

An introduction to the cancer genome and mutational processes in cancer

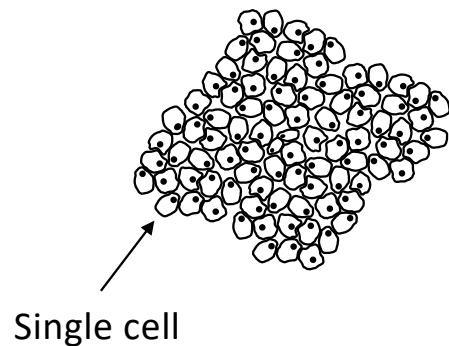


Karolinska
Institutet

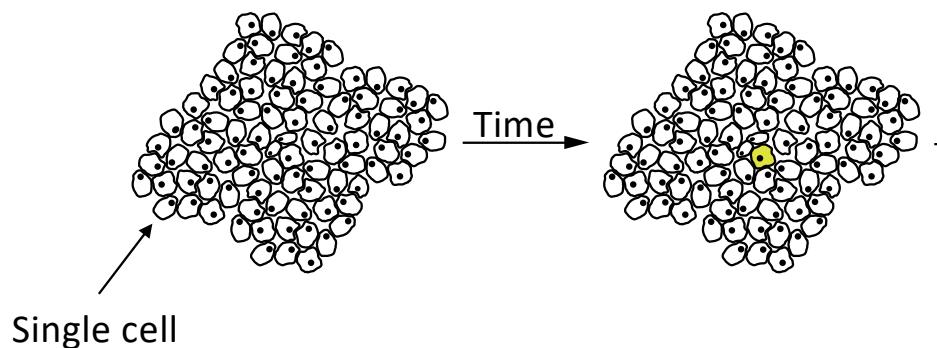
Learning outcomes

- Lectures:
 - show a basic insight into the cancer genome.
 - understand how the cancer genome can be interrogated through tissues and liquid biopsies.
 - understand how to apply technology to obtain relevant information from the cancer genome.
- Labwork
 - use the command line and running bioinformatic tools.
 - visualise data in R.

We are a mosaic of cells



We are a mosaic of cells

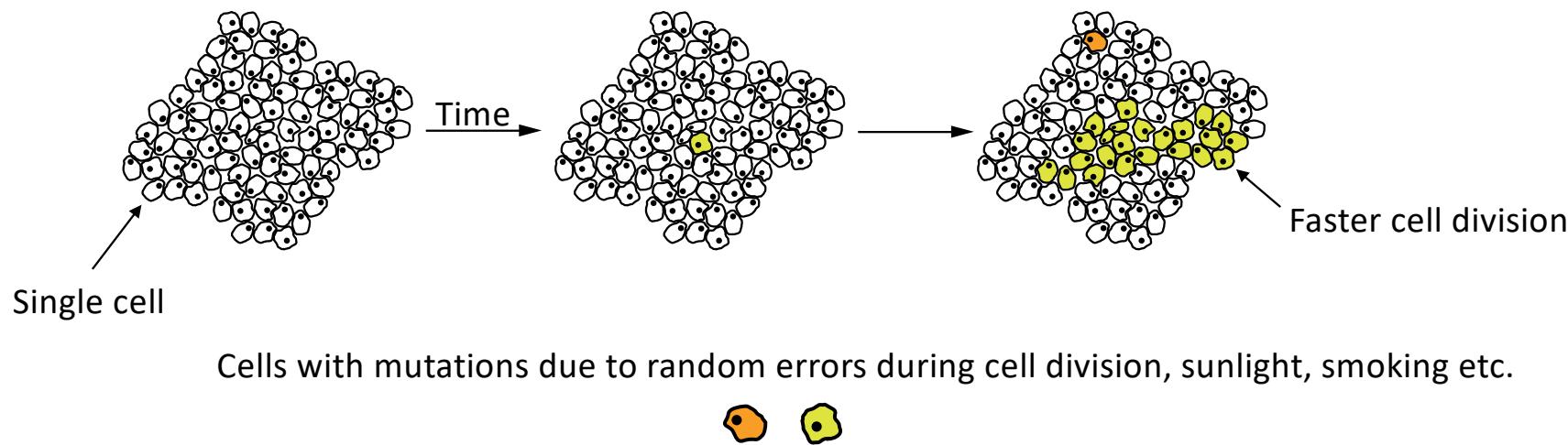


Cells with mutations due to random errors during cell division, sunlight, smoking etc.

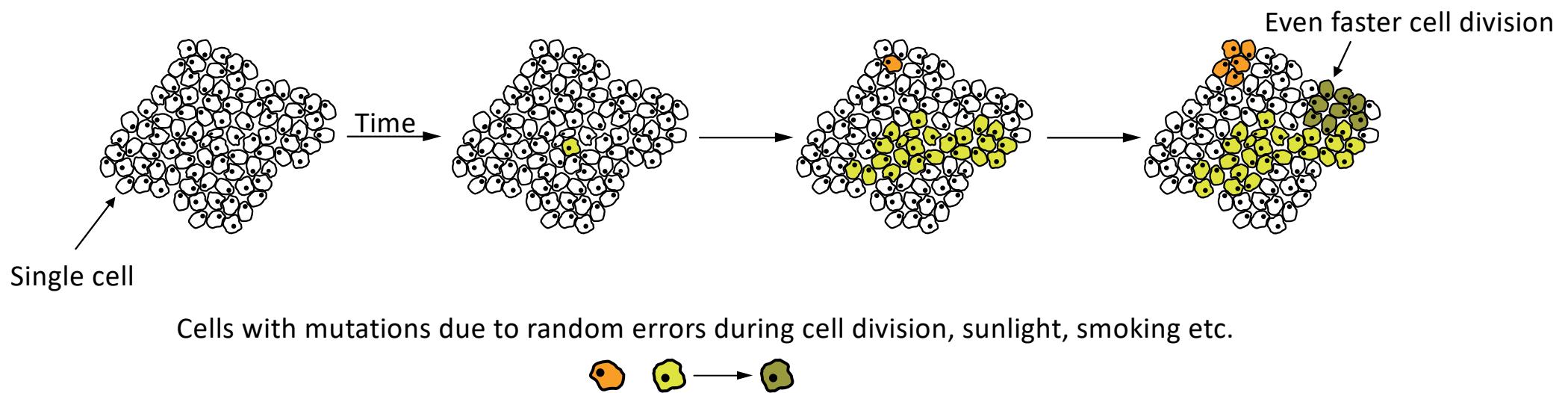


mutations = any type of somatic alteration

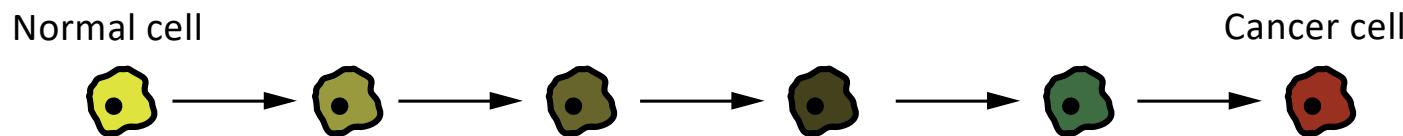
We are a mosaic of cells



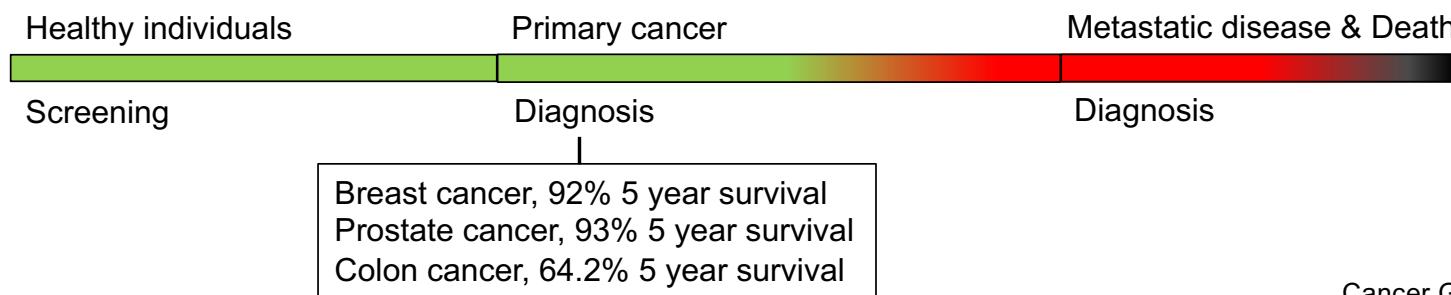
We are a mosaic of cells



We are a mosaic of cells

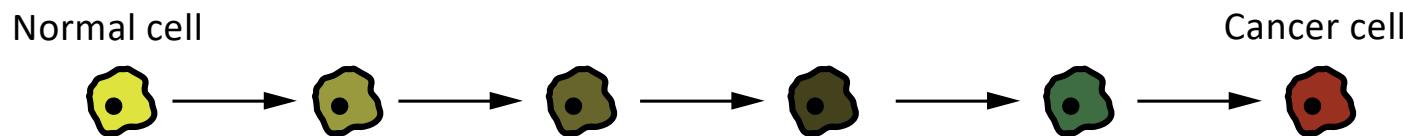


- Cancer occurs through sequential somatic mutations
- Take decades to develop
- Majority of deaths are due to late detection (after 90% of cancers lifespan)
- Potential mortality reduction by >75% if improvements are made in early detection/prevention



Cancer Genome Landscapes, Science 2013

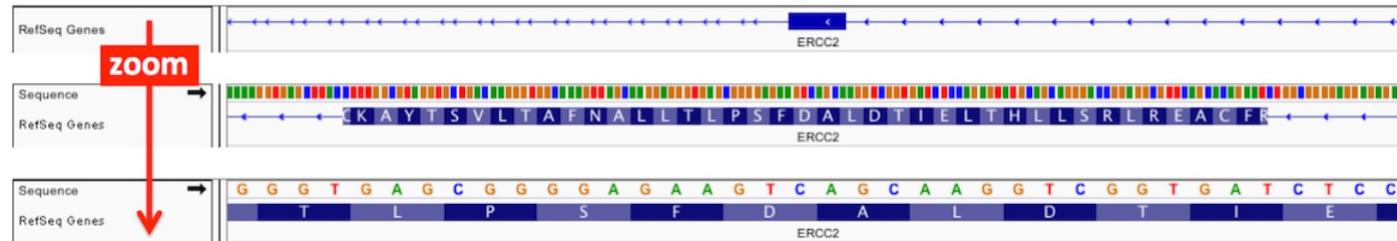
We are a mosaic of cells



- Cancer genomics: the study of the totality of DNA sequence and phenotype differences between tumour cells and normal cells.
- Purpose:
 - to improve treatment selection.
 - to reduce overtreatment.
 - early detection and diagnosis.
 - to reduce mortality.
- Sequencing: the main tool to perform cancer genomics.

The Sequencing revolution

- Sequencing = to determine the order of nucleotides in a DNA molecule.

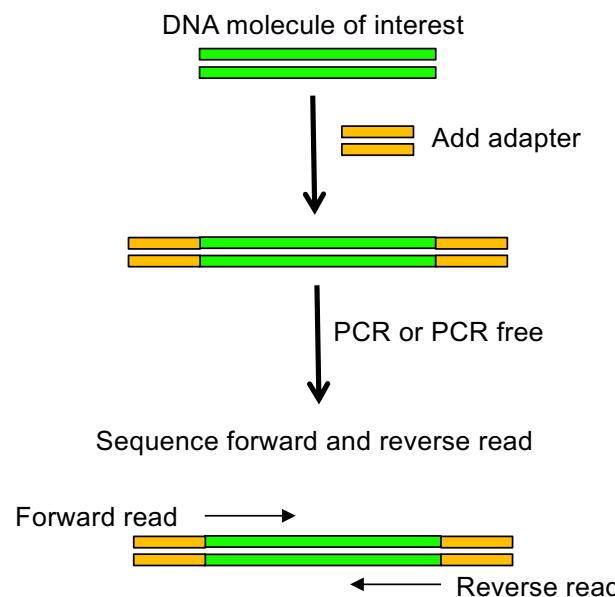


Sequencing:

- DNA
- RNA
- DNA modifications (methylation sequencing)
- Protein localization on DNA

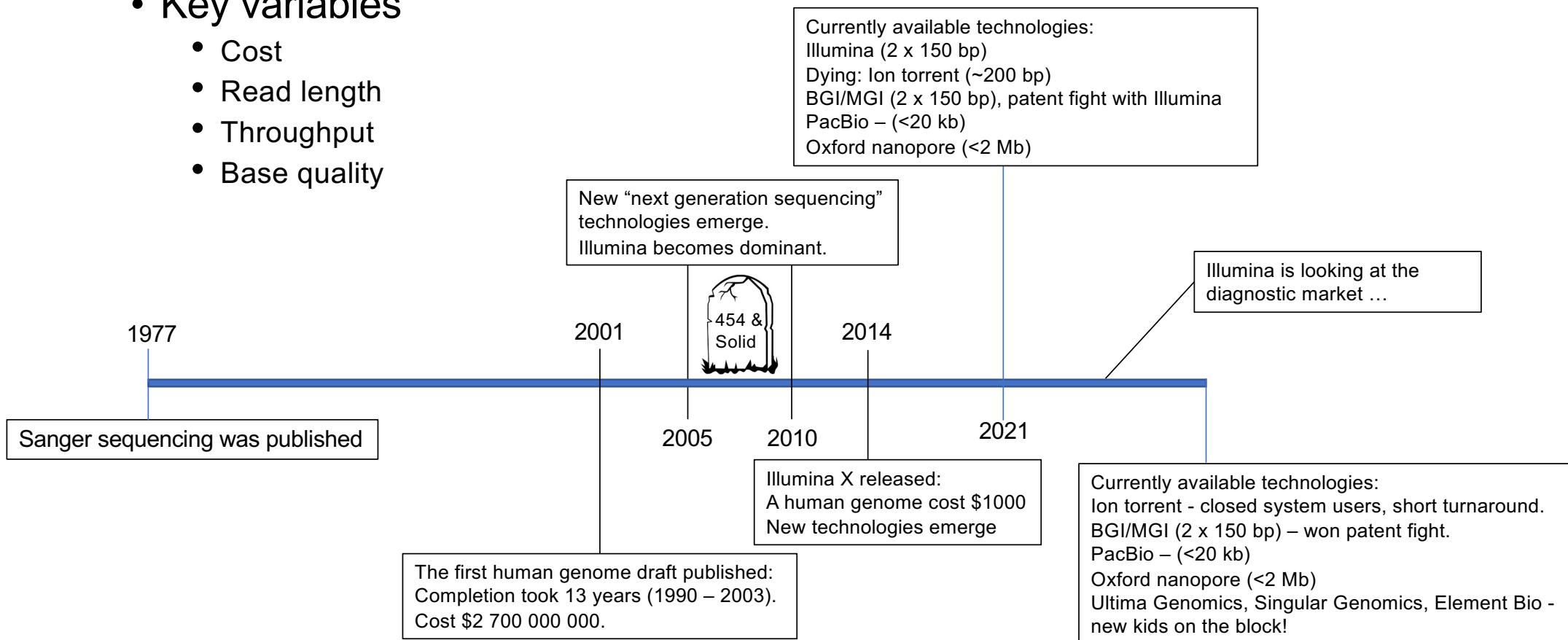
The Sequencing revolution

- Key variables
 - Cost
 - Read length
 - Throughput
 - Base quality/error rate

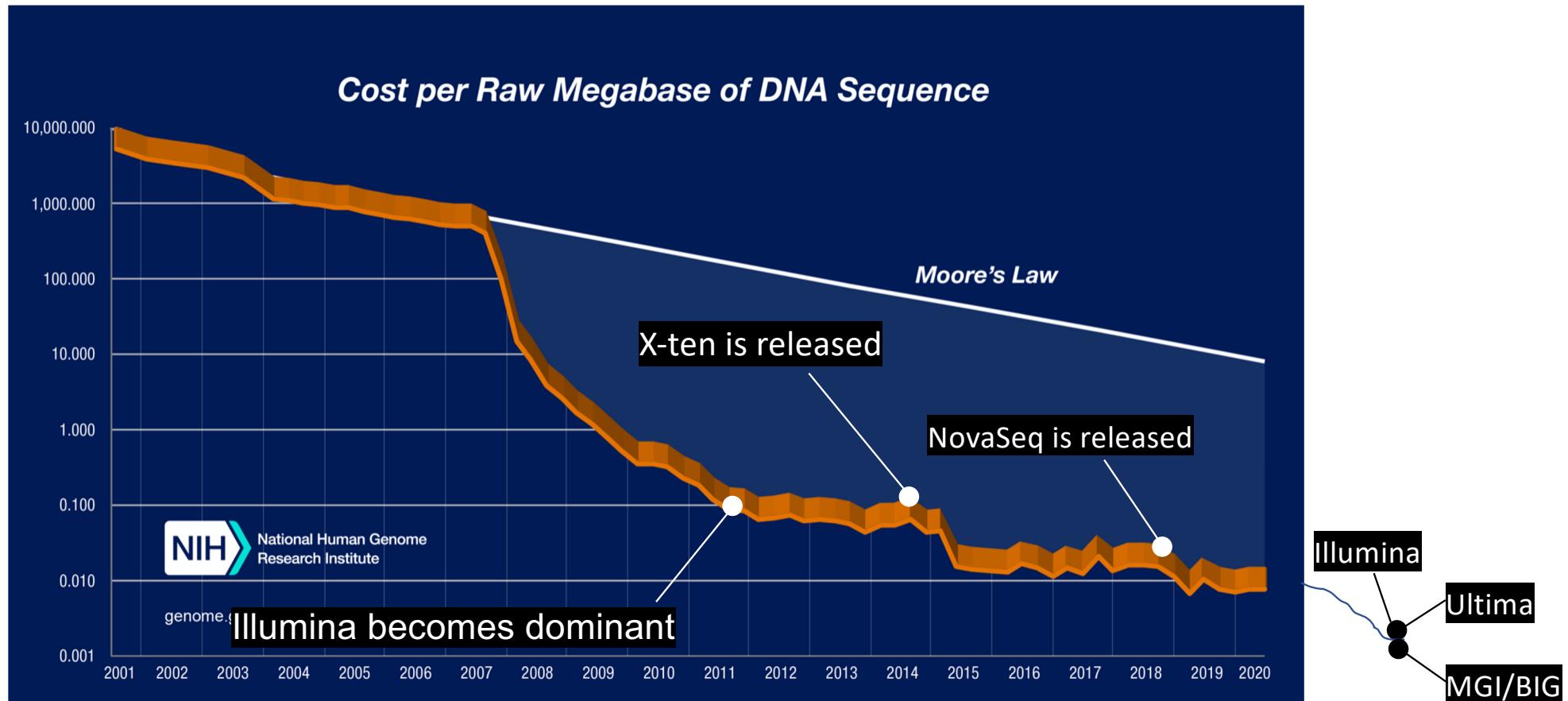


The Sequencing revolution

- Key variables
 - Cost
 - Read length
 - Throughput
 - Base quality

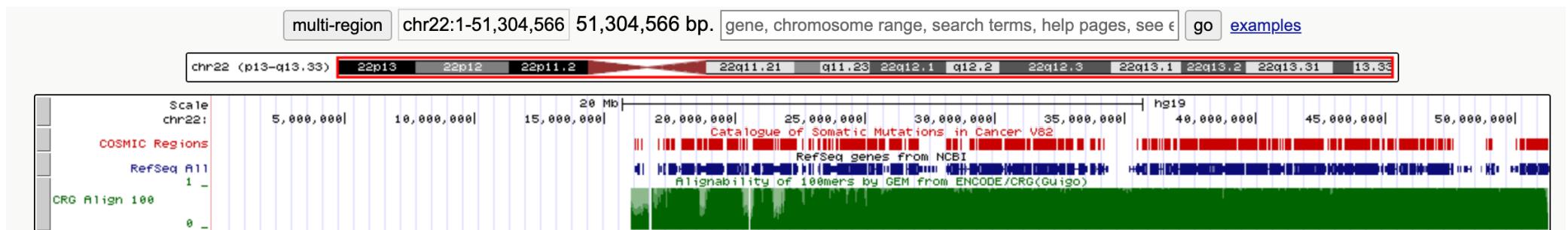


The Sequencing revolution



The Sequencing revolution

- Key variables
 - Cost
 - Read length
 - Throughput
 - Base quality/error rate



The Sequencing revolution

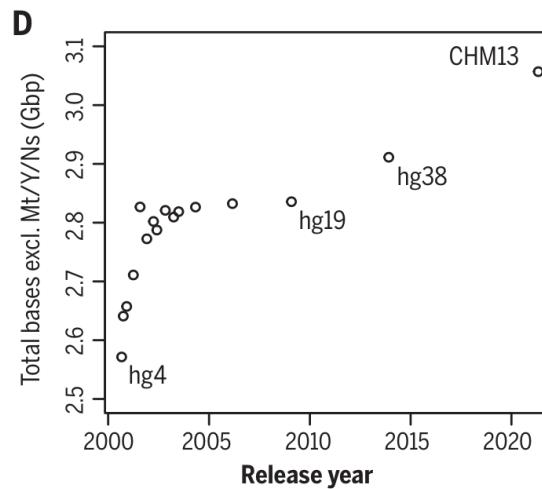
- Current genome build incomplete
 - Merged haplotypes from ~20 people, with a single individual comprising most of the sequence.
- Telomere-to-Telomere (T2T) Consortium present a new genome build T2T-CHM13
 - Using new long-read technologies.
 - Add 200 million base pairs of sequence containing
 - 1956 gene predictions
 - 99 of which are predicted to be protein coding

