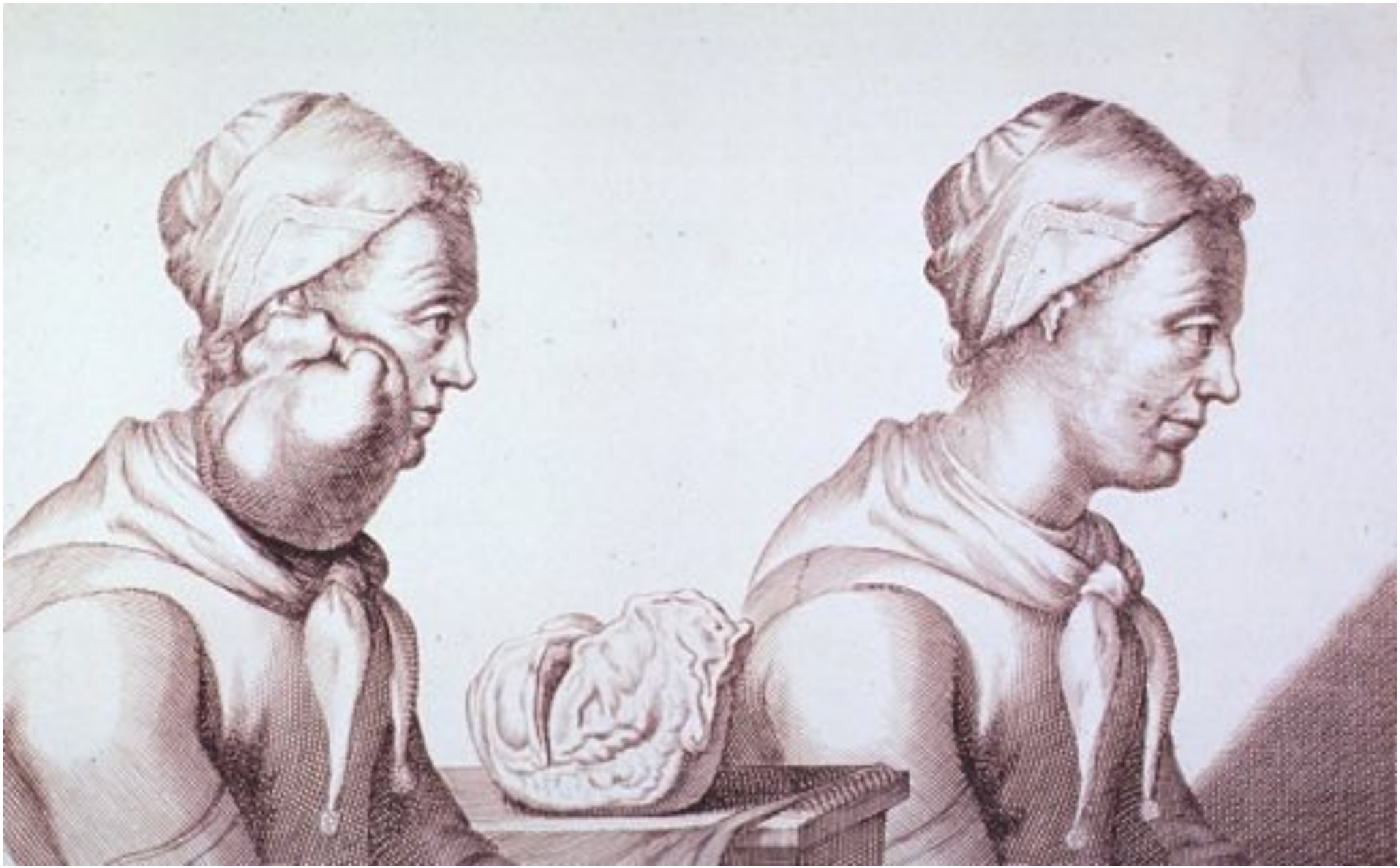
Cancer Genetics & Genomics

Michael Schatz

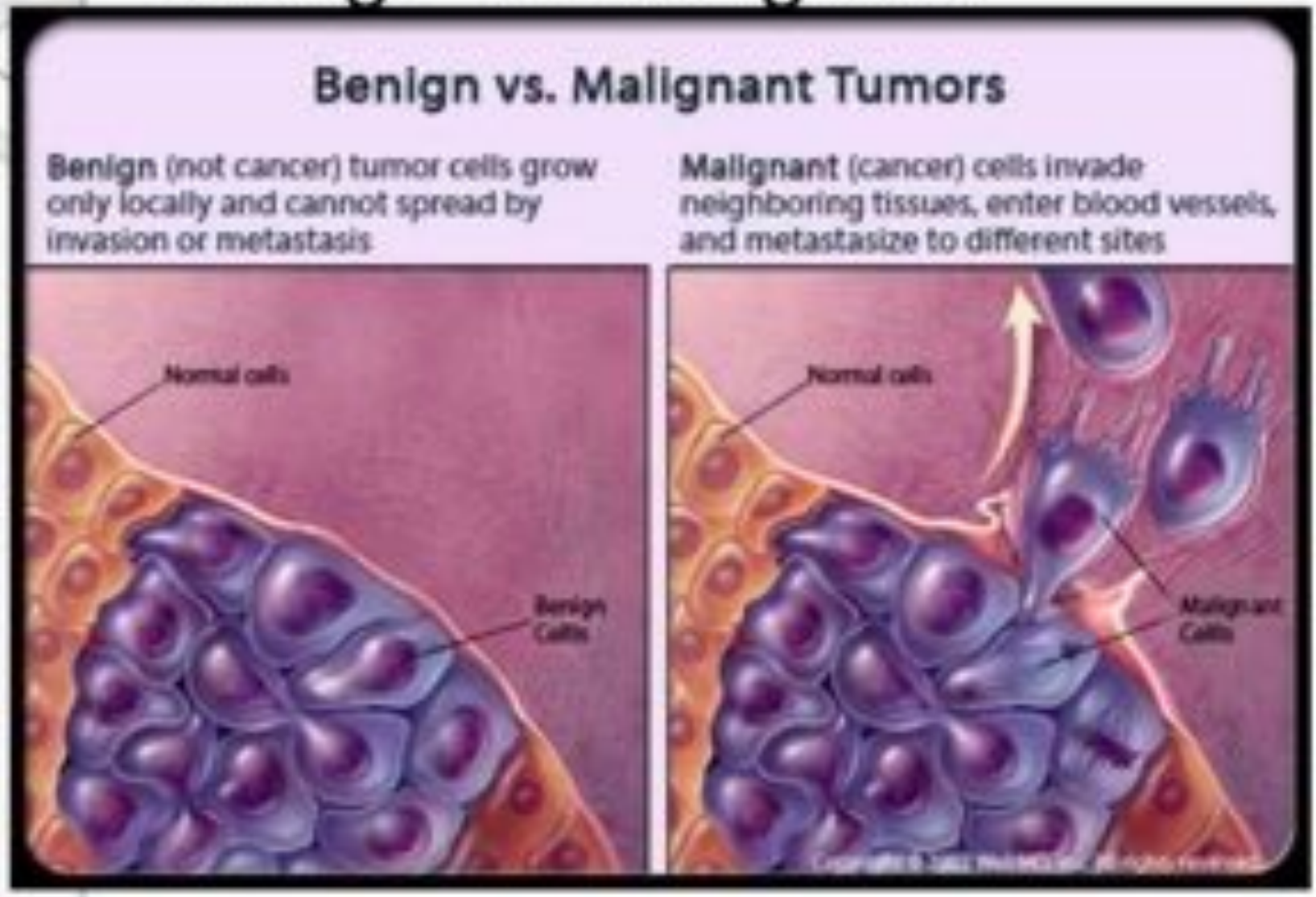
Nov 4, 2019

Lecture 19: Computational Biomedical Research

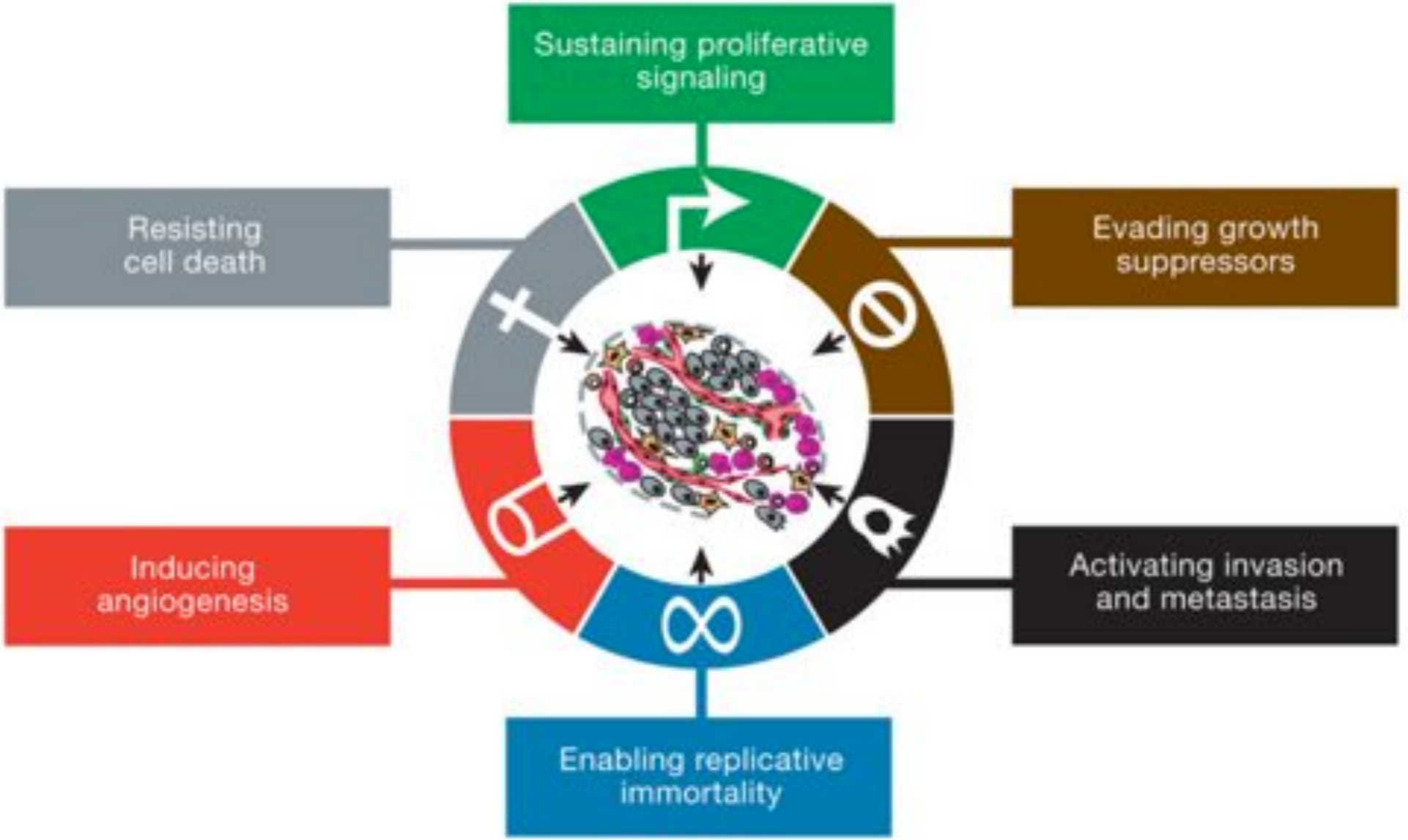


A tumor removed by surgery in 1689.

Benign vs. Malignant

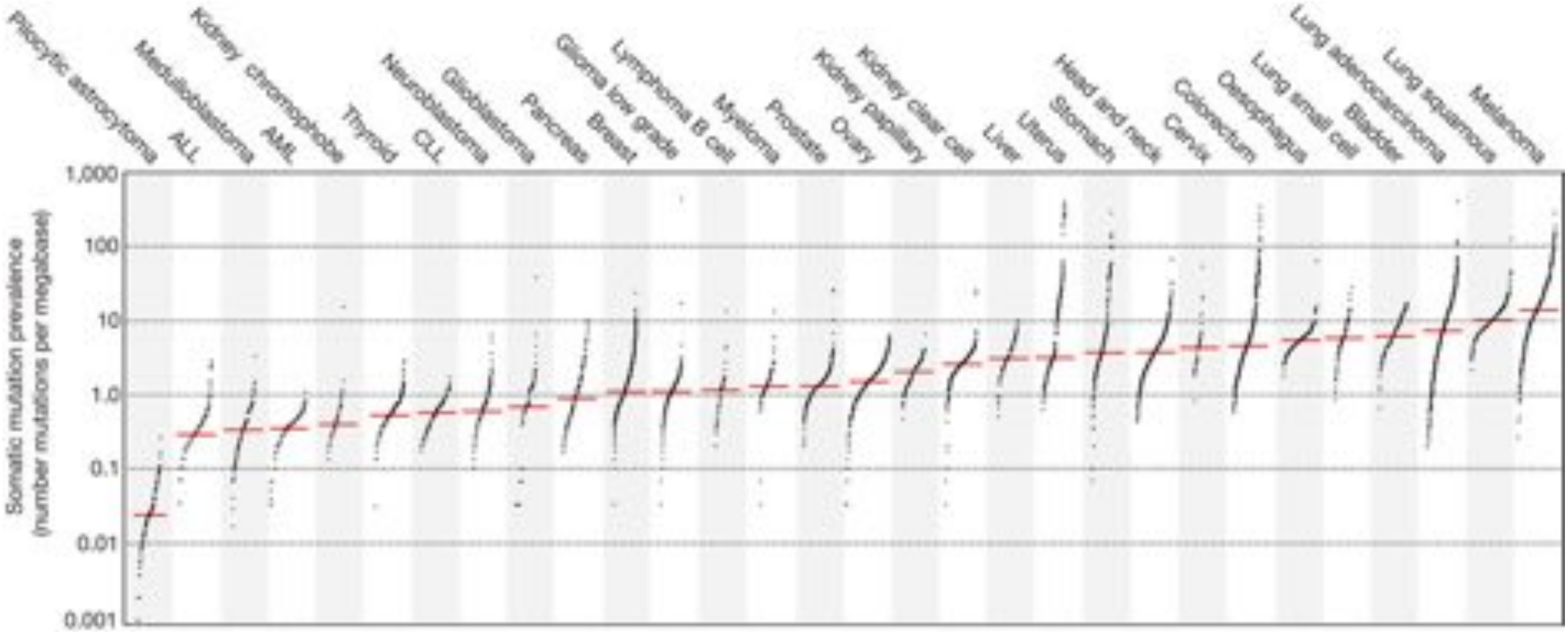


The Six Hallmarks of Cancer



Hallmarks of Cancer
Hanahan and Weinberg (2000) Cell. http://doi.org/10.1016/S0092-8674(00)81683-9

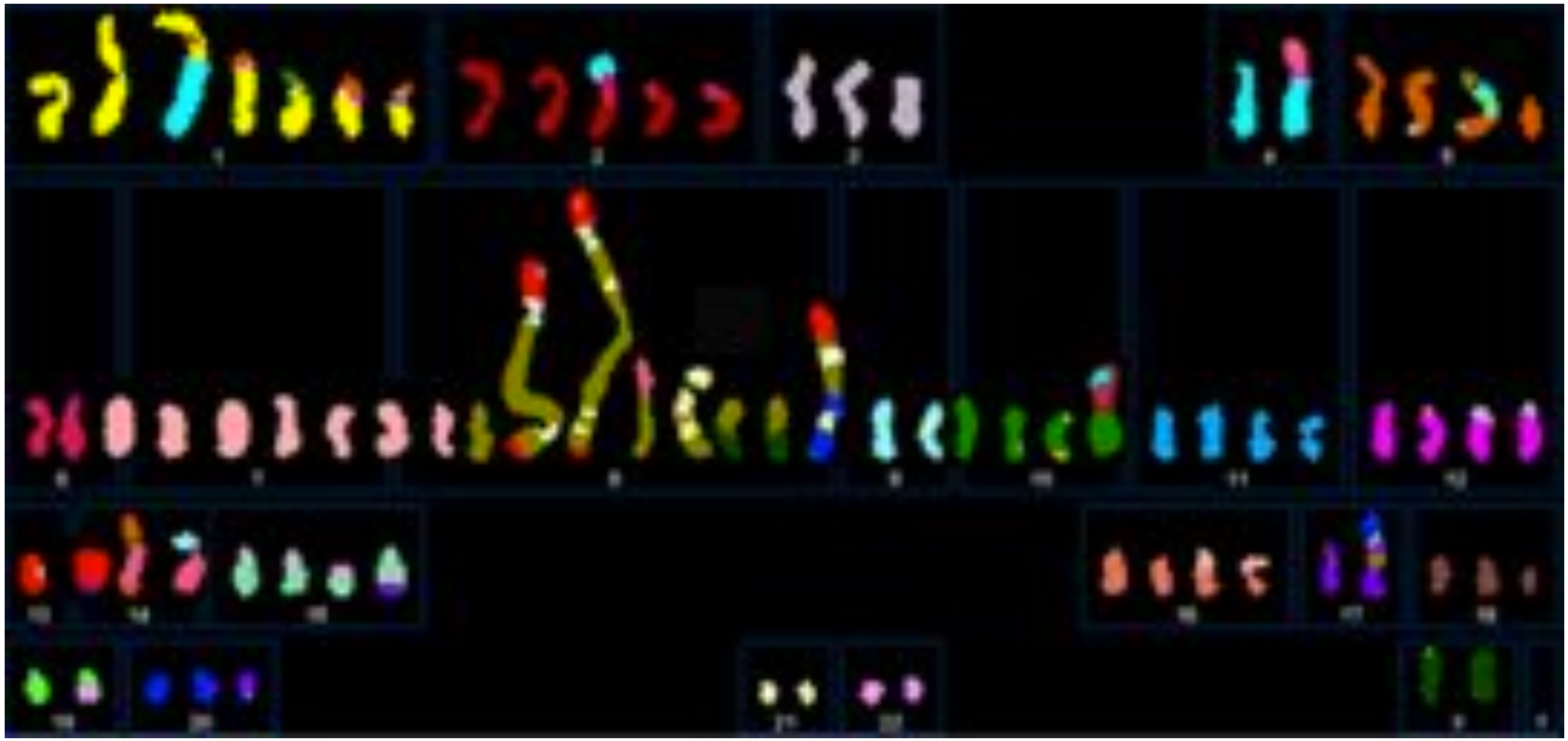
Somatic Mutations In Cancer



Signatures of mutational processes in human cancer
Alexandrov et al (2013) *Nature*. doi:10.1038/nature12477

SK-BR-3

Most commonly used Her2-amplified breast cancer cell line



(Davidson et al, 2000)

