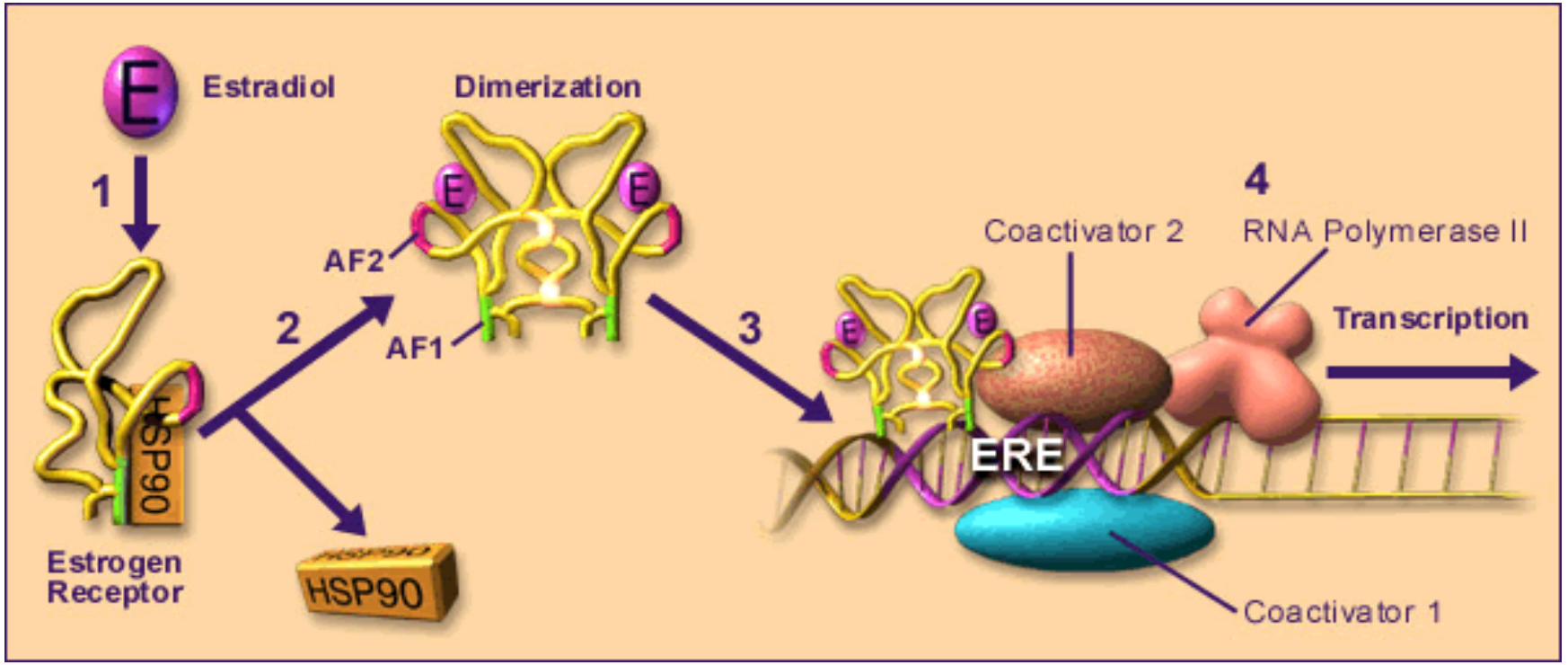
A trispecific antibody targeting HER2 and T cells (CD3xCD28) stimulates regression of HER2-positive and HER2-low breast cancers in a humanized mouse model through a

- **ADCs are modular compounds**. Modifying each component (mAb, linker, payload) may enable us to unlock new therapeutic advancements, with **several innovative ADCs already in early-phase development**
- In addition, **bispecific/trispecific antibodies**, **vaccines** and **cell therapies** may enrich the arsenal of anti-HER2 treatment strategies for breast cancer
- An enlarging pipeline of new drugs offers the opportunity to tailor treatments. Adequate tailoring will need validation of promising **biomarkers**, such as HER2DX and ctDNA
- Drugs and biomarkers will need to be evaluated in adequate **clinical trials**, aimed at identifying the optimal treatment intensity required for each patient, based on the anatomic and biologic risk of each tumor
- An improved understanding of HER2 expression in the low range may allow to extend the benefit of targeting HER2 to a much wider population of patients.

Seung E, et al. Nature. 2022;603(7900):328-334.

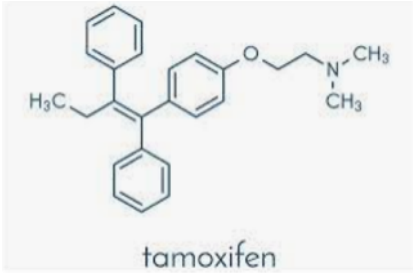
HER2 - human epidermal growth factor receptor 2, also called ERB-B2 (Erb-B2 receptor tyrosine kinase 2)

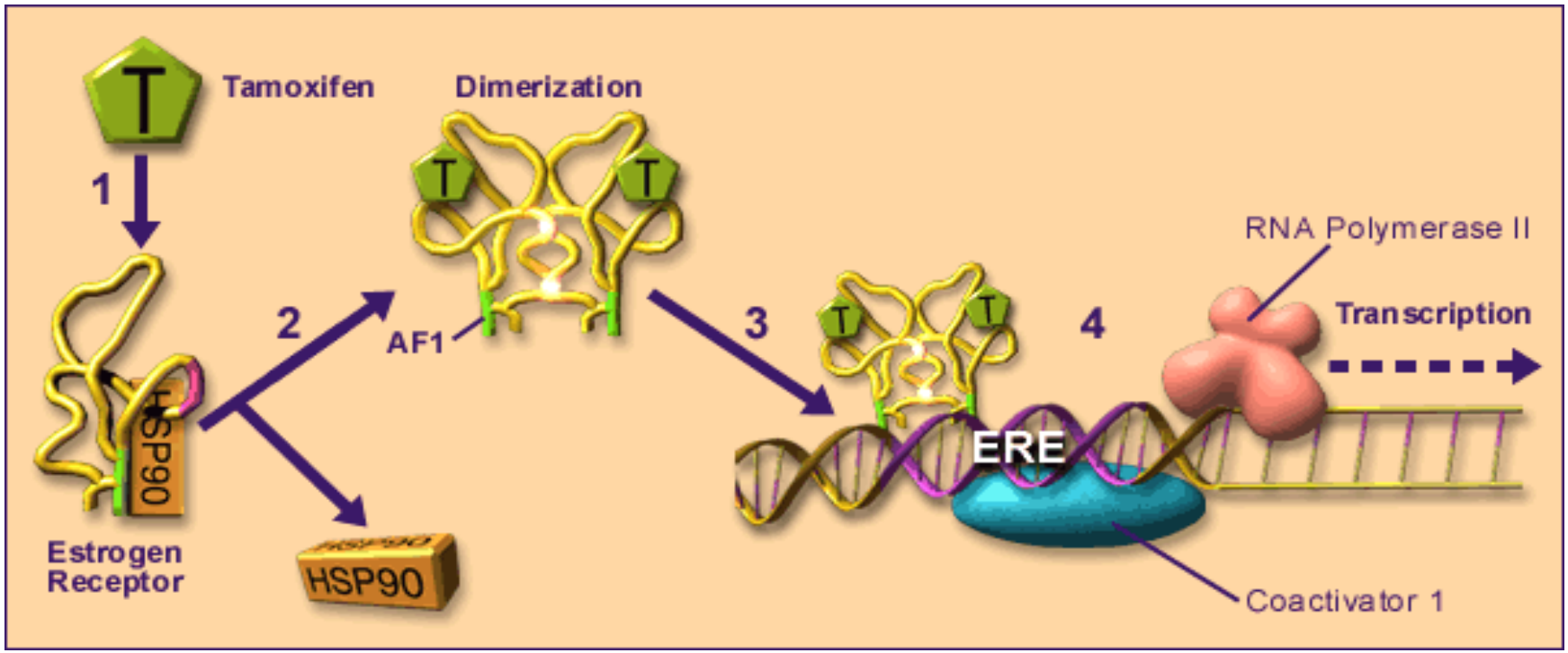
Hormonal dependent breast homeostasis : underlying molecular action of of estradiol



Adapted from Howell A, Osborne CK, Morris C, Wakeling AE. ICI 182, 780 (Faslodex®), development of a novel, "pure" antiestrogen. Cancer 2000; 89: 819.

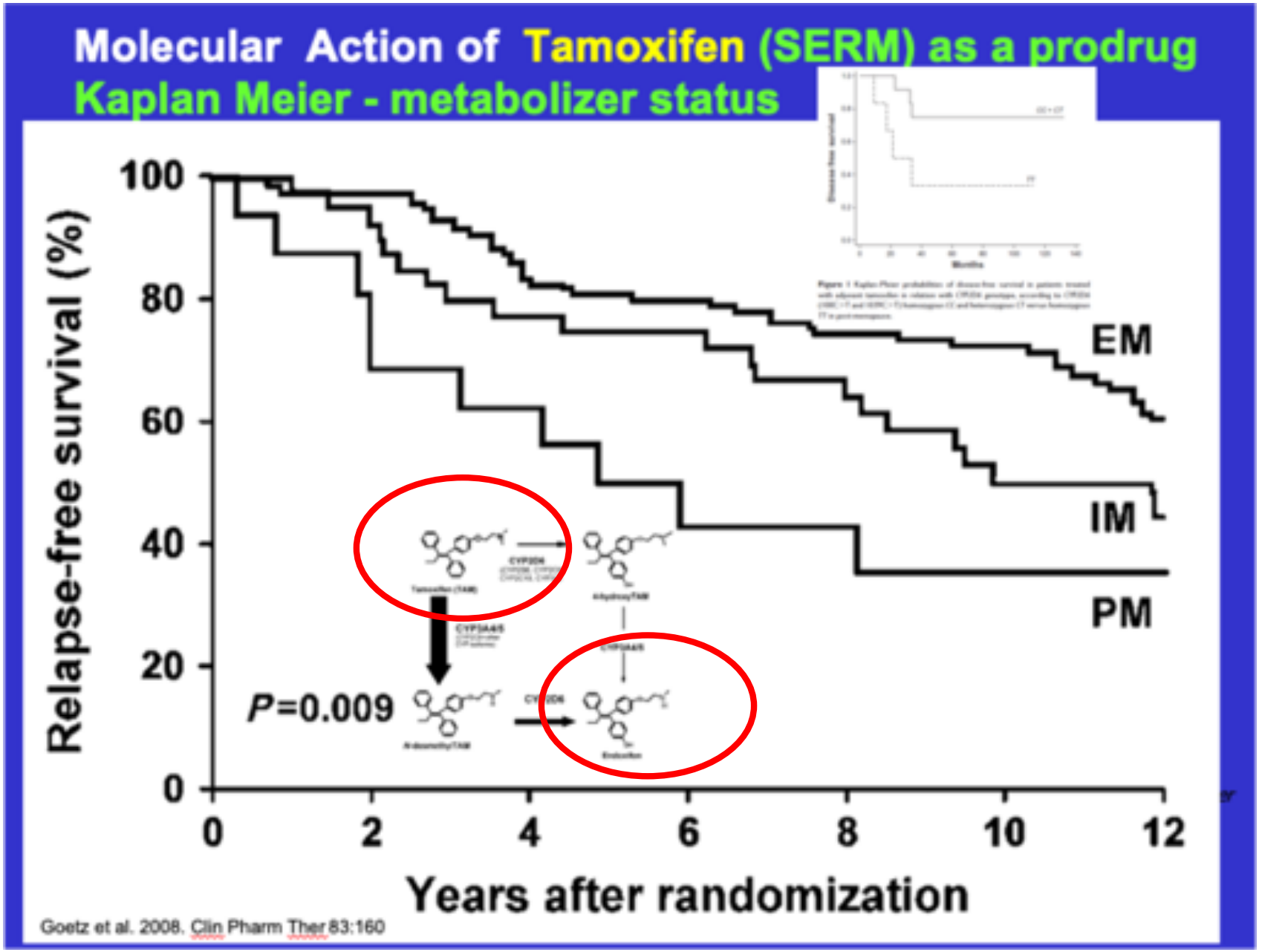
Molecular Action of Tamoxifen (SERM)
90% breast carcinoma hormonal dependent





Adapted from Howell A, Osborne CK, Morris C, Wakeling AE. ICI 182, 780 (Faslodex®), development of a novel, "pure" antiestrogen. *Cancer* 2000; 89: 819.
SERM = selective estrogen receptor modulator

Check metabolizer status of patient - CYP2D6 SNP analysis for optimal individualized therapy

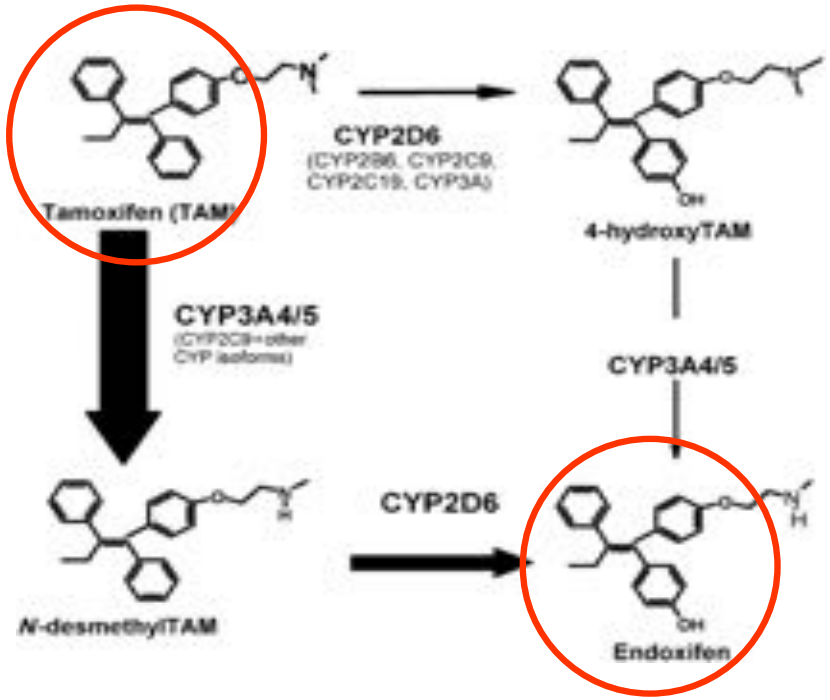


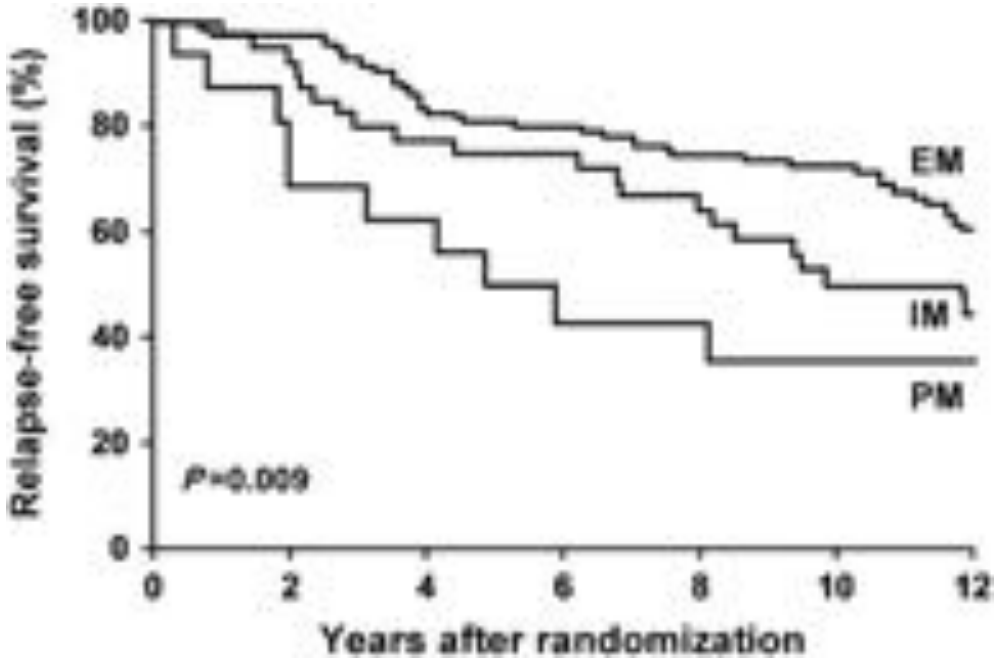
Pharmacogenetics_optimize the dose

- Tamoxifen or TAM (partial ERα agonist) works as prodrug: its metabolite (Endoxifen) is the active principle when administered *per os*

- Endoxifen works anti proliferative on the mammary gland

- Cytochrome CYP2D6 as critical step in the metabolization of TAM into Endoxifen
- <u>CYP2D6 polymorphism</u> analysis allows an optimal invidualized therapy





Personalized therapy : responders vs non responders

Test Systems

"FDA Clears Test for Patient DNA to Screen for Drug Effectiveness"

Wall Street Journal, January 11, 2005

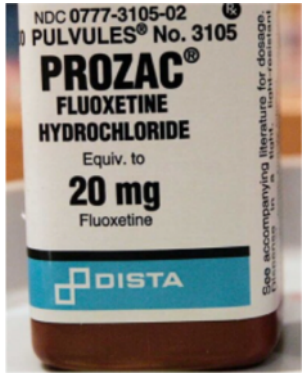
- Chip measures alleles of CYP2C19 and CYP2D6
- Tool to reduce over- and under-dosing
- Estimated 20% reduction in adverse events

Personalized therapy : check BBB transporter status of patient

Neuron 57, 203–209, January 24, 2008 ©2008 Elsevier Inc.

