

R E G I S T E R N O W !

1,000,000,000 CHF investment

7,000,874 hours of work

6,587 experiments

423 researchers

1 medicine



THE MAKING OF AN INNOVATIVE MEDICINE

*Introductory workshops on translational biomedical research,
drug discovery and development*

**BIO-698 resumes Thursday September 11. 2025
4:15 PM @ CM013**



Judge Prof Dr med Olaia Naveiras



With Timothee Ferrari MD PhD cand



Sciences de la Vie -SV



With Justine Epiney MD PhD cand



Mehdi AliGadiri MD PhD cand



Prof Roger G. Clerc

The Making Of An Innovative Medicine – class schedule

Thursday's @ 4-6 PM except 04.12/11.12.25 @2-6 PM



- Session 1: Scope of the course _ general organization _ case study**
11.09.25 *Embracing a career at the heart of biomedical research !?*
CM013
- Session 2: Historical perspective: the modern pharmacy**
18.09.25 *Advent of modern medicines - placebo controlled drug development*
CM013
- Session 3: Introduction to translational research: crossing the bridge**
25.09.25 *A chasm has opened wide between biomedical research and patients in need*
CM013
- Sessions 4-5: Therapeutic target identification I & II**
02-09.10.25 *“me too” vs a wealth of innovative targets _ small MW cpds vs biologicals*
CM013
Early front loading of biomarker identification for cohort stratification
- Session 6: Structure based drug design _ medicinal chemistry_low/high throughput screening assays_ multiple parallel optimization_ML-powered screens**
16.10.25 *Setting up screening assays, the robotics, the million cpds libraries*
CM013
- Session 7: Therapeutic modalities biologicals–peptides : today’s - tomorrow’s pharmacy NBEs**
30.10.25 *Challenges (cost of goods - healthcare payers) and opportunities*
CM013

The Making Of An Innovative Medicine - class schedule

Thursday's @ 4-6 PM except 04.12/11.12.25 @2-6 PM



Session 8: **Personalized Healthcare** PHC _ precision medicine

06.11.25 *How PHC started: from a single case to a paradigm change*

CM013

Session 9: ~~Pharmacogenetic polymorphisms, Pharmacogenomics~~

13.11.25 *Interindividual variability toxicity in response to medicines*

CM013

Session 10: **In vivo pharmacology, investigative toxicology** with Nathalie Brandenberg PhD eMBA CEO

20.11.25 *Preclinical research ends up with IDB's, FDA guidelines for FIH*

CM013

Session 11: **Clinical research**_ phase 0, phase I, II, III, IV with Raphael Sommer PhD Bristol Myers Squibb

27.11.25 *The long and complex experimental procedures with human patients*

CM013

Intellectual property_ integrity in research_my genome vs our genomes

Why are patents essential to new medicine/biotech development

Session 12: **Health Hackathon – Hacking medicine I** with T. Ferrari & M. Ali Gadiri MD PhDs confirmed !

04.12.25 *Pitches –building teams – hacking problem - 5Ws – brainstorm*

starts @ 2PM ! CO017

Session 13: **Health Hackathon – Hacking medicine II** with judges Prof Olaia Naveiras - Prof James Habib

11.12.25 *Building up solutions – make it better - final presentations*

starts @ 2PM ! CO017

! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !

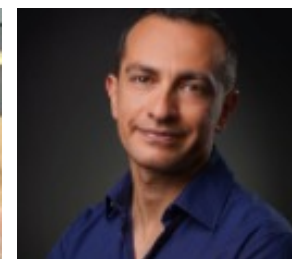
sessions	workshops	speaker/s
S02 (18-09-25)		
historical medicines	penicilin: impact, whose invention ?	
hopping on giant shoulders	prozac at the core of psychiatry	
	vaccine discovery:smallpoxJennerTodaymRNAvaccine	Eugenio
	artemisinin and malaria	
	insulin-Banting Best et al. beagle dog	
	slide51-X-ray image DNA--Rosalind Franklin	
	cyclosporin from soil sample to life saver	
S03 (25-09-25)		
translational research	expanding scope of translational therapies	
from bench to bedside and back	chronotherapy,circadian clock,sex,longevity	Solomon
	CAR-T, TCR-T cell therapies in "cold" tumors	
	Y chrom loss in immune cells drives cancer	
S04 (02-10-25)		
therapeutic target identification	th. target identification using a phenocopy screen	Justine
S05 (09-10-25)		
therapeutic target identification	nocosomial inf/MRSA/phage antibacterials	
	Crispr/Cas9 gene editing huntington disease	
	AI in drug discovery / ML-powered medicine	Lou
	AIDS - Lenacapavir : end of plague ?	
S06 (16-10-25)		
structure based drug design	macrocycles and non druggable targets	Benedikt
	chemoproteomics - NMEs	
	AIDS HIV from deadly virus to chronic disease	
S07 (30-10-25)		
therapeutic modalities - NBEs	rare diseases repurposing medicines	Jana
	biologics on the rise-MABs medicines & more	Eleni
	RNA therapeutics, antisense medicines	
	Wnt pathway - PROTACs vs molecular GLUEs	
S08 (06-11-25)		
PHC personalized healthcare	BRCA1/2 preventive surgery/tumor board	
Human genomics	4P medicine-GWAS-Personalized Health Care	Frederico
	disease enabling biomarkers/micro RNAs	
	AZ-biomarker BD-tau yet still no curative drug	
	centenarian host isoallo-LCA bile acid bacteria	
S09 (12-11-25)		



Workshops The Making Of An Innovative Medicine (today's class)



Prof O Naveiras



Prof J Habib

Session 8 - PHC – advent of **4P** medicine
Preventive, Personalized, Precise, Participative



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 !

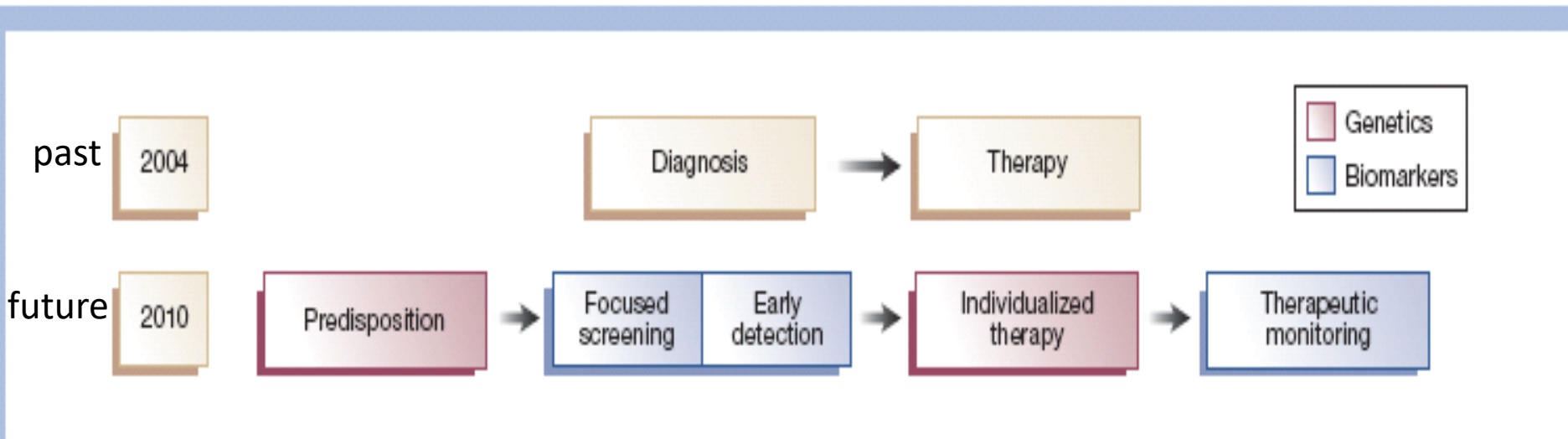
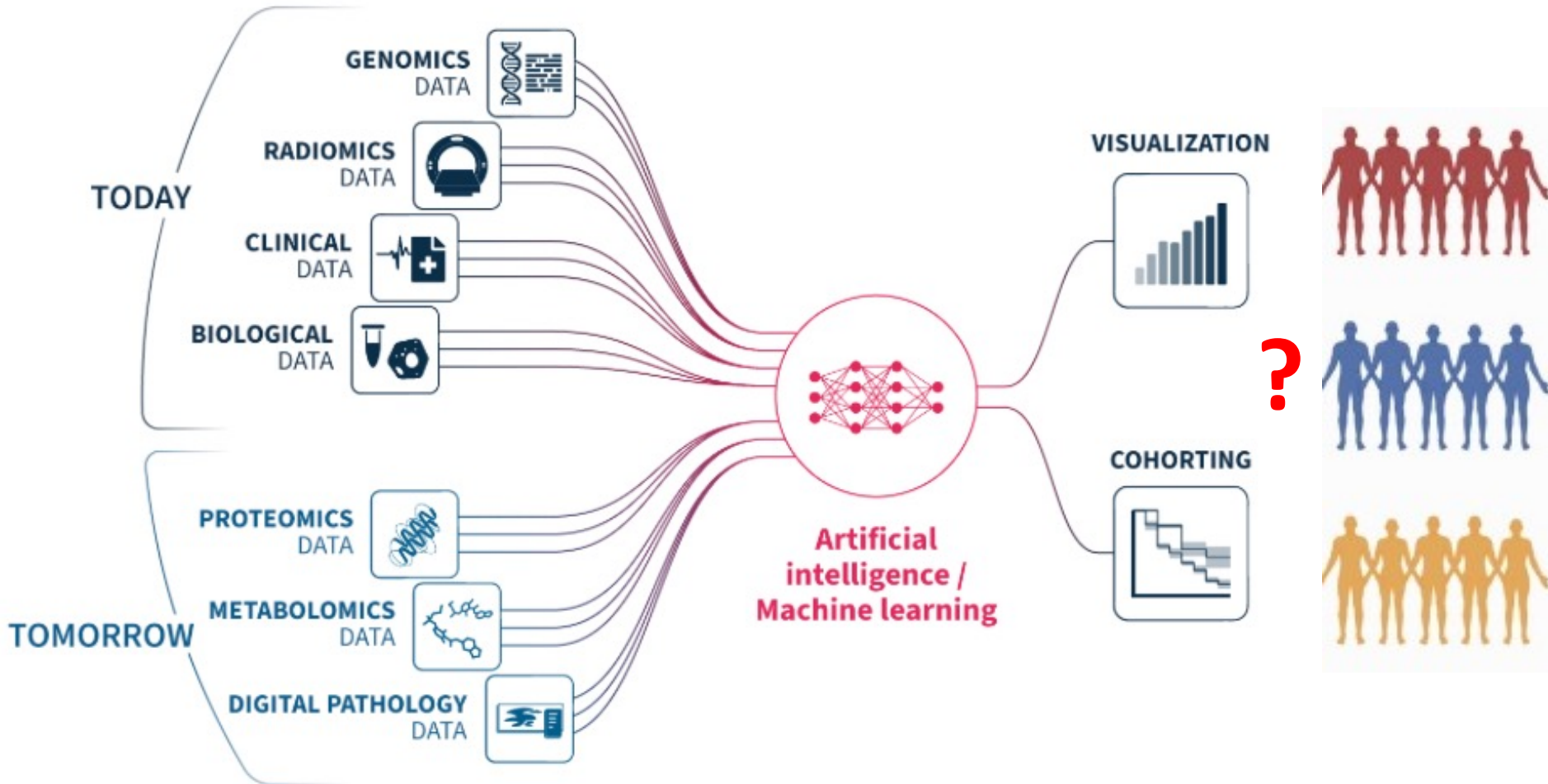


Figure 1 Diagnostic medicine. The role of diagnostics, driven by genetics and the discovery of biomarkers, will grow over the next ten years. Early diagnosis, targeted therapy and disease monitoring will replace the current paradigm of late-stage diagnosis and therapy.

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

Personalized medicine : from a concept the PHC is progressively coming of age



**WHICH MEDICINE TO WHICH COHORT OF PATIENT ?
(the R+D days of « one pill fits all » are over)**

Personalized medicine : non-responders to oncology therapeutics are highly prevalent and very costly



**WHICH MEDICINE TO WHICH COHORT OF PATIENT ?
(the R+D days of « one pill fits all » are over)**

PHC pioneers : the first quantum leap with non hormonal breast cancer



Wednesday, Sep 2, 1998

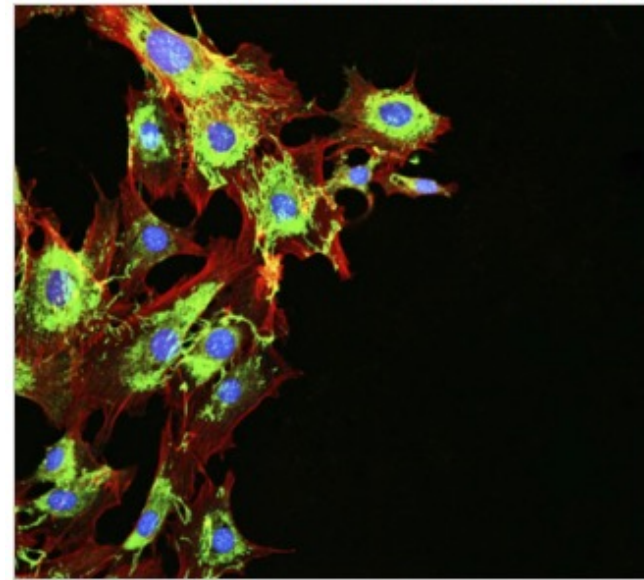
FDA Advisory Committee Recommends Approval of First Monoclonal Antibody for Metastatic Breast Cancer

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

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

Genentech, Inc. (NYSE:G) 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 sizeable fraction of HER2-positive patients. Herceptin lowers the risk of relapse, extends survival and potentiates the efficacy of chemotherapy and immunotherapy.

1998-2023



ÉDITORIAL

La belle histoire de HER2

The great story of HER2

La Lettre du Cancérologue • Vol. XXIV - n° 8 - septembre 2015 | 351

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

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.](#)

HMG2A Is Confirmed To Be Associated with Human Adult Height

Tie-Lin Yang^{1,2}, Yan Guo^{1,2}, Li-Shu Zhang², Qing Tian², Han Yan¹, Yan-Fang Guo¹ and Hong-Wen Deng^{1,2,3*}

¹Key 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

²School of Medicine, University of Missouri – Kansas City, Kansas City, MO 64108, USA

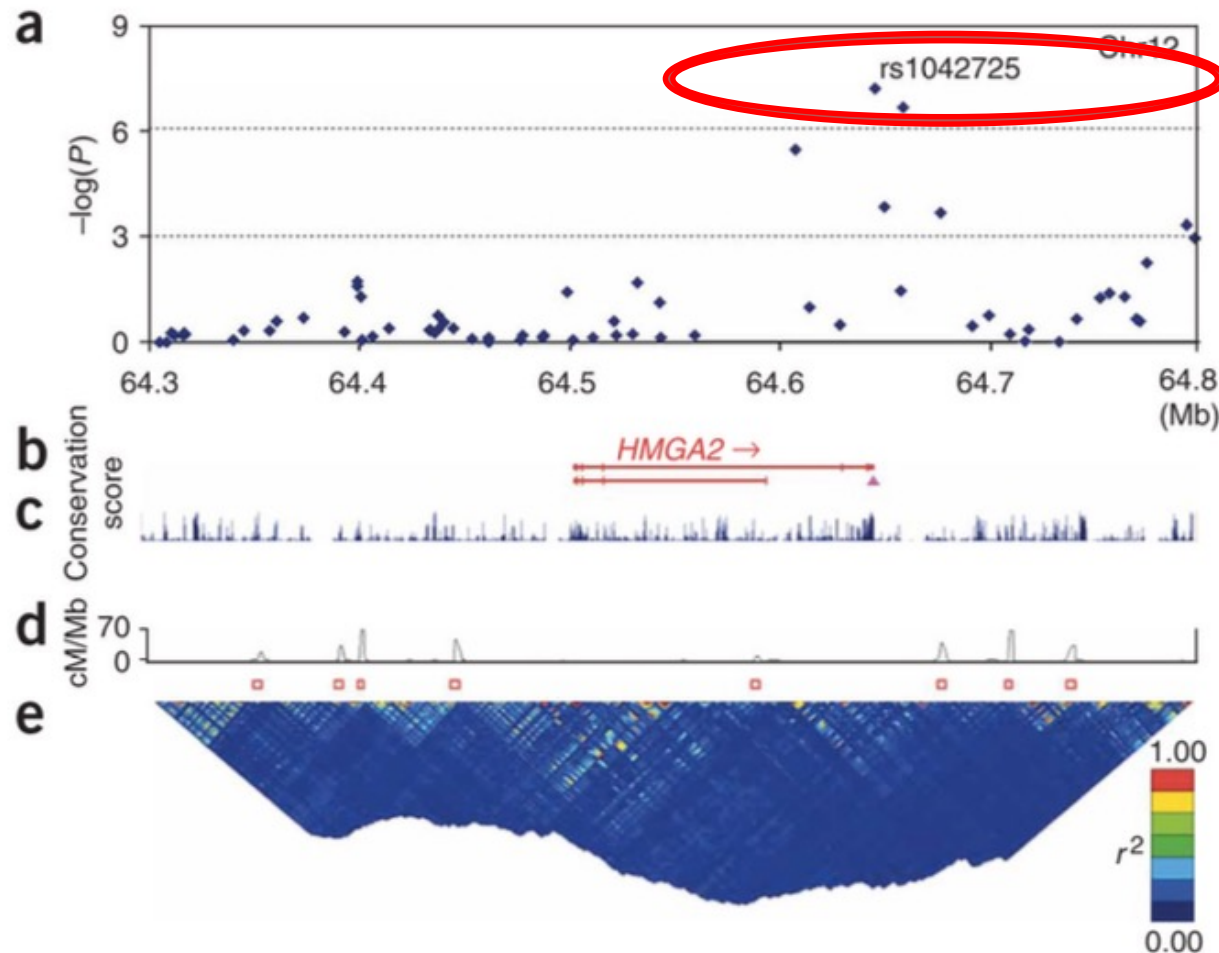
³Center of System Biomedical Sciences, Shanghai University of Science and Technology, Shanghai 200093, P. R. China

Summary

Recent genome-wide association studies have identified a novel polymorphism, rs1042725, in the *HMG2A* gene to



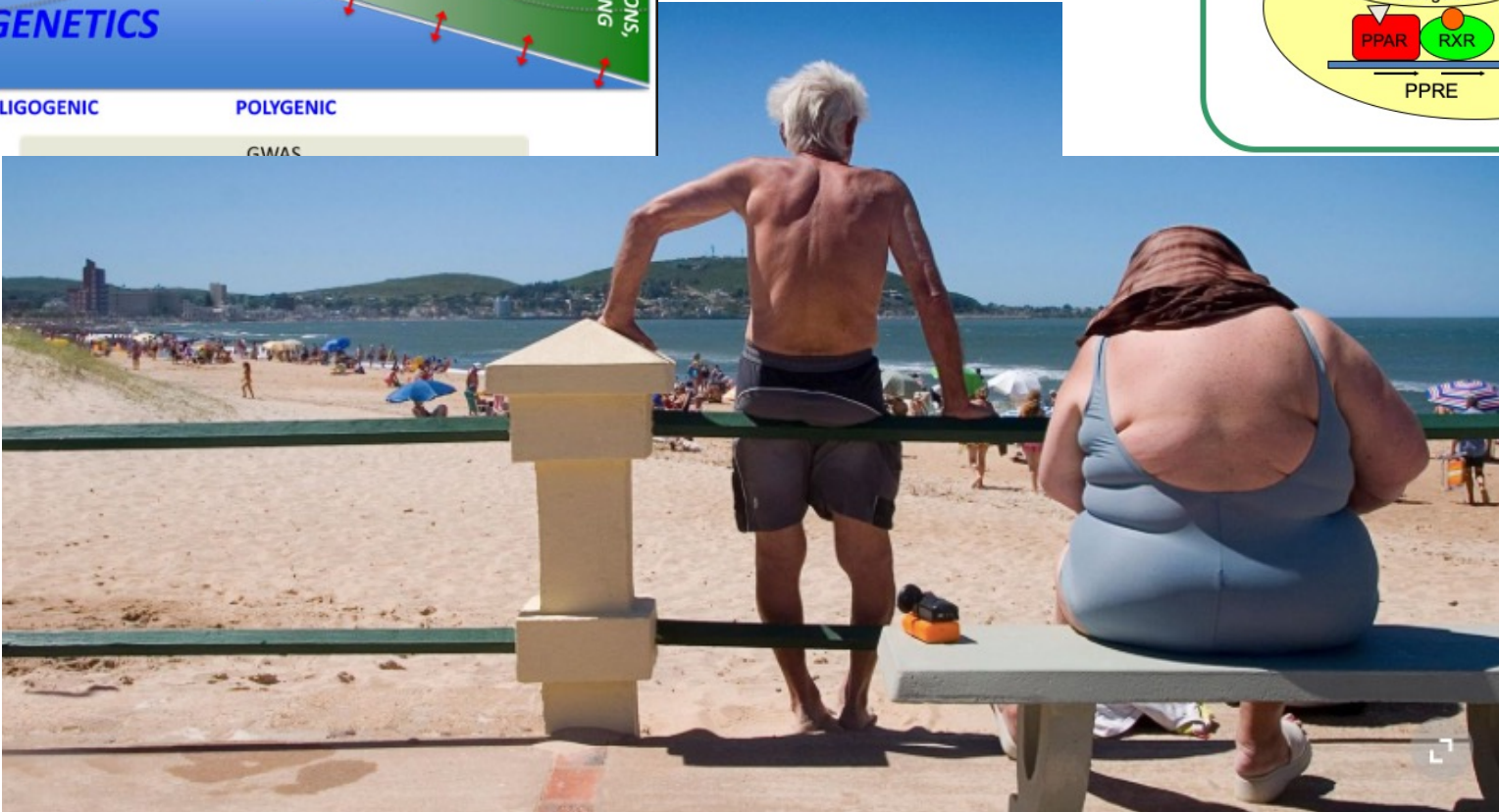
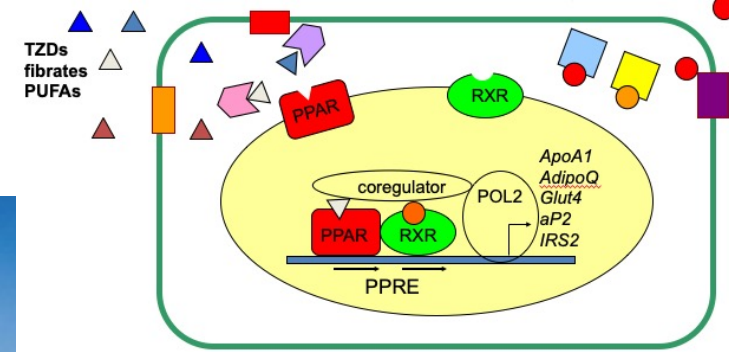
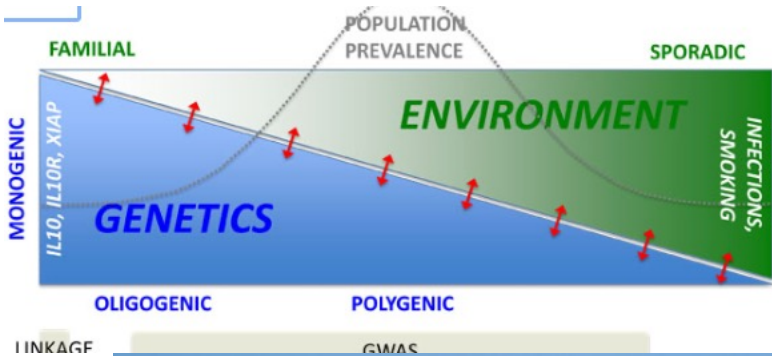
Linkage disequilibrium of the human height HMGA2 locus



Loci are said to be in linkage disequilibrium 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.

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



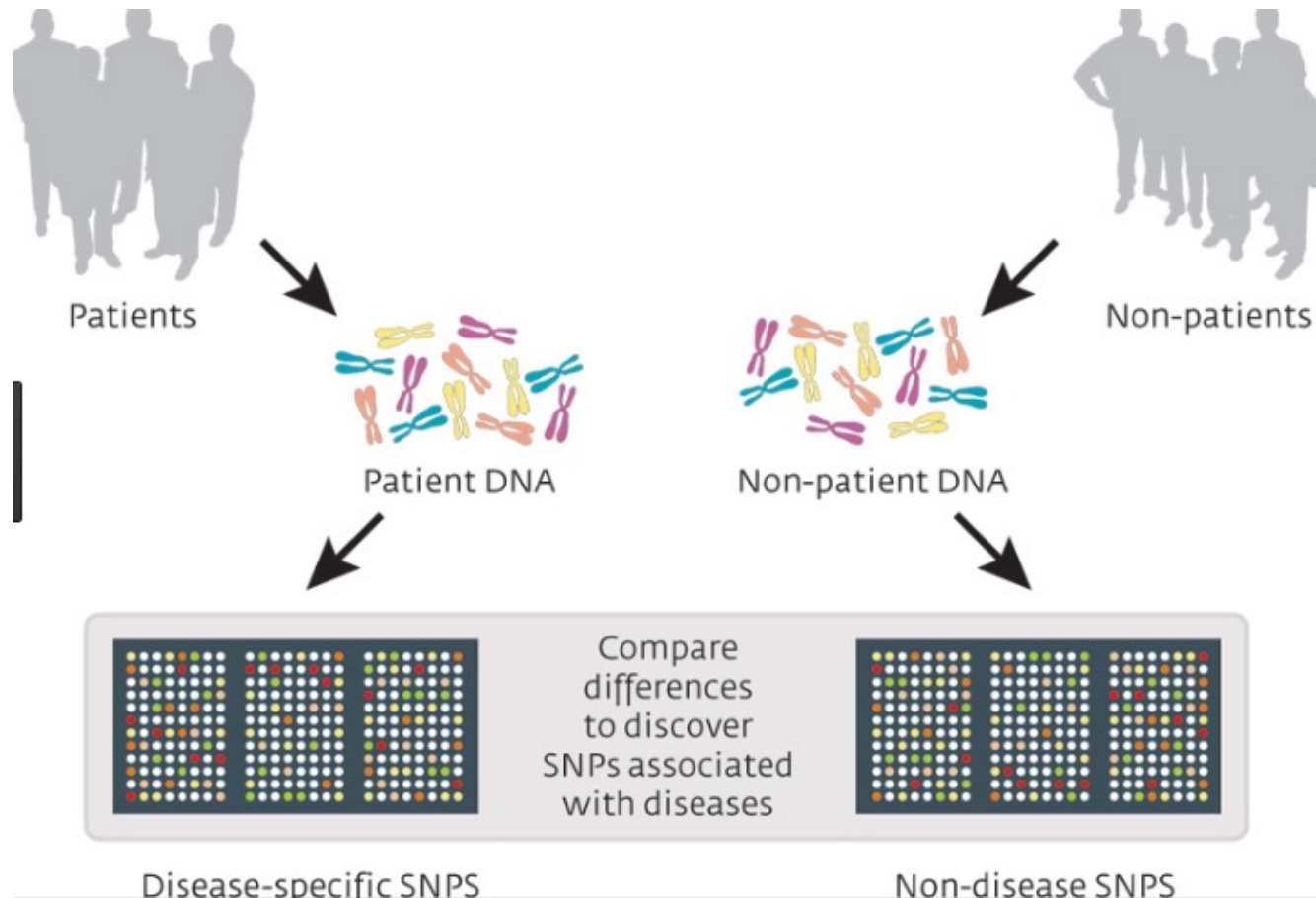
- METABOLIC DISEASES - GENOMES AND ENVIRONMENTAL FACTORS
- THRIFTY GENE HYPOTHESIS-EPIGENETIC IMPACT-PATIENT DERIVED

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



OPPORTUNITIES

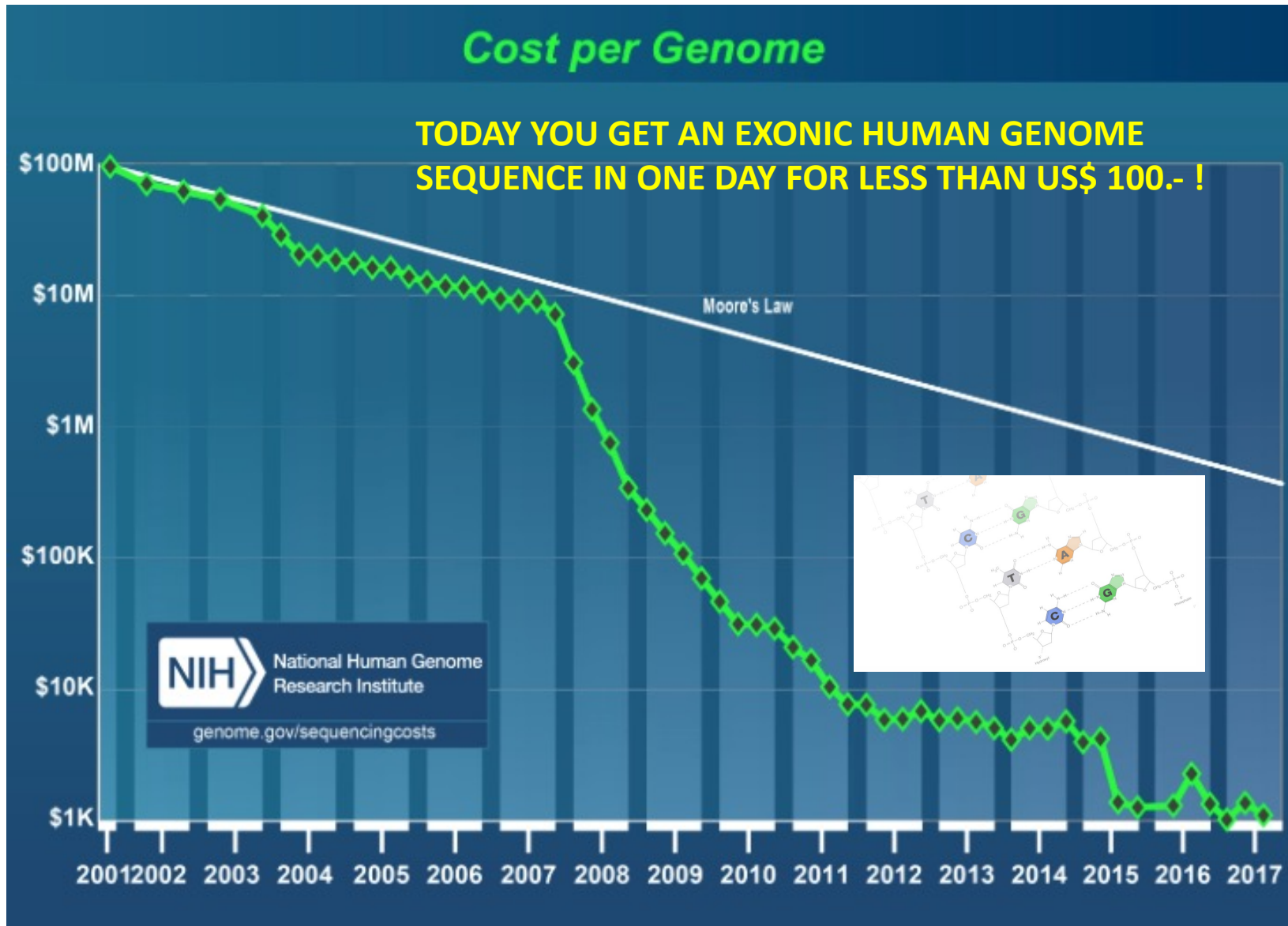
- **Genome Wide Association Studies (GWAS)** looks for *associations* with **Single Nucleotide Polymorphisms (SNPs)** and genetic factors across the whole genome to correlate with particular traits (clinical symptoms, phenotypes) eg. *ApoE4 polymorphism and AZ*