80+ chromosomes,
Many are a patchwork of fragments of other chromosomes

A firestorm in cancer

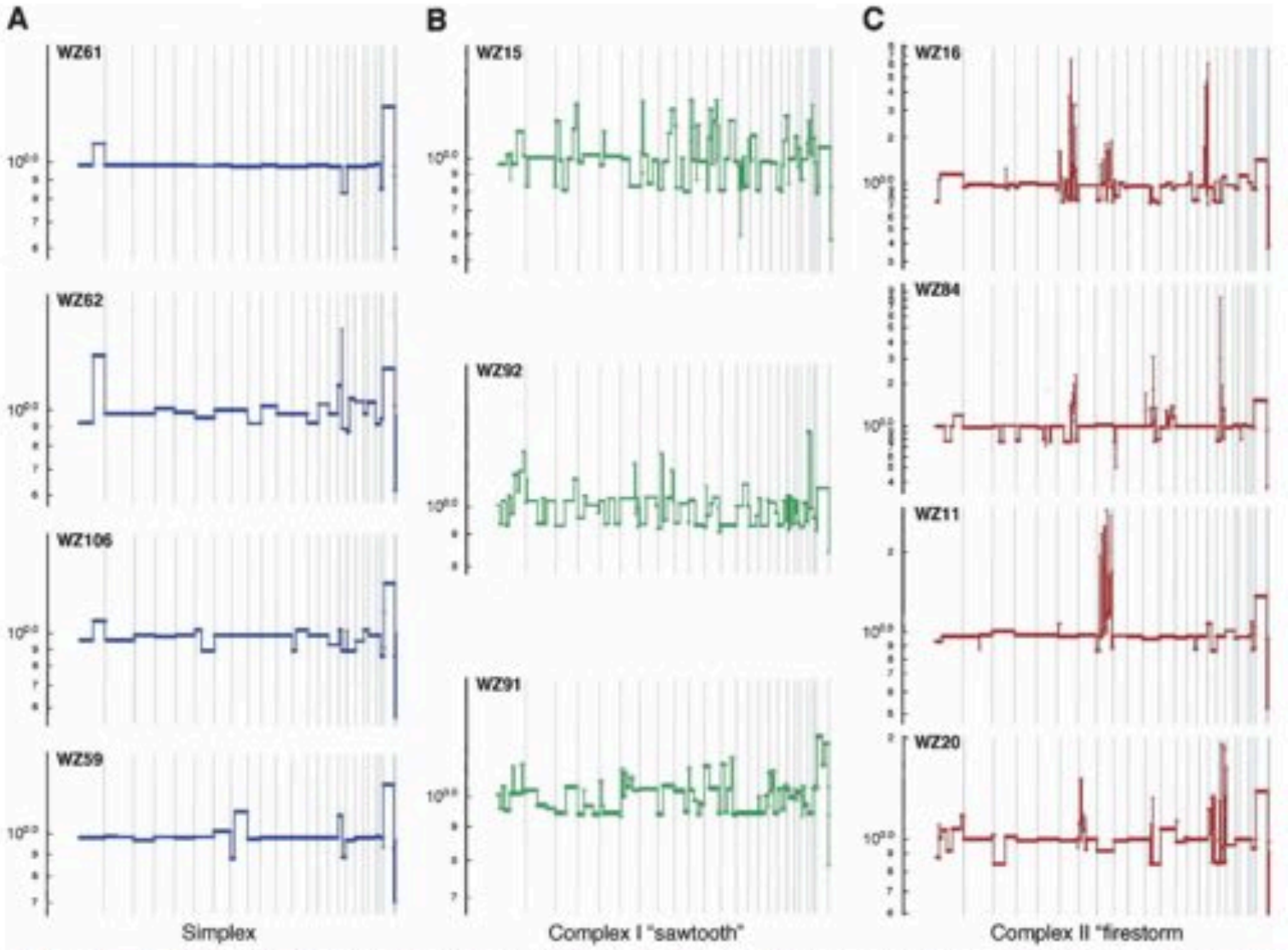
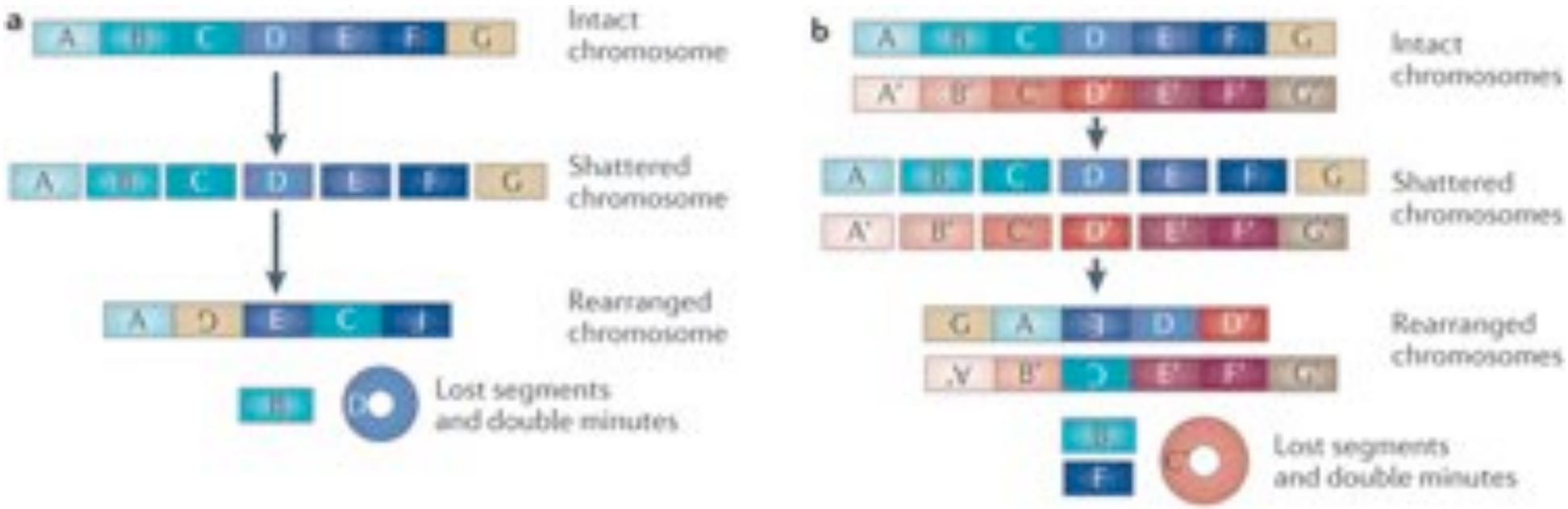


Figure 2. Major types of tumor genomic profiles. Segmentation profiles for individual tumors representing each category: (*A*) simplex; (*B*) complex type I or sawtooth; (*C*) complex type II or firestorm. Scored events consist of a minimum of six consecutive probes in the same state. The *y*-axis displays the geometric mean value of two experiments on a log scale. Note that the scale of the amplifications in *C* is compressed relative to *A* and *B* owing to the high levels of amplification in firestorms. Chromosomes 1–22 plus X and Y are displayed in order from *left* to *right* according to probe position.

Novel patterns of genome rearrangement and their association with survival in breast cancer
Hicks et al (2006) *Genome Research. Doi: 10.1101/gr.5460106*

Aberrations in cancer genomes



Chromothripsis, which literally means 'chromosome shattering', is a phenomenon that has recently been reported to occur in cells harbouring complex genomic rearrangements (CGRs). Has 3 defining characteristics:

(1) Occurrence of remarkable numbers of rearrangements in localized chromosomal regions;
(2) Low number of copy number states (generally between one or two) across the rearranged region;
(3) Alternation in the chromothriptic areas of regions where heterozygosity is preserved with regions presenting loss of heterozygosity (LOH).

Chromothripsis and cancer: causes and consequences of chromosome shattering
Forment et al (2012) Nature Reviews Cancer. doi:10.1038/nrc3352

Hypomethylation distinguishes genes of some human cancers from their normal counterparts

Andrew P. Feinberg & Bert Vogelstein

Cell Structure and Function Laboratory, The Oncology Center, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA

It has been suggested that cancer represents an alteration in DNA, heritable by progeny cells, that leads to abnormally regulated expression of normal cellular genes; DNA alterations such as mutations[1,2], rearrangements[3-5] and changes in methylation[6-8] have been proposed to have such a role. Because of increasing evidence that DNA methylation is important in gene expression (for review see refs 7, 9–11), several investigators have studied DNA methylation in animal tumours, transformed cells and leukaemia cells in culture[8,12-30]. The results of these studies have varied; depending on the techniques and systems used, an increase[12-19], decrease[20-24], or no change[25-29] in the degree of methylation has been reported. To our knowledge, however, primary human tumour tissues have not been used in such studies. We have now examined DNA methylation in human cancer with three considerations in mind: (1) the methylation pattern of specific genes, rather than total levels of methylation, was determined; (2) human cancers and adjacent analogous normal tissues, unconditioned by culture media, were analysed; and (3) the cancers were taken from patients who had received neither radiation nor chemotherapy. In four of five patients studied, representing two histological types of cancer, substantial hypomethylation was found in genes of cancer cells compared with their normal counterparts. This hypomethylation was progressive in a metastasis from one of the patients.

and (3) *Hpa*II and *Hha*I cleavage sites should be present in the regions of the genes.

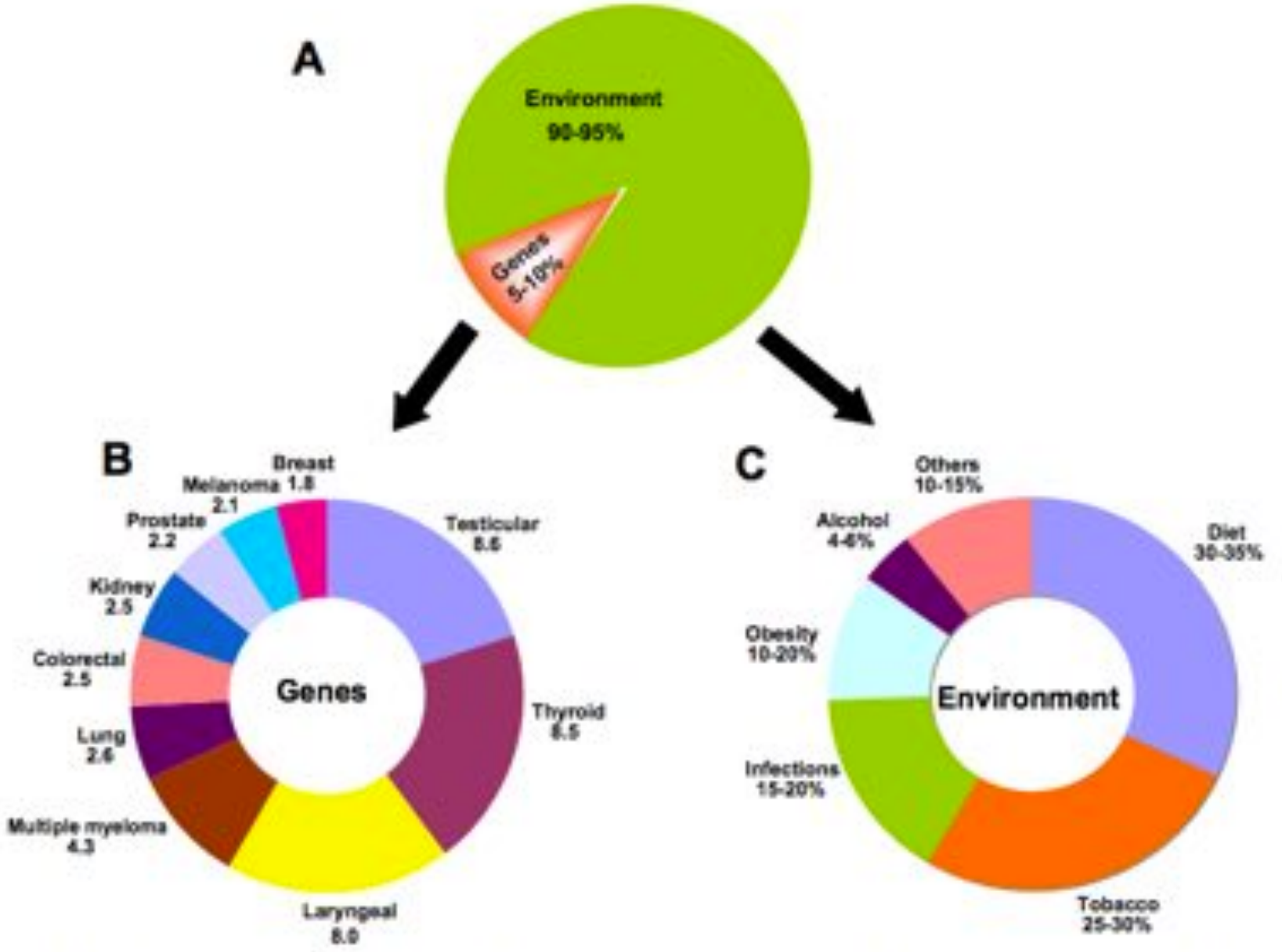
The first cancer studied was a grade D (ref. 43), moderately well differentiated adenocarcinoma of the colon from a 67-yr-old male. Tissue was obtained from the cancer itself and also from colonic mucosa stripped from the colon at a site just outside the histologically proven tumour margin. Figure 1 shows the pattern of methylation of the studied genes. Before digestion with restriction enzymes, all DNA samples used in the study had a size >25,000 base pairs (bp). After *Hpa*II cleavage, hybridization with a probe made from a cDNA clone of human growth hormone (HGH) showed that significantly more of the DNA was digested to low-molecular weight fragments in DNA from the cancer (labelled C in Fig. 1) than in DNA from the normal colonic mucosa (labelled N). In the hybridization conditions used, the HGH probe detected the human growth hormone genes as well as the related chorionic somatotropin

Table 1 Quantitation of methylation of specific genes in human cancers and adjacent analogous normal tissues

Patient	Carcinoma	Probe	Enzyme	% Hypomethylated fragments		
				N	C	M
1	Colon	HGH	*Hpa*II	<10	35	—
			*Hha*I	<10	39	—
		γ-Globin	*Hpa*II	<10	52	—
			*Hha*I	<10	39	—
		α-Globin	*Hpa*II	<10	<10	—
			*Hha*I	<10	<10	—
2	Colon	HGH	*Hpa*II	<10	76	—
			*Hha*I	<10	85	—
		γ-Globin	*Hpa*II	<10	58	—
			*Hha*I	<10	23	—
		α-Globin	*Hpa*II	<10	<10	—
			*Hha*I	<10	<10	—
3	Colon	HGH	*Hpa*II	<10	41	—
			*Hha*I	<10	38	—
		γ-Globin	*Hpa*II	<10	50	—

Nature 301, 89 - 92 (06 January 1983); doi:10.1038/301089a0

Causes of Cancer



Cancer is a Preventable Disease that Requires Major Lifestyle Changes

Anand et al (2008) Pharmaceutical Research. doi: 10.1007/s11095-008-9661-9

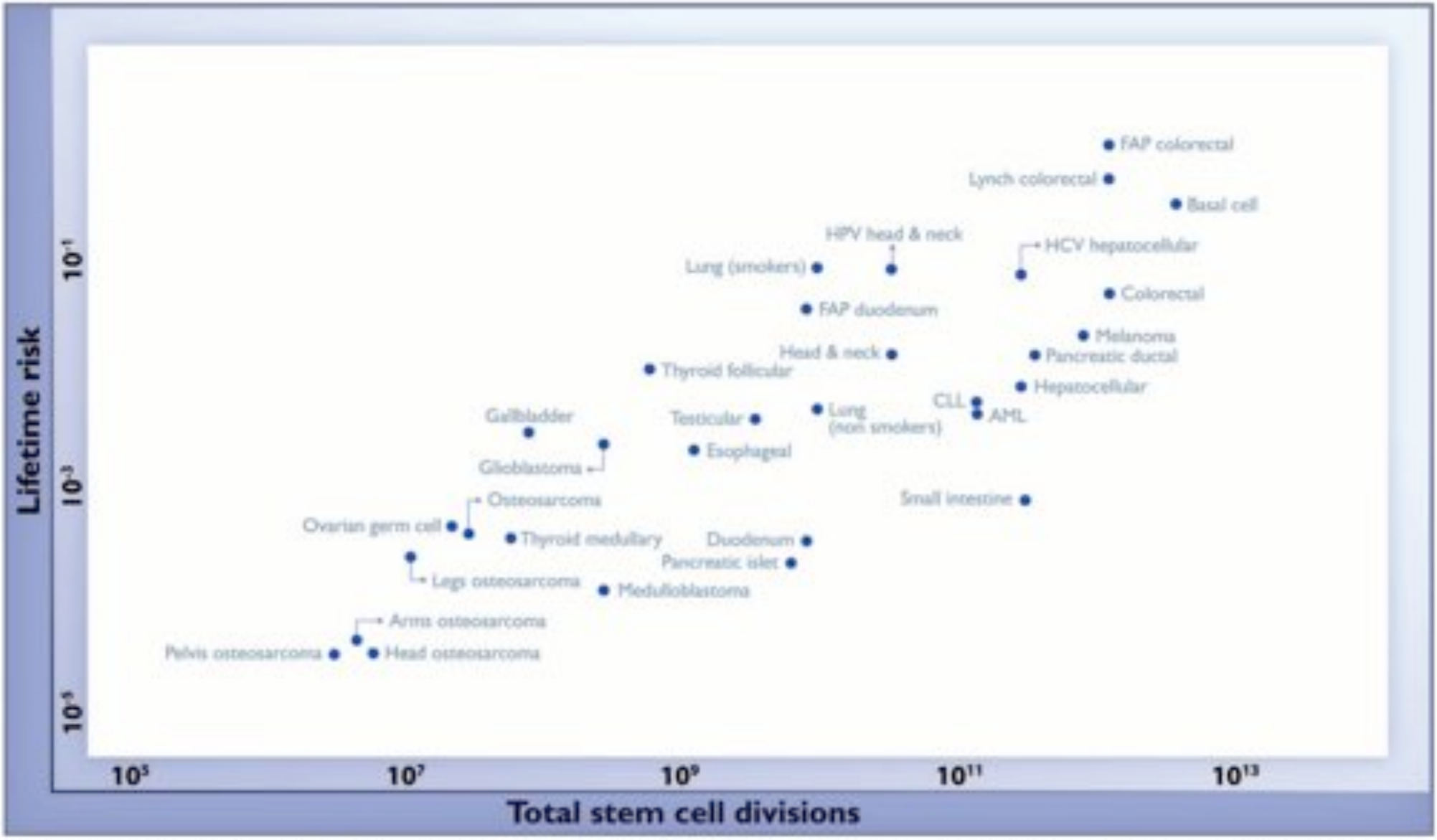
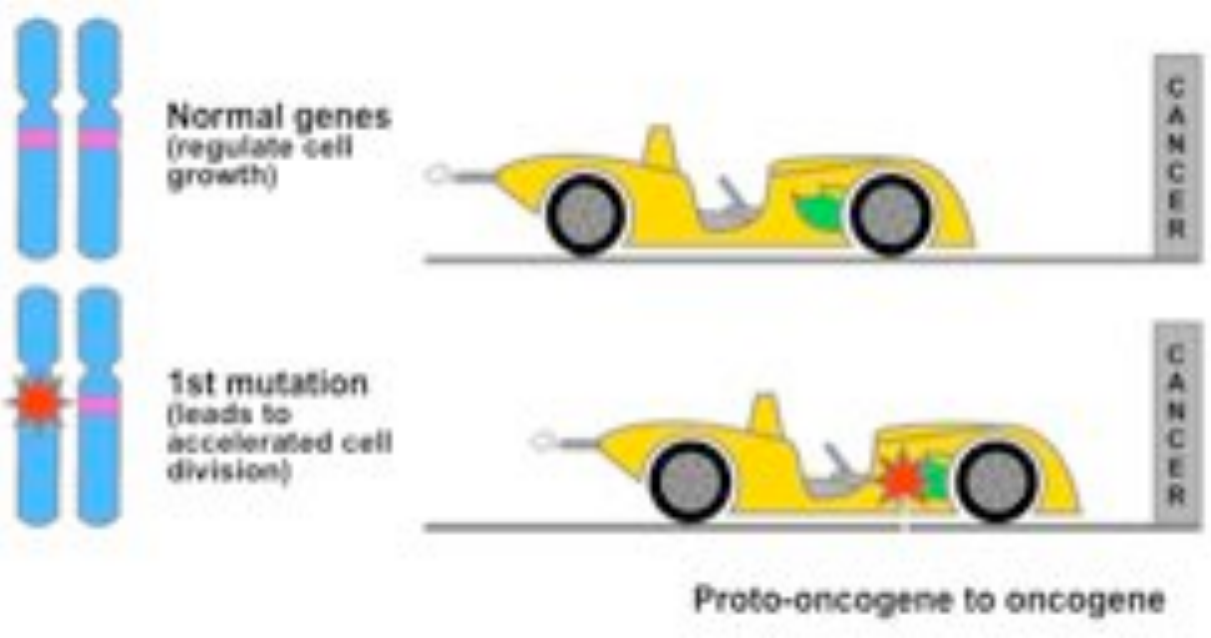


Fig. 1. The relationship between the number of stem cell divisions in the lifetime of a given tissue and the lifetime risk of cancer in that tissue. Values are from table S1, the derivation of which is discussed in the supplementary materials.

