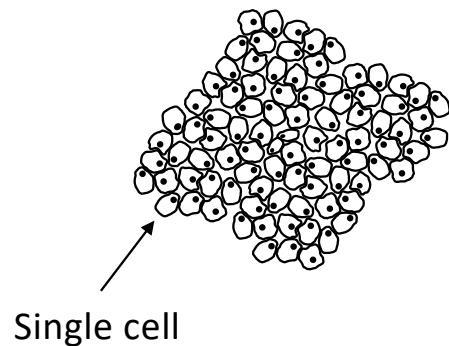


An introduction to the cancer genome and mutational processes in cancer

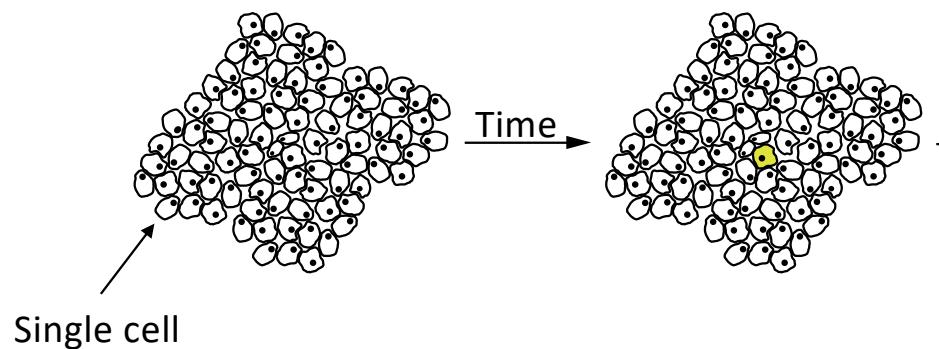


Karolinska
Institutet

We are a mosaic of cells



We are a mosaic of cells

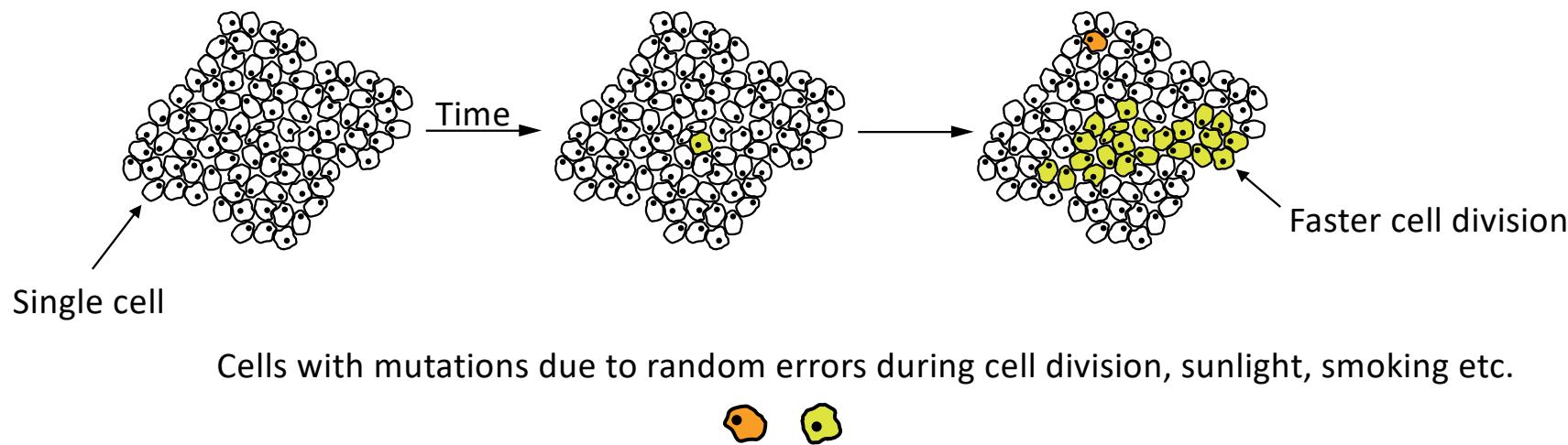


Cells with mutations due to random errors during cell division, sunlight, smoking etc.

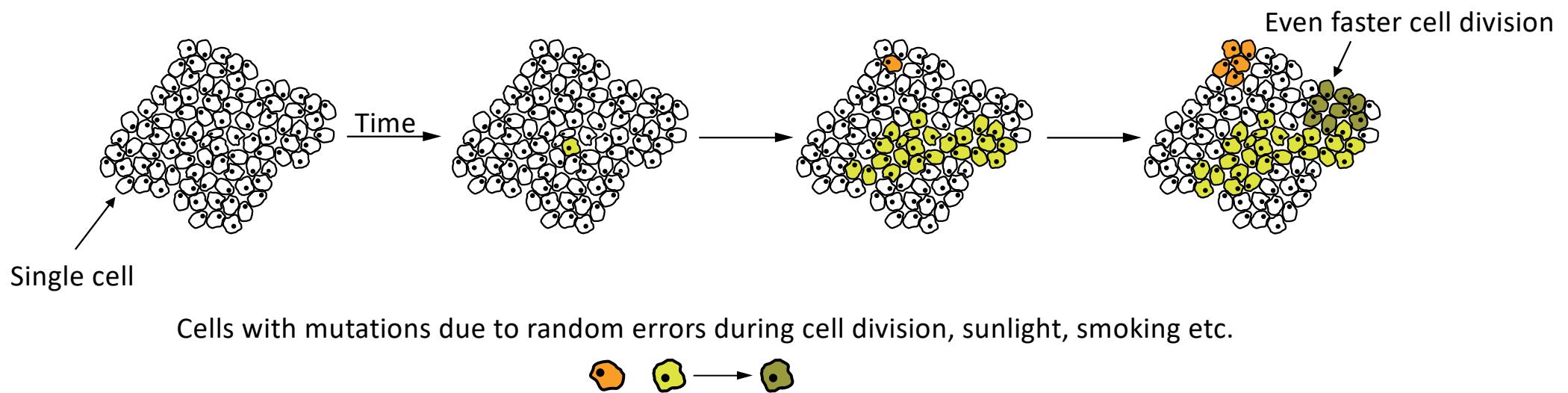


mutations = any type of somatic alteration

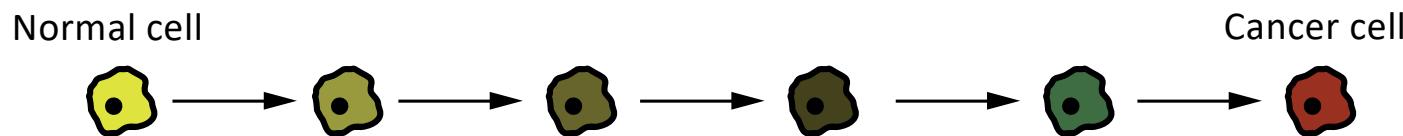
We are a mosaic of cells



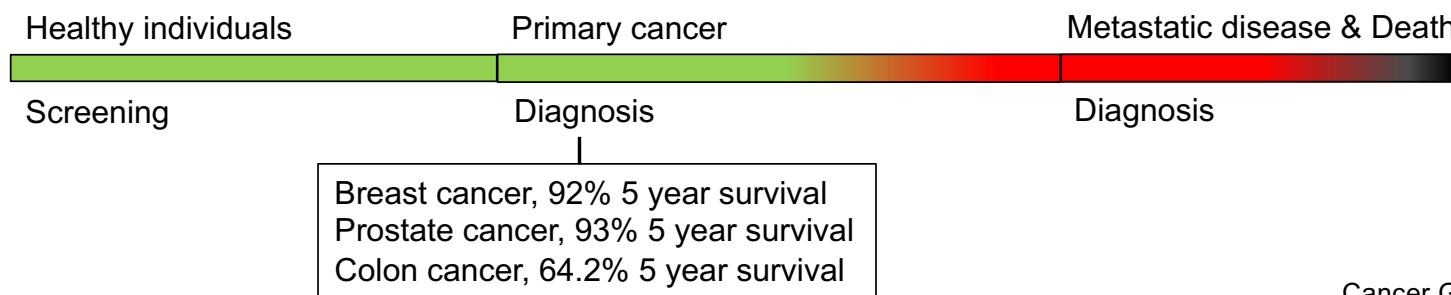
We are a mosaic of cells



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



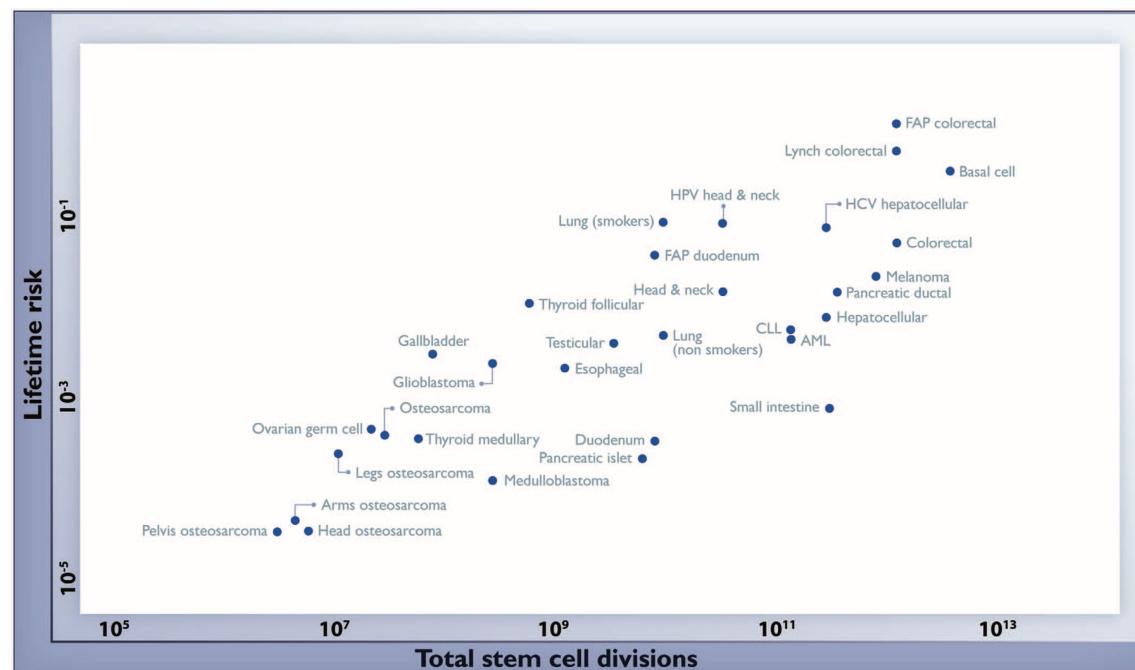
Cancer Genome Landscapes, Science 2013

We are a mosaic of cells

Normal cell



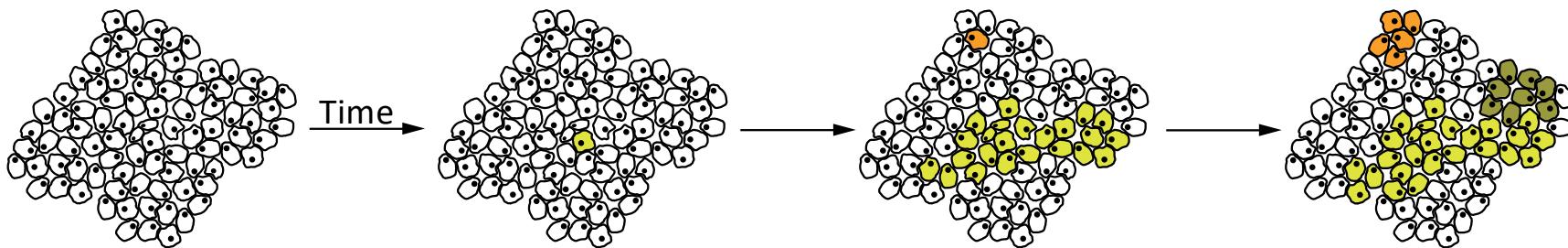
Cancer cell



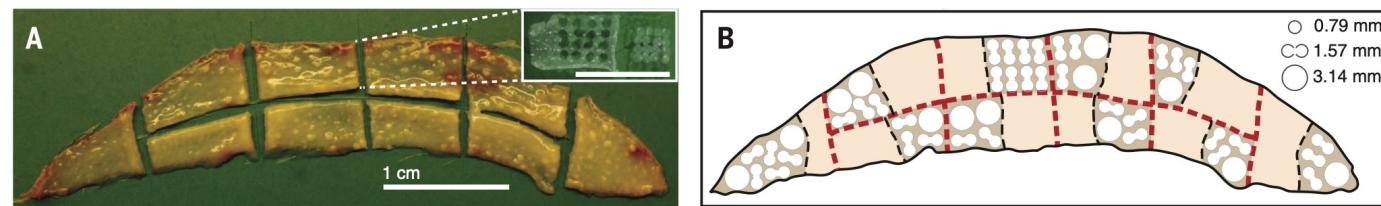
FAP = Familial Adenomatous Polyposis ◊ HCV = Hepatitis C virus ◊ HPV = Human papillomavirus ◊ CLL = Chronic lymphocytic leukemia ◊ AML = Acute myeloid leukemia

Variation in cancer risk among tissues can be explained by the number of stem cell divisions, Science 2015

We are a mosaic of cells



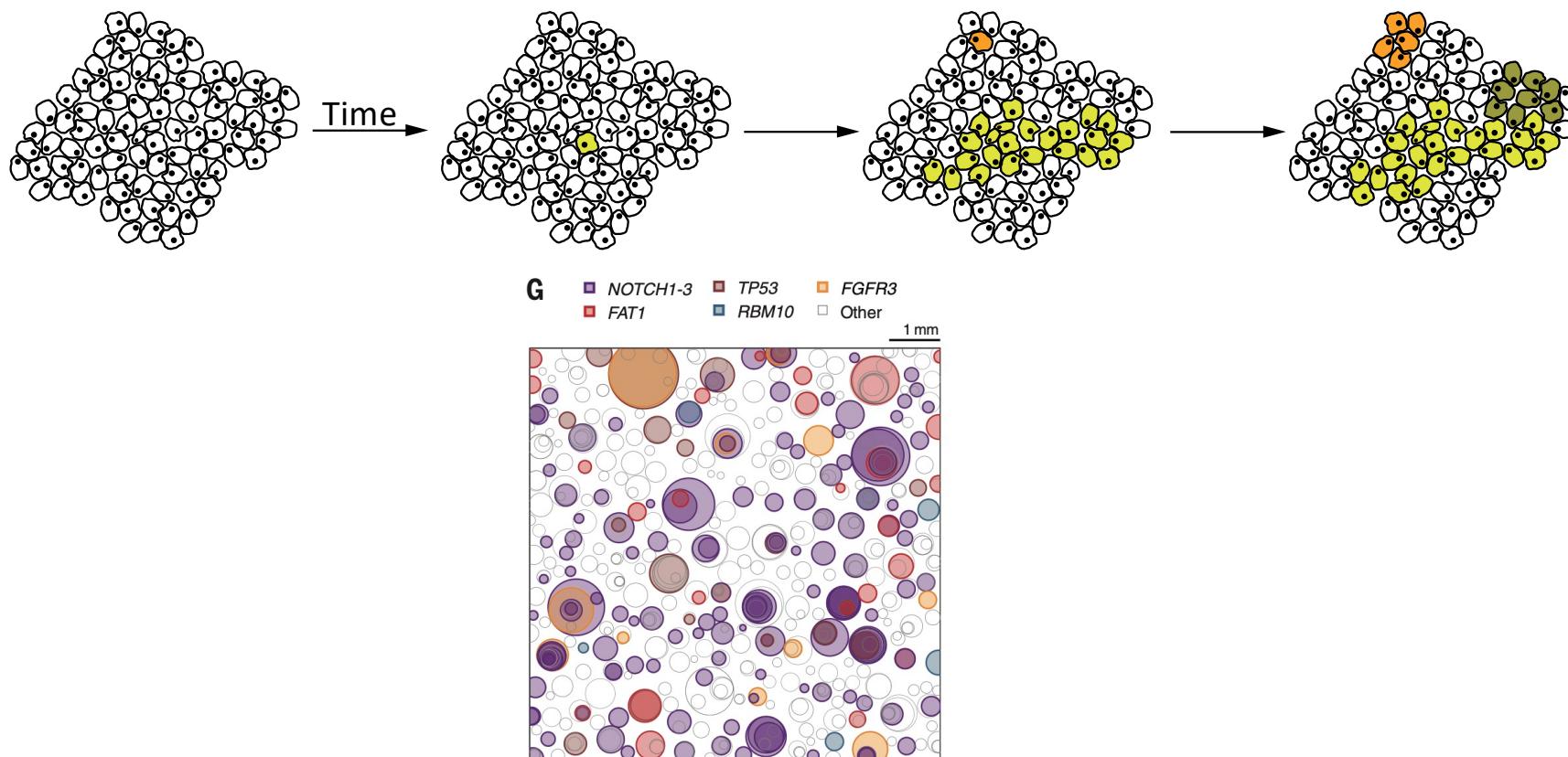
Sequencing of sun-exposed eye lids in mid-age to old people