Neuron

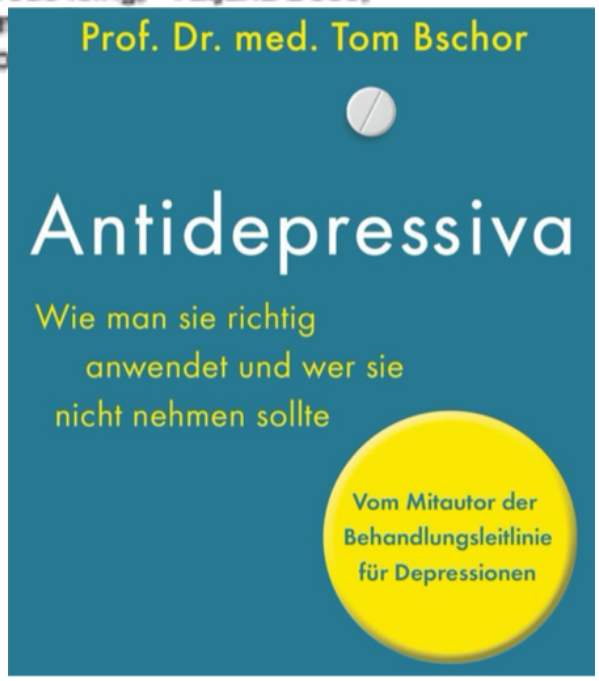
Clinical Study



Polymorphisms in the Drug Transporter Gene *ABCB1* Predict Antidepressant Treatment Response in Depression

Manfred Uhr,[1,*] Alina Tontsch,[1] Christian Namendorf,[1] Stephan Ripke,[1] Susanne Lucae,[1] Marcus Ising,[1] Tatjana Dose,[1] Martin Ebinger,[1] Marcus Rosenhagen,[1] Martin Kohli,[1] Stefan Kloiber,[1] Daria Salyakina,[1] Thom
Michael Specht,[1] Benno Pütz,[1] Elisabeth B. Binder,[1] Bertram Müller-Myhsok,[1] and Florian Ho
[1]Max Planck Institute of Psychiatry, Kraepelinstr. 10, 80804 Munich, Germany
*Correspondence: uhr@mpipsykl.mpg.de
DOI 10.1016/j.neuron.2007.11.017

- Tool to reduce over- and under-dosing
- Estimated 20% reduction in adverse events



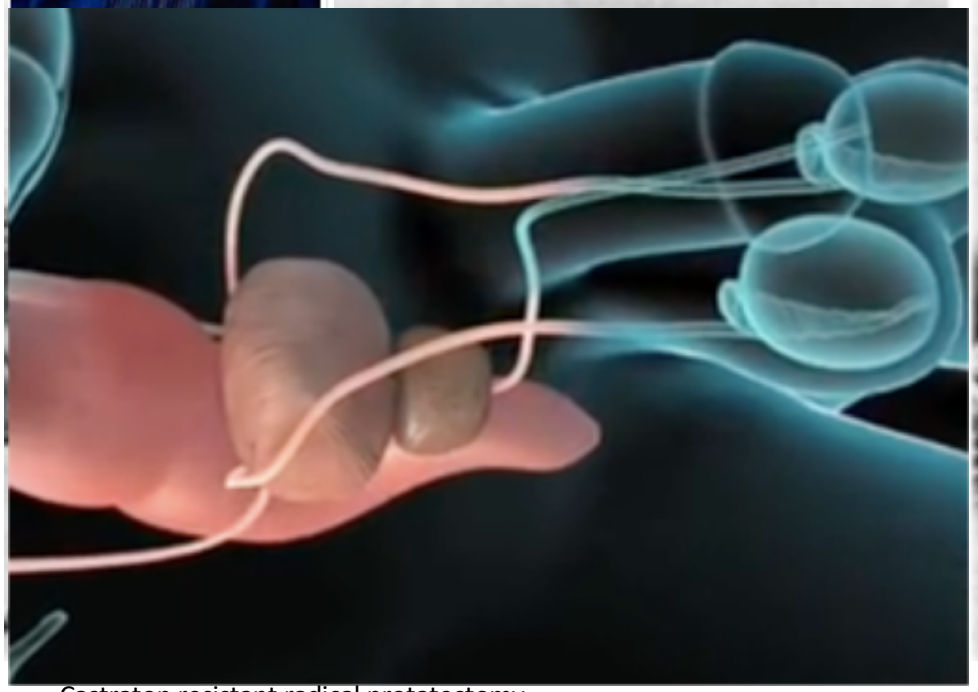
PHC - BRCA1/2 – tumor suppressor genes with high predictive value

Biomarker discovery : BRCA1 discovered in 1994 - DNA repair tumor supressor gene- today a biomarker of breast, endometrium, ovary and prostate cancer (65% cumulative risk) !

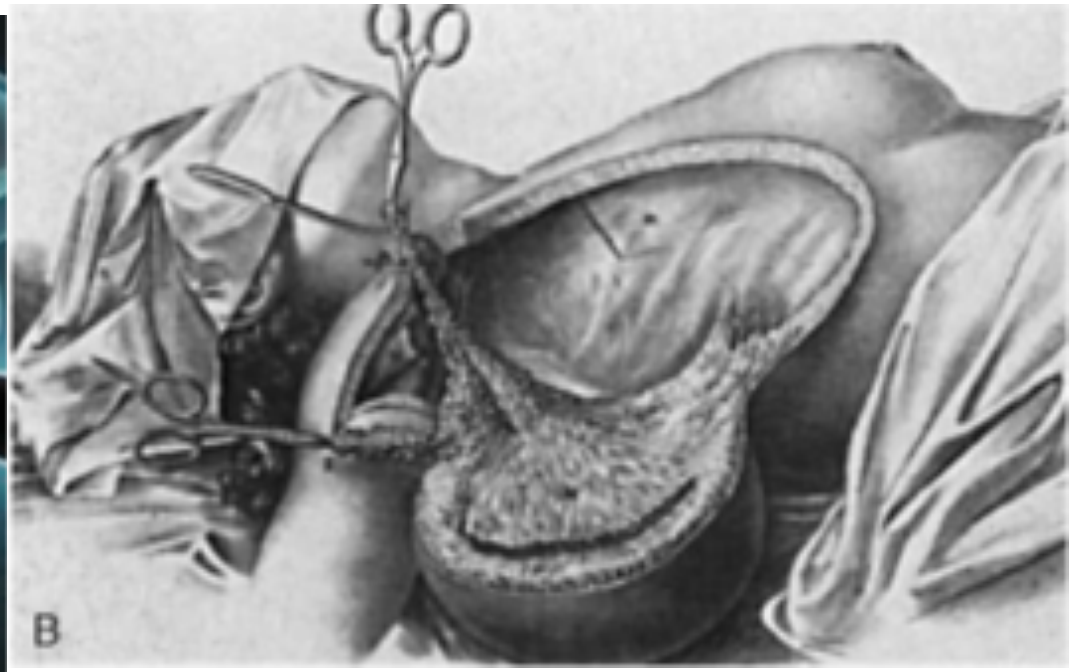
CANCER RESEARCH UK

Let's beat cancer sooner

M-Claire King Berkley CA USA (Lasker award 2014): linking the first oncogene to breast cancer (1994)



Castraton resistant radical protatectomy



William Halsted (1890s): pioneer in radical mastectomy

PHC - BRCA1/2 - the "Angelina effect" : Holliwood celebrities impact on how we seek treatment for health conditions

LOS ANGELES — "I choosed to have a preventive double mastectomy. A simple blood test had revealed that I carried a mutation in the BRCA1 gene (encode protein involved in DNA repair). I lost my mother, grandmother and aunt to cancer. I wanted other women at risk to know about the options. I promised to follow up with any information that could be useful, including about my next preventive surgery, including the removal of my ovaries and fallopian tubes " **Angelina Jolie**

Towards a trend of salpingo-oophorectomy – mastectomy ?

A small percentage of people (about one in 400, or **0.25%** of the population) carry mutated BRCA1 or BRCA2 genes with significant cumulative risk of ovarian, breast, pancreas, uterine, prostate cancers incidence

PHC - BRCA1 – preventive areola/nipple sparing mastectomy

DOI 10.1245/s10434-010-1365-9

SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

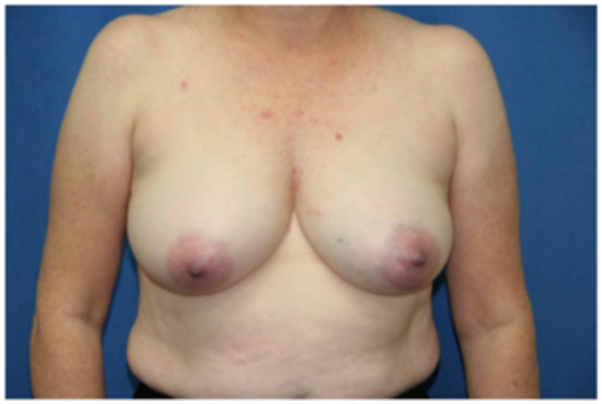
Areola and Nipple-Areola-Sparing Mastectomy for Breast Cancer Treatment and Risk Reduction: Report of an Initial Experience in a Community Hospital Setting

Jay K. Harness, MD, FACS[1], Thomas S. Vetter, MD[2], and Arthur H. Salibian, MD[1]

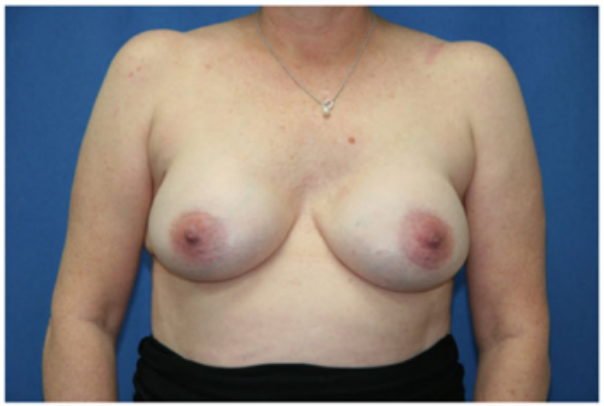
[1]St. Joseph Hospital, The Center for Cancer Treatment and Prevention, Orange, CA; [2]Aesthetic and Institute, University of California, Irvine, Orange, CA

30% to 60% of women report sensation in the nipple, especially over time

NSM - a safe option for most women with preventive or early breast cancer diagnosis



Pre-op Bilateral NAS Mastectomies



Post-op Bilateral NAS Mastectomies

PHC - BRCA1/2 are an integrated part in clinical oncology practice.

Box 1 | *BRCA* mutations in women with breast and ovarian cancer

Studies indicate that it is worthwhile to screen all patients with invasive ovarian cancer or certain types of breast cancer, as more than 10% of tests will identify a *BRCA1* or *BRCA2* mutation (see table below).

Group	Proportion with *BRCA* mutations
Women with invasive ovarian cancer (all ages)	12%
Jewish women with breast cancer (all ages)	11%
Families with two or more cases of breast cancer in women under 50 years of age	12%

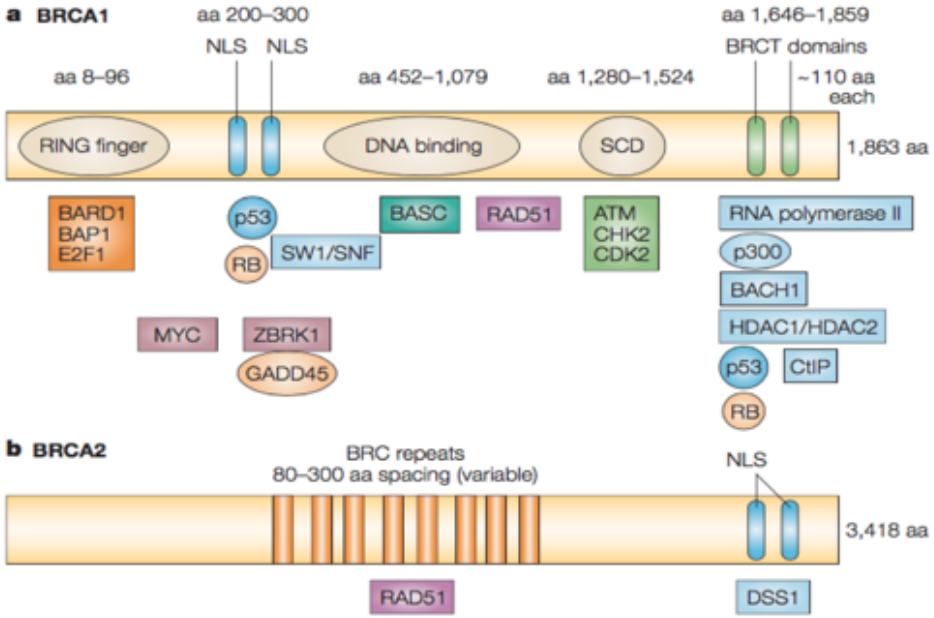


Figure 1 | **BRCA1 and BRCA2 functional domains, and selected binding partners.**

"When mutated larger incidence of mutational rate. It gave me an estimated 87 percent risk of breast cancer and a 50 percent risk of ovarian cancer" Angelina Jolie

Narod S and Foulkes W. 2004. Nature Reviews Cancer 4: 666-676

PHC – familial heritable negative BRCA1/2 breast cancers – more GWAS

BRCA1/2-negative, high-risk breast cancers (*BRCAX*) for Asian women: genetic susceptibility loci and their potential impacts

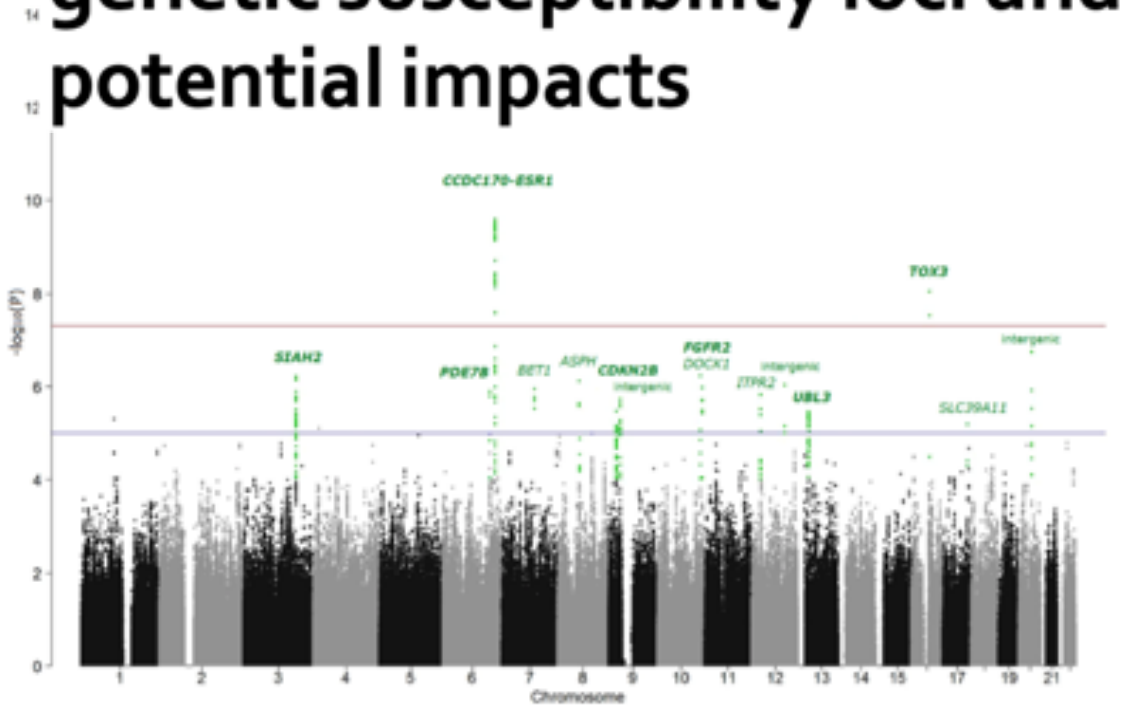


Figure 1. Manhattan plot. The red horizontal line represents the genome-wide significance threshold of p-value $= 5.0 \times 10^{-8}$ and the blue horizontal line represents the suggestive significance threshold of p-value $= 1.0 \times 10^{-5}$. For significantly associated regions, SNPs with p-value less than 10^{-3} are highlighted in green and the replicated genes are marked in bold.