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

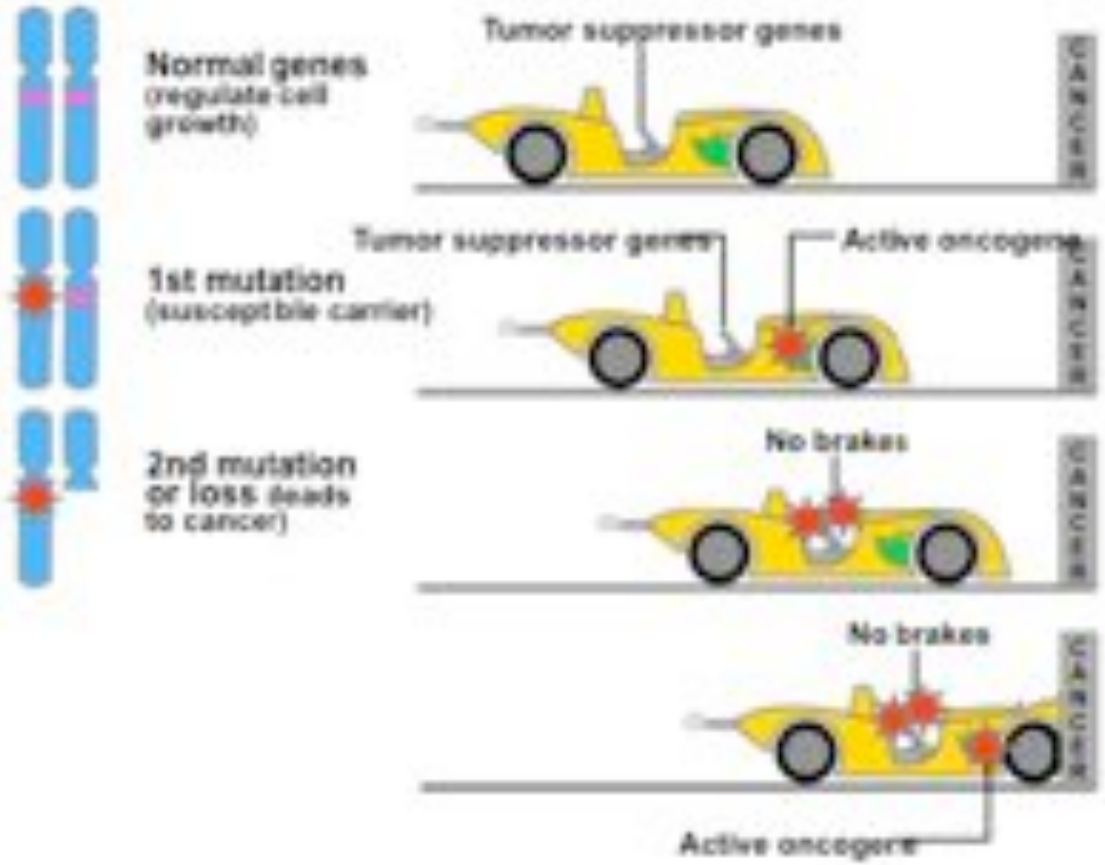
Tomasetti and Vogelstein (2015) Science. DOI: 10.1126/science.1260825

Oncogenes



- ***HER-2/neuHER-2/neu:*** encodes for a cell surface receptor that can stimulate cell division. The HER-2/neu gene is amplified in up to 30% of human breast cancers.
- ***RAS:*** The Ras gene products are involved in kinase signaling pathways that ultimately control transcription of genes, regulating cell growth and differentiation.
- ***MYC:*** The Myc protein is a transcription factor and controls expression of several genes.
- ***SRC:*** First oncogene ever discovered. The Src protein is a tyrosine kinase, which regulates cell activity.
- ***hTER:*** Codes for an enzyme (telomerase) that maintains chromosome ends.

Tumor Suppressors



- ***TP53:*** a transcription factor that regulates cell division and cell death.
- ***Rb:*** alters the activity of transcription factors and therefore controls cell division.
- ***APC:*** controls the availability of a transcription factor.
- **PTEN:** acts by opposing the action of PI3K, which is essential for anti-apoptotic, pro-tumorogenic Akt activation.

TP53: The first and most important tumor suppressor

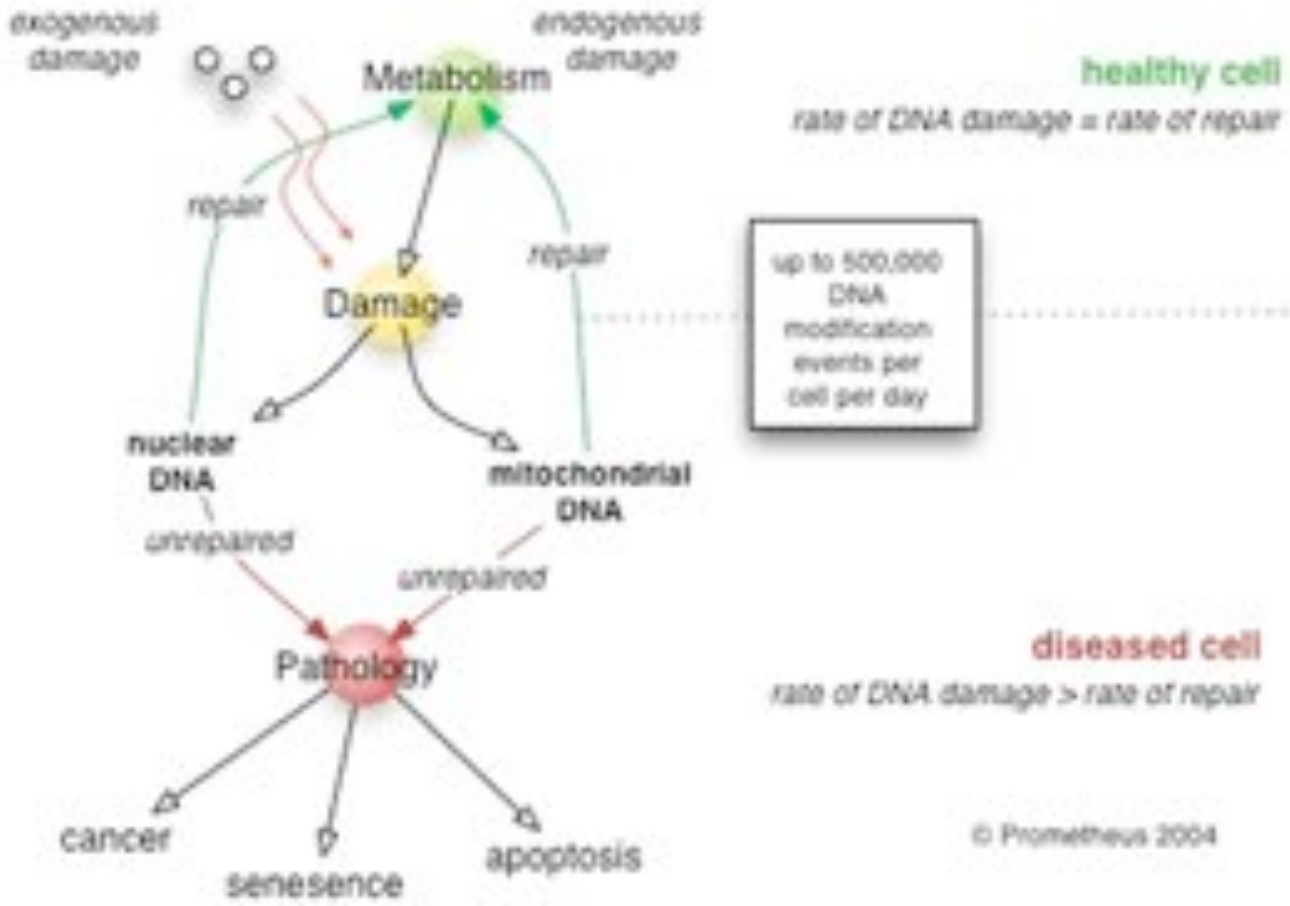
Mechanism of inactivating p53	Typical tumours	Effect of inactivation
Amino-acid-changing mutation in the DNA-binding domain	Colon, breast, lung, bladder, brain, pancreas, stomach, oesophagus and many others	Prevents p53 from binding to specific DNA sequences and activating the adjacent genes
Deletion of the carboxy-terminal domain	Occasional tumours at many different sites	Prevents the formation of tetramers of p53
Multiplication of the MDM2 gene in the genome	Sarcomas, brain	Extra MDM2 stimulates the degradation of p53
Viral infection	Cervix, liver, lymphomas	Products of viral oncogenes bind to and inactivate p53 in the cell, in some cases stimulating p53 degradation
Deletion of the $p14^{ARF}$ gene	Breast, brain, lung and others, expecially when p53 itself is not mutated	Failure to inhibit MDM2 and keep p53 degradation under control
Mislocalization of p53 to the cytoplasm, outside the nucleus	Breast, neuroblastomas	Lack of p53 function (p53 functions only in the nucleus)

Figure 1 **The many ways in which p53 may malfunction in human cancers.**

>10,000 known mutations
>17,000 publications

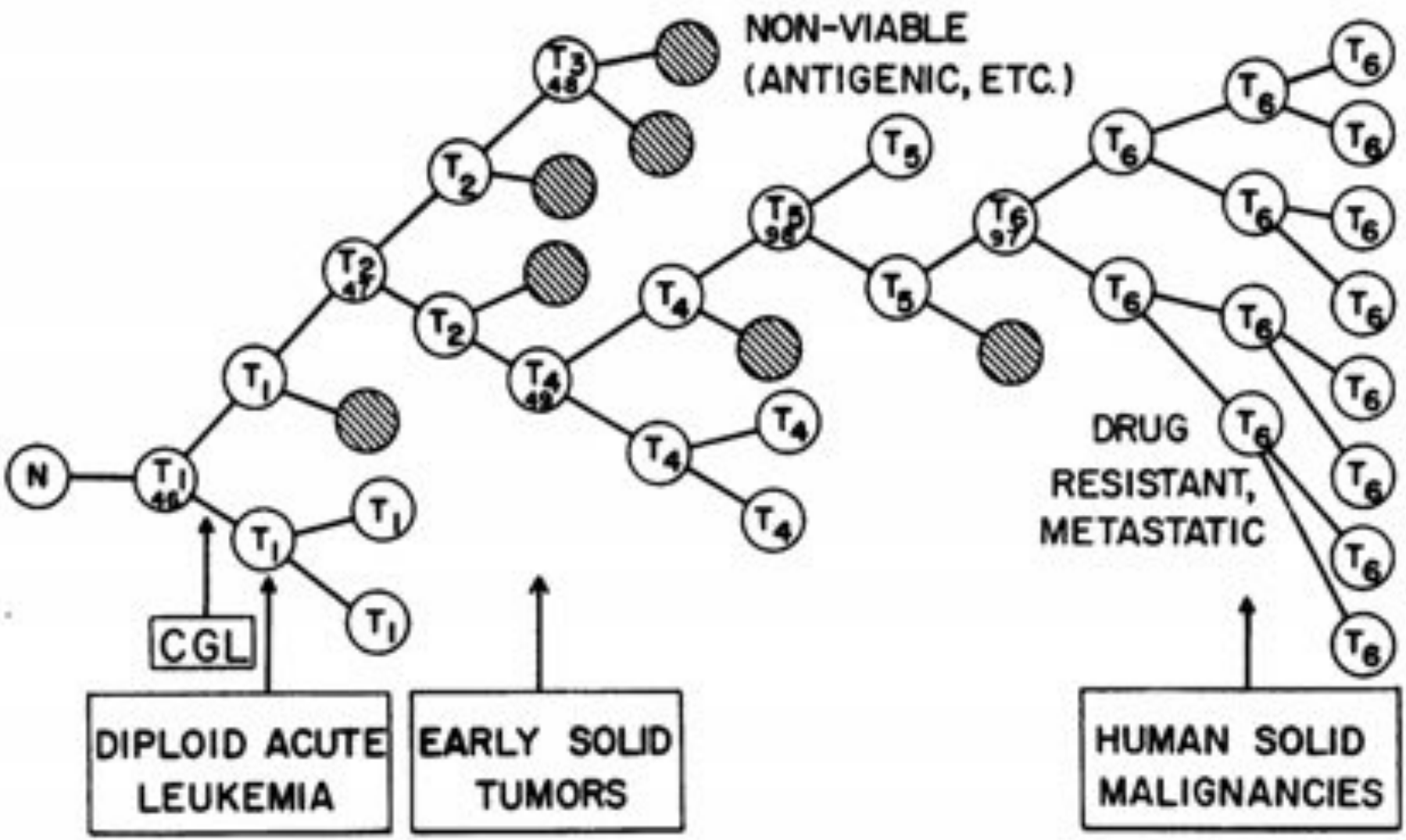
Surfing the p53 network
Volgelstein et al (2000) Nature. DOI: 10.1038/35042675

DNA Repair Genes



BRCA1 and BRCA2 (breast cancer type 1/2 susceptibility genes)
Normally expressed in the cells of breast and other tissue, where they help repair damaged DNA, or destroy cells if DNA cannot be repaired. They are involved in the repair of chromosomal damage with an important role in the error-free repair of DNA double-strand breaks

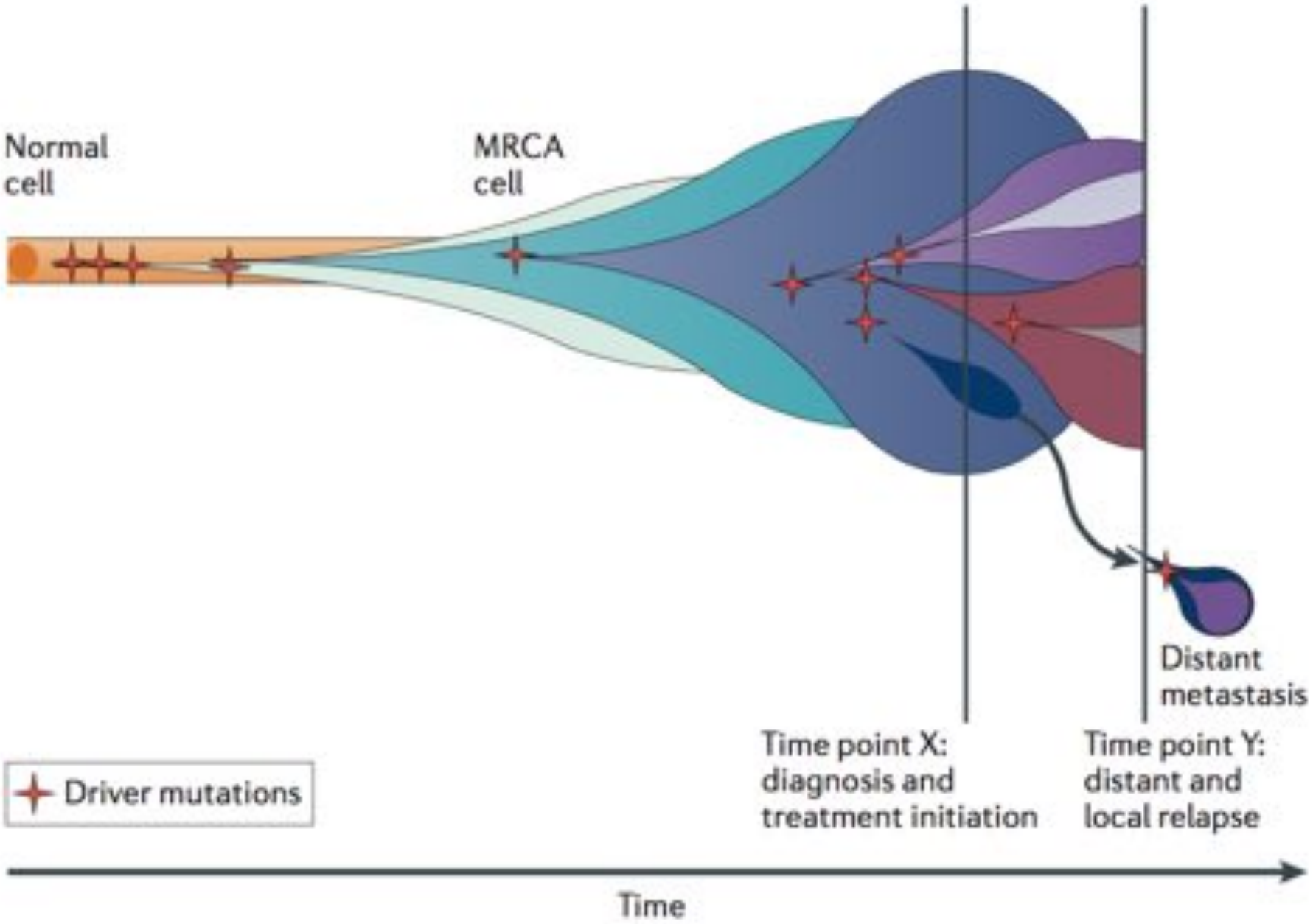
Tumor Evolution



The Clonal Evolution of Tumor Cell Populations

Peter C. Nowell (1976) *Science.* 194(4260):23-28 DOI: 10.1126/science.959840

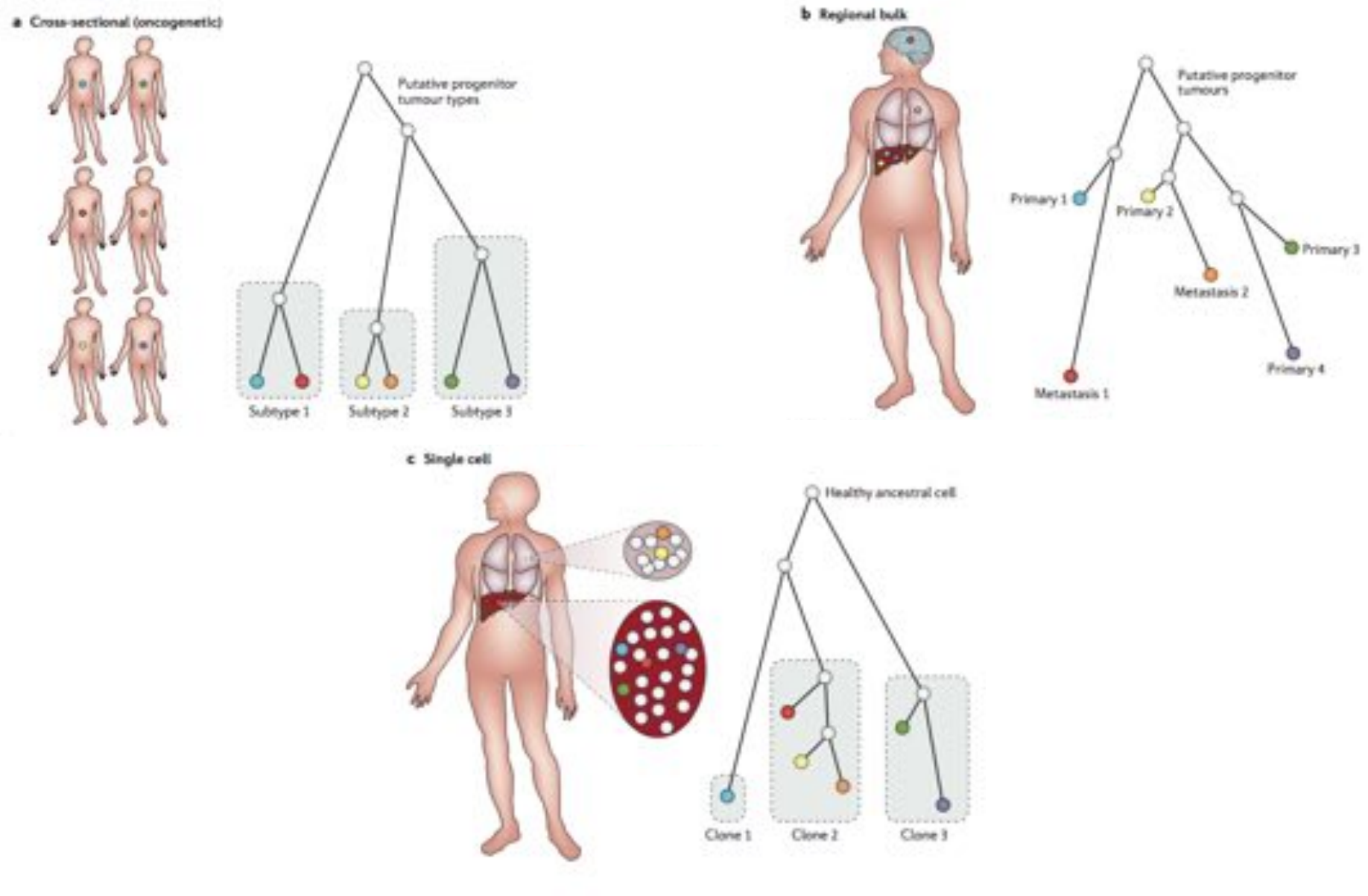
Tumor Evolution



Evolution of the cancer genome

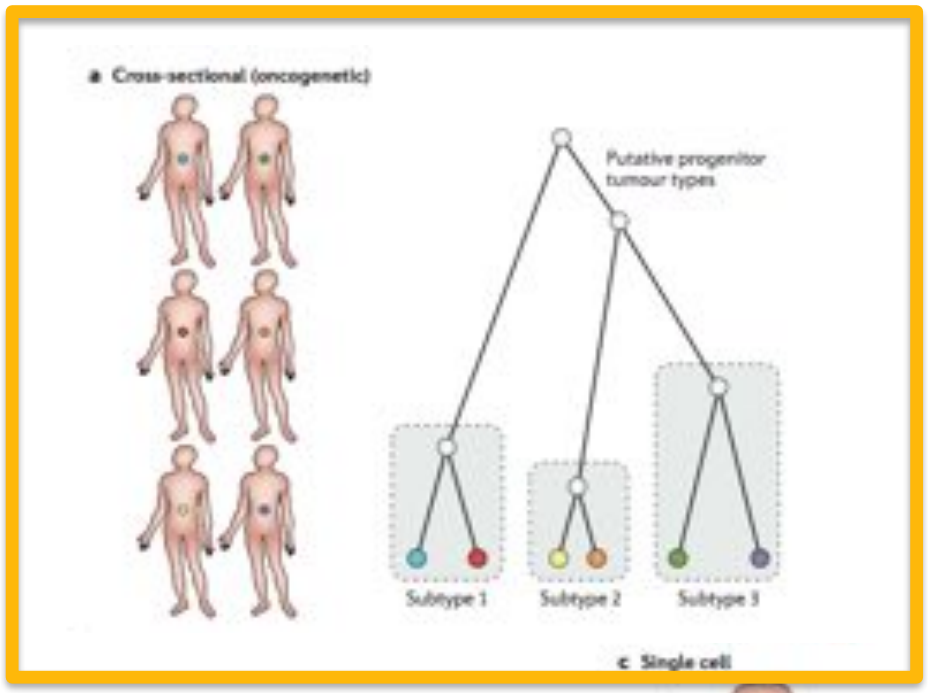
Yates & Campbell (2012) Nature Review Genetics. doi:10.1038/nrg3317