SPECIAL SECTION COMPLETING THE HUMAN GENOME

RESEARCH ARTICLE

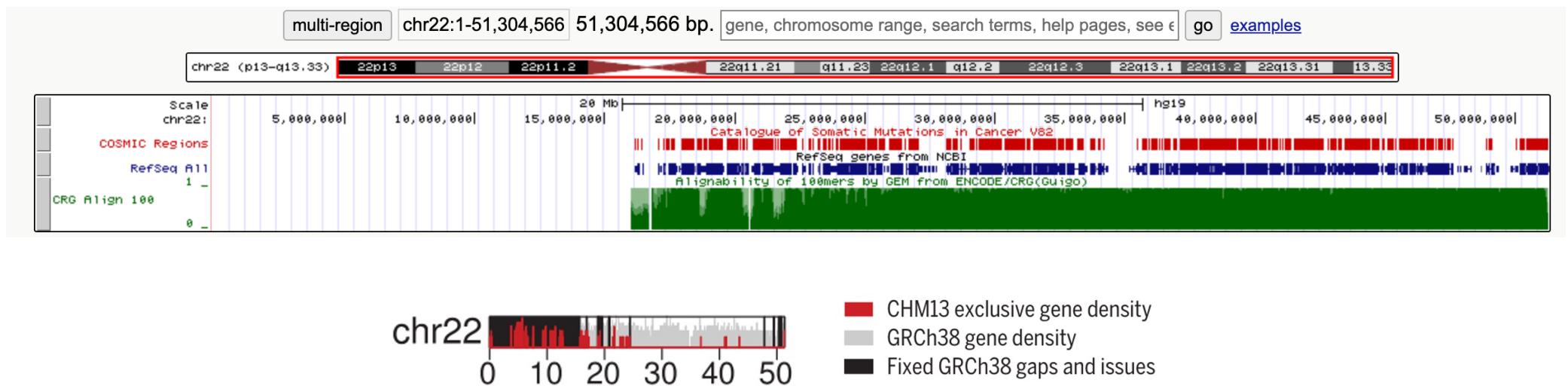
HUMAN GENOMICS

The complete sequence of a human genome

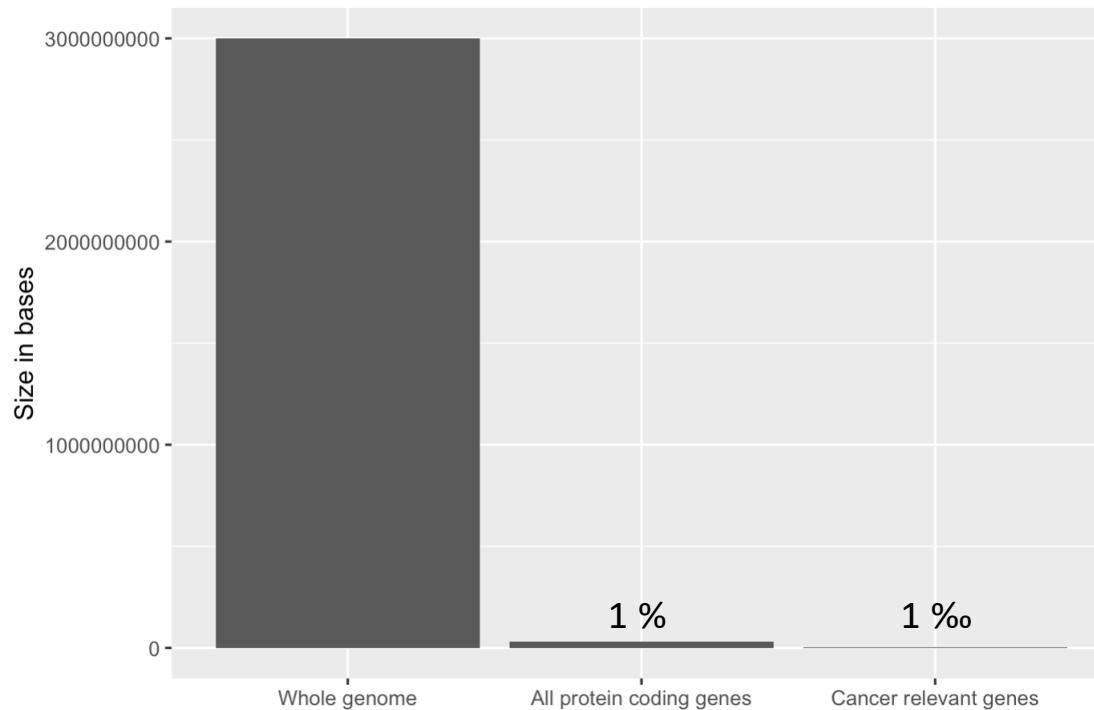


The Sequencing revolution

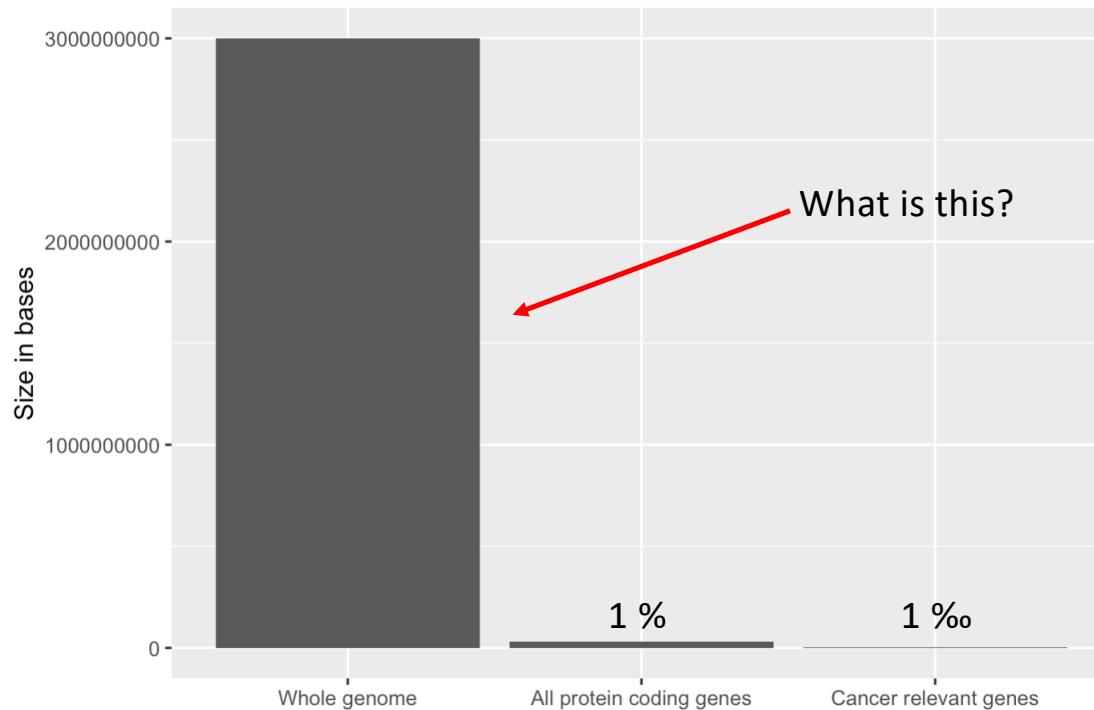
- Key variables
 - Cost
 - Read length
 - Throughput
 - Base quality/error rate



Part of the genome with somatic alterations with known importance for cancer



Part of the genome with somatic alterations with known importance for cancer



The power of epigenetic regulation

Worm



Arabidopsis



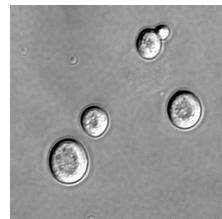
~27,000 protein coding genes

Sea Urchin



~23,000 protein coding genes

Yeast



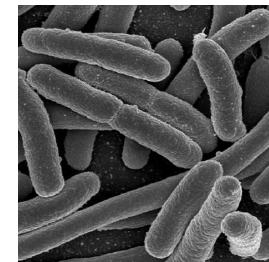
~5,800 protein coding genes

Human



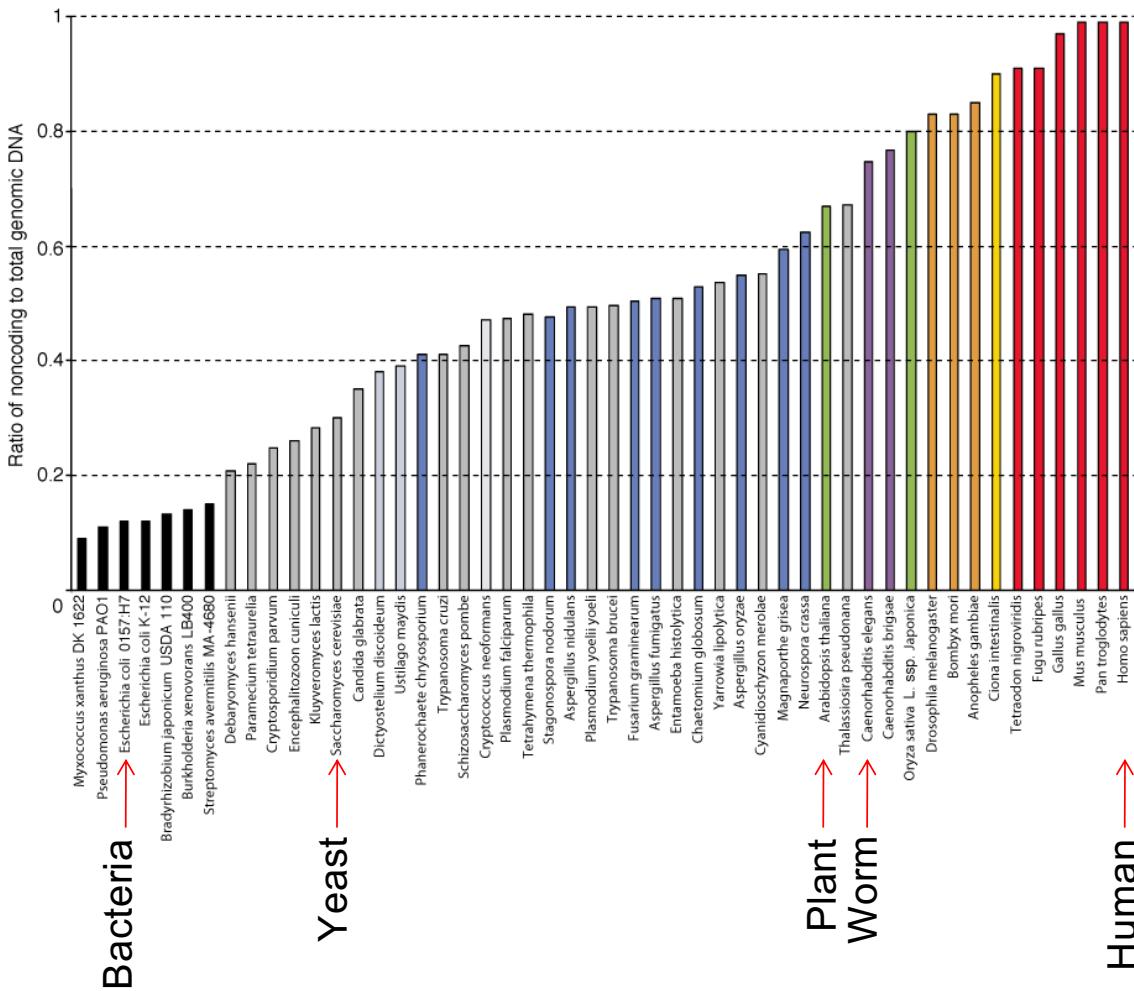
~20,500 protein coding genes

Bacteria

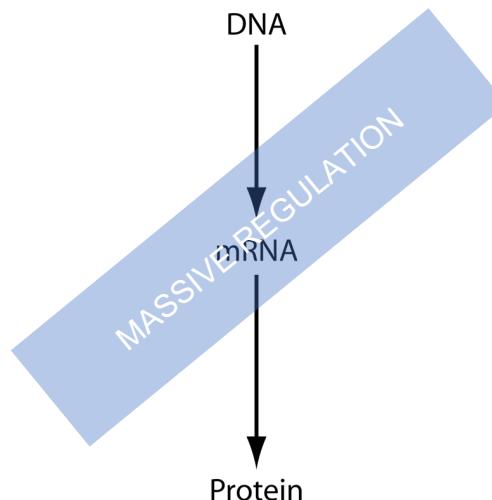
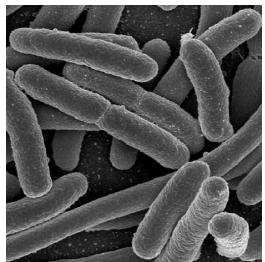


~4,580 protein coding genes

The power of epigenetic regulation



The power of epigenetic regulation



The power of epigenetic regulation

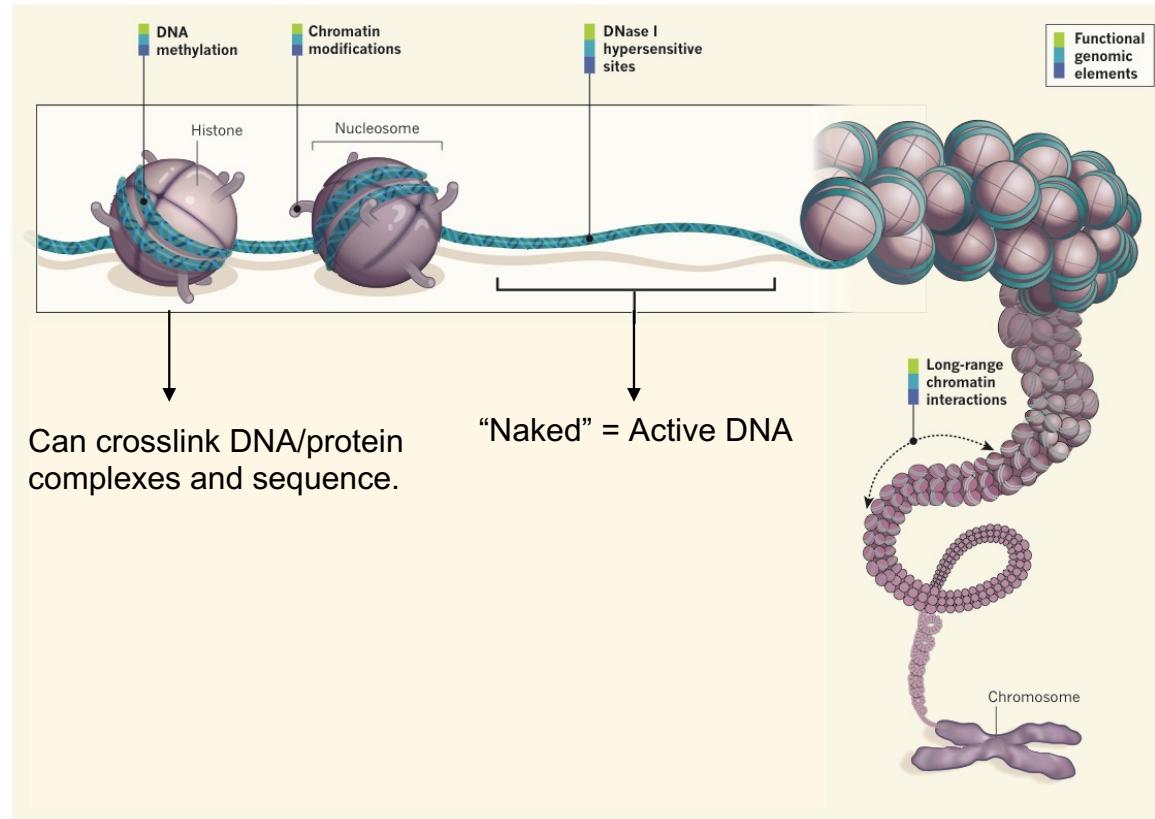
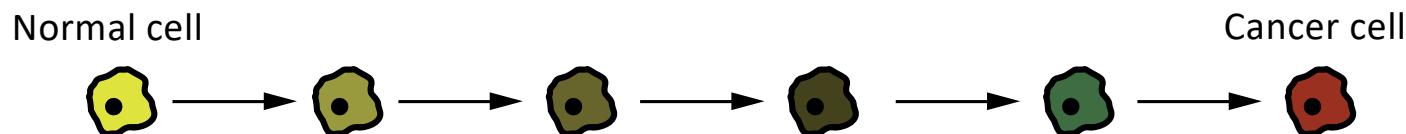


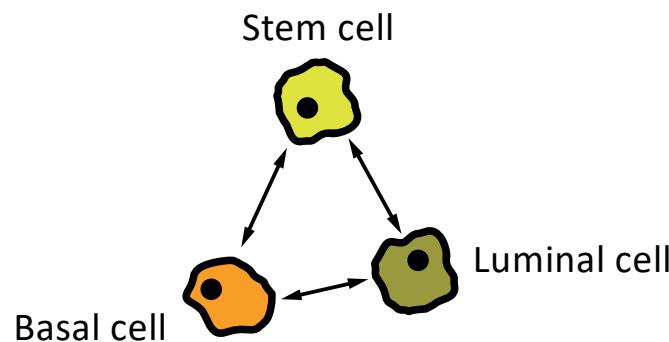
Figure from Nature Reviews

We are a mosaic of cells

Cancer occurs through sequential somatic mutations



Cancer cells can change phenotype without altering the DNA

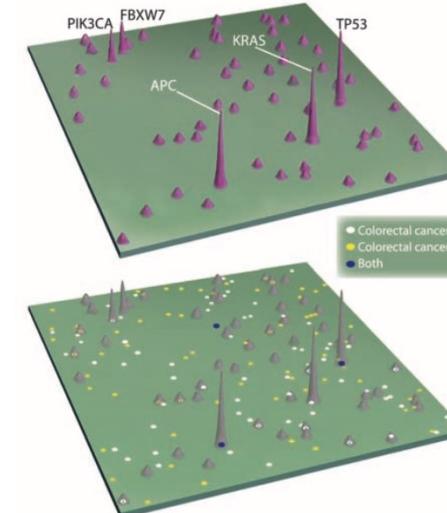


Summary

- Cancer occurs through sequential somatic mutations.
 - Take decades to develop.
 - Majority of deaths are due to late detection (after 90% of cancers lifespan).
- Cancer genomics: the study of the totality of DNA sequence and phenotype differences between tumour cells and normal cells.
- Sequencing is the main tool to perform cancer genomics.
- The sequencing revolution has facilitated a tsunami of new knowledge since 2010.
- Cancer cells can change phenotype/epigenetic state without acquiring somatic alterations.

Sequencing revolution = allowed accumulation of new knowledge

- Knowledge = “to some extent” limited to what can be measured and is affordable.
- But ... first set of “genome-wide” data was generated before it was affordable.
 - Whole genome amplification x 2
 - Sanger sequencing
 - 11 breast- and colorectal cancers
 - The first take on “the long tail”

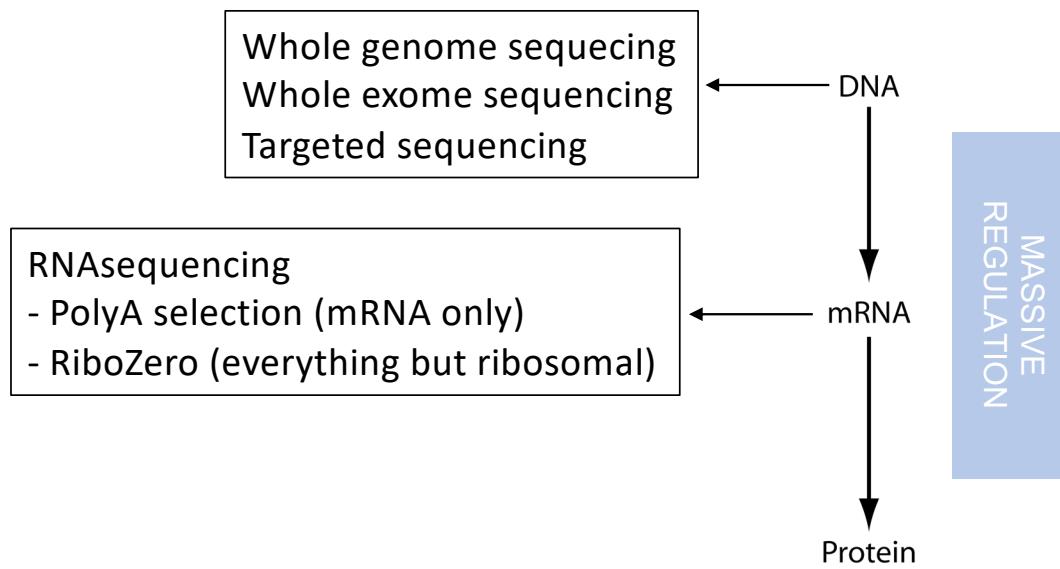


The Genomic Landscapes of Human Breast and Colorectal Cancers
Laura D. Wood, *et al.*
Science **318**, 1108 (2007);
DOI: 10.1126/science.1145720

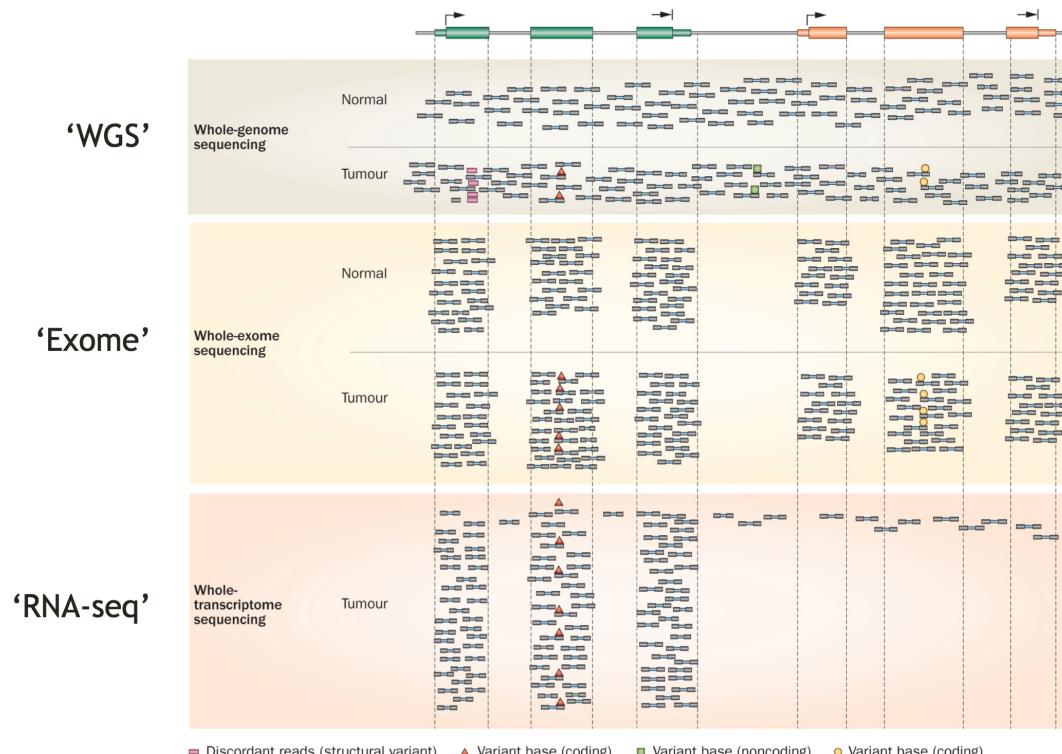


The Consensus Coding Sequences of Human Breast and Colorectal Cancers
Tobias Sjöblom, *et al.*
Science **314**, 268 (2006);
DOI: 10.1126/science.1133427