High burden and pervasive positive selection of somatic mutations in normal human skin, Science 2015

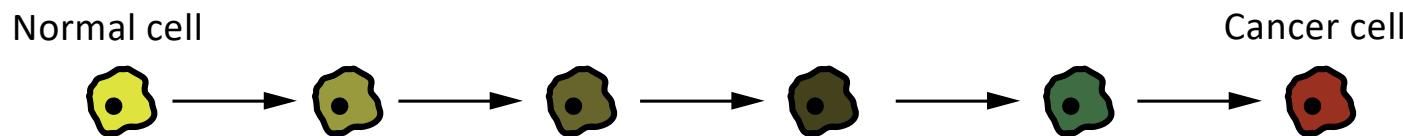
Menti - clones

We are a mosaic of cells



High burden and pervasive positive selection of somatic mutations in normal human skin, Science 2015

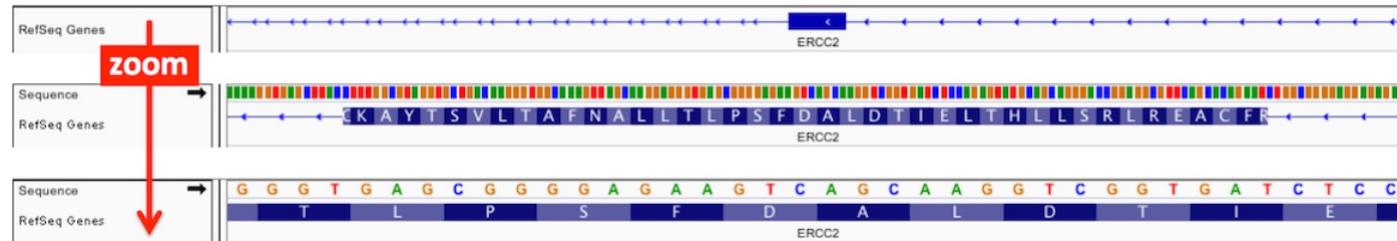
We are a mosaic of cells



- 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.

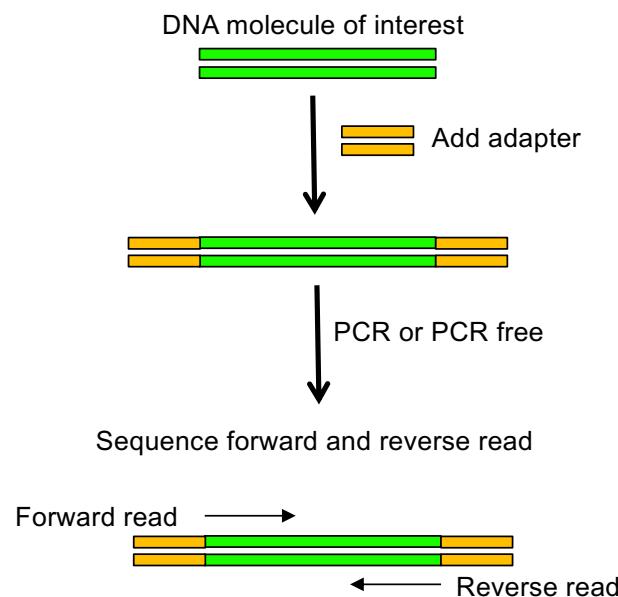


Sequencing:

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

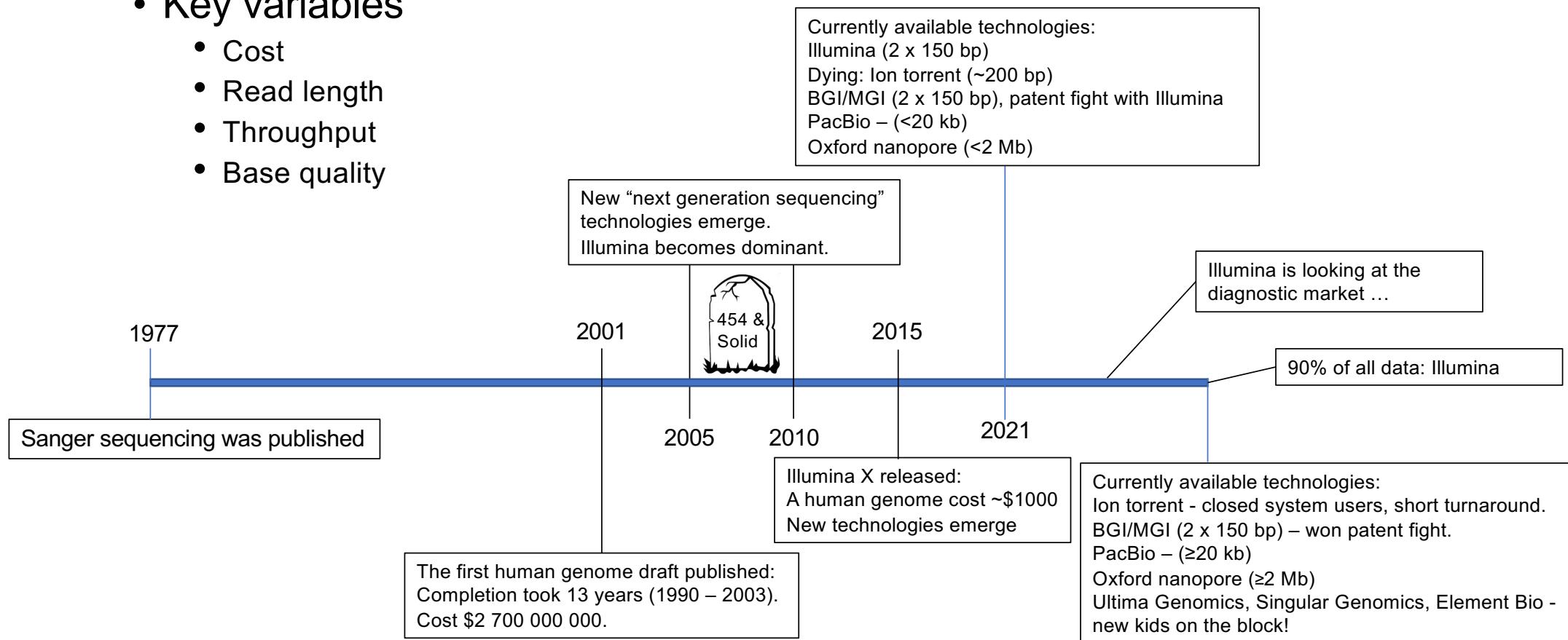
The Sequencing revolution

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

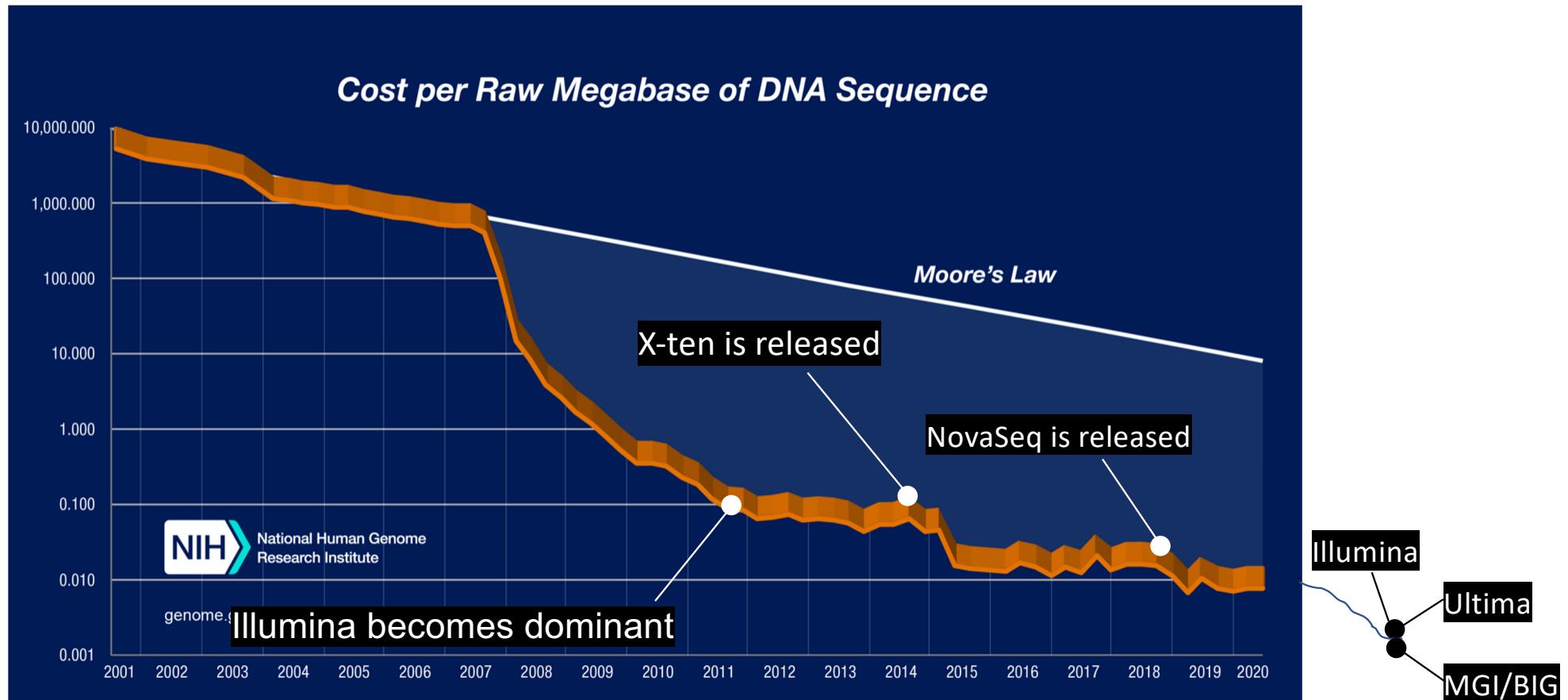


The Sequencing revolution

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



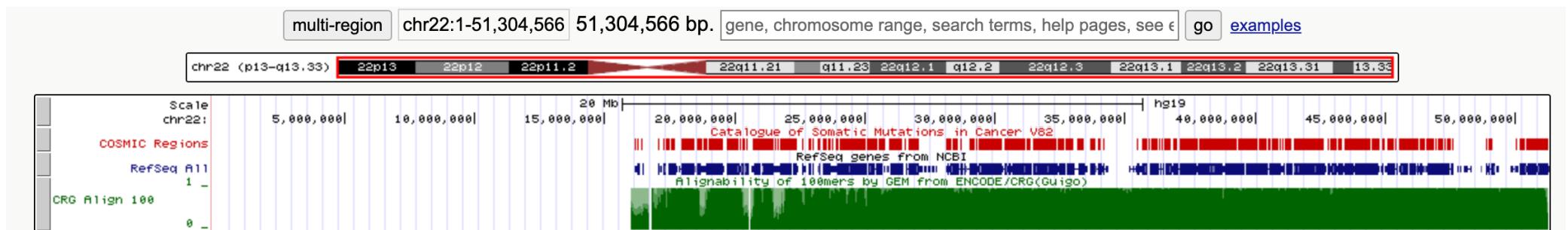
The Sequencing revolution



Menti – cost of WGS

The Sequencing revolution

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



The human genome

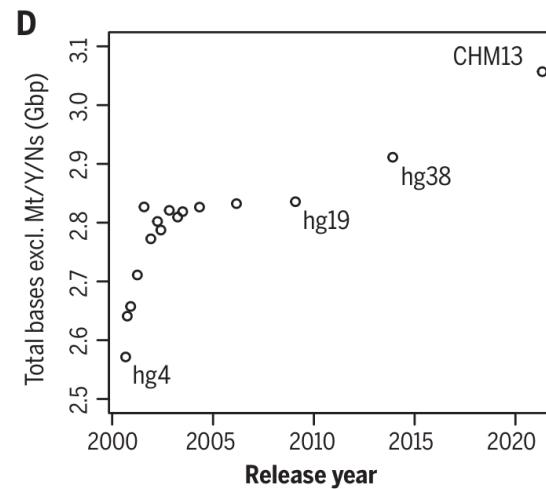
- Current genome build incomplete
 - Merged haplotypes from ~20 people, with a single individual comprising most of the sequence.
- Telomere-to-Telomere (T2T) Consortium present a new genome build T2T-CHM13
 - Using new long-read technologies.
 - Illumina (2 x 150 bp for reference)
 - PacBio (≤ 25 kb)
 - Nanopore (≤ 4 Mb)
 - 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