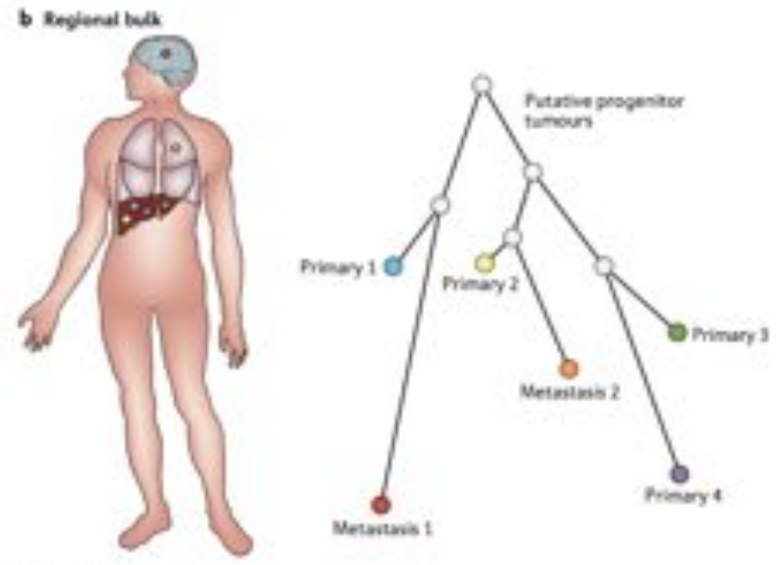
Tumor Heterogeneity

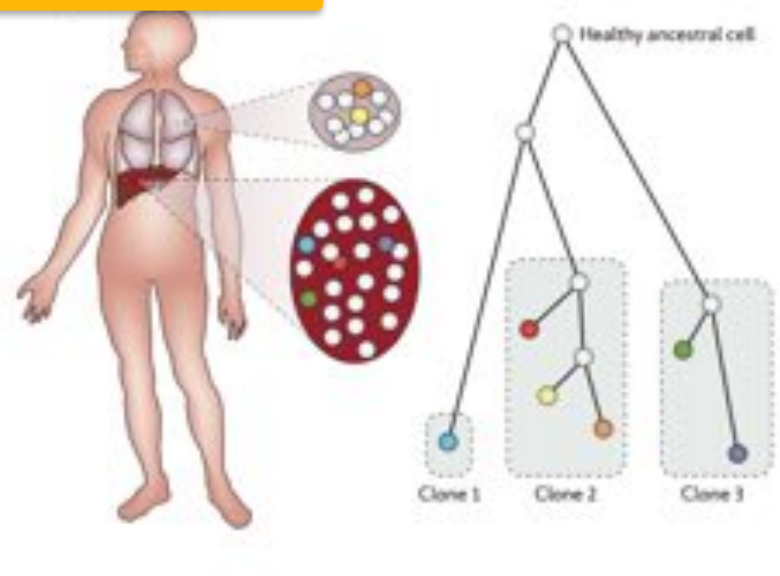


The evolution of tumour phylogenetics: principles and practice
Schwarz and Schaffer (2017) *Nature Reviews Genetics. doi:10.1038/nrg.2016.170*

Tumor Heterogeneity



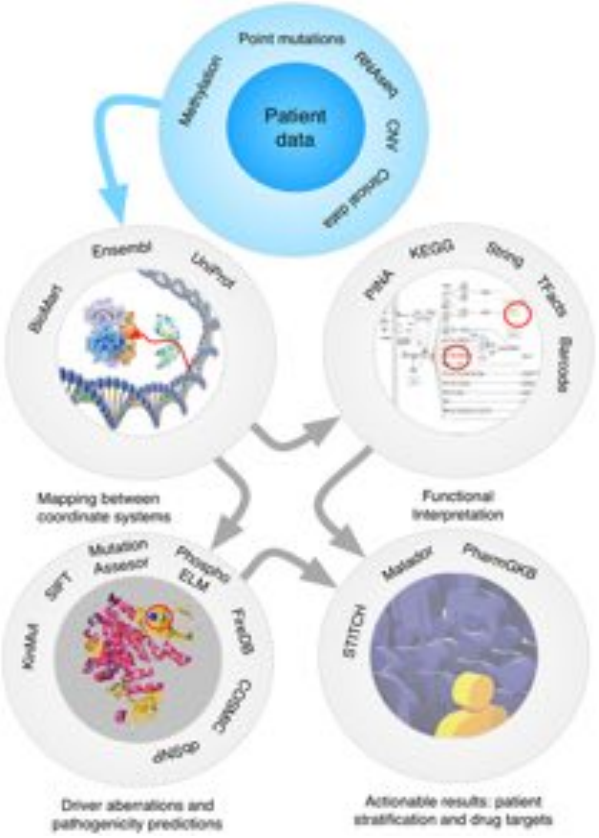




The evolution of tumour phylogenetics: principles and practice
Schwarz and Schaffer (2017) *Nature Reviews Genetics. doi:10.1038/nrg.2016.170*

Cancer Mutation Analysis

Analysis Steps	Disciplines	Techniques	Challenges
Sequencing, alignment, and Variant calling.	NGS bioinformatics, alignments, and databasing.	Data management, alignment and variant calling, and quality control.	Sample preparation, clonal mosaicism, and alignment efficiency and biases.
Consequence Analysis. Mutation Recurrence. Classification of driver-passenger mutations.	Structural bioinformatics, regulatory genomics, and biostatistics.	Pathogenicity predictions and recurrence statistics.	Predicting effect of mutations on protein function, regulation, splicing, etc. Establishing mutational background
Pathway and functional analysis.	Systems Biology, pathway modeling, and Interactomics.	Enrichment statistics and network analysis.	Multiple pathway definitions and violated statistical assumptions.
Integration, Visualization, and disease centered interpretation.	Application development, Man-machine interfaces, Pharmacogenomics, Text-mining, and Information management.	Data integration and visualization.	Multiple, heterogeneous, experimental data sources, database formats, and software resources. Biomedical expertise required.



Vazquez M, de la Torre V, Valencia A (2012) Chapter 14: Cancer Genome Analysis. PLOS Computational Biology 8(12): e1002824. https://doi.org/10.1371/journal.pcbi.1002824
http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002824

PLOS | COMPUTATIONAL BIOLOGY

First Cancer Genome

nature Vol 456 6 November 2008 doi:10.1038/nature07485

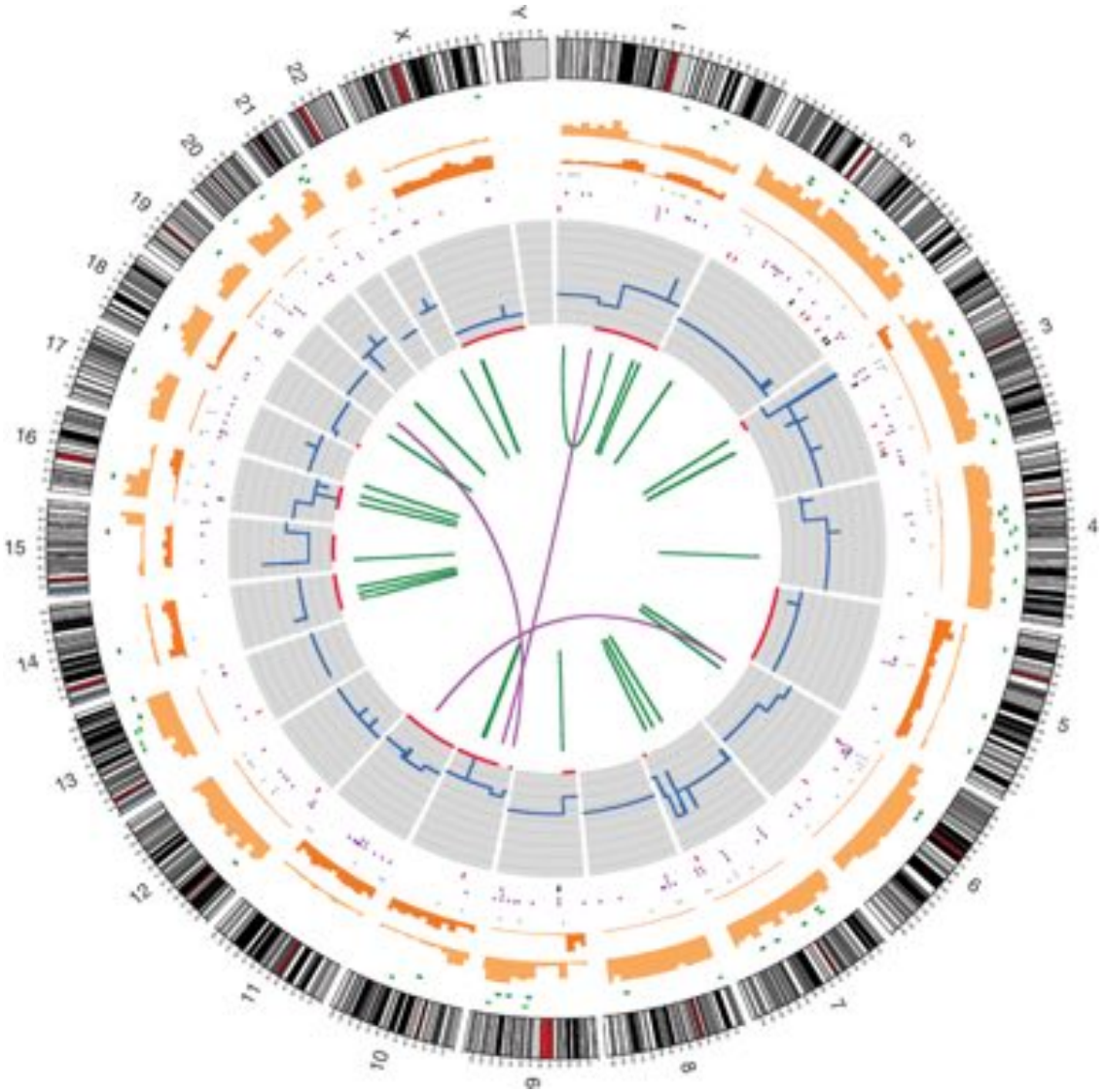
ARTICLES

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

Timothy J. Ley[1,2,3,4]*, Elaine R. Mardis[2,3]*, Li Ding[2,3], Bob Fulton[3], Michael D. McLellan[3], Ken Chen[3], David Dooling[3], Brian H. Dunford-Shore[3], Sean McGrath[3], Matthew Hickenbotham[3], Lisa Cook[3], Rachel Abbott[3], David E. Larson[3], Dan C. Koboldt[3], Craig Pohl[3], Scott Smith[3], Amy Hawkins[3], Scott Abbott[3], Devin Locke[3], LaDeana W. Hillier[3,4], Tracie Miner[3], Lucinda Fulton[3], Vincent Magrini[2,3], Todd Wylie[3], Jarret Glasscock[3], Joshua Conyers[3], Nathan Sander[3], Xiaoqi Shi[3], John R. Osborne[3], Patrick Minx[3], David Gordon[3], Asif Chinwalla[3], Yu Zhao[1], Rhonda E. Ries[1], Jacqueline E. Payton[5], Peter Westervelt[1,4], Michael H. Tomasson[1,4], Mark Watson[5,4,3], Jack Baty[6], Jennifer Ivanovich[6,7], Sharon Heath[1,4], William D. Shannon[1,4], Rakesh Nagarajan[6,3], Matthew J. Walter[1,4], Daniel C. Link[1,4], Timothy A. Graubert[1,4], John F. DiPersio[1,4] & Richard K. Wilson[2,3,4]

Acute myeloid leukaemia is a highly malignant haematopoietic tumour that affects about 13,000 adults in the United States each year. The treatment of this disease has changed little in the past two decades, because most of the genetic events that initiate the disease remain undiscovered. Whole-genome sequencing is now possible at a reasonable cost and timeframe to use this approach for the unbiased discovery of tumour-specific somatic mutations that alter the protein-coding genes. Here we present the results obtained from sequencing a typical acute myeloid leukaemia genome, and its matched normal counterpart obtained from the same patient's skin. We discovered ten genes with acquired mutations; two were previously described mutations that are thought to contribute to tumour progression, and eight were new mutations present in virtually all tumour cells at presentation and relapse, the function of which is not yet known. Our study establishes whole-genome sequencing as an unbiased method for discovering cancer-initiating mutations in previously unidentified genes that may respond to targeted therapies.

First Melanoma Genome

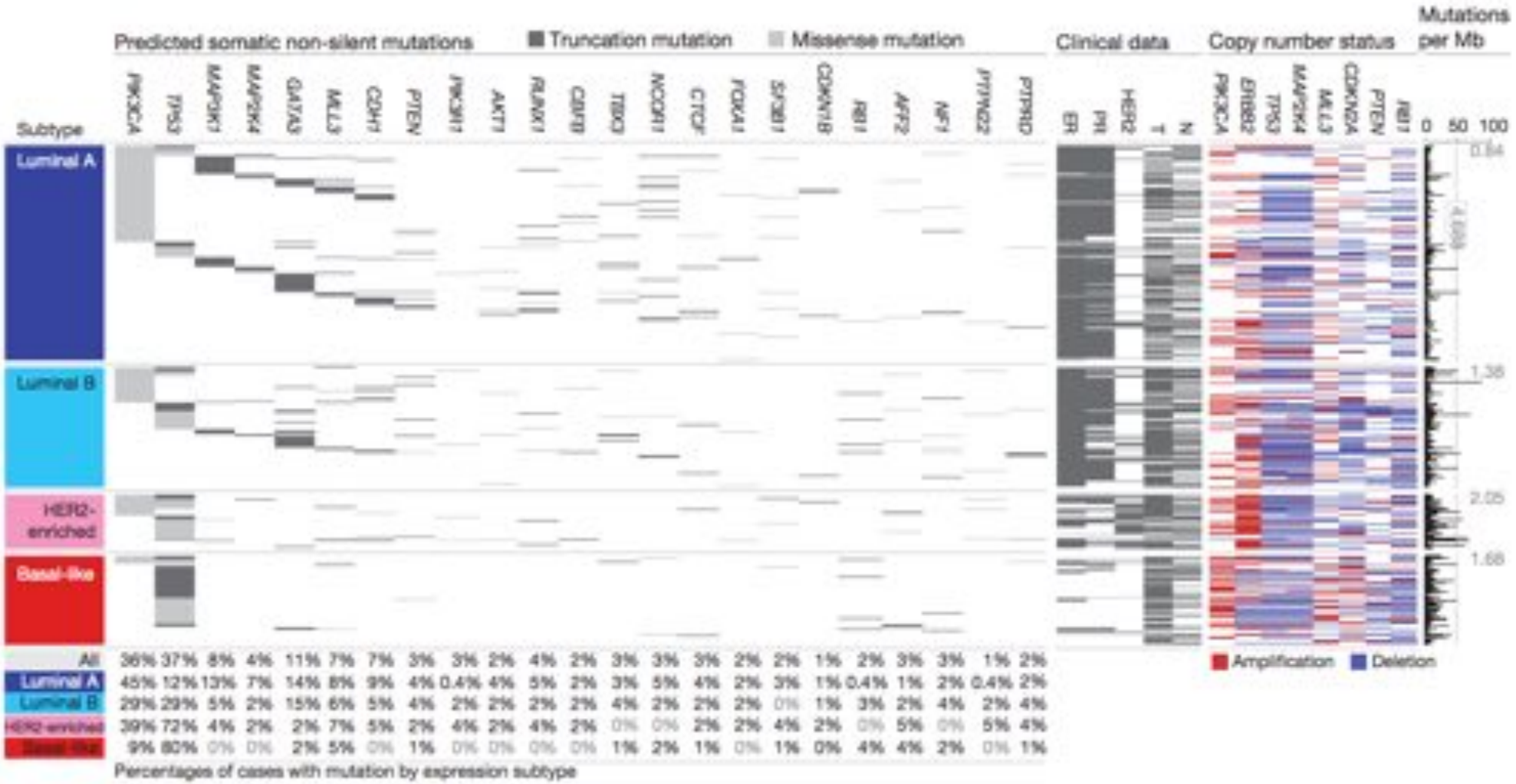


- Insertions (light-green rectangles);
- Deletions (dark-green rectangles);
- Heterozygous (light-orange bars) and Homozygous (dark-orange bars) Substitutions
- Coding substitutions (coloured squares: silent in grey, missense in purple, nonsense in red and splice site in black);
- Copy number (blue lines); regions of LOH (red lines);
- Intrachromosomal rearrangements (green lines);
- Interchromosomal rearrangements (purple lines).