Next Gen DNA sequencing (NGS) : superseded by computer development technologies



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



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



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

Next Gen Sequencing [NGS]

- History of DNA Sequencing

- Maxam-Gilbert
- Sanger
- ABI

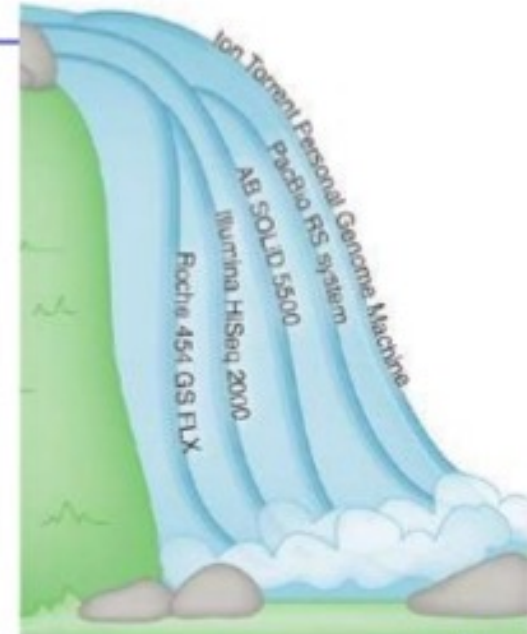
Human Genome: 1990-2000

- NGS Technologies:

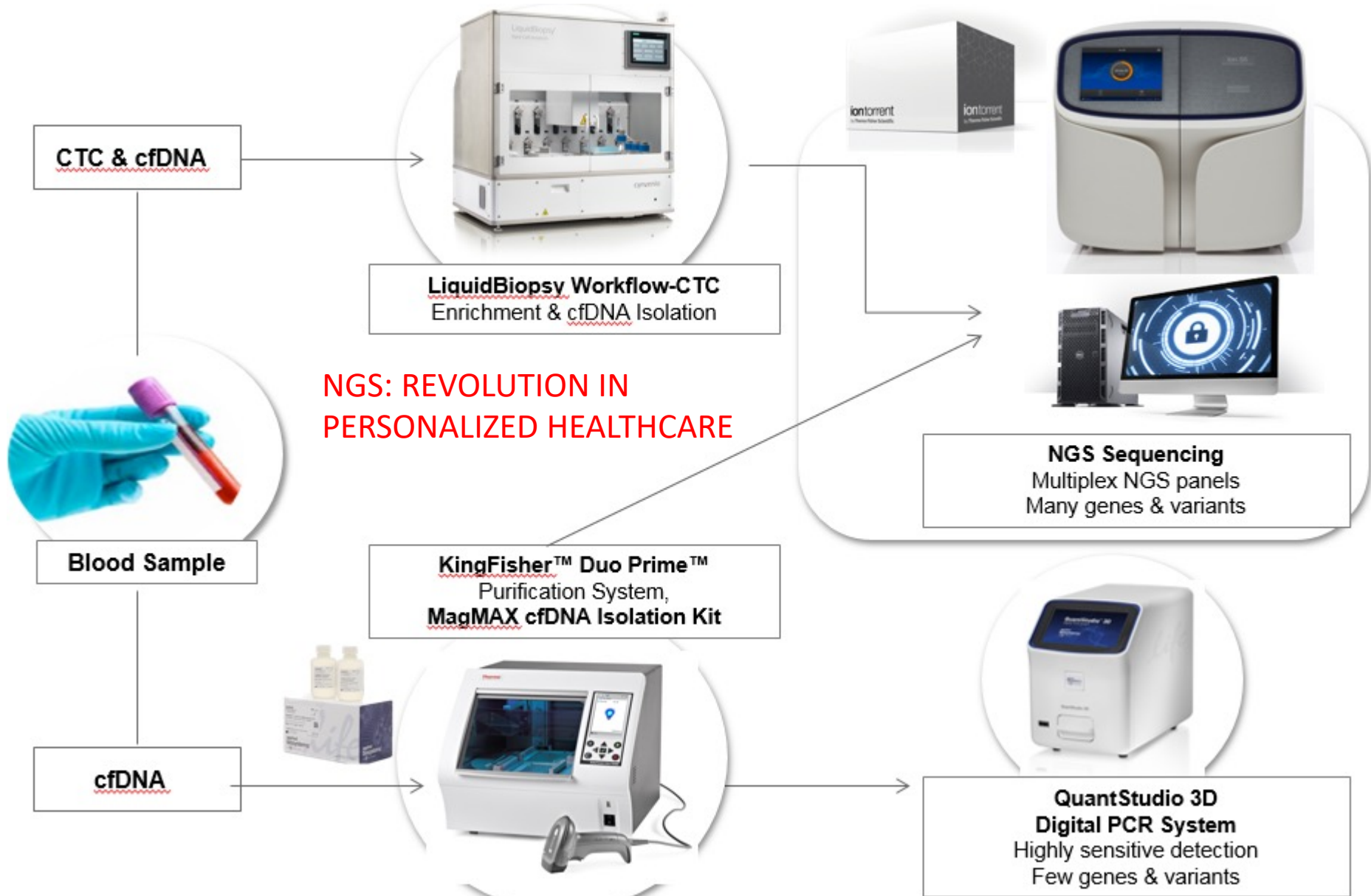
- 454, Illumina, PacBio, ABI, Helicos,
- Ion Torrent, Nanopores

- Applications:

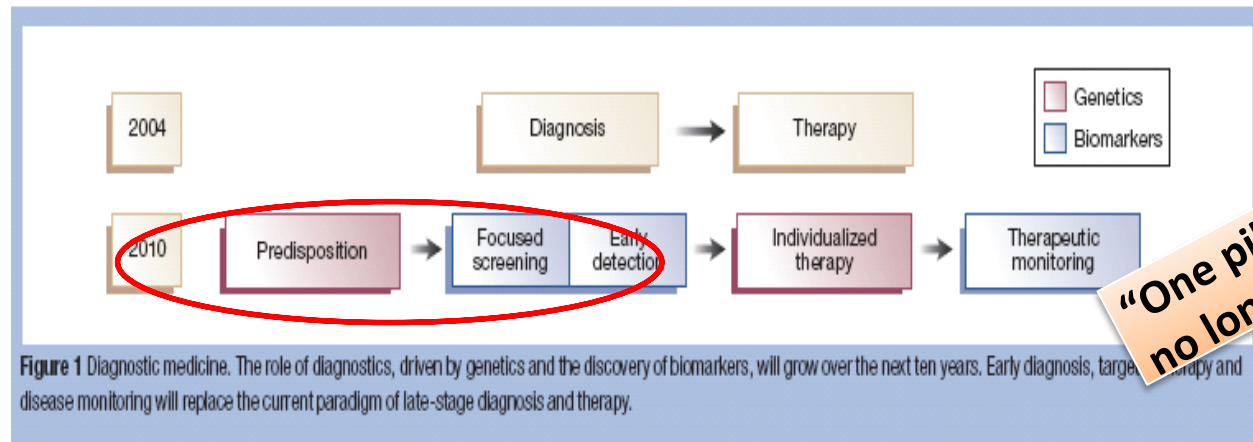
- Genomes, RNASeq, ChIPSeq, CGH, CancerGenome
, Environmental



Liquid biopsies_Next Generation Sequencing NGS



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 medicine 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 ?**

EACH INDIVIDUAL – EACH GROUP OF PATIENT IS UNIQUE



Jeder Mensch ein Einzelstück

Was macht uns einzigartig? Diese Frage philosophisch anzugehen, würde hier zu weit führen. Streng wissenschaftlich gesehen, ist es jedoch das Erbgut, das jeden Menschen zum Einzelstück macht. Genauer gesagt, jene fünf Prozent unserer Gene, die von Person zu Person variieren und damit theoretisch unendlich viele Variationen zulassen. Wäre ja auch langweilig, wenn wir alle gleich wären, oder?

100 000

Jahre ist es her, seit die ersten Menschen den afrikanischen Kontinent verliessen. Vergleiche des Erbguts verschiedener Völker aus aller Welt belegen, dass jeder heute lebende Mensch mit diesen Auswanderern verwandt ist. Wir sind also alle Afrikaner.



46

Chromosomen befinden sich in einer einzigen Zelle. Aneinandergefügt und ausgebreitet würde das eine Länge von 1,8 Metern ergeben.



> 30

Jahre bleiben menschliche DNA-Spuren stabil. Ein Umstand, den sich die Kriminalistik zunutze macht, um Täter auch nach Jahren noch zu identifizieren.

> 95

Prozent beträgt die genetische Übereinstimmung von uns Menschen. Nur eine kleine Abweichung im Erbgut macht uns also einzigartig. Ausnahme: eineige Zwillinge – sie sind natürliche Klone.



57

Jahre bräuchte man theoretisch, wenn man die 3 Milliarden Buchstaben umfassende Sequenz unseres genetischen Materials vorzutragen wünschte. Dies bei 100 Buchstaben pro Minute ohne Pausen für Essen, Trinken und Schlafen.



30 000

Gene besitzt der Mensch – soweit die Wissenschaft es weiss. Die genaue Anzahl ist jedoch noch nicht endgültig erforscht; deshalb kann auch in Zukunft mit einigen Überraschungen gerechnet werden.

2000

Gen-Defekte trägt jeder Mensch in sich. Diese können zu Krankheiten führen – müssen es aber zum Glück nicht.

100 000 000 000 000

spricht einhundert Billionen oder 100^{12} oder hunderttausend Milliarden – aus so vielen Zellen setzt sich der Mensch zusammen. In jeder einzelnen Zelle befinden sich 23 Chromosomenpaare, die jeweils etwa 1300 einzelne Gene enthalten.



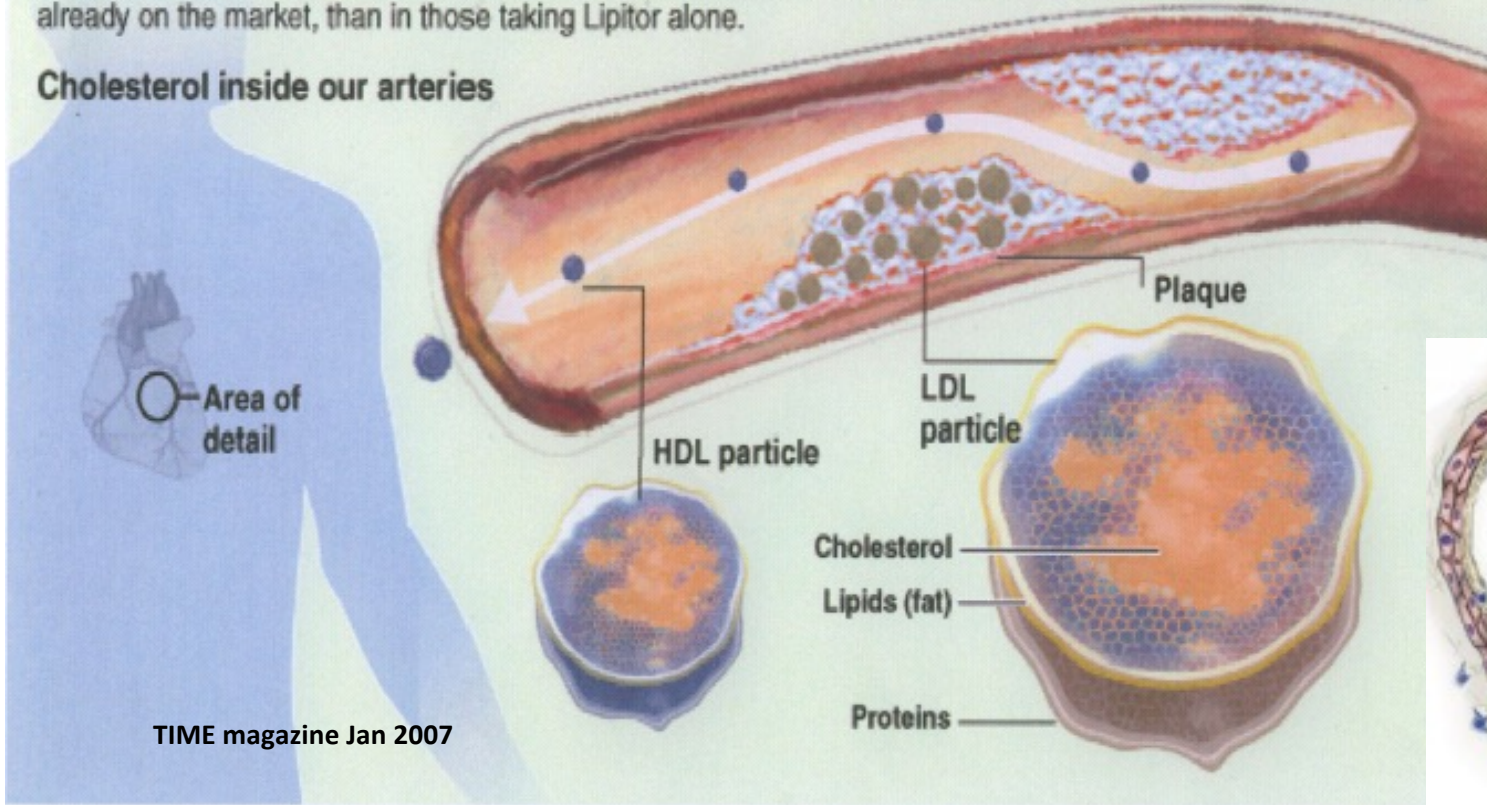


There are still too many undiagnosed causes of early mortality
eg. atheroma plaque ruptures with NO predictive disease enabling biomarker

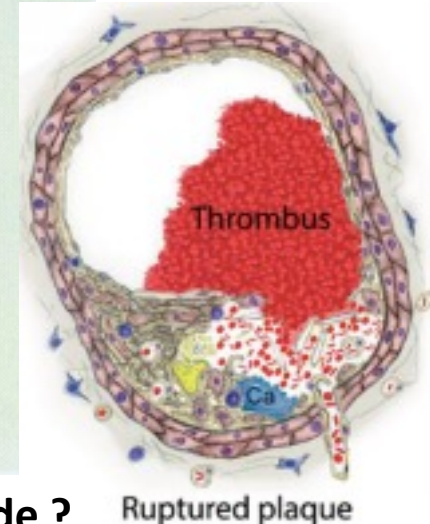
Higher Death Rate in Study Lead Pfizer to Halt Experimental Drug Development

Pfizer's experimental drug, torcetrapib, increases so-called "good" cholesterol, or HDL, as much as 50 percent. The company stopped developing the drug after a study involving 15,000 patients was halted when 60 percent more deaths were reported among those taking torcetrapib in combination with Lipitor, a Pfizer cholesterol drug already on the market, than in those taking Lipitor alone.

Cholesterol inside our arteries



TIME magazine Jan 2007



Ruptured plaque

The days of evidence based medicine are over ?? Do we want AI at bedside ?



The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Limits to Personalized Cancer Medicine

Ian F. Tannock, M.D., Ph.D. and John A. Hickman, D.Sc.

Rapid advances in the molecular biology of tumors, including the identification of multiple driver mutations, have been described. There should also be a clear message to patients that personalized cancer medicine has not led to gains in survival or its quality and is an appropriate strategy only within well-designed clinical trials.

RESEARCH PROGRAMS

There is a strong focus on personalized medicine by large cancer centers and those who fund research. In his State of the Union address, President Barack Obama announced that he had allocated \$215 million in the 2016 U.S. budget



The NEW ENGLAND JOURNAL of MEDICINE

RESPONSE

In our article, we were careful to point out that groups of patients defined according to biomarkers such as women with HER2-expressing breast cancers or people with BRAF V600E mutations in melanoma or with BCR-ABL in chronic myeloid leukemia benefited from appropriately targeted therapy. We agree with Clark and Chabner that this type of precision medicine remains an important aspect of current therapy, although we are less sure that it provides directions for future advances, given the emergence of resistance that limits its effects.² Our critique was directed rather at the expectation that the molecular characterization of individual tumors by genetic sequencing or other means would allow the selection of effective targeted therapies that would have a profound effect on outcome.

Ian F. Tannock, M.D., Ph.D.

Princess Margaret Cancer Centre, Toronto, ON, Canada

Early front loading biomarkers for preventive medicine and cohort stratification in clinical research : implementing 4P medicine

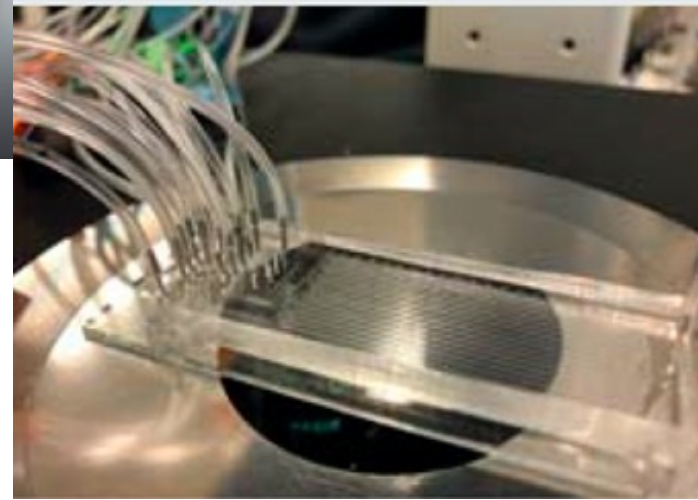


Diabète & Nutrition www.diabetnutrition.ch	HbA1c %	Glycémie mmol/L
😊	4,4	4,4
	4,7	4,9
	5,0	5,4
	5,3	5,8
	5,6	6,3
	5,9	6,8
	6,0	7,0
	6,2	7,3
	6,5	7,8
😐	7,0	8,6
	7,2	8,9
	7,5	9,4
😞	7,7	9,7
	8,0	10,2
	8,3	10,6
	8,6	11,1
	9,0	11,8
	9,2	12,1
	9,8	13,0
	10,0	13,4
	10,4	14,0
	11,0	14,9
12,0	16,5	

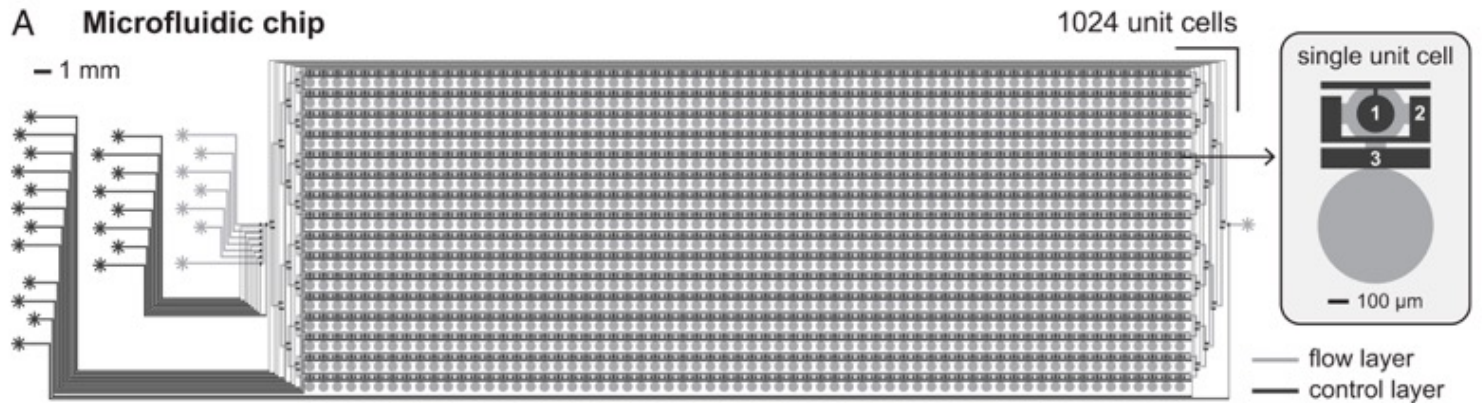
Glycosylated hemoglobin HbA1c -microfluidic guided nano-immunoassay



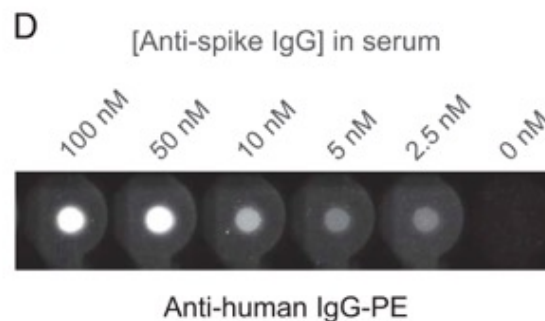
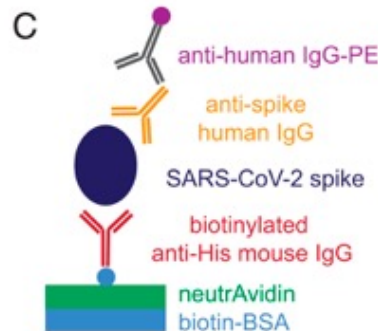
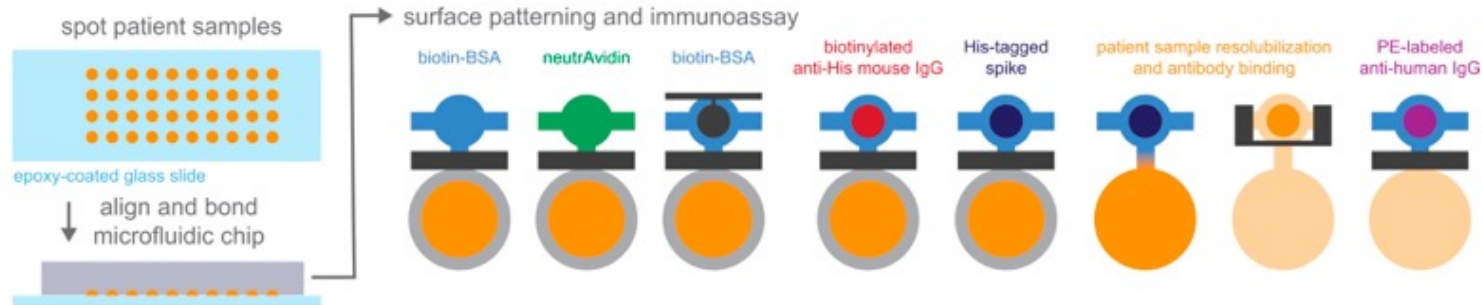
Greg Michelin MD PhD EPFL CEO Naialabs with Hon Ming Yip PhD and Evan Olson PhD



Biomarker discovery by Nialabs in preventive medicine eg SarsCoV2 screens in community/herd immunity



B Experimental overview



Lancet Infect Dis. 2022 Jun; 22(6): 767–768.

Published online 2022 Apr 14. doi: 10.1016/S1473-3099(22)00267-5

PMCID: PMC9009838

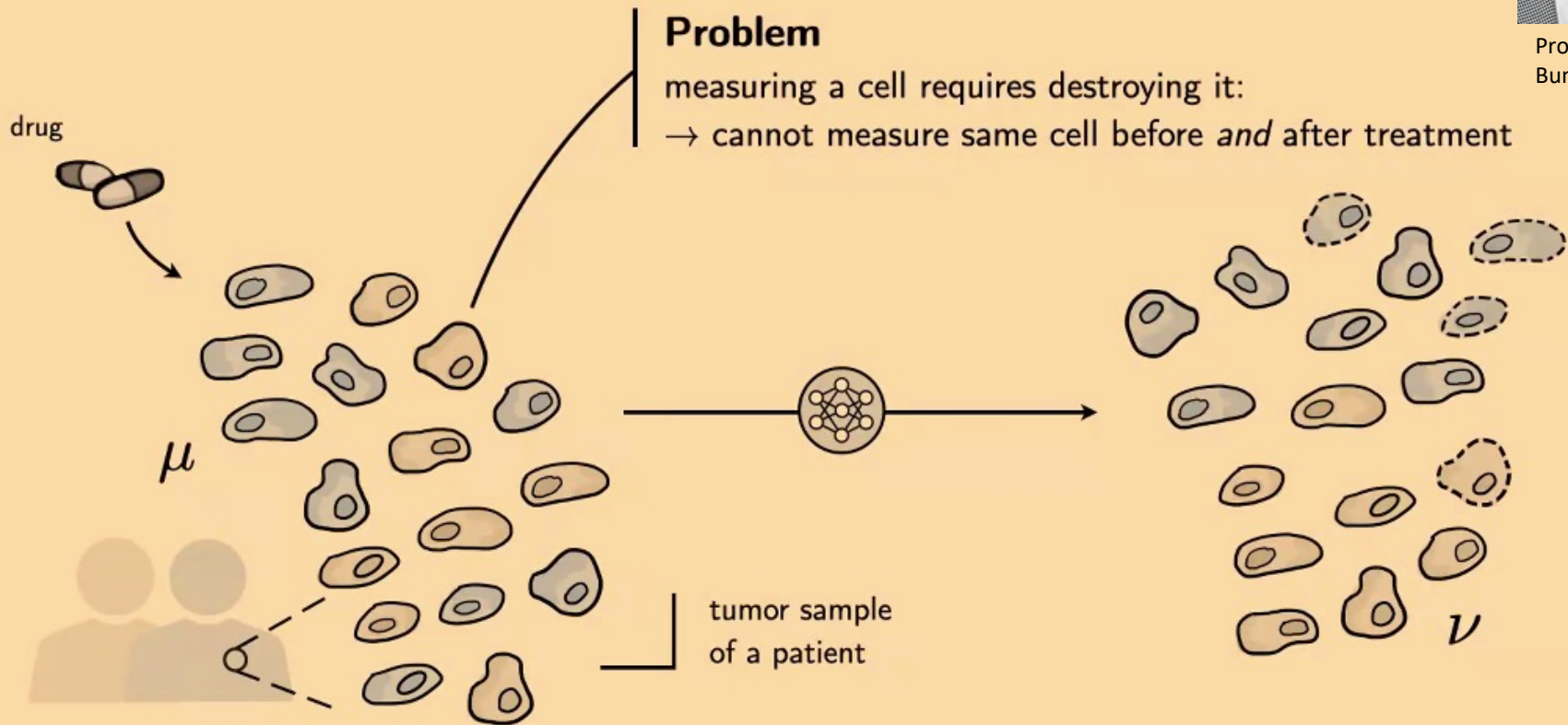
PMID: 35429994

Elsa Lorthe,^a Mathilde Bellon,^{f,i} Julie Berthelot,^a Grégoire Michielin,^j
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Idris Guessous,^{d,h} Sebastian J Maerkl,^j Isabella Eckerle,^{b,e,f,i} Silvia
Stringhini,^{a,h,l} and SEROCov-Schools Study Group, on behalf of the

Predicting treatment responses using ML-powered generative algorithms



Prof Charlotte
Bunne

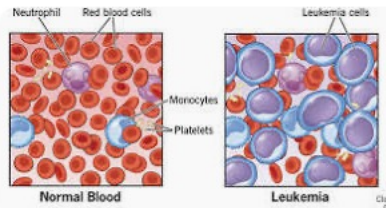




Leukemia diagnosis using ML-powered generative algorithms



Prof Olaia Naveiras



AI revolution : integrative artificial intelligence outperforming standard histopathology !?