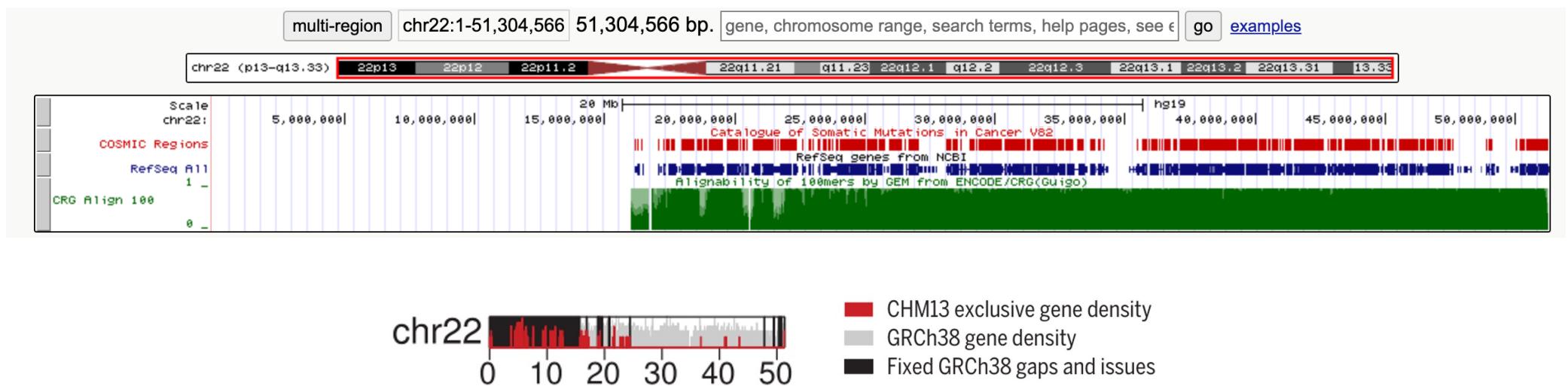
The complete sequence of a human genome



The human genome

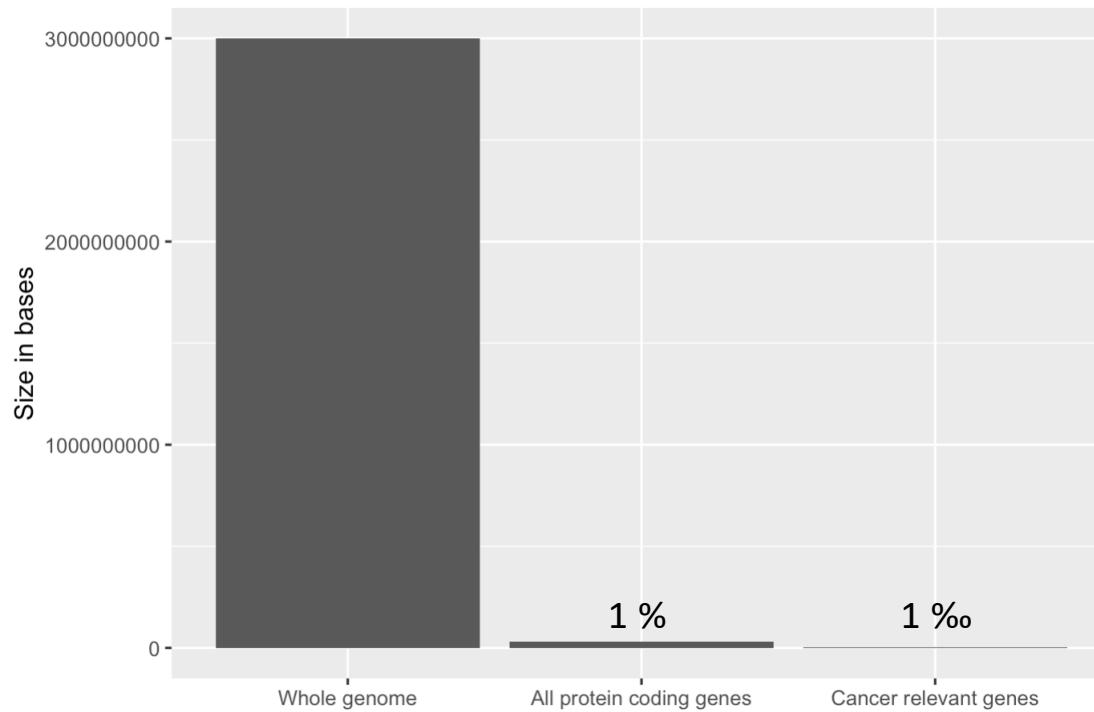
- Key variables

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

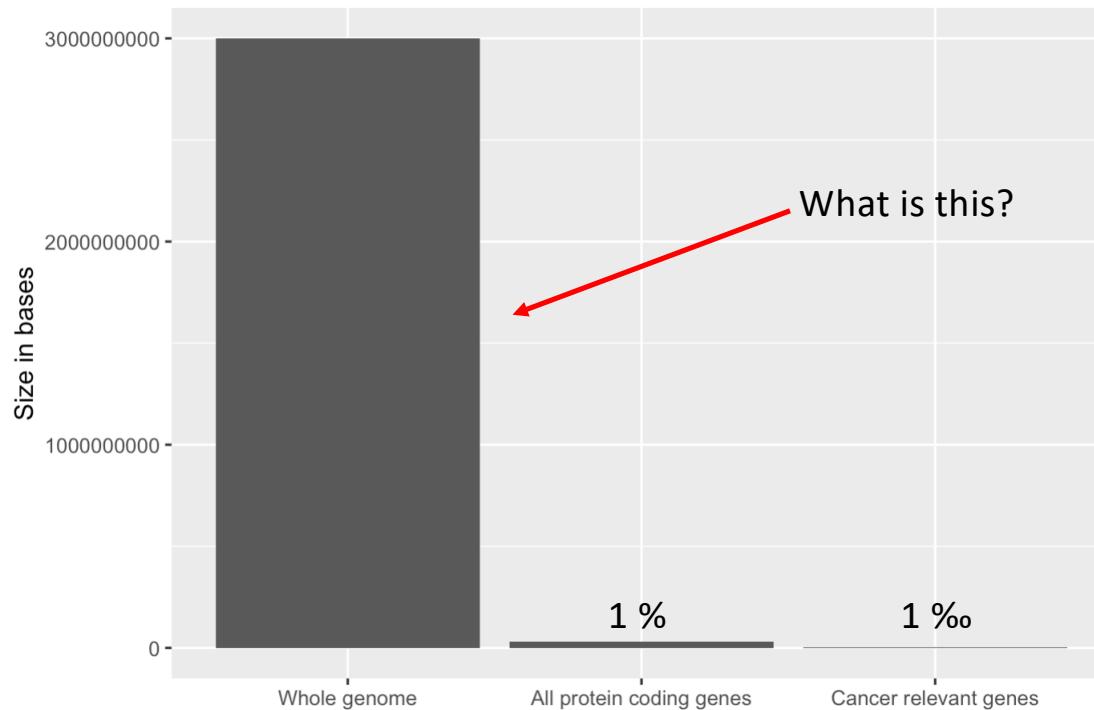


Menti – fraction of genome
needed for diagnostic assays

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



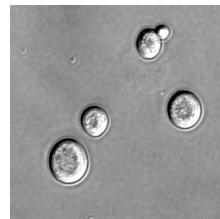
~27,000 protein coding genes

Sea Urchin



~23,000 protein coding genes

Yeast



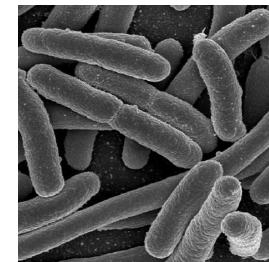
~5,800 protein coding genes

Human



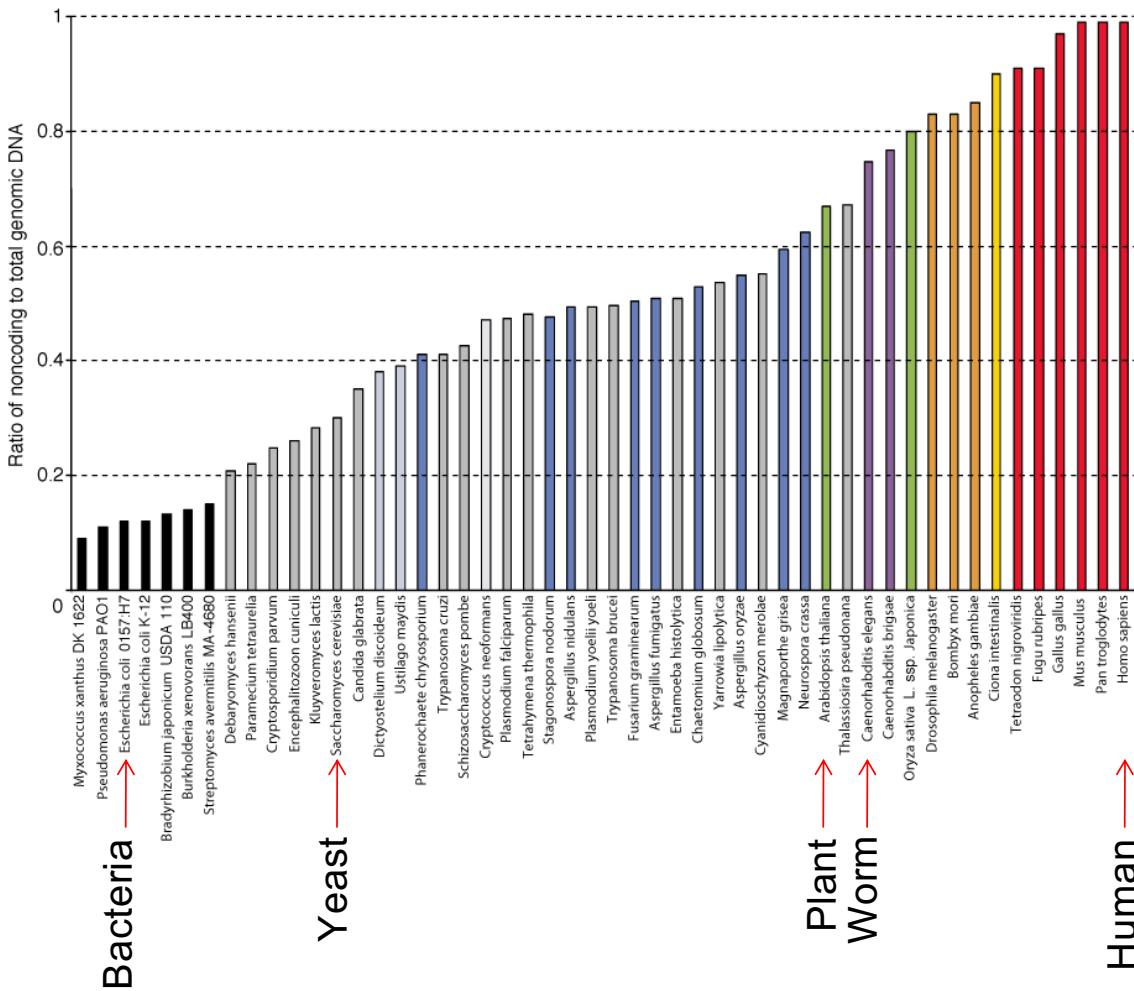
~20,500 protein coding genes

Bacteria

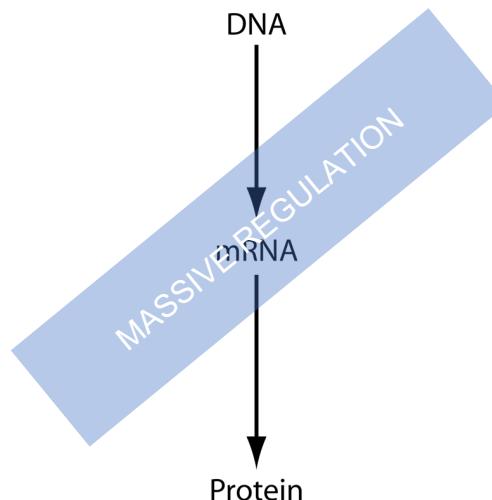
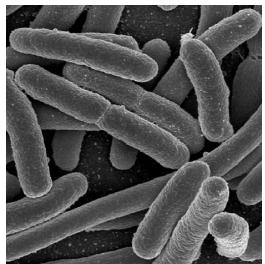


~4,580 protein coding genes

The power of epigenetic regulation



The power of epigenetic regulation



The power of epigenetic regulation

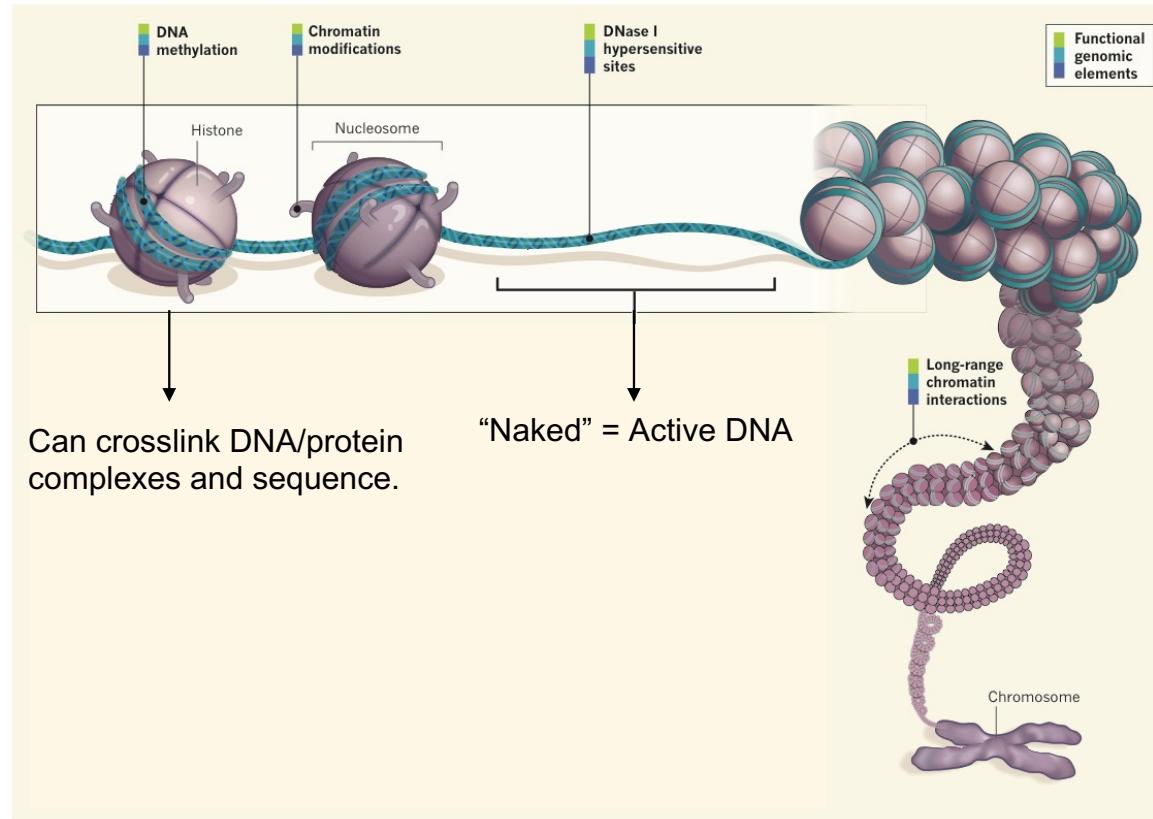
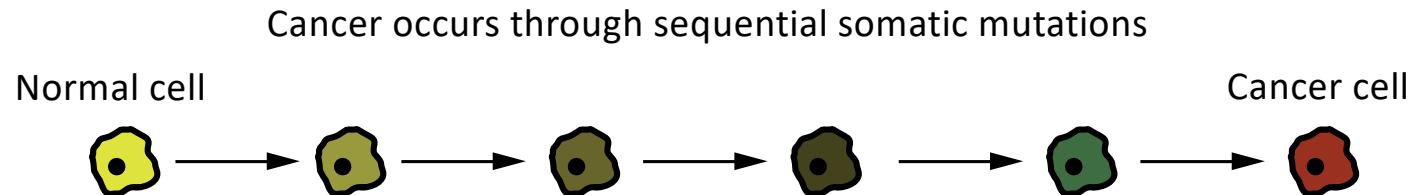
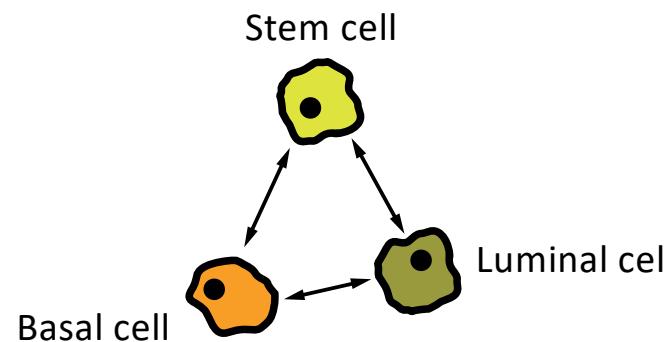