A comprehensive catalogue of somatic mutations from a human cancer genome

Pleasance et al (2010) Nature. doi:10.1038/nature08658

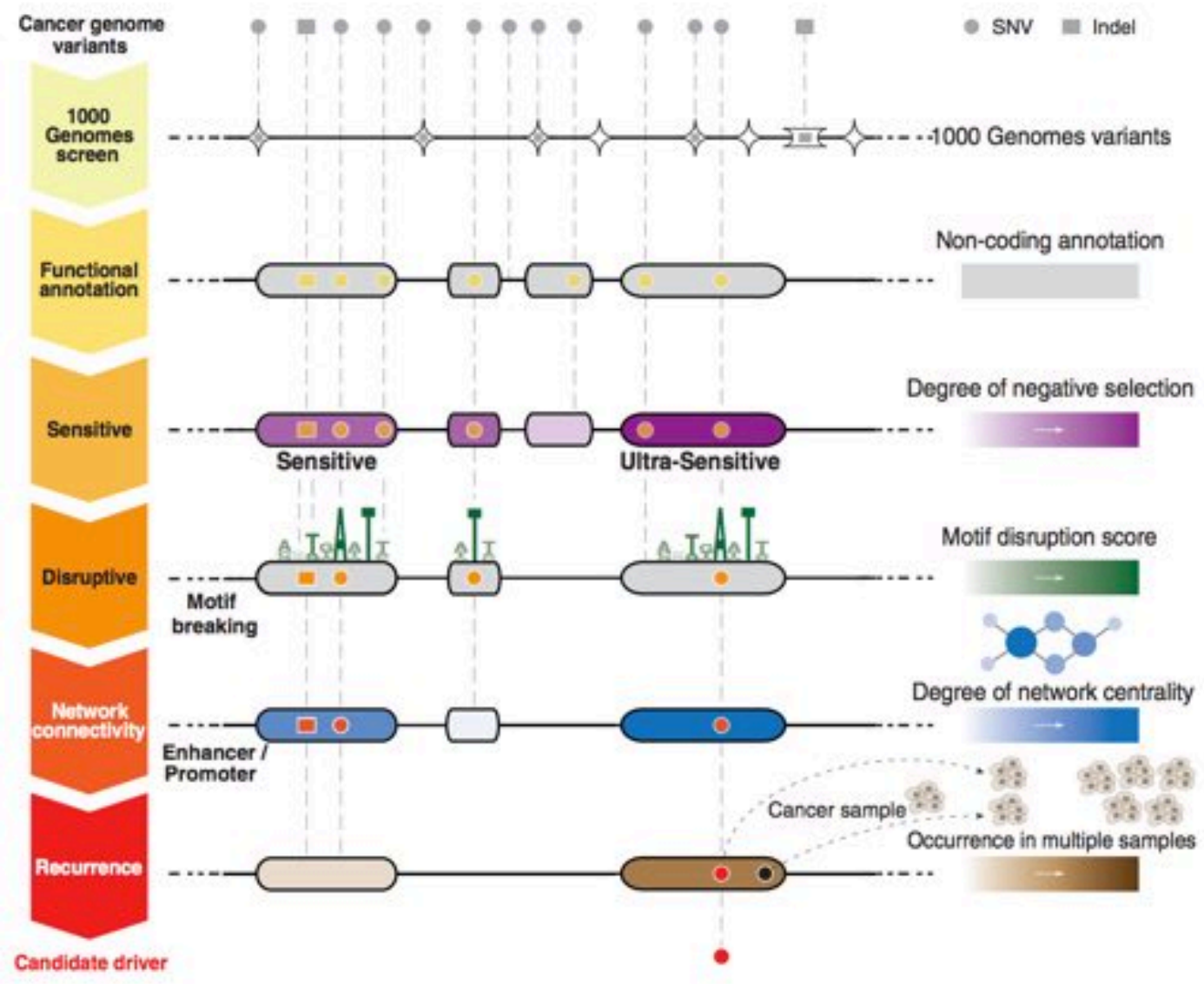
Mutations in Breast Cancer



Comprehensive molecular portraits of human breast tumours

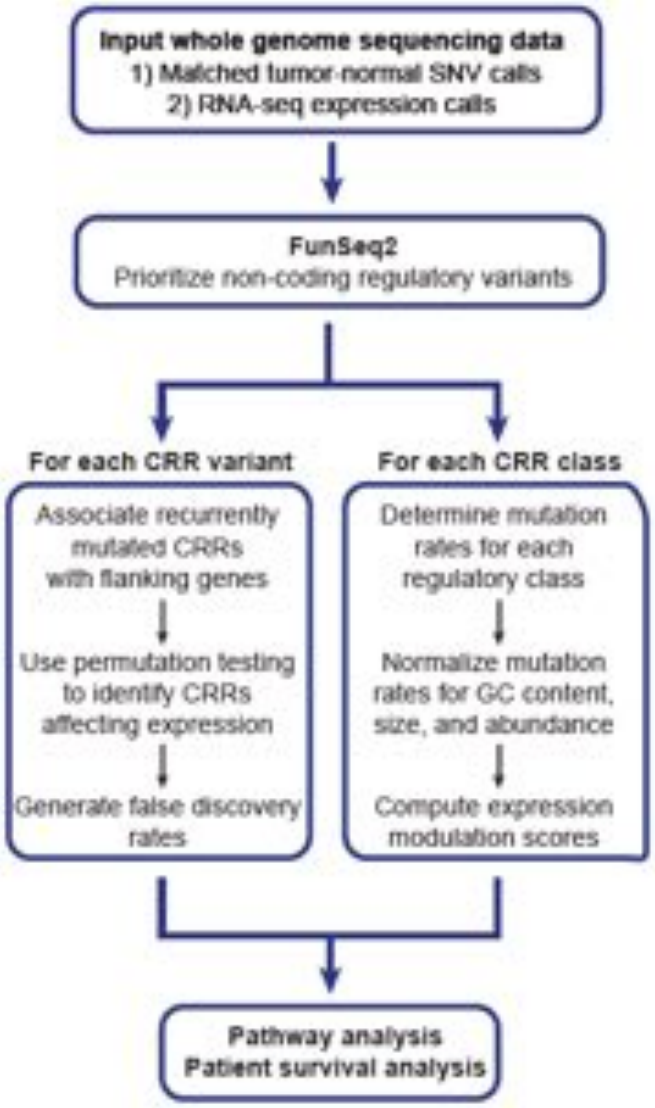
Cancer Genome Atlas Network (2012) Nature. doi:10.1038/nature11412

Finding Driving Mutations



Integrative Annotation of Variants from 1092 Humans: Application to Cancer Genomics
Khurana et al (2013) Science. DOI: 10.1126/science.1235587

Regulatory mutations in PDAC



Coding alterations of PDAC are now fairly well established but non-coding mutations (NCMs) largely unexplored

•Developed GECCO to analyze the thousands of somatic mutations observed from hundreds of tumors to find potential drivers of gene expression and pathogenesis

•NCMs are enriched in known and novel pathways

•NCMs correlate with changes in gene expression

•NCMs can demonstrably modulate gene expression

•NCMs correlate with novel clinical outcomes

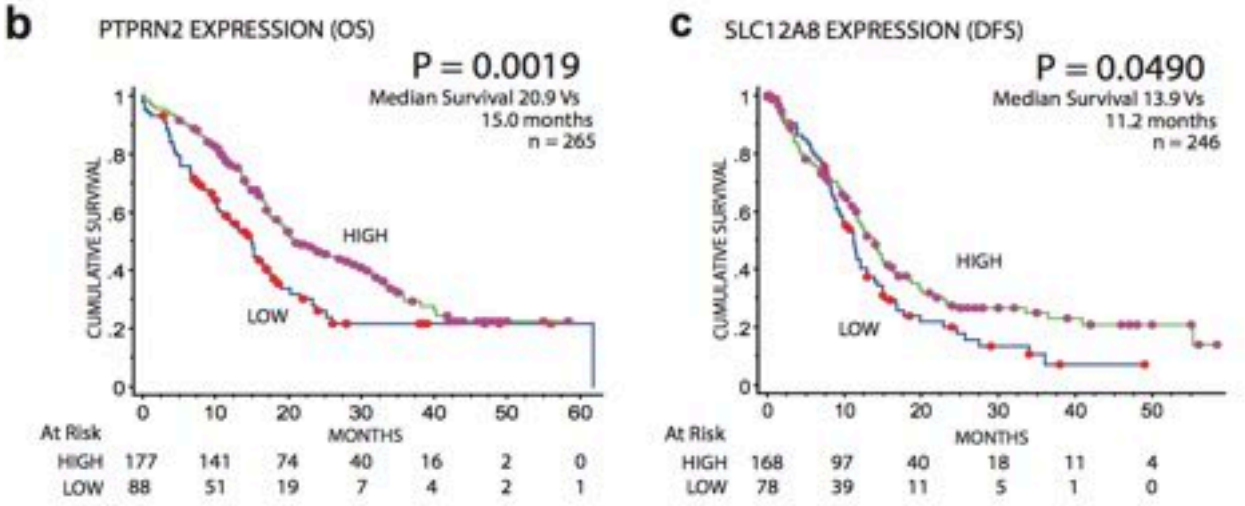
NCMs are an important mechanism for tumor genome evolution

Recurrent noncoding regulatory mutations in pancreatic ductal adenocarcinoma
Feigin, M, Garvin, T et al. (2017) Nature Genetics. doi:10.1038/ng.3861

Driving Non-Coding Mutations

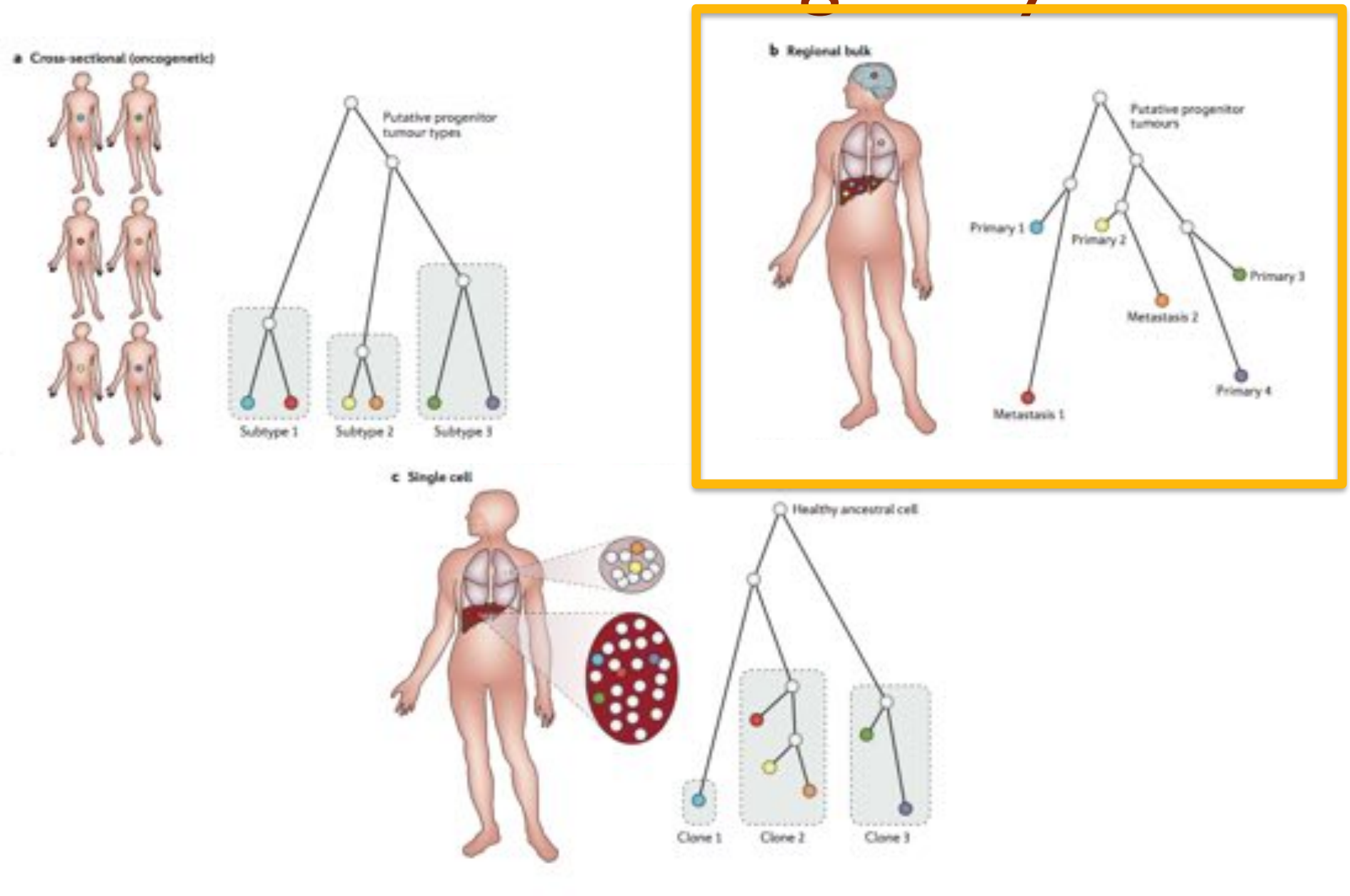
a **NCMs correlate with gene expression changes**

CRR (MUT#)	Nearest gene	MUT allele	WT allele	Fold change	*p*-value	q-value
MAX (5)	*PTPRN2*	0.82	10.92	0.075	0.00593	0.09689
FOSL2 (7)	*KCNQ1*	0.85	6.39	0.133	0.02456	0.18212
TAF7 (9)	*SNRPN*	0.46	3.4	0.135	0.00818	0.11818
NFKB1 (7)	*GYPC*	1.08	7.29	0.148	0.01845	0.15157
TAF1 (6)	*PDPN*	2.09	13.08	0.160	0.03544	0.22016
BCLAF1 (5)	*PRSS12*	1.07	6.46	0.166	0.01107	0.14144
MAFK (3)	*SOX5*	0.29	1.63	0.178	0.02851	0.20379
POU2F2 (6)	MIR4420	8.16	40.24	0.203	0.01773	0.15157
WRNIP1 (3)	*IKZF1*	0.64	3.15	0.203	0.01811	0.15157
GATA3 (3)	*PCLO*	0.35	1.67	0.210	0.01113	0.14144
JUND (3)	TUSC7	0.98	4.53	0.216	0.02909	0.20560
REST (3)	*MTERF4*	1.46	5.78	0.253	0.02209	0.16542
GATA1 (3)	*FNIP2*	7.59	18.32	0.414	0.02588	0.18929
CEBPB (3)	*PNPLA8*	5.69	13.62	0.418	0.01726	0.15157
EGR1 (5)	*SLC12A8*	4.34	7.99	0.542	0.04185	0.23823
SIN3A (3)	*FAM192A*	20.31	30.48	0.666	0.01788	0.15157



Recurrent noncoding regulatory mutations in pancreatic ductal adenocarcinoma
Feigin, M, Garvin, T et al. (2017) Nature Genetics. doi:10.1038/ng.3861

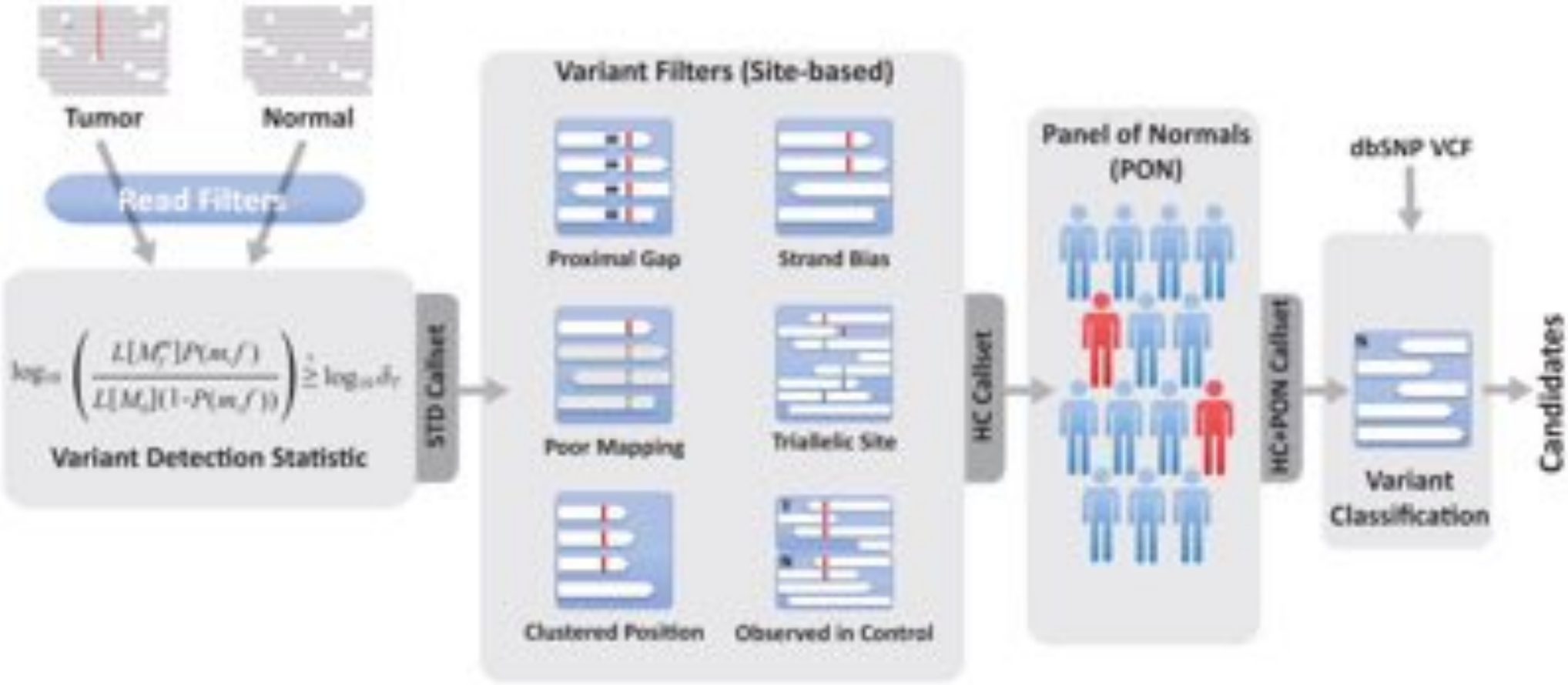
Tumor Heterogeneity



The evolution of tumour phylogenetics: principles and practice

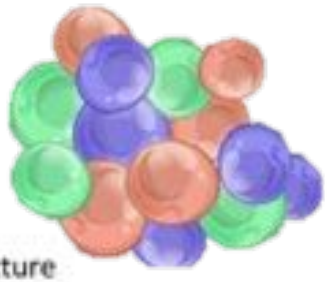
Schwarz and Schaffer (2017) *Nature Reviews Genetics. doi:10.1038/nrg.2016.170*

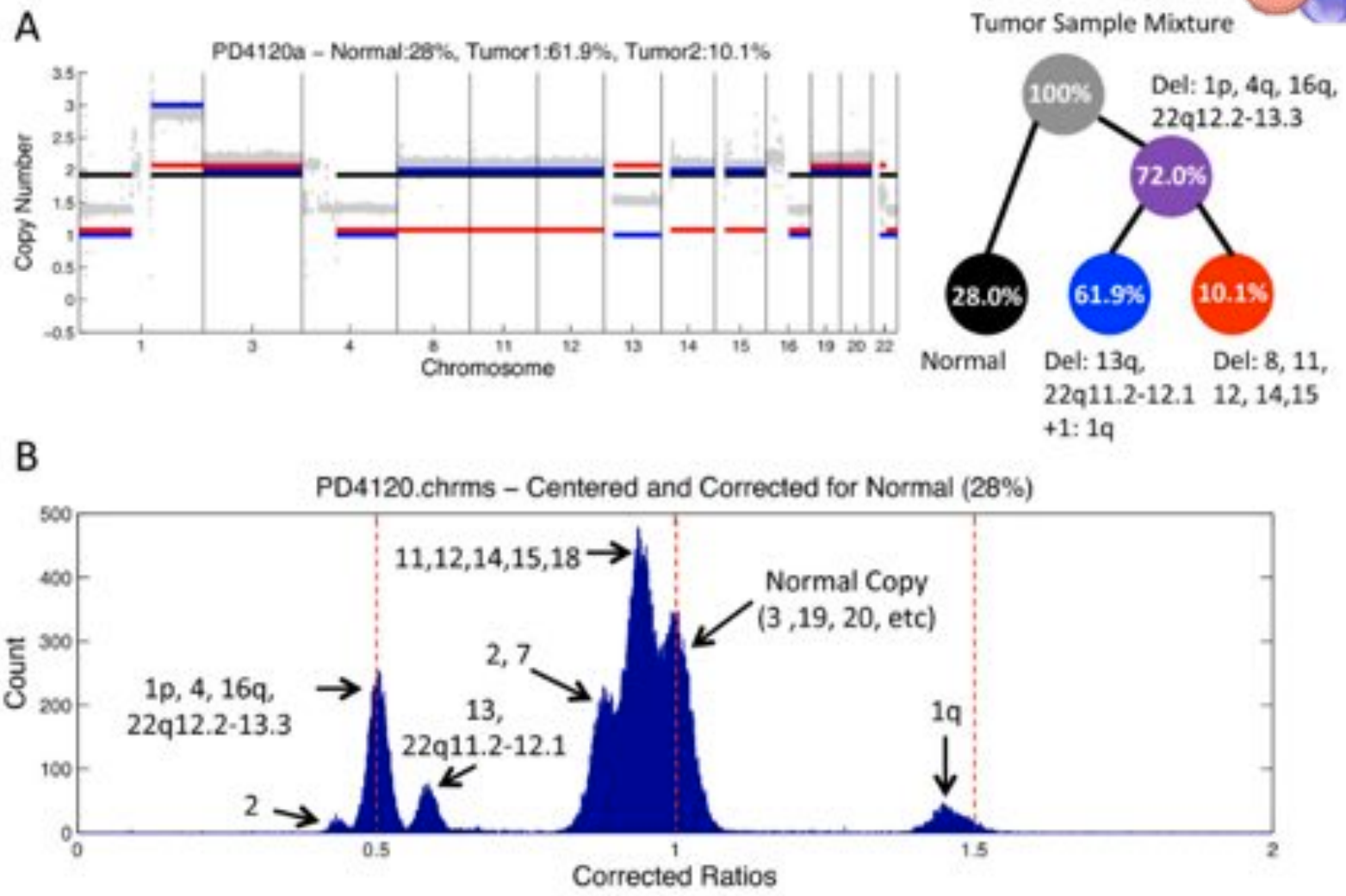
Tumor-Normal Pairs



Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples
Cibulskis et al (2013) Nature Biotech. doi:10.1038/nbt.2514