MODERN PATHOLOGY



Journal homepage: <https://modernpathology.org/>

Sarkis et al 2023.Modern Pathology 36: issue 4 April 2023

Research Article

MarrowQuant 2.0: A Digital Pathology Workflow Assisting Bone Marrow Evaluation in Experimental and Clinical Hematology

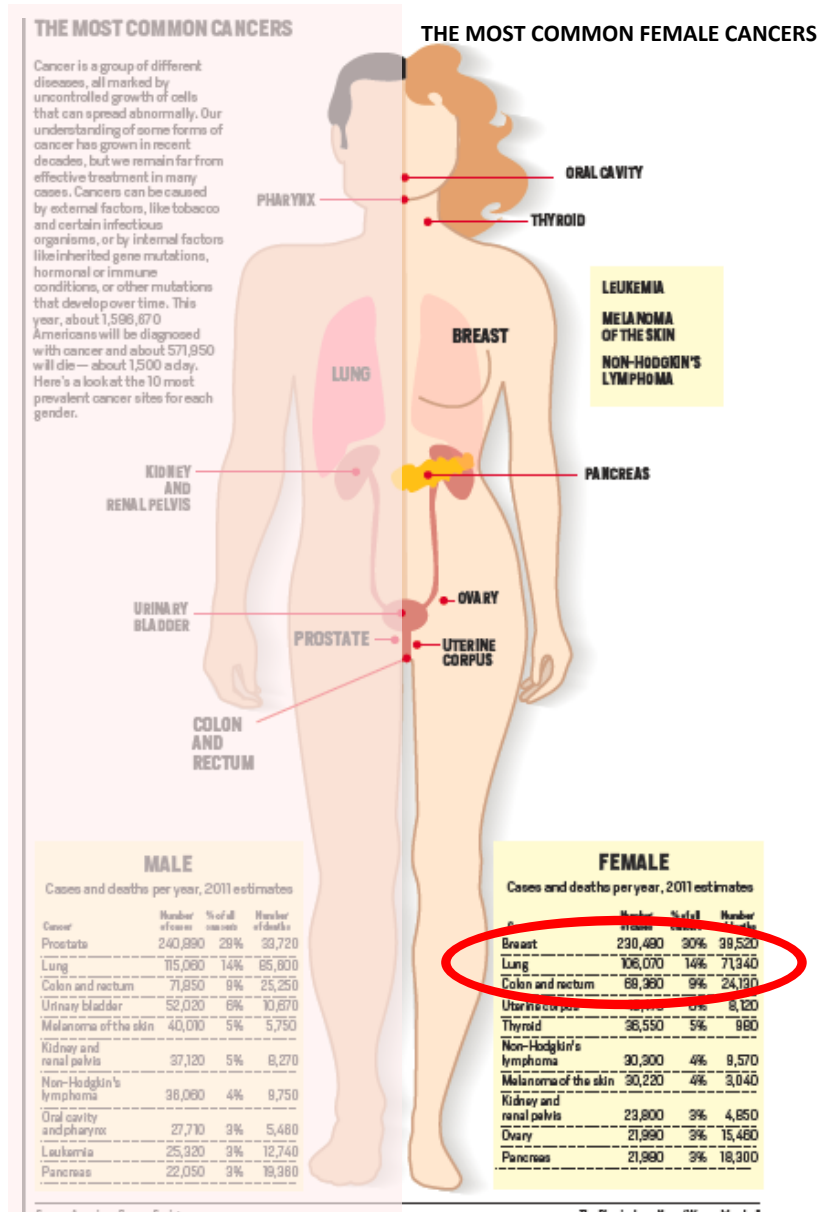
Rita Sarkis^{a,b,c}, Olivier Burri^d, Claire Royer-Chardon^e, Frédérica Schyrr^a, Sophie Blum^a, Mariangela Costanza^f, Stephane Cherix^g, Nathalie Piazzon^e, Carmen Barcena^{e,h}, Bettina Bisig^e, Valentina Nardiⁱ, Rossella Sarro^{e,j}, Giovanna Ambrosini^k, Martin Weigert^l, Olivier Spertini^f, Sabine Blum^f, Bart Deplancke^m, Arne Seitz^d, Laurence de Leval^e, Olaia Naveiras^{a,f,*}

^a Laboratory of Regenerative Hematopoiesis, Institute of Bioengineering & ISREC, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland; ^b Department of Biomedical Sciences, University of Lausanne (UNIL), Lausanne, Switzerland; ^c Laboratory of Systems Biology and Genetics, Institute of Bioengineering, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland; ^d BioImaging and Optics Core Facility, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; ^e Institute of Pathology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital and Lausanne University, Lausanne, Switzerland; ^f Hematology Service, Departments of Oncology and Laboratory Medicine, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland; ^g Department of Orthopaedics and Traumatology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; ^h Department of Pathology, Hospital 12 de Octubre, Madrid, Spain; ⁱ Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts; ^j Institute of Pathology, Ente Ospedaliero Cantonale (EOC), Locarno, Switzerland; ^k Bioinformatics Competence Center (BICC), UNIL/EPFL Lausanne, Switzerland; ^l Institute of Bioengineering, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland; ^m Laboratory of Systems Biology and Genetics, Institute of Bioengineering, School of Life Sciences, Ecole Polytechnique Fédérale de

Disease enabling biomarker_driving innovation in PHC: from an exemplary clinical practice of PHC



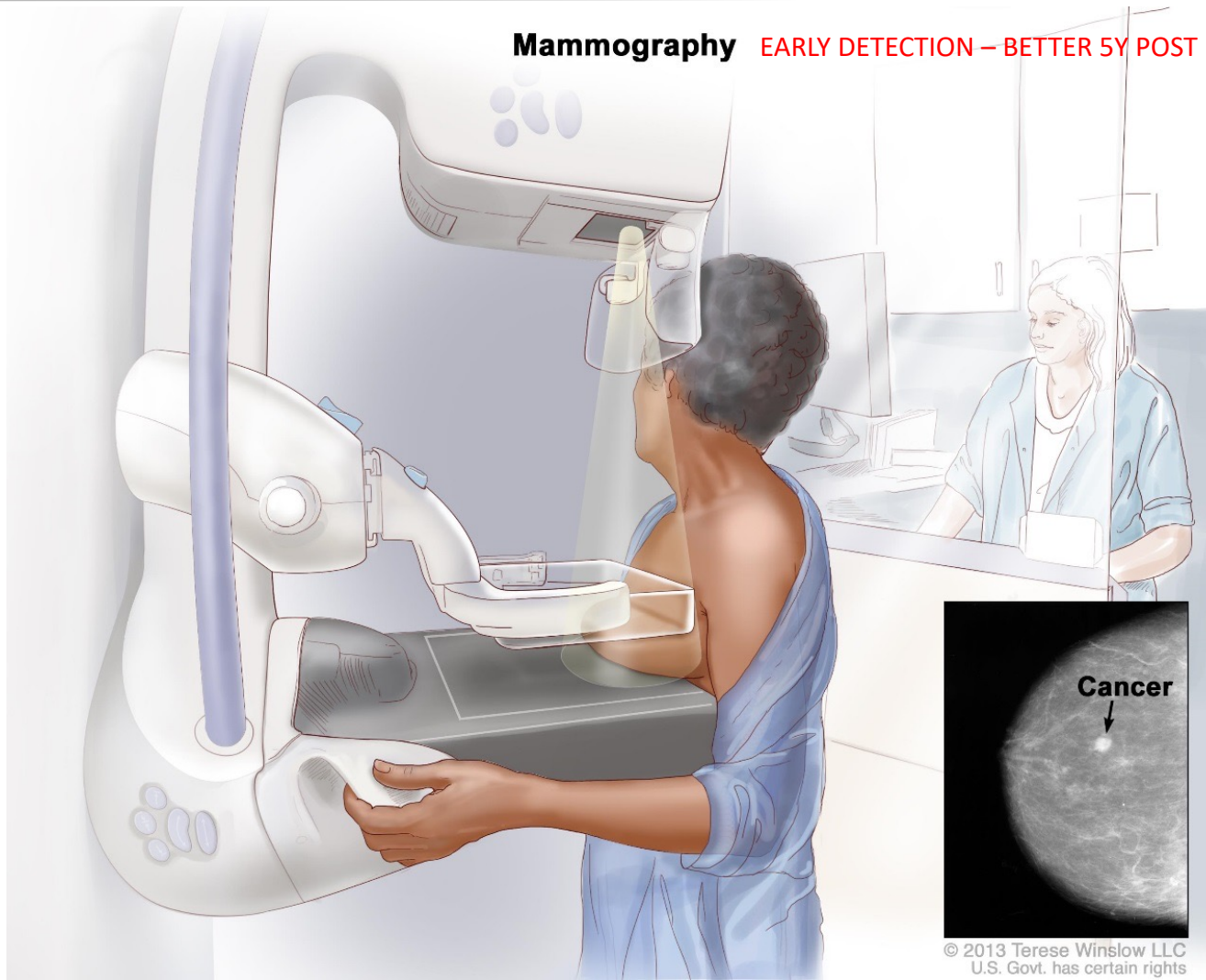
October :
breast cancer
awareness
month !



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

CANCER DIAGNOSTIC
REMAINS A MAJOR
CHALLENGE !

The first PHC quantum leap with breast cancer

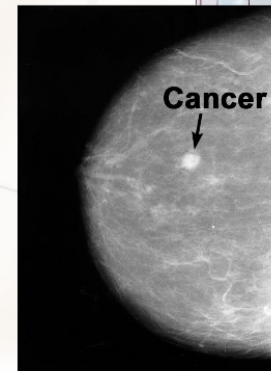


Mammography EARLY DETECTION – BETTER 5Y POST DIAGNOSIS SURVIVAL

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



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

Disease enabling biomarker_breast cancer prevention - exemplary clinical practice of PHC



Le cancer du sein en chiffres

Durant le mois d'octobre, l'accent est mis sur la prévention de ce cancer typiquement féminin. En Suisse, douze femmes sur cent développent une tumeur dans la poitrine au cours de leur vie. Heureusement, une détection précoce leur sauve la vie dans la majorité des cas.

Texte: Martina Frei

6239

femmes développent en moyenne un cancer du sein chaque année en Suisse. Leur âge moyen est de 64 ans.

80%

soit 4 femmes sur 5 avec un cancer du sein conservent leur poitrine.

En Suisse, sur 100 femmes, 12 développent un cancer du sein au cours de leur vie. L'âge joue un rôle: le risque augmente à partir de 45 ans.

Et entre leur 50^e et leur 60^e anniversaire, 25 femmes sur 1000 en sont atteintes. Chez les 60-70 ans, ce chiffre grimpe même à 36 sur 1000 et chez les 70-80 ans, il est encore de 34.

33%

Une bonne hygiène de vie permet d'éviter environ un cancer du sein sur trois après la ménopause. Les facteurs importants sont les suivants:

- l'exercice physique
- une alimentation équilibrée
- un poids corporel sain
- pas de fumée
- une consommation d'alcool limitée
- si possible, pas de traitement hormonal de substitution.

2

Deux gènes appelés BRCA1 ou BRCA2 peuvent être responsables des cancers du sein. 5 à 10 cancers du sein sur 100 sont héréditaires.

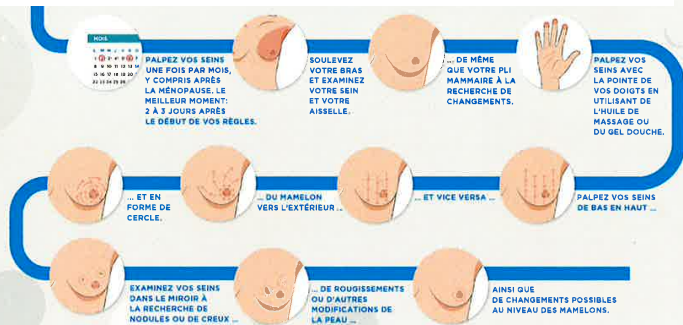
18%

de tous les décès par cancer chez les femmes en Suisse sont dus au cancer du sein. Le cancer du sein est donc tout aussi dangereux que le cancer du poumon, le cancer du côlon arrivant en troisième position.

1369

femmes en Suisse meurent en moyenne chaque année d'un cancer du sein. Leur âge moyen de décès est de 75 ans.

cancer prevention – appropriate breast palpation



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

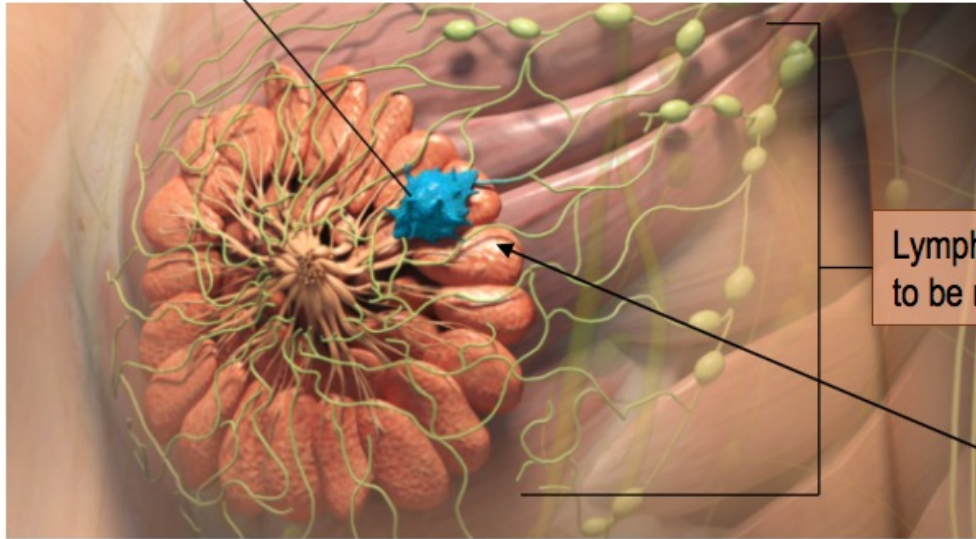
1369 terminal patient

PHC : breast cancer



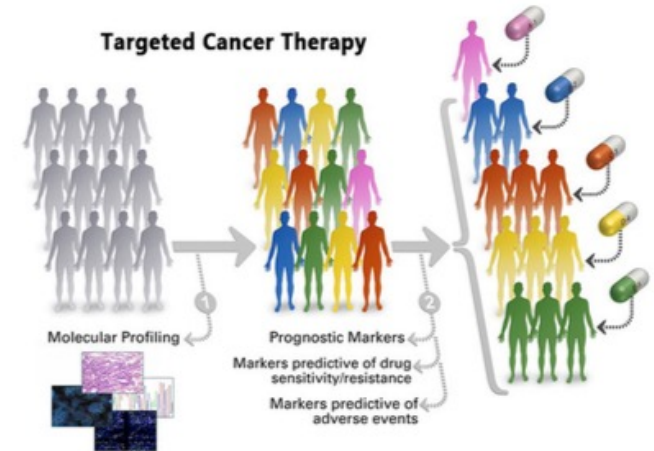
Targeted Cancer Therapy – Breast Cancer

Breast cancer



Lymph nodes to be removed

©harabicherbalmedicine.com



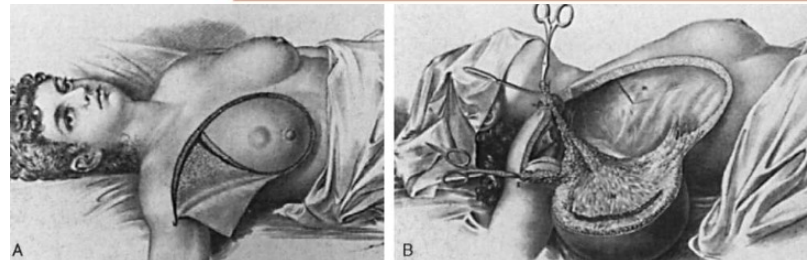
@www.puhuahospital.com

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



Let's beat cancer sooner

William Halsted (1890s): pioneer in radical mastectomy



William S. Halsted (1850-1922): american surgeon and pioneer in radical mastectomy and antiseptis

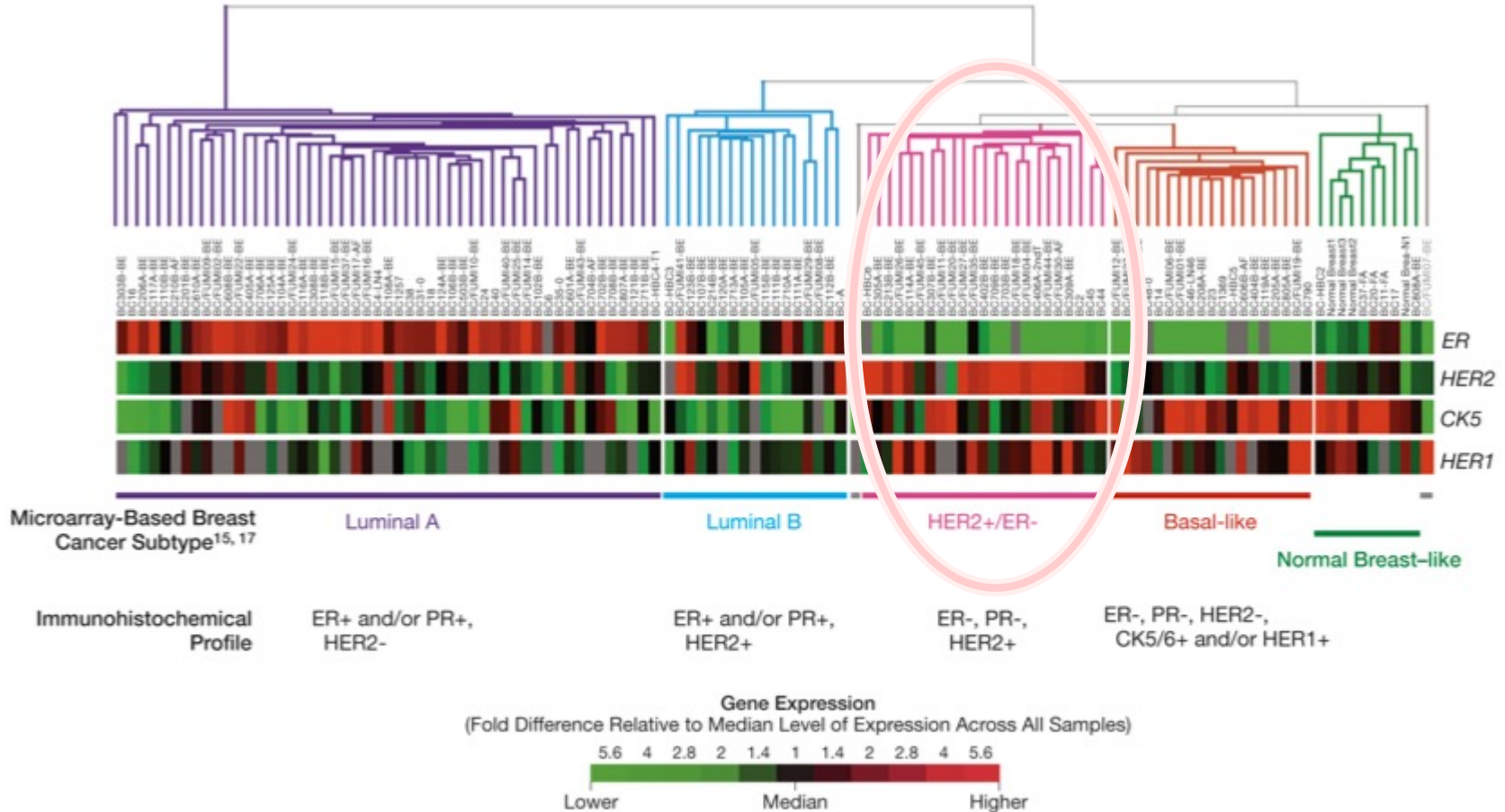


Despite Halsted's lifelong battles with addiction, not only cocaine but later morphine, he revolutionized surgery in America by elevating three concepts: anesthesia to control pain, fine instruments to stop bleeding, and antiseptis to prevent infection. One intern observed that the surgeon's technique was so measured and precise that "there was never a moment of anxiety. I could not believe my eyes. It was like stepping into a new world."

William Halsted in a surgical theater

IMAGE : ALAN MASON CHESNEY MEDICAL ARCHIVES

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



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

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VOLUME 347

DECEMBER 19, 2002

NUMBER 25



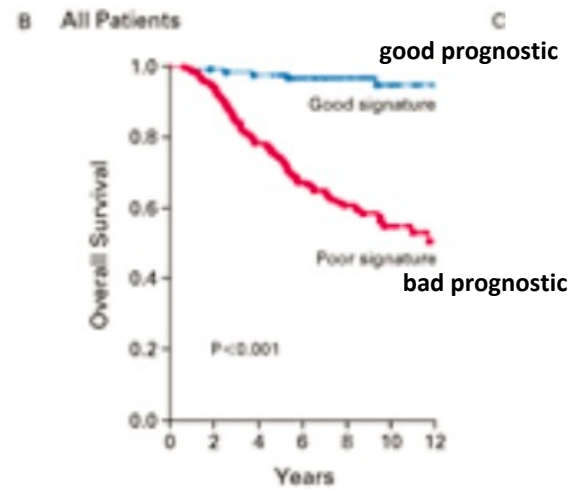
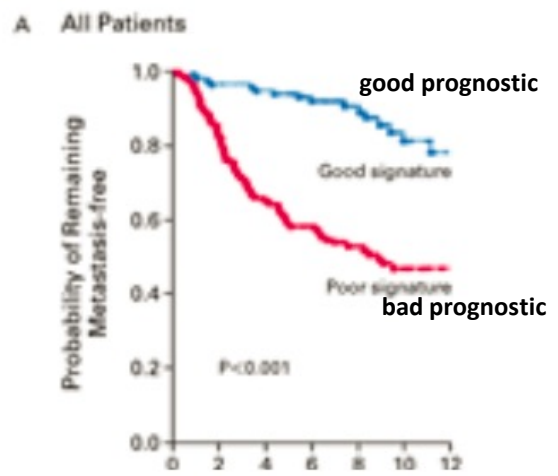
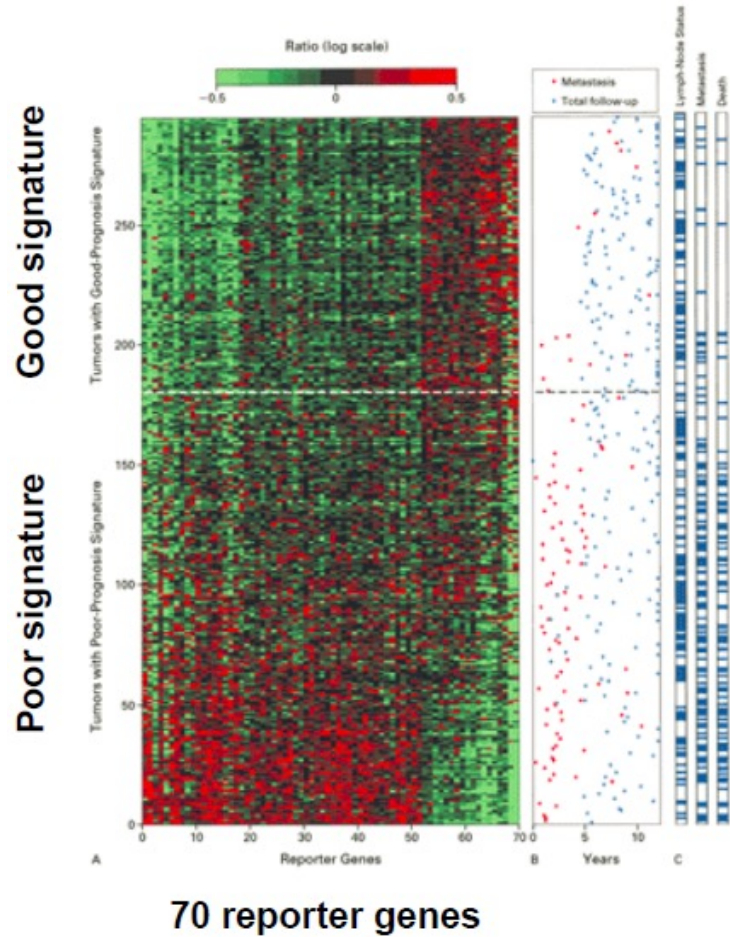
A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

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 AT SMA, 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.

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



Wednesday, Sep 2, 1998

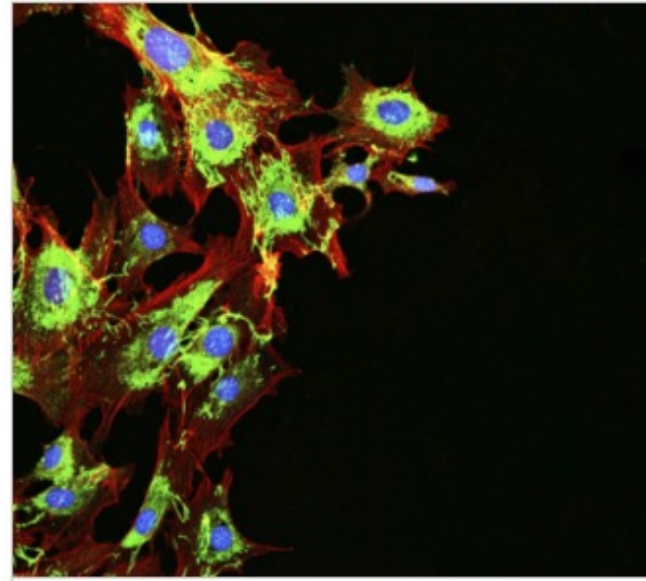
FDA Advisory Committee Recommends Approval of First Monoclonal Antibody for Metastatic Breast Cancer

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

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

Genentech, Inc. (NYSE:G) 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 sizeable fraction of HER2-positive patients. Herceptin lowers the risk of relapse, extends survival and potentiates the efficacy of chemotherapy and immunotherapy.

1998-2023



ÉDITORIAL

La belle histoire de HER2

The great story of HER2

La Lettre du Cancérologue • Vol. XXIV - n° 8 - septembre 2015 | 351

- 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 ▾

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.

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 prognostic factors. It may play a role in

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

PMID: 3798106

[Indexed for MEDLINE]



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. Hynes²

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.]

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HER-2/neu amplification and overexpression in primary human breast can [Anticancer Res. 1992]

The association of HER-2/neu amplification with

Publication types

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



AI revolution : integrative intelligence outperforms standard histopathology !



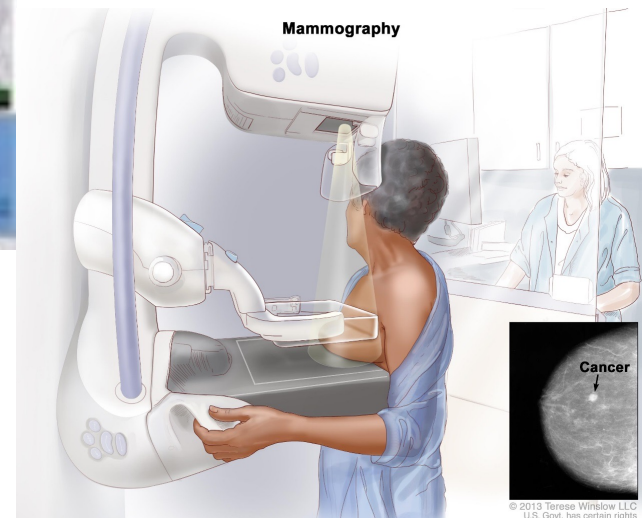
A healthy cell may hold as many as **20,000 HER2** proteins whereas a highly overexpressing cell as much as **2×10^6 receptors**, hence HER2 grading scores.

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

~10-15% breast cancers test HER2 positive !

90% breast cancer are hormonal dependent (tamoxifen responsive)

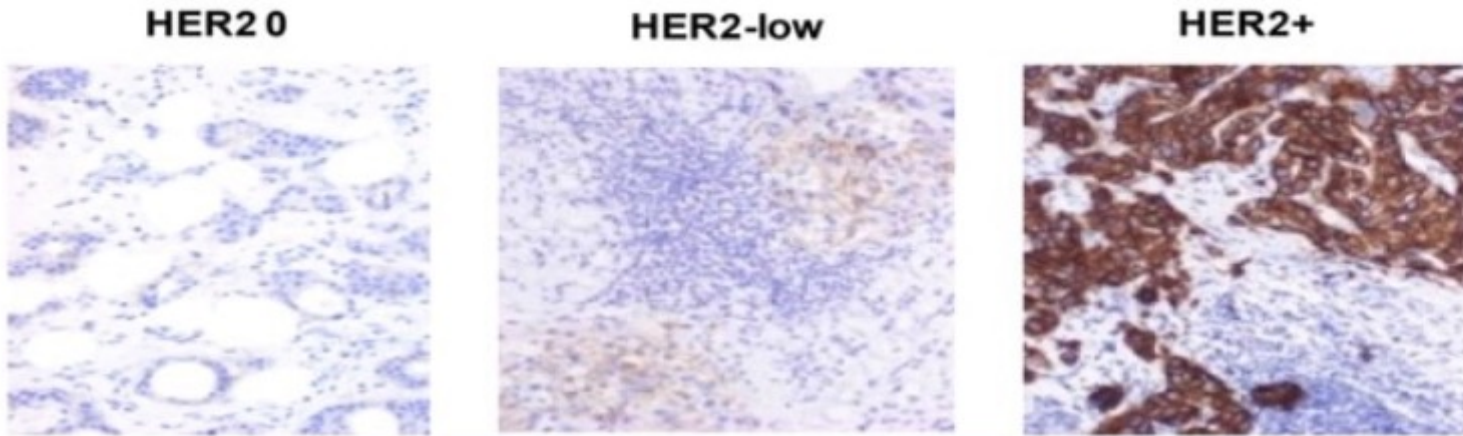
disease diagnosis: machine learning assisted screens may search through thousands of calcified breast regions



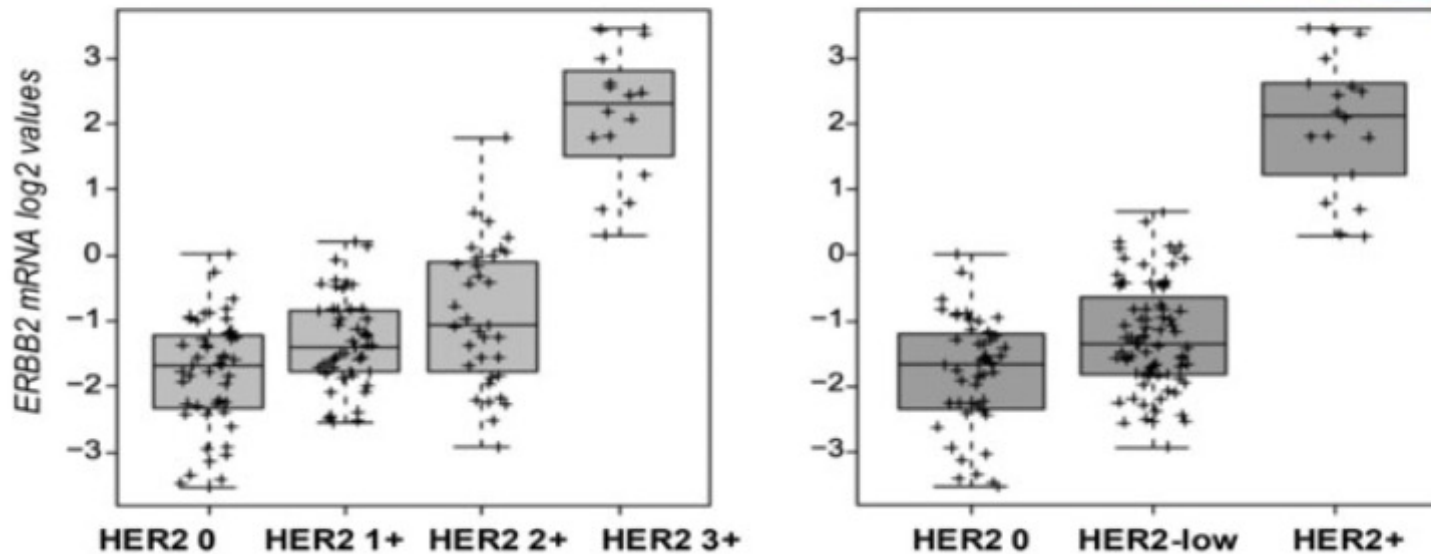
© 2013 iStockphoto.com
U.S. Govt. has certain rights

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

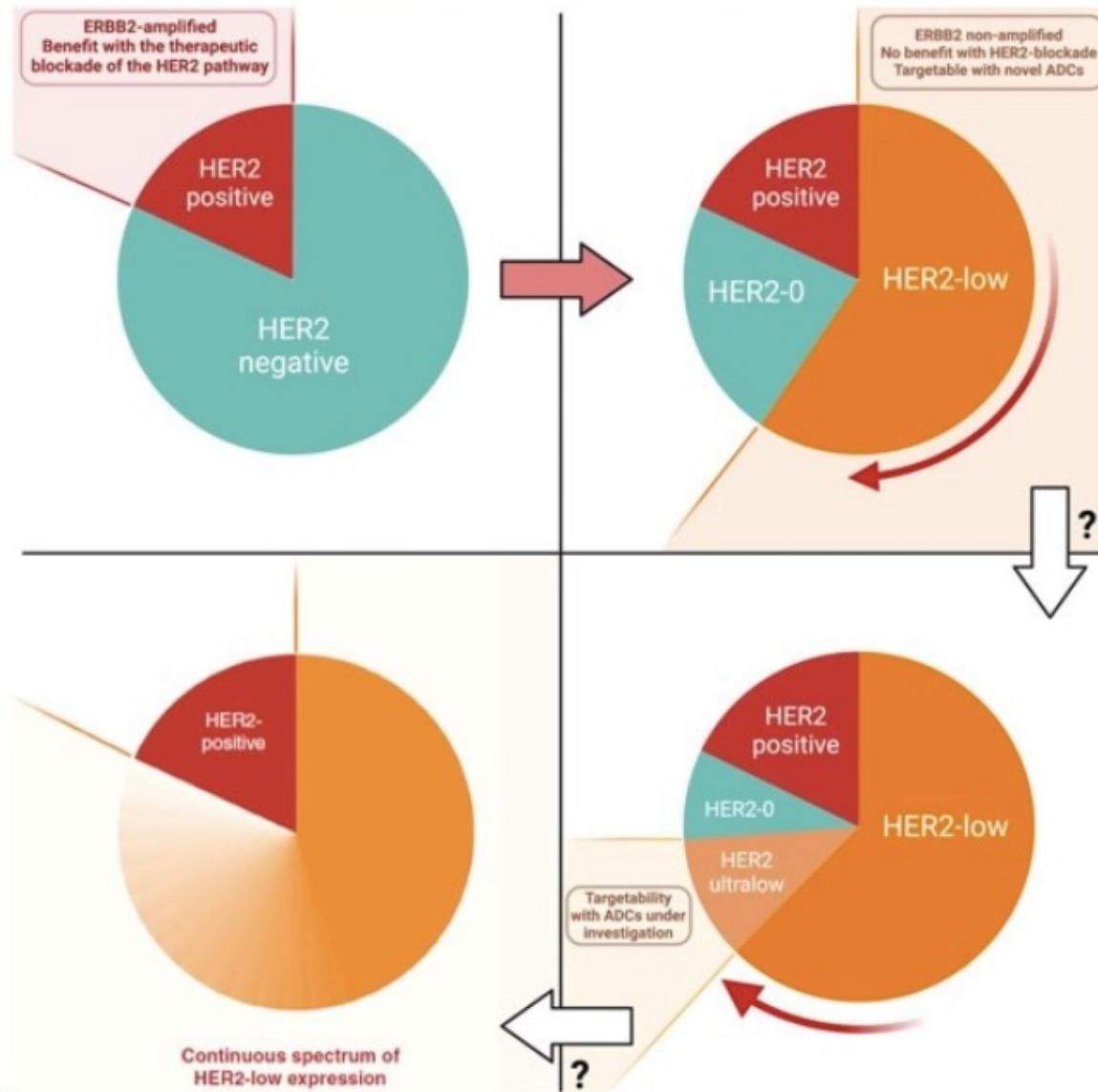
PHC_ Two decades of HER2 targeting: the unfinished revolution in breast cancer



HER2 protein
HER2 mRNA



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



PHC_ HER2 biomarker_pioneer driver of personalized oncology



Human Epidermal Growth Factor (HER2) Testing

HER2, or human epidermal growth factor 2, is a special protein on the surface of breast cells that controls the growth of cancer.