Figure from Nature Reviews

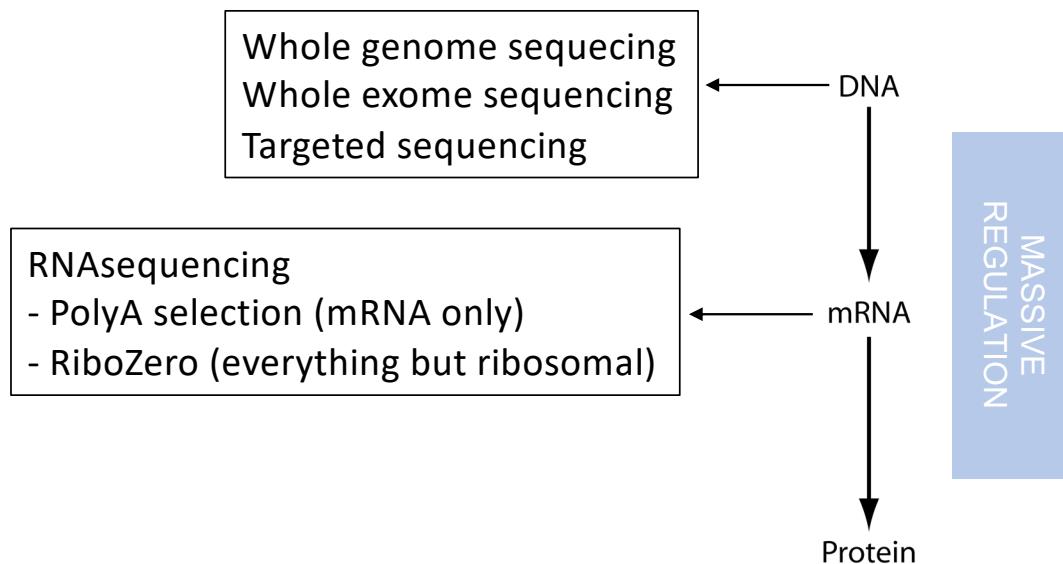
We are a mosaic of cells



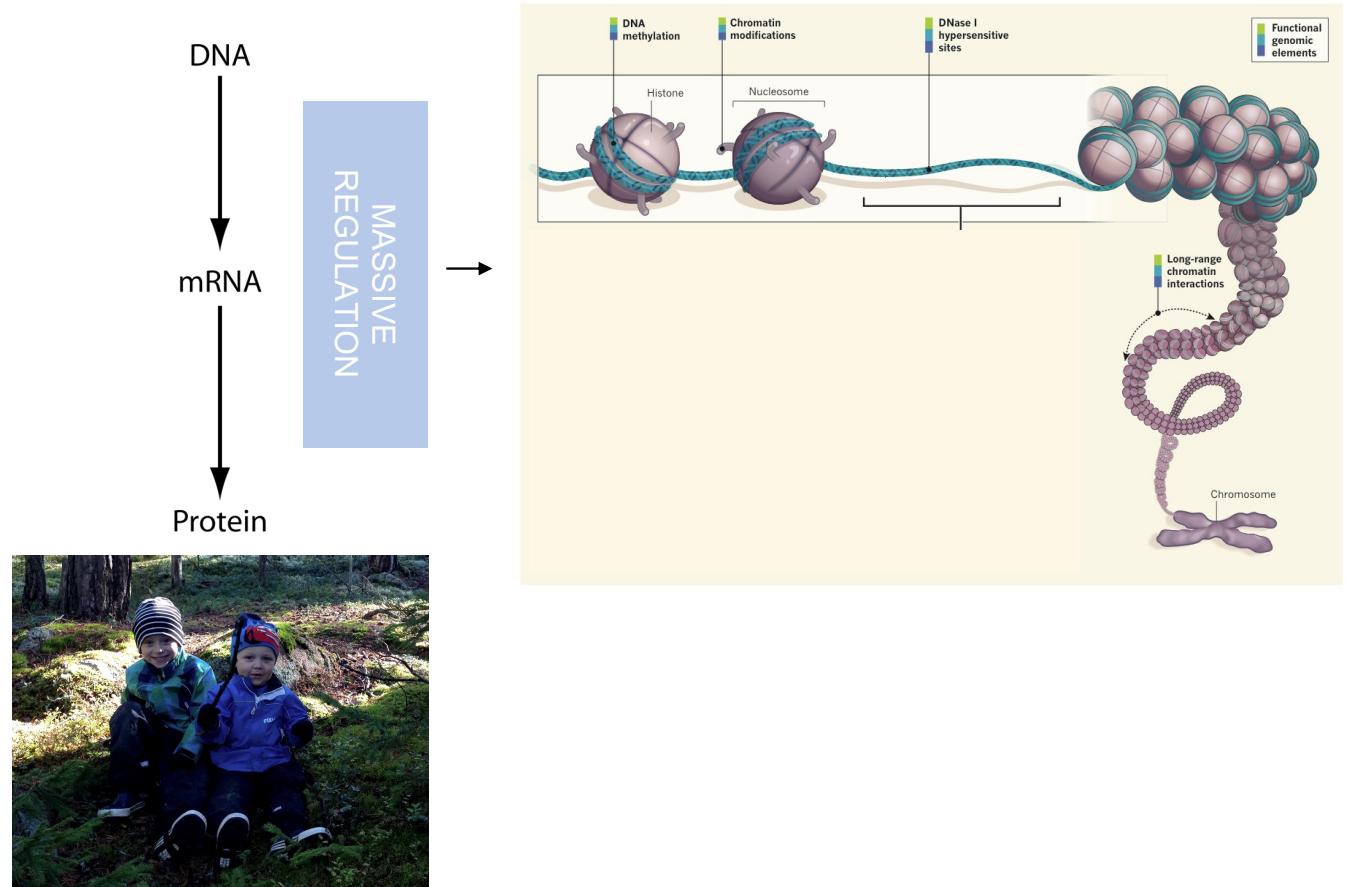
Cancer cells can change phenotype without altering the DNA



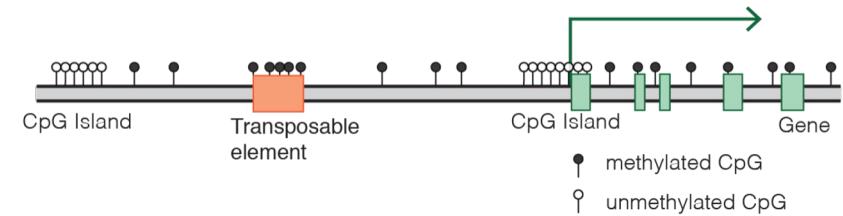
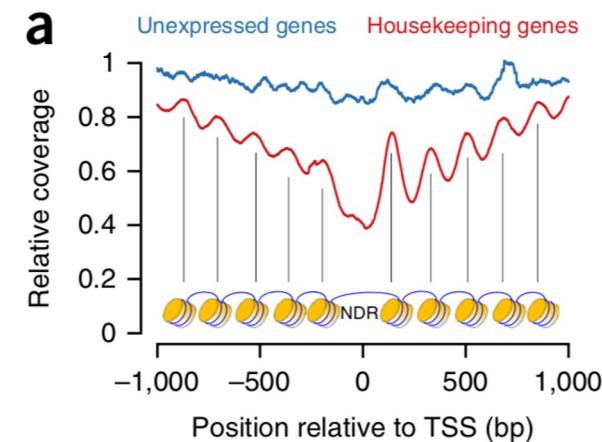
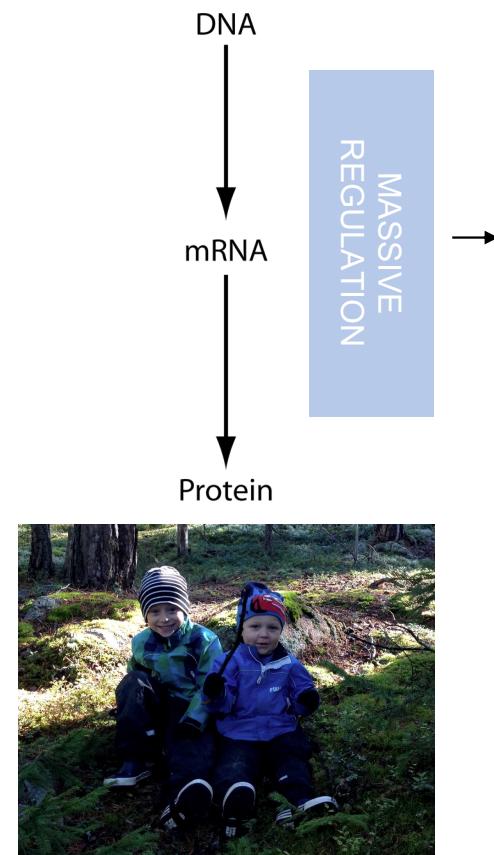
Sequencing revolution = allowed accumulation of new knowledge



Sequencing revolution = allowed accumulation of new knowledge



Sequencing revolution = allowed accumulation of new knowledge

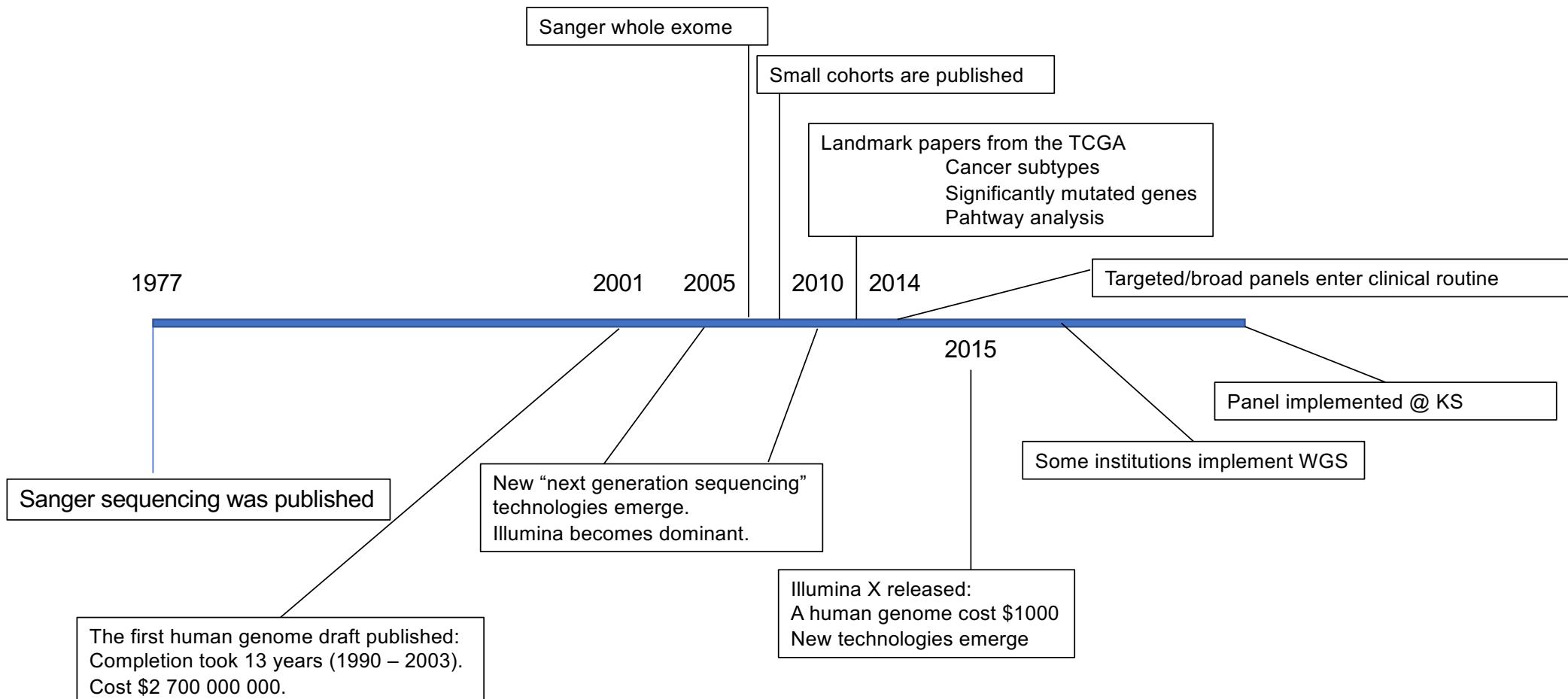


Inferring expressed genes by whole-genome sequencing of plasma DNA, Nature genetics 2016
 Sensitive tumour detection and classification using plasma cell-free DNA methylomes, Nature 2018

Summary

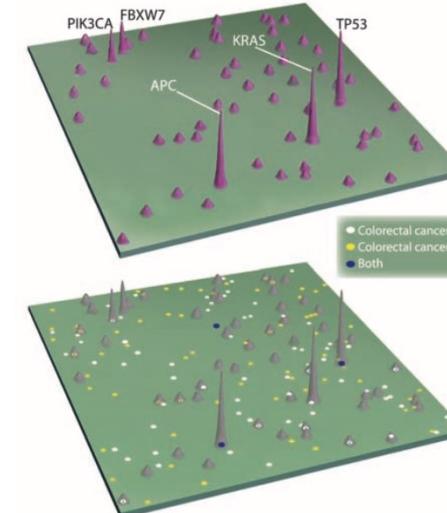
- Cancer occurs through sequential somatic mutations.
 - Take decades to develop.
 - Majority of deaths are due to late detection (after 90% of cancers lifespan).
- Cancer genomics: the study of the totality of DNA sequence and phenotype differences between tumour cells and normal cells.
- Sequencing 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.

The Sequencing revolution



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”

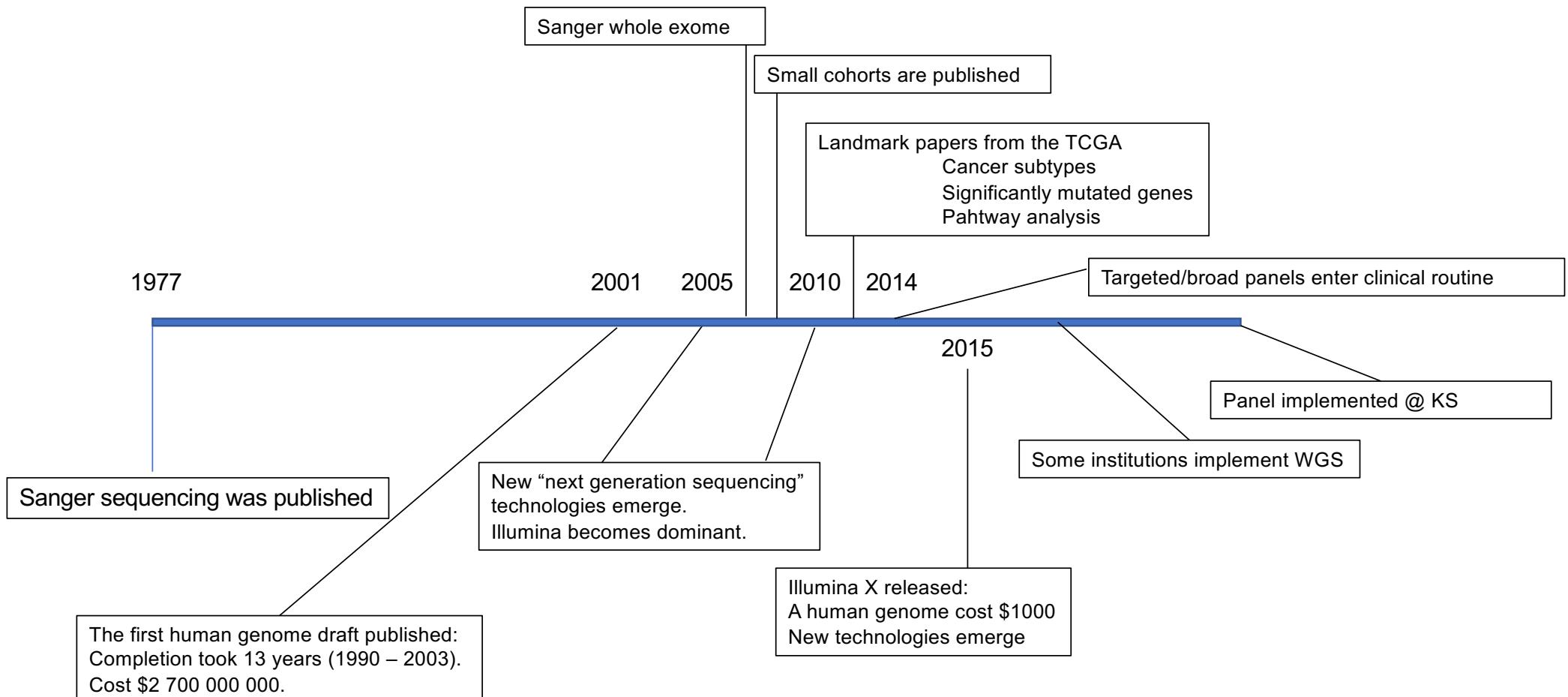


The Genomic Landscapes of Human Breast and Colorectal Cancers
Laura D. Wood, *et al.*
Science **318**, 1108 (2007);
DOI: 10.1126/science.1145720