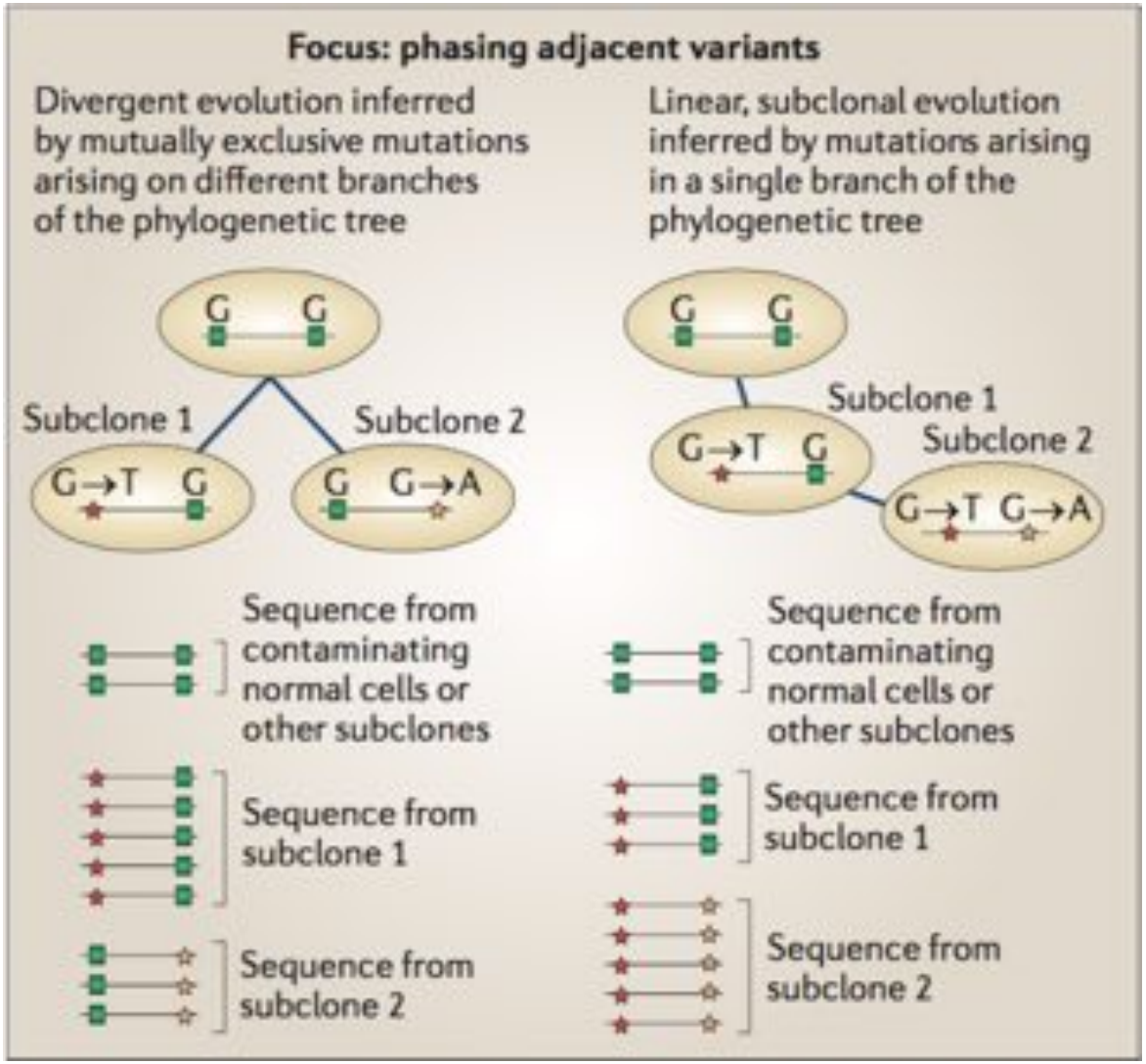
Bulk Heterogeneity





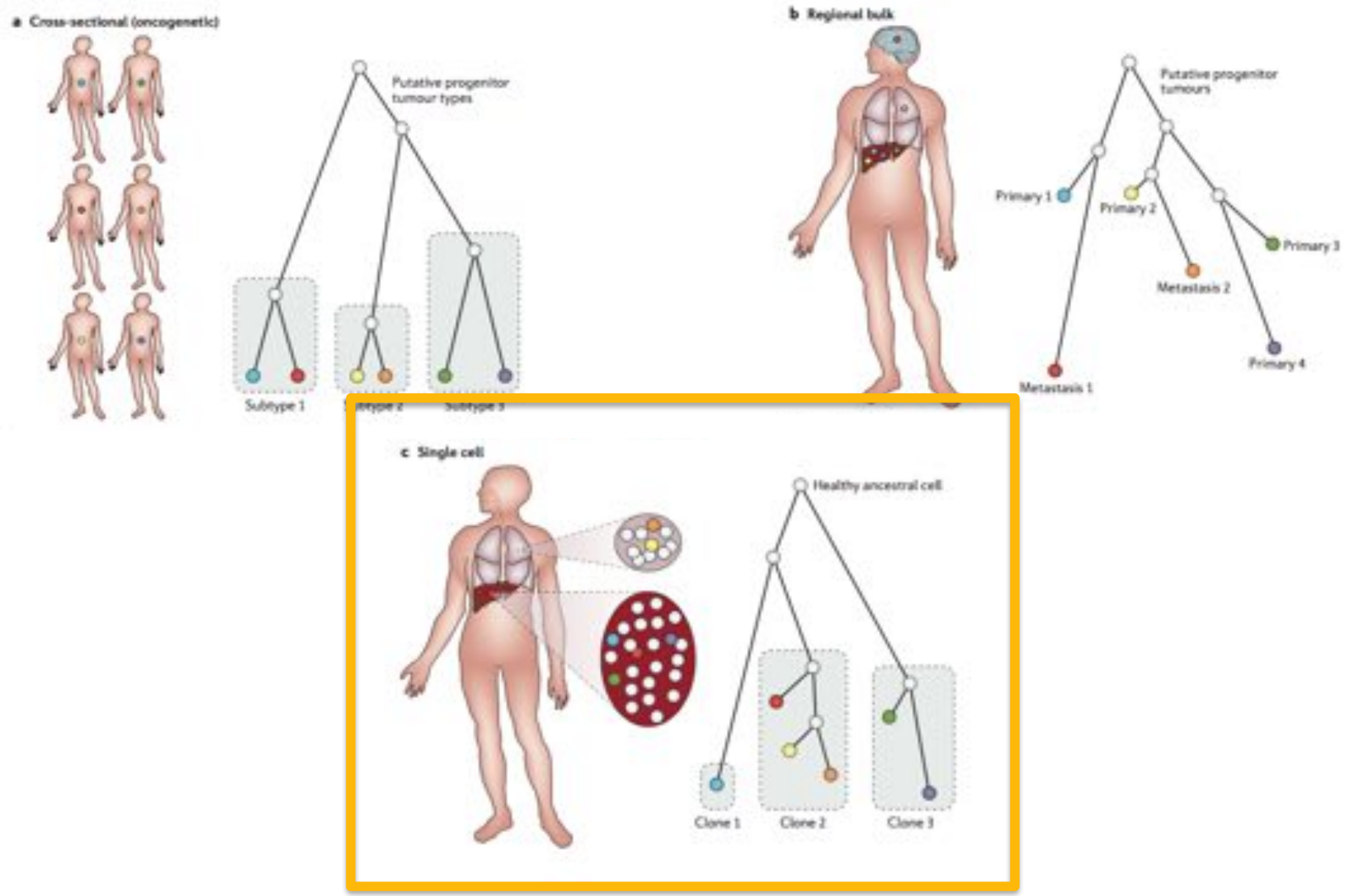
THetA: inferring intra-tumor heterogeneity from high-throughput DNA sequencing data
Oesperet al (2013) Genome Biology. DOI: 10.1186/gb-2013-14-7-r80

Somatic Variant Detection



Evolution of the cancer genome
Yates & Campbell (2012) Nature Review Genetics. doi:10.1038/nrg3317

Tumor Heterogeneity



The evolution of tumour phylogenetics: principles and practice

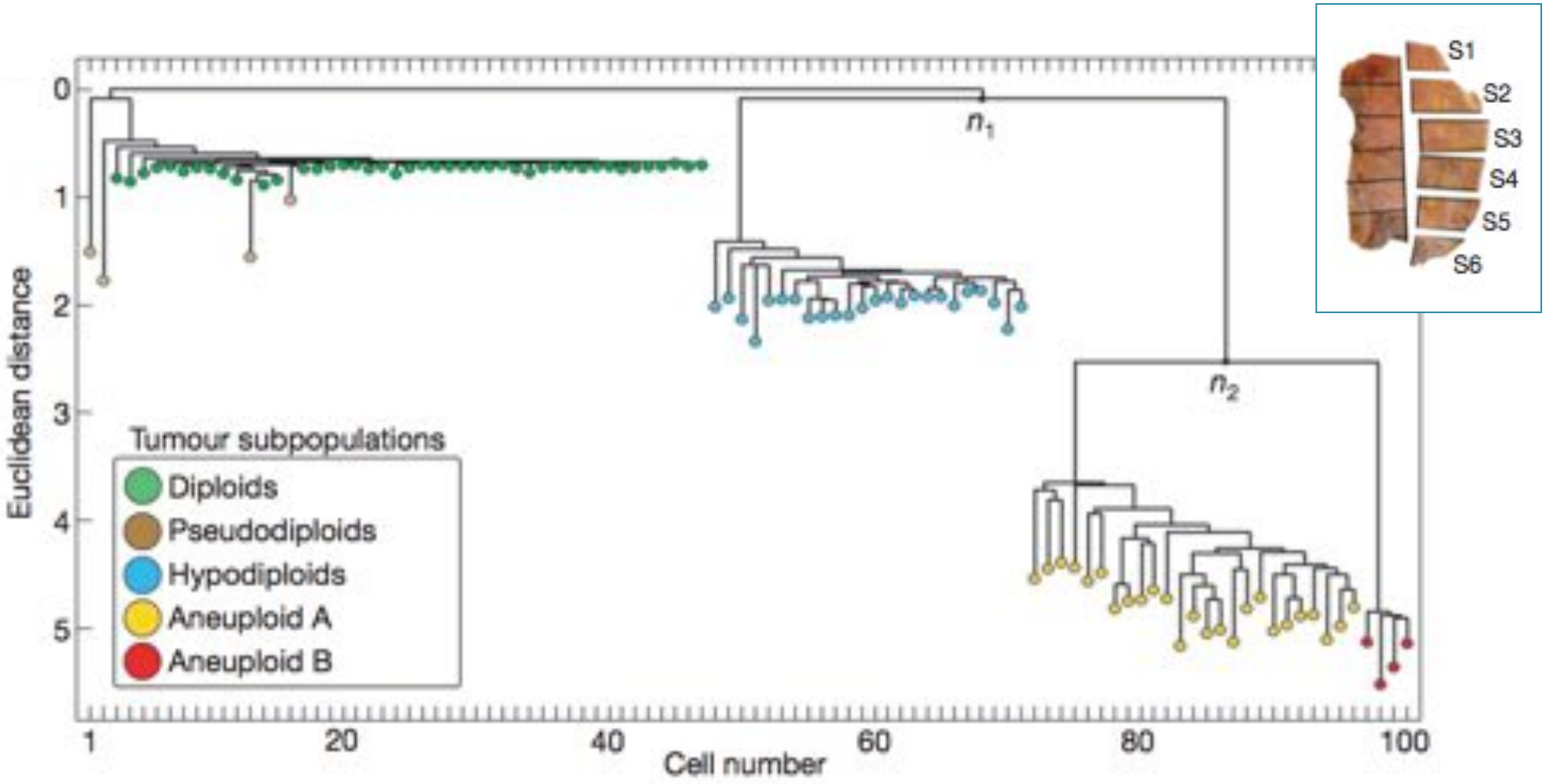
Schwarz and Schaffer (2017) *Nature Reviews Genetics. doi:10.1038/nrg.2016.170*

LETTER

doi:10.1038/nature09807

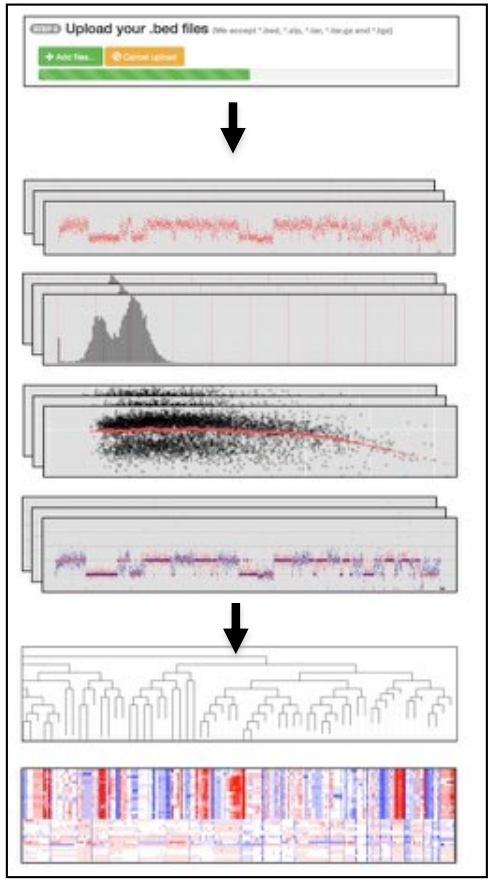
Tumour evolution inferred by single-cell sequencing

Nicholas Navin[1,2], Jude Kendall[1], Jennifer Troge[1], Peter Andrews[1], Linda Rodgers[1], Jeanne McIndoo[1], Kerry Cook[1], Asya Stepansky[1], Dan Levy[1], Diane Esposito[1], Lakshmi Muthuswamy[3], Alex Krasnitz[1], W. Richard McCombie[1], James Hicks[1] & Michael Wigler[1]



Gingko

http://qb.cshl.edu/ginkgo



Interactive Single Cell CNV analysis & clustering

- Easy-to-use, web interface, parameterized for binning, segmentation, clustering, etc
- Per cell through project-wide analysis in any species

Compare MDA, DOP-PCR, and MALBAC

- DOP-PCR shows superior resolution and consistency

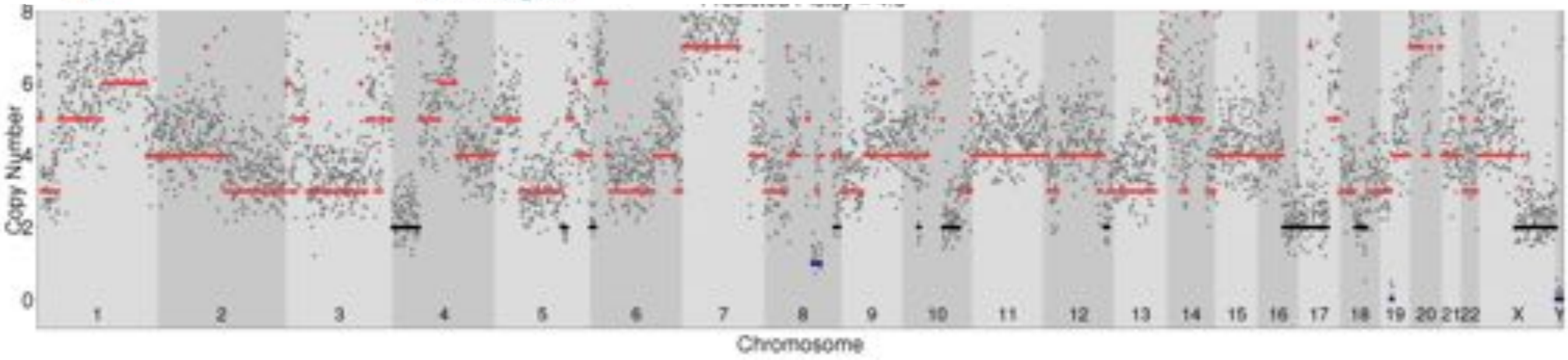
Available for collaboration

- Analyzing CNVs with respect to different clinical outcomes
- Extending clustering methods, prototyping scRNA

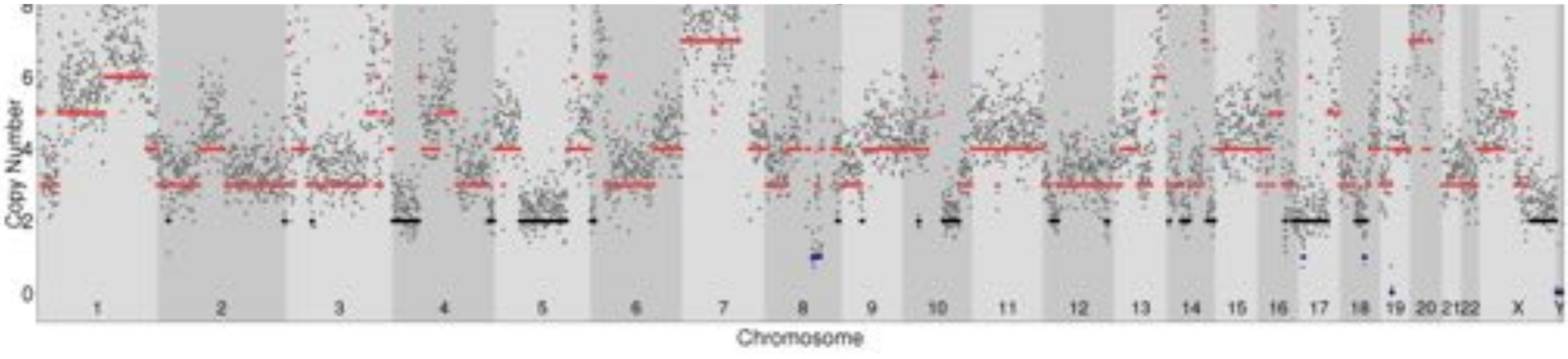
Interactive analysis and assessment of single-cell copy-number variations.
Garvin et al. (2015) Nature Methods doi:10.1038/nmeth.3578