"When mutated larger incidence of mutational rate. It gave me an estimated 87 percent risk of breast cancer and a 50 percent risk of ovarian cancer"
Angelina Jolie

Lee JY et al. 2018 Nature Reports 8:15263

PHC reaches Hollywood and the LA community

What is the societal value of such a DNA test ?
the Angelina Jolie effect :

a debate on disease predisposition biomarkers !

BIG DATA INFORM PATIENTS eg. ON PREDISPOSITION TO GET AZ, MI, ETC.

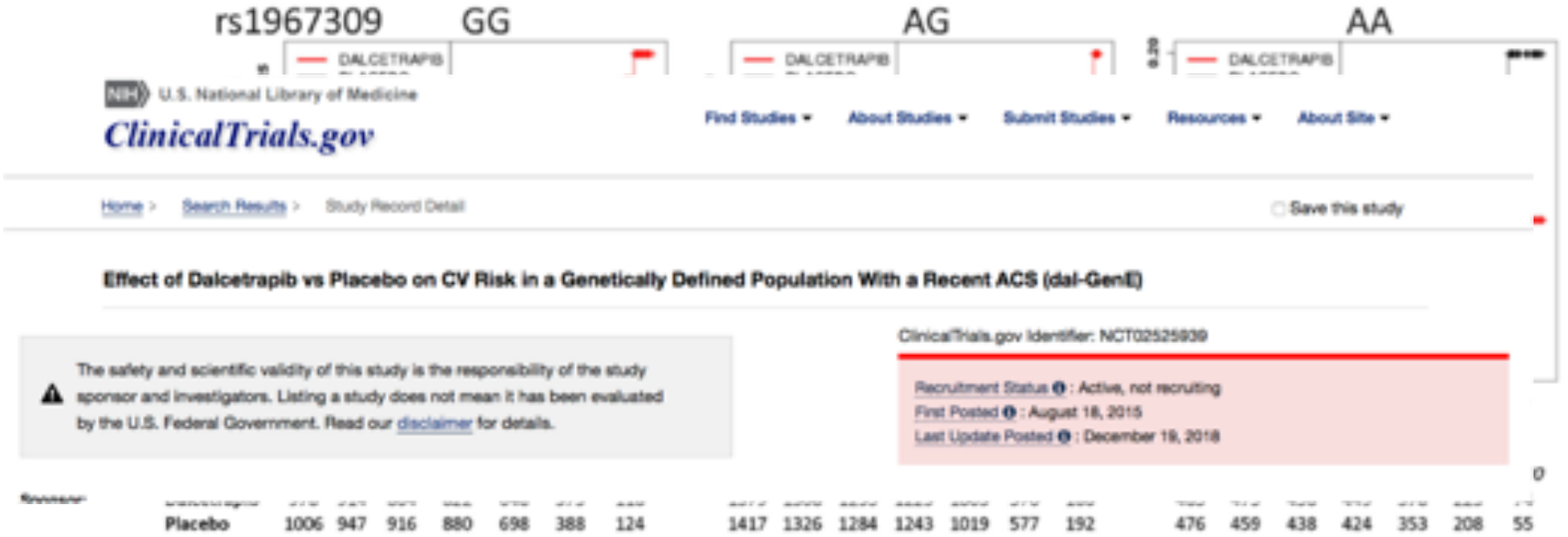
OR ANY OTHER NON REVERSIBLE PATHOLOGICAL AILMENTS !

FAR REACHING CONSEQUENCES : ARE WE THEN FREE TO DECIDE ABOUT ENDING OUR LIFES ? (eg. Exit, Dignitas) BASED ON PREDISPOSITION BIOMARKERS ?

Pharmacogenomics – MI phase 3 clinical trial on GWAS stratification : first personalized cardio metabolism clinical trial

DalCor PHARMACEUTICALS

Treatment Effect by *ADCY9* Genotypes in dal-OUTCOMES



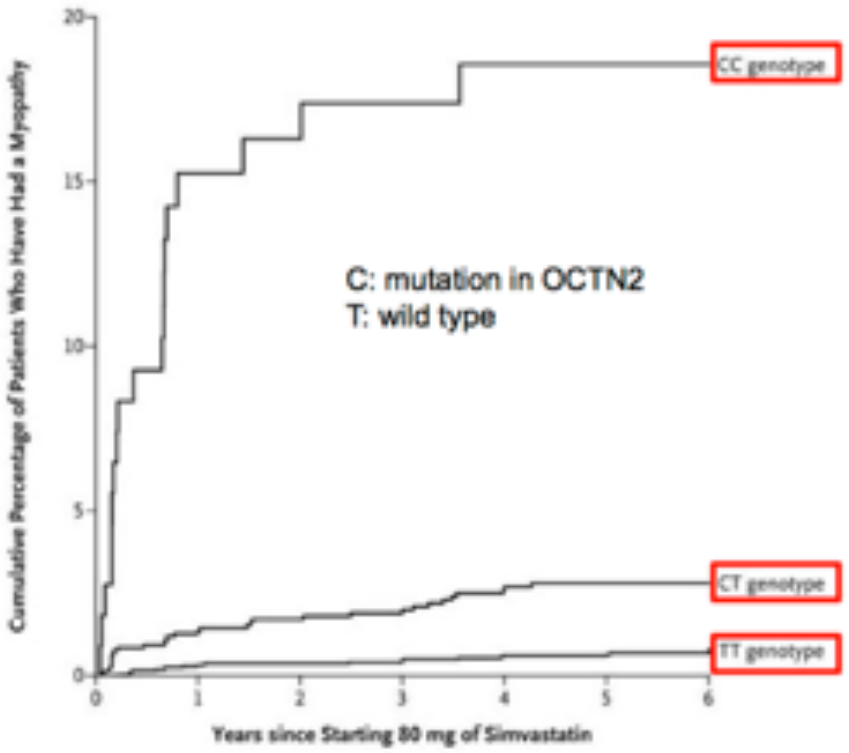
Events: Composite of CHD death, resuscitated cardiac arrest, non-fatal myocardial infarction, unstable angina with objective evidence of ischemia, atherothrombotic stroke and unanticipated coronary revascularization

igure. Kaplan–Meier curves of accumulating cardiovascular events in the dalcetrapib and placebo arms broken down according to the enotypes at rs1967309 in the *ADCY9* (adenylate cyclase type 9) gene. CHD indicates coronary heart disease.

GWAS – cadiomyocyte transporter OCTN2 and statin myopathies

Myopathies associated with statins (HMGCoA inhibitors)

- 85 patients with myopathy and 90 controls (SEARCH Trial)
- All treated with 80 mg/d simvastatin
- Genome-wide association study for genetic risk factors for myopathy
- SNP rs4149056 is a good predictor for myopathy
- SNP rs4149056 is in the vicinity of OATP1B1, which carries statins into hepatocytes



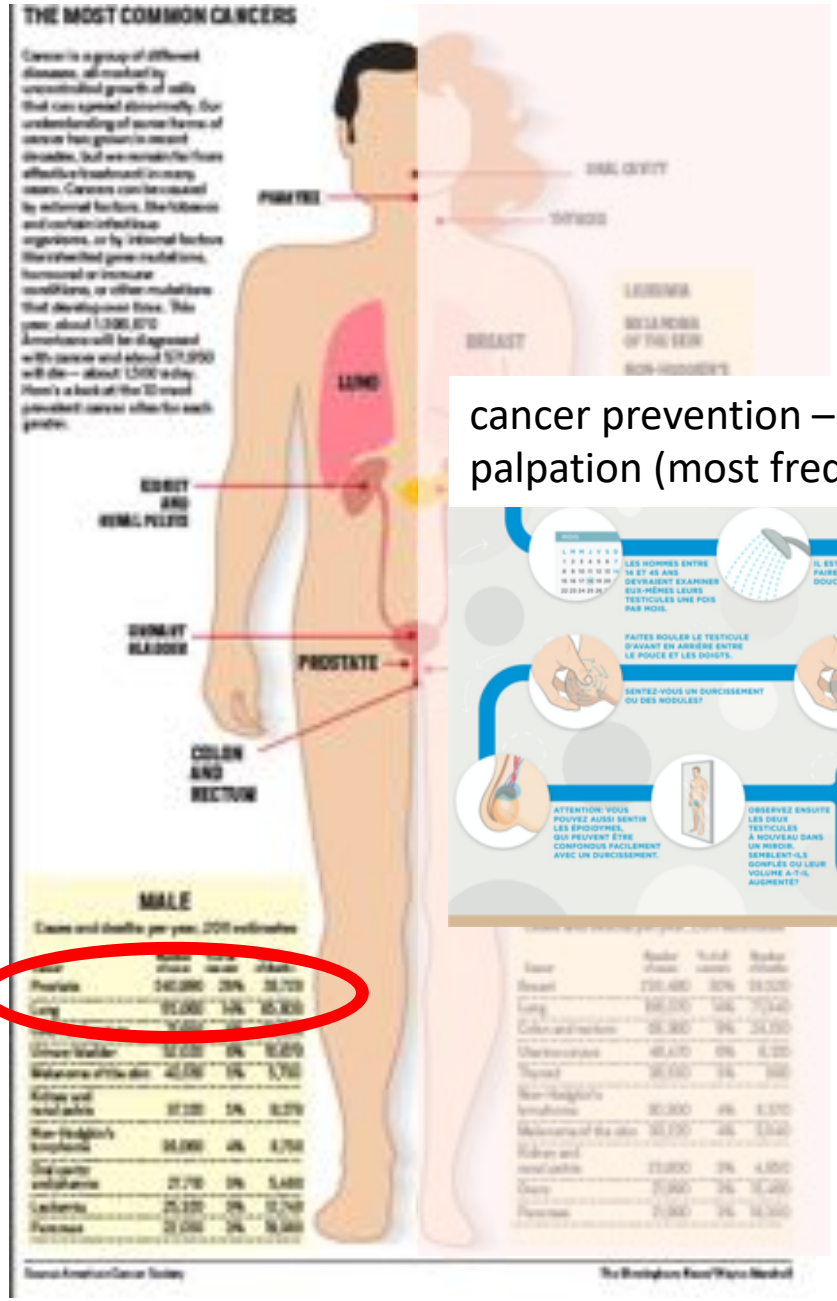
N Engl J Med 2008;359:789-99

Disease biomarker_driving innovation in oncology: examplary clinical practice of PHC

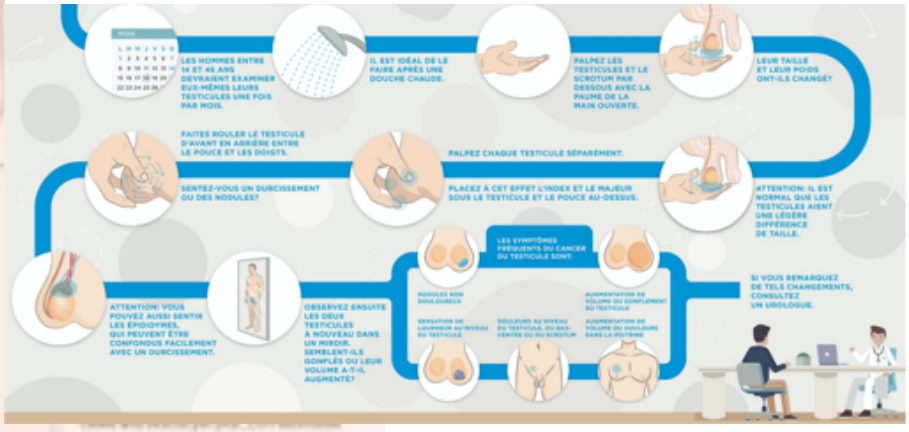
november

CANCER AT DIAGNOSTIC: WHAT IS THE STAGE OF THE DISEASE ?

CANCER DIAGNOSTIC REMAINS A MAJOR CHALLENGE !



cancer prevention – appropriate testicular palpation (most frequent age 14-45 y old)



(no biomarker yet for testicular carcinome !)

PHC – hormonal prostate cancer - biomarker PSA

PSA : **P**rostate **S**pecific **A**ntigen

PHC_ biomarker PSA at use in cancer screening

The PSA Test

J'aime 168 | Tweet | Partager | 8 | A A

What is Prostate Specific Antigen (PSA)?

Prostate Specific Antigen (PSA) is a protein produced within the prostate gland and is secreted into seminal fluid.

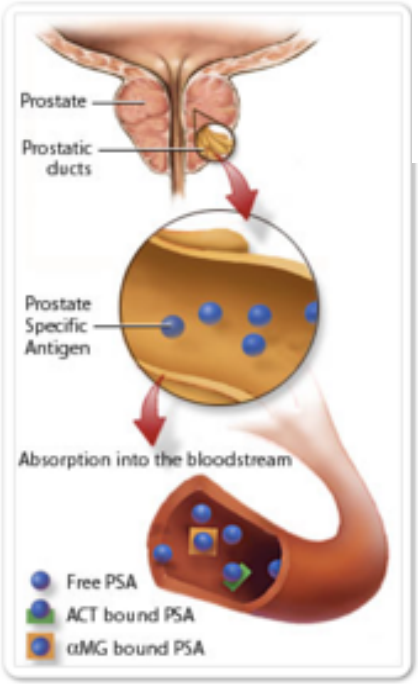
There are two types of PSA:

1. Free PSA: moves freely in the blood as it is unbound to other proteins
2. Complex PSA: attached to other proteins as it moves around the blood

Free PSA comes from benign prostatic hyperplasia (BPH), an enlargement of the prostate. The higher the amount of free PSA, the less likely prostate cancer will be found as prostate cancer cells produce more complex PSA.

What is the PSA test?

The PSA test is a simple blood test, taken from the arm, which measures the amount of PSA protein in the blood. It is common for PSA to be found in the blood in very small concentrations. Higher levels of PSA may indicate the presence of cancer, but can also be an indicator of other prostate conditions.



Prostate Cancer Canada graciously acknowledges the Princess Margaret Cancer Centre for sharing this image with us.

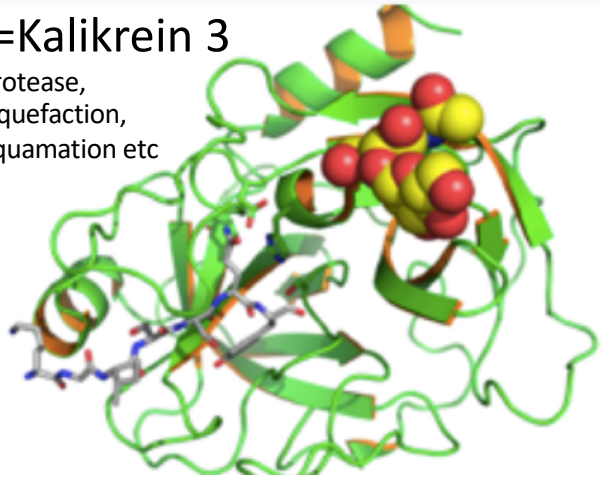
What are the benefits and limitations of the PSA test?

Benefits	Limitations
May indicate the presence of cancer in its earliest stages.	May lead to unnecessary tests and treatment.
Simple blood test (not harmful).	Cannot distinguish between slow growing and advanced cancer.
Currently only test we have as red flag to indicate follow-up.	The PSA test cannot diagnose prostate cancer but can tell you if there's a problem with the prostate.

THE NEED FOR AN ACCURATE BIOMARKER IS DRIVEN BY THE FEAR OF UNNECESSARY BIOPSIES ON THE ONE HAND, AND THE MORE DANGER RISK OF MISSING A TREATABLE CANCER ON THE OTHER !

PSA =Kalikrein 3

serine protease,
semen liquefaction,
skin desquamation etc



Ongoing efforts are targeted at identifying new serum markers that will have greater diagnostic accuracy for prostate cancer, particularly those that can predict aggressive tumours whose treatment will save lives

The Prostate Cancer Prevention Trial, which biopsied patients with normal PSA levels, estimated a negative predictive value of 85% for a PSA value <4.0ng/ml (false negative rates)

Consistently positive PSA : robotic prostate ablation (DaVinci) (video)

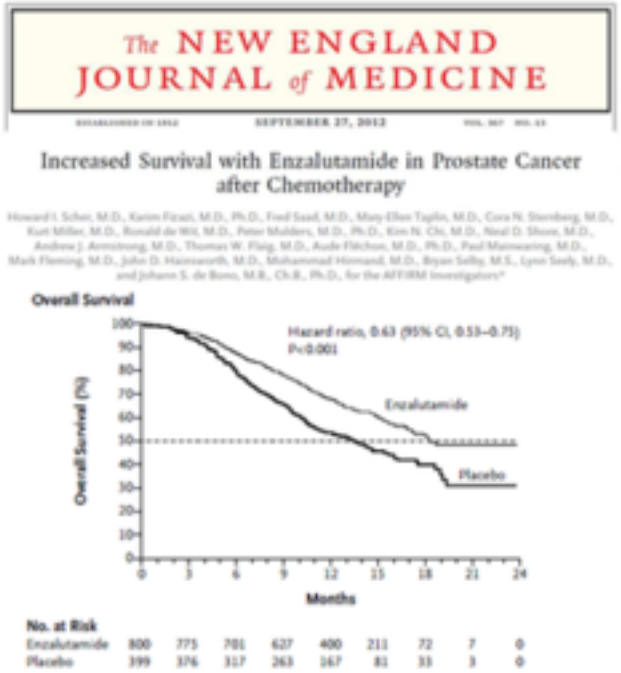
Consistently positive PSA : robotic prostate ablation (DaVinci) (video)
“the surgeon takes care of the tumor, not from the mets !”