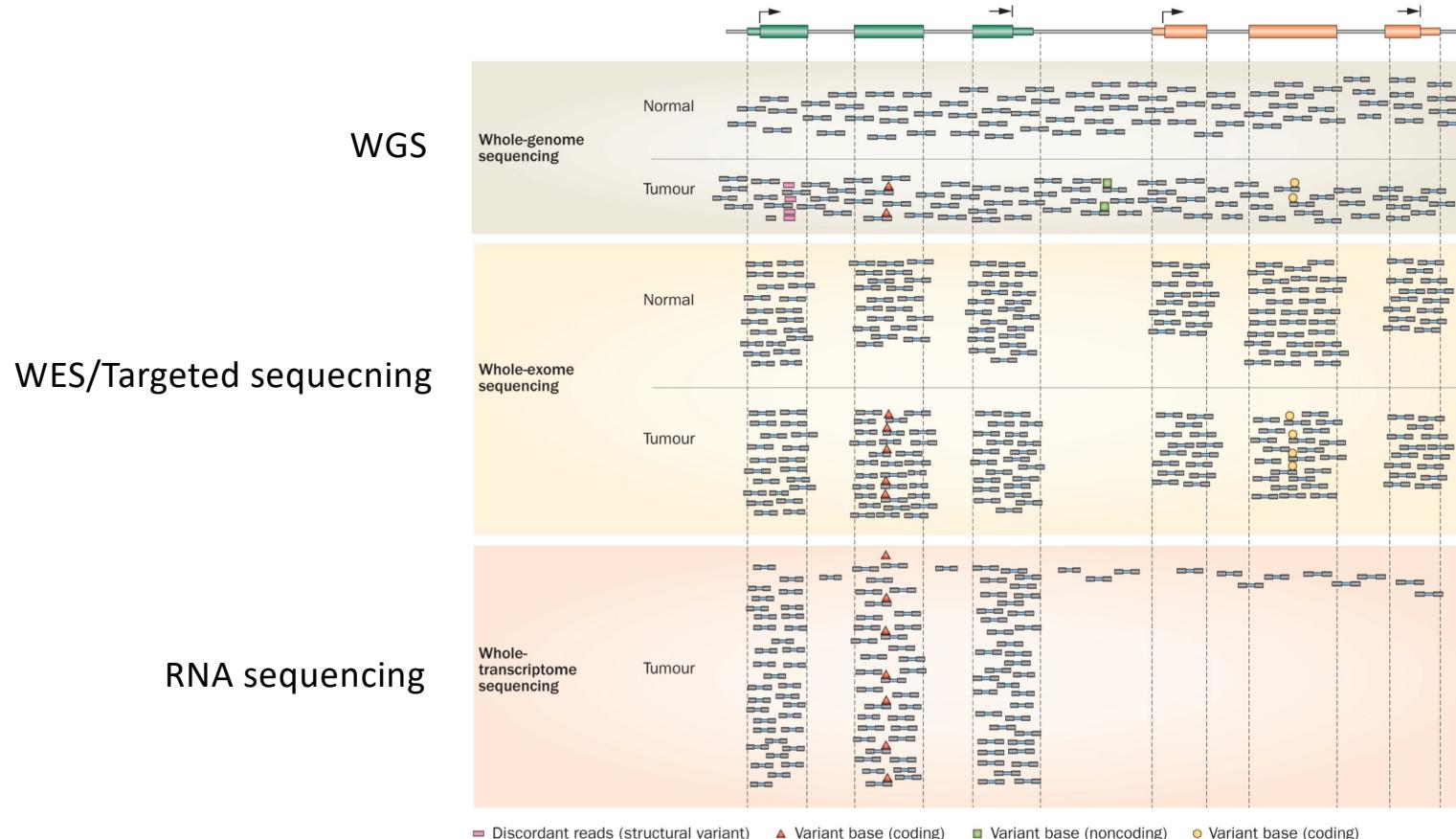


The Consensus Coding Sequences of Human Breast and Colorectal Cancers
Tobias Sjöblom, *et al.*
Science **314**, 268 (2006);
DOI: 10.1126/science.1133427

The Sequencing revolution



Sequencing revolution = allowed accumulation of new knowledge



These three data types = course focus

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

International consortia and other initiatives

- ICGC
 - International Cancer Genome Consortium
 - WGS + RNAseq
- TCGA
 - The Cancer Genome Atlas
 - WES + RNAseq + Methylation profiling
- Memorial Sloan Kettering
 - Panel-sequencing of hundreds of thousands locally advanced/advanced cases
- The Hartwig Foundation
 - WGS + RNAseq on ~7000 cases in a clinical trial context

WGS = whole genome sequencing.

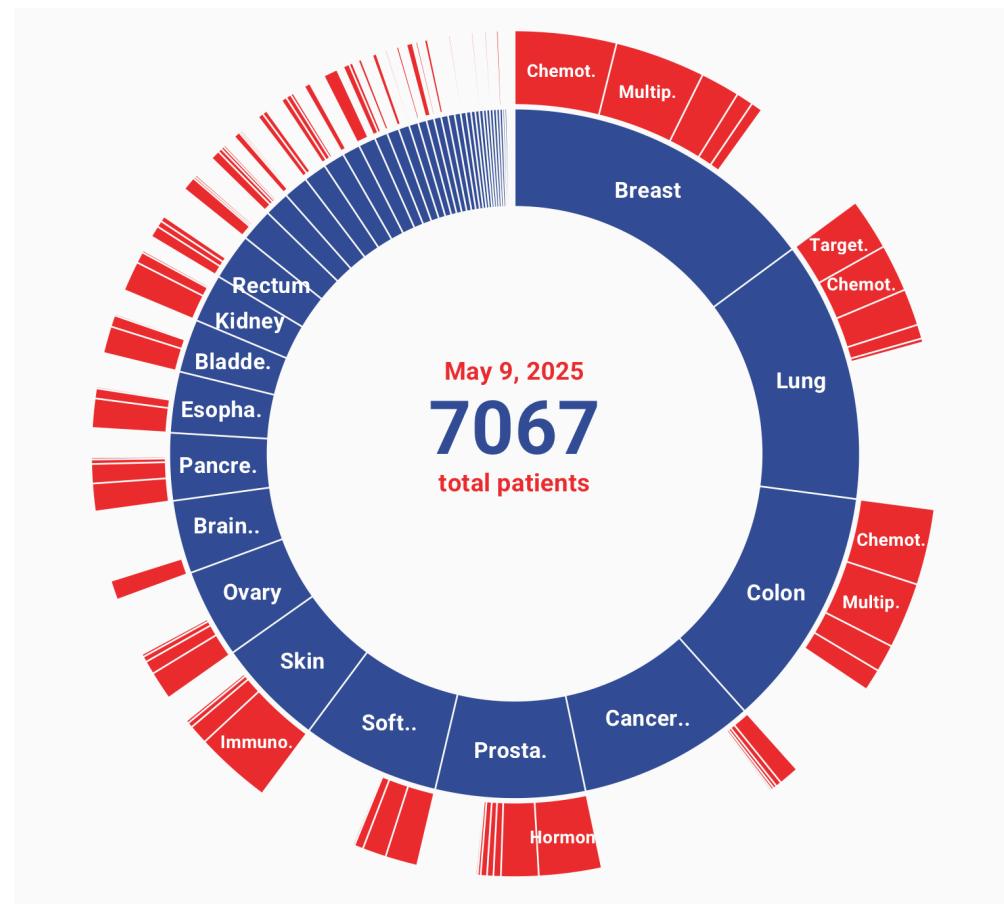
WES/WEX = whole exome sequencing.

RNA-seq = RNA sequencing.

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

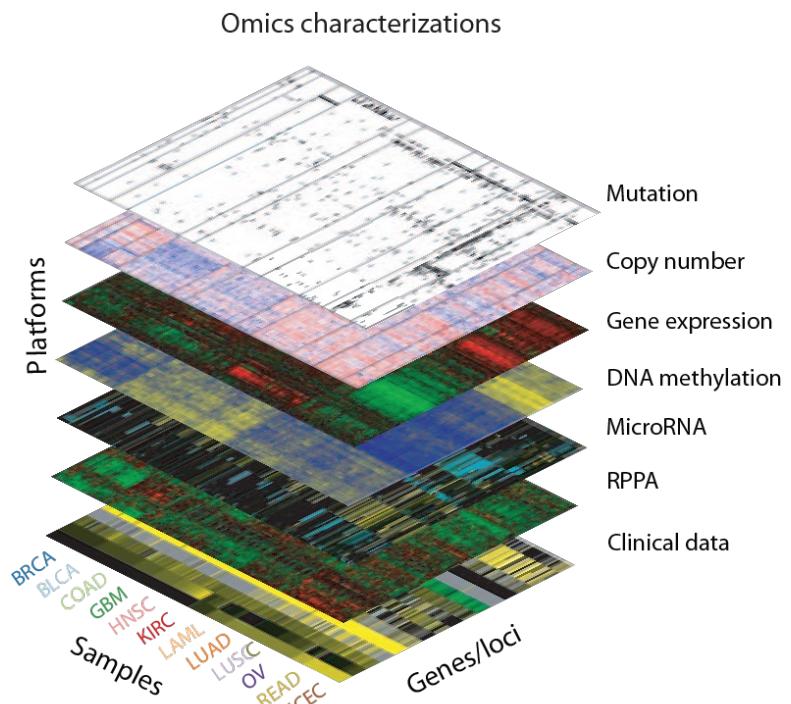
Hartwig foundation data – available via google cloud

- Application via web page
- <https://www.hartwigmedicalfoundation.nl/en/>
- Whole genome
- Whole transcriptome
- Clinical data



International consortia and other initiatives

- Complex data has been applied in TCGA etc.
 - E.g methylation
 - Need large cohorts for meaningful interpretation



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

Breast cancer – an example

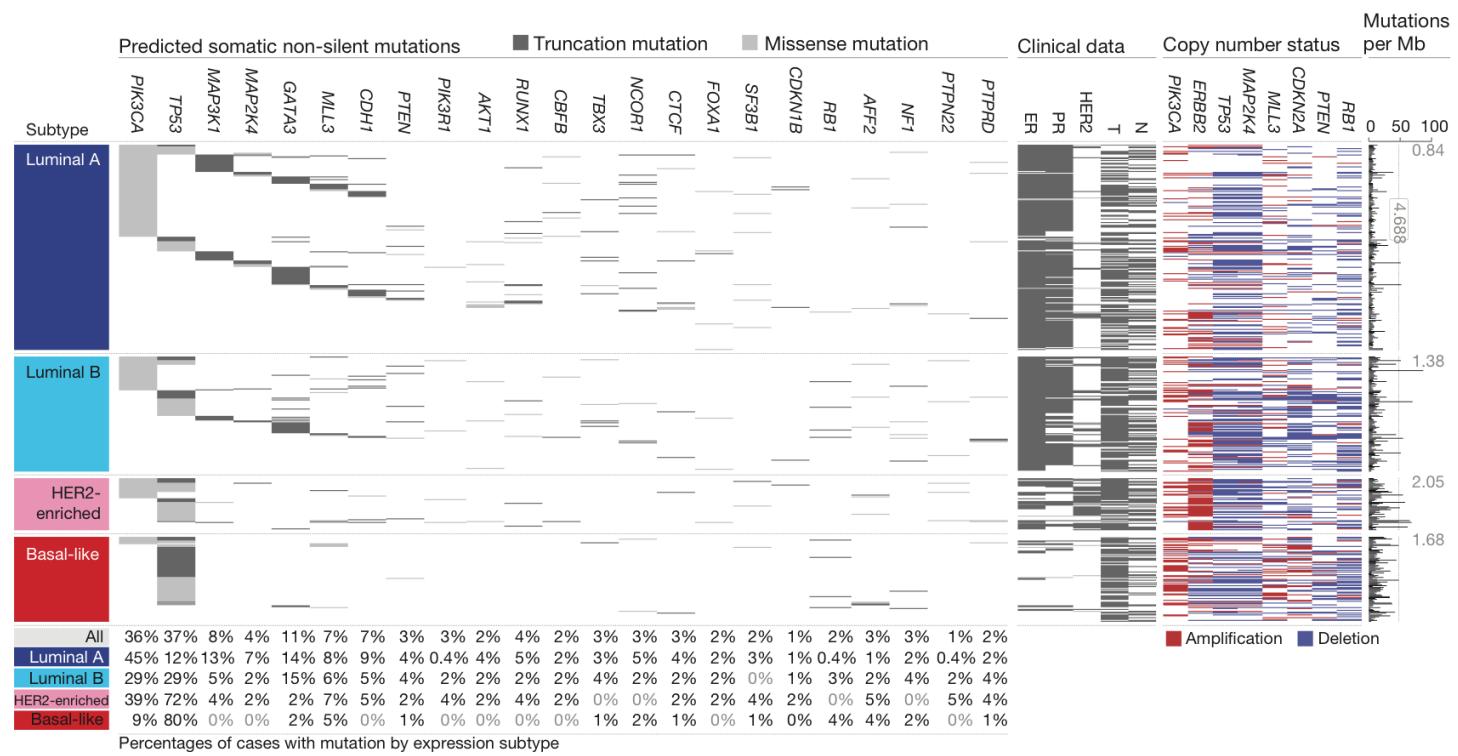
ARTICLE

doi:10.1038/nature11412

Comprehensive molecular portraits of human breast tumours

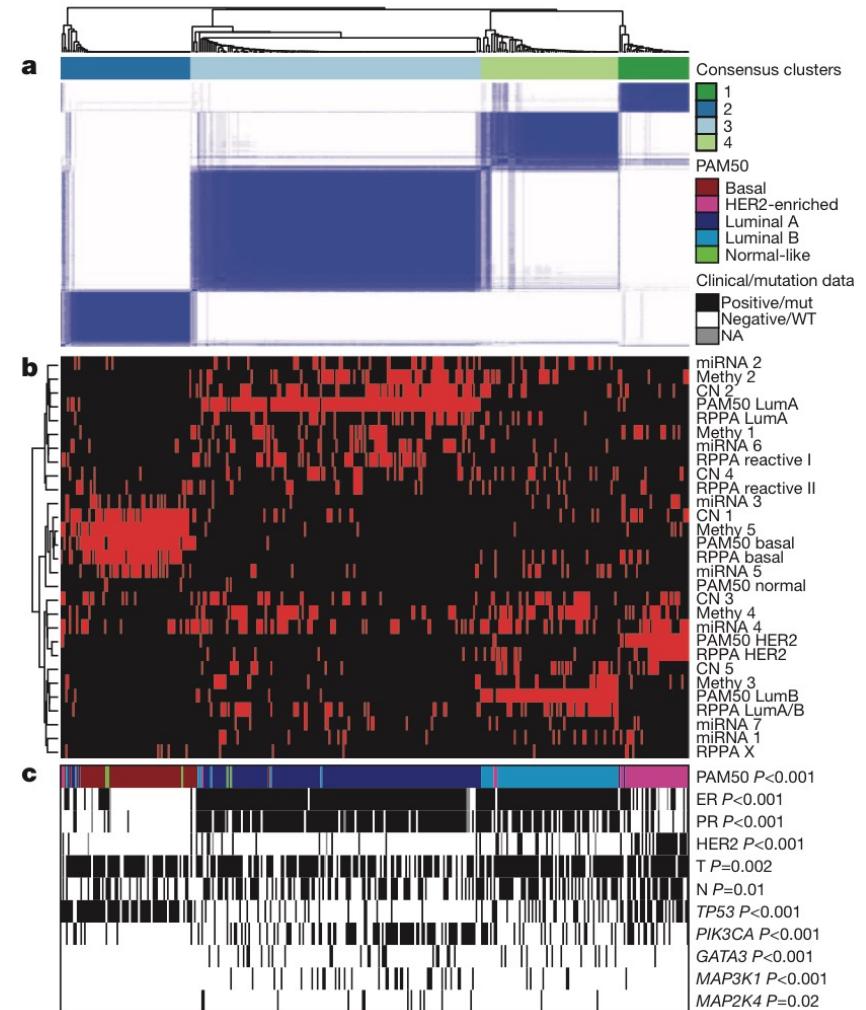
The Cancer Genome Atlas Network*

~500 patients with multiple data types



Breast cancer – an example

- The breast cancer subtypes were re-identified by the other data-types
- Subtype:
 - 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