The levels of HER2 in your tumor help your doctor plan your treatment options.

When is HER2 testing done?

You have been newly diagnosed with breast cancer

You have breast cancer that has come back after treatment

Your cancer has spread to other parts of the body

How is HER2 testing done?

Immunohistochemistry (IHC) measures the levels of HER2 protein on the surface of the cancer cells.

In-situ hybridization (ISH) measures the copies of the HER2 gene within one cancer cell.

HER2 test results can be

HER2 POSITIVE

High levels of the HER2 protein and/or many copies of the HER2 gene are found in your tumor sample.

Treatment Options
HER2-targeted therapy, such as trastuzumab (Herceptin), lapatinib (Tykerb), pertuzumab (Perjeta), and a do-trastuzumab emtansine (T-DM1: Kadcyla)

HER2 NEGATIVE

No or low levels of the HER2 protein and/or few copies of the HER2 gene are found in your tumor sample.

Treatment Options
HER2-targeted therapy is not recommended. Your doctor will suggest other treatment options.



Sometimes, retesting is needed

The levels of the HER2 protein and/or the number of copies of the HER2 gene fall between the limits for HER2 positive and HER2 negative.

Testing may need to be done again, either on a different tumor sample or with a different test. Even then, results may not be conclusive. You and your doctor will discuss what this means for treatment.



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.

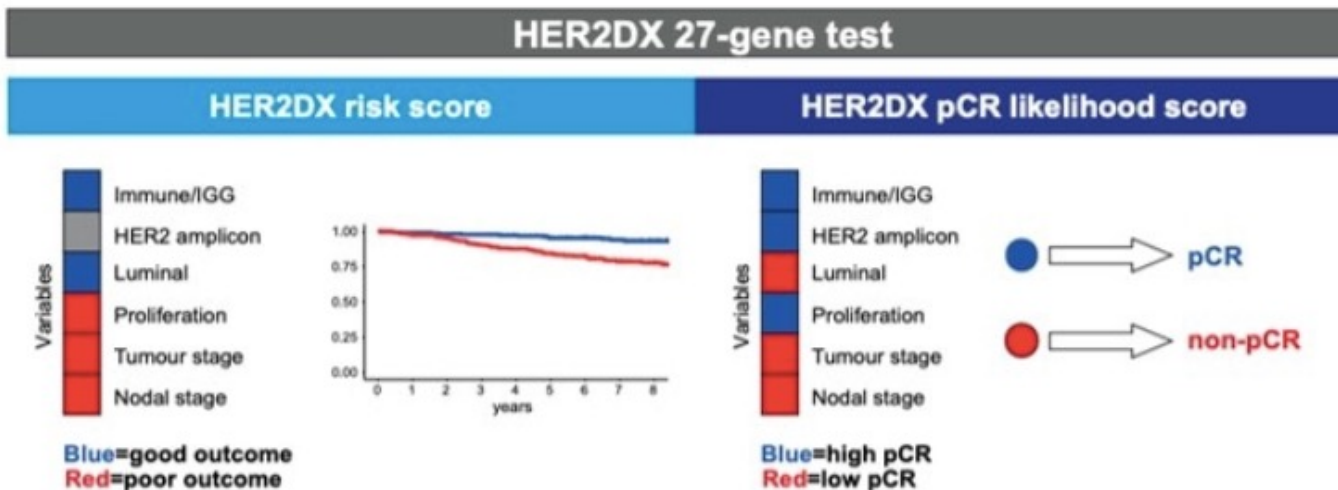
- Stratification of clinical cohorts trials based on biopses ! biomarker is key !
- **Frontloading biomarker search** is now common practice in translational research!

PHC_ a supervised M-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.

Pioneering personalized Healthcare _ Herceptin and Perjeta



Breast cancer

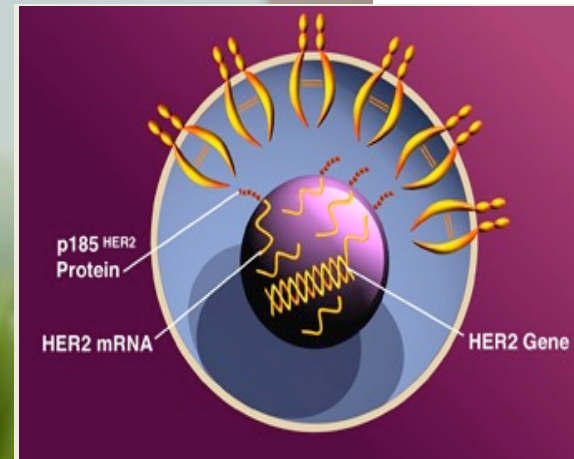
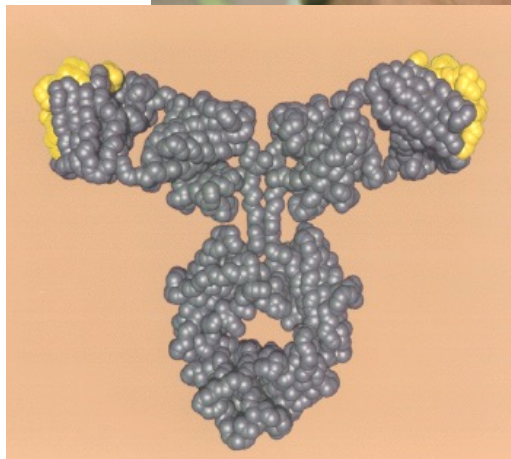
700,000 newly diagnosed patients in Europe and USA -- 200,000 death cases

1 woman over 10 undergoes a breast cancer during her lifetime

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

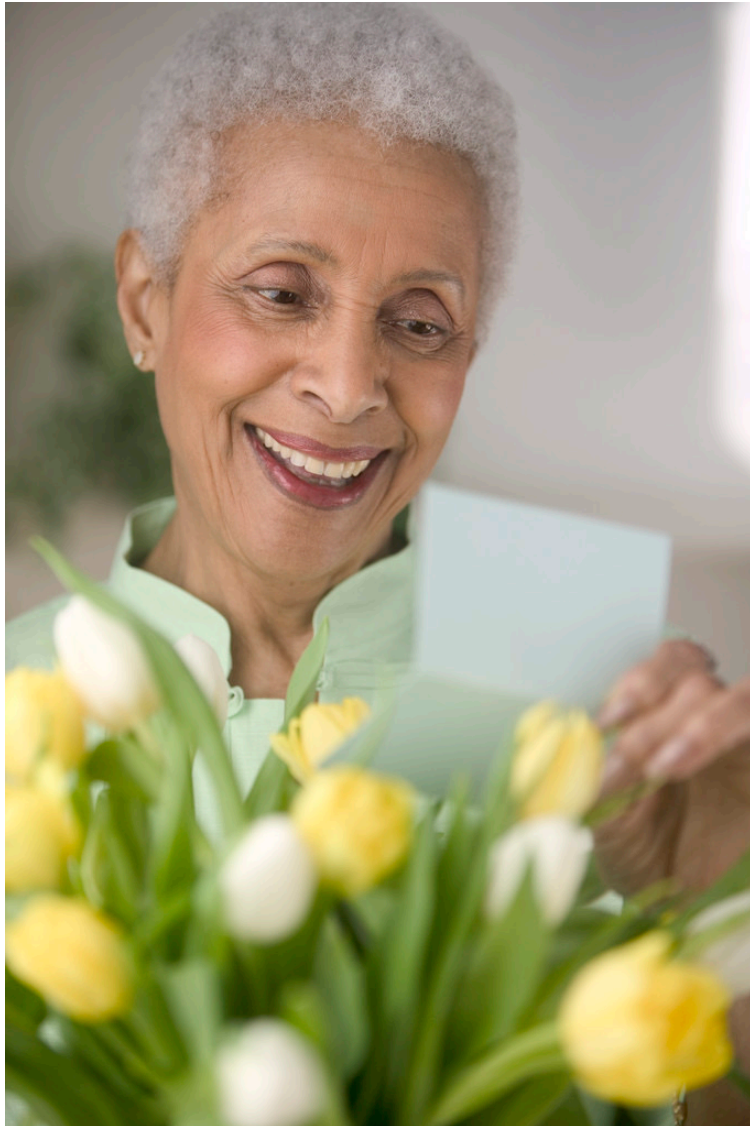
1/3 of all patients: 3 years life extension

NB :Katrin S. is not a simulated patient !



Katrin S. enrolment

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



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 celebrating her 55th birthday...

on January 12, 2006, almost 10 years later !



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

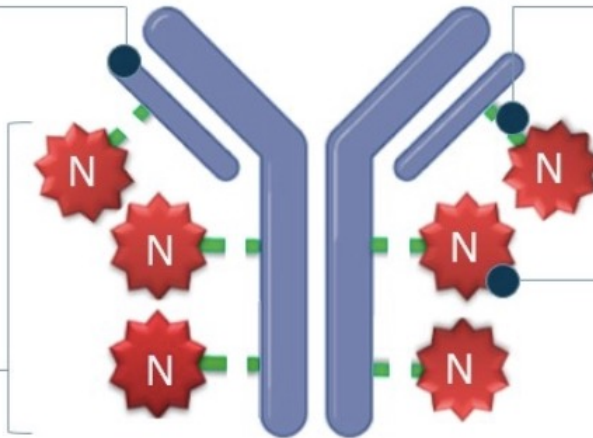


Antibody

- New formats (eg, antibody fragments)
- Half-life extension
- CDR-masking technologies
- Enhanced drug delivery

DAR

- Higher drug-to-antibody ratios



Cleavable linker

- Several chemistries
- Tumor-specific triggers

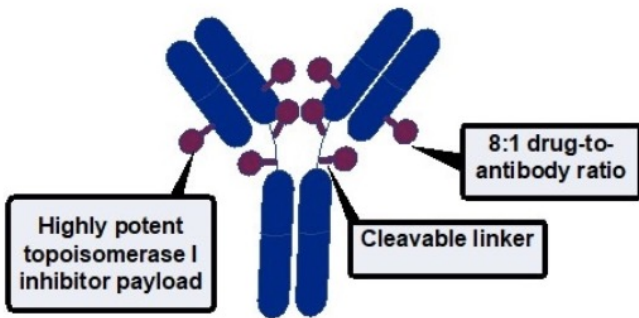
Novel Payloads

- Match right payload MOA for right target/patient population
- Alternative warheads, eg, targeted agents in both tumor and tumor microenvironment

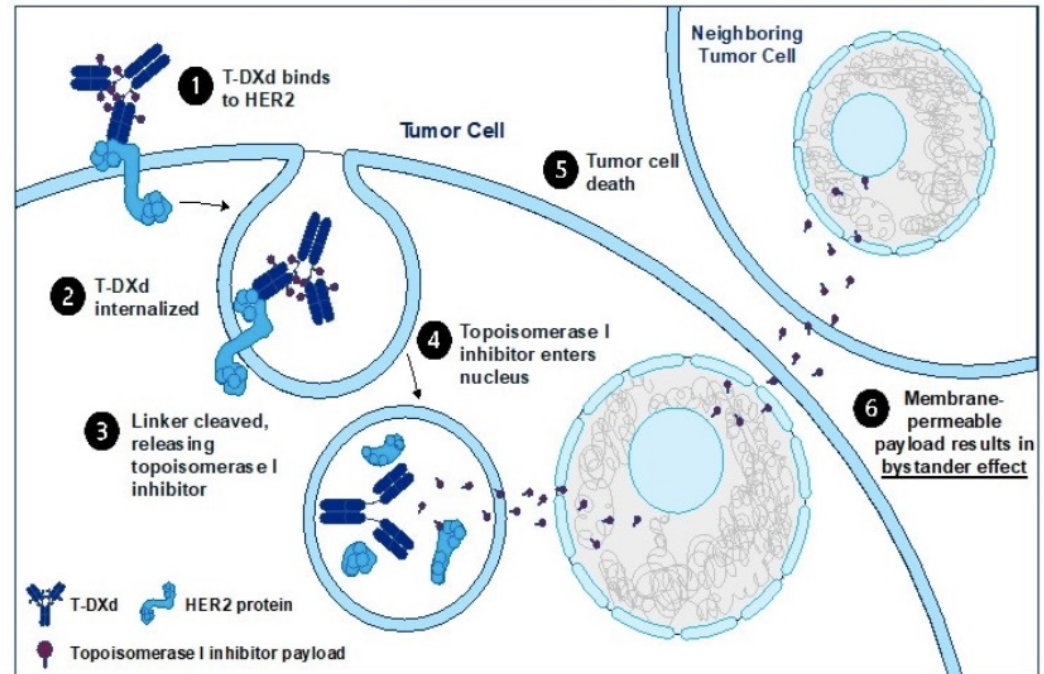
HER2 - human epidermal growth factor receptor 2, also called ERB-B2 (Erb-B2 receptor tyrosine kinase 2)



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

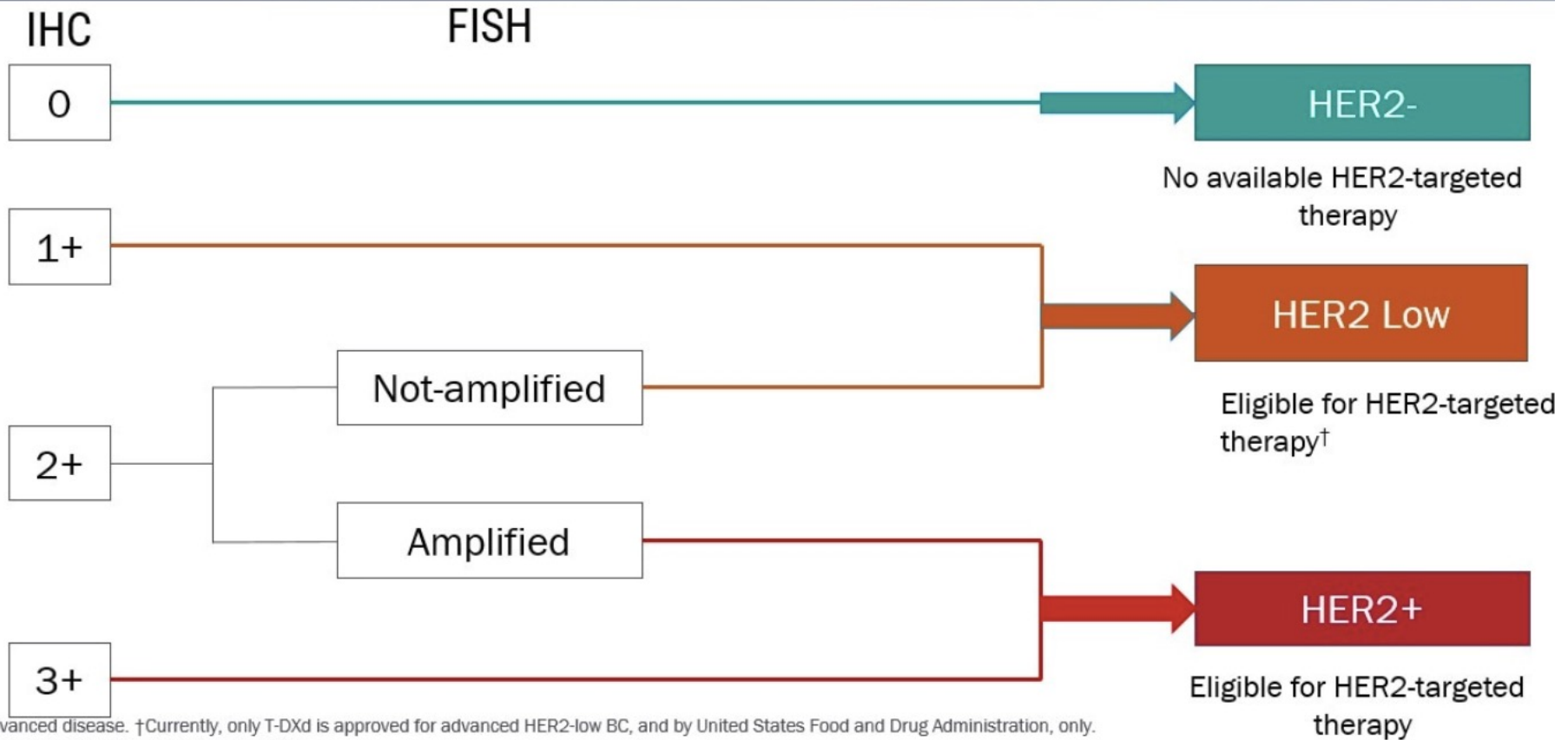


Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

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



Today It Is Clinically Essential to Report HER2 IHC Results*



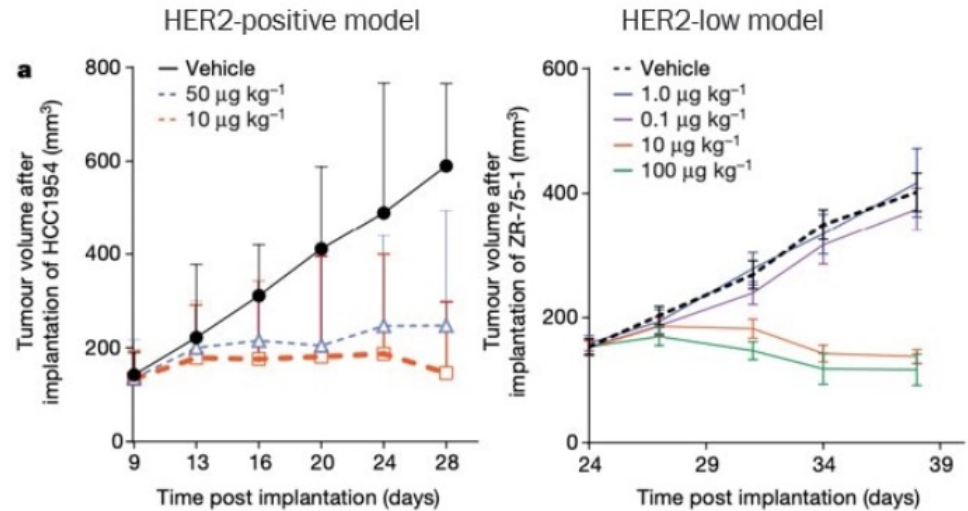
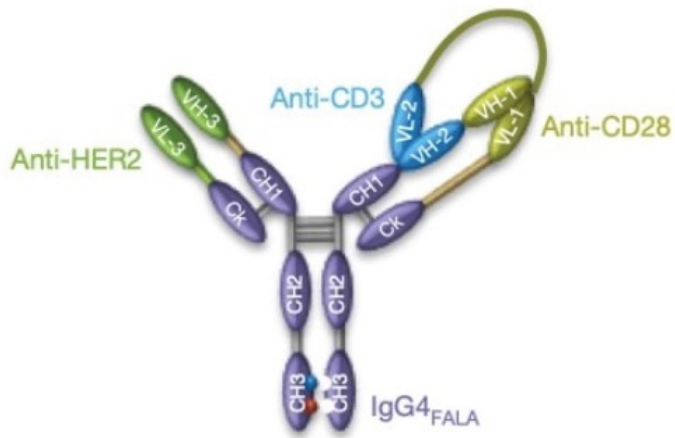
HER2 - human epidermal growth factor receptor 2, also called ERB-B2 (Erb-B2 receptor tyrosine kinase 2)

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



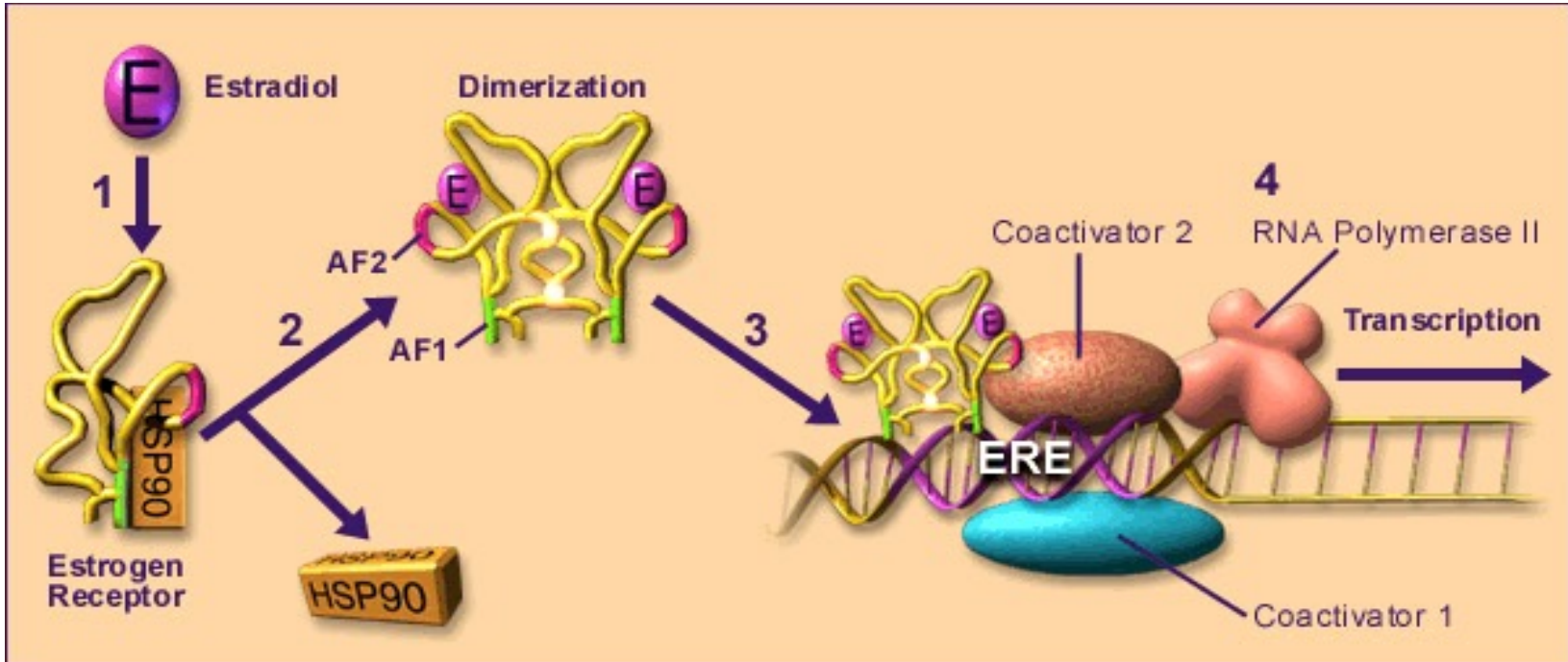
A trispecific antibody targeting HER2 and T cells (CD3xCD28) stimulates regression of HER2-positive and HER2-low breast cancers in a humanized mouse model through a

- **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)

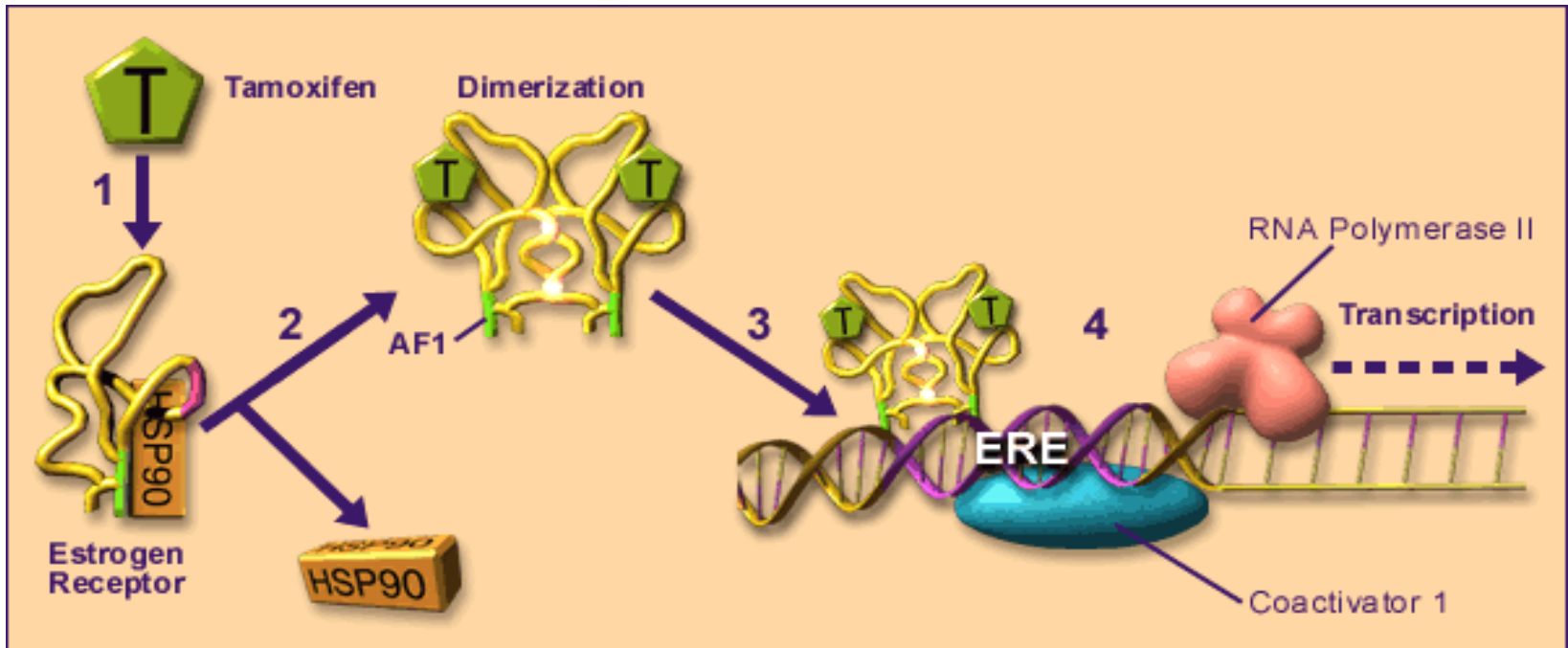
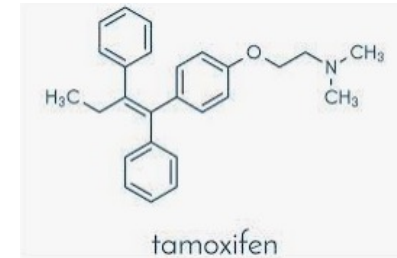
Hormonal dependent breast homeostasis : underlying molecular action of of estradiol



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



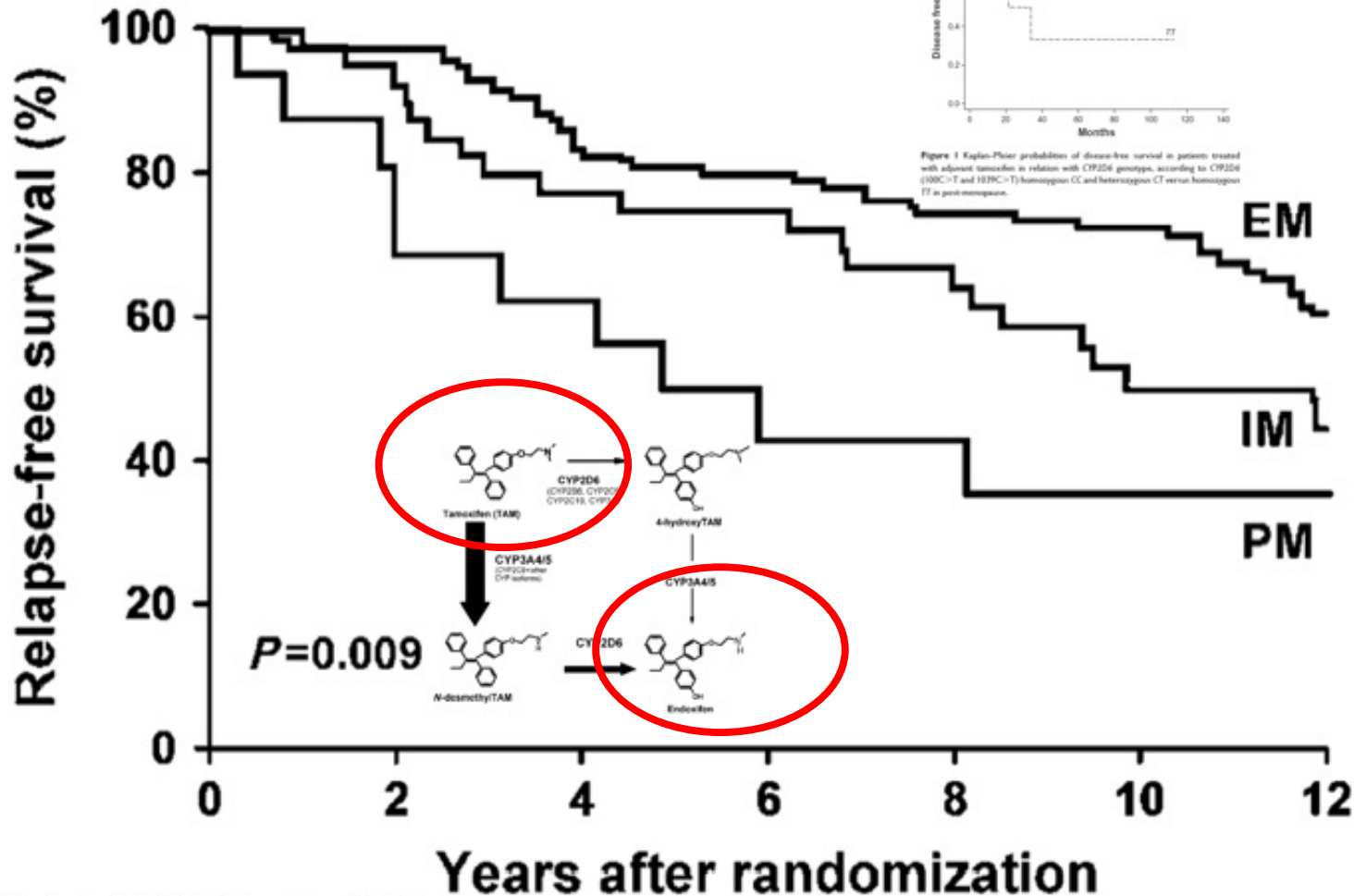
Adapted from Howell A, Osborne CK, Morris C, Wakeling AE. ICI 182,780 (Faslodex®), development of a novel, "pure" antiestrogen. *Cancer* 2000; 89: 819.