Sequencing revolution = allowed accumulation of new knowledge



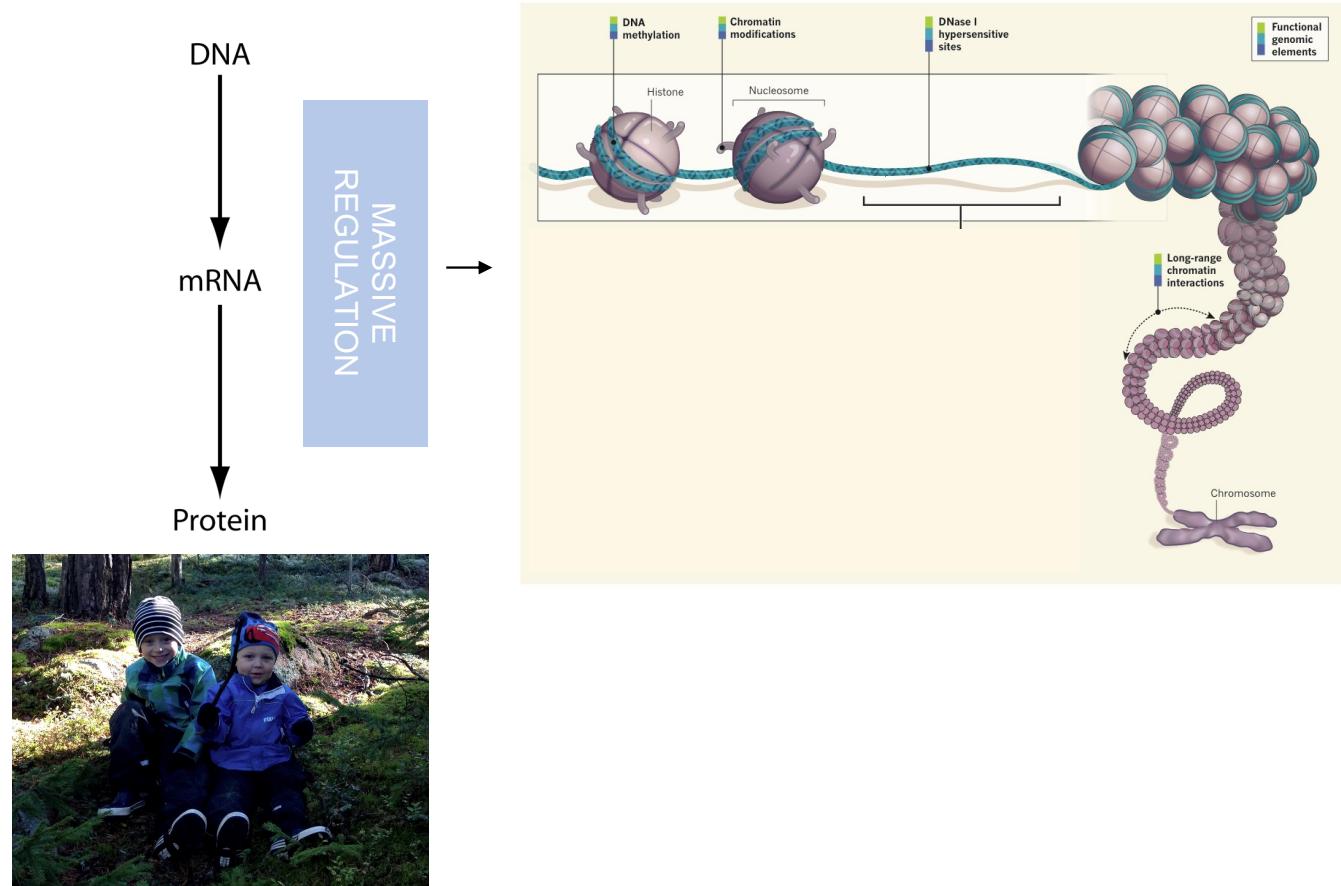
Sequencing revolution = allowed accumulation of new knowledge



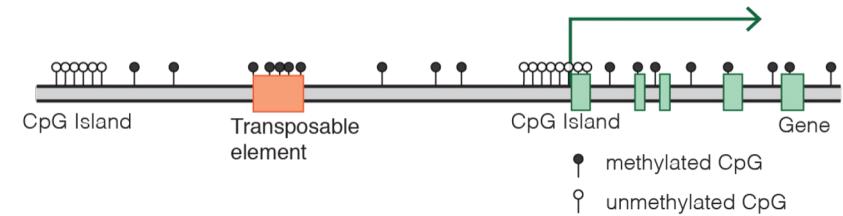
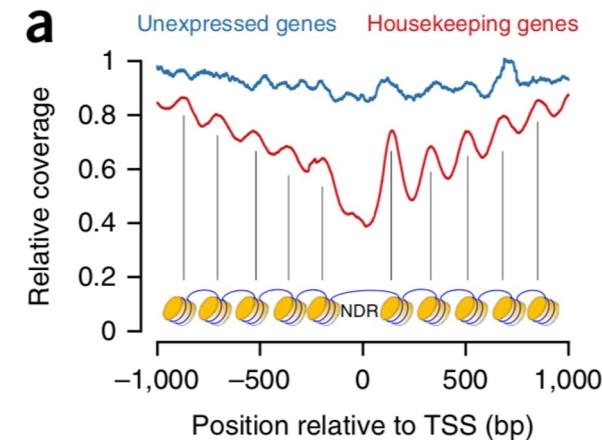
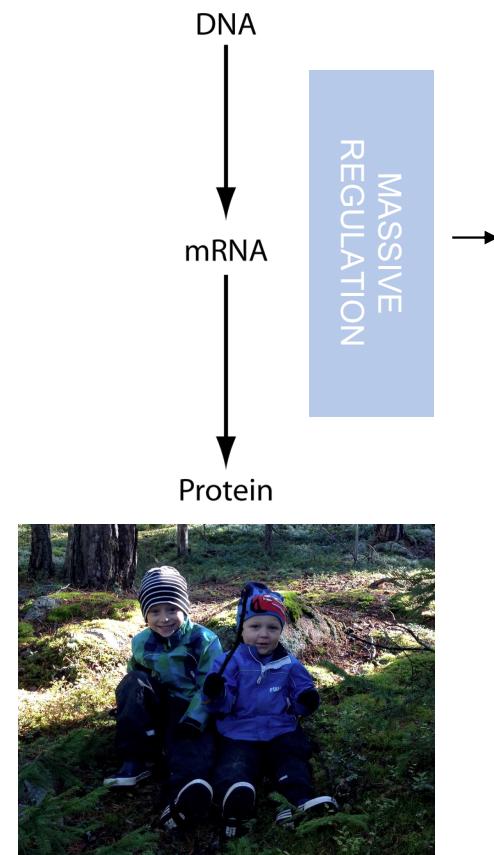
These three data types = course focus

Figure from <https://github.com/griffithlab/pmbio.org>

Sequencing revolution = allowed accumulation of new knowledge



Sequencing revolution = allowed accumulation of new knowledge



Inferring expressed genes by whole-genome sequencing of plasma DNA, Nature genetics 2016
 Sensitive tumour detection and classification using plasma cell-free DNA methylomes, Nature 2018

International consortia and other initiatives

- ICGC
 - International Cancer Genome Consortium
 - WGS + RNAseq on ~3000 cases
- TCGA
 - The Cancer Genome Atlas
 - WES + RNAseq + Methylation profiling etc on ~15000 cases
- Memorial Sloan Kettering
 - Panel-sequencing of >50.000 locally advanced/advanced cases
- The Hartwig Foundation
 - WGS + RNAseq on ~5000 cases in a clinical trial context

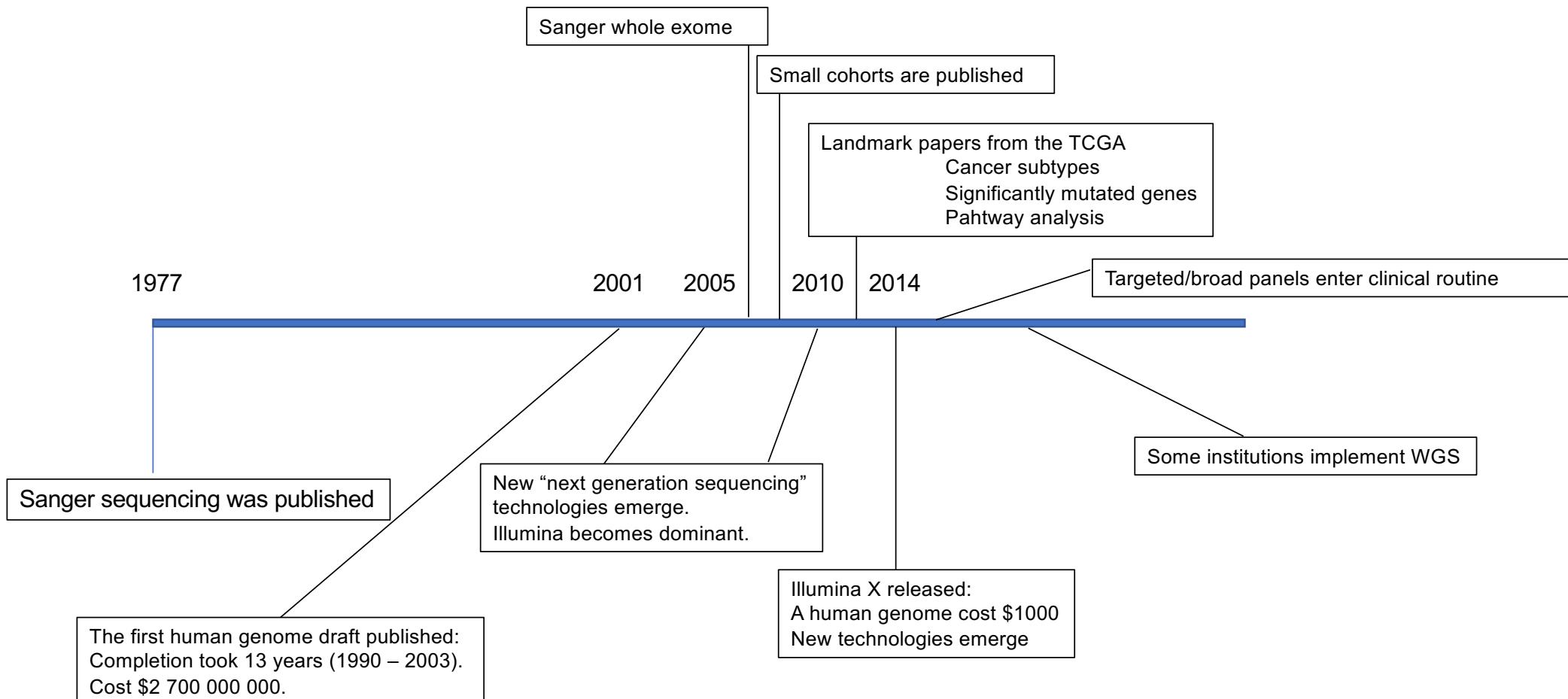
WGS = whole genome sequencing.

WES/WEX = whole exome sequencing.

RNA-seq = RNA sequencing.

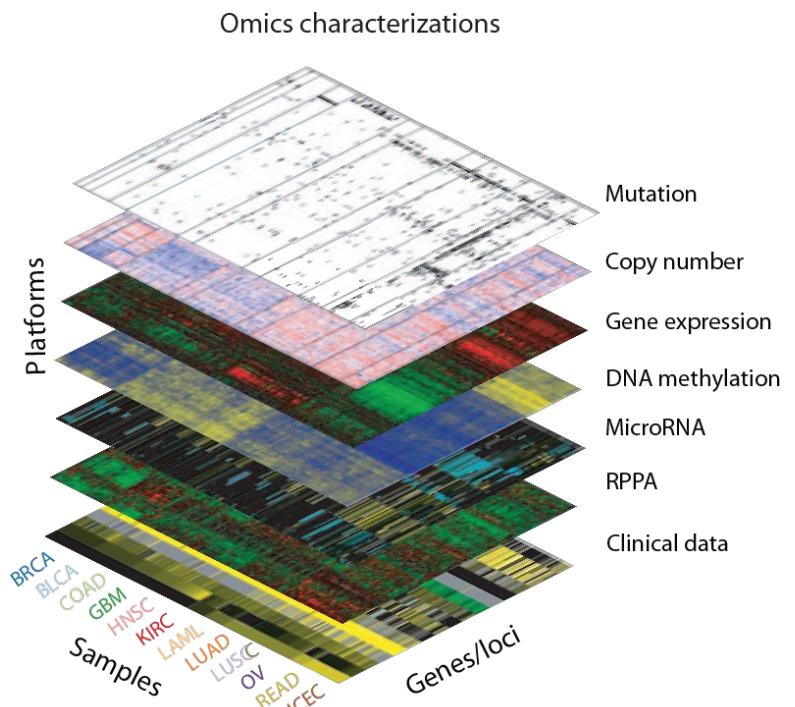
Targeted/panel sequencing = sequencing of selected parts of the human genome.

The Sequencing revolution



International consortia and other initiatives

- Course focus
 - DNA sequencing
 - RNA sequencing
 - Meaningful interpretation of single samples
- Complex data
 - E.g methylation
 - Need large cohorts for meaningful interpretation



The Cancer Genome Atlas Pan-Cancer analysis project, Nature Genetics 2013

Breast cancer – an example

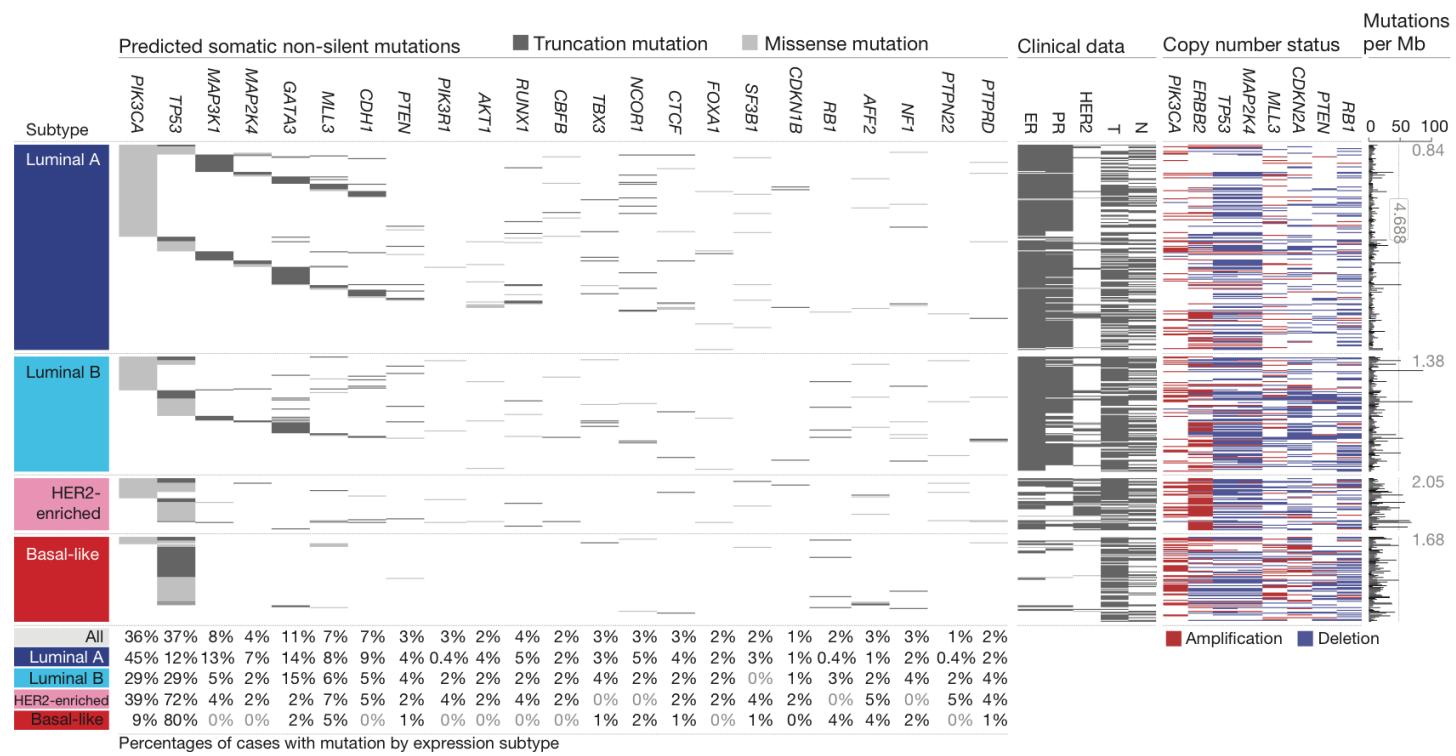
ARTICLE

doi:10.1038/nature11412

Comprehensive molecular portraits of human breast tumours

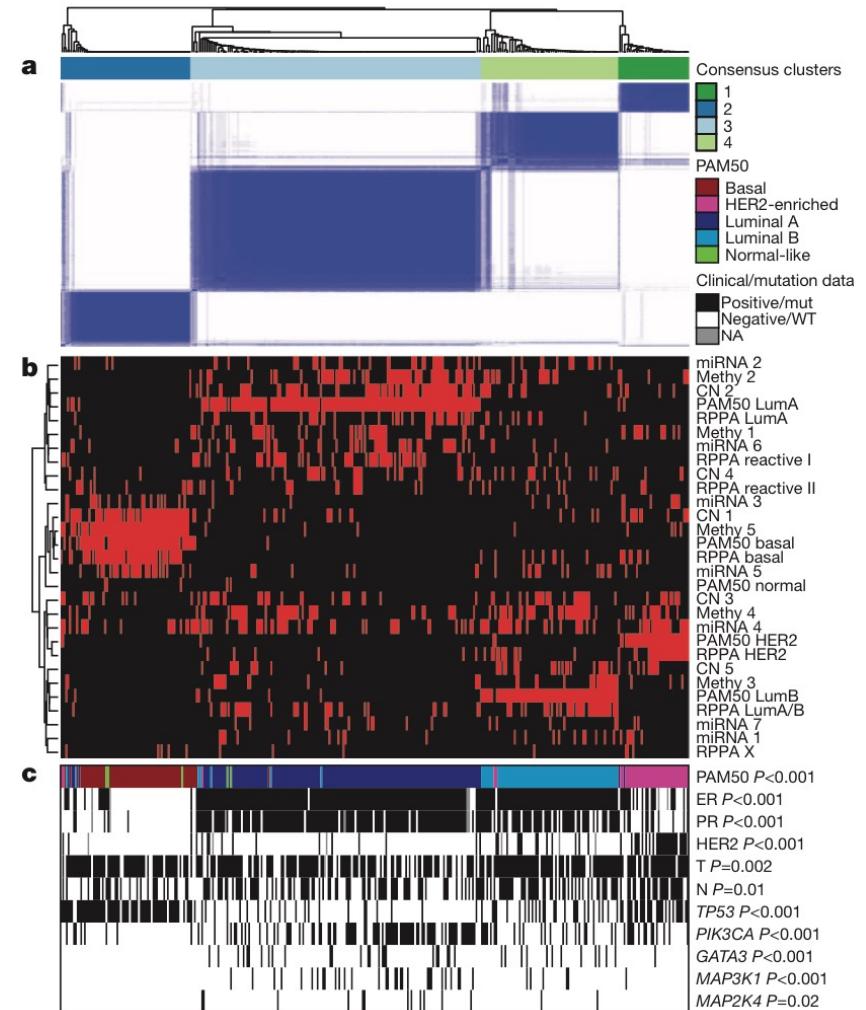
The Cancer Genome Atlas Network*

~500 patients with multiple data types



Breast cancer – an example

- Cancer subtype
 - **NCI dictionary definition:**
 - Describes the smaller groups that a type of cancer can be divided into, based on certain characteristics of the cancer cells.
 - These characteristics include how the cancer cells look under a microscope and whether there are certain substances in or on the cells or certain changes to the DNA of the cells.
 - **For me:**
 - a fraction of cancers of a certain histological origin with a distinct molecular phenotype.
 - Example: Breast cancer subtypes (Basal, HER2, Luminal A and Luminal B).