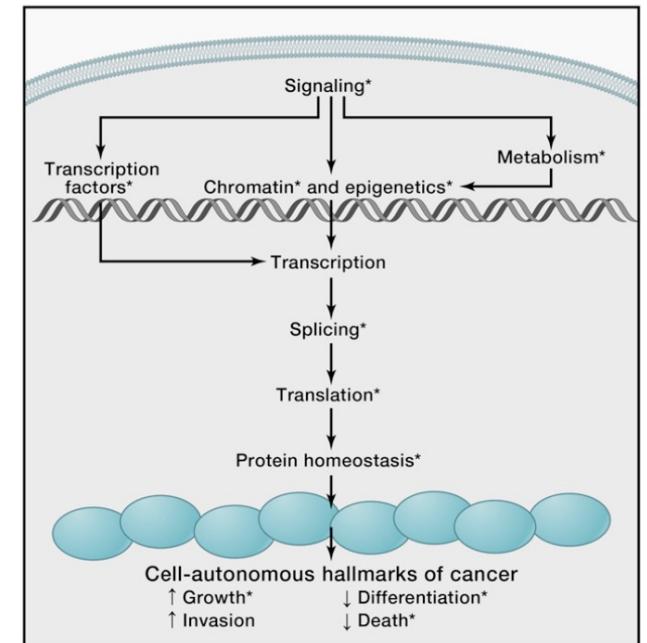


Leading Edge
Review

Cell

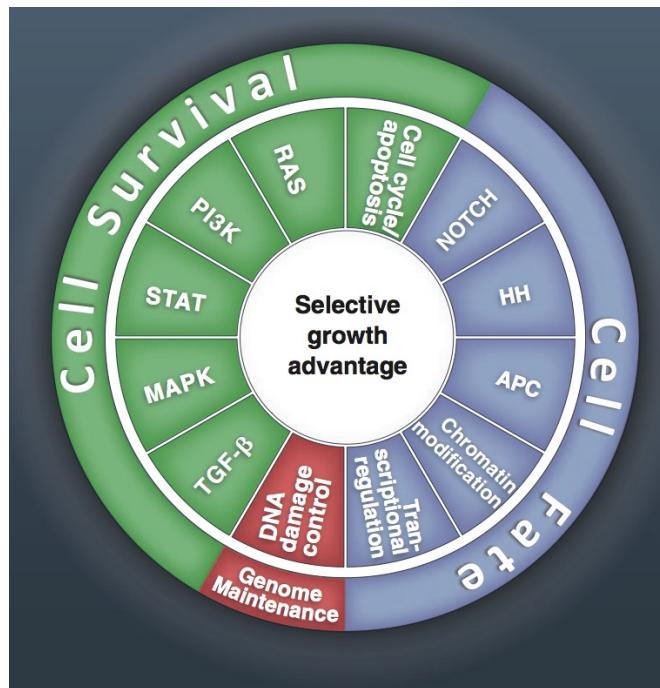
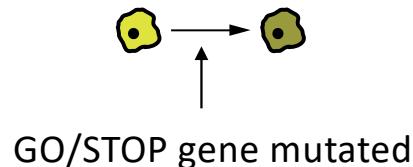
Lessons from the Cancer Genome

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



Driver mutations in key genes

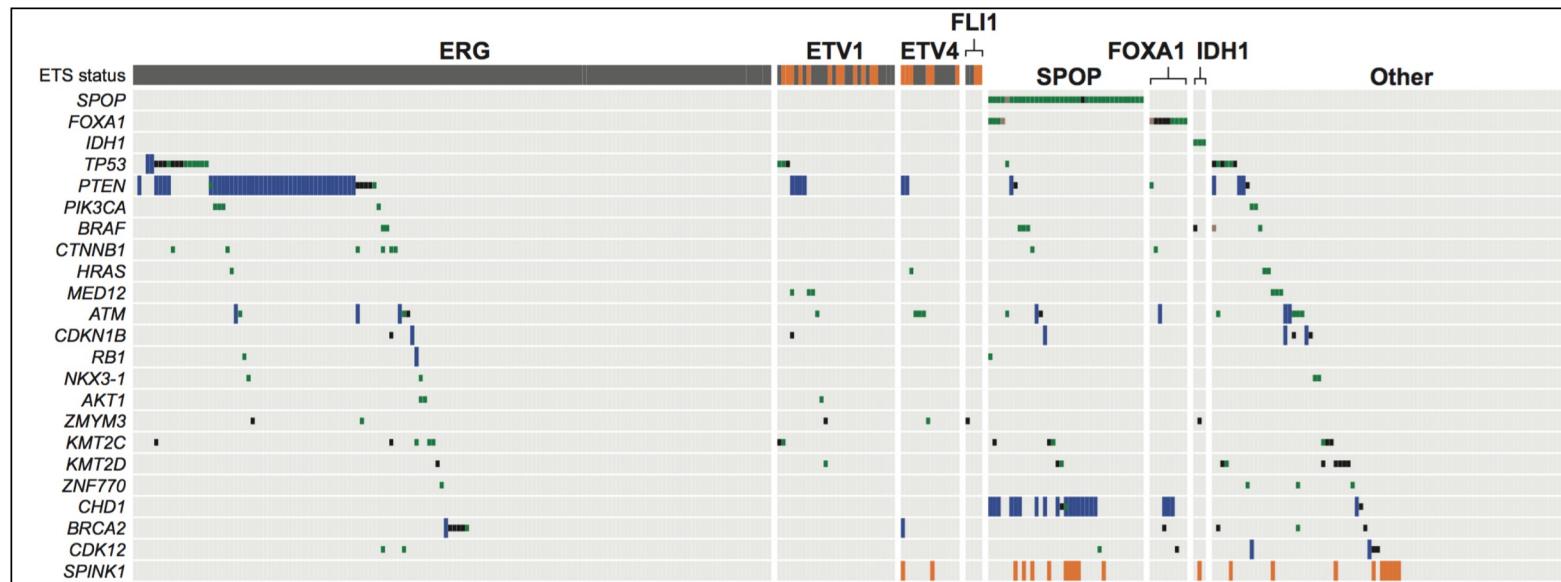
- Most cancers have four to eight mutations in “driver” genes causing a selective growth advantage
 - “GO” genes (oncogenes)
 - “STOP” genes (tumor suppressor genes)



Cancer Genome Landscapes, Science 2013

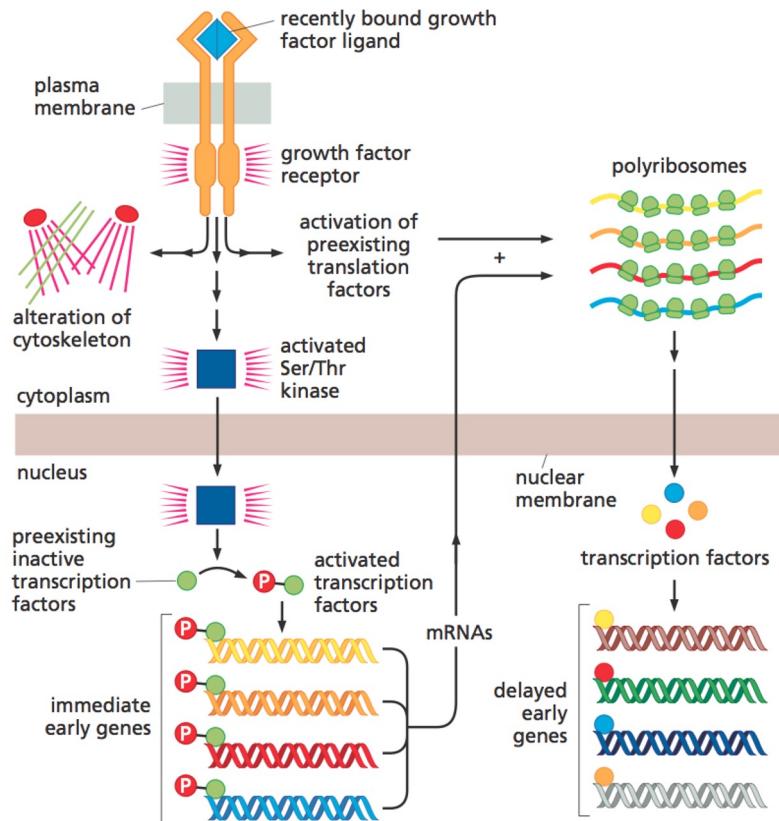
Intra disease heterogeneity

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



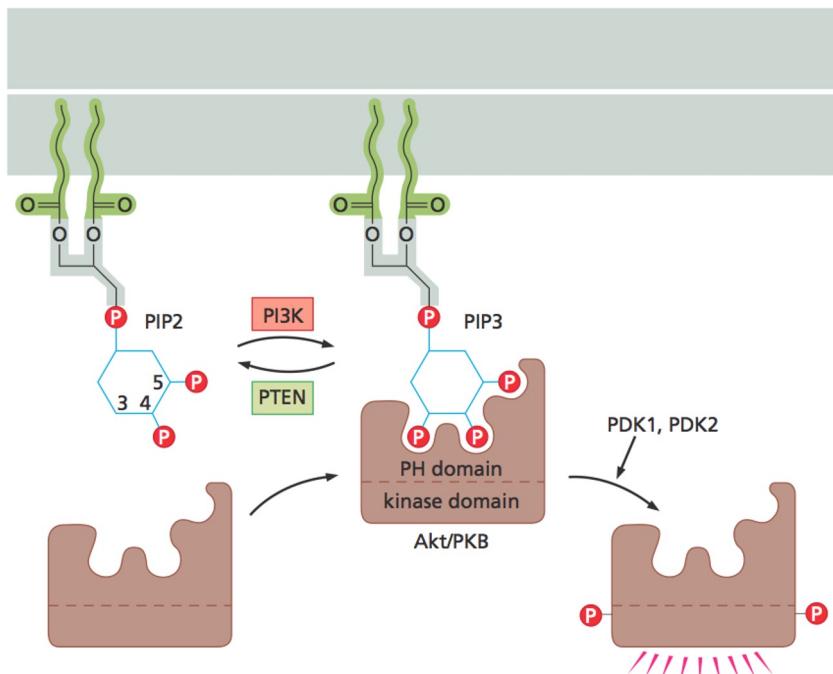
The molecular taxonomy of primary prostate cancer, Cell, 2015

Unifying pathways



Biology of Cancer, Weinberg

Unifying pathways – an example

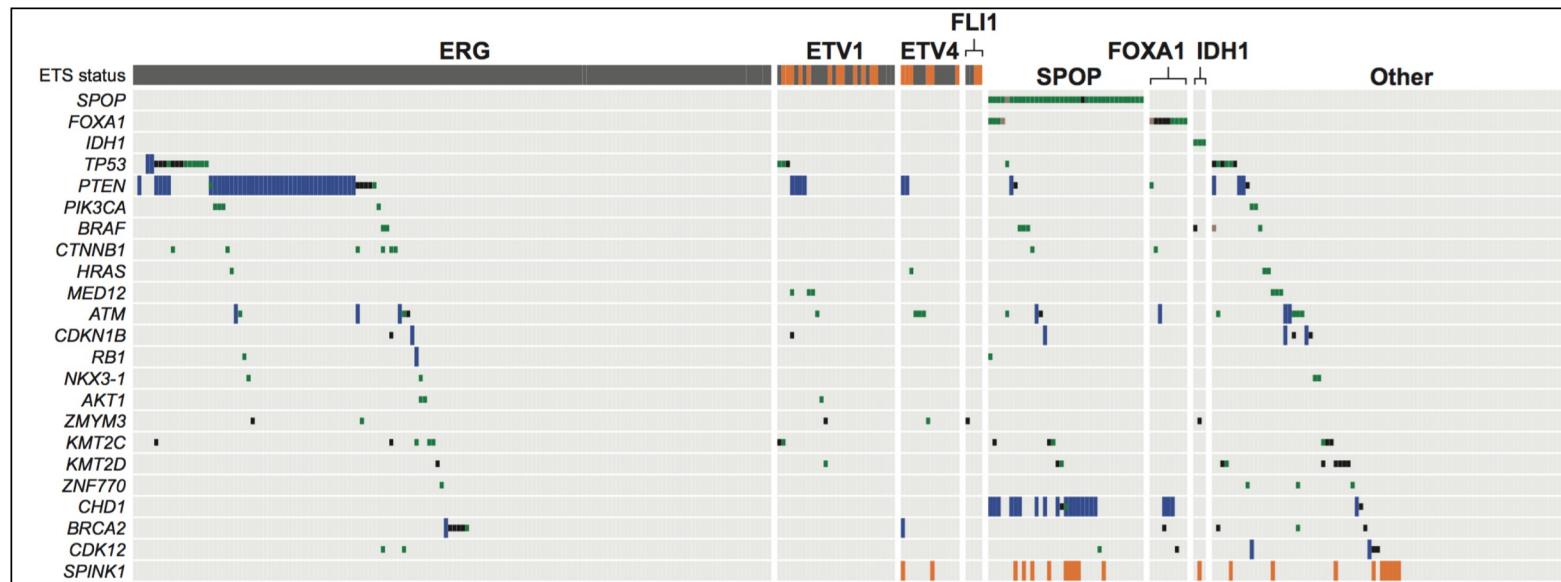


PI3K = Oncogene. A gene when activated by mutation gives a growth advantage

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

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

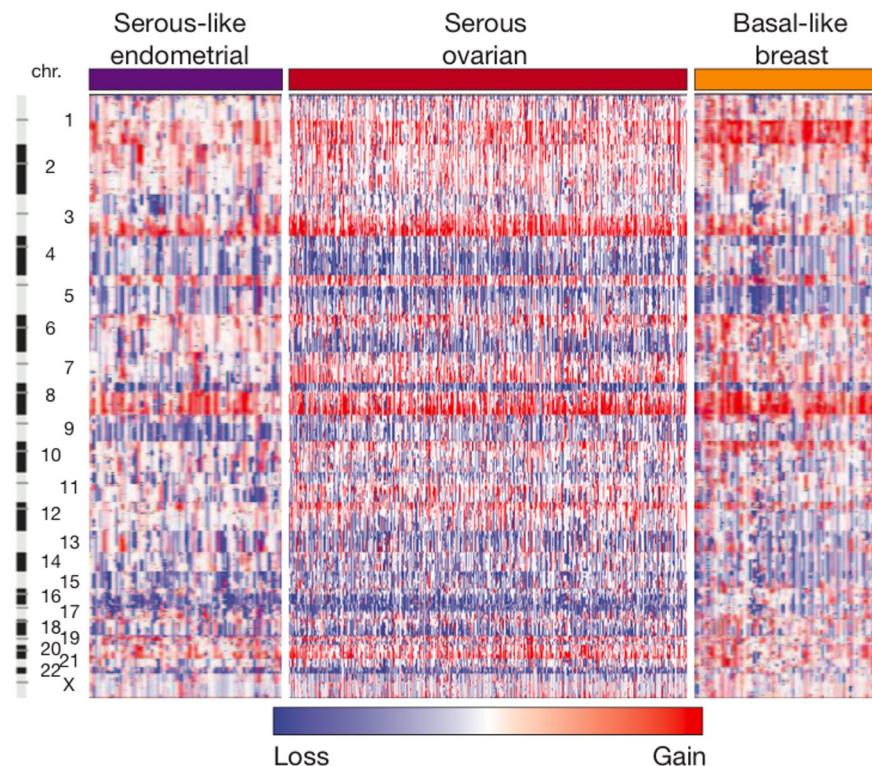
Inter disease homogeneity

Almost all cancer drivers are mutated in all cancers BUT at different frequencies

TP53-mutated cancer signature the same in multiple organs

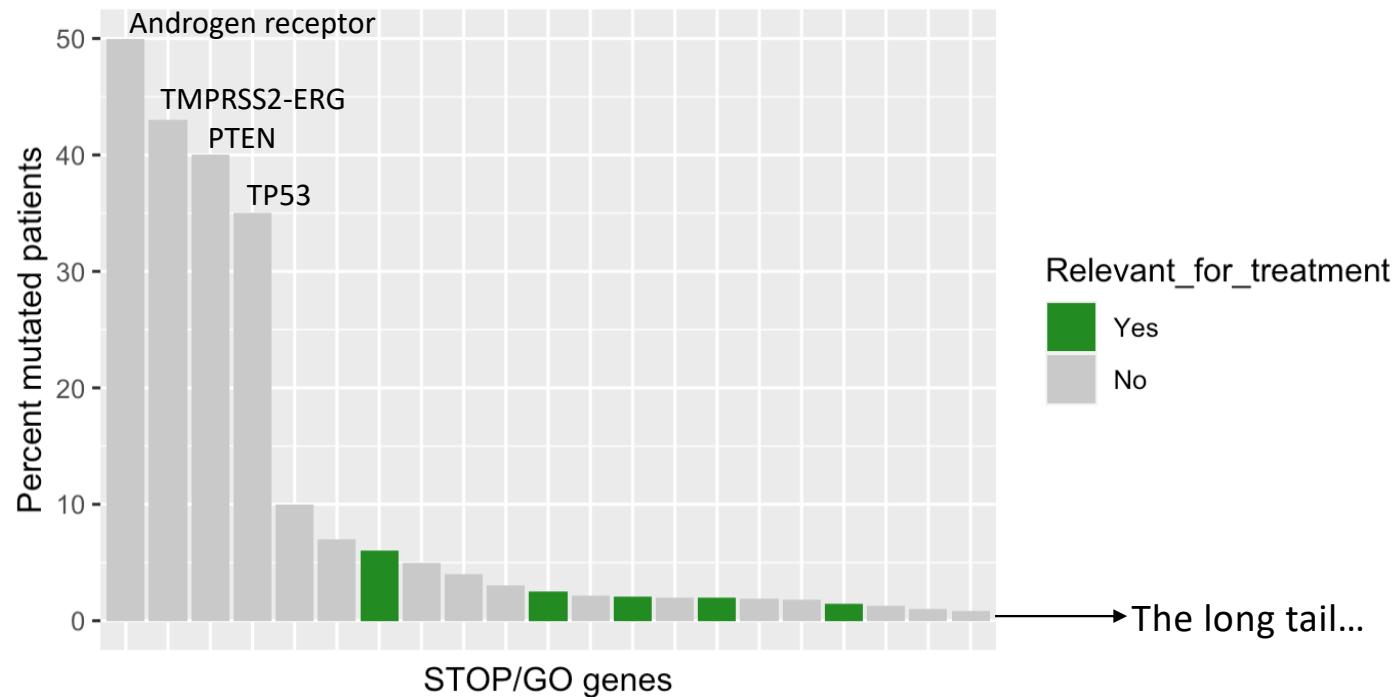
Similarities suggest pan-cancer treatment possibilities

Stage-shift from organ-based to genomic-based treatment rationales?