SERM = selective estrogen receptor modulator

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



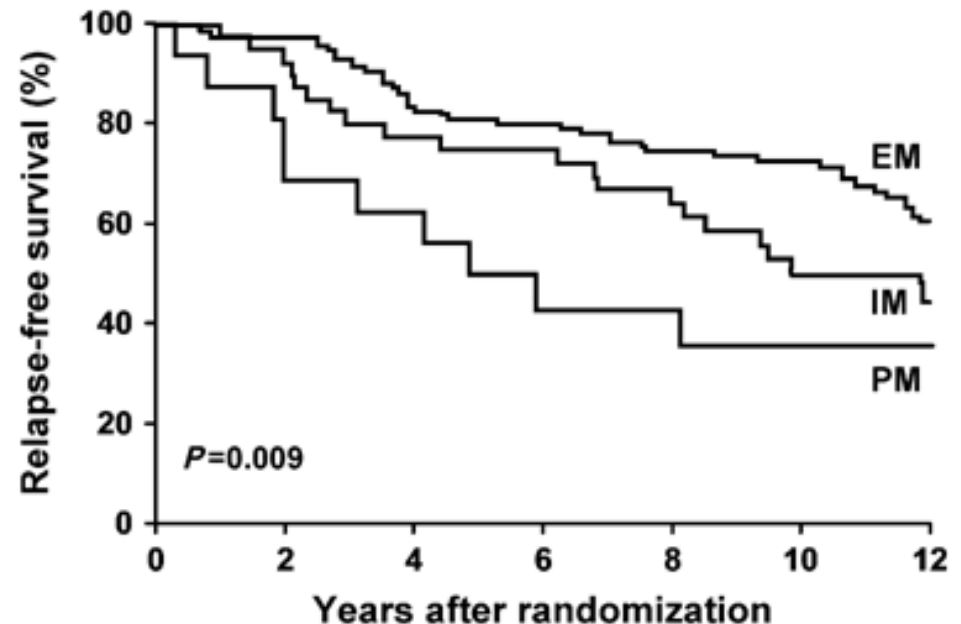
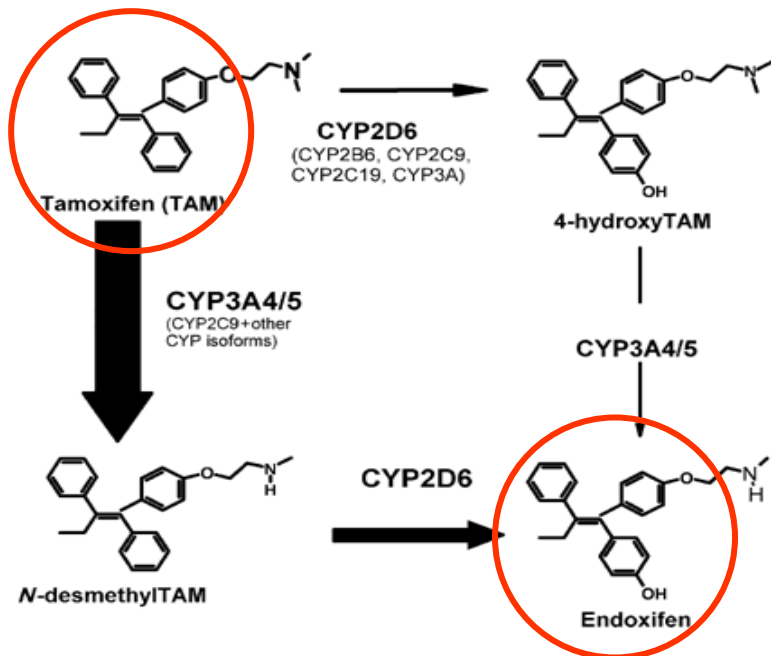
Molecular Action of Tamoxifen (SERM) as a prodrug Kaplan Meier - metabolizer status



Pharmacogenetics_optimize the dose



- Tamoxifen or TAM (partial ER α 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
- CYP2D6 polymorphism analysis allows an optimal individualized 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

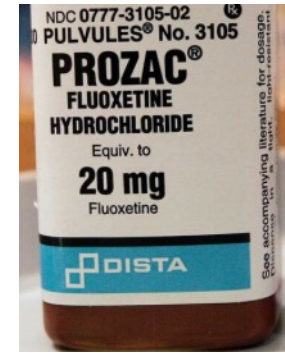


Neuron 57, 203–209, January 24, 2008 ©2008 Elsevier Inc.

Neuron

Clinical Study

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



Cell
PRESS

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

¹Max 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

Prof. Dr. med. Tom Bschor



Antidepressiva

Wie man sie richtig
anwendet und wer sie
nicht nehmen sollte

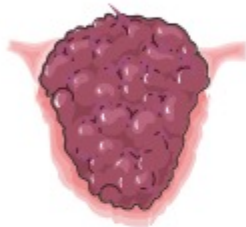
Vom Mitautor der
Behandlungsleitlinie
für Depressionen

PHC – front loading biomarker discovery



Macroscopy

Morphological alterations



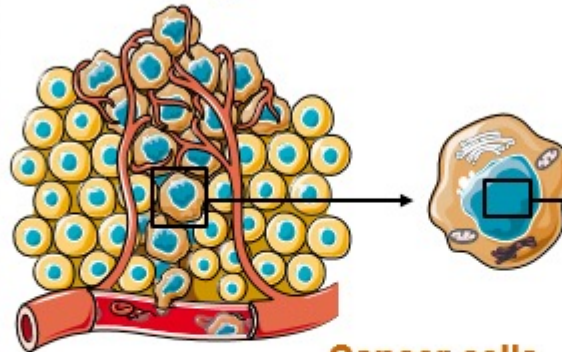
Tumor



AI - ML POWERED IMAGING ALGORITHMS

Histology

Histological biomarkers



Cancer cells



Molecular analyses

Molecular biomarkers



DNA/RNA



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

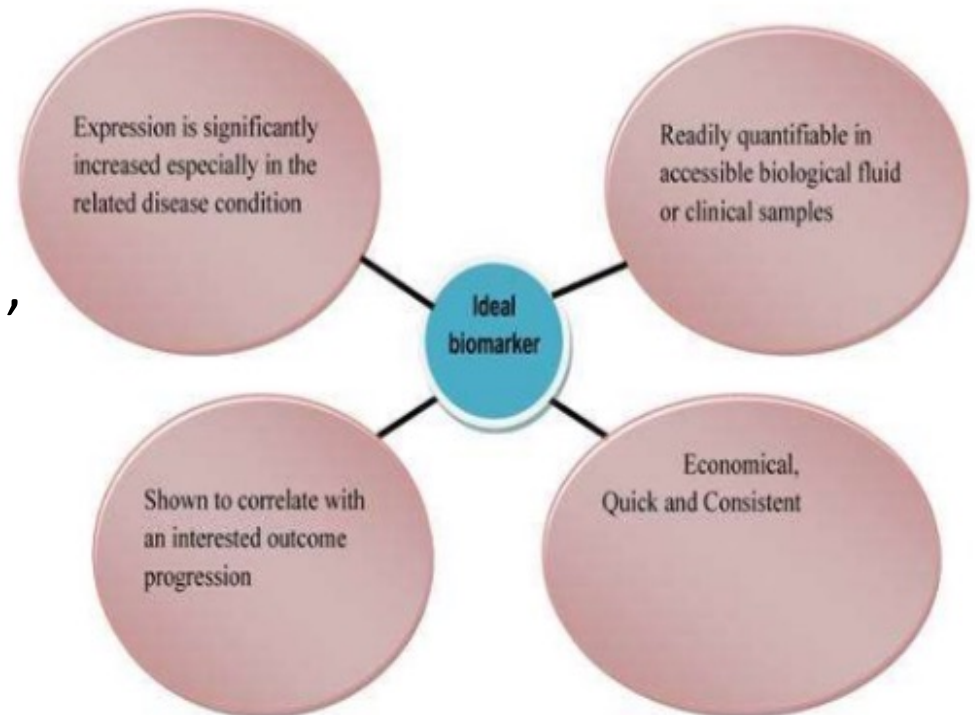
Genomics: GWAS, microarrays, PCR, RT-PCR, microRNAs

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

Imaging: biopsies, IVUS, IRM

Metabolomics: metabolites, metabolic pathways

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



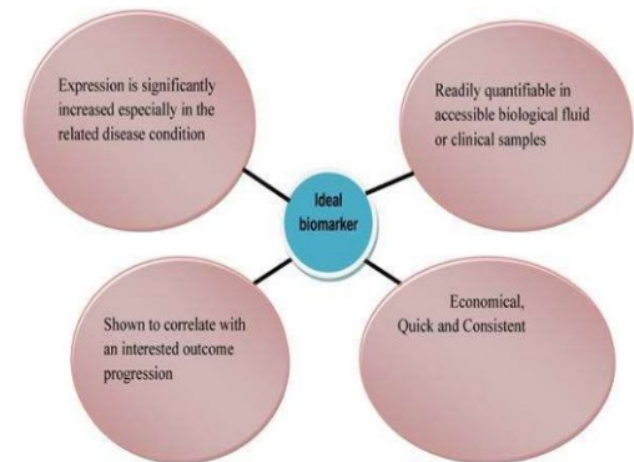


“Any substance, structure or process that can be measured in the body or its product and influence or predict the incidence of outcome or disease.” WHO international programme on chemical safety 2001

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

	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....



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			miR-25, -223, -1254, -574-5p, -29c, -21, -155, -182, -197, -125b, -205, -30d miR-21, -126, -210, 486-5p, let-7f, -30e-3p, -155, -197, -182 INCREASE	
Lung cancer	miR-25, miR-223 miR-1254, miR-574-5p			LUNG miRNA-146b, -221, let-7a, -155, -17-5p, -27a, -106a, -361-3p, -625* miR-205, -19a, -19b, -30a, -20a DECREASE	
Prostate	miR-155, miR-197, miR-182 miR-375, miR-141 MiR-107, miR-574-3P miR-205, miR-214			PROSTATE miR-141, -375, -18a, -107, -378*, -200a, -200c, -210, -375 miR-221 miR-409-3p INCREASE DECREASE	
Pancreatic	Index I (4 miRNAs) and index II (10 miRNAs)				
Hepatocellular carcinoma	miR-16, miR-199a MiR-15b, miR-130b, and miR-16			BREAST miRNA-155, -21, -214, -182, -1, -92a, -133a, -133b, let-7b, let-7q, 18b, -148b, -409-3p, -801, -10b, -373, -127-3p, -376a, -652, -484 miR-195, -202 INCREASE DECREASE miR-30a	
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			COLORECTAL miR-29a, -21, 18a, 29c, let-7g, let7a, -1229, 1246, -150, 223, 23a miR-29a, -92a, -221, -141, -601, -760 miR-31, -181b, -92a, -203 miR-34a, -18a, -29a INCREASE DECREASE	
Gastric cancer	miR-18a miR-122, miR-192	Serum Plasma	Up Differential	Diagnosis of CRC lymph node metastasis GC vs. healthy cor	(31)
Ovarian cancer	miR-205, miR-let-7f	Plasma	Differential	Epithelial ovarian c	
				CANCER LIVER miR-1, -25, -92a, -206, -375, let-7f, 885-5p, -21, -122, -223, -222, -221, -101 INCREASE DECREASE miR-16, -199a, -15b, -130b	
				GASTRIC miR-196a, -378 miR-17-5p, -21, -106a, -106b, -199a-3p, -146a, -148a, -16, -25, 92a, 451, 486-5p, -18 miR-106, 17, -21, -200c, -421 INCREASE DECREASE miR-375 let-7a, -195-5p, -122, -192	



Cell Reports

report

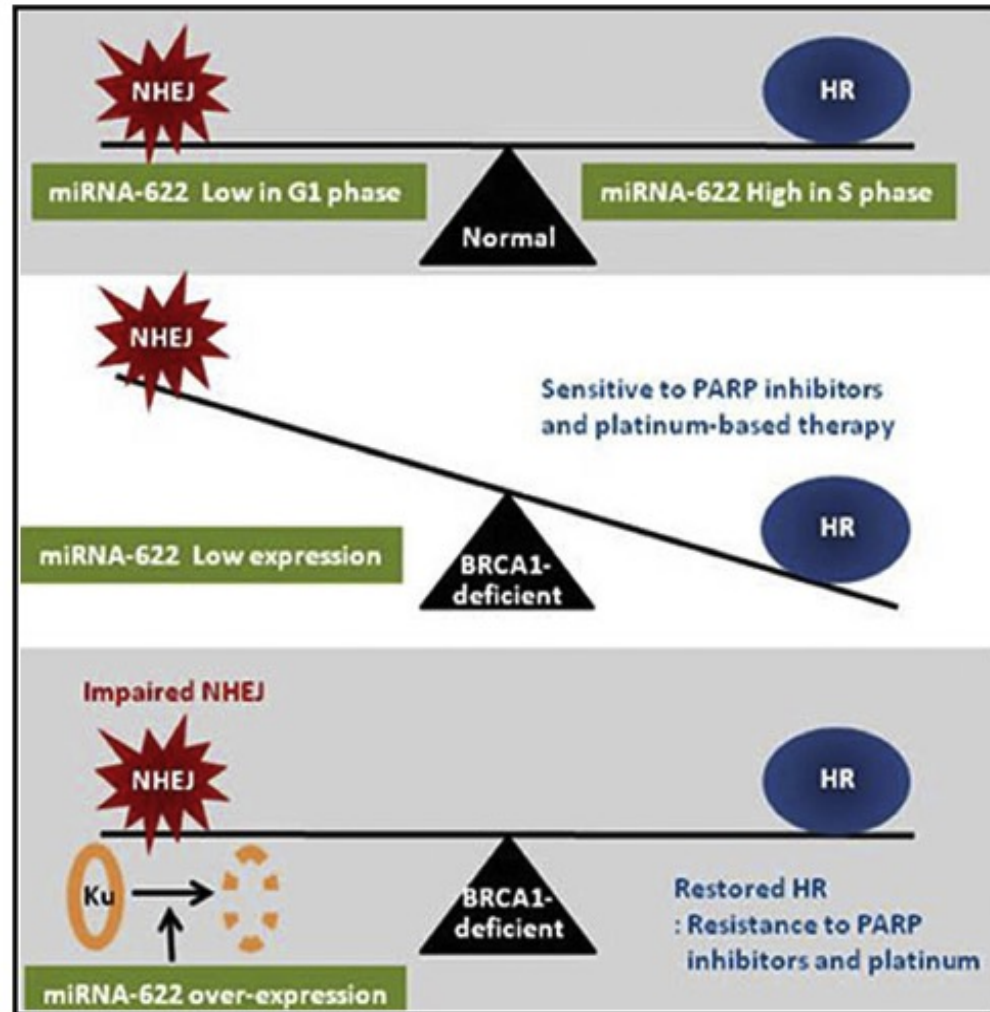
Platinum and PARP Inhibitor Resistance Due to Overexpression of MicroRNA-622 in *BRCA1*-Mutant Ovarian Cancer

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**

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

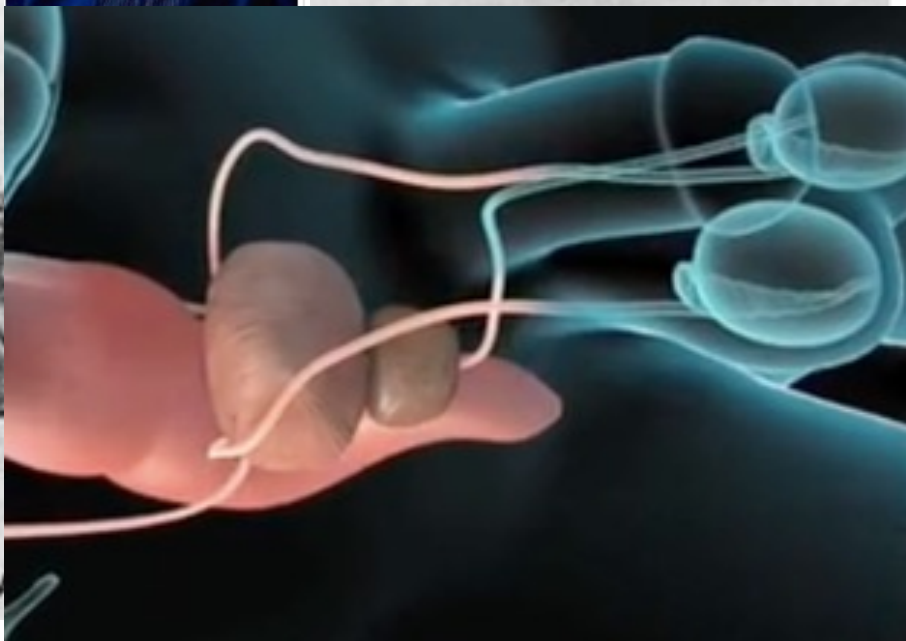


Biomarker discovery : BRCA1 discovered in 1994 - DNA repair tumor suppressor gene- today a biomarker of breast, endometrium, ovary and prostate cancer (65% cumulative risk) !

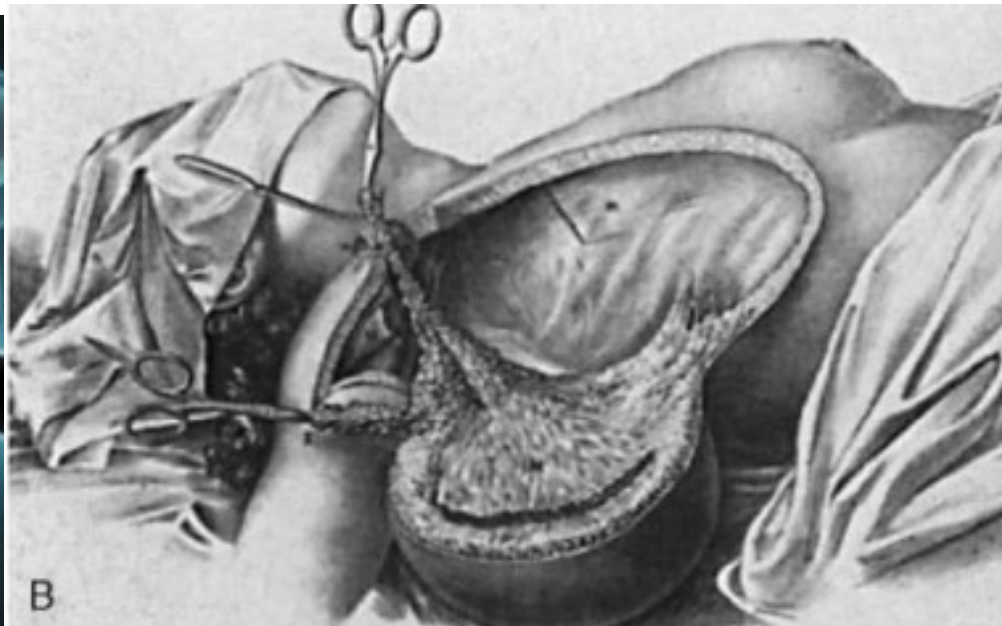


Let's beat cancer sooner

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



Castration resistant radical prostatectomy



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,** and aggressive prostate cancers incidence





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, FACS¹, Thomas S. Vetter, MD², and Arthur H. Salibian, MD¹

¹St. Joseph Hospital, The Center for Cancer Treatment and Prevention, Orange, CA; ²Aesthetic 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-on 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 <i>BRCA</i> 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%

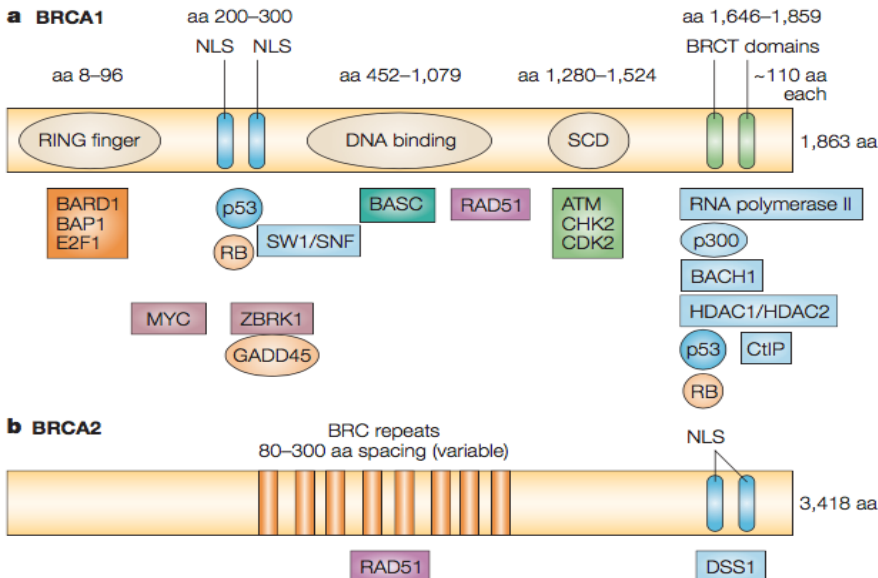
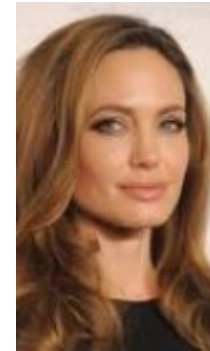


Figure 1 | BRCA1 and BRCA2 functional domains, and selected binding partners.

"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



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

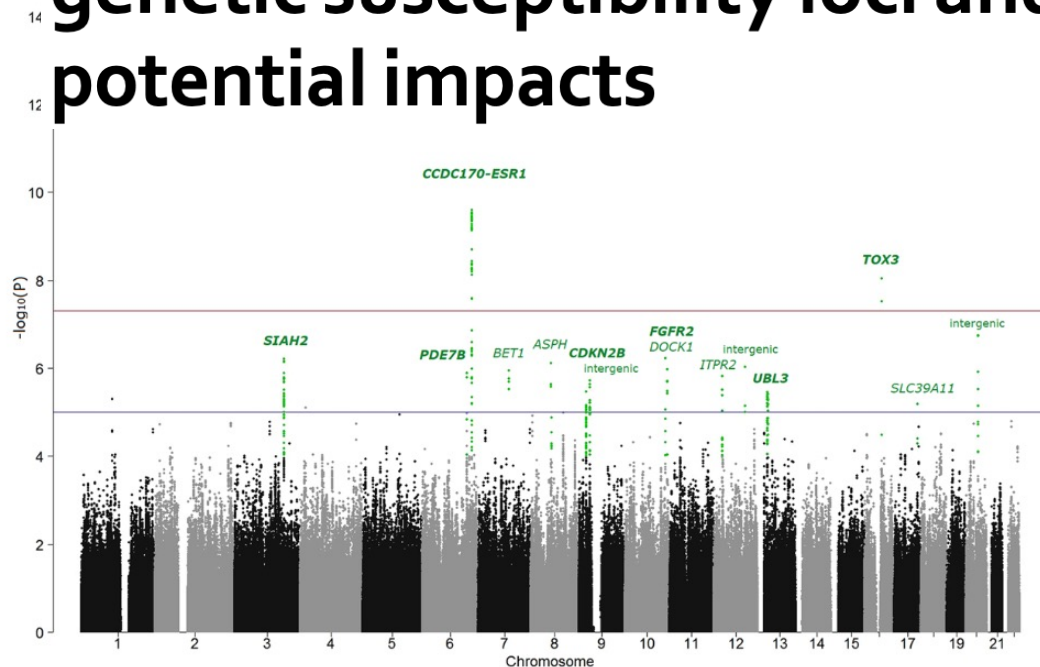
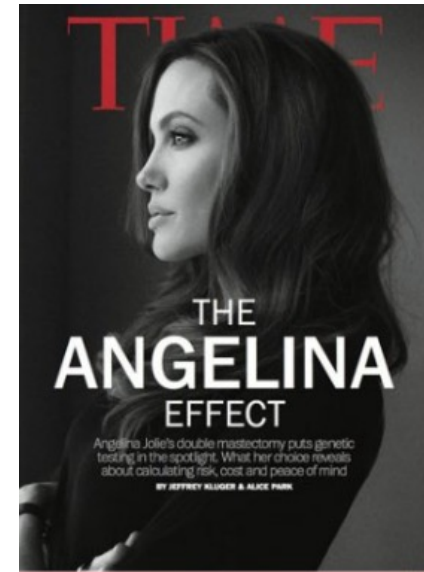


Figure 1. Manhattan plot. The red horizontal line represents the genome-wide significance threshold of p -value = 5.0×10^{-8} and the blue horizontal line represents the suggestive significance threshold of p -value = 1.0×10^{-5} . For significantly associated regions, SNPs with p -value less than 10^{-3} 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



**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.

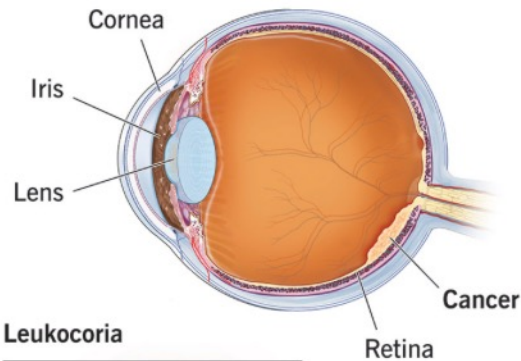
OR ANY OTHER NON REVERSIBLE PATHOLOGICAL AILMENTS !

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

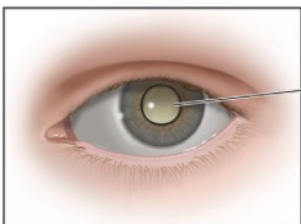
A. Knudson – two hits hypothesis in tumor suppressor genes



Retinoblastoma

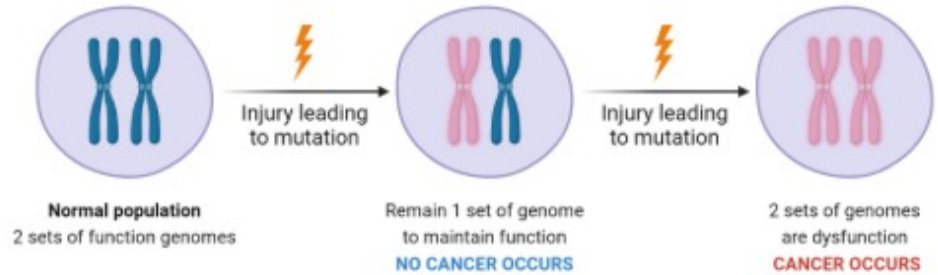


Leukocoria

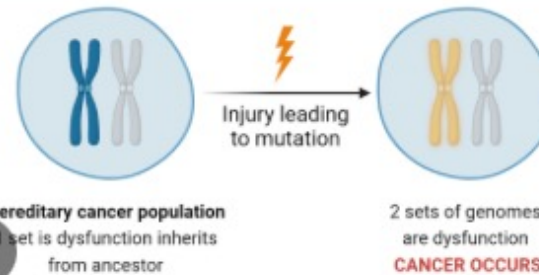


Pale-colored retina

General Population



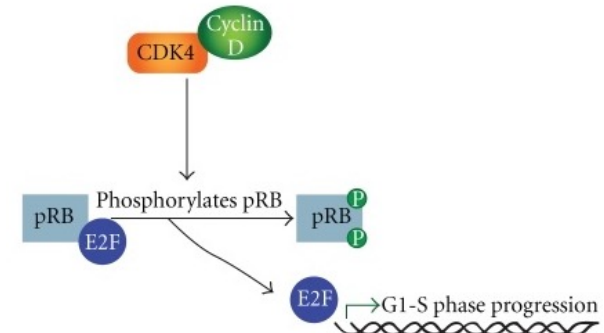
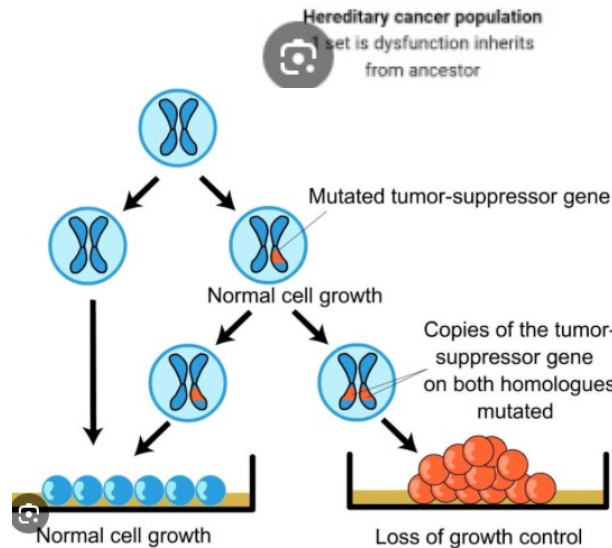
Hereditary Cancer Population



Knudson's Two-Hit Hypothesis

suggests that cancer develops through two mutations in tumor suppressor genes. In hereditary cases, one mutation is inherited, requiring only one additional mutation. Sporadic cancers need two acquired mutations. This model, exemplified by retinoblastoma, advanced cancer genetics, guiding genetic testing and targeted therapies.

References: Nat Rev Cancer. 2001 Nov;1(2):157-62.