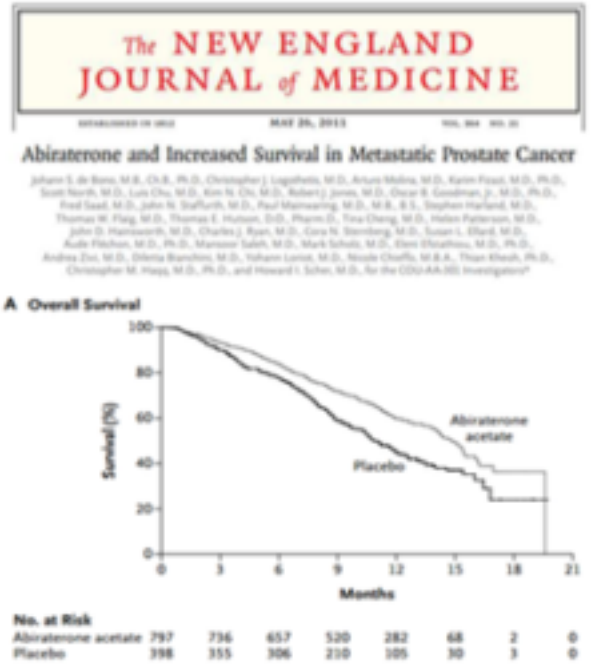
Prostate cancer : resistance and PSA controled hormonal chemotherapy

Metastatic prostate Cancer

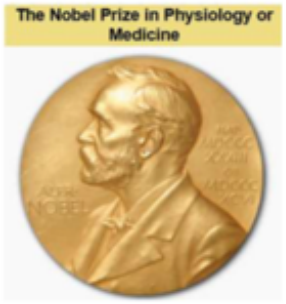
Hormon-Targets: Steroidhormonbiosynthesis

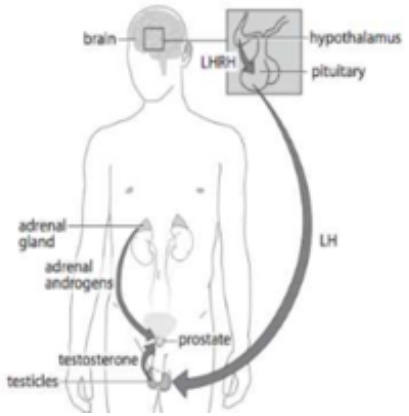
This was the first discovery that showed that cancer can be controlled by hormonal chemicals





Approximately 15% to 25% of patients with CRPC do not respond to first-line treatment with either abiraterone or enzalutamide, meaning that their prostate-specific antigen (PSA) values do not decrease or their tumours do not regress.

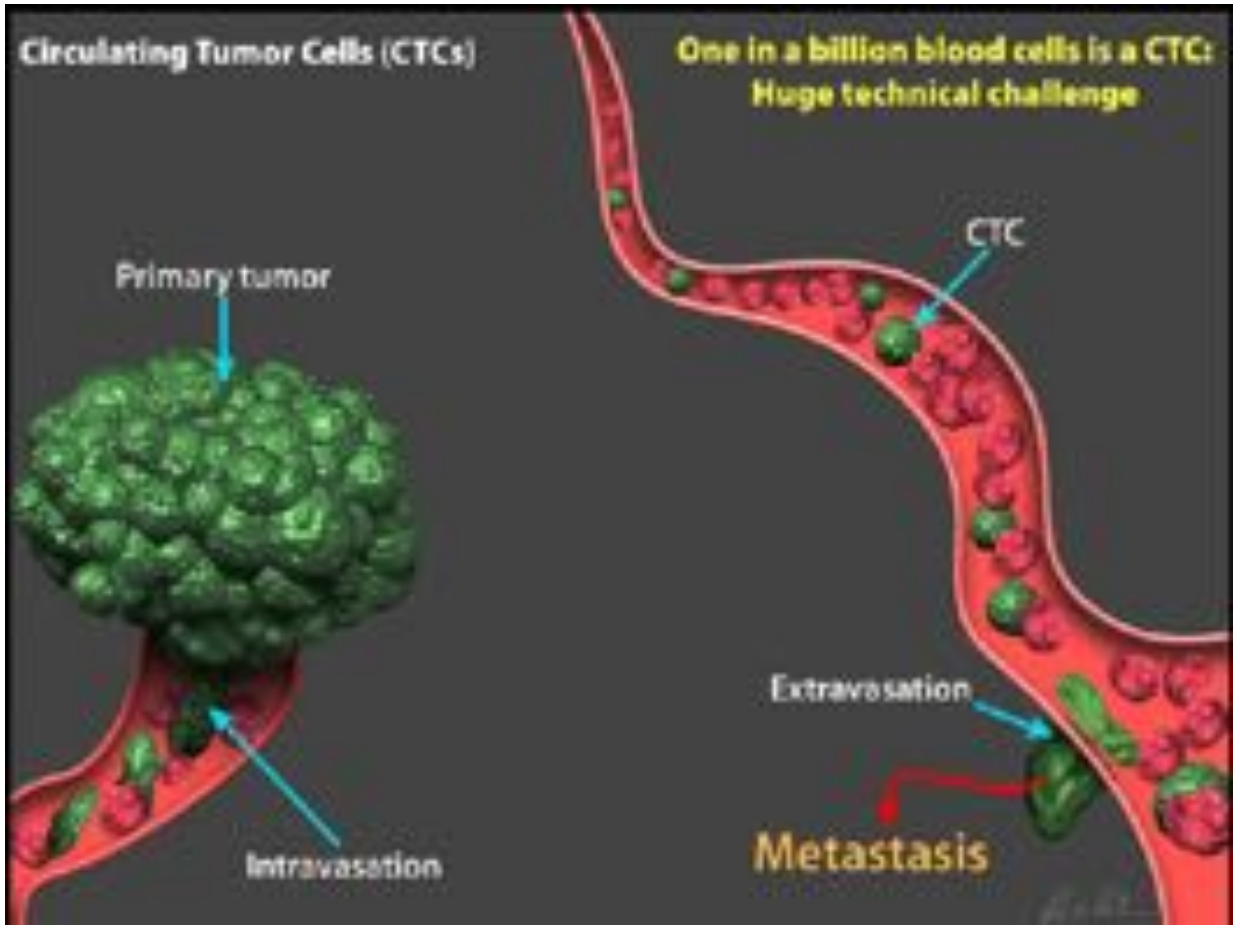




CASTRATION RESISTANT PROSTATE CANCER
CYP17A1 inhibitor (abiraterone): androgen synthesis blocker. AR (androgen receptor) antagonist enzalutamide (SARM) therapy
PROTAC androgene receptor-VHL ub ligase

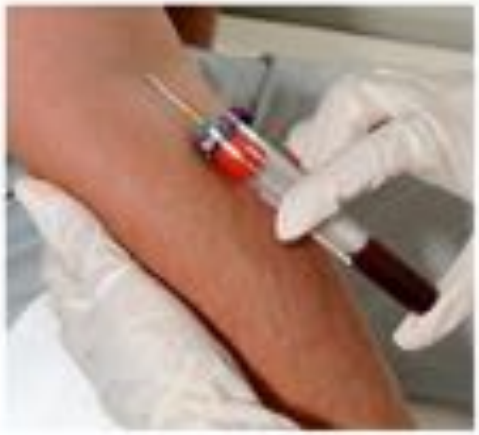
Circulating Tumor Cells - CTCs

- **CTCs MAY ORIGINATE FROM DIFFERENT PARTS OF THE PRIMARY TUMOR !**
- **90% OF CANCER RELATED DEATHS ARE DUE TO DEVELOPMENT OF METASTASIS**
- **7 MILLIONS PATIENTS WORDWIDE DIE EVERY YEAR OF CANCER METASTASIS (NOT FROM PRIMARY TUMOR) !**
- **NOBODY KNOWS HOW TO PREVENT FORMATION OF METASTASIS** !



Liquid biopsies_ into the future of personalized medicine !

MIT Technology Review



Liquid Biopsy

Fast DNA-sequencing machines are leading to simple blood tests for cancer.

10 Breakthrough Technologies 2015

- Introduction
- Magic Leap
- Nano-Architecture
- Car-to-Car Communication
- Project Loon
- **Liquid Biopsy**
- Megascale Desalination
- Apple Pay
- Brain Organoids
- Supercharged Photosynthesis
- Internet of DNA
- Archive of Past Lists

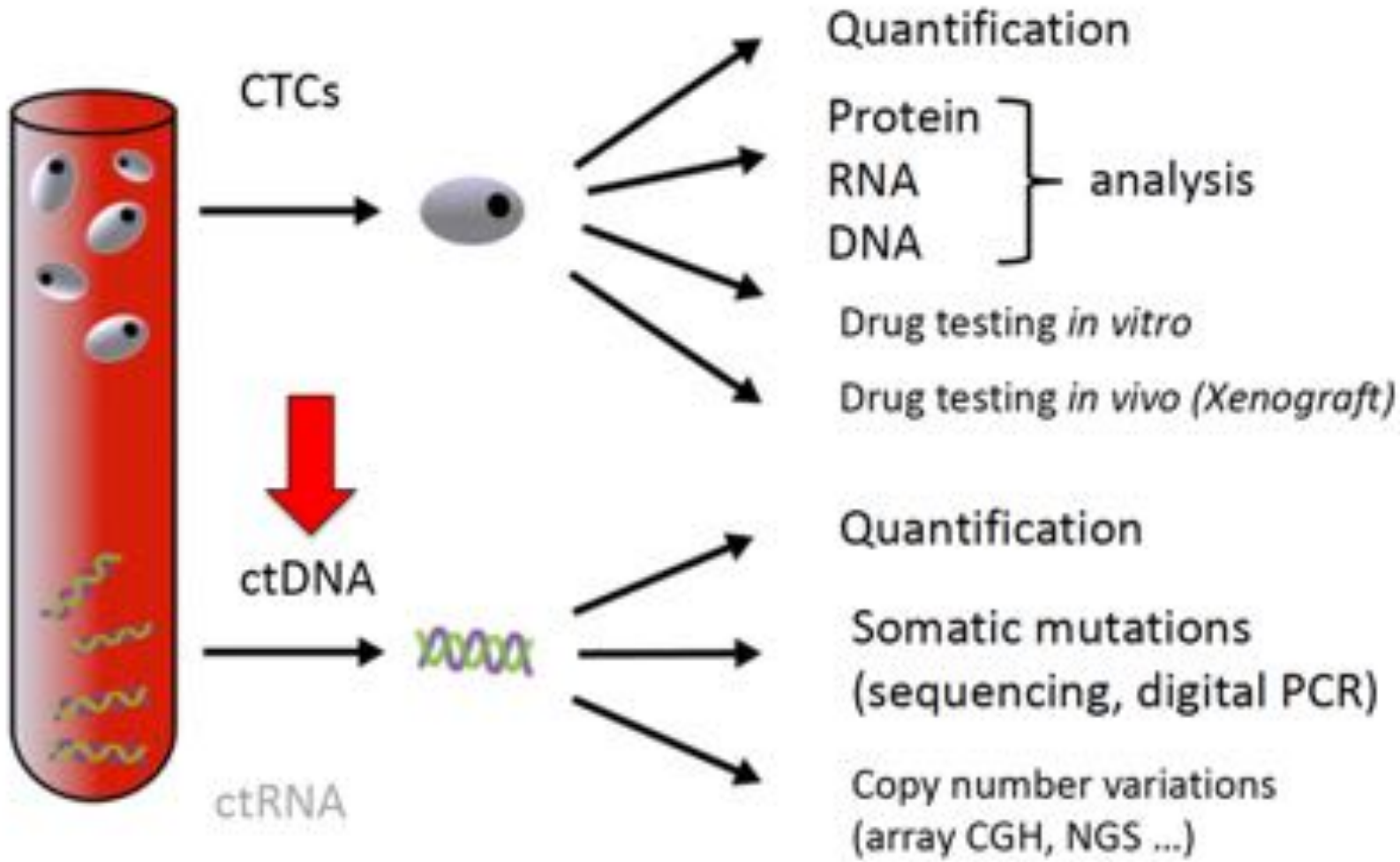
Culturing ex vivo circulating patient derived cancer tumor cells (CTCs) allows to test various drug suceptiblity in vitro, and to tailor cancer metastasis therapy

Circulating Tumor Cells CTCs

- **CTCs MAY ORIGINATE FROM DIFFERENT PARTS OF THE PRIMARY TUMOR !**
- **90% OF CANCER RELATED DEATHS ARE DUE TO DEVELOPMENT OF METASTASIS**
- **7 MILLIONS PATIENTS WORDWIDE DIE EVERY YEAR OF CANCER METASTASIS (NOT FROM PRIMARY TUMOR) !**
- **NOBODY KNOWS HOW TO PREVENT FORMATION OF METASTASIS !**

PHC – liquid biopsies and biomarker discovery

liquid biopsies : what is in there ? Overcoming tumor heterogeneity !



CTCs: circulating tumor cancer cells (glioma excepted?). Solid biopsies are frustrating as they rely on the evasive cancer drug resistance of the primary tumor !

CTCs cluster profiling can be used non invasively to monitor drug susceptibility in patients !

Patient tailored liquid biopsies during the course of disease : real time personalized diagnostic