Integrated genomic characterization of endometrial carcinoma, TCGA, Nature 2013

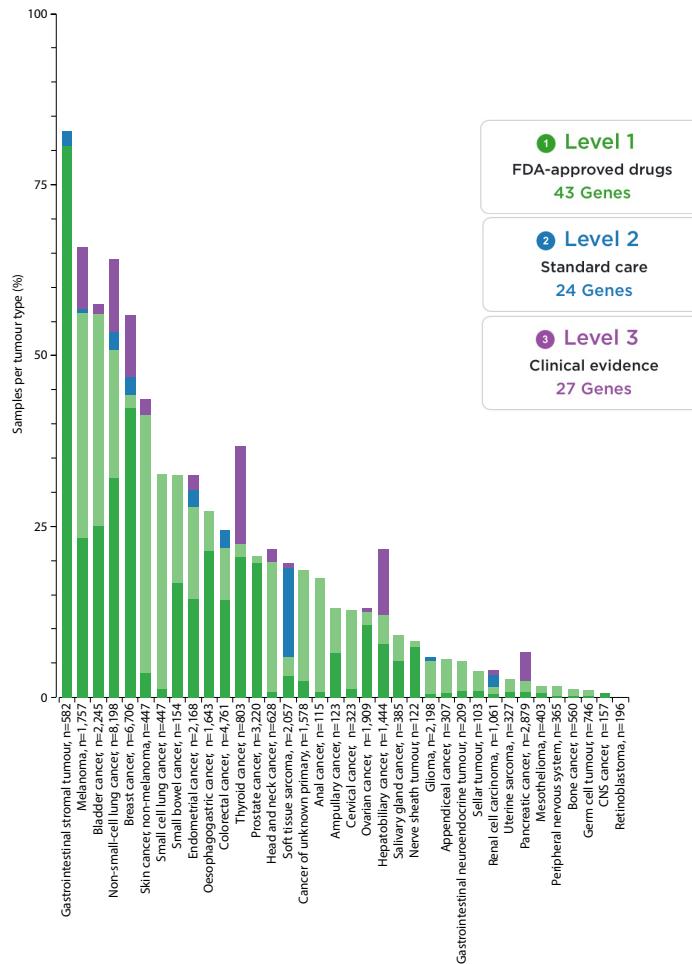
Driver mutations in metastatic castrate resistant prostate cancer



- 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.

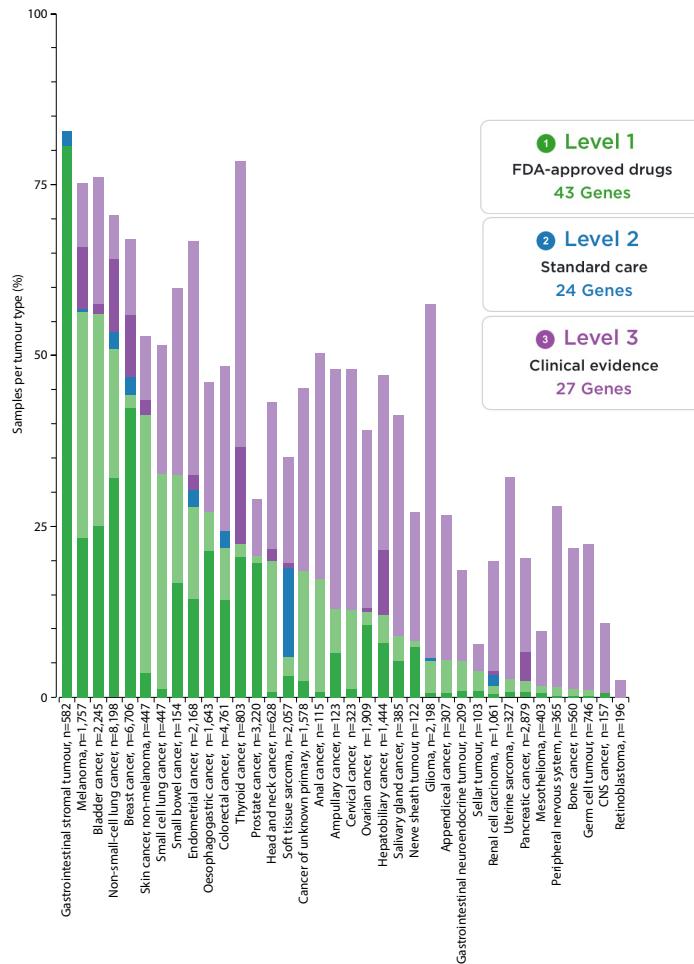
Clinically actionable STOP/GO genes

- 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.



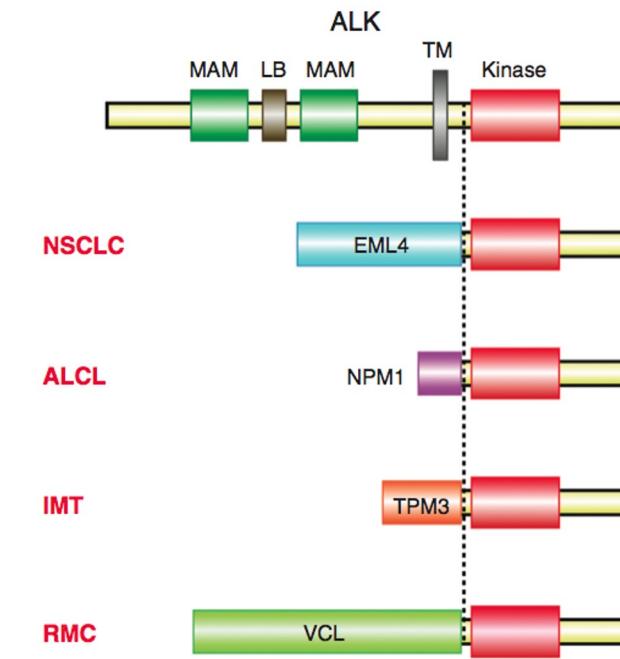
Inter disease homogeneity

ALK (Anaplastic lymphoma kinase)

Protein tyrosine kinase acting as driver in multiple cancers of different origin =

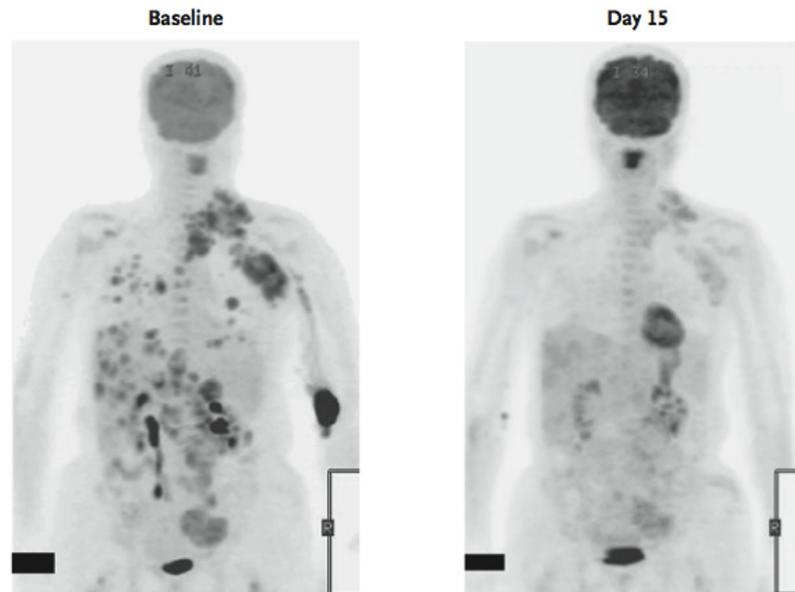
Alkomas

Inhibitors are effective across a range of different histologies



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

Inter disease heterogeneity



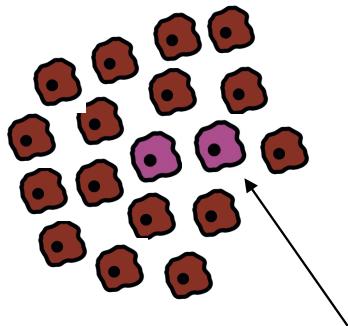
Vemurafenib is highly effective in BRAF V600E mutated melanoma but not colorectal cancer

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

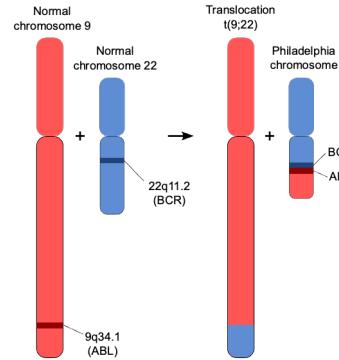
Targeted therapy and advanced cancer

- 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.



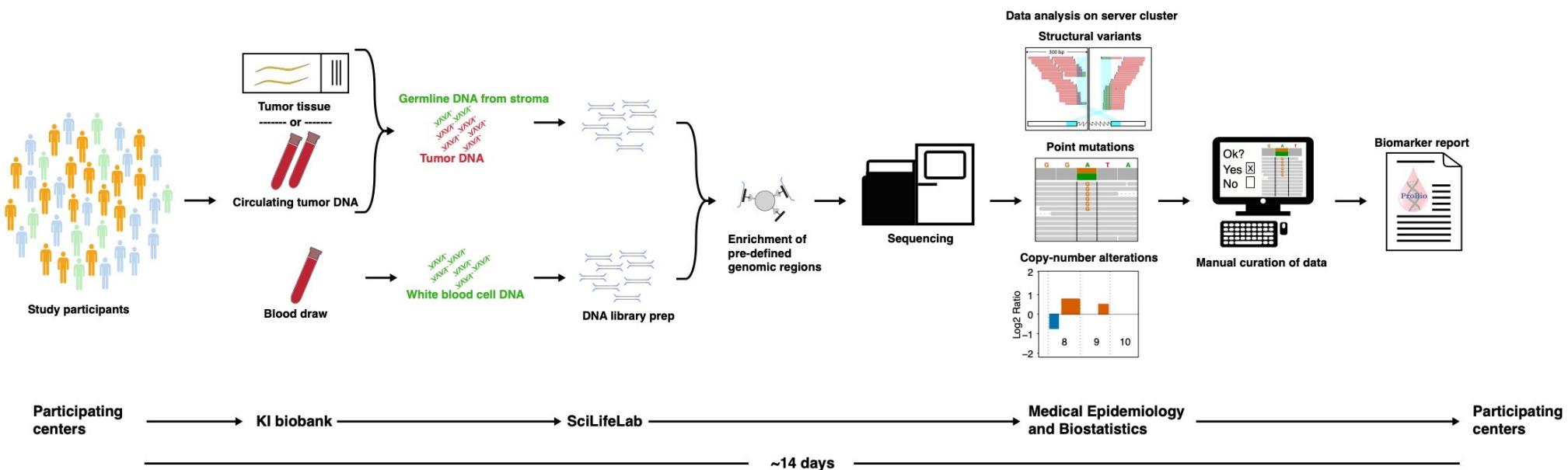
Pre-existing resistant clone

CML, the Philadelphia chromosome



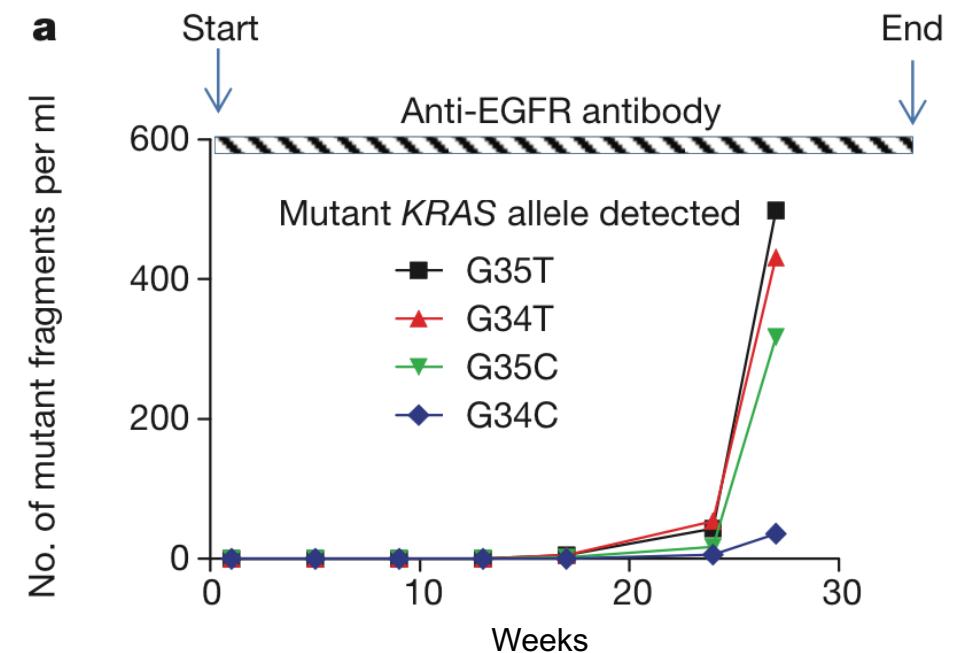
Drugs targeting the BCR-ABL protein.
CML is now a chronic disease

Circulating tumor DNA



Why targeted mono-therapy fail in metastatic disease

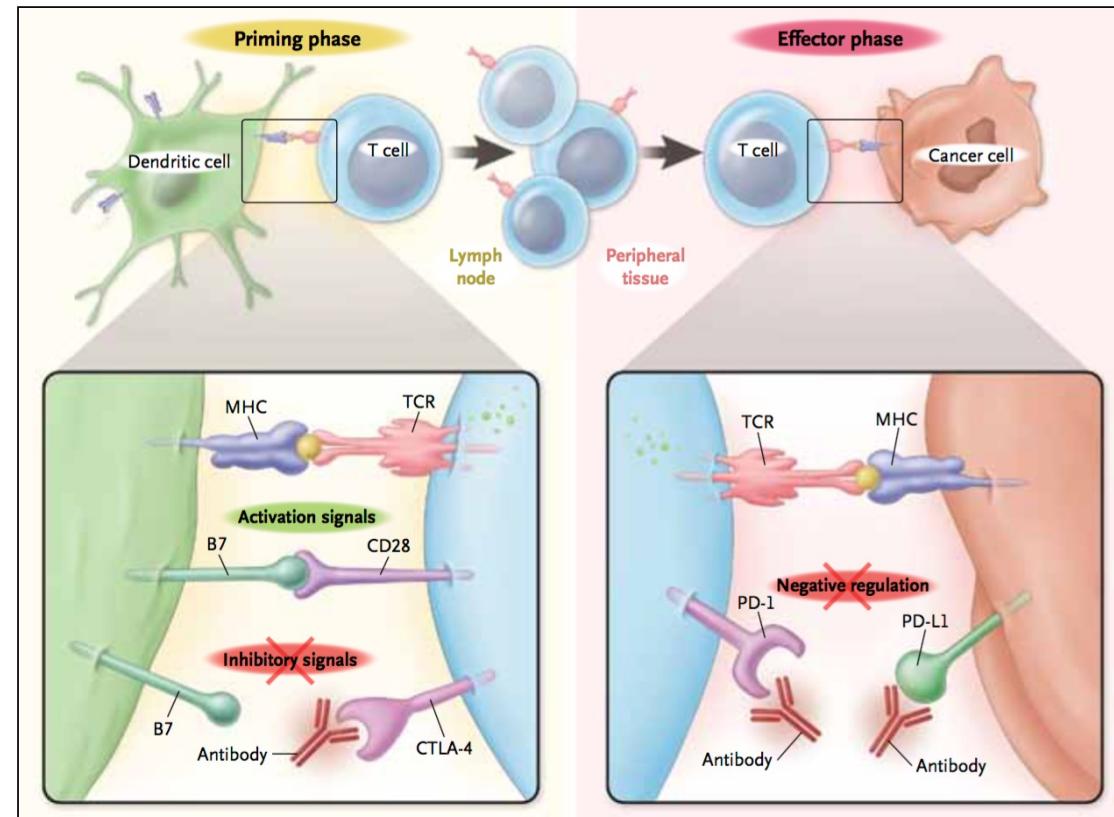
- Metastatic patients basically always contain resistant clones to targeted monotherapy
 - Inevitable due to random errors during cell-division
 - Combinations the way forward hitting on orthogonal functions.
 - Side effects ...