Two early great reviews in 2013


CANCER GENOMICS
www.sciencemag.org/special/cancergenomics

REVIEW

Cancer Genome Landscapes

Bert Vogelstein, Nickolas Papadopoulos, Victor E. Velculescu, Shabin Zhou,
 Luis A. Diaz Jr., Kenneth W. Kinzler*

- Insights into mutational processes causing cancer
- Structural variant patterns
- New categories of significantly mutated genes
- The long tail of driver variants
- Heterogeneity (within the same tumor, between tumors of the same diagnosis, between cancers of different diagnoses)
- ...
- The main take-homes summarized in a couple of slides

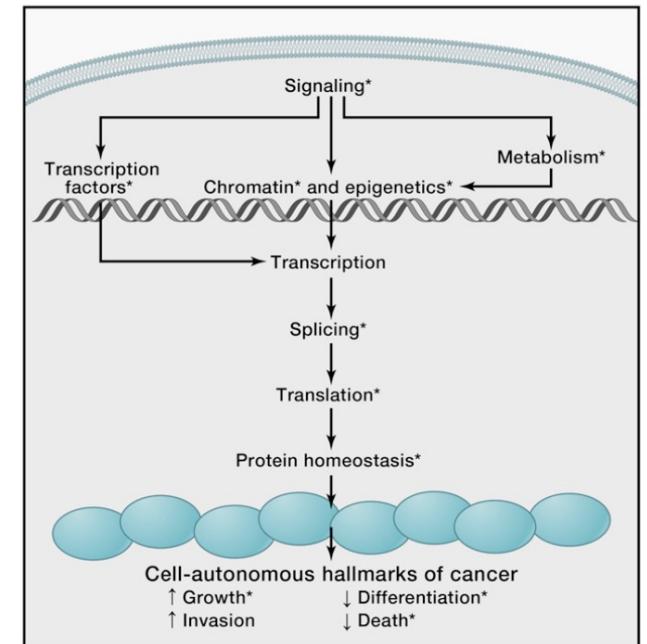


Leading Edge
Review

Cell

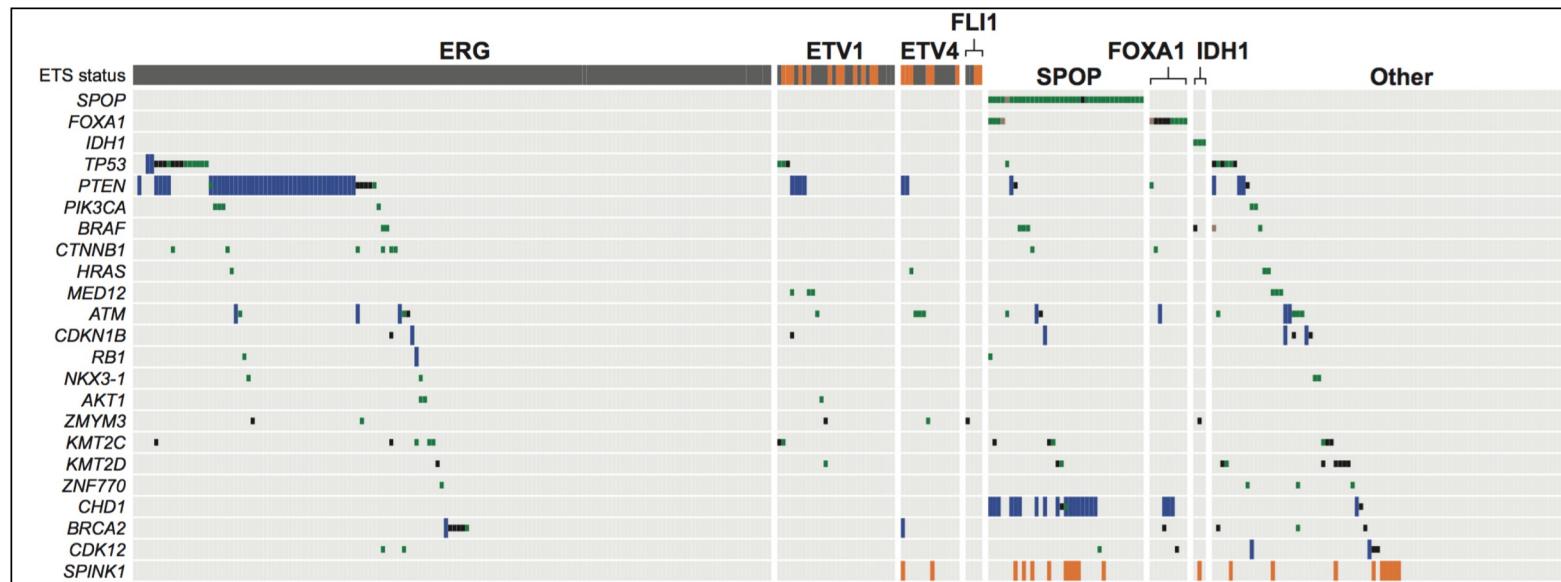
Lessons from the Cancer Genome

Levi A. Garraway^{1,2,4} and Eric S. Lander^{3,4,5,*}



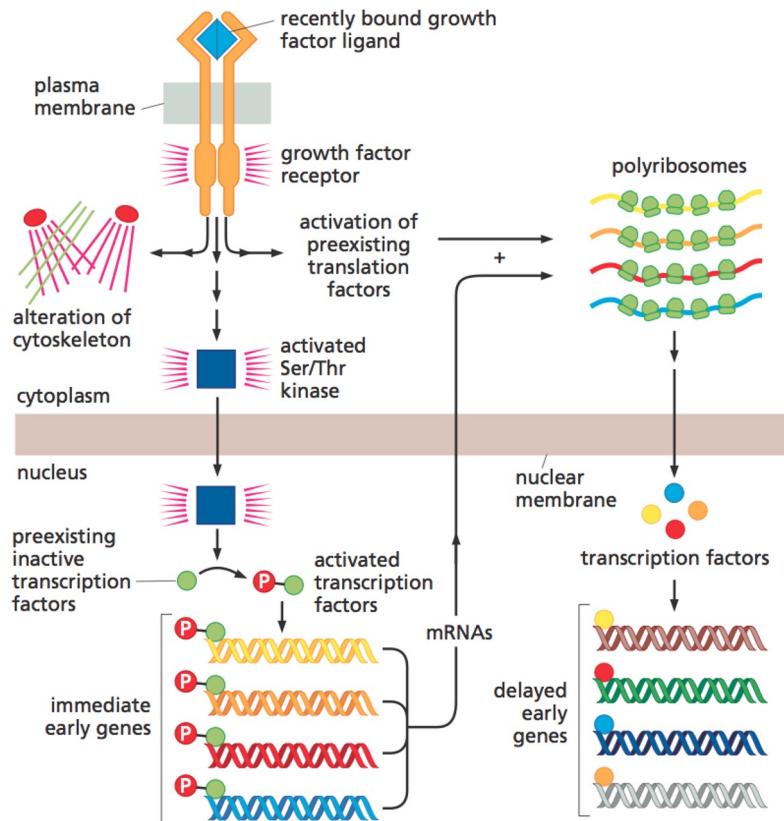
Intra disease heterogeneity

- Localized prostate cancer – intra disease heterogeneity
- Subtypes, defined by the main driver detected in precursor lesions



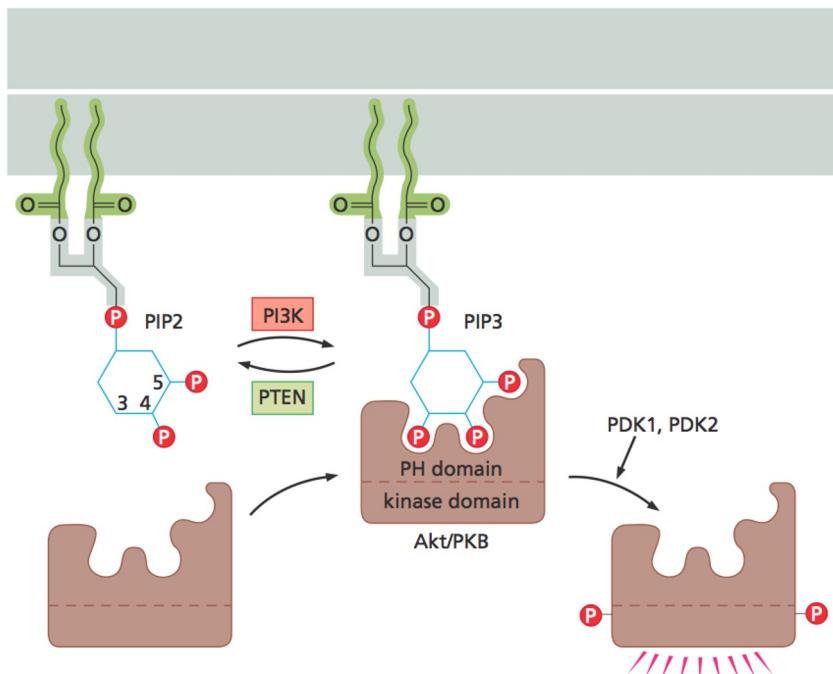
The molecular taxonomy of primary prostate cancer, Cell, 2015

Unifying pathways



Biology of Cancer, Weinberg

Unifying pathways – an example

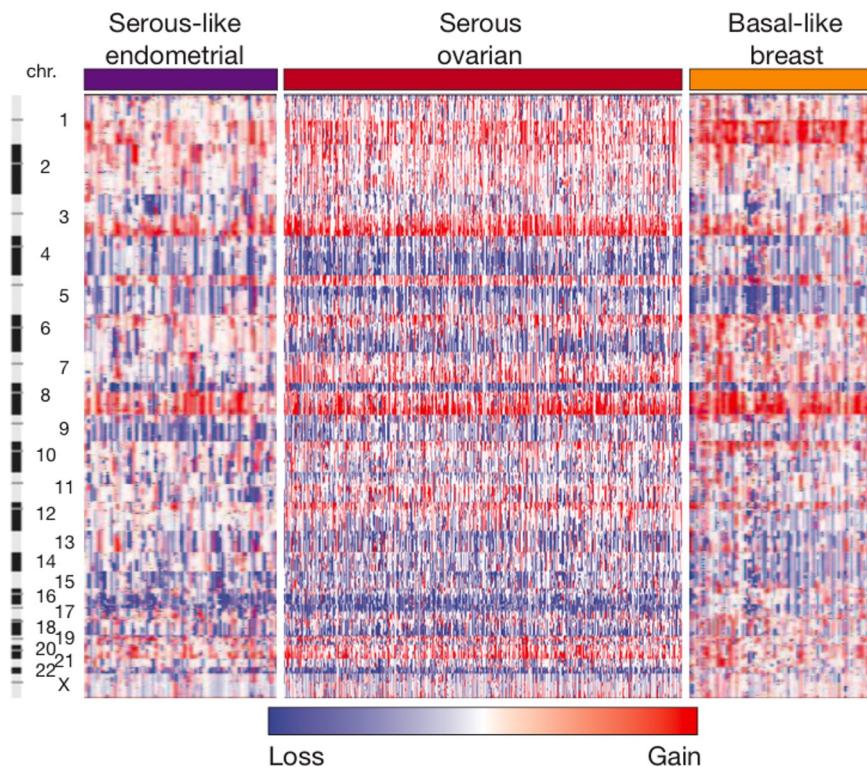


PI3K = Oncogene. A gene when activated by mutation gives a growth advantage

PTEN = Tumor suppressor gene. A gene when inactivated by mutation gives a growth advantage

Inter disease homogeneity

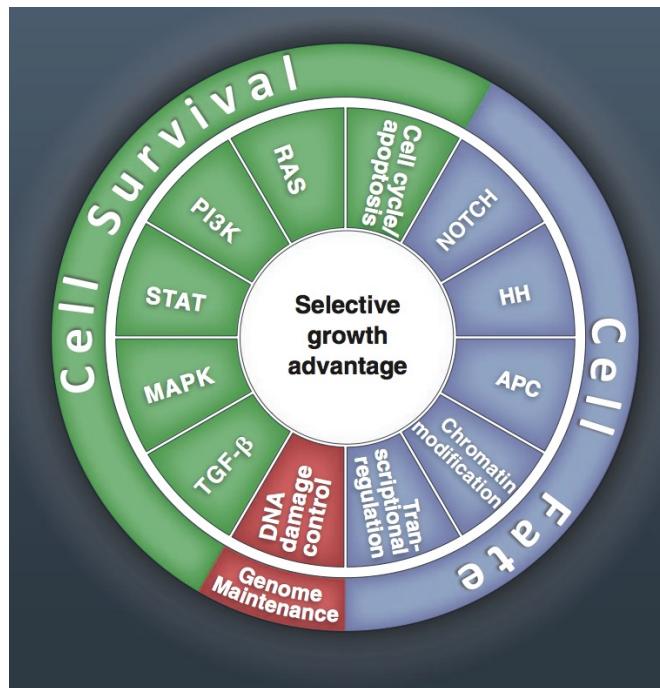
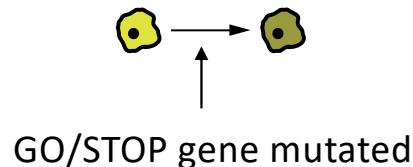
- Almost all cancer drivers are mutated in all cancers BUT at different frequencies
- TP53-mutated cancer signature the same in multiple organs
- Similarities suggest pan-cancer treatment possibilities
- Stage-shift from organ-based to genomic-based treatment rationales?



Integrated genomic characterization of endometrial carcinoma, TCGA, Nature 2013

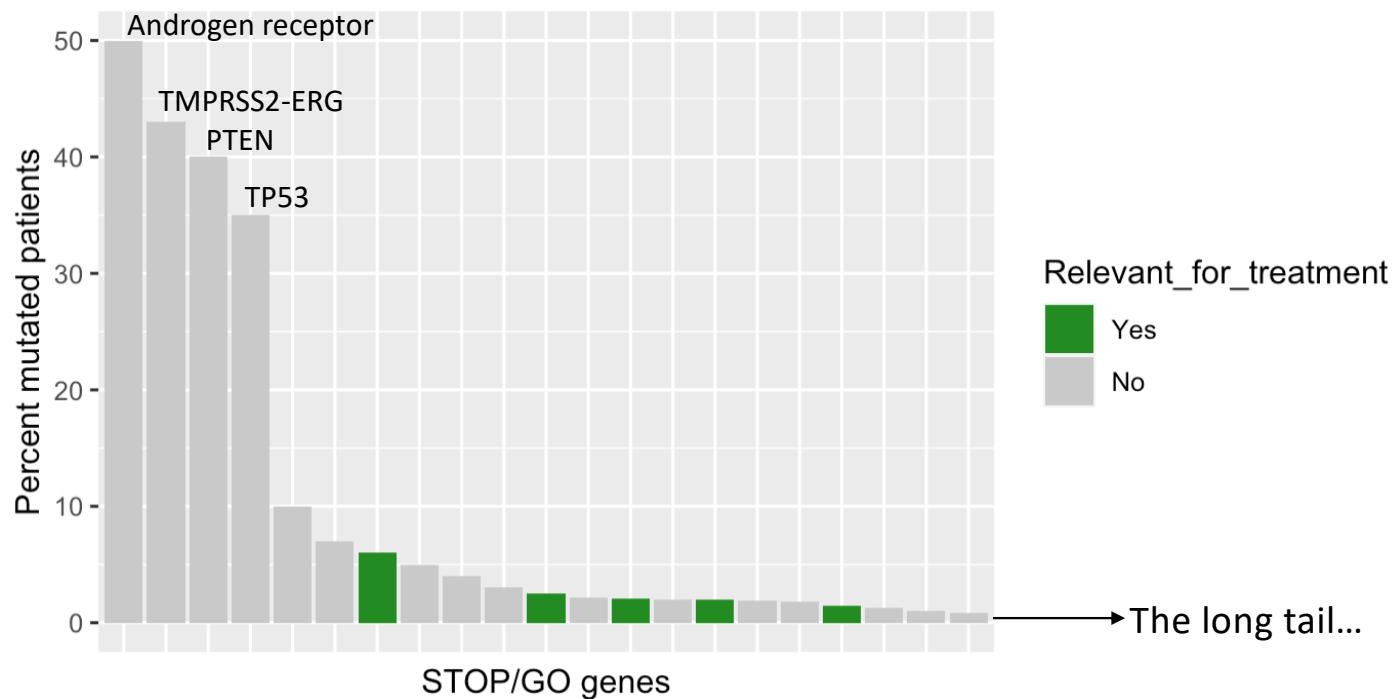
Driver mutations in key genes

- Most cancers have four to eight mutations in to eight “driver” genes causing a selective growth advantage
 - “GO” genes (oncogenes)
 - “STOP” genes (tumor suppressor genes)



Cancer Genome Landscapes, Science 2013

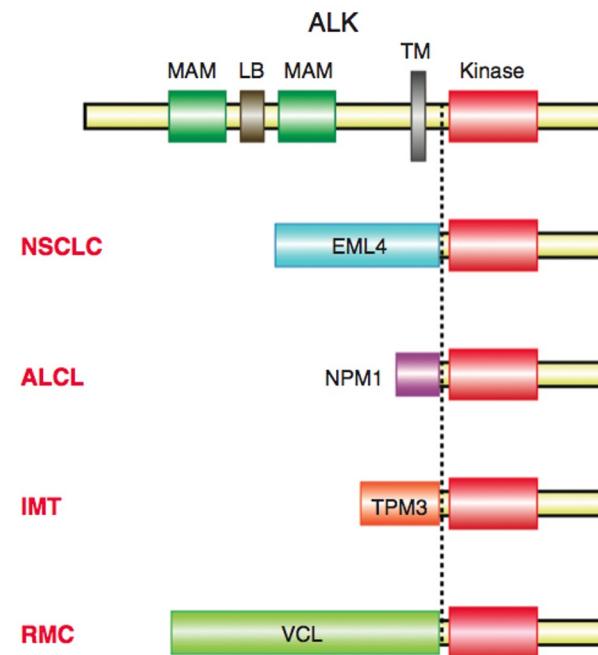
Driver mutations in metastatic castrate resistant prostate cancer



- Sum(the long tail of actionability) – can be a large fraction of patients: approximately 15% of advanced prostate cancer cases harbor treatment-relevant alterations.
 - Treatment-relevant = an approved drug exist that target exactly that alteration, approved for prostate- or other cancer types.

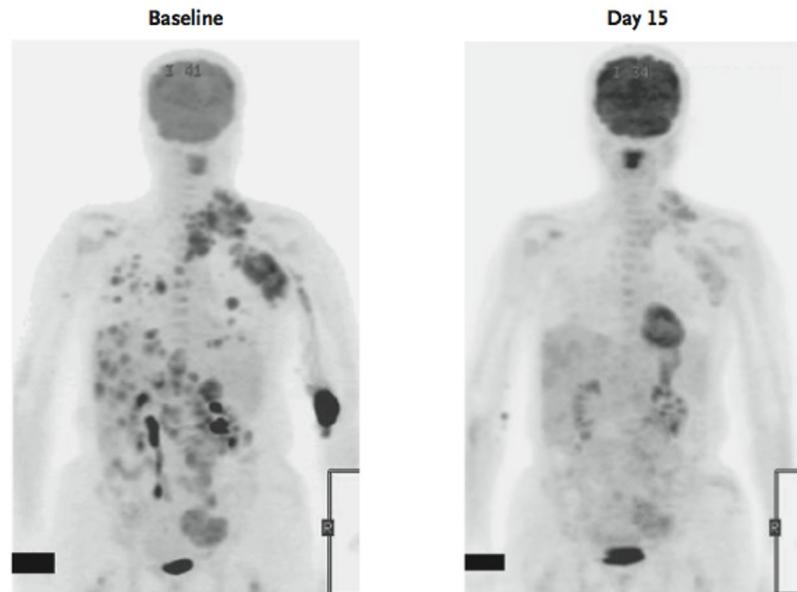
Inter disease homogeneity

- ALK (Anaplastic lymphoma kinase)
 - Protein tyrosine kinase acting as driver in multiple cancers of different origin = Alkomas
 - Inhibitors are effective across a range of different histologies



ALKoma: A Cancer Subtype with a Shared Target, CD, 2012

Inter disease heterogeneity

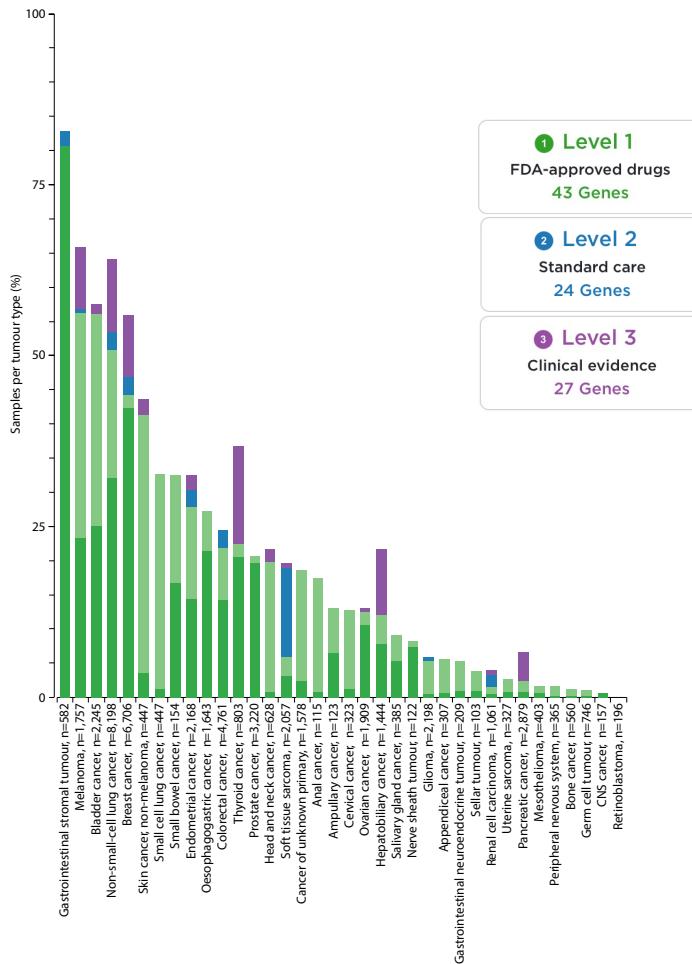


- Vemurafenib is highly effective in BRAF V600E mutated melanoma but not colorectal cancer
- Each drug – diagnosis combination need to be evaluated in a clinical trial

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma, NEJM, 2010
PLX4032 in metastatic colon cancer patients with mutant BRAF tumors, JCM 2010

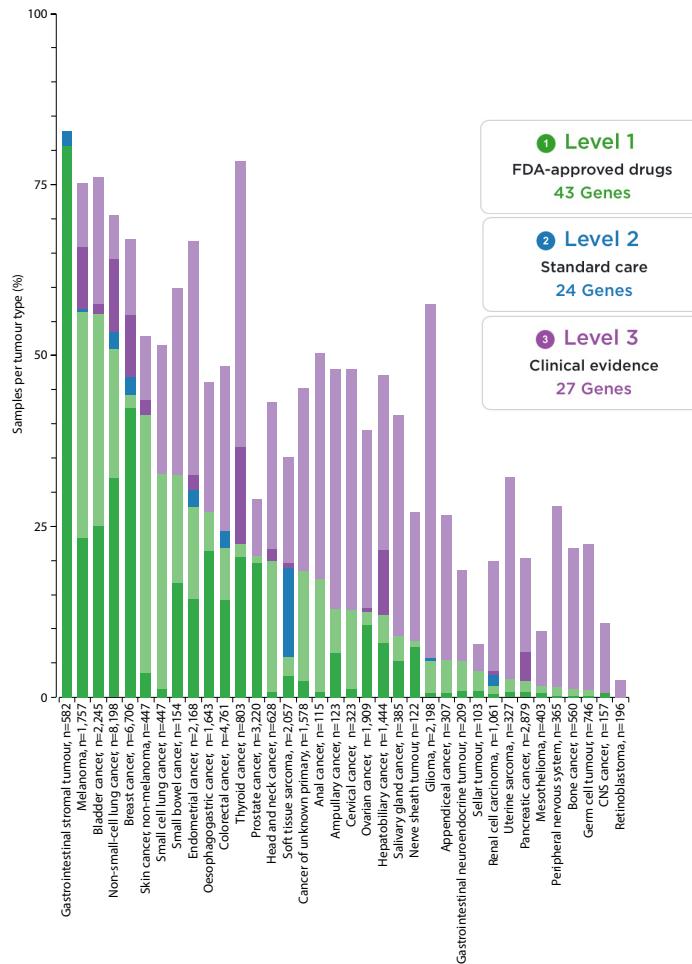
Clinically actionable STOP/GO genes

- Chemotherapy
 - Damage rapidly dividing cells
- Targeted therapy
 - Targets e.g. a specific protein
- 94 STOP/GO genes associated to specific treatments/diagnoses/stages



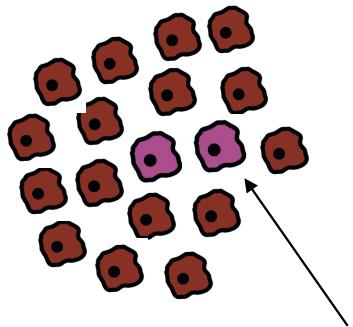
Clinically actionable STOP/GO genes

- Chemotherapy
 - Damage rapidly dividing cells
- Targeted therapy
 - Targets e.g. a specific protein
- 94 STOP/GO genes associated to specific treatments/diagnoses/stages
- Off label use = motivation for broad genomic analysis for all patients.