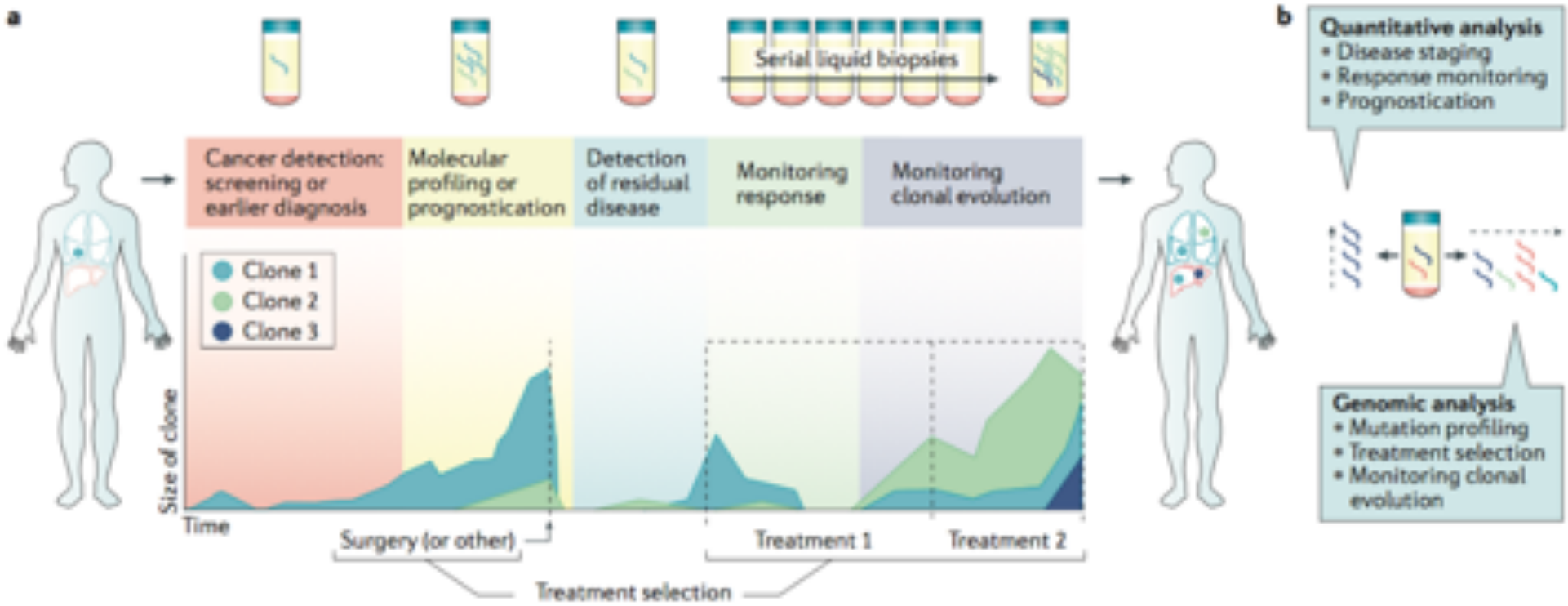
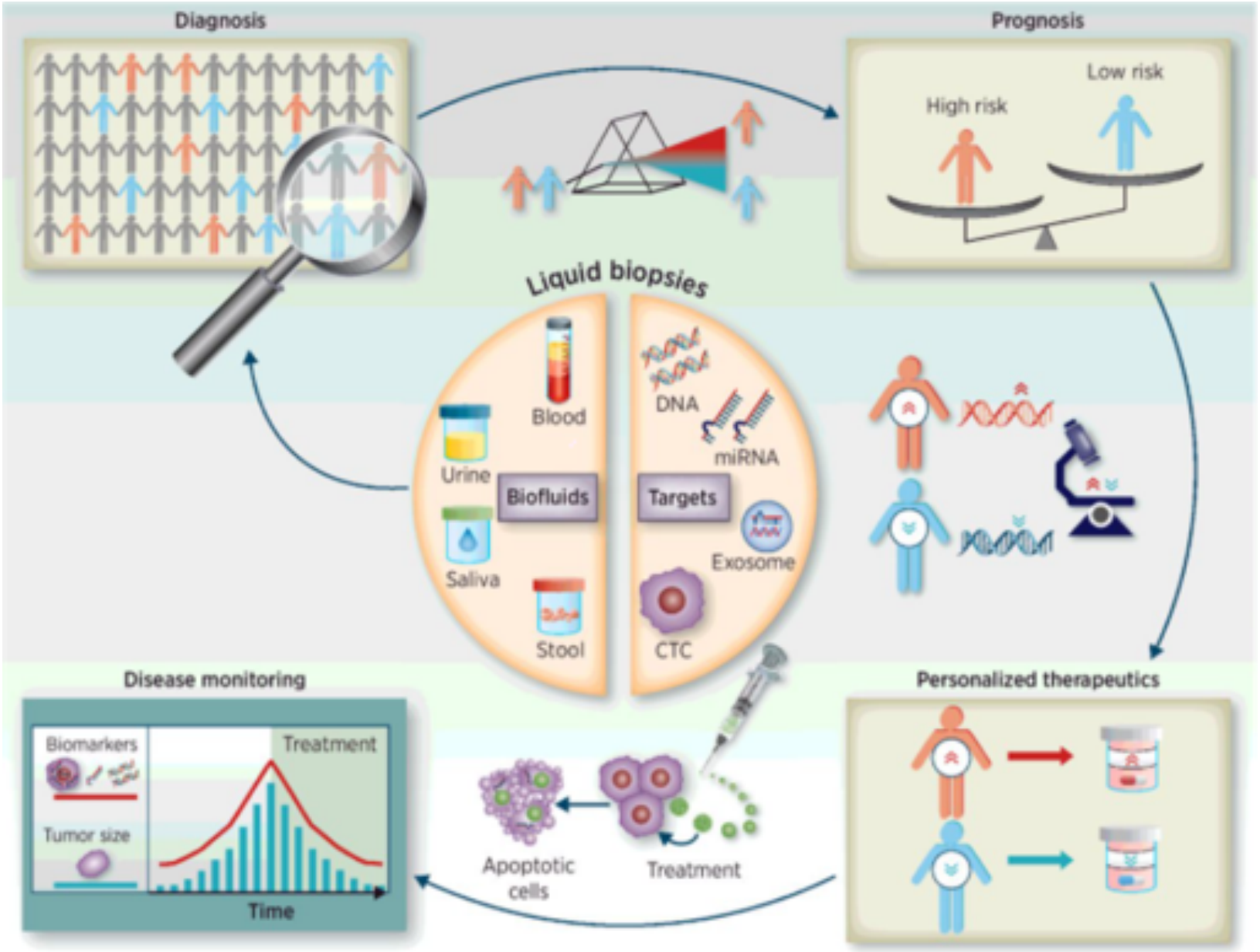


Figure 1 | **Applications of circulating tumour DNA analysis during the course of disease management. a** | A schematic

Acute metastases may be kept up as a chronic disease upon serial liquid biopsies and evasive cancer drug resistance scrutiny

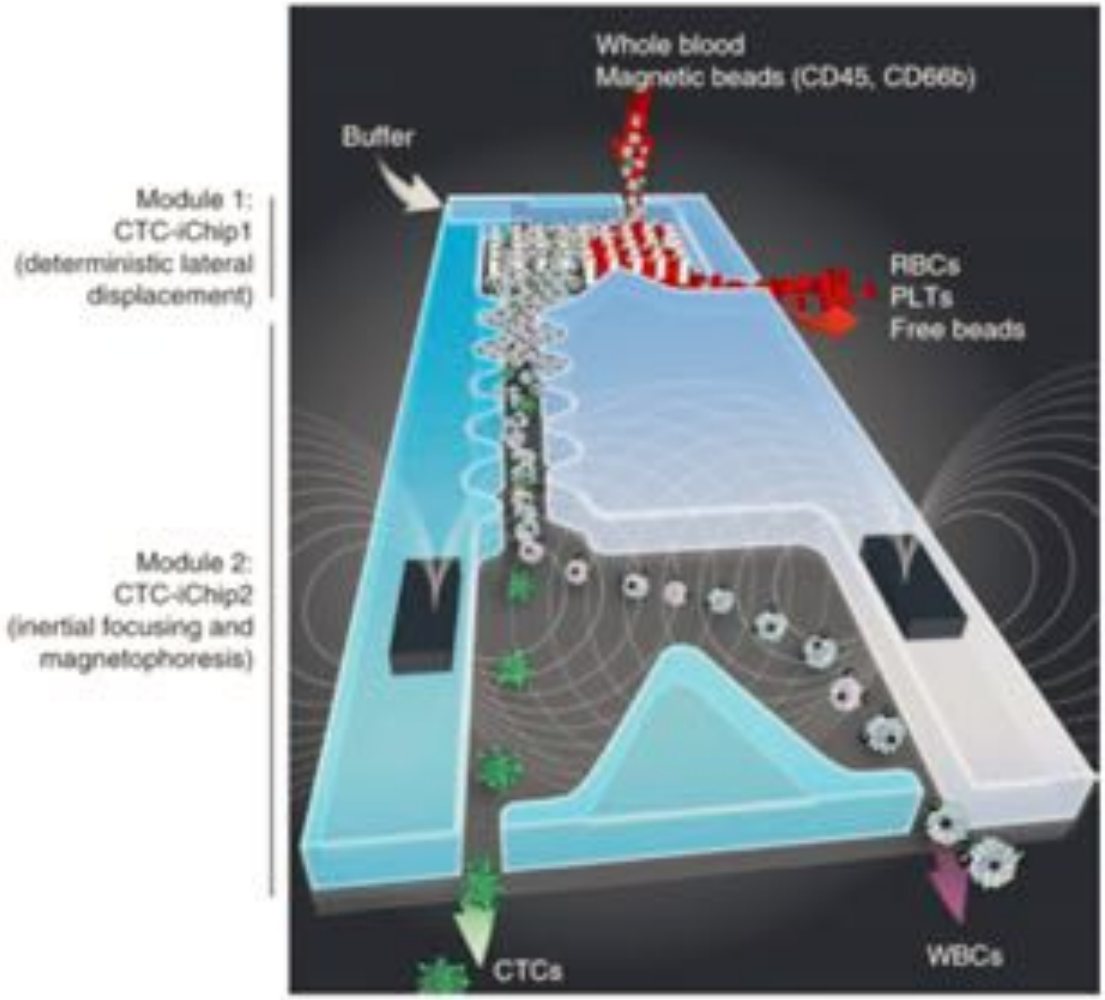
Van et al. 2017 Nature Cancer 17.223-238

Patient tailored metastasis evasive cancer drug resistance



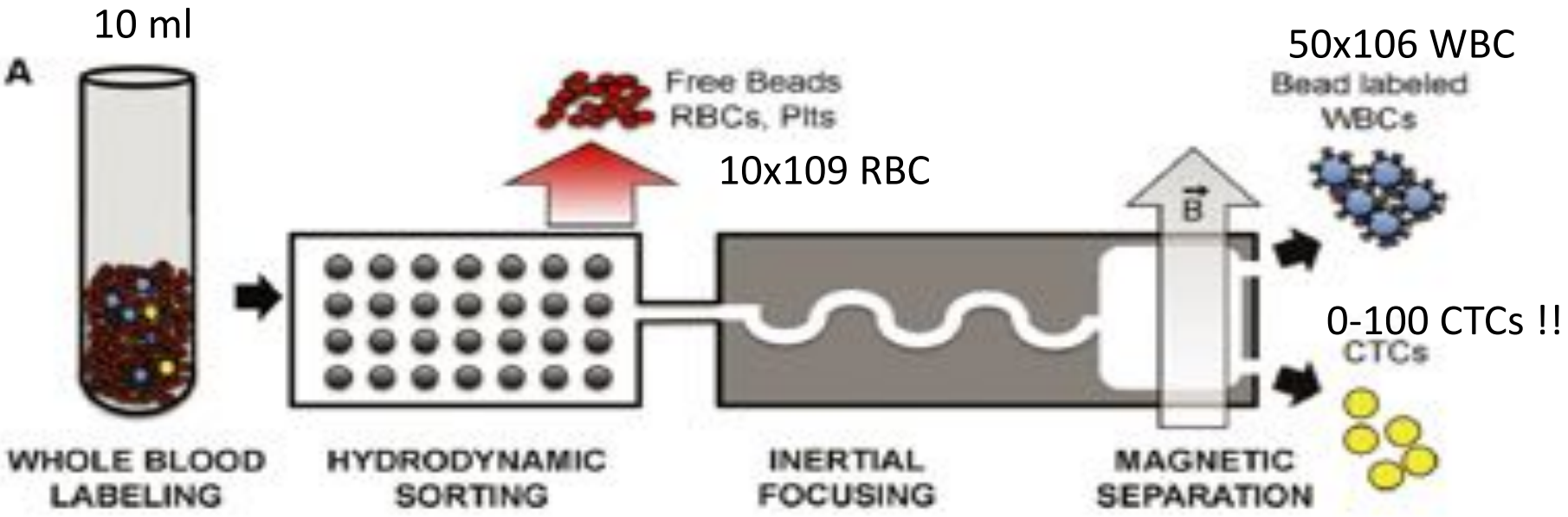
Microfluidics/magnetophoresis allows to separate CTCs from whole blood

Negative selection (Markers) – e.g. "CTC-iChip"



Ozkumur et al., ***Science Transl Med***, *2013*
Karabacak et al., ***Nature Protocols***, *2014*

Microfluidics allows to separate CTCs from whole blood !



CTCs MAY ORIGINATE FROM DIFFERENT PARTS OF THE PRIMARY TUMOR !!

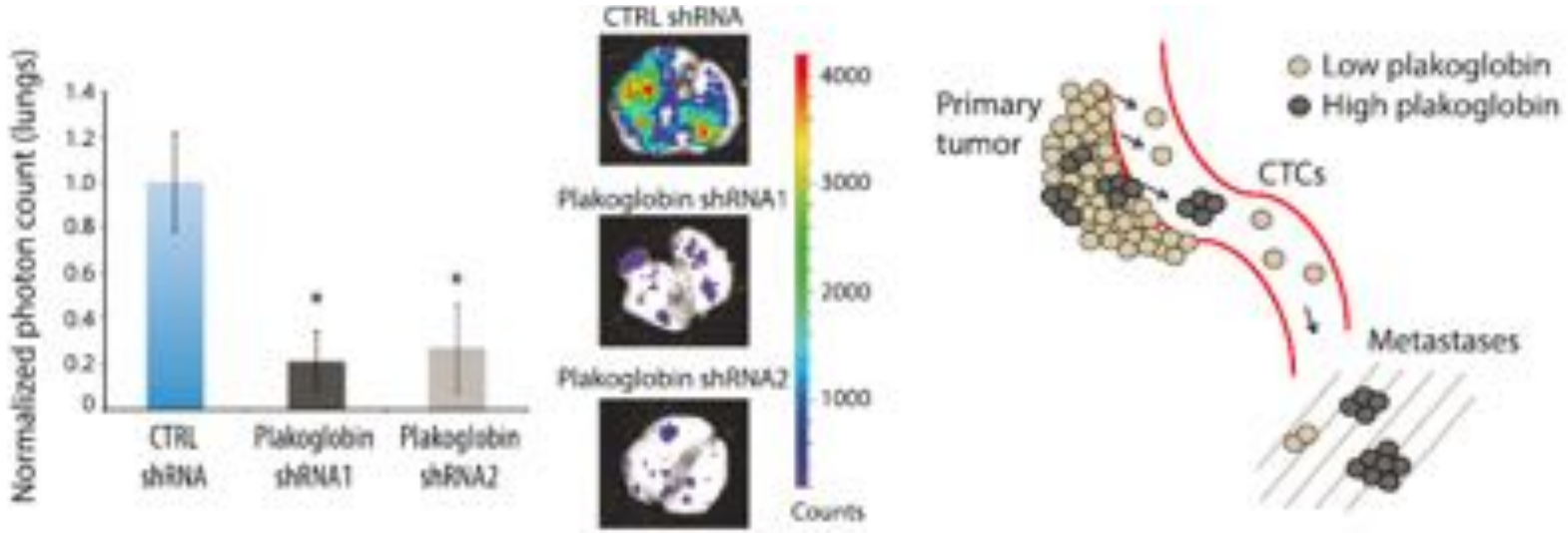


Figure 7. Plakoglobin Is Required for CTC Cluster Formation and Lung Metastasis

Aceto et al. 2014 Cell 158:1110-1122

CTCs from whole blood can traverse the capillary bed !