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



Treatment Effect by *ADCY9* Genotypes in dal-OUTCOMES

rs1967309 GG AG AA

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

Home > Search Results > Study Record Detail Save this study

Effect of Dalcetrapib vs Placebo on CV Risk in a Genetically Defined Population With a Recent ACS (dal-GenE)

ClinicalTrials.gov Identifier: NCT02525939

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

Recruitment Status ⓘ : Active, not recruiting
 First Posted ⓘ : August 18, 2015
 Last Update Posted ⓘ : December 19, 2018

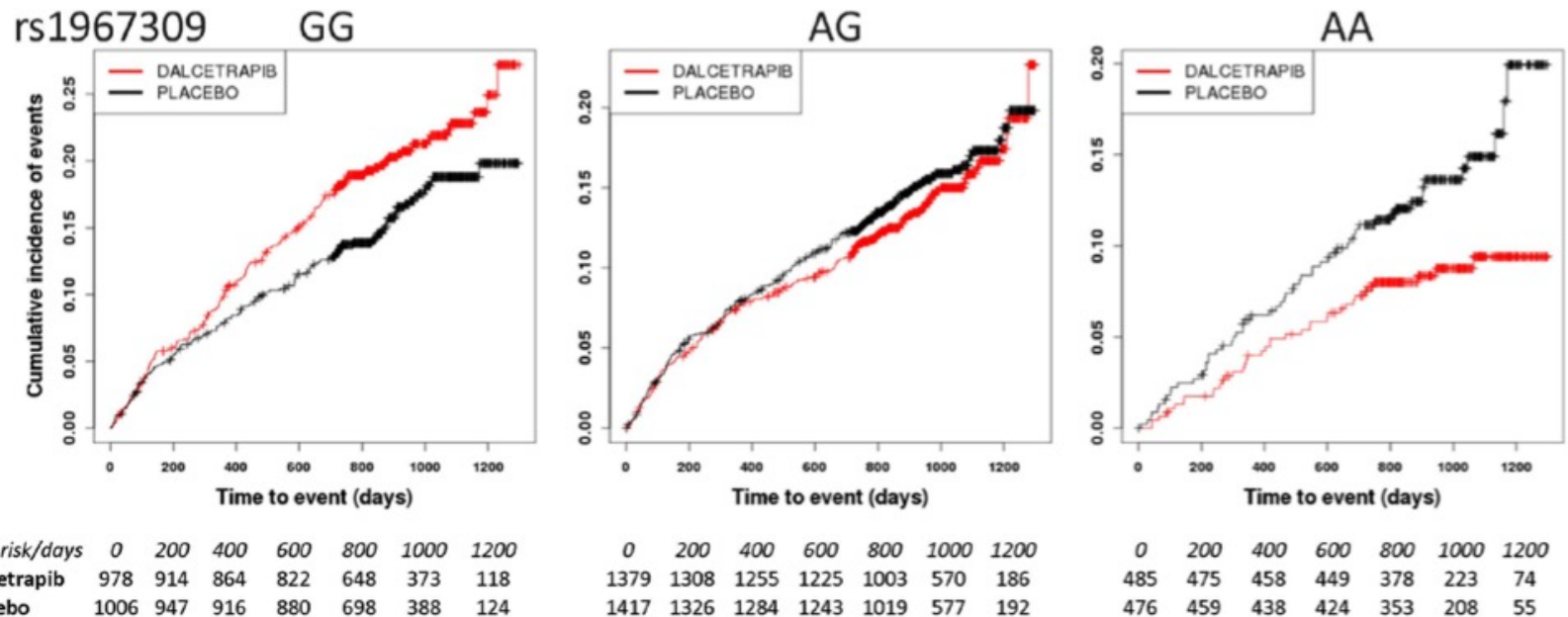
Sponsor	Placebo	1006	947	916	880	698	388	124	1417	1326	1284	1243	1019	577	192	476	459	438	424	353	208	55
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Events: Composite of CHD death, resuscitated cardiac arrest, non-fatal myocardial infarction, unstable angina with objective evidence of ischemia, atherothrombotic stroke and unanticipated coronary revascularization

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



Treatment Effect by *ADCY9* Genotypes in dal-OUTCOMES



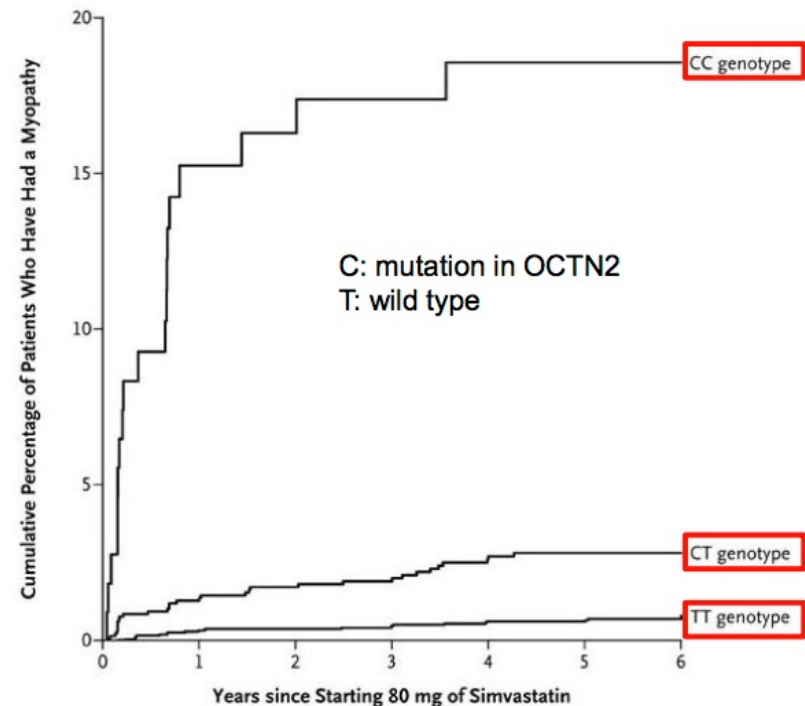
Events: Composite of CHD death, resuscitated cardiac arrest, non-fatal myocardial infarction, unstable angina with objective evidence of ischemia, atherothrombotic stroke and unanticipated coronary revascularization

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



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





The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

TO THE EDITOR

Although we agree with many of the points made by Tannock and Hickman about the limits of precision medicine for patients with cancer, we disagree with the final conclusion “that personalized cancer medicine has not led to gains in survival or its quality.” Gains in both survival and quality of life have occurred with agents targeted at specific molecular subtypes of cancer, including human epidermal growth factor receptor 2 (HER2)–expressing breast cancers, BRAF V600E mutations in melanoma, BCR–ABL in chronic myeloid leukemia, hormonal receptors in breast and prostate cancers, and CD20 in lymphomas.¹⁻³ Higher rates of progression-free survival have been observed with these

Disease biomarker_driving innovation in oncology: exemplary clinical practice of PHC



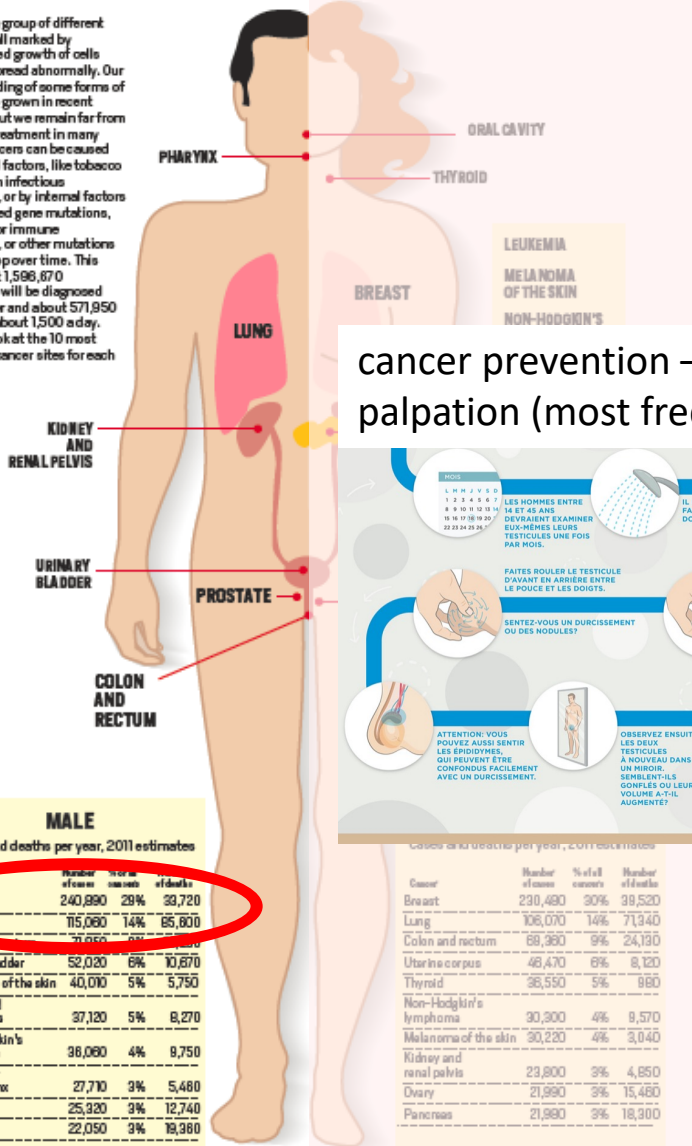
November testicular cancer awareness month

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

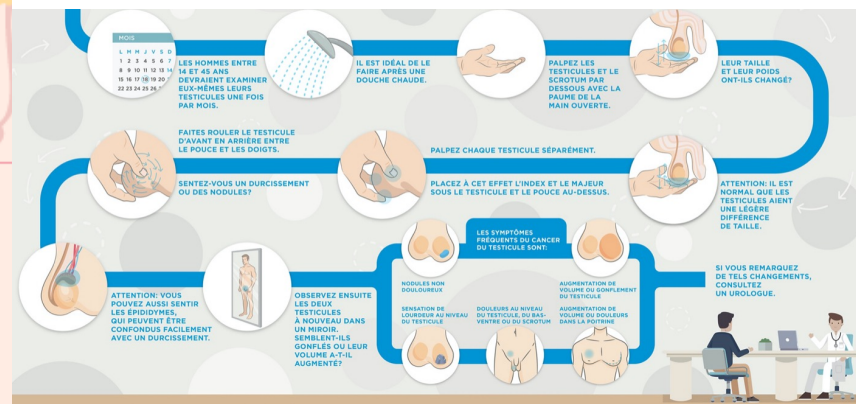
CANCER DIAGNOSTIC REMAINS A MAJOR CHALLENGE !

THE MOST COMMON CANCERS

Cancer is a group of different diseases, all marked by uncontrolled growth of cells that can spread abnormally. Our understanding of some forms of cancer has grown in recent decades, but we remain far from effective treatment in many cases. Cancers can be caused by external factors, like tobacco and certain infectious organisms, or by internal factors like inherited gene mutations, hormonal or immune conditions, or other mutations that develop over time. This year, about 1,596,870 Americans will be diagnosed with cancer and about 571,950 will die—about 1,500 a day. Here's a look at the 10 most prevalent cancer sites for each gender.



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



MALE

Cases and deaths per year, 2011 estimates

Cancer	Number of cases	% of total cases	Number of deaths
Prostate	240,890	29%	39,720
Lung	115,060	14%	65,800
Colon and rectum	70,250	9%	32,300
Urinary bladder	52,020	6%	10,870
Melanoma of the skin	40,070	5%	5,750
Kidney and renal pelvis	37,120	5%	8,270
Non-Hodgkin's lymphoma	36,060	4%	9,750
Oral cavity and pharynx	27,710	3%	5,480
Leukemia	25,320	3%	12,740
Pancreas	22,050	3%	19,380

Source: American Cancer Society

FEMALE


Cases and deaths per year, 2011 estimates

Cancer	Number of cases	% of total cases	Number of deaths
Breast	230,490	30%	39,520
Lung	106,070	14%	71,340
Colon and rectum	69,980	9%	24,130
Uterine corpus	48,470	6%	8,120
Thyroid	36,550	5%	980
Non-Hodgkin's lymphoma	30,300	4%	8,570
Melanoma of the skin	30,220	4%	3,040
Kidney and renal pelvis	23,800	3%	4,850
Ovary	21,990	3%	15,480
Pancreas	21,980	3%	18,300

The Birmingham News/Wynne Marshall

(no clinically validated specific biomarker yet for testicular carcinoma !)
PSA = surrogate marker

PHC – hormonal prostate cancer - biomarker PSA

An anatomical illustration of the male reproductive system, focusing on the prostate gland. The prostate is shown as a textured, reddish-brown, walnut-shaped organ situated below the bladder and in front of the rectum. It is surrounded by various ducts and vessels, including the ureters and vas deferens. The bladder is depicted as a larger, smooth, pinkish structure above the prostate. The rectum is shown as a large, pinkish structure to the left of the prostate. The entire diagram is set against a black background.

Prostate gland

PSA : Prostate Specific Antigen

PHC_ surrogate biomarker PSA at use in cancer screening



The PSA Test



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

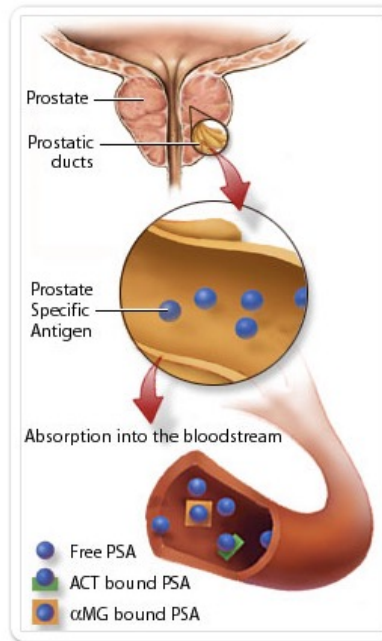
Free PSA comes from benign prostatic hyperplasia (BPH), an enlargement of the prostate. The higher the amount of free PSA, the less likely prostate cancer will be found as prostate cancer cells produce more complex PSA.

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.

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.

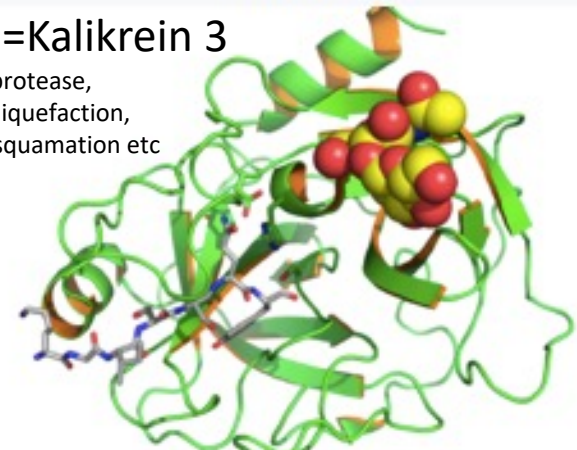


Prostate Cancer Canada graciously acknowledges the Princess Margaret Cancer Centre for sharing this image with us.

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

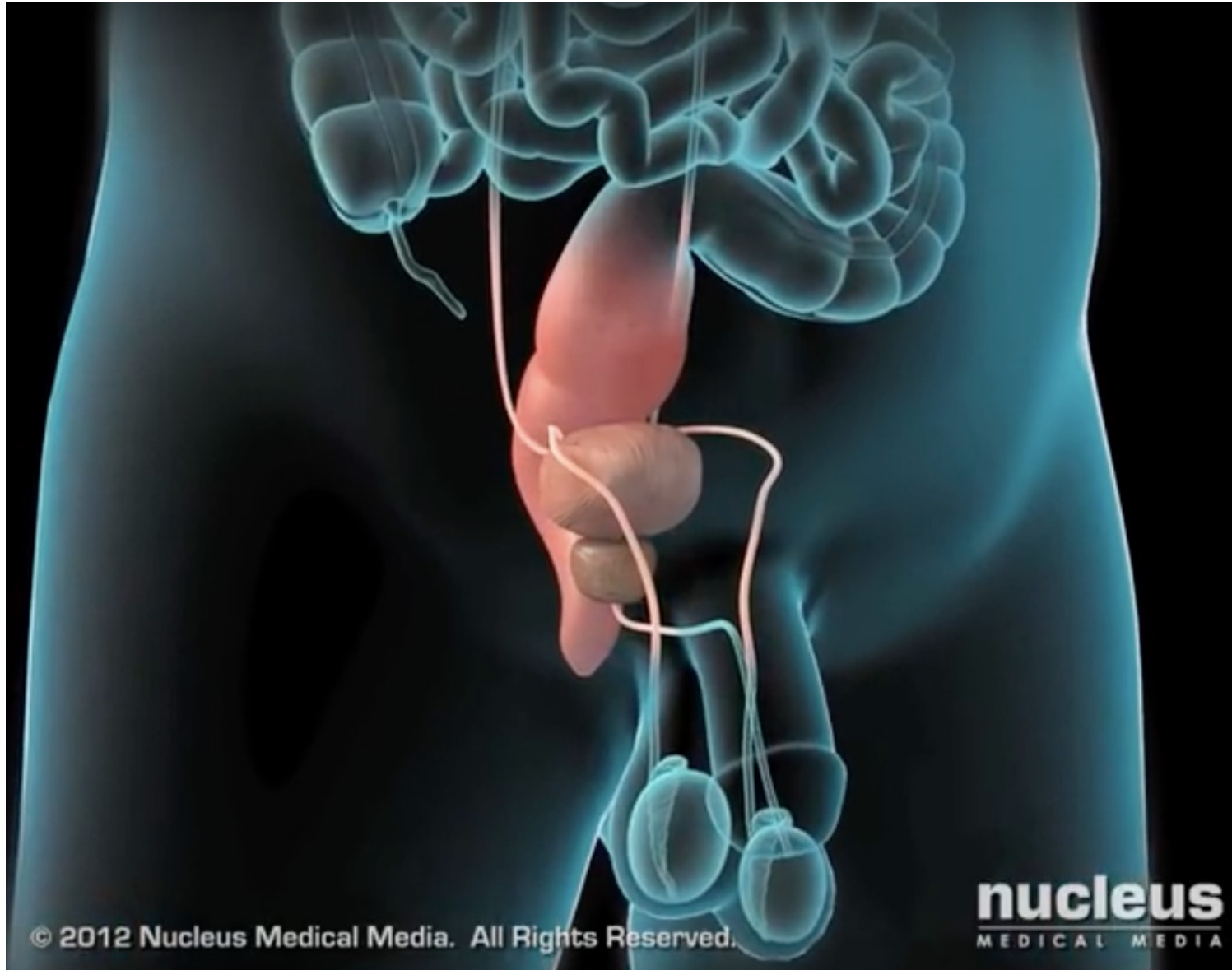
serine protease,
semen liquefaction,
skin desquamation etc



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 !”



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nucleus
MEDICAL ART

Prostate cancer : resistance and PSA controled hormonal chemotherapy



Metastatic prostate Cancer Hormon-Targets: Steroidhormonbiosynthesis

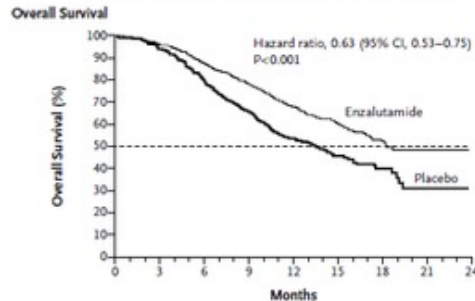
Approximately 15% to 25% of patients with CRPC do not respond to first-line treatment with either abiraterone or enzalutamide, meaning that their prostate-specific antigen (PSA) values do not decrease or their tumours do not regress.

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



Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

Howard I. Scher, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Mary-Ellen Taplin, M.D., Cora N. Sternberg, M.D., Kurt Miller, M.D., Ronald de Wit, M.D., Peter Mulders, M.D., Ph.D., Kim N. Chi, M.D., Neal D. Shore, M.D., Andrew J. Armstrong, M.D., Thomas W. Flaig, M.D., Audie Filchun, M.D., Ph.D., Paul Mainwaring, M.D., Mark Fleming, M.D., John D. Hainsworth, M.D., Mohammad Hirmand, M.D., Bryan Selby, M.S., Lynn Seely, M.D., and Johann S. de Bono, M.B., Ch.B., Ph.D., for the AFFIRM Investigators*

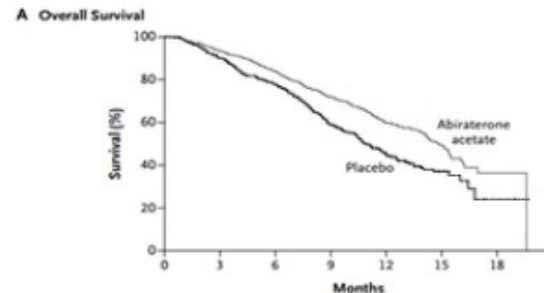


No. at Risk	0	3	6	9	12	15	18	21	24
Enzalutamide	800	775	701	627	400	211	72	7	0
Placebo	399	376	317	263	167	81	33	3	0



Abiraterone and Increased Survival in Metastatic Prostate Cancer

Johann S. de Bono, M.B., Ch.B., Ph.D., Christopher J. Logothetis, M.D., Arturo Molina, M.D., Karim Fizazi, M.D., Ph.D., Scott North, M.D., Luis Chu, M.D., Kim N. Chi, M.D., Robert J. Jones, M.D., Oscar S. Goodman, Jr., M.D., Ph.D., Fred Saad, M.D., John H. Staffurth, M.D., Paul Mainwaring, M.D., M.B., B.S., Stephen Mariani, M.D., Thomas W. Flaig, M.D., Thomas E. Hutson, D.O., Ph.D., Tina Cheng, M.D., Helen Patterson, M.D., John D. Hainsworth, M.D., Charles J. Ryan, M.D., Cora N. Sternberg, M.D., Susan I. Eland, M.D., Audie Filchun, M.D., Ph.D., Mansoor Saleh, M.D., Mark Scholz, M.D., Elton Efstathiou, M.D., Ph.D., Andrea Zivi, M.D., Daniela Brundini, M.D., Valérie Loriot, M.D., Shihua Chen, M.B.A., Tapan Khushi, Ph.D., Christopher M. Hagg, M.D., Ph.D., and Howard I. Scher, M.D., for the COU-AA-301 Investigators*



No. at Risk	0	3	6	9	12	15	18	21
Abiraterone acetate	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

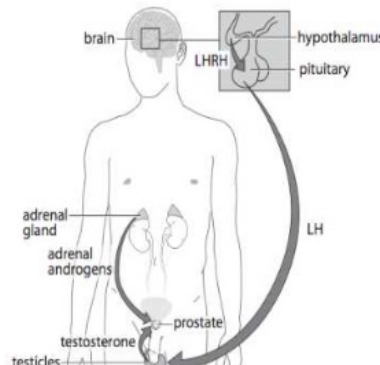
Charles Brenton Huggins



Charles Brenton Huggins

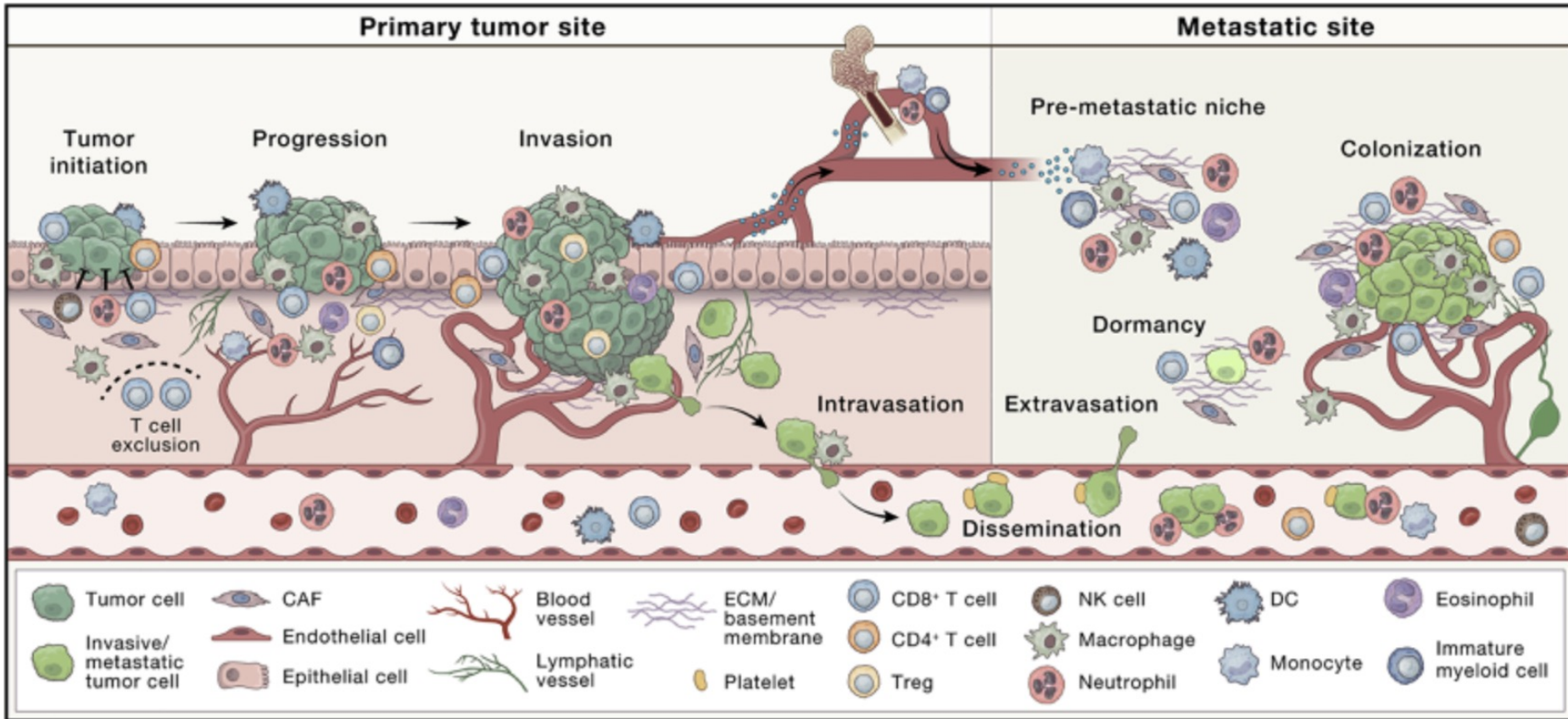
Born September 22, 1901
Halifax, Nova Scotia

The Nobel Prize in Physiology or Medicine



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

Microenvironmental of primary tumor progression and metastasis

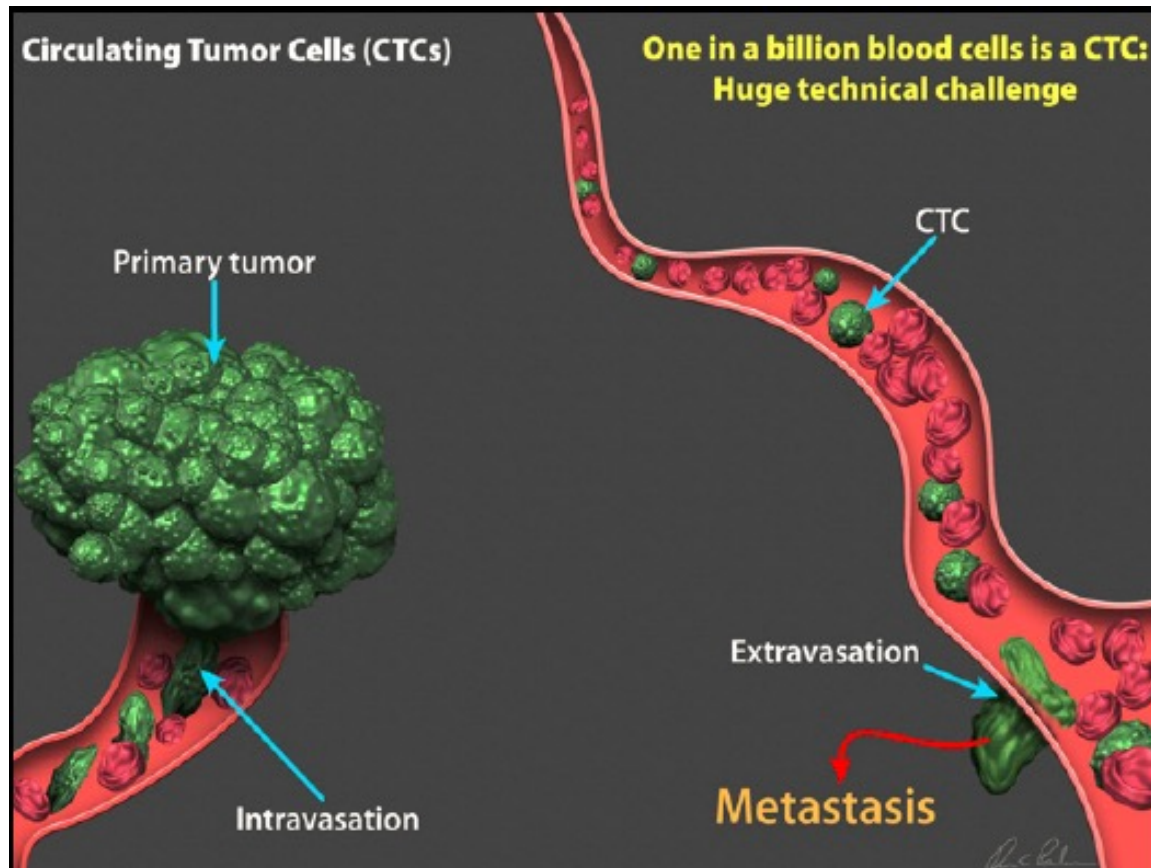


From J. Joyce et al 2023 Cancer Cell 41: 375-403

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 WORLDWIDE DIE EVERY YEAR OF CANCER METASTASIS (NOT FROM PRIMARY TUMOR) !
- NOBODY KNOWS HOW TO PREVENT FORMATION OF METASTASIS !