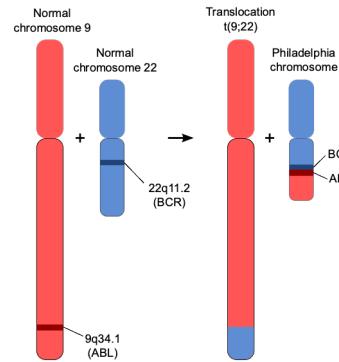
Targeted therapy and advanced cancer

- Treatments can prolong life, with better side effect profile than e.g. chemotherapy.
 - Resistance mutations exist for most already before start of treatment.
- Exceptions exist.



Pre-existing resistant clone

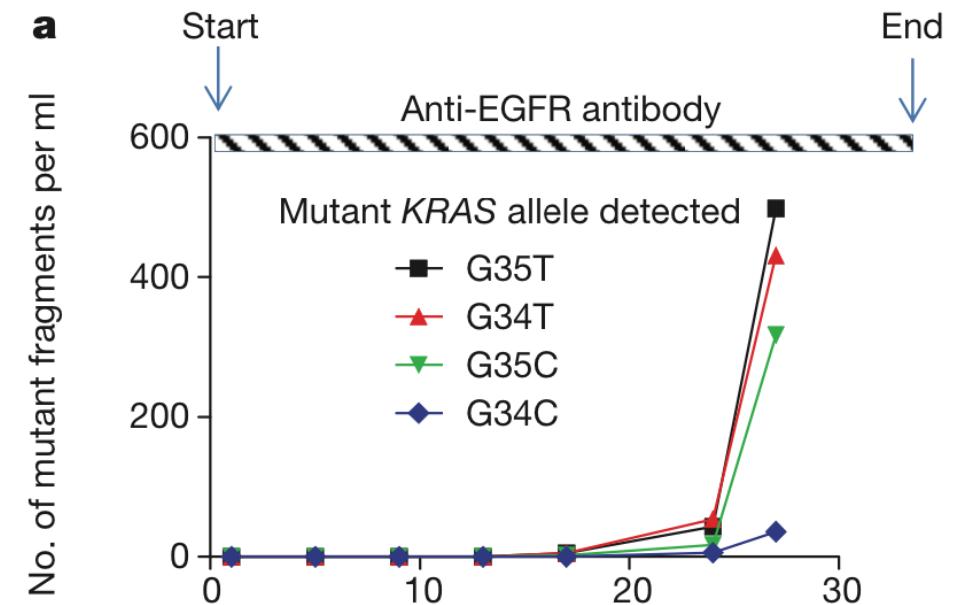
CML, the Philadelphia chromosome



Drugs targeting the BCR-ABL protein.
CML is now a chronic disease

Why targeted mono-therapy fail in metastatic disease

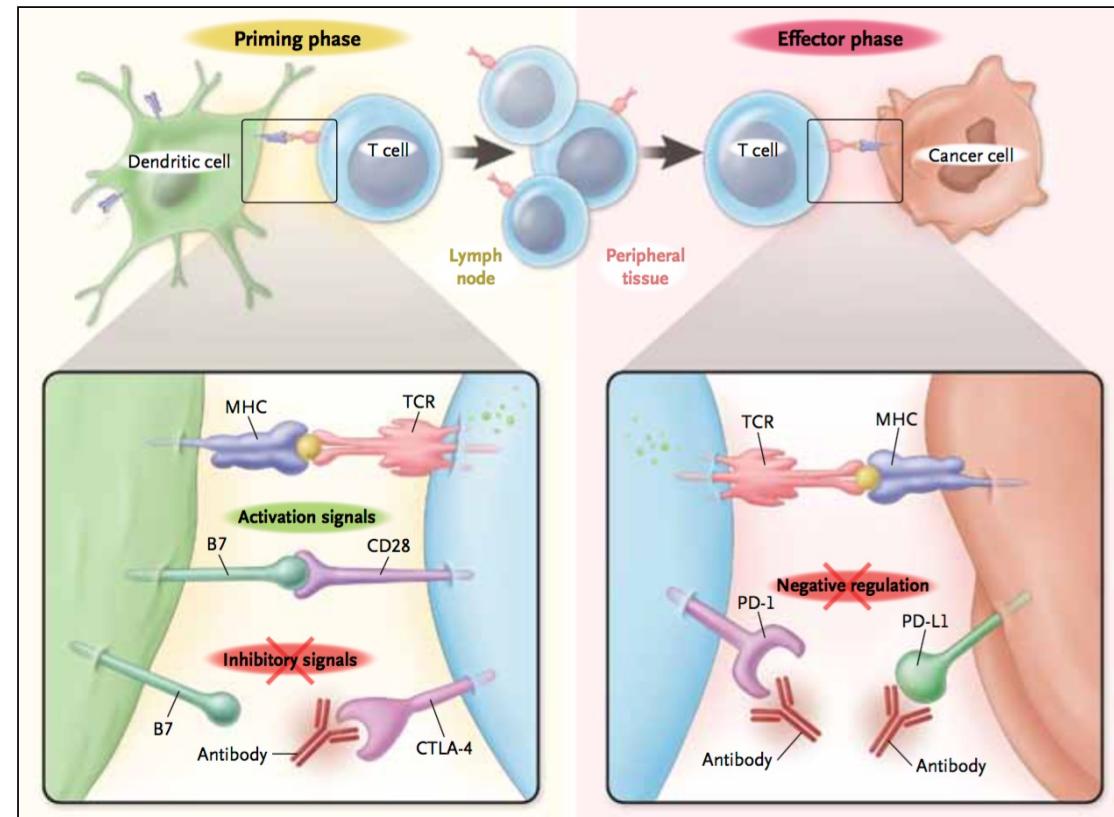
- Metastatic patients basically always contain resistant clones to targeted monotherapy
 - Inevitable due to random errors during cell-division
 - Combinations the way forward hitting on orthogonal functions.
 - Side effects ...



The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers, Nature, 2012
 Evolutionary dynamics of cancer in response to targeted combination therapy, ELife, 2013

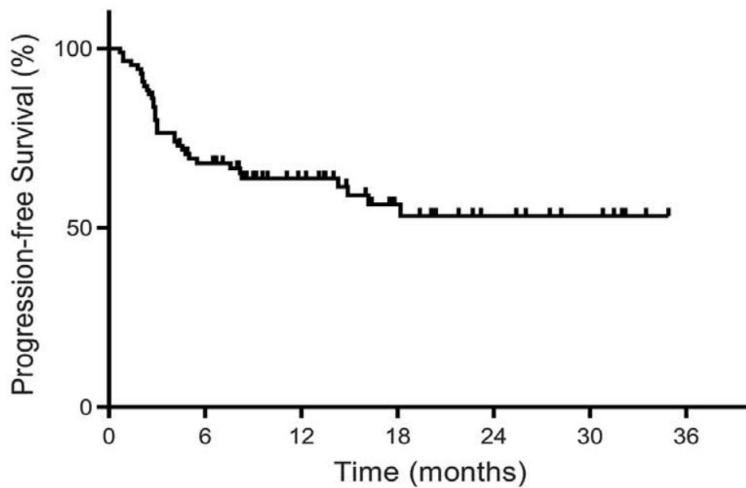
Immunotherapy – the exception from the rule

- Immune-modulating antibodies seem to be an exception



Immunotherapy – the exception from the rule

- Advanced cancers.
- 12 different tumour types treated with PD-1 antibody.
- 53% with objective radiographic responses.
- 21% with complete responses.
- Lead to pan-cancer approval of pembrolizumab in the US.
 - Still not in the EU...



RESEARCH

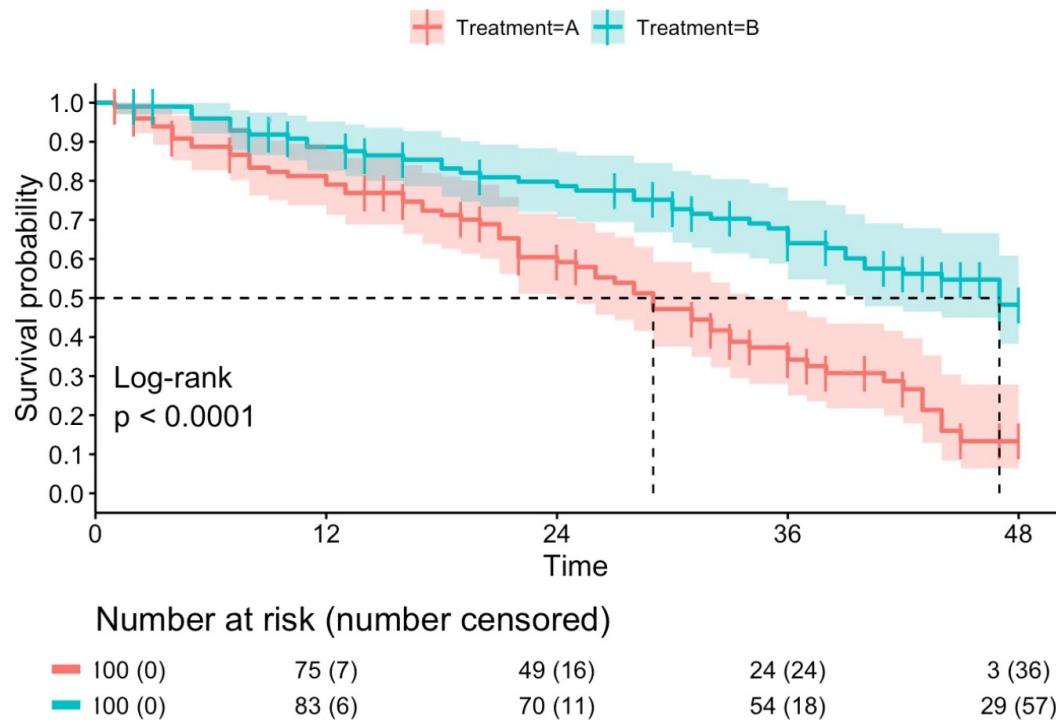
CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,^{1,2,3} Jennifer N. Durham,^{1,2,3*} Kellie N. Smith,^{1,3*} Hao Wang,^{3*} Bjarne R. Bartlett,^{2,4*} Laveet K. Aulakh,^{2,4} Steve Lu,^{2,4} Holly Kemberling,³ Cara Wilt,³ Brandon S. Luber,³ Fay Wong,^{2,4} Nilofer S. Azad,^{1,3} Agnieszka A. Rucki,^{1,3} Dan Laheru,² Ross Donehower,³ Atif Zaheer,³ George A. Fisher,⁶ Todd S. Crocenzi,⁷ James J. Lee,⁸ Tim F. Greten,⁹ Austin G. Duffy,⁹ Kristen K. Ciombor,¹⁰ Aleksandra D. Eyring,¹¹ Bao H. Lam,¹¹ Andrew Joe,¹¹ S. Peter Kang,¹¹ Matthias Holdhoff,³ Ludmila Danilova,^{1,3} Leslie Cope,^{1,2} Christian Meyer,³ Shihbin Zhou,^{1,3,4} Richard M. Goldberg,¹² Deborah K. Armstrong,³ Katherine M. Bever,³ Amanda N. Fader,¹³ Janis Taube,^{1,3} Franck Housseau,^{1,3} David Spetzler,¹⁴ Nianqing Xiao,¹⁴ Drew M. Pardoll,^{1,3} Nickolas Papadopoulos,^{3,*} Kenneth W. Kinzler,^{3,4} James R. Eshleman,¹⁵ Bert Vogelstein,^{1,3,4} Robert A. Anders,^{1,3,15} Luis A. Diaz Jr.^{1,2,3,1,†}

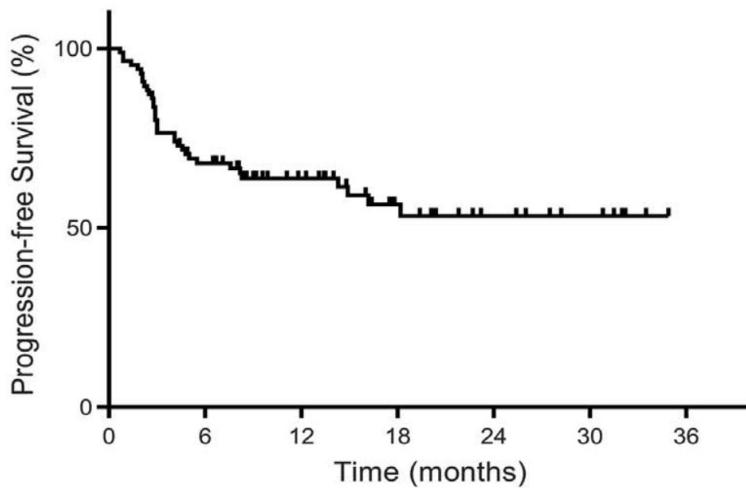
Science, 2017

Kaplan-Meier curves in 30 sec ...



Immunotherapy – the exception from the rule

- Advanced cancers.
- 12 different tumour types treated with PD-1 antibody.
- 53% with objective radiographic responses.
- 21% with complete responses.
- Lead to pan-cancer approval of pembrolizumab in the US.
 - Still not in the EU...



RESEARCH

CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,^{1,2,3} Jennifer N. Durham,^{1,2,3*} Kellie N. Smith,^{1,3*} Hao Wang,^{3*} Bjarne R. Bartlett,^{2,4*} Laveet K. Aulakh,^{2,4} Steve Lu,^{2,4} Holly Kemberling,³ Cara Wilt,³ Brandon S. Luber,³ Fay Wong,^{2,4} Nilofer S. Azad,^{1,3} Agnieszka A. Rucki,^{1,3} Dan Laheru,² Ross Donehower,³ Atif Zaheer,³ George A. Fisher,⁶ Todd S. Crocenzi,⁷ James J. Lee,⁸ Tim F. Greten,⁹ Austin G. Duffy,⁹ Kristen K. Ciombor,¹⁰ Aleksandra D. Eyring,¹¹ Bao H. Lam,¹¹ Andrew Joe,¹¹ S. Peter Kang,¹¹ Matthias Holdhoff,³ Ludmila Danilova,^{1,3} Leslie Cope,^{1,2} Christian Meyer,³ Shihbin Zhou,^{1,3,4} Richard M. Goldberg,¹² Deborah K. Armstrong,³ Katherine M. Bever,³ Amanda N. Fader,¹³ Janis Taube,^{1,3} Franck Housseau,^{1,3} David Spetzler,¹⁴ Nianqing Xiao,¹⁴ Drew M. Pardoll,^{1,3} Nickolas Papadopoulos,^{3,*} Kenneth W. Kinzler,^{3,4} James R. Eshleman,¹⁵ Bert Vogelstein,^{1,3,4} Robert A. Anders,^{1,3,15} Luis A. Diaz Jr.^{1,2,3,1,†}

Science, 2017

Immunotherapy – the exception from the rule

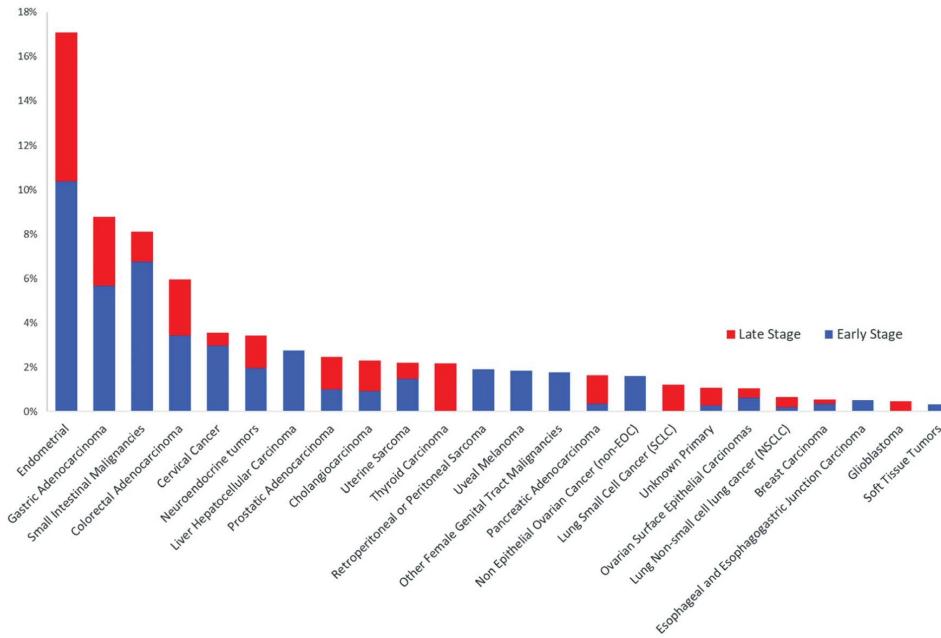
RESEARCH

CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,^{1,2,3} Jennifer N. Durham,^{1,2,3*} Kellie N. Smith,^{1,3*} Hao Wang,^{3*}
 Bjørne R. Bartlett,^{2,4*} Laveet K. Aulakh,^{2,4} Steve Lu,^{2,4} Holly Kemberling,³ Cara Wilt,³
 Brandon S. Lubet,³ Fay Wong,^{2,4} Nilofer S. Azad,^{1,3} Agnieszka A. Rucki,^{1,3} Dan Laheru,²
 Ross Donehower,² Atif Zaheer,³ George A. Fisher,⁶ Todd S. Crocenzi,⁷ James J. Lee,⁸
 Tim F. Greten,⁹ Austin G. Duffy,⁹ Kristen K. Ciombor,¹⁰ Aleksandra D. Eyring,¹¹
 Bao H. Lam,¹¹ Andrew Joe,¹¹ S. Peter Kang,¹¹ Matthias Holdhoff,³ Ludmila Danilova,^{1,3}
 Leslie Cope,^{1,3} Christian Meyer,³ Shihbin Zhou,^{1,3,4} Richard M. Goldberg,¹²
 Deborah K. Armstrong,³ Katherine M. Bever,³ Amanda N. Fader,¹³ Janis Taube,^{1,3}
 Franck Housseau,^{1,3} David Spetzler,¹⁴ Nianqing Xiao,¹⁴ Drew M. Pardoll,^{1,3}
 Nickolas Papadopoulos,^{3,*} Kenneth W. Kinzler,^{3,4} James R. Eshleman,¹⁵
 Bert Vogelstein,^{1,3,4} Robert A. Anders,^{1,3,15} Luis A. Diaz Jr.^{1,2,3,1,†}

Science, 2017



Classification and characterization of microsatellite instability across 18 cancer types, Nature Medicine 2016