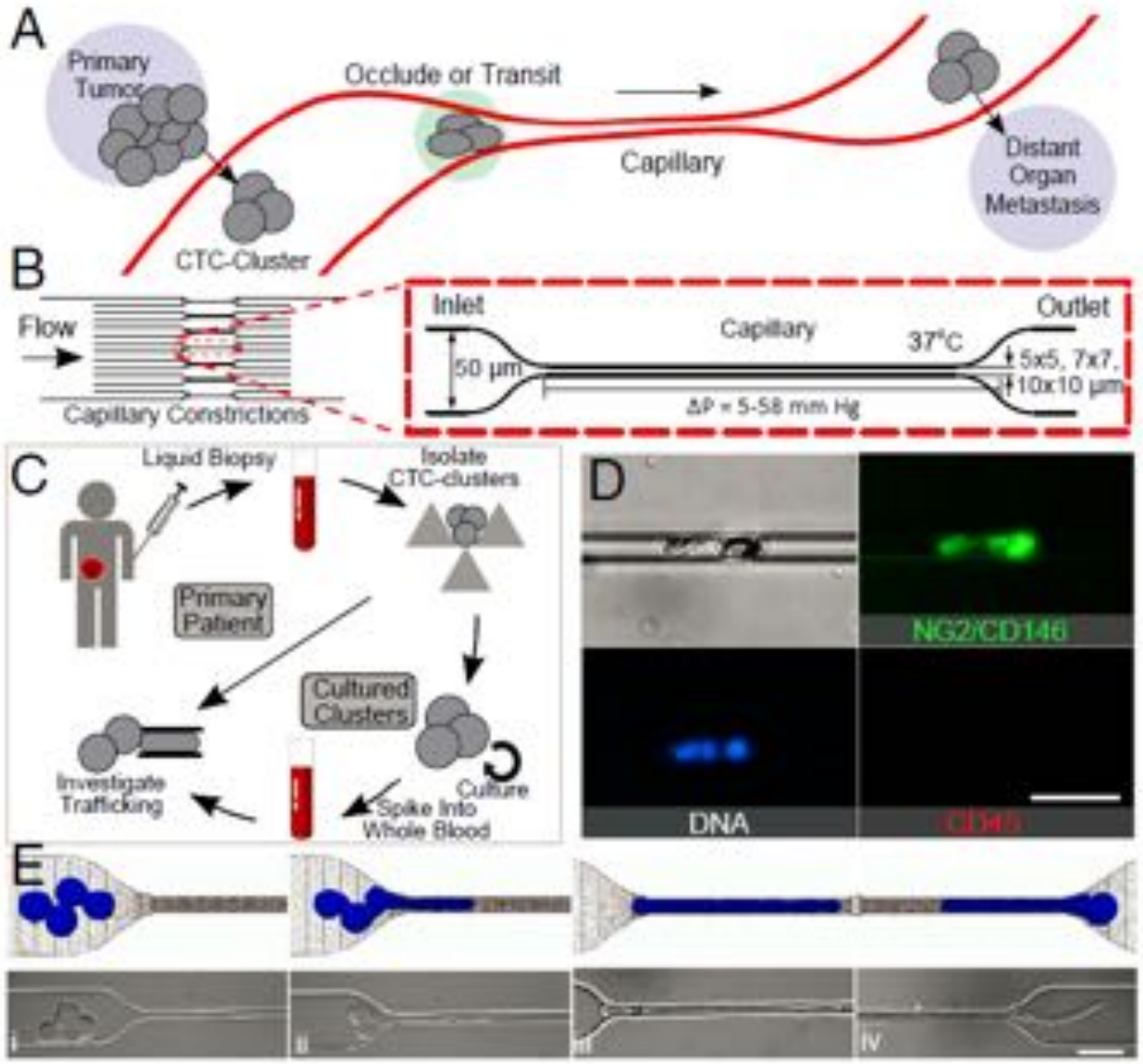
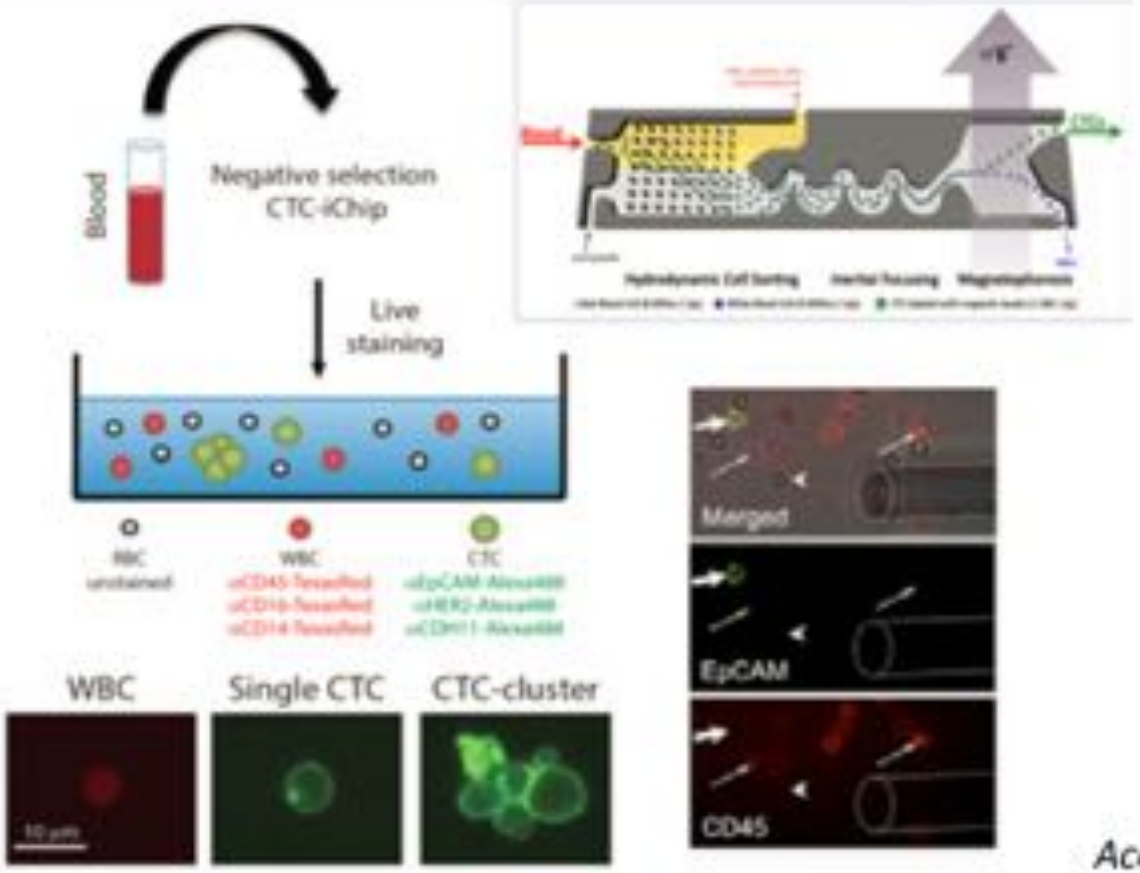


Fig. 1. (*A*) Diagram of CTC clusters occluding or transiting through capillary

Aceto et al. 2014 Cell 158:1110-1122

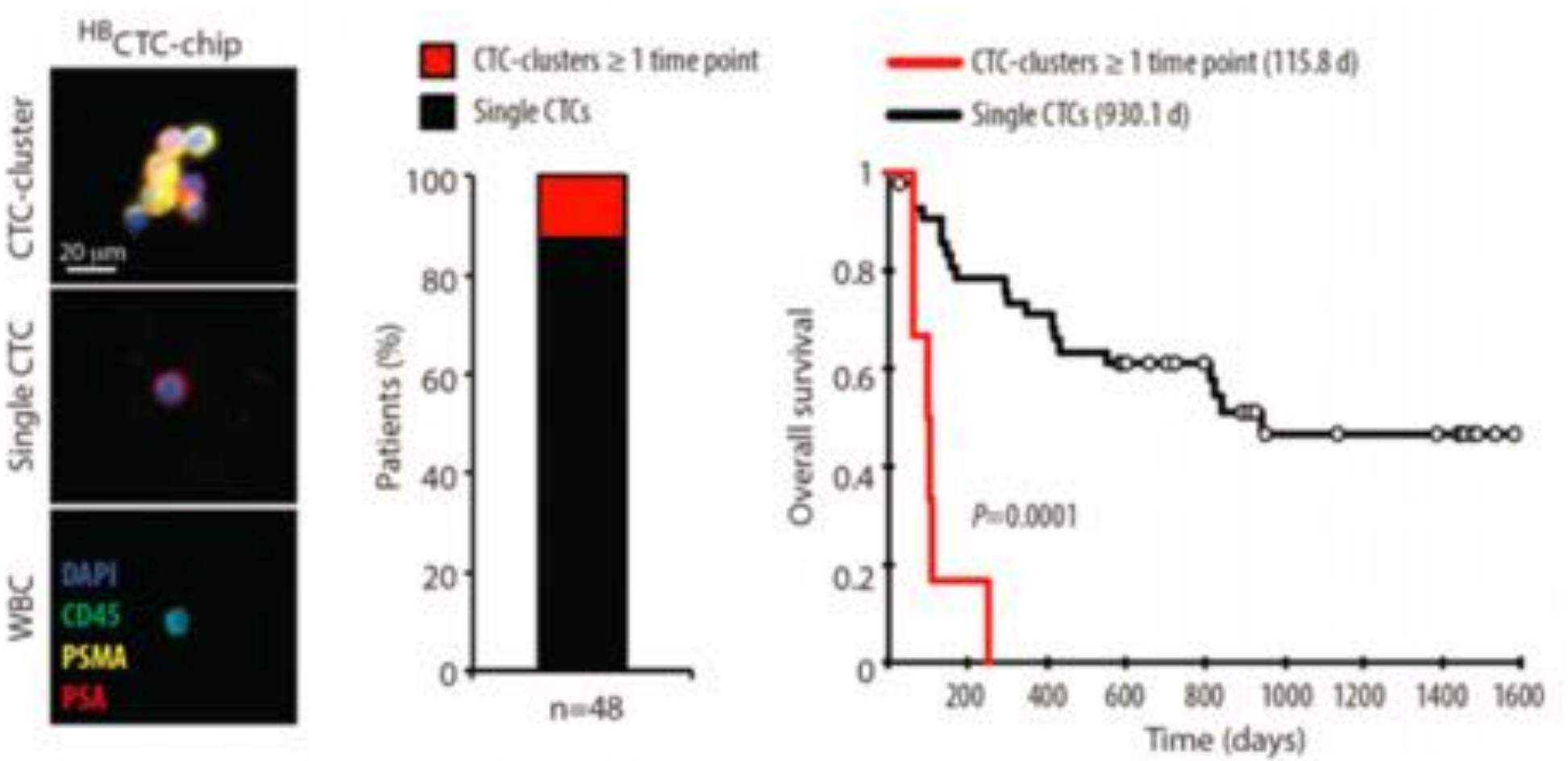
Single cell RNA sequencing of CTC and CTC clusters

CTCs from patients with breast cancers:
- Cell surface staining (EpCAM, HER2, CDH11) for micromanipulator and RNA seq



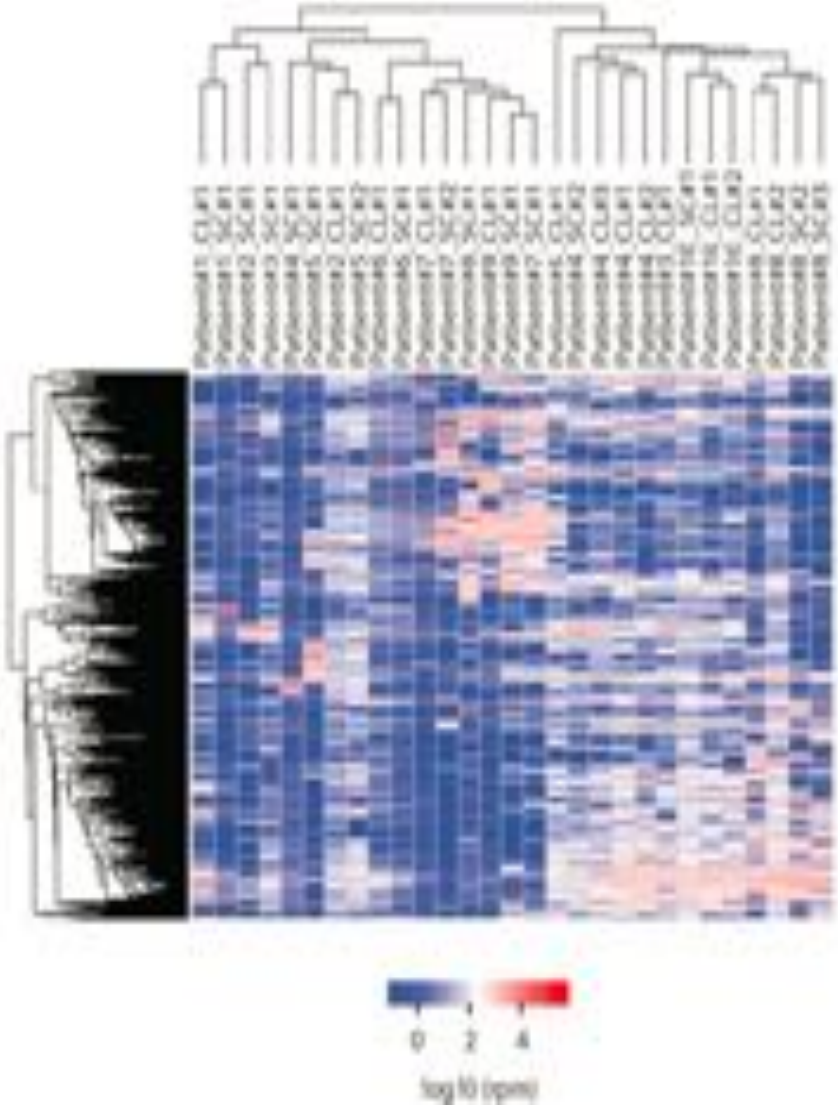
*Aceto et al., **Cell**, 2014*

CTC clusters in patients with metastatic prostate cancer

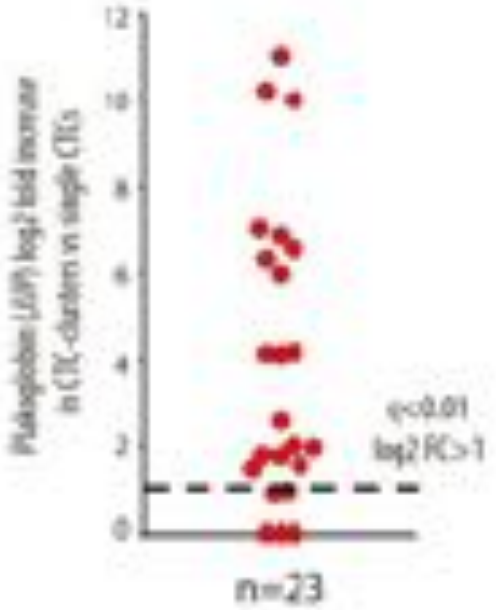


CTC clusters demonstrate increased metastatic potential compared to single CTCs

Single cell transcriptomics of CTC vs CTC clusters

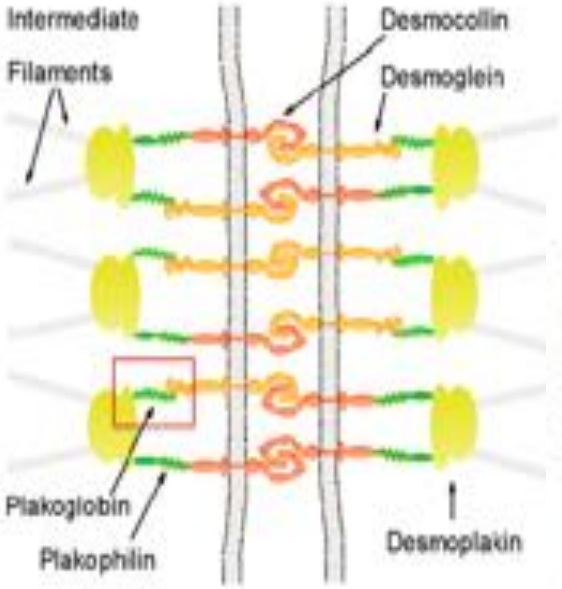


Plakoglobin increased ~215-fold in clusters vs Single CTCs

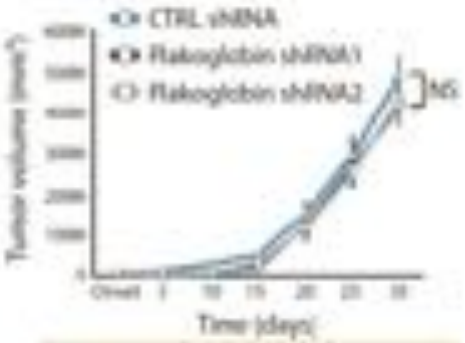


*Aceto et al., **Cell**, 2014*

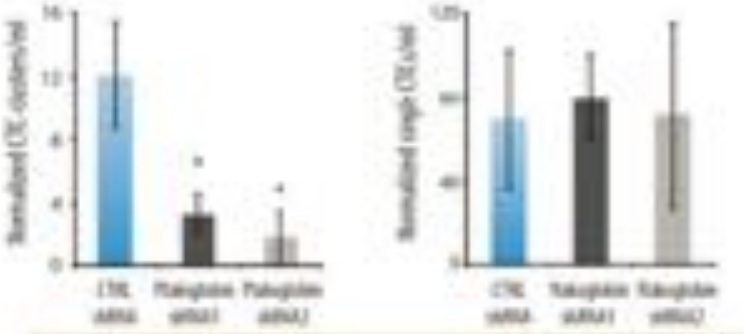
CTC vs CTC clusters in tumor metastasis



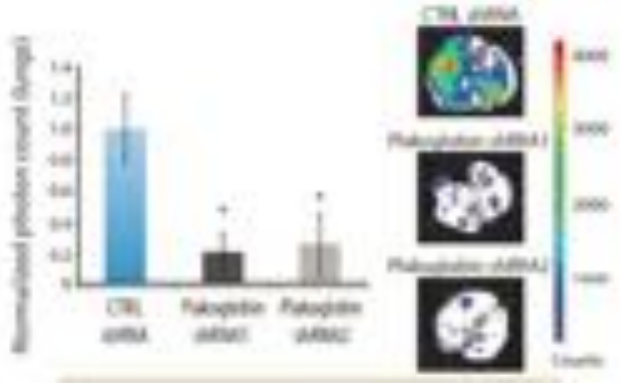
Plakoglobin knock down in primary tumor suppresses lung metastasis



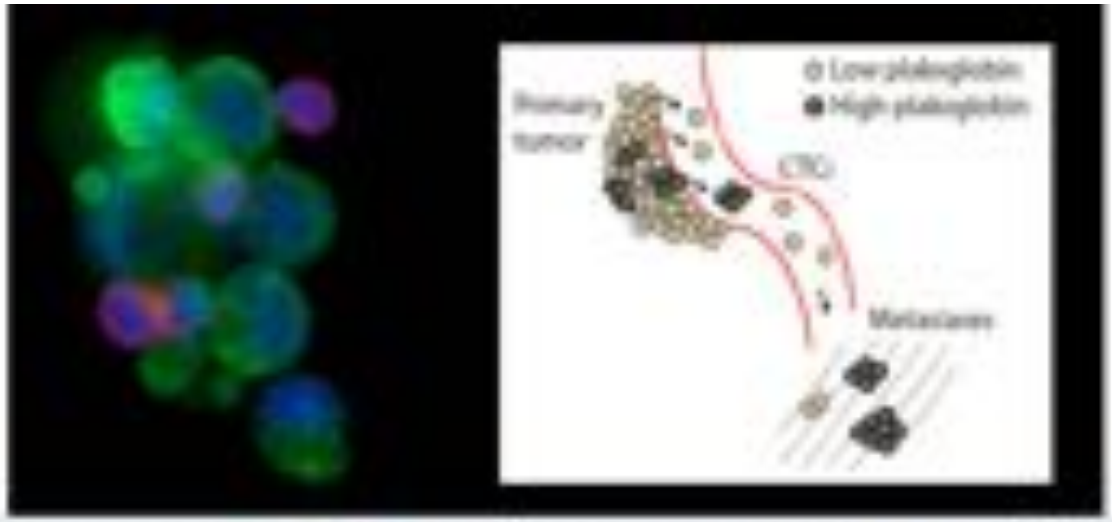
No change in growth of primary tumor xenograft