Realtime CNV Analysis

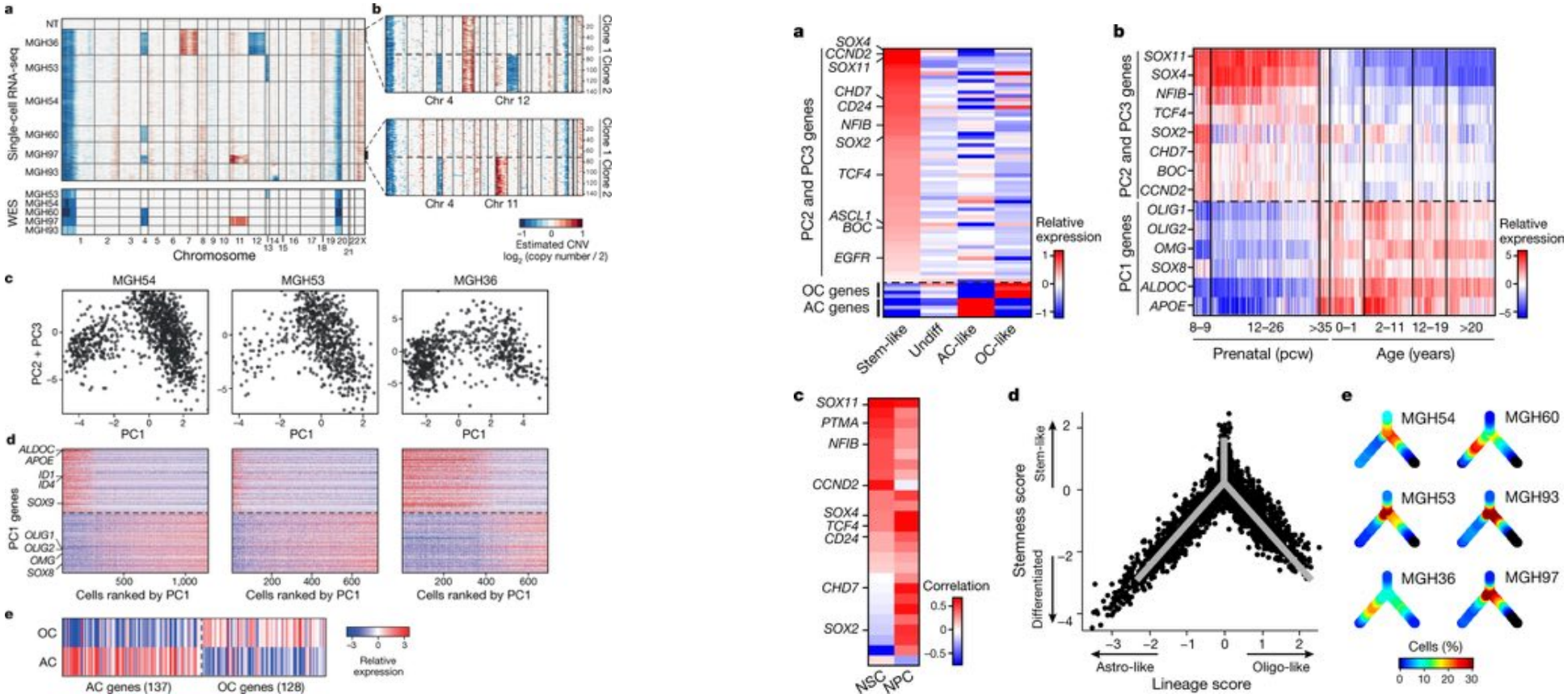
Oxford NANOPORE Technologies



illumina®

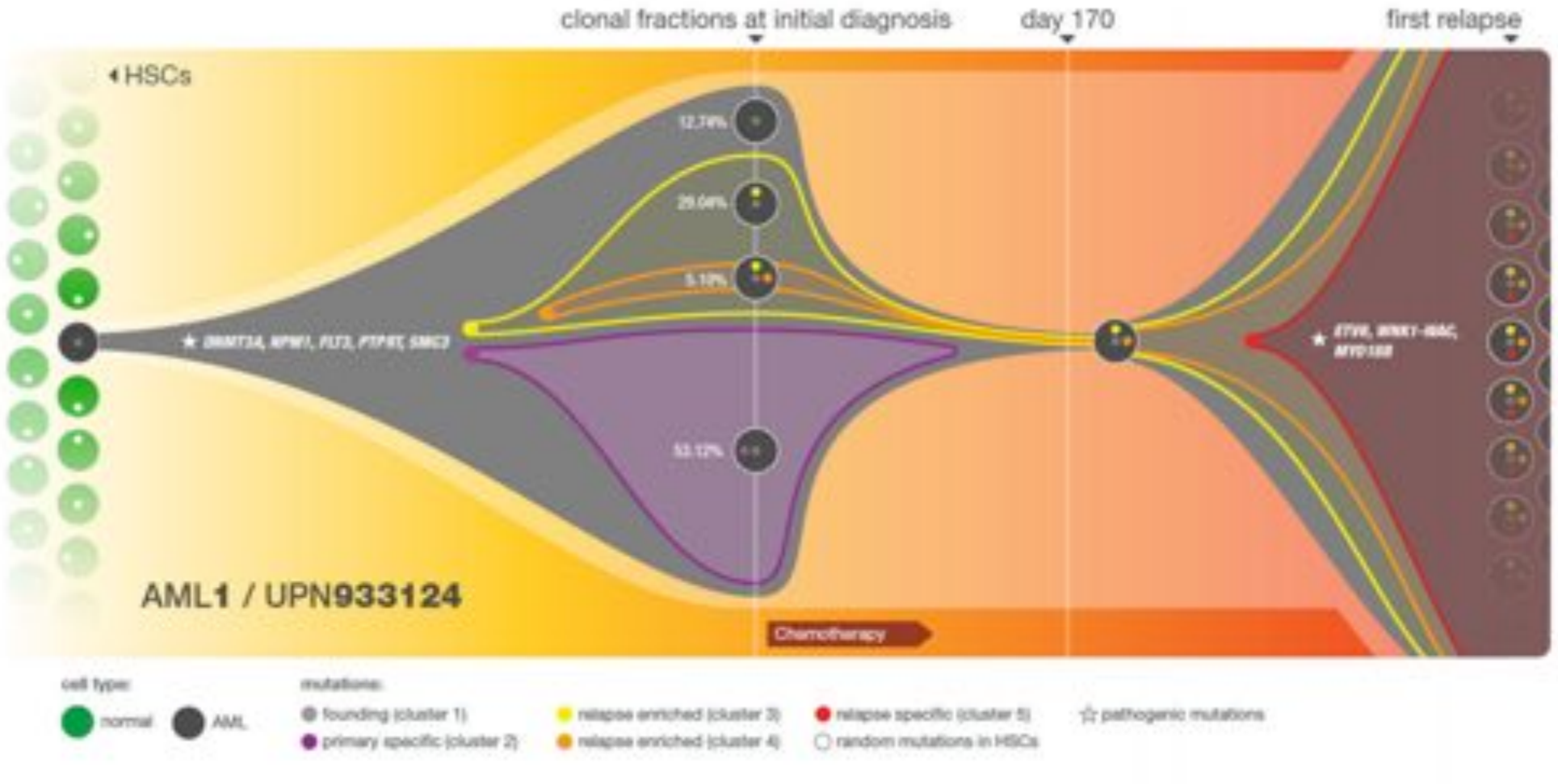


Single Cell RNA-seq of Cancer



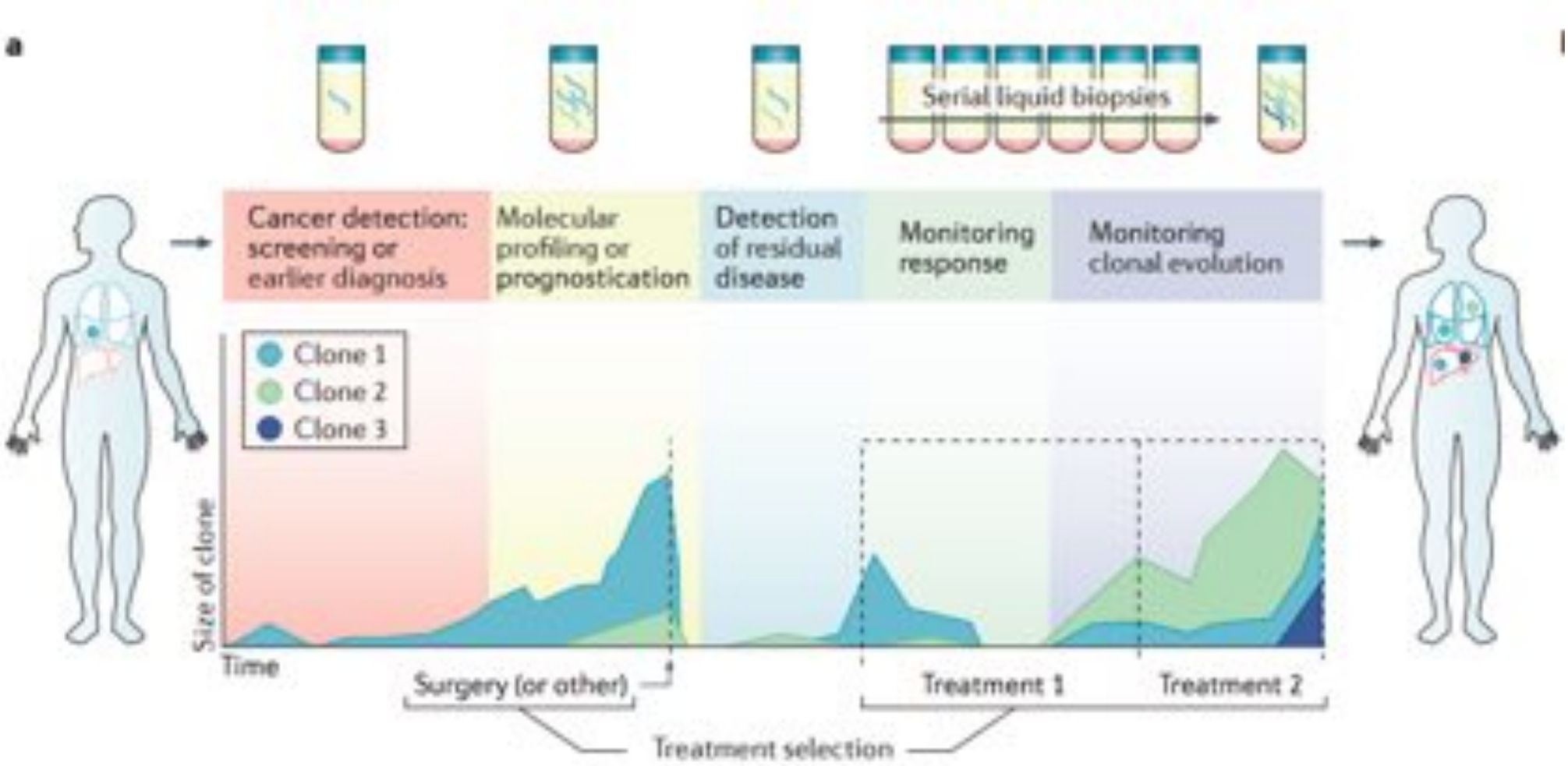
Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma
Tirosh et al (2016) Nature. doi:10.1038/nature20123

Tumor Heterogeneity and Treatment



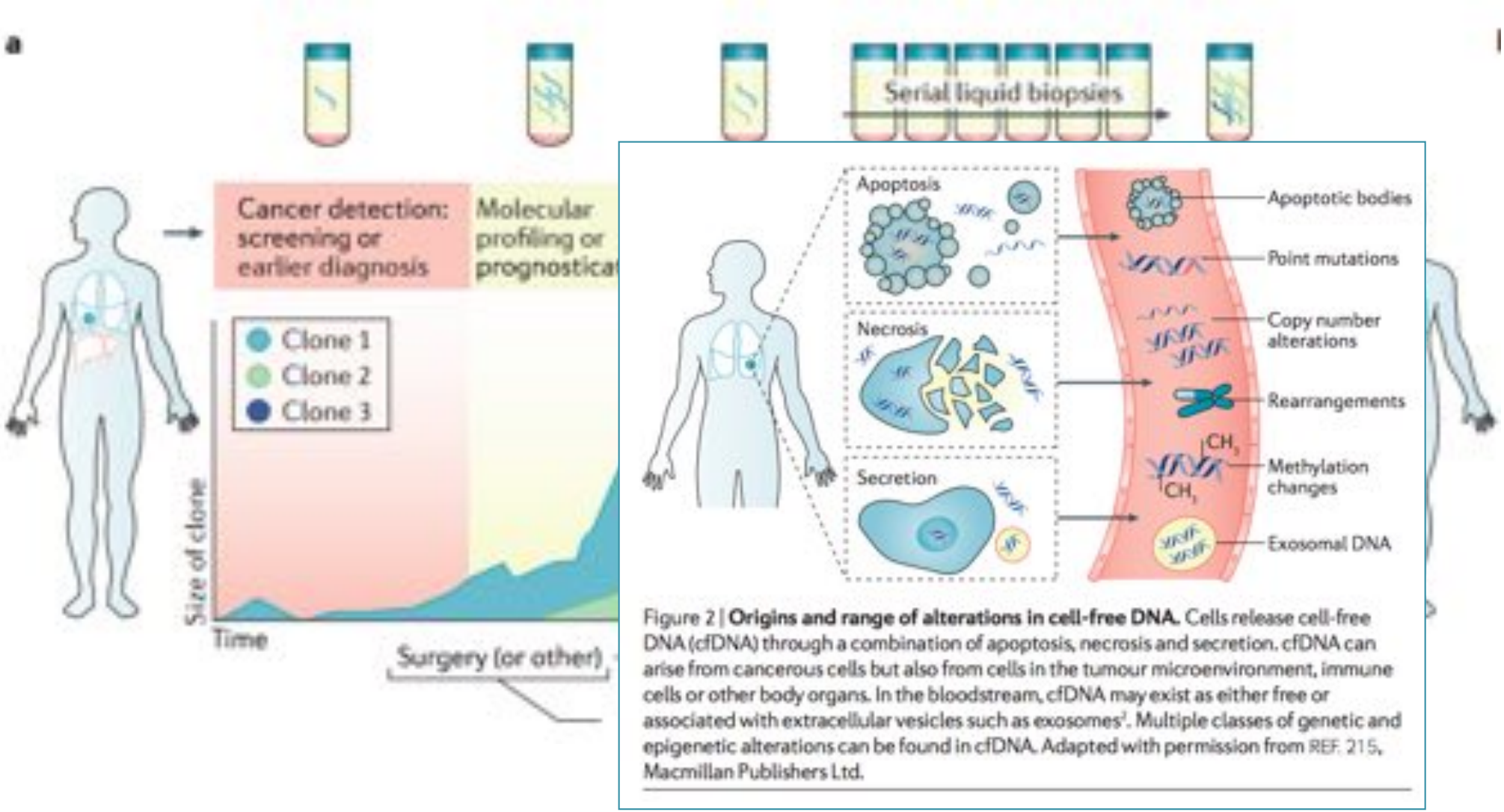
Clonal evolution in relapsed acute myeloid leukemia revealed by whole genome sequencing
Ding et al (2012) Nature. doi:10.1038/nature10738

Liquid Biopsies



Liquid biopsies come of age: towards implementation of circulating tumour DNA
Wan et al (2017) Nature Review Cancer. doi:10.1038/nrc.2017.7

Liquid Biopsies



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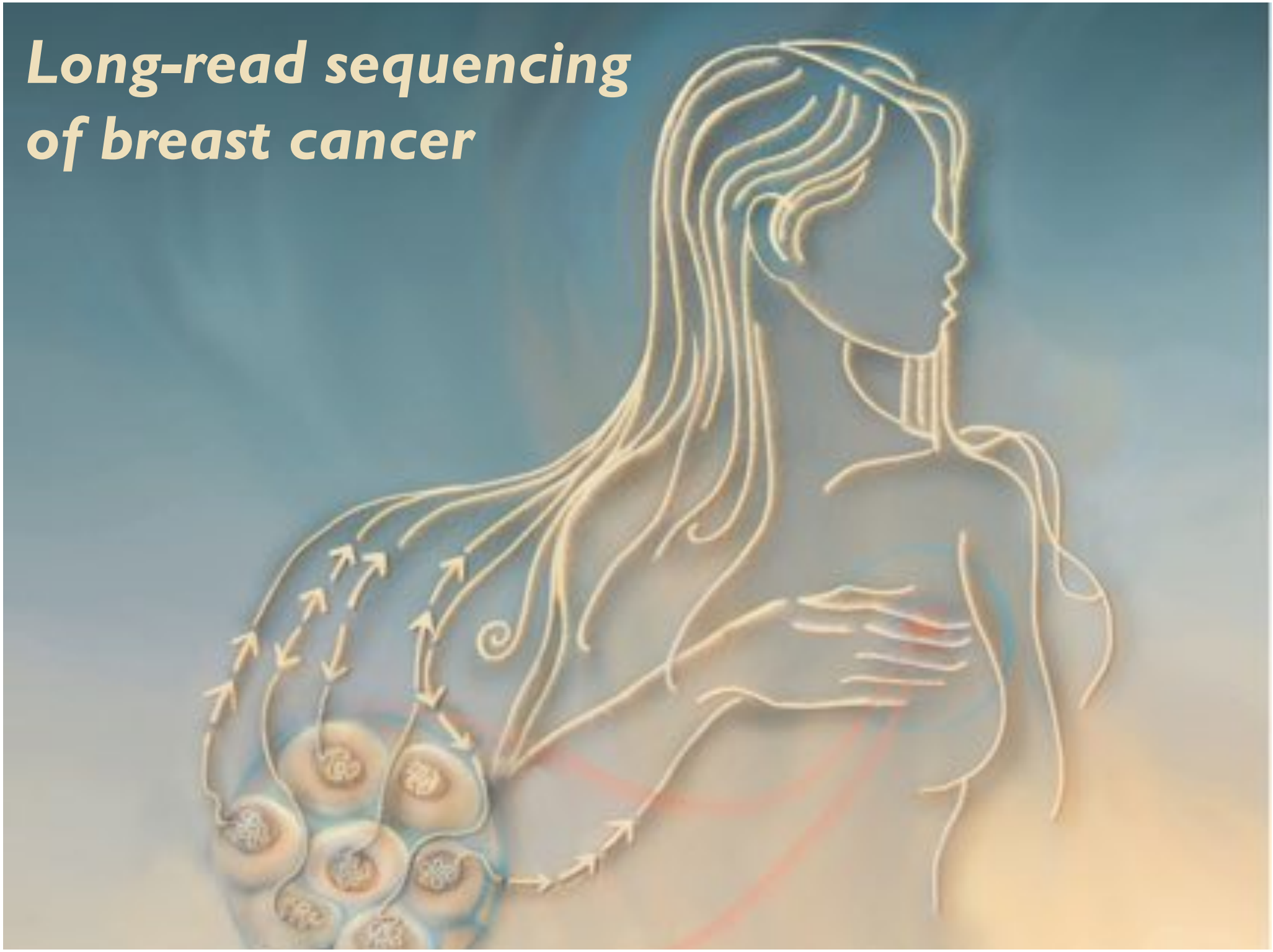
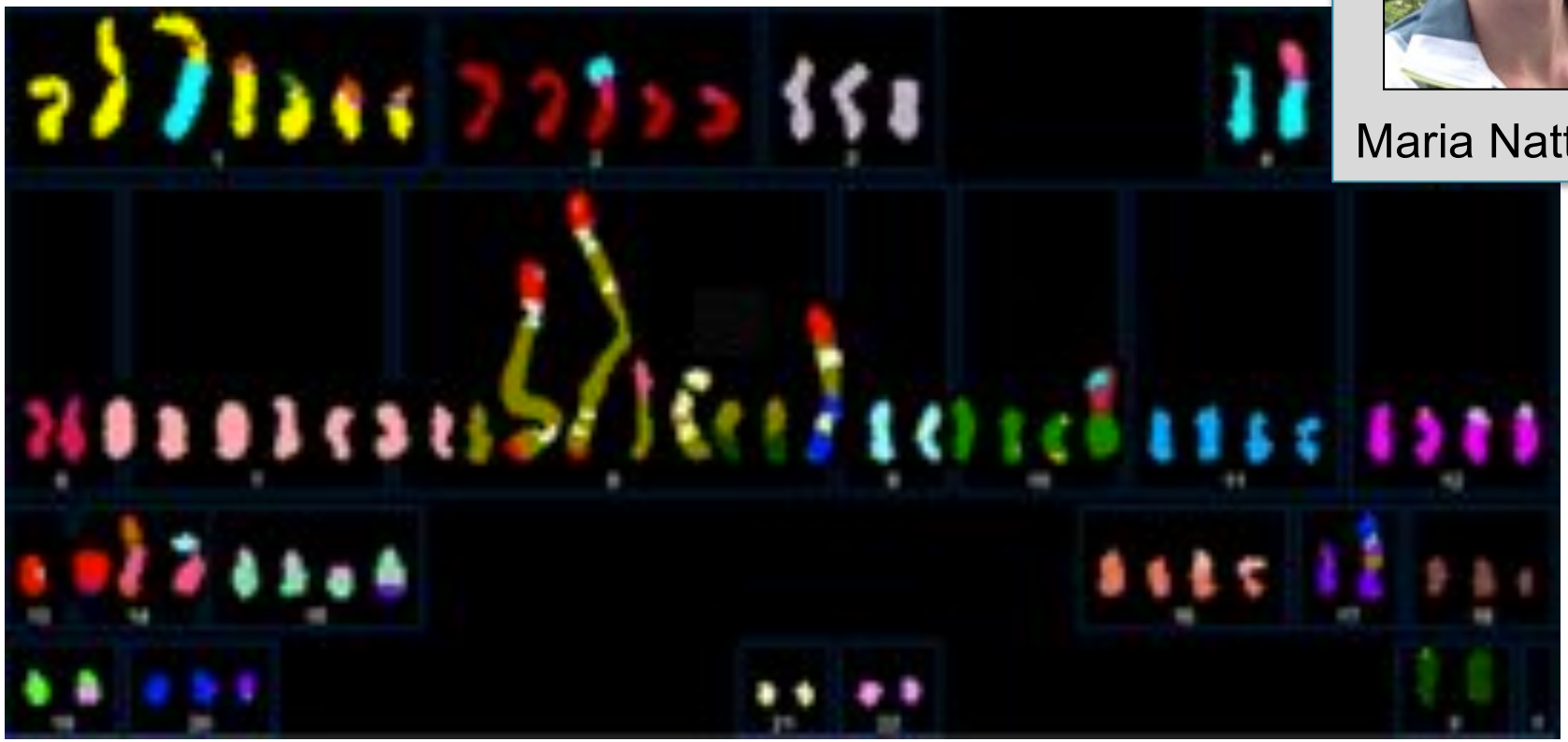
Long-read sequencing of breast cancer