The long tail – a cancer phenotype example

Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients

Ahmet Zehir^{1,13}●, Ryma Benayed^{1,13}, Ronak H Shah¹, Ajayzuddin Syed¹, Sumit Middha¹●, Hyunjae R Kim¹●, Preethi Srinivasan¹, Jianqiong Gao², Debyani Chakravarty², Sean M Devlin³, Matthew D Hellmann⁴, David A Barroo⁵, Alison M Schram⁶, Meen Hameed¹, Snjezana Dogan¹, Dara S Ross¹, Jaclyn F Hechtman¹, Deborah F Delair¹, JinJuan Yao¹, Diana L Mandelker¹, Donovan T Cheng^{1,13}, Raghu Chandramohan^{1,12}, Abhinitta S Mohanty¹, Ryan N Ptashkin¹, Gowtham Jayakumaran¹, Meera Prasad¹, Mustafa H Syed¹, Anoop Balakrishnan Rema¹●, Zhen Y Liu¹, Khedoudja Nafa¹, Justyna Sadowska¹, Jacklyn Casanova¹●, Ruben Bacares¹, Iwona J Kiecka¹, Anna Razumova¹, Julie B Son¹, Lisa Stewart¹, Tessara Baldi¹, Kerryn A Mullaney¹, Hikmat Al-Ahmadi¹, Efsevia Vakanian¹, Adam A Abeshouse¹, Alexander V Penson^{3,6}, Philip Jonsson^{3,6}, Niedzica Camacho¹, Matthew T Chang^{3,6}, Helen H Won¹, Benjamin F Gross², Ritika Kundra², Zachary J Hein², Hsiao-Wei Chen², Sarah Phillips², Hongxin Zhang², Jiaojiao Wang², Angelica Ochoa², Jonathan Wills⁷, Michael Eubank², Stacy B Thomas¹●, Stuart M Gards⁸, Dalicia N Reales³, Jesse Galie⁸, Robert Durany⁸, Ron Cambrria³, Wassim Abida⁴, Andrea Cercek⁴, Darren R Feldman⁴, Mirinal M Gounder⁴, A Ari Hakim⁹, James J Harding⁴, Gopa Iyer¹●, Yelena Y Janjigian⁴, Emmet J Jordan⁴, Ciara M Kelly⁴, Maeve A Lower¹, Luc G T Morris⁹, Antonio M Omuro¹⁰, Nitya Raj⁴, Pedram Razavi⁴, Alexander N Shoushtari⁴●, Neerav Shukla¹¹, Tara E Soumerai⁴, Anna M Varghese⁴, Rona Yaeger⁴, Jonathan Coleman⁸, Bernard Bochner⁸, Gregory J Riely⁴, Leonard B Saltz⁴, Howard I Scher⁴, Paul J Sabbatini⁴, Mark E Robson¹, David S Klimstra¹, Barry S Taylor^{2,3,6}, Jose Baselga^{4,6}, Nikolaus Schultz^{2,3,6}, David M Hyman⁴, Maria E Arcila¹, David B Solit^{2,3,6}, Marc Ladanyi¹● & Michael F Berger^{2,3,6}

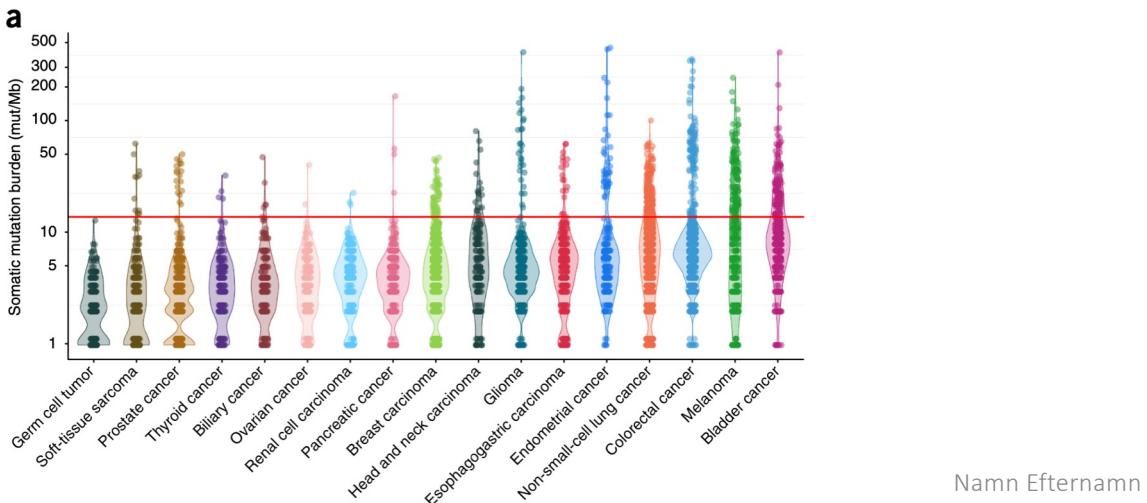
- ~400 genes interrogated in 10,000 patients
 - Detection of relevant variants in 9% with low tumor purity
 - 11% enrolled in genetically matched clinical trials
 - Detection of unexpected gene fusions (e.g. BRAF in prostate cancer)
 - Detection of hypermutated cancers

The long tail – a cancer phenotype example

Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients

Ahmet Zehir^{1,13}●, Ryma Benayed^{1,13}, Ronak H Shah¹, Ajayuddin Syed¹, Sumit Middha¹●, Hyunjae R Kim¹●, Preethi Srinivasan¹, Jianqiong Gao², Debayan Chakravarty², Sean M Devlin³, Matthew D Hellmann⁴, David A Barroo⁵, Alison M Schram⁶, Meen Hameed¹, Snjezana Dogan¹, Dara S Ross¹, Jaclyn F Hechtman¹, Deborah F Delair¹, JinJuan Yao¹, Diana L Mandelker¹, Donovan T Cheng^{1,13}, Raghu Chandramoham^{1,12}, Abhinitta S Mohanty¹, Ryan N Ptashkin¹, Gowtham Jayakumaran¹, Meera Prasad¹, Mustafa H Syed¹, Anoop Balakrishnan Rema¹●, Zhen Y Liu¹, Khedoudja Nafa¹, Laetitia Borsig¹, Justyna Sadowska¹, Jacklyn Casanova¹●, Ruben Bacares¹, Ivona J Kieckel¹, Anna Razumova¹, Julie B Son¹, Lisa Stewart¹, Tessara Baldi¹, Kerry A Mullaney¹, Hikmat Al-Ahmadie¹, Efsevia Vakanian¹, Adam A Abeshouse¹, Alexander V Penson^{3,6}, Philip Jonsson^{3,6}, Niedzica Camacho¹, Matthew T Chang^{1,6}, Helen H Won¹, Benjamin F Gross², Ritika Kundra², Zachary J Hein², Hsiao-Wei Chen², Sarah Phillips², Hongxin Zhang², Jiaojiao Wang², Angelica Ochoa², Jonathan Wills⁷, Michael Eubank⁷, Stacy B Thomas⁷●, Stuart M Gards⁸, Dalicia N Reales⁹, Jesse Galie⁹, Robert Durany⁹, Roe Cambrria⁹, Wassim Abida⁹, Andrea Cercek⁹, Darren R Feldman⁹, Mirna M Gounder⁴, A Ari Hakim¹⁰, James J Harding⁴, Gopa Iyer¹¹●, Yelena Y Janjigian⁴, Emmet J Jordan¹, Ciara M Kelly⁴, Maeve A Lower¹², Luc G T Morris⁹, Antonio M Omuro¹⁰, Nitya Raj⁴, Pedram Razavi¹, Alexander N Shoultzari¹²●, Neerav Shukla¹¹, Tara E Soumerai⁴, Anna M Varghese⁴, Rona Yaeger¹, Jonathan Coleman⁸, Bernard Bochner⁸, Gregory J Riely⁴, Leonard B Saltz⁴, Howard I Scher⁴, Paul J Sabbatini¹, Mark E Robson¹, David S Klimstra¹, Barry S Taylor^{2,3,6}, Jose Baselga^{4,6}, Nikolaus Schultz^{2,3,6}, David M Hyman⁴, Maria E Arcila¹, David B Solit^{2,3,6}, Marc Ladanyi^{1,6} & Michael F Berger^{1,2,6}

- ~400 genes interrogated in 10,000 patients
 - Detection of relevant variants in 9% with low tumor purity
 - 11% enrolled in genetically matched clinical trials
 - Detection of unexpected gene fusions (e.g. BRAF in prostate cancer)
 - Detection of hypermutated cancers

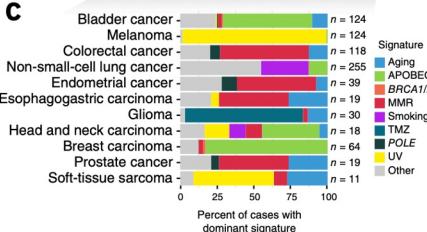
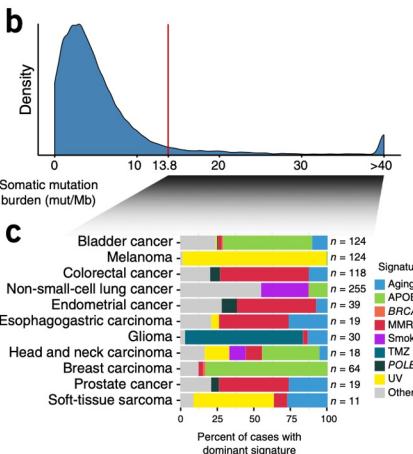
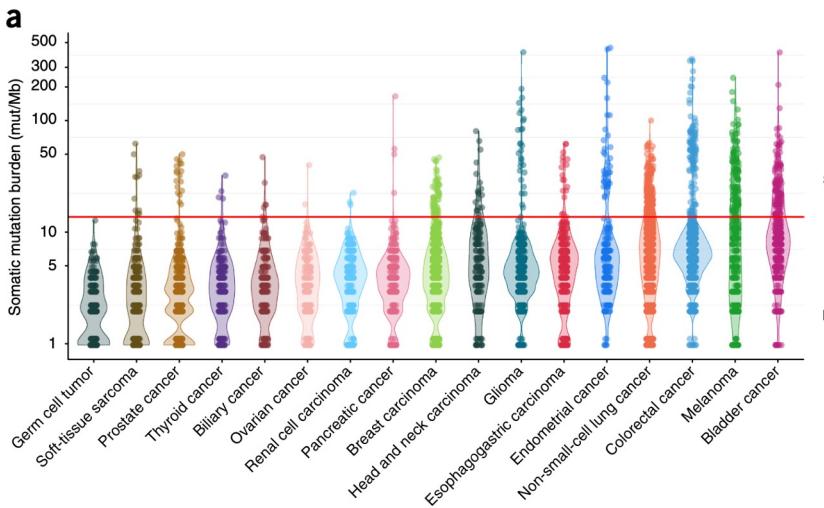


The long tail – a cancer phenotype example

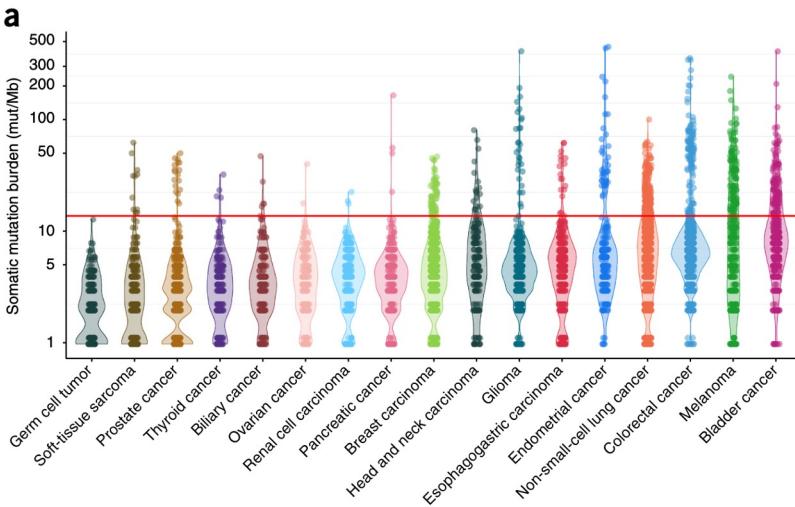
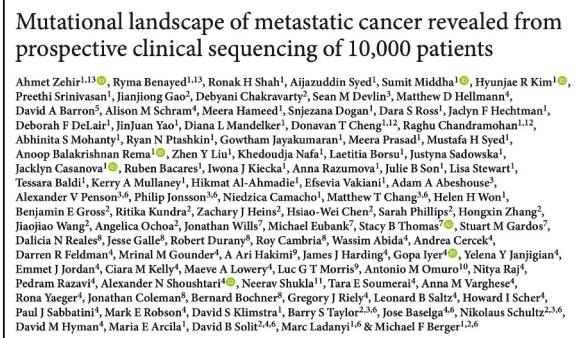
Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients

Ahmet Zehir^{1,13}●, Ryma Benayed^{1,13}, Ronak H Shah¹, Aijazuddin Syed¹, Sumit Middha¹●, Hyunjae R Kim¹●, Preethi Srinivasan¹, Jianqiong Gao², Debayan Chakravarty², Sean M Devlin³, Matthew D Hellmann⁴, David A Barroo⁵, Alison M Schram⁶, Meen Hameed¹, Snjezana Dogan¹, Dara S Ross¹, Jaclyn F Hechtman¹, Deborah F Delair¹, JinJian Yao¹, Diana L Mandelker¹, Donovan T Cheng^{1,13}, Raghu Chandramoham^{1,12}, Abhinitta S Mohanty¹, Ryan N Ptashkin¹, Gowtham Jayakumaran¹, Meera Prasad¹, Mustafa H Syed¹, Anoop Balakrishnan Rema¹●, Zhen Y Liu¹, Khedoudja Nafa¹, Laetitia Borsig¹, Justyna Sadowska¹, Jacklyn Casanova¹●, Ruben Bacares¹, Ivona J Kieckel¹, Anna Razumova¹, Julie B Son¹, Lisa Stewart¹, Tessara Baldi¹, Kerryn A Mullaney¹, Hikmat Al-Ahmadie¹, Efsevia Vakanian¹, Adam A Abeshouse¹, Alexander V Penson^{1,6}, Philip Jonsson^{1,6}, Niedzica Camacho¹, Matthew T Chang^{1,6}, Helen H Won¹, Benjamin E Gross², Ritika Kundra², Zachary J Hein², Hsiao-Wei Chen², Sarah Phillips², Hongxin Zhang², Jiaojiao Wang², Angelica Ochoa², Jonathan Wills⁷, Michael Eubank⁷, Stacy B Thomas⁷●, Stuart M Gards⁸, Dalicia N Reales⁹, Jesse Galie⁹, Robert Durany⁹, Roy Cambray⁹, Wassim Abida⁹, Andrea Cercek⁹, Darren R Feldman⁹, Mirna M Gounder⁹, A Ari Hakim⁹, James J Harding⁹, Gopa Iyer¹●, Yelena Y Janjigian⁴, Emmet J Jordan¹, Ciara M Kelly⁴, Maeve A Lowery¹, James P Morris⁹, Antonio M Omuro¹⁰, Nitya Raj⁴, Pedram Razavi⁴, Alexander N Shoushtari⁴●, Neerav Shukla¹¹, Tara E Soumerai⁴, Anna M Varghese⁴, Rona Yaeger⁴, Jonathan Coleman⁸, Bernard Bochner⁸, Gregory J Riely⁴, Leonard B Saltz⁴, Howard I Scher⁴, Paul J Sabbatini¹, Mark E Robson¹, David S Klimstra¹, Barry S Taylor^{2,3,6}, Jose Baselga^{4,6}, Nikolaus Schultz^{2,3,6}, David M Hyman⁴, Maria E Arcila¹, David B Solit^{2,4,6}, Marc Ladanyi^{1,6} & Michael F Berger^{1,2,6}

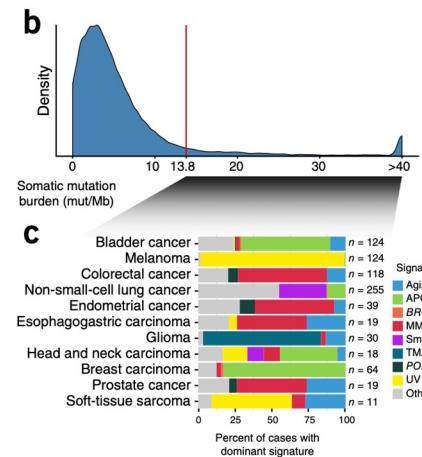
- ~400 genes interrogated in 10,000 patients
- Detection of relevant variants in 9% with low tumor purity
- 11% enrolled in genetically matched clinical trials
- Detection of unexpected gene fusions (e.g. BRAF in prostate cancer)
- Detection of hypermutated cancers



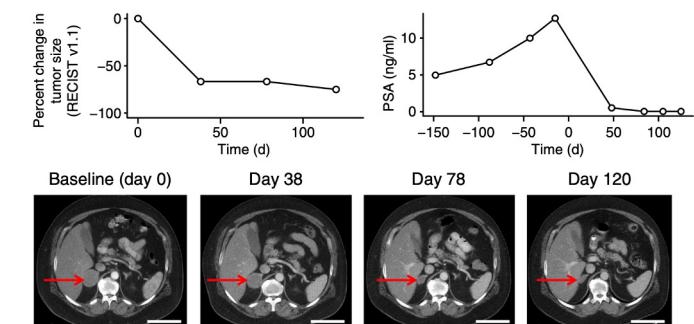
The long tail – a cancer phenotype example



- ~400 genes interrogated in 10,000 patients
- Detection of relevant variants in 9% with low tumor purity
- 11% enrolled in genetically matched clinical trials
- Detection of unexpected gene fusions (e.g. BRAF in prostate cancer)
- Detection of hypermutated cancers



Metastatic prostate cancer with MSI+ treated with immunomodulators

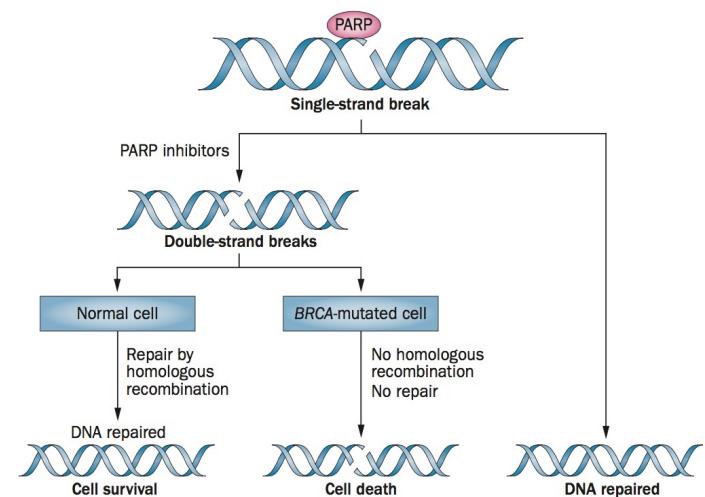


Summary

- Two cancers of the same histological origin may have no common somatic denominator.
- Not total chaos – a limited number of pathways are affected.
- The concept of the long tail.
- Cancers with different histological origin but common drivers may have genomic similarities providing a rationale for drug repurposing.
- Drug repurposing does not always work - the concept of pan-can treatment needs to be evaluated for each drug target combination x histological origin.
- Resistance occurs even if treatment is targeted for most metastatic cancers. Immunotherapy is the exception.

How to identify new effective treatment-biomarker combinations

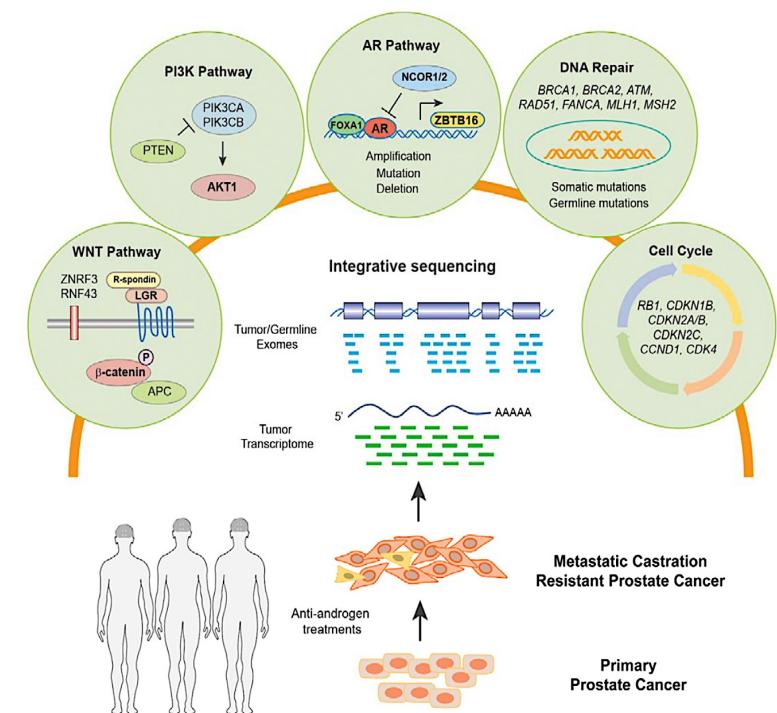
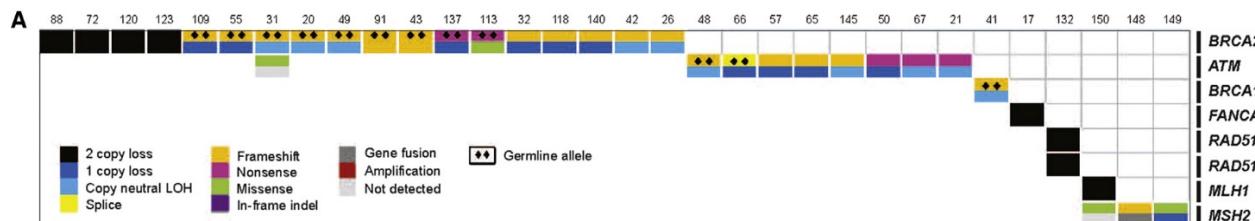
- Old fashion trials:
 - Unselected patients.
 - New drug vs. old standard of care or placebo.
- Biomarker driven trials possible after the sequencing revolution.
- PARP-inhibitors, an example.
 - PARP (poly ADP-ribose polymerases) are important for the repair of single-strand breaks (SSBs) in DNA.
 - Cancers with homologous recombination repair deficiency are sensitive to PARP inhibition.