Reduced CTC-clusters, but not single CTCs, from primary tumor xenograft



CTC vs CTC clusters in tumor metastasis



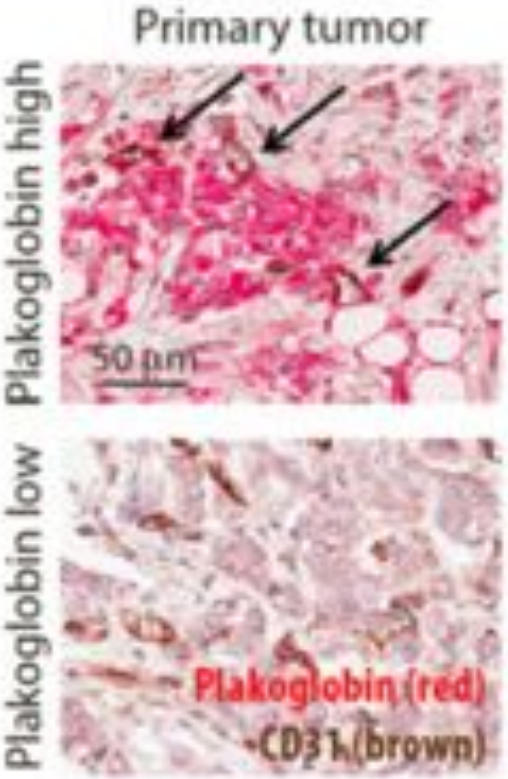
1. CTC-clusters originate from ***individual tumor deposits*** and are not the result of intravascular tumor cell aggregation

2. CTC-clusters are ***rare but highly metastasis-competent***, accounting for half of metastatic lesions in mouse model

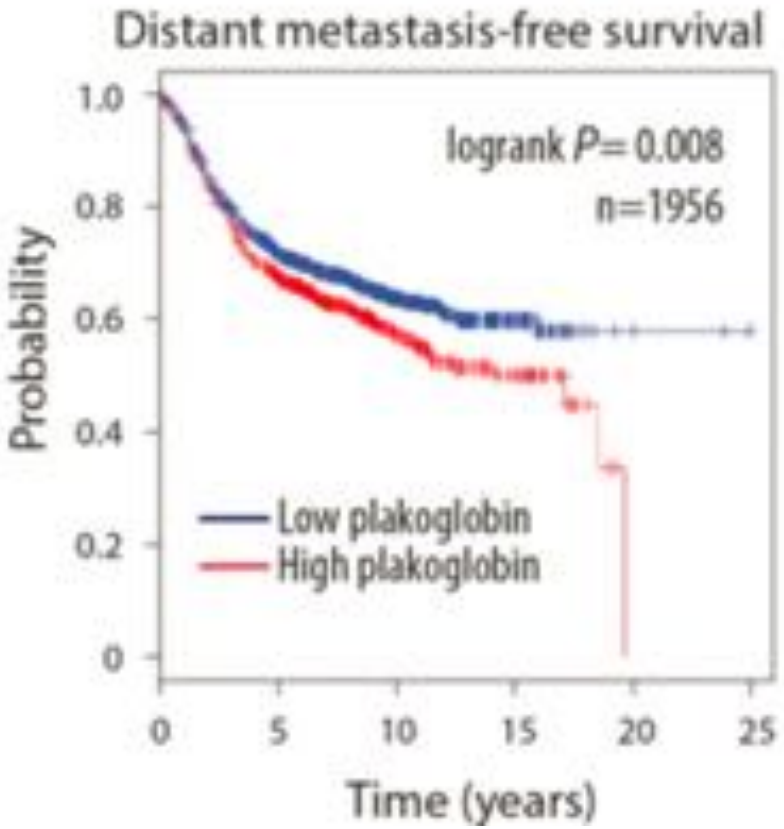
3. ***Plakoglobin*** helps tether CTCs within clusters, thereby enhancing metastatic spread

Plakoglobin in primary breast cancer tumors

Heterogeneous expression in primary tumors



Higher metastatic risk in high expressing tumors



PATIENT TAILORED metastasis evasive cancer drug resistance screen

Table 1. Mutations detected in cultured CTC lines.

Case	Gene	DNA	Protein	Allele frequency†	In pretreatment tumor‡	In multiple CTC lines	Known mutation§
BRx33‖	ESR1	A1613G	D538G	0.24	–	–	Br,# En
	NUMA1	C5501T	S1834L	0.39	–	–	Br
BRx07‖	TP53	G853A	E285K	0.99	No	–	Bl, Br, Co, HN, Lu
	PIK3CA	A3140T	H1047L	1	No	–	Br, Co, GBM, HN, K$_i$, Lu, Me, Mel, Ov, En
	FGFR2	T1647A	N549K	0.46	No	–	Br, En
	CDH1	C790T	Q264*	1	Yes	–	Br
	APC	G7225A	G2409R	0.47	Yes	–	Mel
	DGKQ	G2530A	D844N	0.55	–	–	Lu
	MAML2	A2569G	M857V	0.52	–	–	Lu
BRx68	TP53	C1009T	R337C	0.99	No	Yes	Br, Co, HN, Hem, Ov
	ESR1	A1610C	Y537S	0.47	No	Yes	Br#, En
	PIK3CA	A3140G	H1047R	0.7	Yes	Yes	Br, Co, GBM, HN, K$_i$, Lu, Me, Mel, Ov, En
	MSN	G1153A	E385K	0.25	–	–	En
BRx50‖	ESR1	T1607C	L536P	0.06††	–	–	Br#
	IKZF1	G1444T	G482C	0.09	–	–	Hem
	BRCA2¶	T6262del	L2039fs	–	–	–	Br (germ line)
BRx42	PIK3CA	G3145C	G1049R	0.60	Yes	Yes	Br, En, K$_i$
	PIK3CA	C1097G	P366R	0.54	–	–	Br
	KRAS	G35T	G12V	0.99	No	Yes	Br, Co, Hem, Es, GBM, Lu, Ov, En
	IGF1R	G3613A	A1205T	0.06	–	–	Hem
BRx61	TP53	G610T	E204*	0.98	No	Yes	Bl, Br, K$_i$, Lu, Ov

†Mutant allele frequency within oligoclonal cultured CTC populations was calculated as the ratio of mutant sequence reads to total reads for each gene. ‡Where sufficient material was available for analysis, matched archival pretreatment tumor specimens were subjected to Sanger sequencing to confirm selected mutations

Patient tailored metastasis evasive cancer drug resistance screen

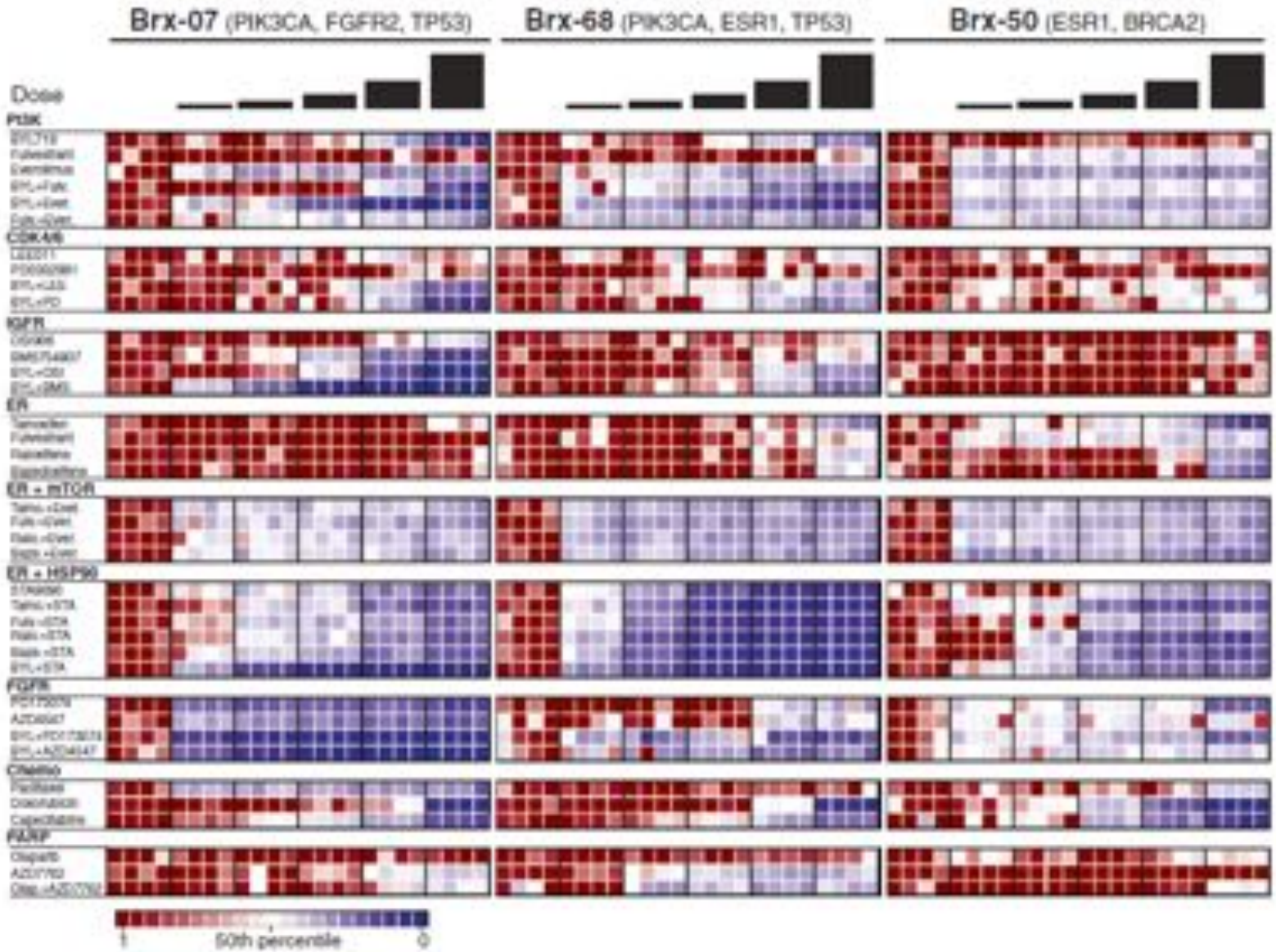


Fig. 2. Drug sensitivity of cultured CTCs. Heatmaps representing cell viability after treatment of BRx-07, BRx-68, and BRx-50 CTC lines with selected anti- dose, with each concentration tested in quadruplicate. Drug concentrations a tested in table S3. Signal from viable cells remaining after drug treatment

Yu et al. Daniel A Haber lab. 2014 Science 345:216-220

Patient tailored metastasis evasive cancer drug resistance screen

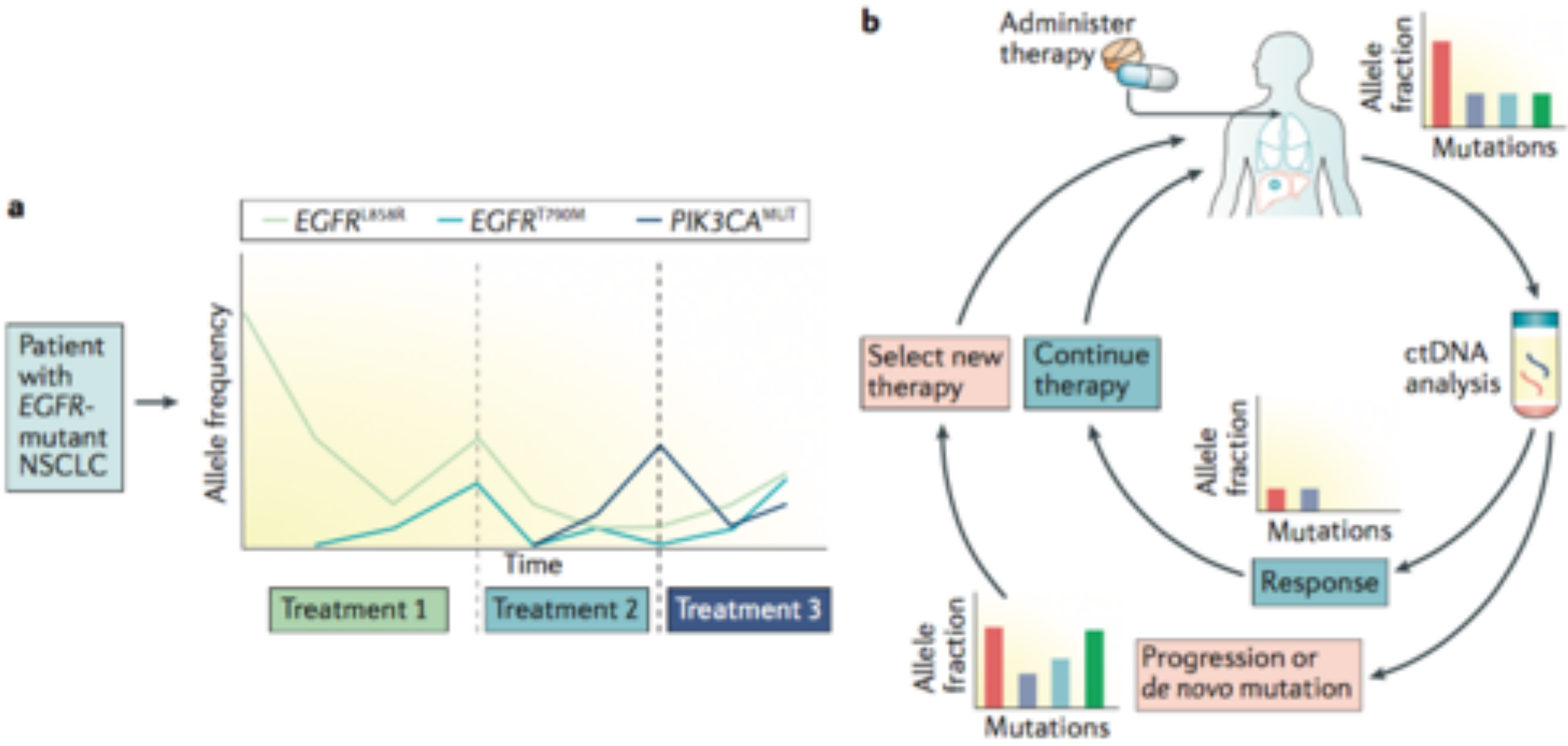
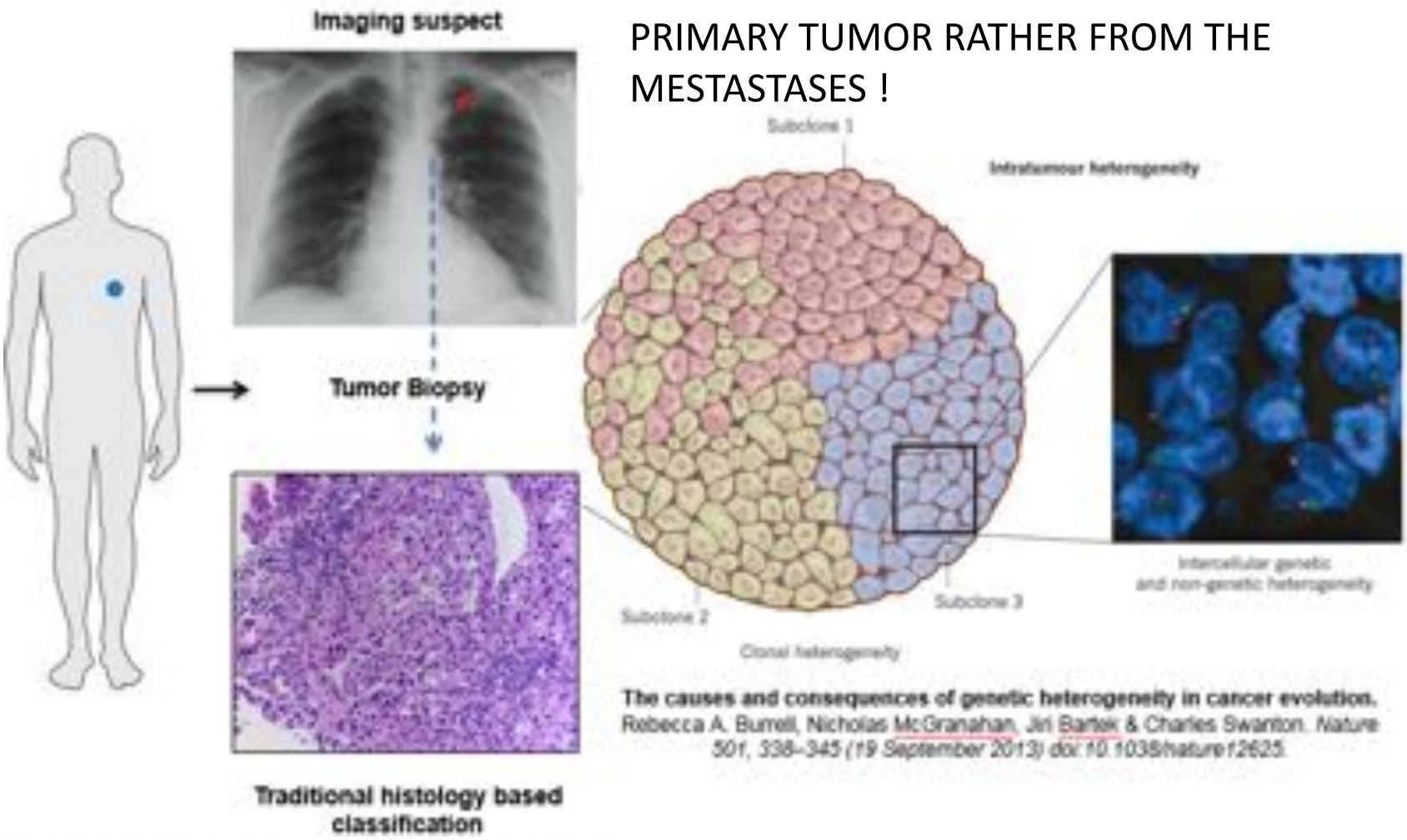