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

Liquid Biopsy

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



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

Circulating Tumor Cells CTCs

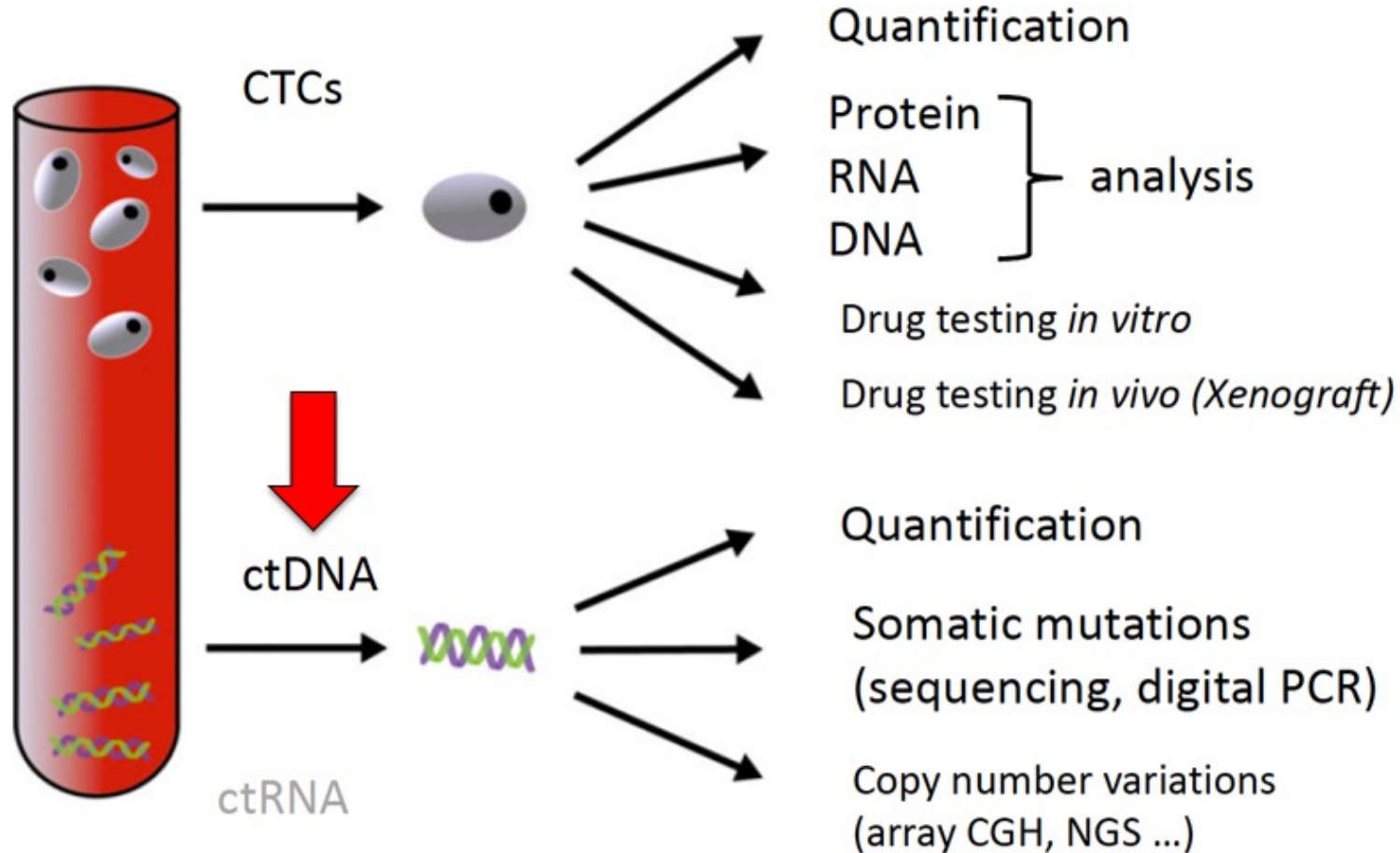


- **CTCs MAY ORIGINATE FROM DIFFERENT PARTS OF THE PRIMARY TUMOR !**
- **90% OF CANCER RELATED DEATHS ARE DUE TO DEVELOPMENT OF METASTASIS**
- **7 MILLIONS PATIENTS WORDWIDE DIE EVERY YEAR OF CANCER METASTASIS (NOT FROM PRIMARY TUMOR) !**
- **NOBODY KNOWS HOW TO PREVENT FORMATION OF METASTASIS !**





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



REVIEWS

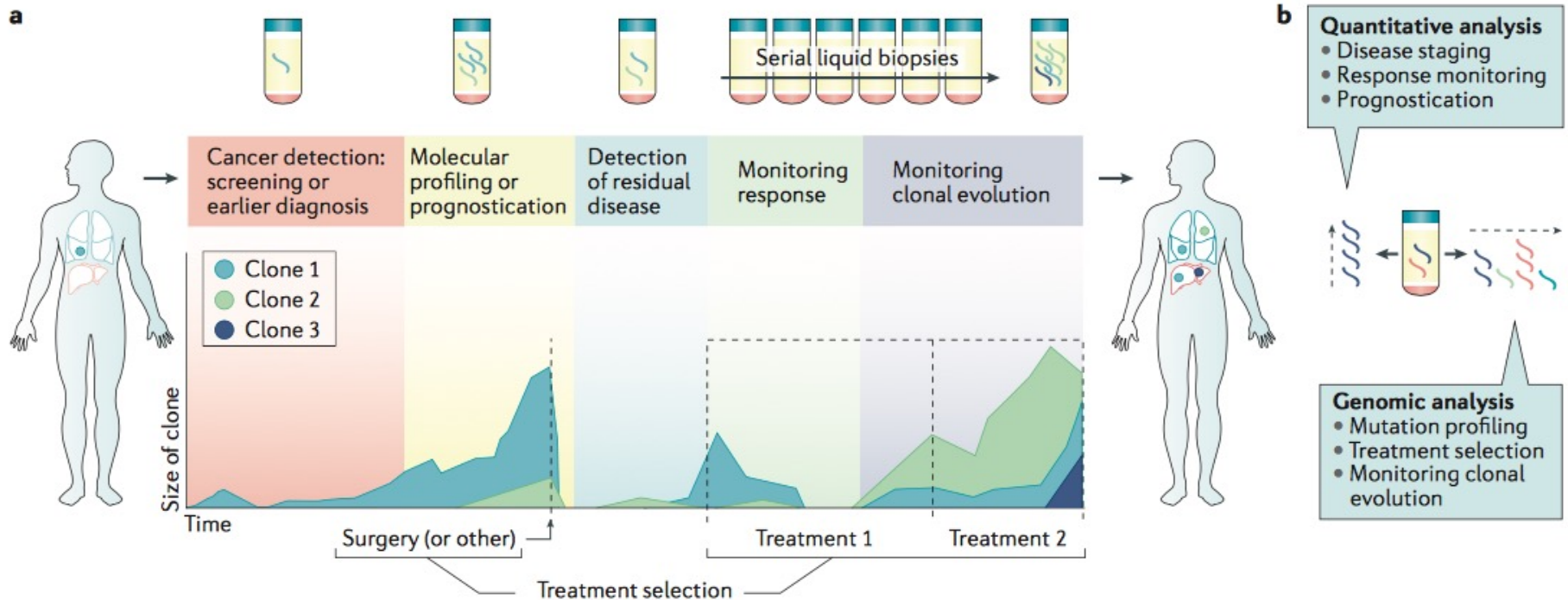
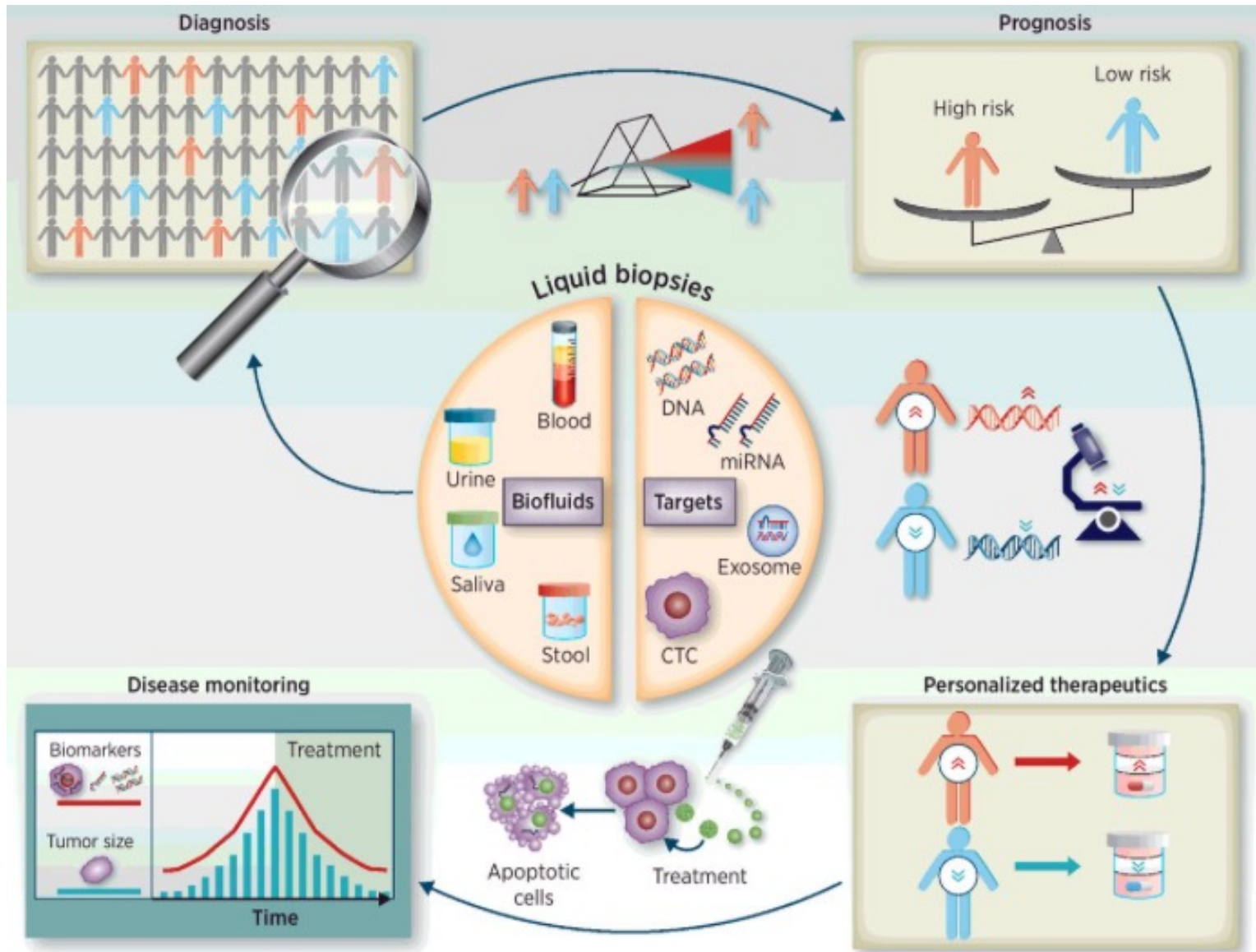


Figure 1 | Applications of circulating tumour DNA analysis during the course of disease management. **a** | A schematic

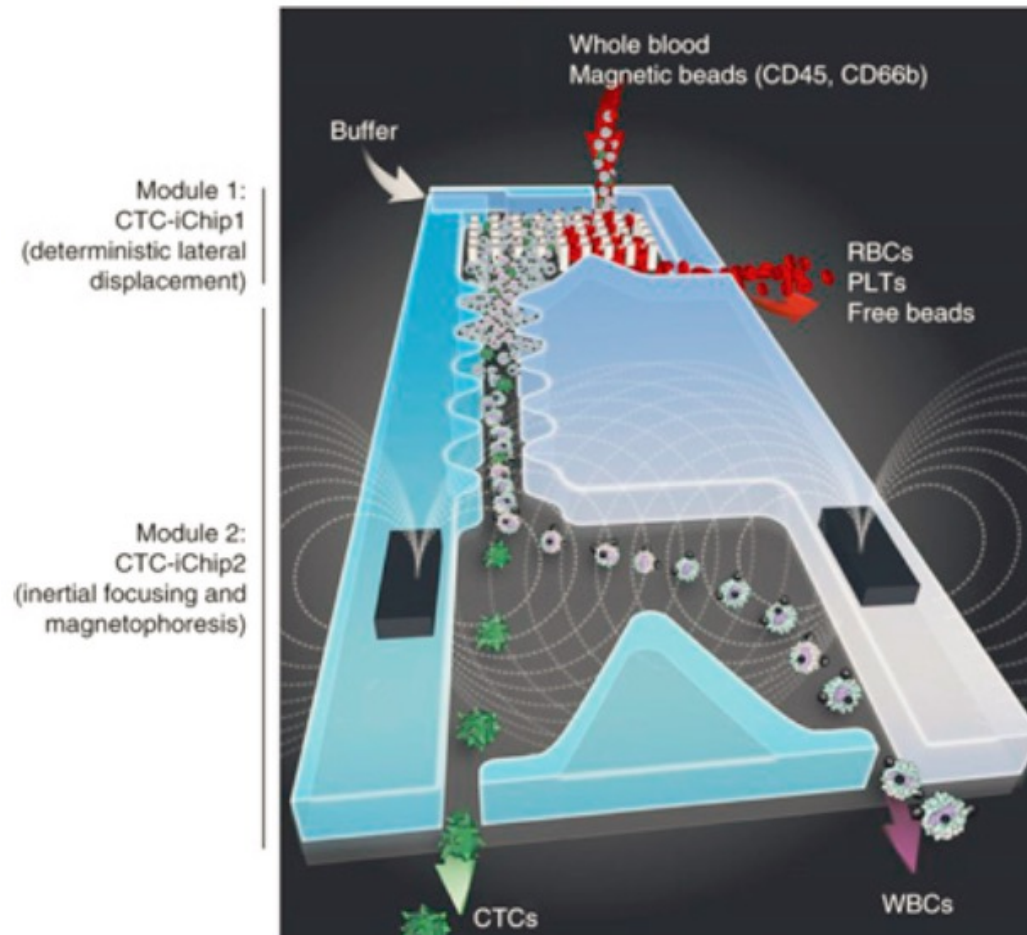
Acute metastases may be kept up as a chronic disease upon serial liquid biopsies and evasive cancer drug resistance scrutiny

Patient tailored metastasis evasive cancer drug resistance

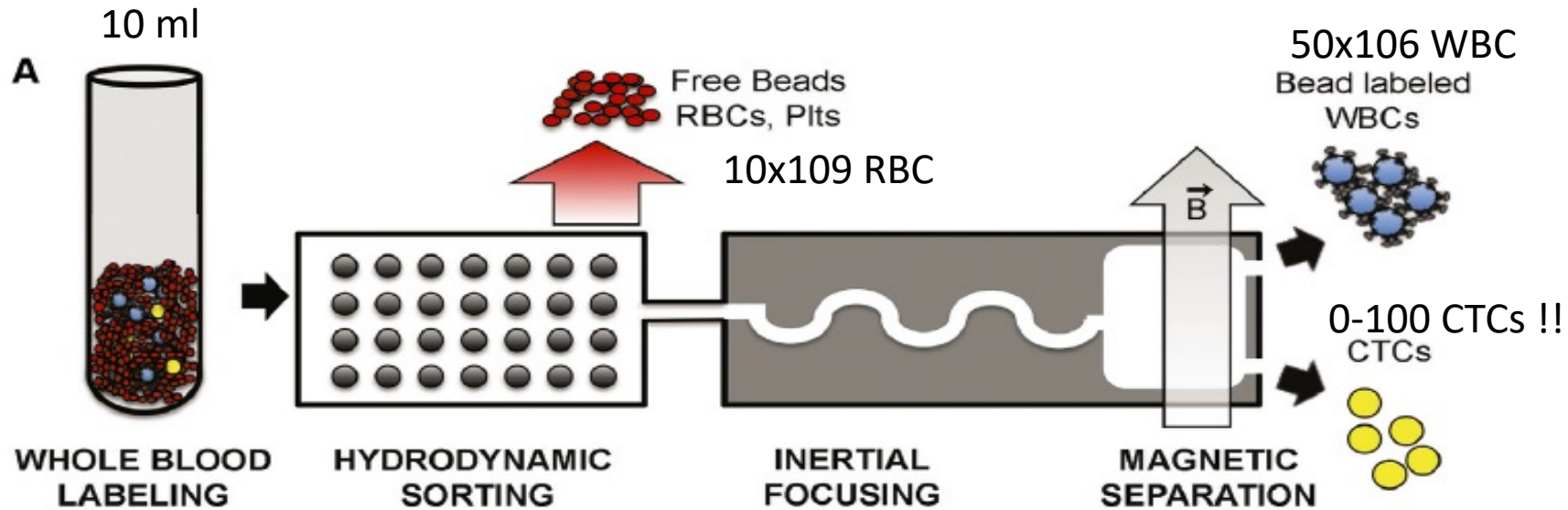




Negative selection (Markers) – e.g. “CTC-iChip”



Microfluidics allows to separate CTCs from whole blood !



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

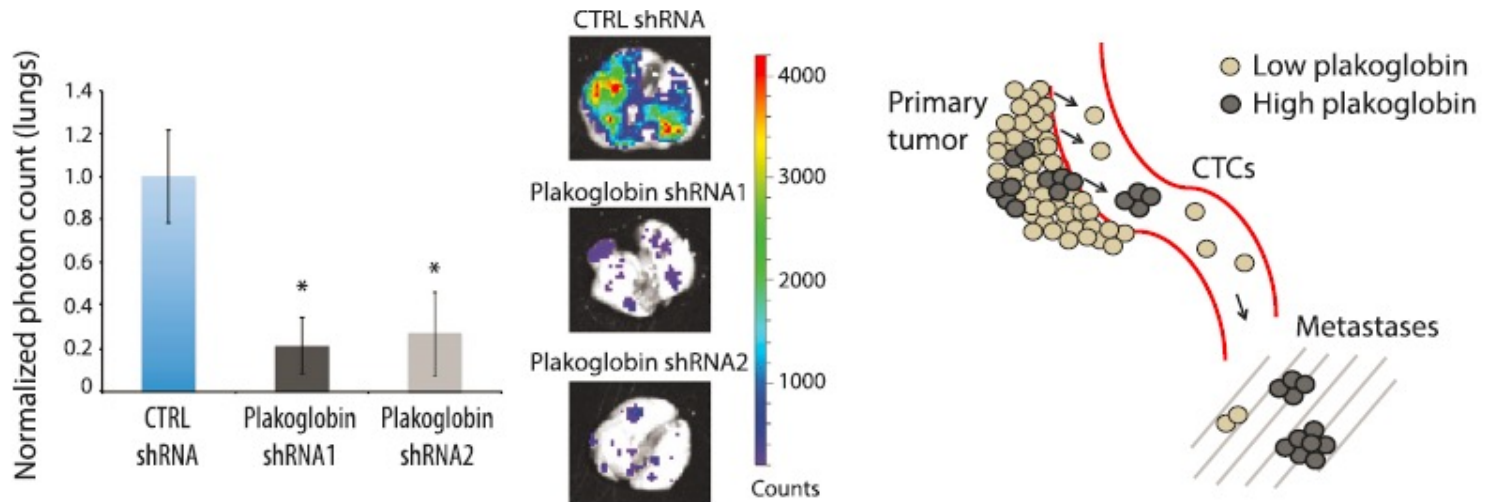


Figure 7. Plakoglobin Is Required for CTC Cluster Formation and Lung Metastasis

CTCs from whole blood can traverse the capillary bed !

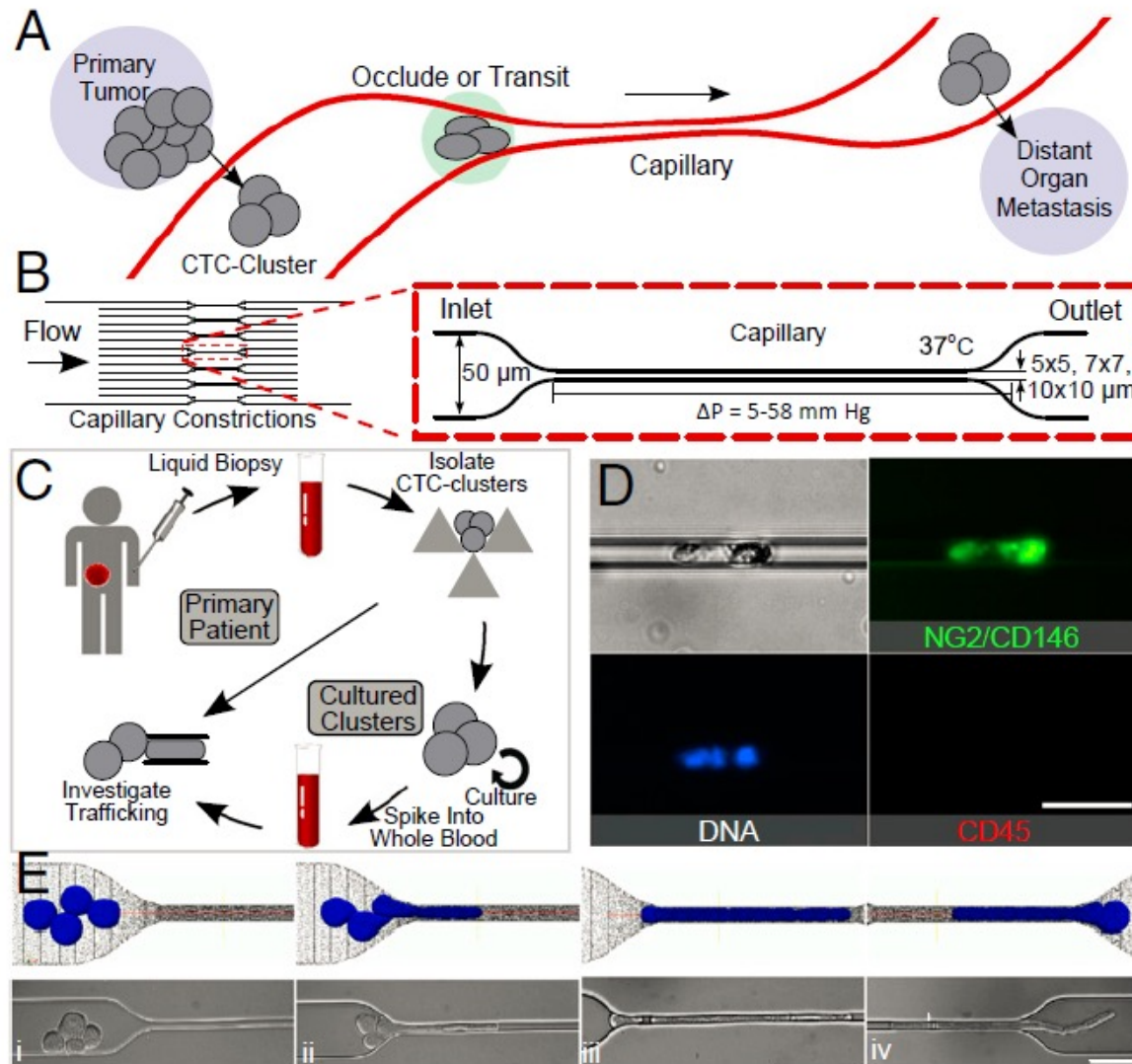
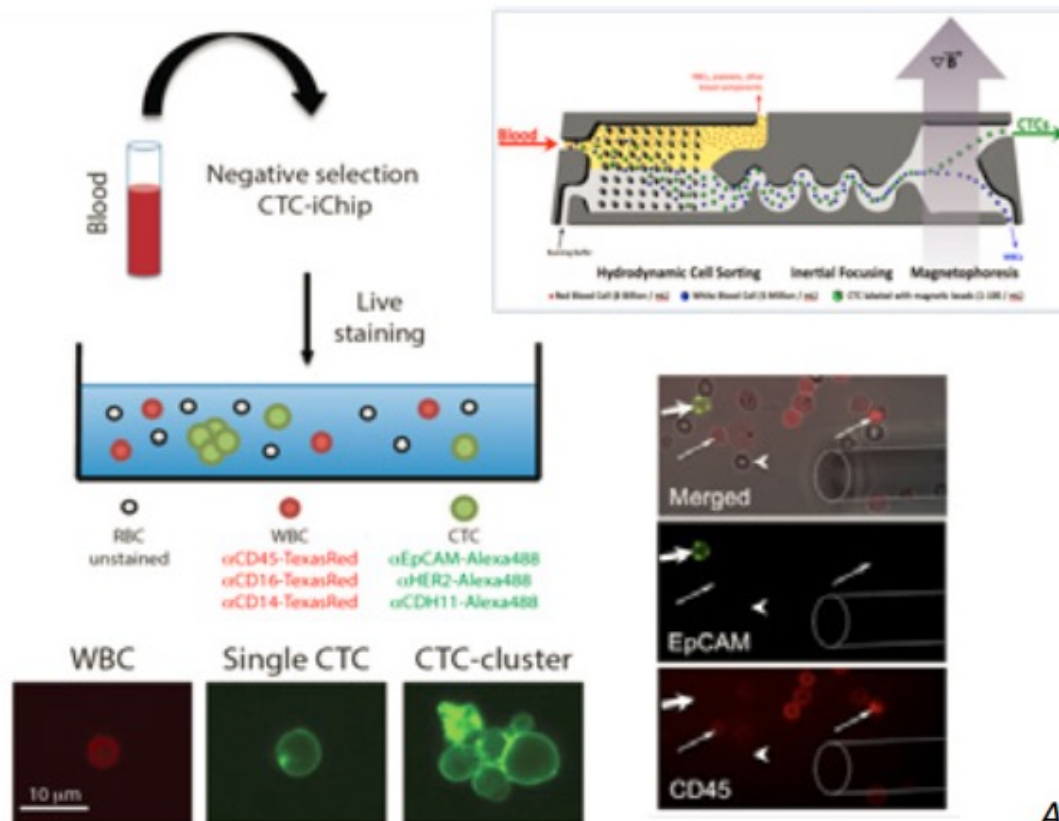


Fig. 1. (A) Diagram of CTC clusters occluding or transiting through capillary

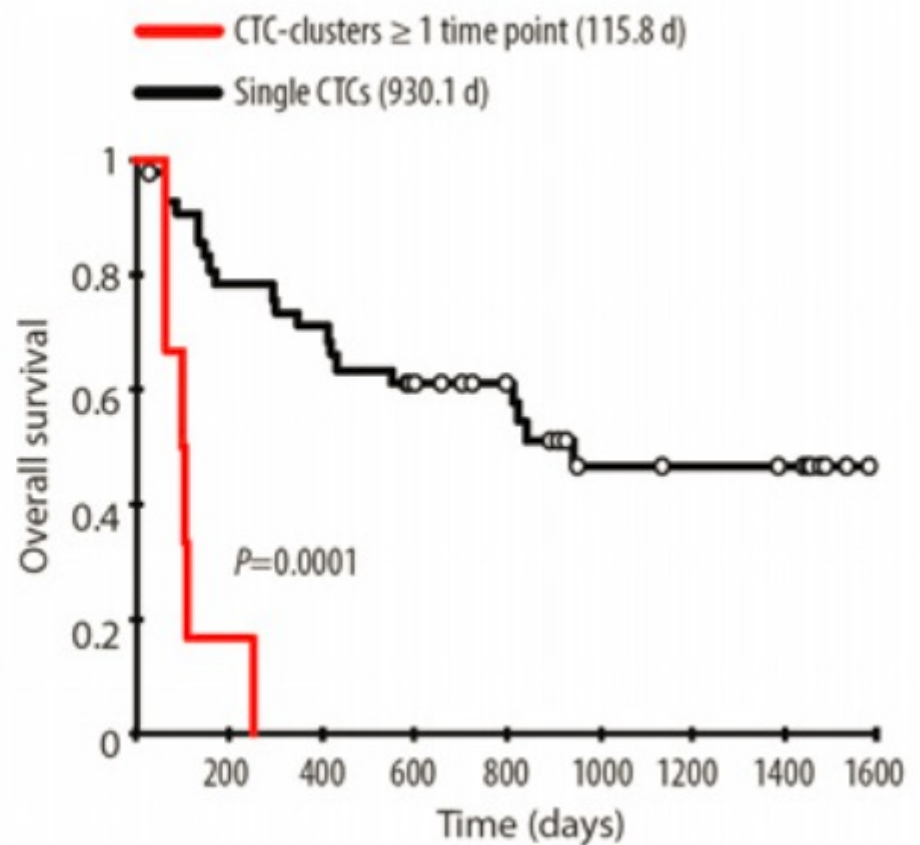
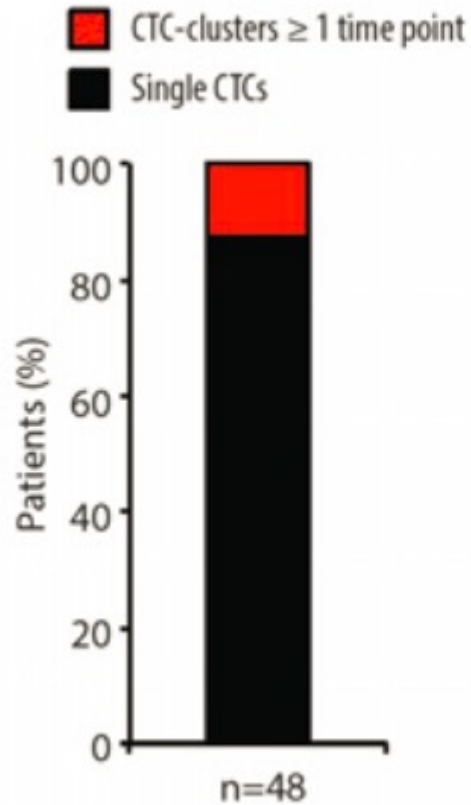
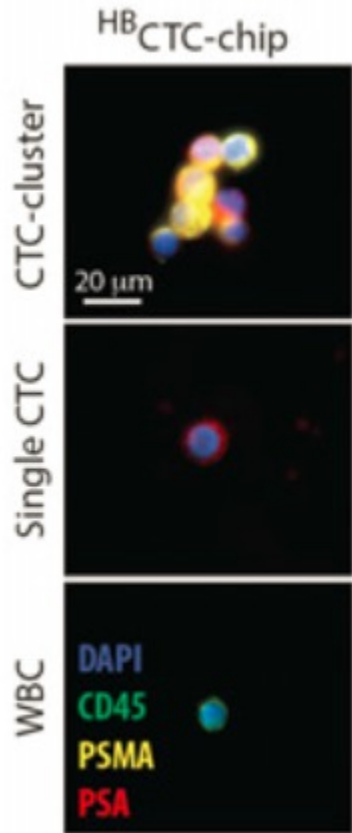


CTCs from patients with breast cancers:

- Cell surface staining (EpCAM, HER2, CDH11) for micromanipulator and RNA seq

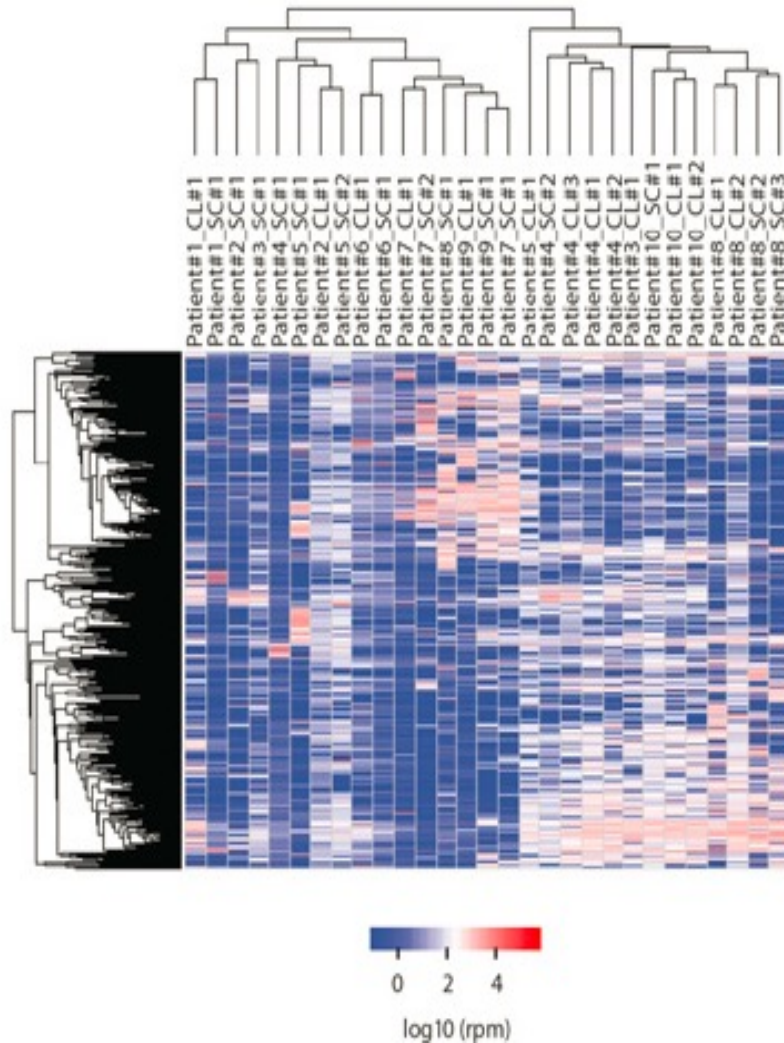


CTC clusters in patients with metastatic prostate cancer

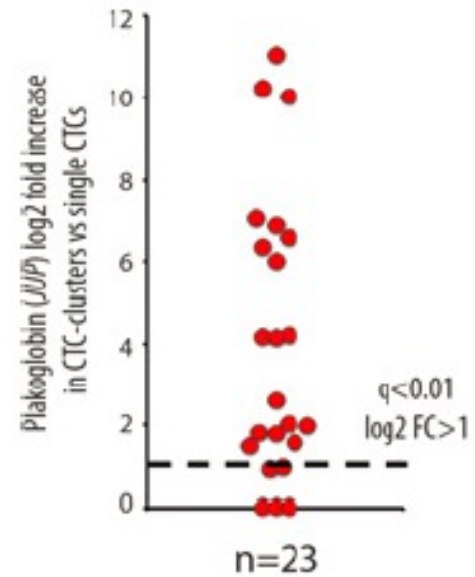


CTC clusters demonstrate increased metastatic potential compared to single CTCs

Single cell transcriptomics of CTC vs CTC clusters

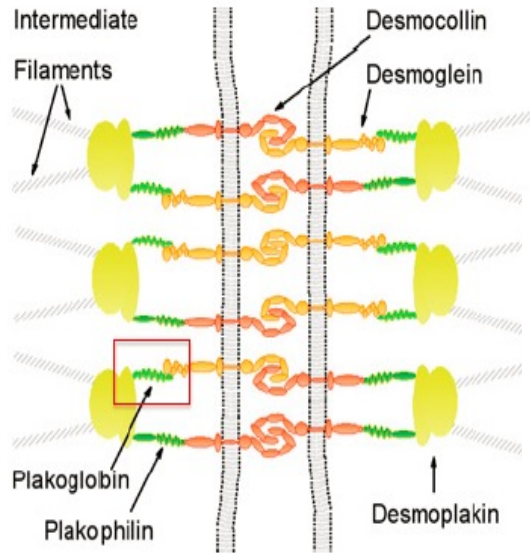


Plakoglobin increased
~215-fold in clusters vs
Single CTCs

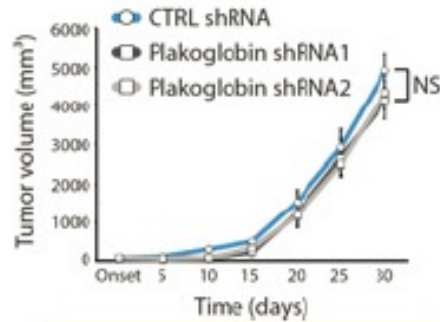


Aceto et al., *Cell*, 2014

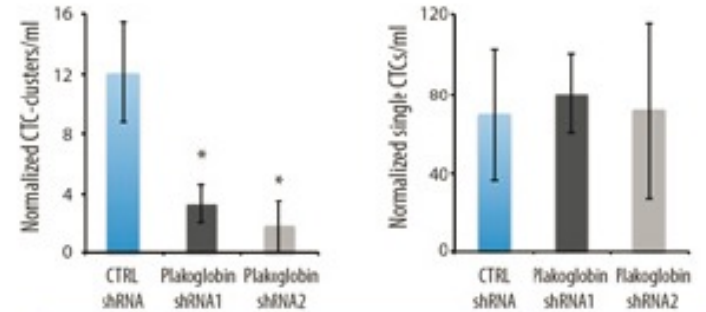
CTC vs CTC clusters in tumor metastasis



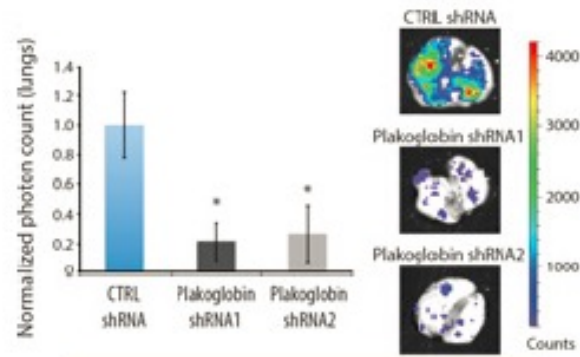
Plakoglobin knock down in primary tumor suppresses lung metastasis