Sonnenblick et al, Nat. Rev., 2014;

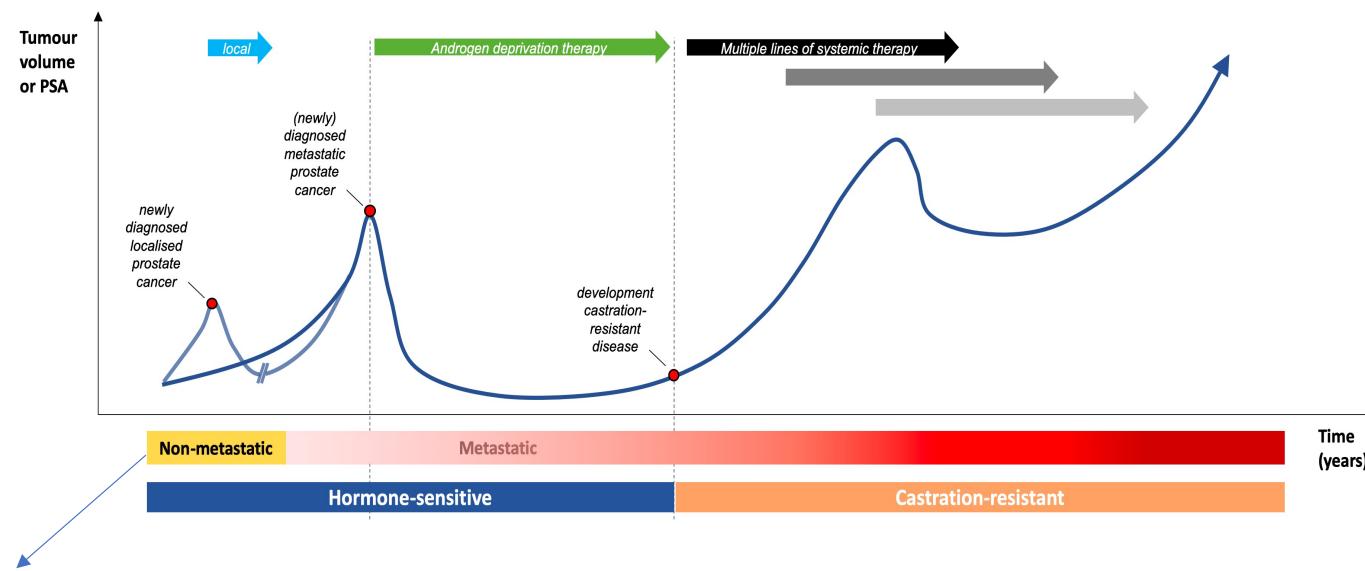
PARP trials in prostate cancer

- Advanced prostate cancer has great potential for precision medicine.
- Robinson et al, Cell, 2015.
 - Whole exome and transcriptome sequencing.
 - 150 individuals.
 - DNA-repair deficiency in 20%.
 - Other potential treatment relevant variants.



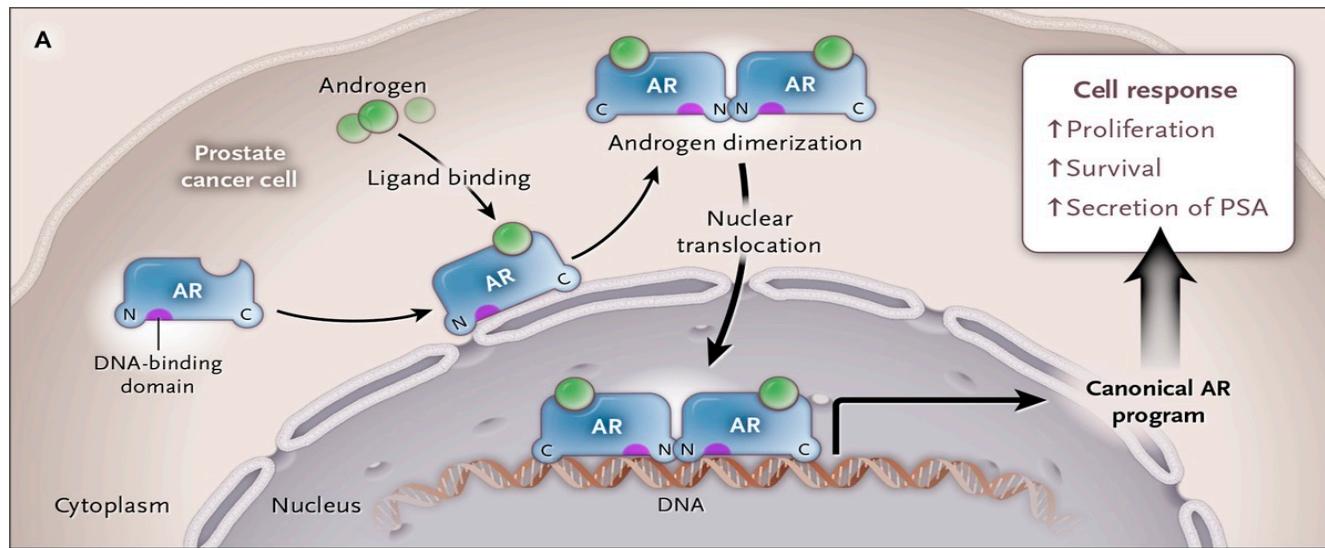
Prostate cancer - background

- Prostate cancer will be used as an example throughout the course



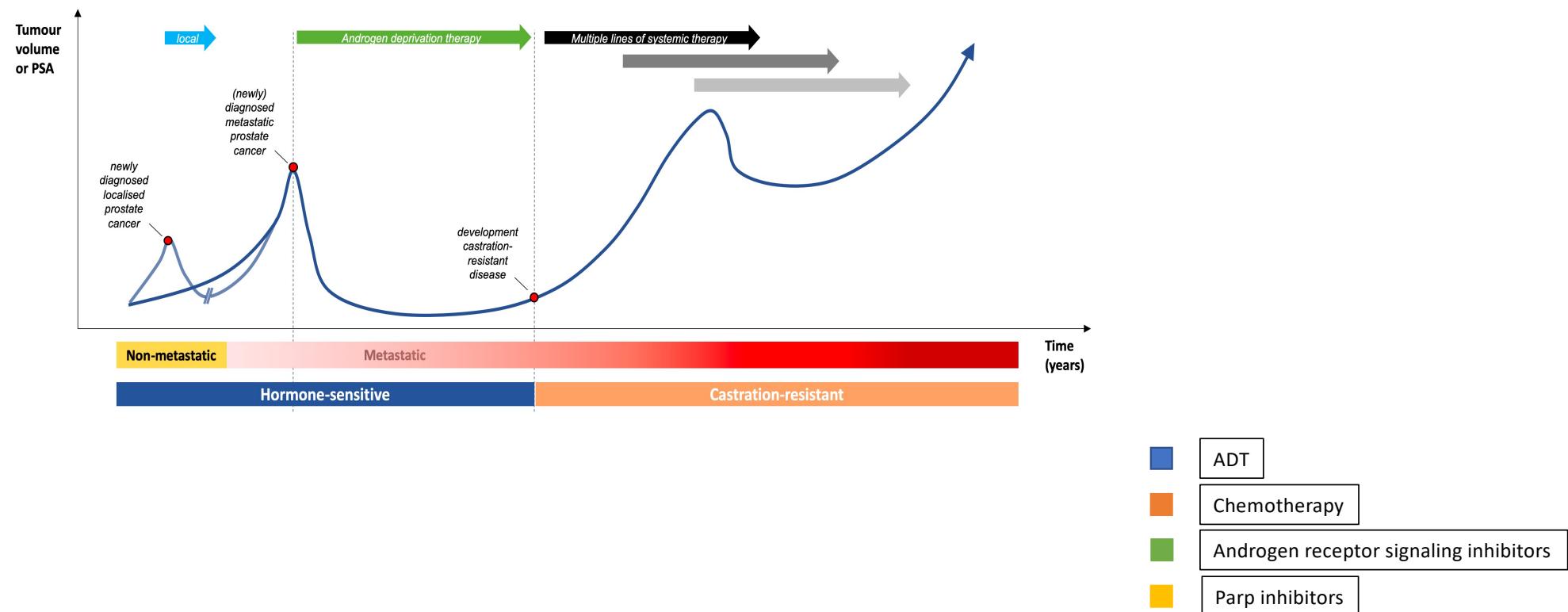
- Whom to treat to avoid overtreatment

Prostate cancer - background



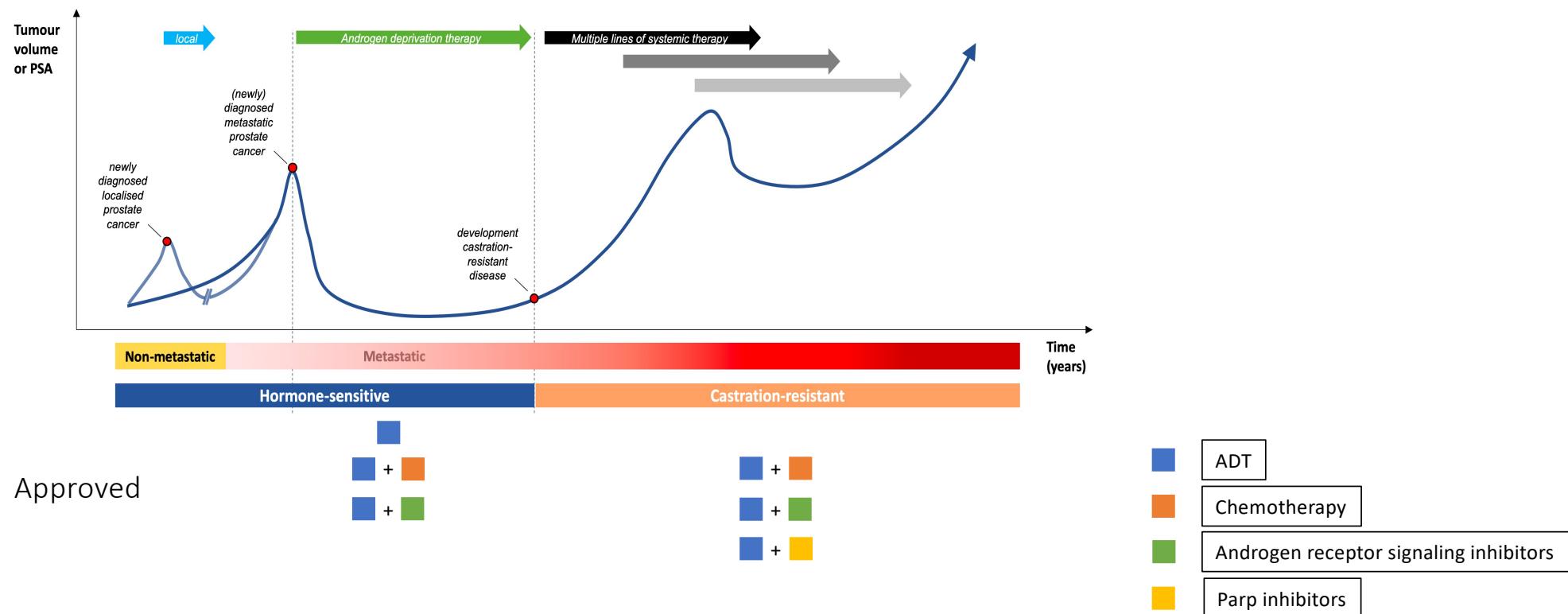
Prostate cancer - background

- Many new drugs but without companion diagnostics.



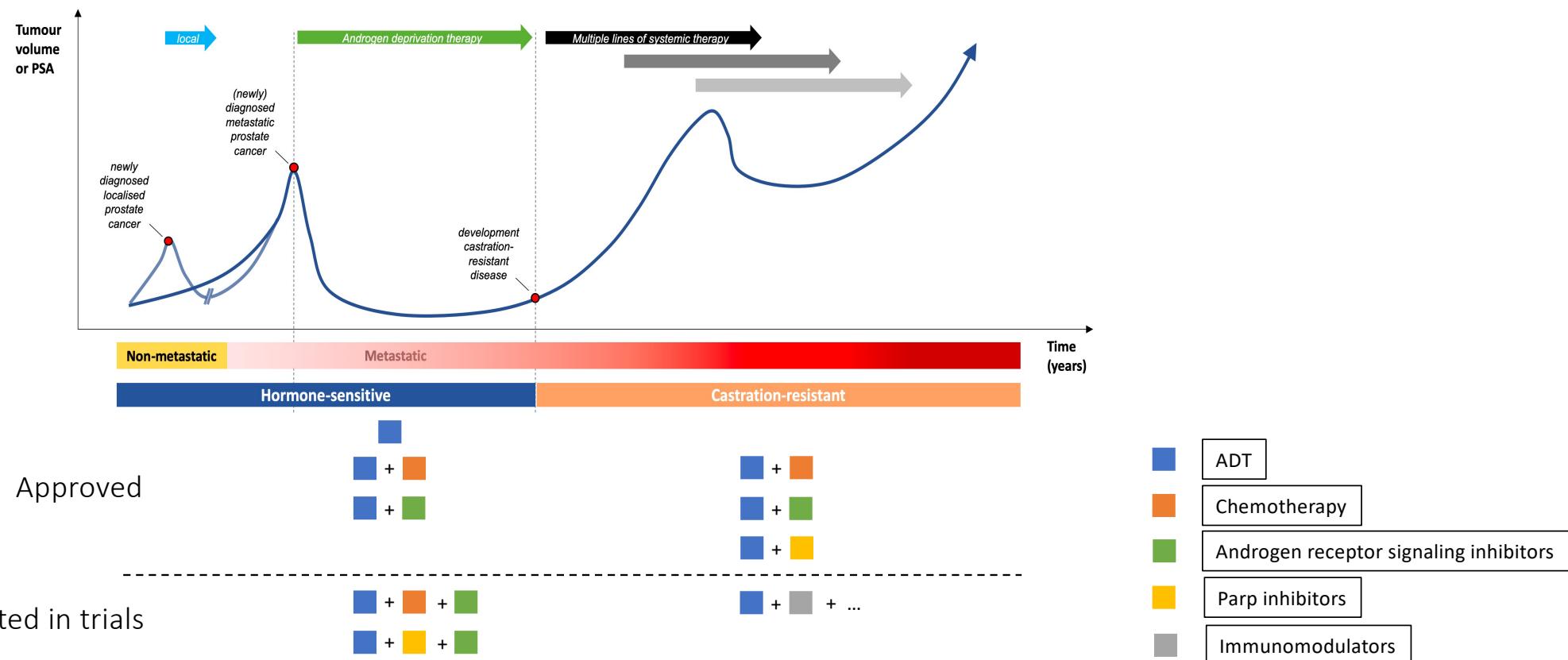
Prostate cancer - background

- A large proportion of prostate cancer patients will develop or are diagnosed with advanced **metastatic disease**.
- Many new drugs but without companion diagnostics.



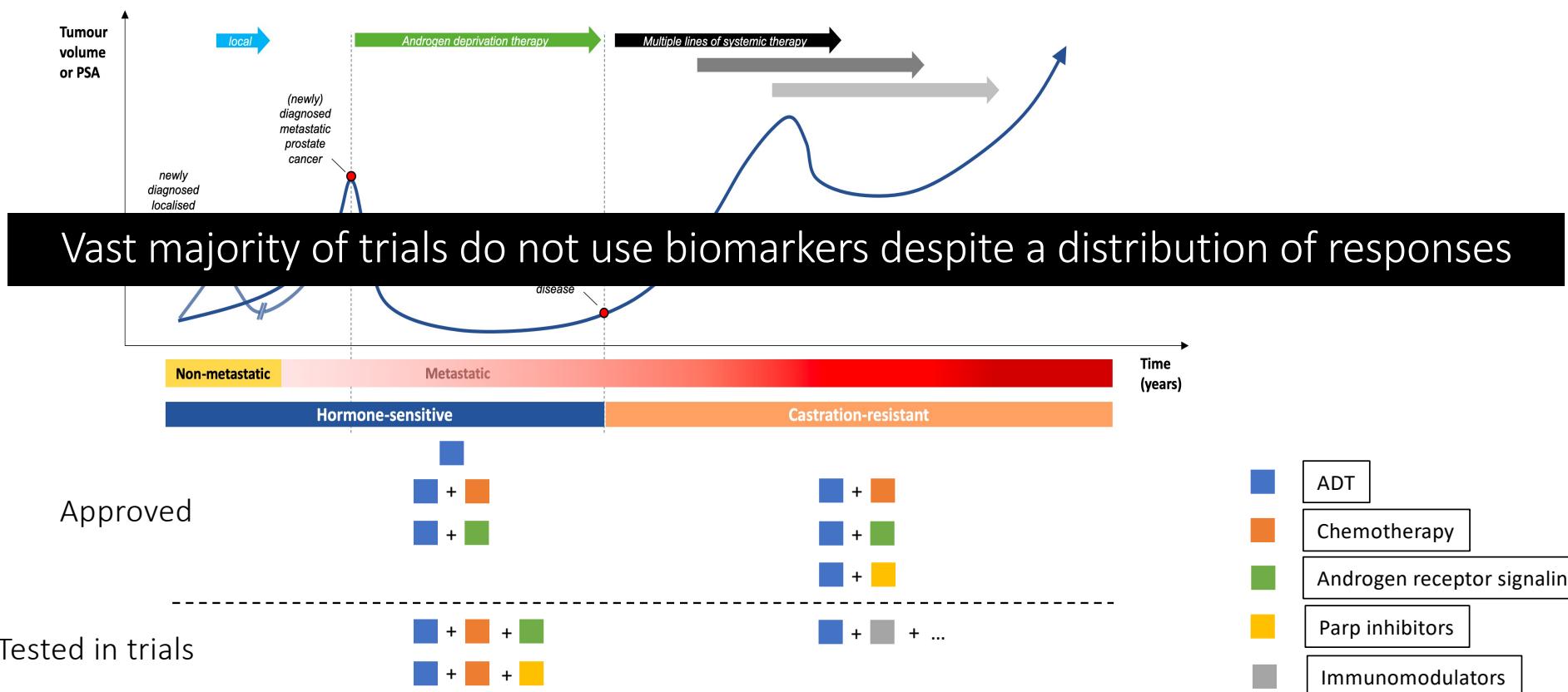
Prostate cancer - background

- A large proportion of prostate cancer patients will develop or are diagnosed with advanced **metastatic disease**.
- Many new drugs but without companion diagnostics.



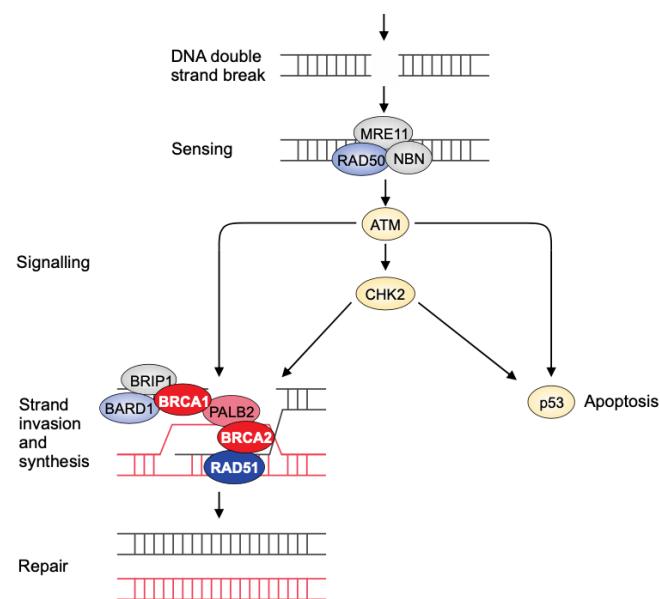
Prostate cancer - background

- A large proportion of prostate cancer patients will develop or are diagnosed with advanced **metastatic disease**.
- Many new drugs but without companion diagnostics.



PARP trials in prostate cancer

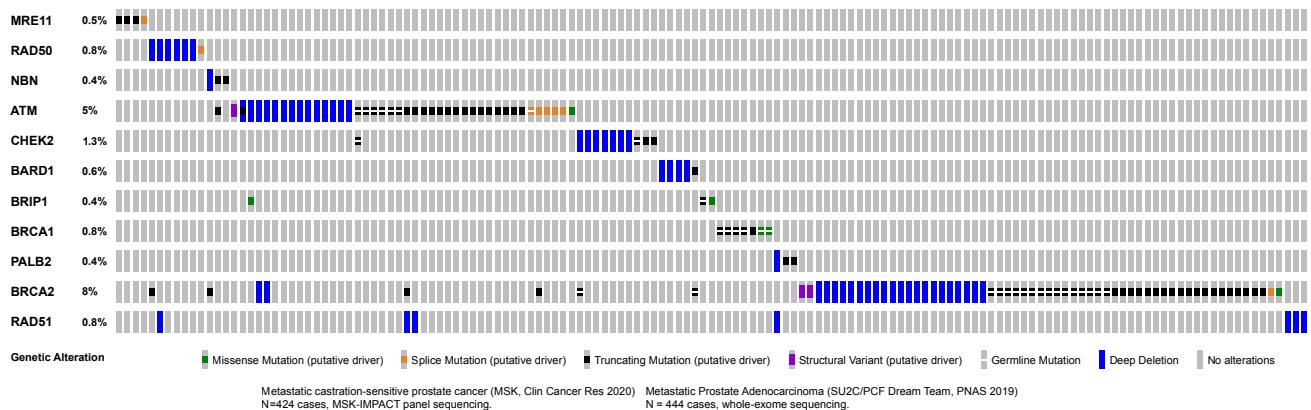
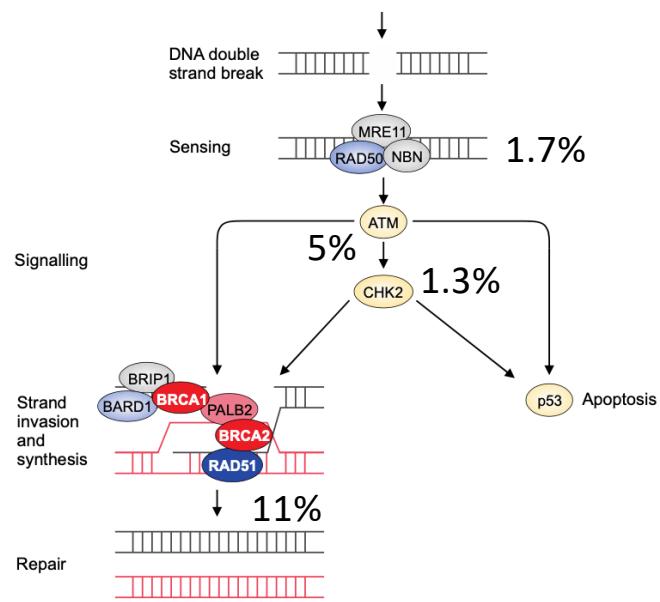
- Multiple studies among various cancers demonstrate that responses are confined to the BRCA-complex.