Figure 5 | **Adaptive or reactive treatment paradigms using liquid biopsies. a** | During systemic anticancer therapy,

Van et al. 2017 Nature Cancer 17: 223-238

PHC - tumor heterogeneity

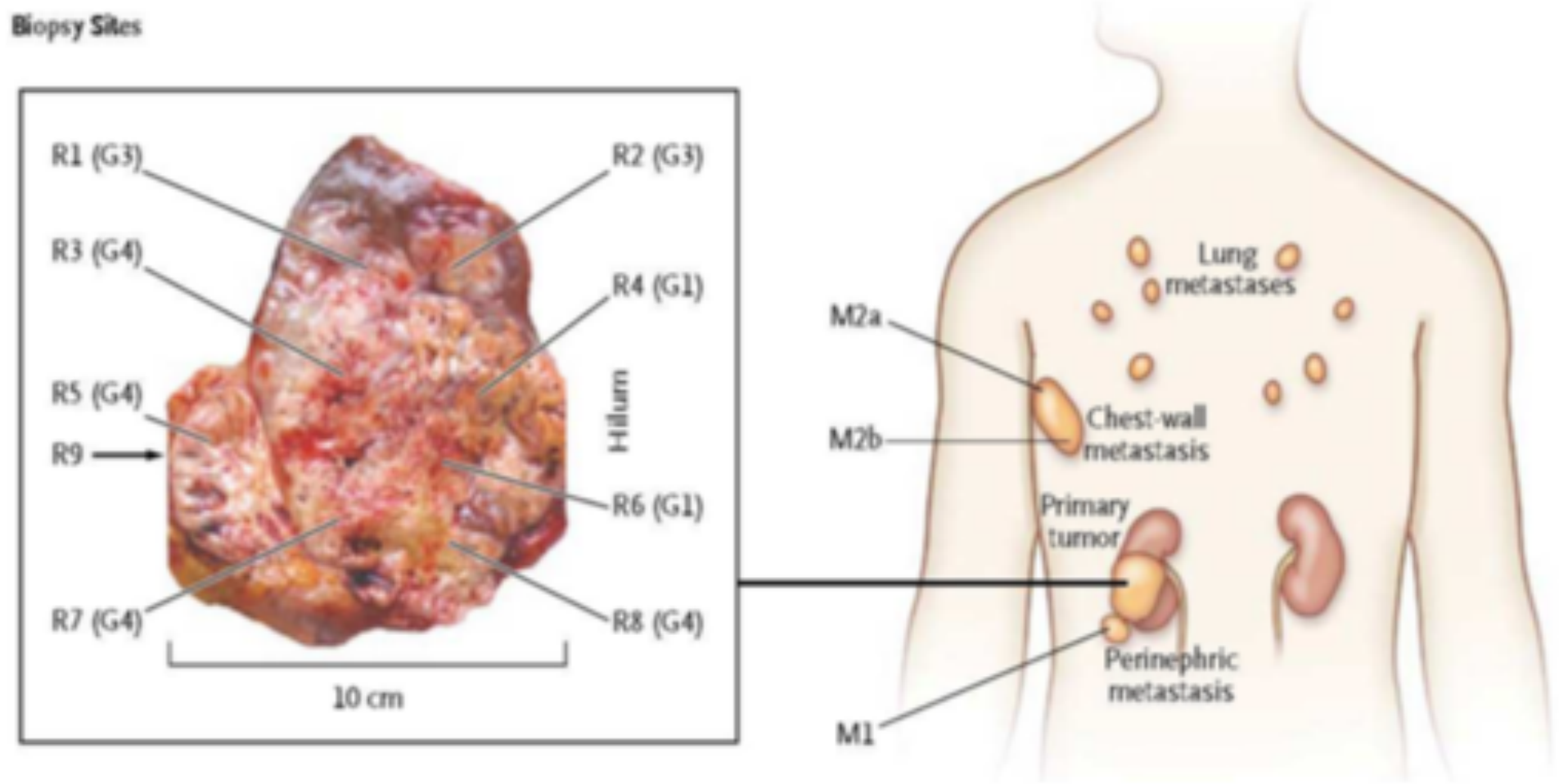
PRIMARY TUMORS ARE HETEROGENOUS, HENCE DIFFICULT TO CONSIDER FOR THE ONCOLOGIST ! PEOPLE DO NOT SUCCUMB ANYMORE FROM THE PRIMARY TUMOR RATHER FROM THE MESTASTASES !



The causes and consequences of genetic heterogeneity in cancer evolution.
Rebecca A. Burrell, Nicholas McGranahan, Jiri Bartek & Charles Swanton. *Nature 501, 338–345 (19 September 2013) doi:10.1038/nature12625*

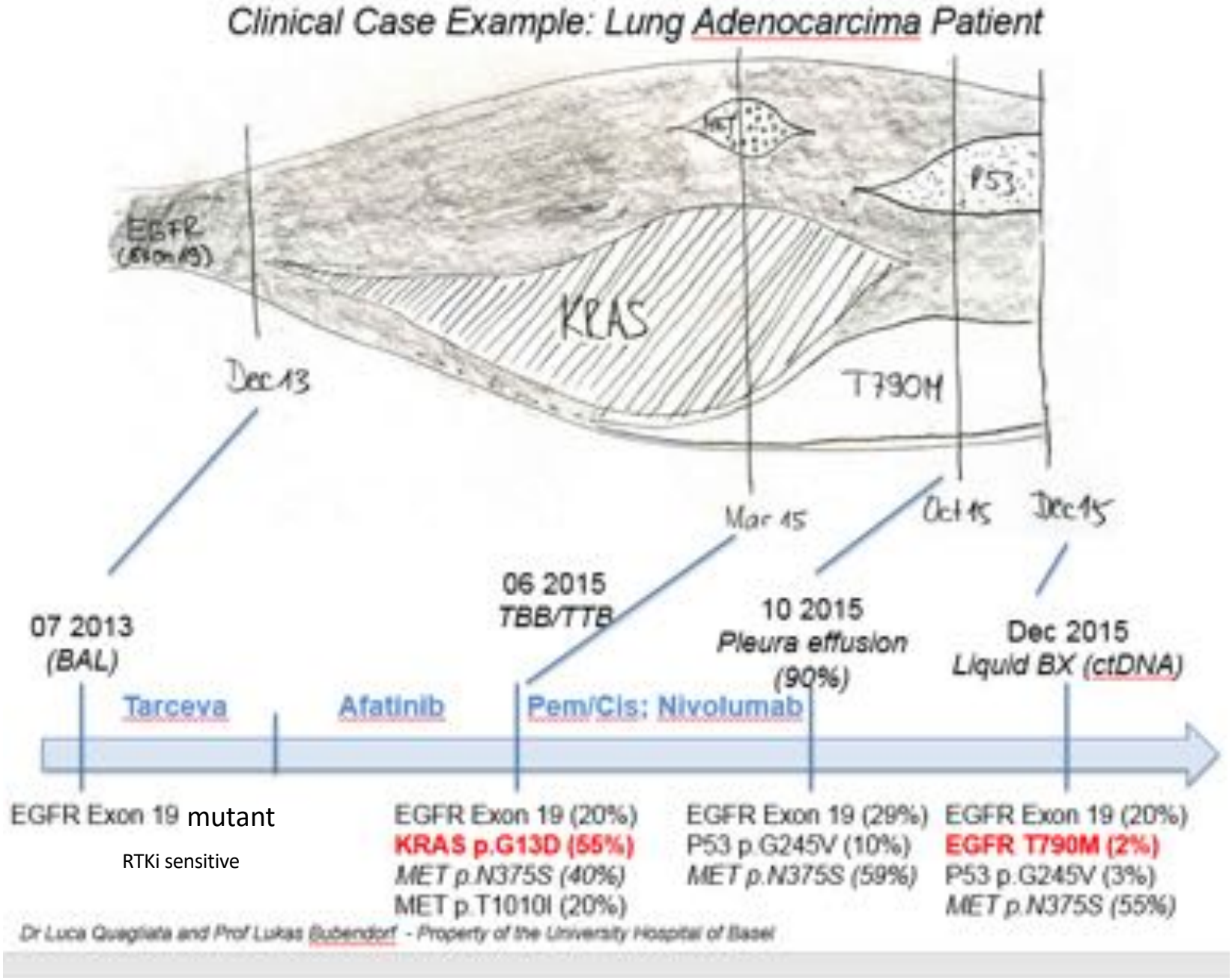
VARIOUS CTCs CLUSTERS MAY ORIGINATE FROM ALL THE DIFFERENT PARTS OF THE PRIMARY TUMOR !!

Intratumor heterogeneity and multiregion
Sequencing branched Evolution



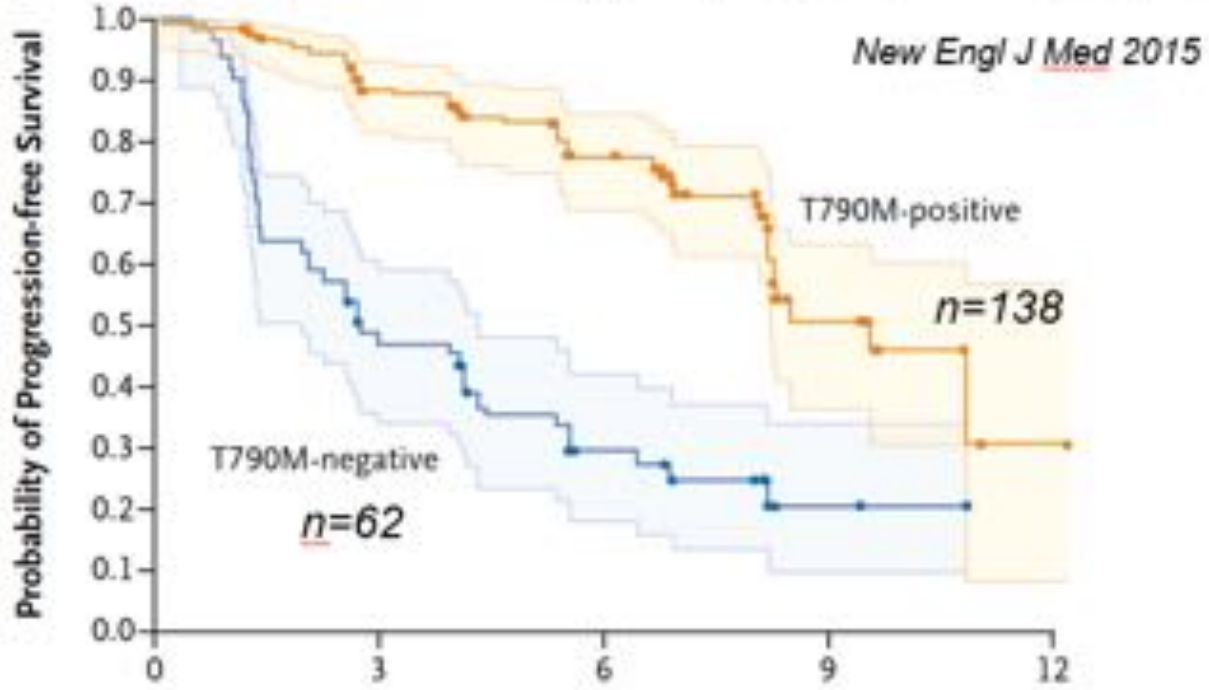
Grelinger M, NEJM 2012

PHC_ tumour heterogeneity



AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

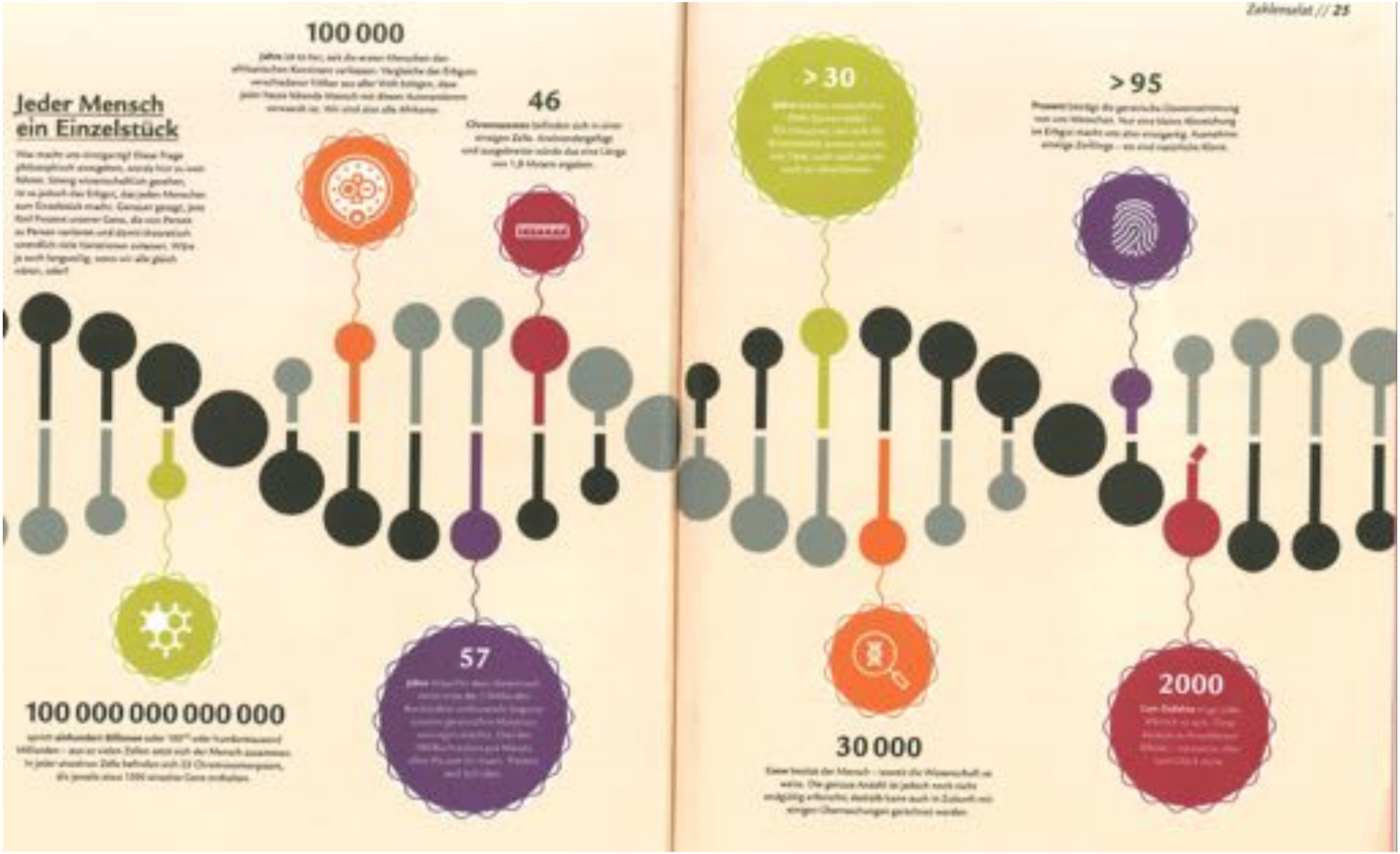
Pasi A. Jänne, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D.,



Osimertinib (3rd generation TKI):
- Partial or full remission in ca. 60% of patients
- Approved for the resistant NSLC (by FDA)

AZD9291 active on EGFR mutants

EACH INDIVIDUAL – EACH PATIENT IS UNIQUE



THANK YOU.....

DO YOU HAVE ANY QUESTIONS ?

Das was wir machen, richtig machen, sonst liegen lassen !

Ce que nous faisons, faisons le bien sans quoi pas la peine !

What we do, do it right, otherwise forget about it !

Roger G.Clerc, your obedient servant