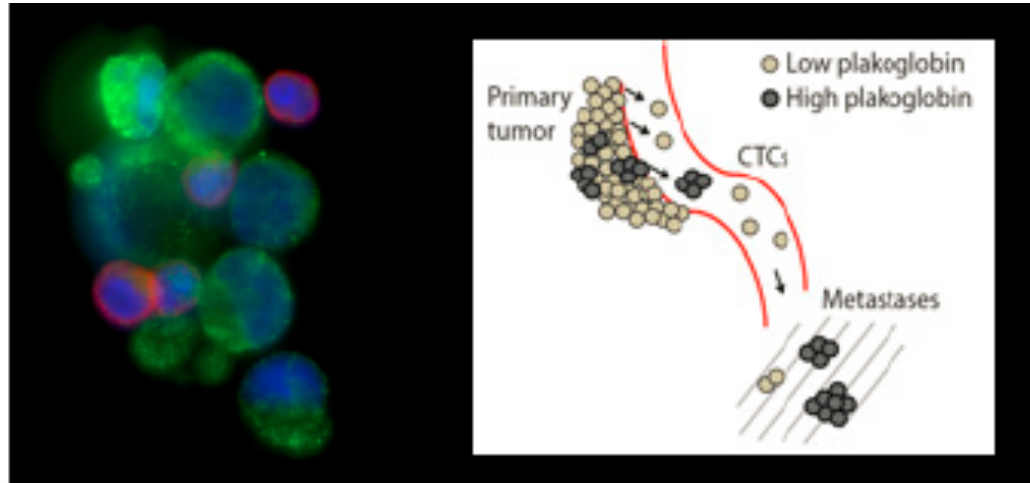


No change in growth of primary tumor xenograft



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



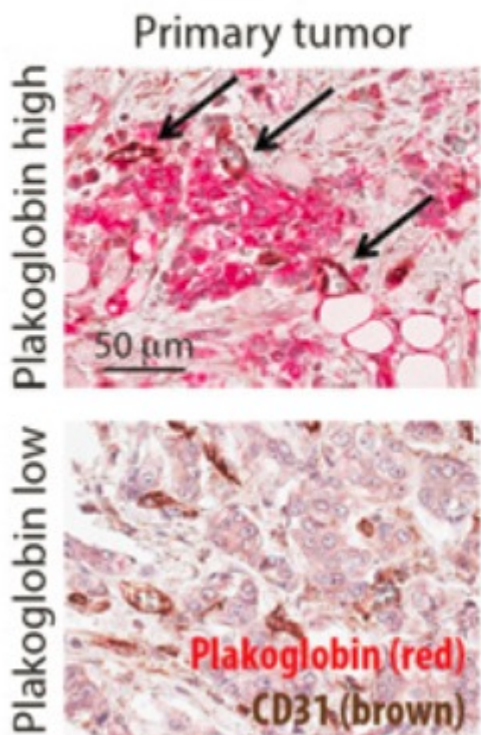


1. CTC-clusters originate from *individual tumor deposits* and are not the result of intravascular tumor cell aggregation
2. CTC-clusters are *rare but highly metastasis-competent*, accounting for half of metastatic lesions in mouse model
3. *Plakoglobin* helps tether CTCs within clusters, thereby enhancing metastatic spread

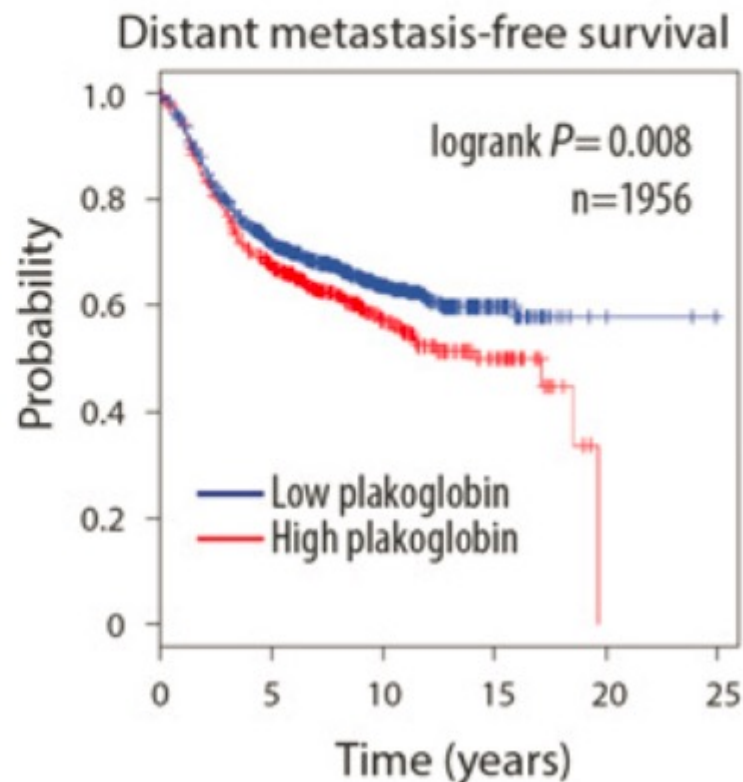
Plakoglobin in primary breast cancer tumors



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

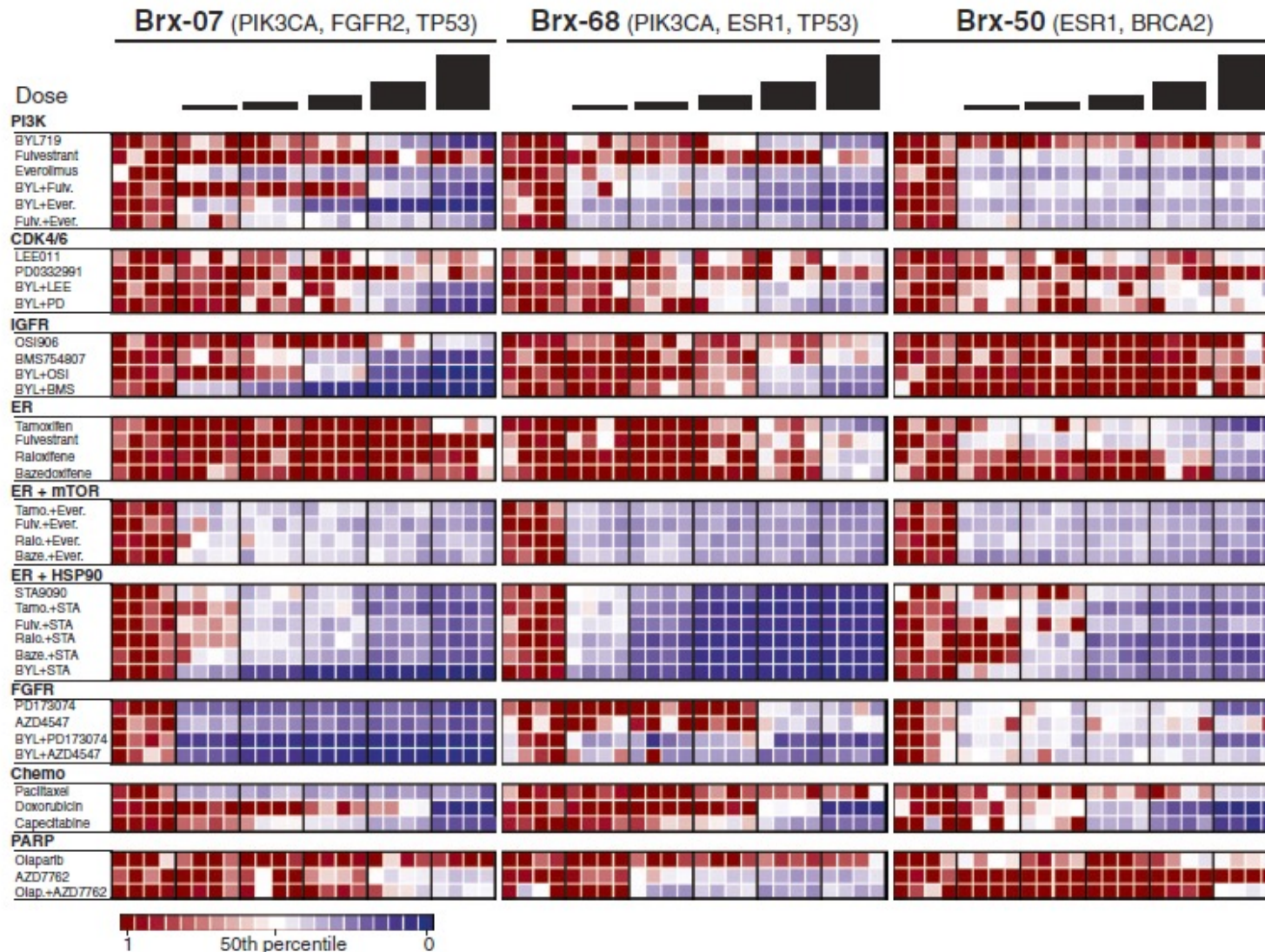


Fig. 2. Drug sensitivity of cultured CTCs. Heatmaps representing cell viability after treatment of BRx-07, BRx-68, and BRx-50 CTC lines with selected anti-

dose, with each concentration tested in quadruplicate. Drug concentrations are listed in table S3. Signal from viable cells remaining after drug treatment

Patient tailored metastasis evasive cancer drug resistance screen

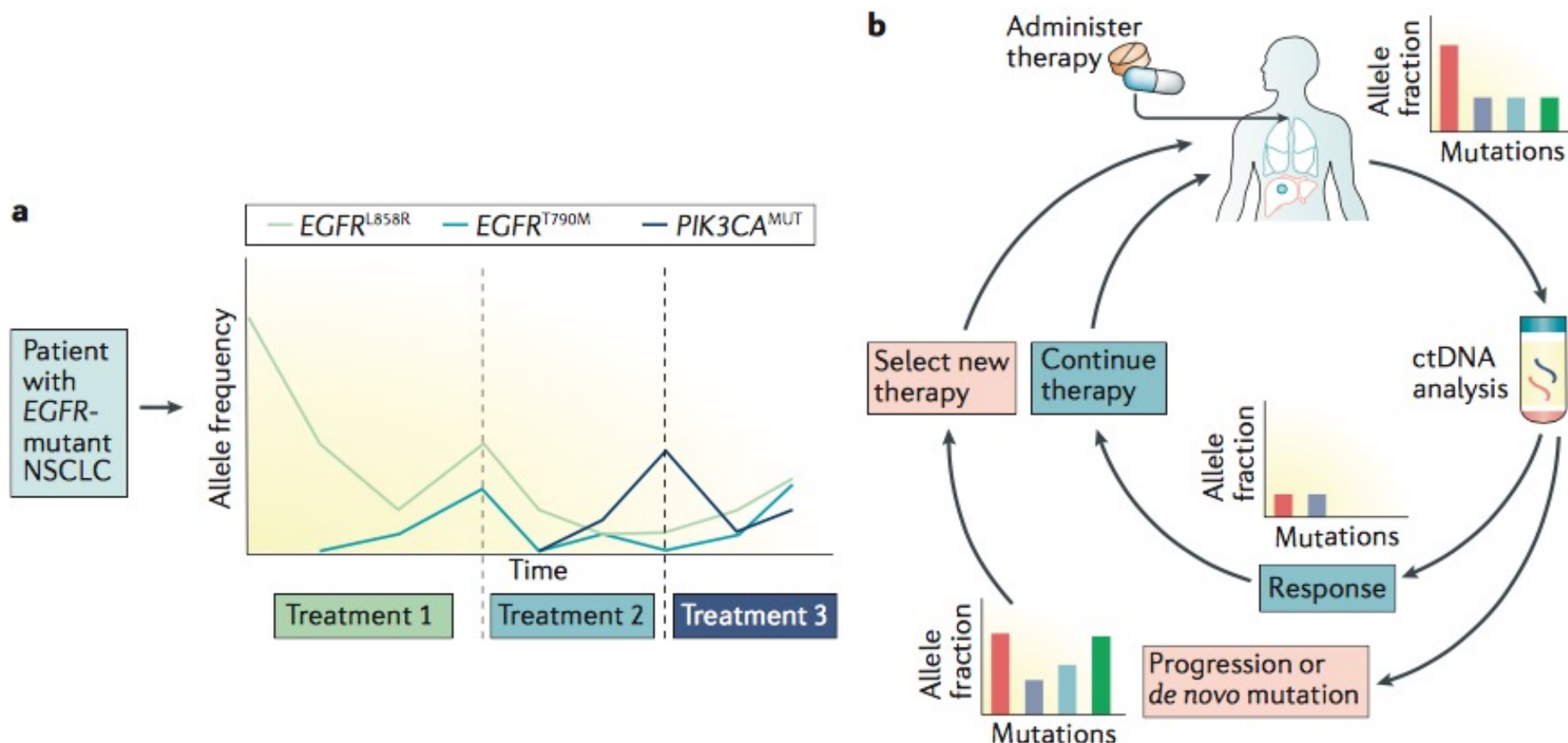
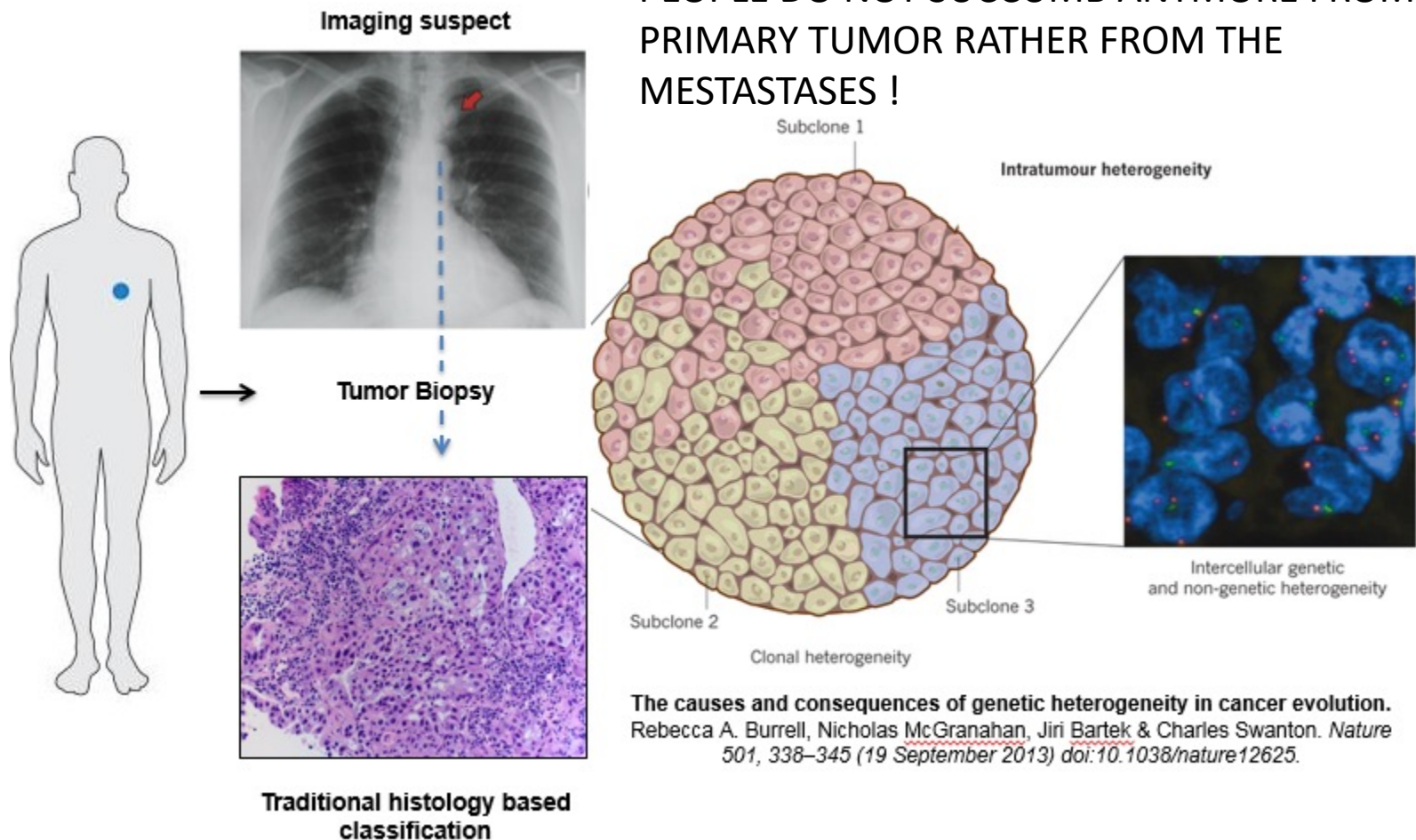


Figure 5 | **Adaptive or reactive treatment paradigms using liquid biopsies.** **a** | During systemic anticancer therapy,

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 !



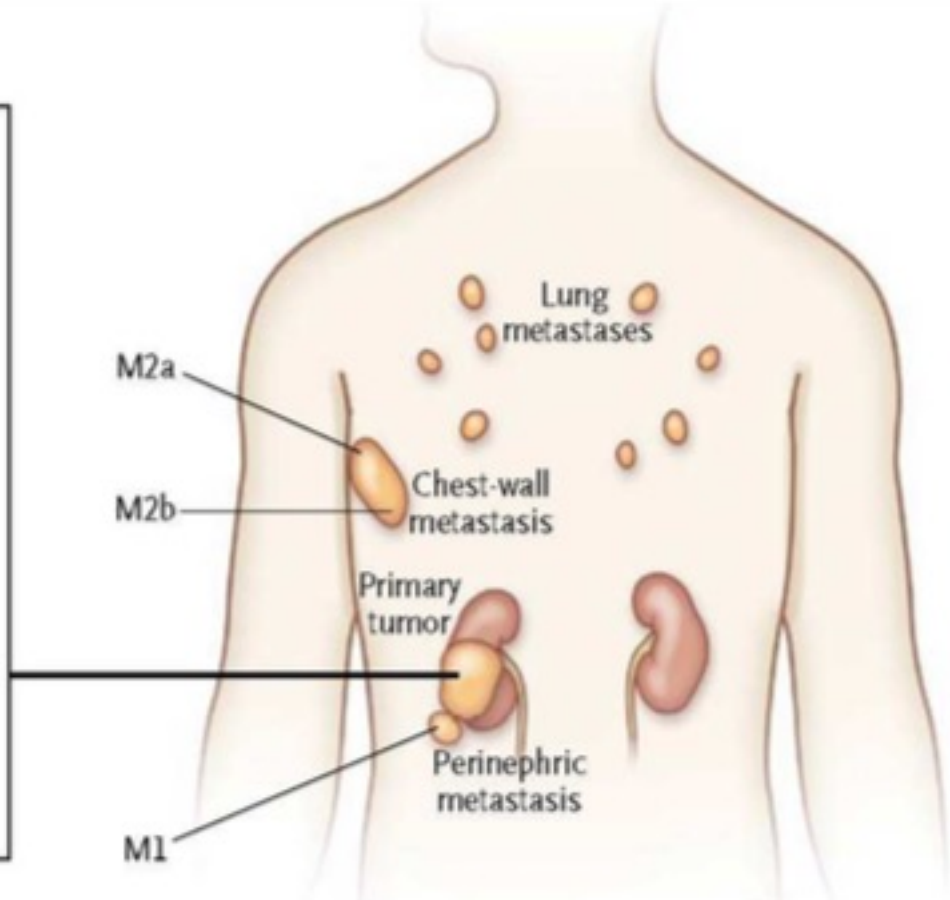
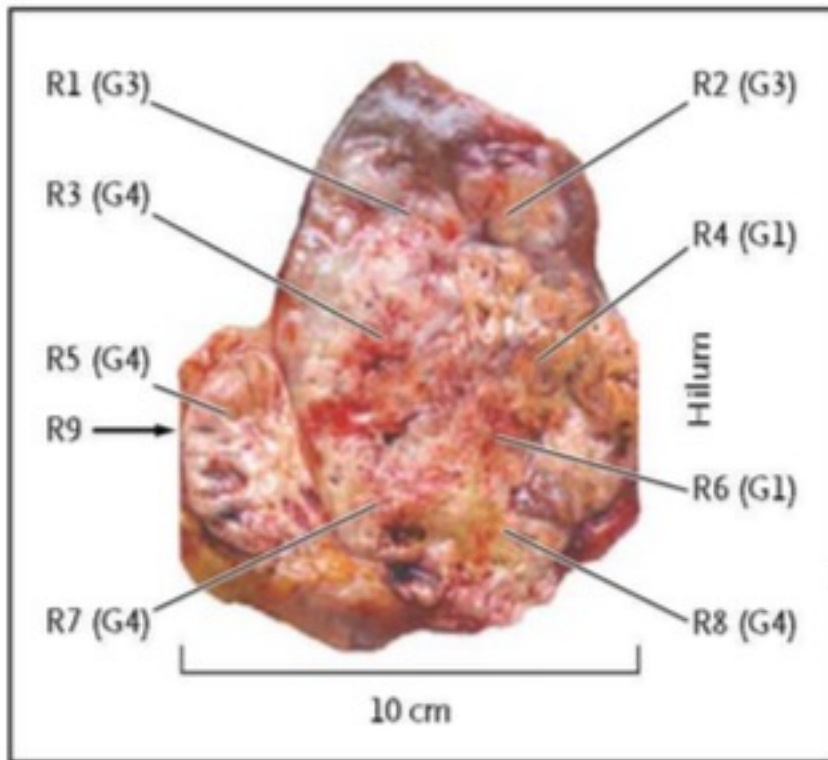
The causes and consequences of genetic heterogeneity in cancer evolution.
Rebecca A. Burrell, Nicholas McGranahan, Jiri Bartek & Charles Swanton. *Nature* 501, 338–345 (19 September 2013) doi:10.1038/nature12625.

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



Intratumor heterogeneity and multiregion Sequencing branched Evolution

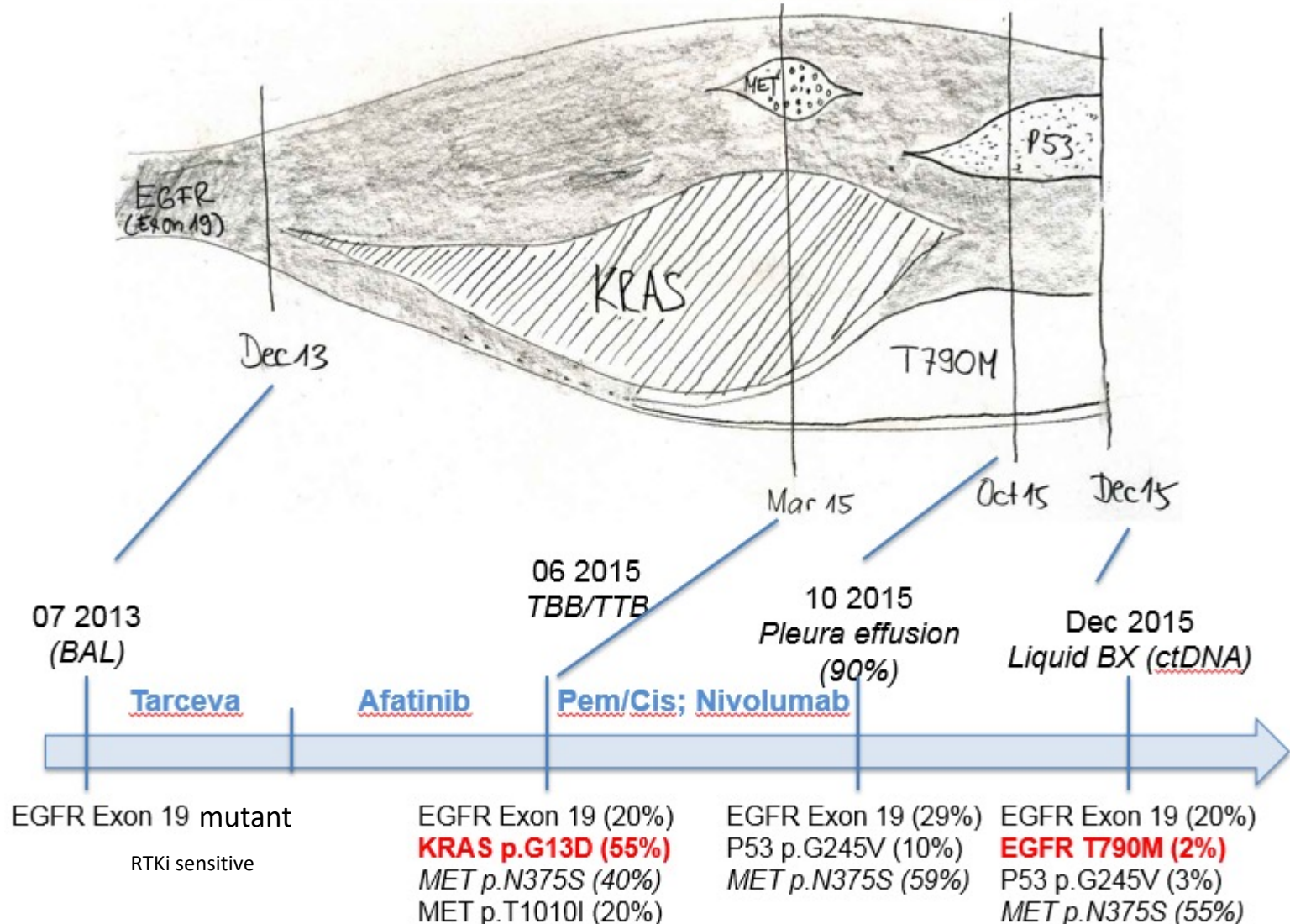
Biopsy Sites



PHC_ tumour heterogeneity



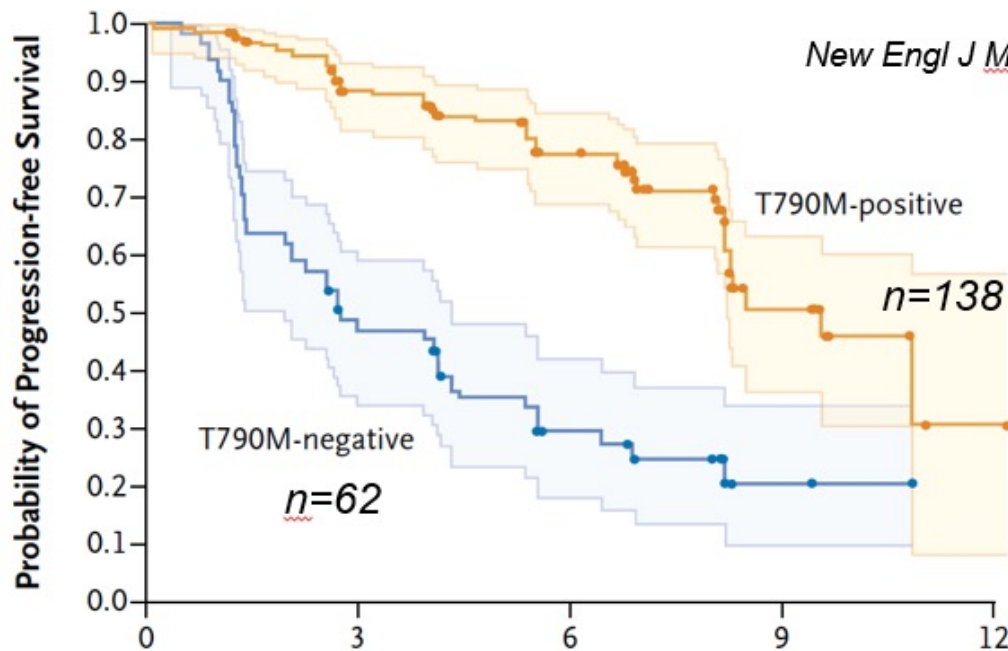
Clinical Case Example: Lung Adenocarcinoma Patient





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



THANK YOU.....

DO YOU HAVE ANY QUESTIONS ?



How our thoughts can impact on your body : psychosomatic symptoms



Today's QUIZ



1	2 main options to modulate a therapeutic target
2	antagomirs
3	medicinal chemistry
4	personalized healthcare
5	animal pharmacology for obesity diabetes
6	biomarker
7	tumor suppressor gene (two hits hypothesis A.Knudson)
8	circulating tumor cells

A	extravasation of cells to build metastases
B	any analyte from body fluids or tissues
C	stratify patient cohorts according to biomarker
D	small MW cpds OR biologicals (eg Mabs)
E	synthesis of clinically approved small MW cpds
F	block miRs (micro RNA)
G	ob/ob mouse (leptin pathway)
H	regulate cell cycle, apoptosis, etc when mutated tumorigenic, eg Rb

1	__
2	__
3	__
4	__
5	__
6	__
7	__
8	__

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1	<u>D</u>
2	<u>E</u>
3	<u>E</u>
4	<u>C</u>
5	<u>G</u>
6	<u>B</u>
7	<u>H</u>
8	<u>A</u>