Polak, Nature Genetics, 2017

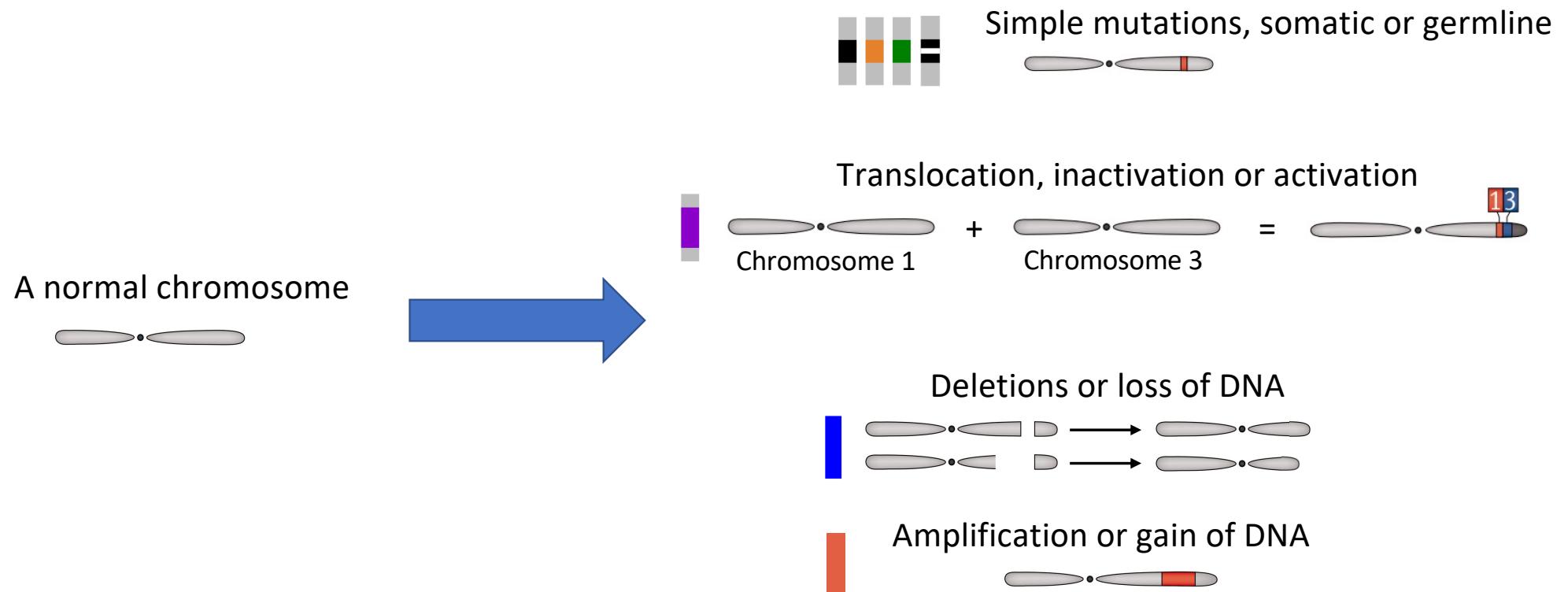
PARP trials in prostate cancer

- Multiple studies among various cancers demonstrate that responses are confined to the BRCA-complex.

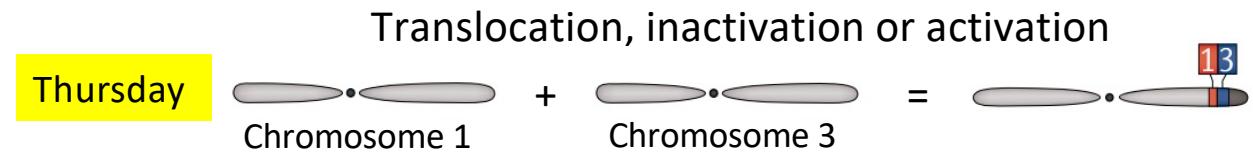


Polak, Nature Genetics, 2017

Type of somatic/germline alteration

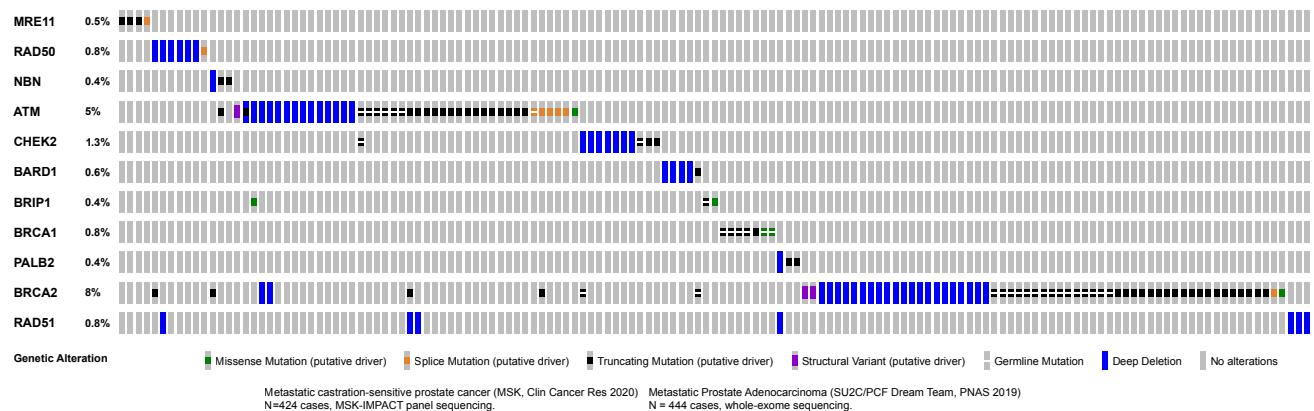
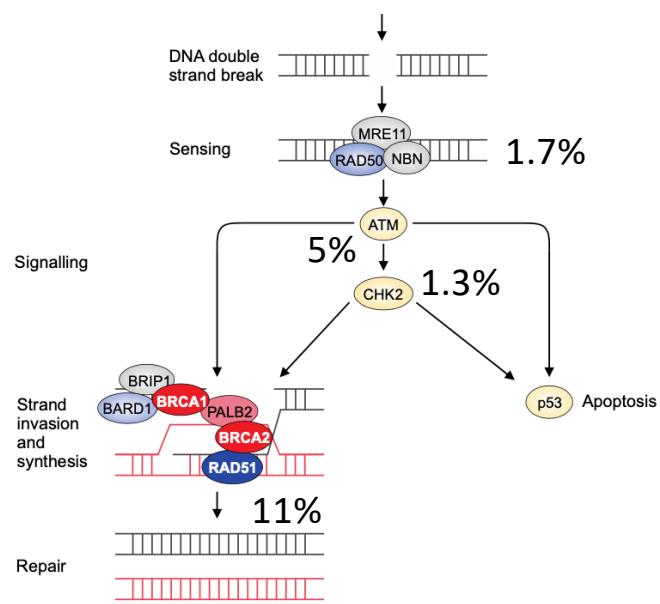


Type of somatic/germline alteration



PARP trials in prostate cancer

- Multiple studies among various cancers demonstrate that responses are confined to the BRCA-complex.



Polak, Nature Genetics, 2017

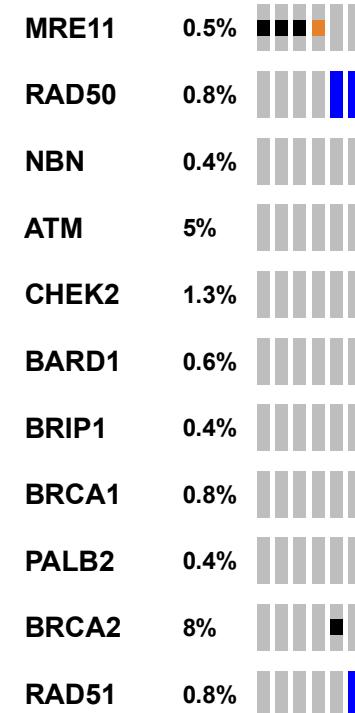
PARP trials in prostate cancer

- The profound trial, led to Olaparib approval in Europe and US.
- Phase III trial
- Biomarker driven:
 - Genes with a "direct" or "indirect" role in homologous recombination repair.
 - Cohort A: Patients with at least one alteration in BRCA1, BRCA2, or ATM.
 - Cohort B: Patients with alterations in any of the other 12 specified genes.

ORIGINAL ARTICLE

Olaparib for Metastatic Castration-Resistant Prostate Cancer

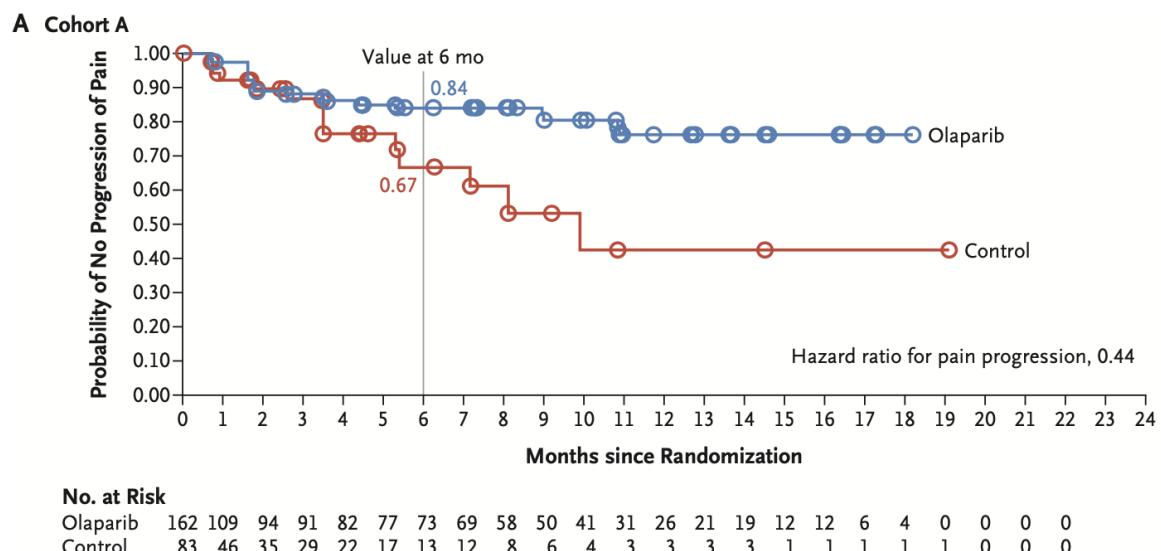
J. de Bono, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, N. Mehra, C. Goessl, J. Kang, J. Burgents, W. Wu, A. Kohlmann, C.A. Adelman, and M. Hussain



Genetic Alteration

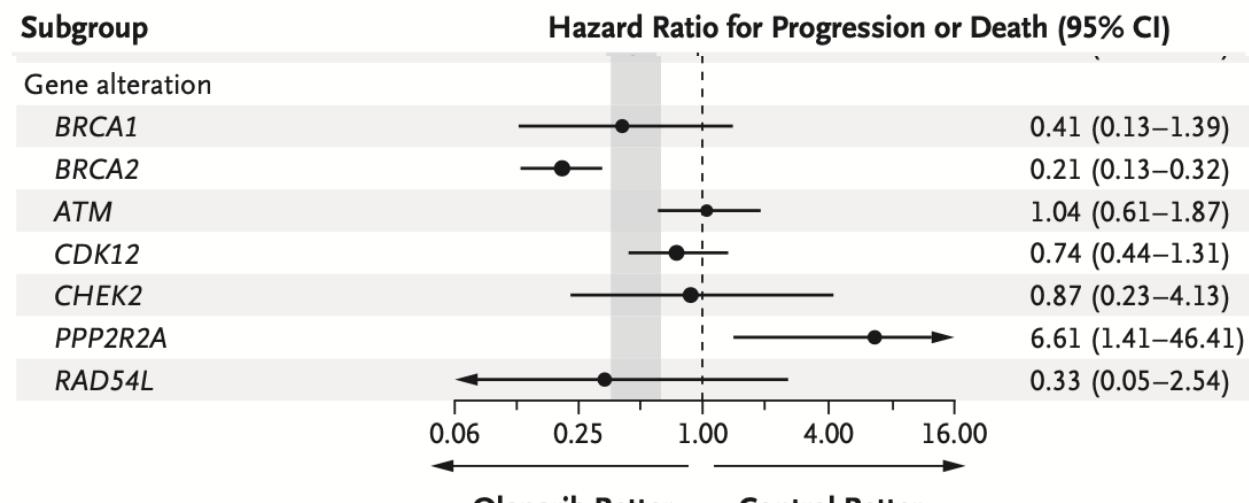
PARP trials in prostate cancer

- Treatment arms:
 - Olaparib.
 - Standard of care.
- Standard of care: getting "the same" drug again but from another vendor.
- Cross-over allowed between arms.
- Only BRCA1/2 approved in Europe.
- ATM + BRCA1/2 approved in US.



PARP trials in prostate cancer

- Hazard ratio: A measure of how often a particular event happens in one group compared to how often it happens in another group, over time.



Remember, control = placebo

PARP trials in prostate cancer



Vinay Prasad MD MPH @VPrasadMDMPH

PROfound is a PROfoundly unethical trial

Here is why [thread]

Or listen to the podcast if you prefer...
soundcloud.com/plenarysession...

ORIGINAL ARTICLE

Olaparib for Metastatic Castration-Resistant Prostate Cancer

Johann de Bono, M.B., Ch.B., Ph.D., Joaquin Mateo, M.D., Ph.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Neal Shore, M.D., Shahneen Sandhu, M.D., Kim N. Chi, M.D., Oliver Sartor, M.D., Neeraj Agarwal, M.D., David Olmos, M.D., Ph.D., Antoine Thiery-Vuillemin, M.D., Ph.D., Przemyslaw Twardowski, M.D., *et al.*

May 28, 2020
N Engl J Med 2020; 382:2091-2102
DOI: 10.1056/NEJMoa1911440

Purchase this article
Print Subscriber? Activate your online access.

ADVERTISEMENT

Have you considered fasting and...

3:51 AM · Sep 27, 2020

<https://www.plenarysessionpodcast.com>

How to identify new effective treatment-biomarker combinations

- There is space for academic initiatives.
- Hartwig Medical Foundation is an independent foundation partly funded by philanthropy.
- The foundation has no profit motive.
- Started the DRUP (drug repurposing) trial.
- Whole genome + transcriptome sequencing.



LETTER

<https://doi.org/10.1038/s41586-019-1600-x>

The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs

D. L. van der Velden^{1,2†}, L. R. Hoes^{1,2,3,2†}, H. van der Wijngaart^{2,3,4,2†}, J. M. van Berge Henegouwen^{2,3,5,2†}, E. van Werkhoven⁶, P. Roepman⁷, R. L. Schilsky⁸, W. W. J. de Leng⁹, A. D. R. Huittema^{10,11}, B. Nuijen¹¹, P. M. Nederlof¹², C. M. L. van Herpen¹³, D. J. A. de Groot¹⁴, L. A. Devriesel¹⁵, A. Hoeben¹⁶, M. J. A. de Jonge¹⁷, M. Chalabi¹⁸, E. F. Smit^{2,19}, A. J. de Langen¹⁹, N. Mehra¹³, M. Labots⁴, E. Kapiteijn⁵, S. Sleijfer^{2,17}, E. Cuppen^{3,7,20}, H. M. W. Verheul^{14,15}, H. Gelderblom⁵ & E. E. Voest^{1,2,3*}

Article

Pan-cancer whole-genome analyses of metastatic solid tumours

<https://doi.org/10.1038/s41586-019-1689-y>

Received: 9 September 2018

Accepted: 20 September 2019

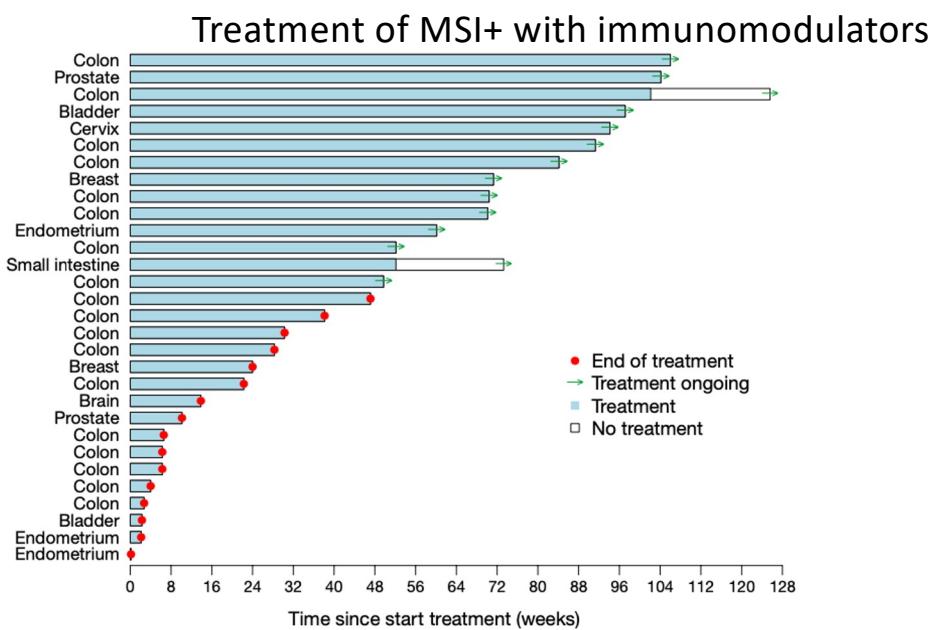
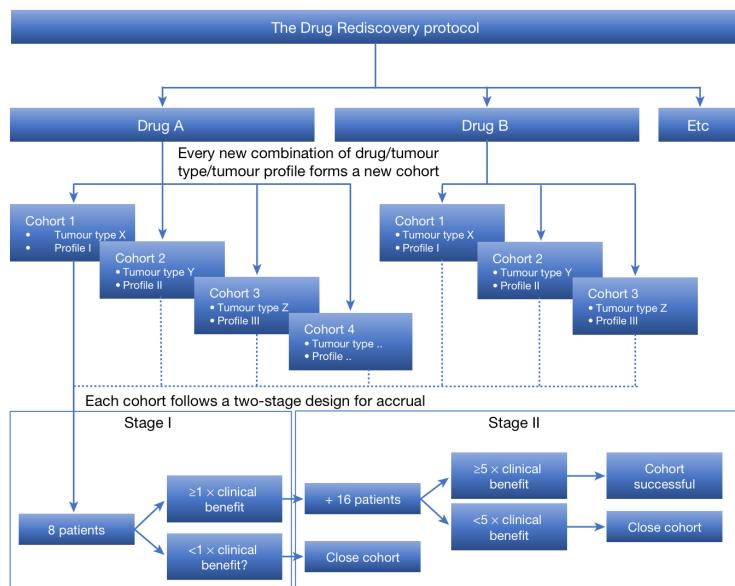
Published online: 23 October 2019

Open access

Peter Priestley^{1,2,2†}, Jonathan Baber^{1,2,2†}, Martijn P. Lolkema^{3,4}, Neeltje Steeghs^{3,5}, Ewart de Brujin¹, Charles Shale², Korneel Duyvesteyn¹, Susan Haldari^{1,3}, Arne van Hoeck⁶, Wendy Onstenk^{1,3,4}, Paul Roepman¹, Mircea Voda¹, Haiko J. Bloemendaal^{1,2}, Vivianne C. G. Tjan-Heijnen⁹, Carla M. L. van Herpen⁵, Mariette Labots¹⁰, Petronella O. Witteveen¹¹, Egbert F. Smit^{3,5}, Stefan Sleijfer^{3,4}, Emile E. Voest^{3,5} & Edwin Cuppen^{1,3,6*}

Drug repurposing – being evaluated in the DRUP trial

- The Center for Personalized Cancer Treatment
 - 45 hospitals in the Netherlands, 219 patients reported
- Structured evaluation of off-target drugs in collaboration with drug companies
- First paper with a focus on pan-cancer MSI+
 - Approval in NE, payment per response ...



The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs, Nature 2019

Immunomodulators in metastatic prostate cancer

- Immunomodulators still not approved for MSI+ prostate cancer (4% of patients).
- MSI- prostate cancer patients do not gain from immunotherapy.
- Multiple phase III trials with pembrolizumab.
 - Unselected patients.
 - Combination of enzalutamide based on week small study data.
 - All negative.

February 28, 2023 6:45 am ET

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today provided updates on two Phase 3 trials, KEYNOTE-641 and KEYNOTE-789. Merck is discontinuing the Phase 3 KEYNOTE-641 trial evaluating KEYTRUDA® (pembrolizumab), Merck's anti-PD-1 therapy, in combination with enzalutamide and androgen deprivation therapy (ADT) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) based on the recommendation of an independent Data Monitoring Committee. At an interim analysis, KEYTRUDA in combination with enzalutamide and ADT did not demonstrate an improvement in radiographic progression-free survival (rPFS) or overall survival (OS), the trial's dual primary endpoints, compared to placebo plus enzalutamide and ADT, and crossed a pre-specified futility boundary for OS. Merck is informing study investigators of the decision and advises patients in the study to speak to their physician regarding treatment.

Summary

- The sequencing revolution has set the stage for biomarker driven clinical trials
- Unfortunately – companies often allow the potential for profit triumph over the best design.
- There is room for academically driven trials, however, this is difficult due to the resources required.

Questions?