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

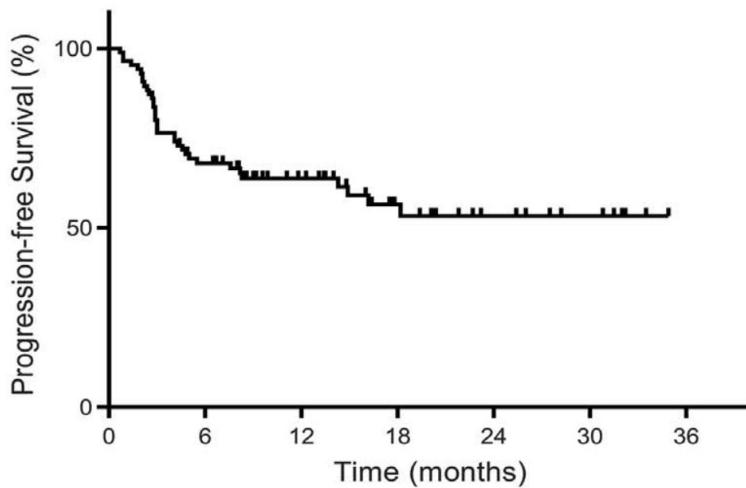
Immunotherapy – the exception from the rule

- 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

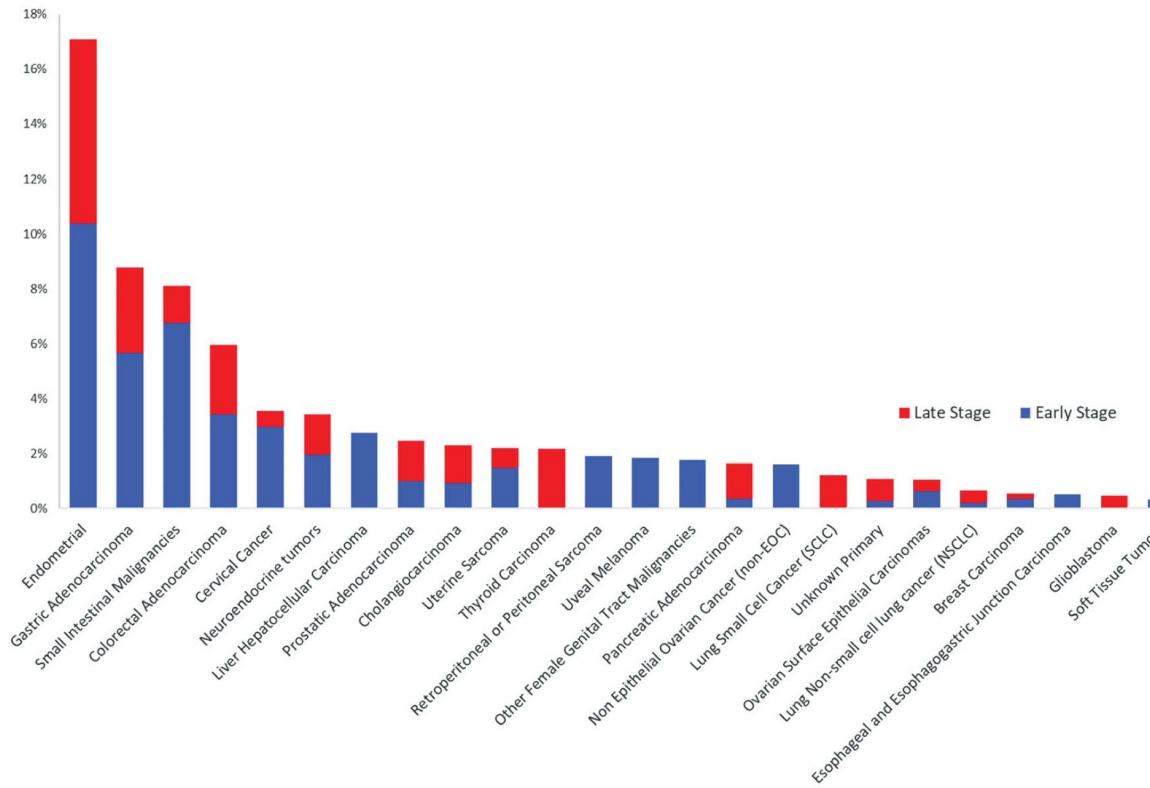
CANCER BIOMARKERS

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

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Science, 2017

Immunotherapy – the exception from the rule



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

RESEARCH

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The long tail – a cancer phenotype example

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

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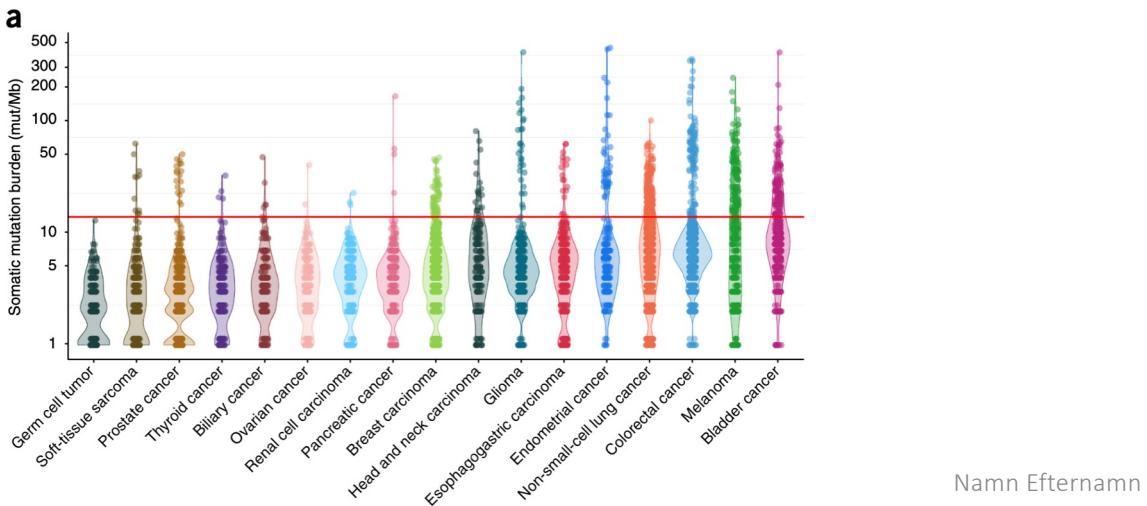
- ~400 genes interrogated in 10,000 patients
 - Detection of relevant variants in 9% with low tumor purity
 - 11% enrolled in genetically matched clinical trials
 - Detection of unexpected gene fusions (e.g. BRAF in prostate cancer)
 - Detection of hypermutated cancers

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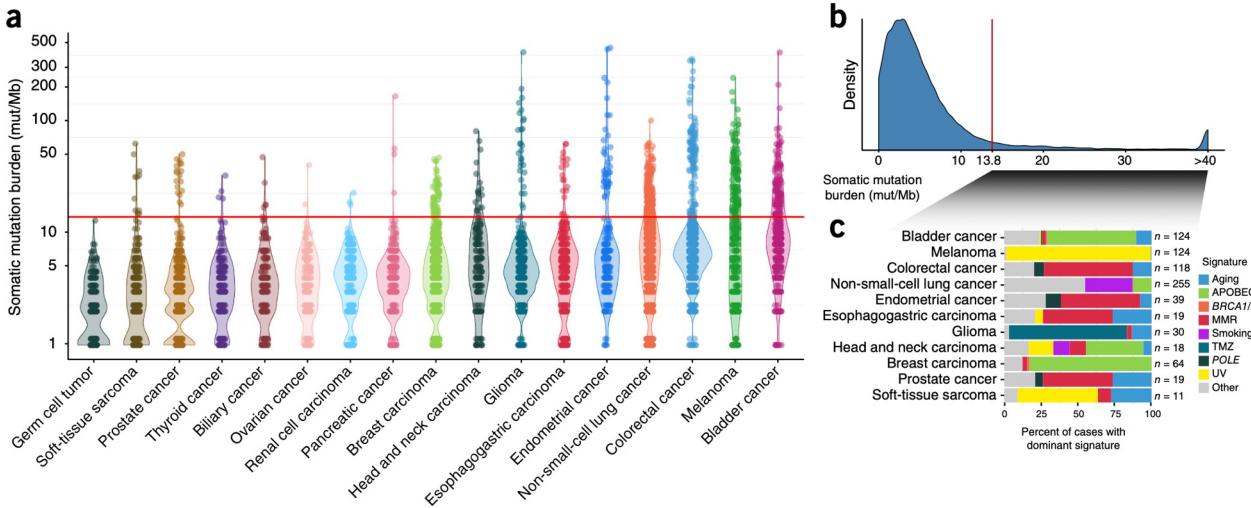


The long tail – a cancer phenotype example

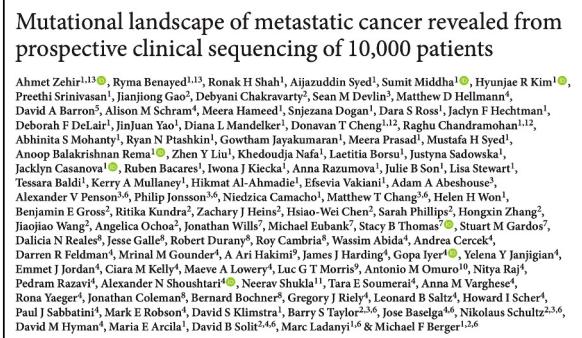
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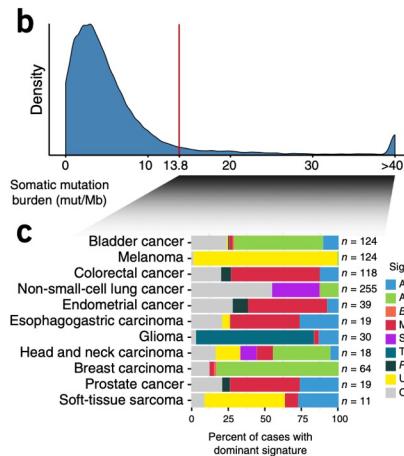
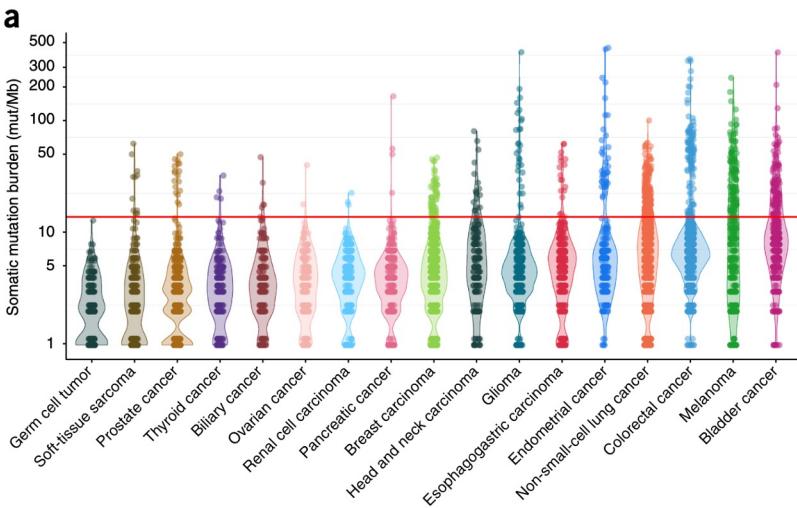
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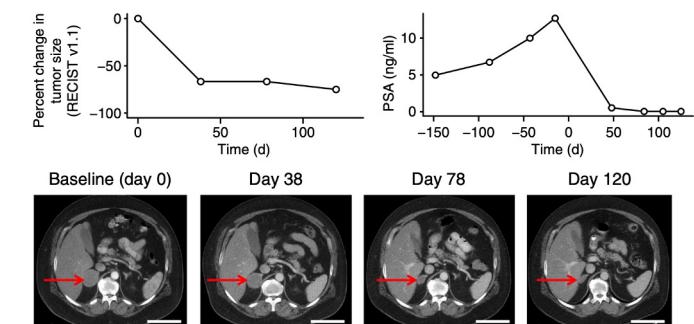
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Metastatic prostate cancer with MSI+ treated with immunomodulators



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

- 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

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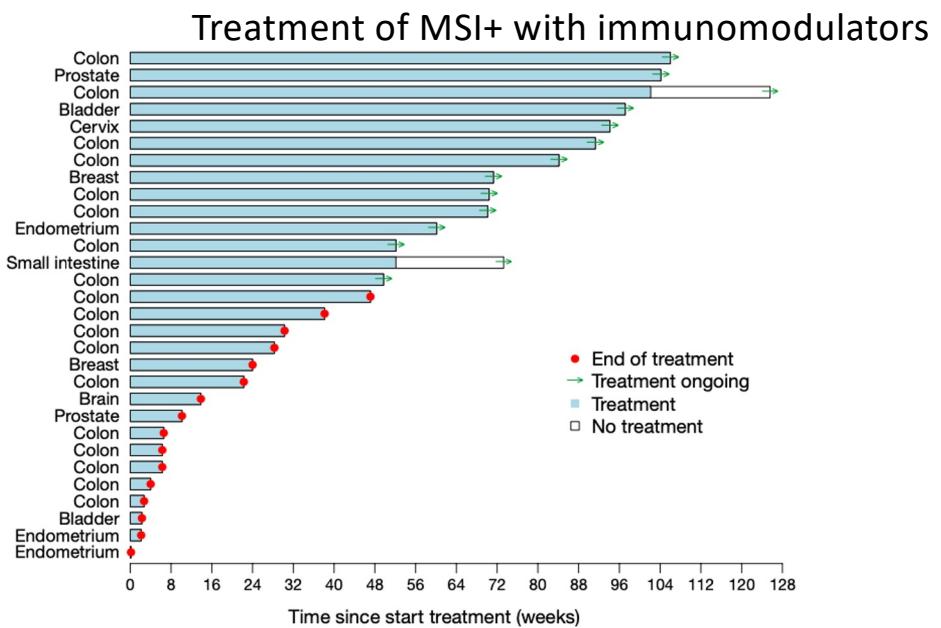
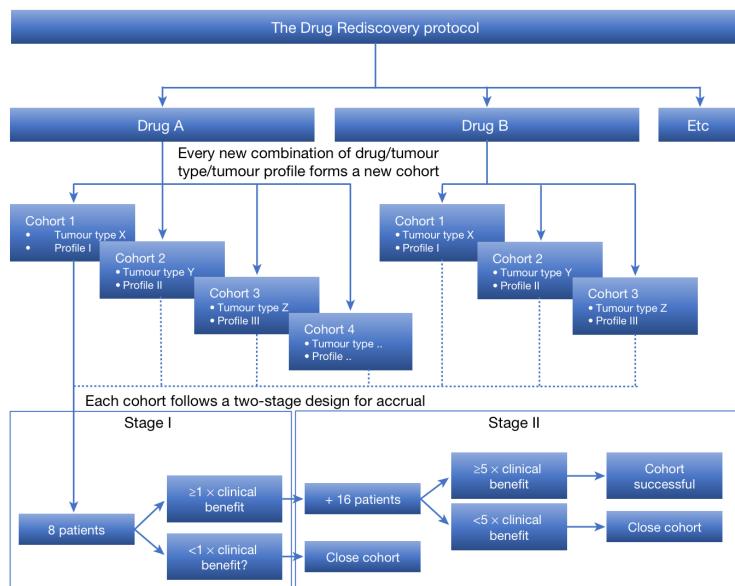
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Open access

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 Duvvesteyn¹, 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?