SK-BR-3


Maria Nattestad

Most commonly used Her2-amplified breast cancer



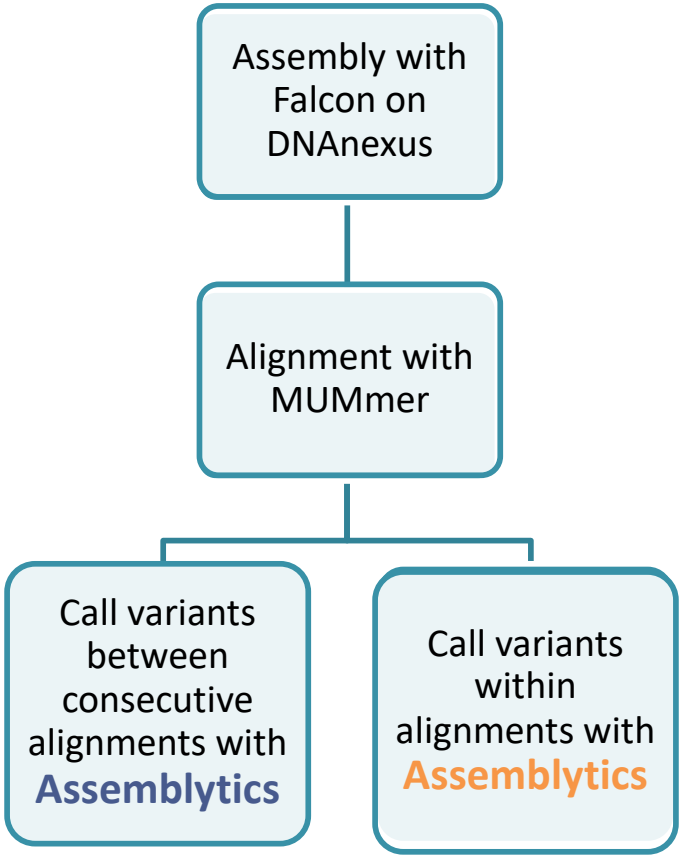
(Davidson et al, 2000)

Can we resolve the complex structural variations, especially around Her2?

Recent collaboration between JHU, CSHL and OICR to *de novo* assemble and analyze the complete cell line genome with PacBio long reads

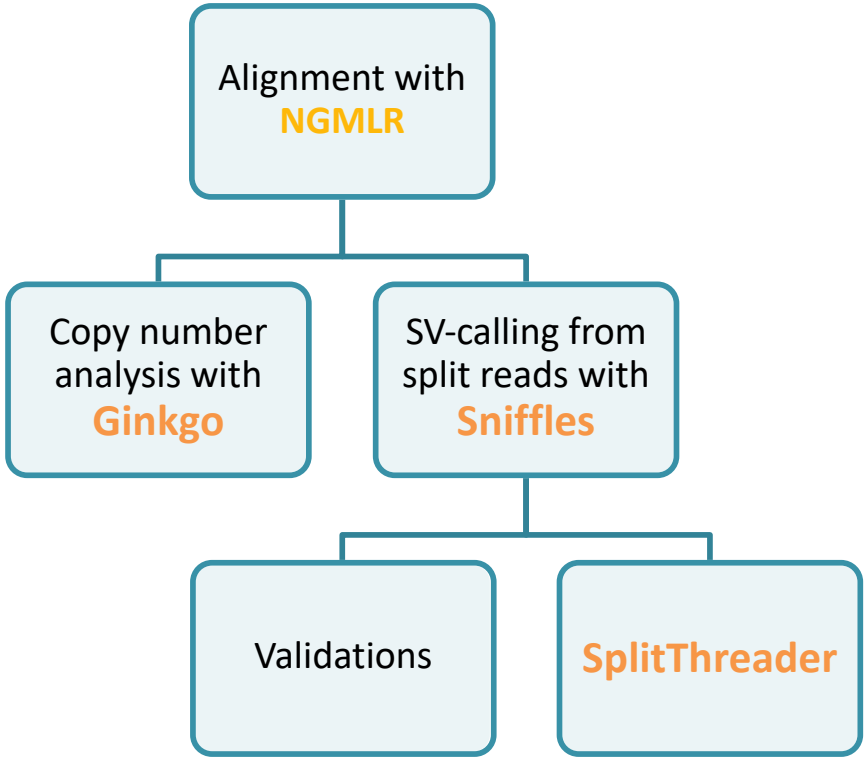
Structural Variation Analysis

Assembly-based



~ 11,000 structural variants
50 bp to 10 kbp

Split-Read based

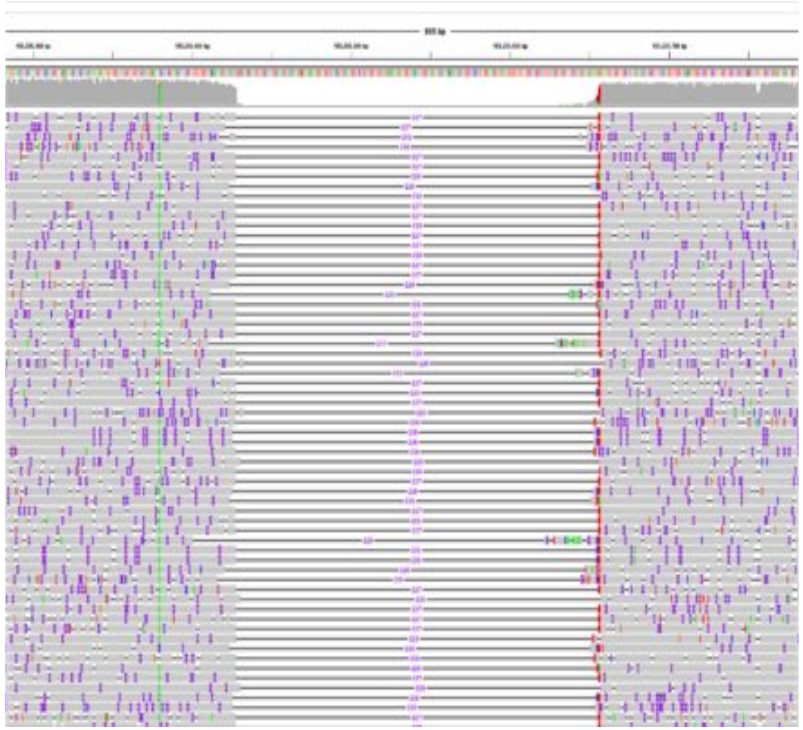


~ 20,000 structural variants
Including many inter-chromosomal rearrangements

NGMLR + Sniffles

BWA-MEM:

NGMLR:



NGMLR: Convex scoring model to accommodate many small gaps from sequencing errors along with less frequent but larger SVs

Accurate detection of complex structural variations using single molecule sequencing
Sedlazeck, Rescheneder et al (2018) *Nature Methods. doi:10.1038/s41592-018-0001-7*

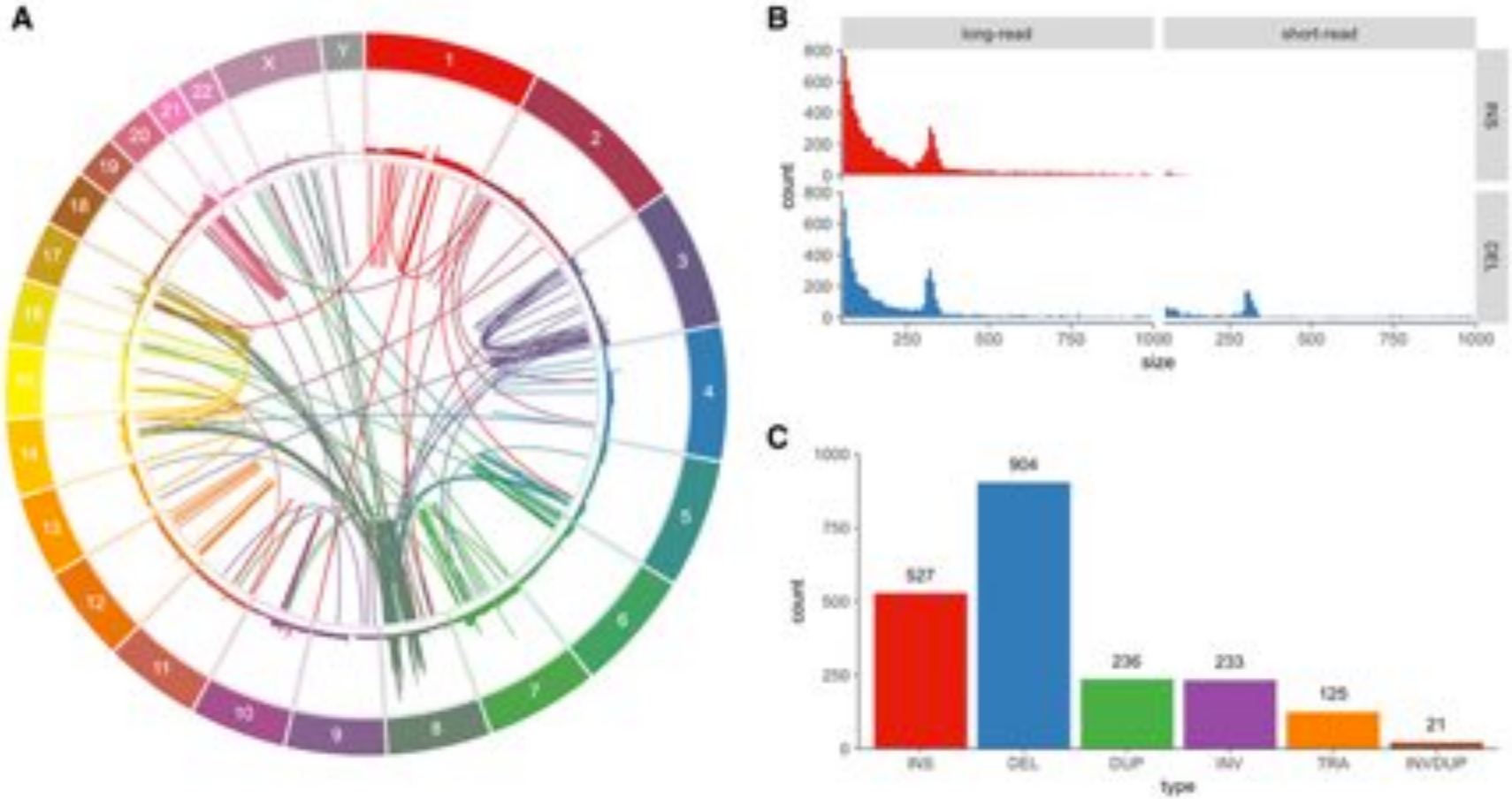


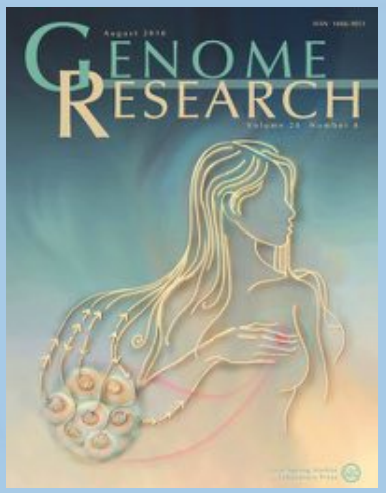
Figure 1. Variants found in SK-BR-3 with PacBio long-read sequencing. (*A*) Circos (Krzywinski et al. 2009) plot showing long-range (larger than 10 kbp or inter-chromosomal) variants found by Sniffles from split-read alignments, with read coverage shown in the *outer* track. (*B*) Variant size histogram of deletions and insertions from size 50 bp up to 1 kbp found by long-read (Sniffles) and short-read (SURVIVOR 2-caller consensus) variant calling, showing similar size distributions for insertions and deletions from long reads but not for short reads, where insertions are greatly underrepresented. (*C*) Sniffles variant counts by type for variants above 1 kbp in size, including translocations and inverted duplications.

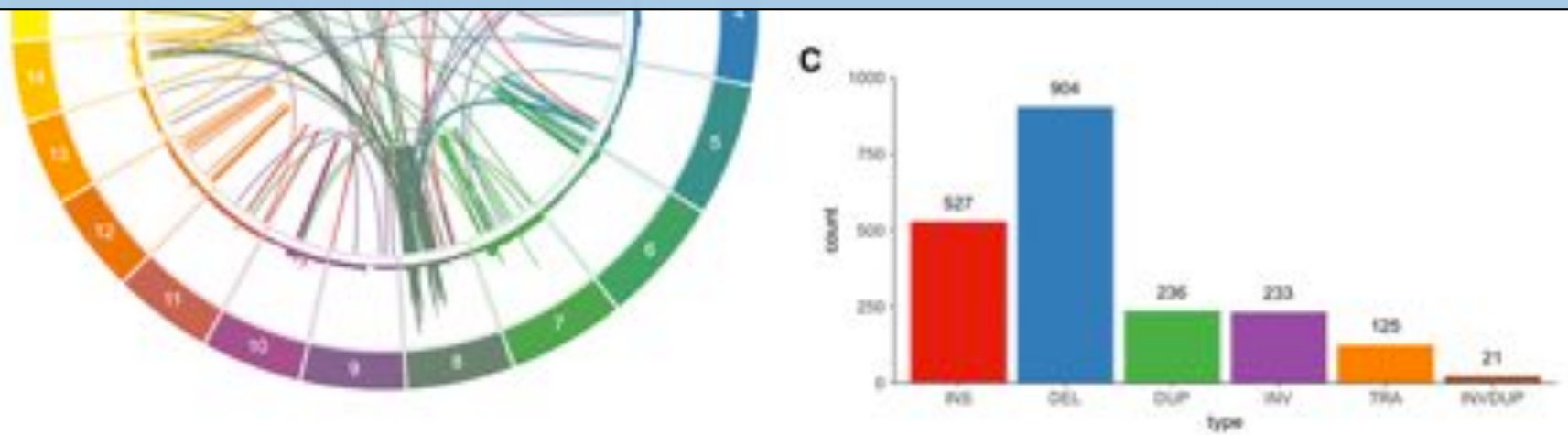
Complex rearrangements and oncogene amplifications revealed by long-read DNA and RNA sequencing of a breast cancer cell line

Nattestad et al. (2018) *Genome Research.* doi: 10.1101/gr.231100.117

Highlights

- Finding 10s of thousands of additional variants
- PCR validation confirms high accuracy of long reads
- Detect many novel gene fusions
- Identify early vs late mutations in the cancer





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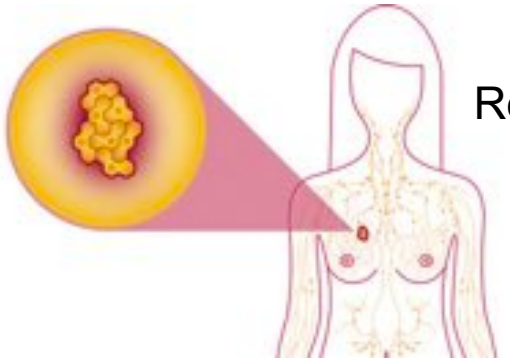
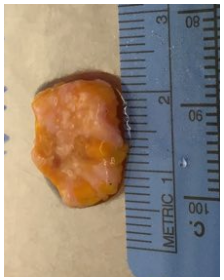
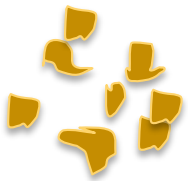
Taking Nanopore Sequencing into the Clinic



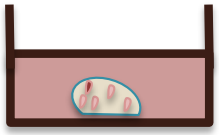
Resected primary tumor



Mechanical/ enzymatic



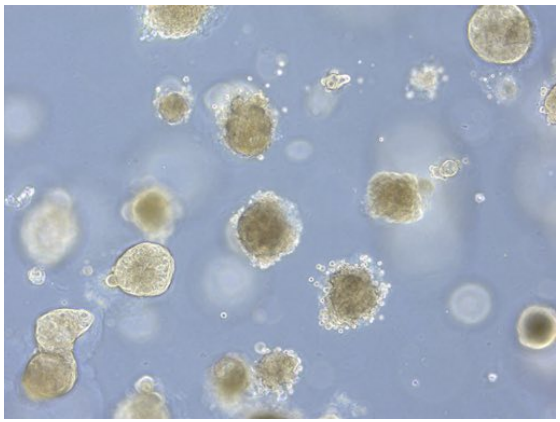
Purification



Plating on Matrigel

Add growth factors

Tumor organoids in culture



- ✓ Stable Growth in 3D
- ✓ Recapitulate tumor pathology & treatment response
- ✓ Maintenance of tissue/tumor heterogeneity
- ✓ "2017 Method of the Year" - Nature Methods

CSH

David Spector

Northwell Health

Karen Kostroff

Preliminary Structural Variations Analysis

	Total	Deletions	Duplications	Insertions	Inversions	Translocations
All SVs in normal	9816	5225	578	3727	130	156
All SVs in tumor	13737	7020	988	5292	202	235
SVs only in tumor (Also exclude NA12878)	3662	1805	420	1250	98	89

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engadget

Latest in Tomorrow

Genesis unveils Mint concept EV for urban fashionistas

CRISPR gene editing has been used on humans in the US

Twitter says new tools automatically flag 38 percent of abusive tweets

NASA's TESS spacecraft finds its first Earth-sized exoplanet

CRISPR gene editing has been used on humans in the US

It's part of a trial that could rethink medicine.

38 246

The first human trials in the US for CRISPR gene editing are officially underway. A University of Pennsylvania in Philadelphia spokesman has confirmed to NPR that two cancer patients, one with myeloma and one with sarcoma, have received CRISPR treatments after standard treatment didn't hold. The trial removes, modifies and reinserts immune cells in hopes they'll destroy cancerous cells.