BIMM 194

Genomics & Cancer Treatment

Lecture 2

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UC San Diego

http://thegrantlab.org/bimm194

Today's Menu

Cancer Fundamentals	What is cancer and what causes it?
Cancer Genomics	How do we identify genomic changes in cancer and new targets for therapy.
Targeted Therapy & Monitoring	How are genomic approaches influencing cancer detection, monitoring & treatment?
Cancer Immunotherapy	How can genomics be used to harness the patient's own immune system to fight cancer?

What is Cancer?

“Cancer is a name given to a collection of related diseases, where some of the body’s cells begin to divide without stopping and spread into surrounding tissue”

Source: https://www.cancer.gov

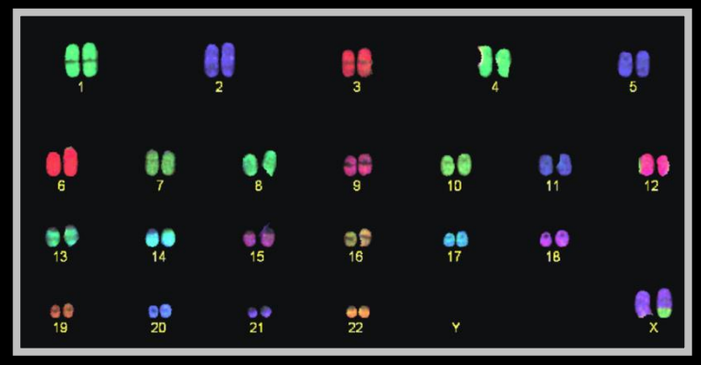
NIH-NCI

Cancer is a disease of the Genome

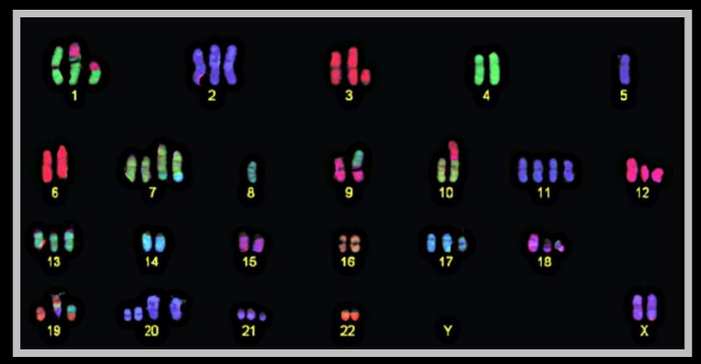
- Caused by changes to genes that control the way our cells function, especially how they **grow and divide**.

- A major challenge in treating cancer is that every tumor is different: Each person's cancer has a unique combination of genetic changes (both "driver" & "passenger").

- As the cancer continues to grow, additional changes will occur.



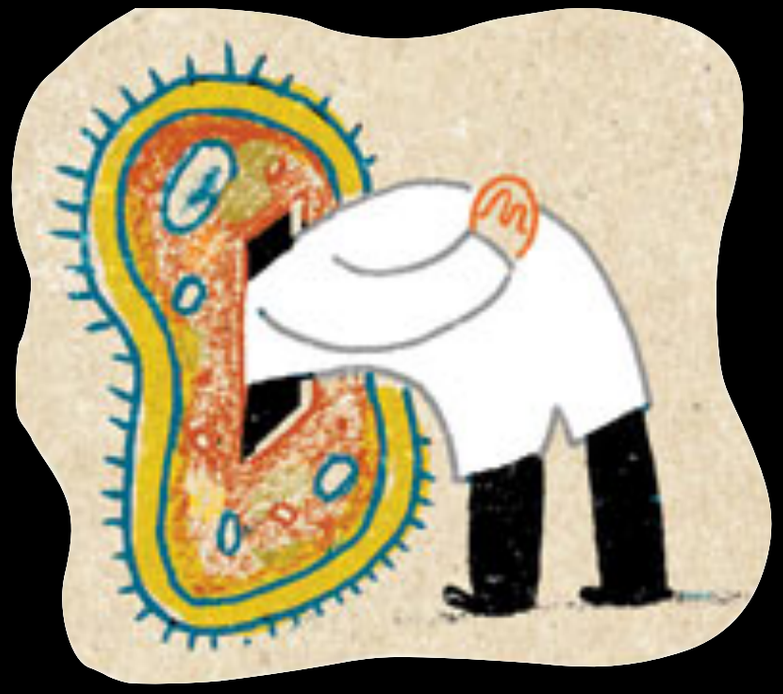
Healthy 46 chromosomes



Example cancer 59 chromosomes

Goals of Cancer Genome Research

- Identify changes in the genomes of tumors that drive cancer progression
- Identify new targets for therapy
- Select drugs based on the genomics of the tumor
- Provide early cancer detection and treatment response monitoring
- Utilize cancer specific mutations to derive neoantigen immunotherapy approaches



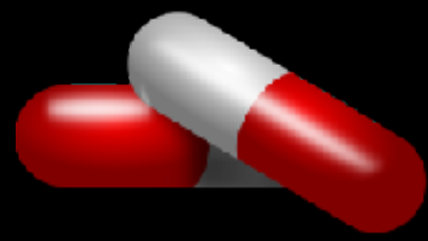
Finding Cancer Drivers

Motivation for adopting a genomics approach…

- Cancer is caused by mutations to specific genes

A G C T ⟶ A G **A** T

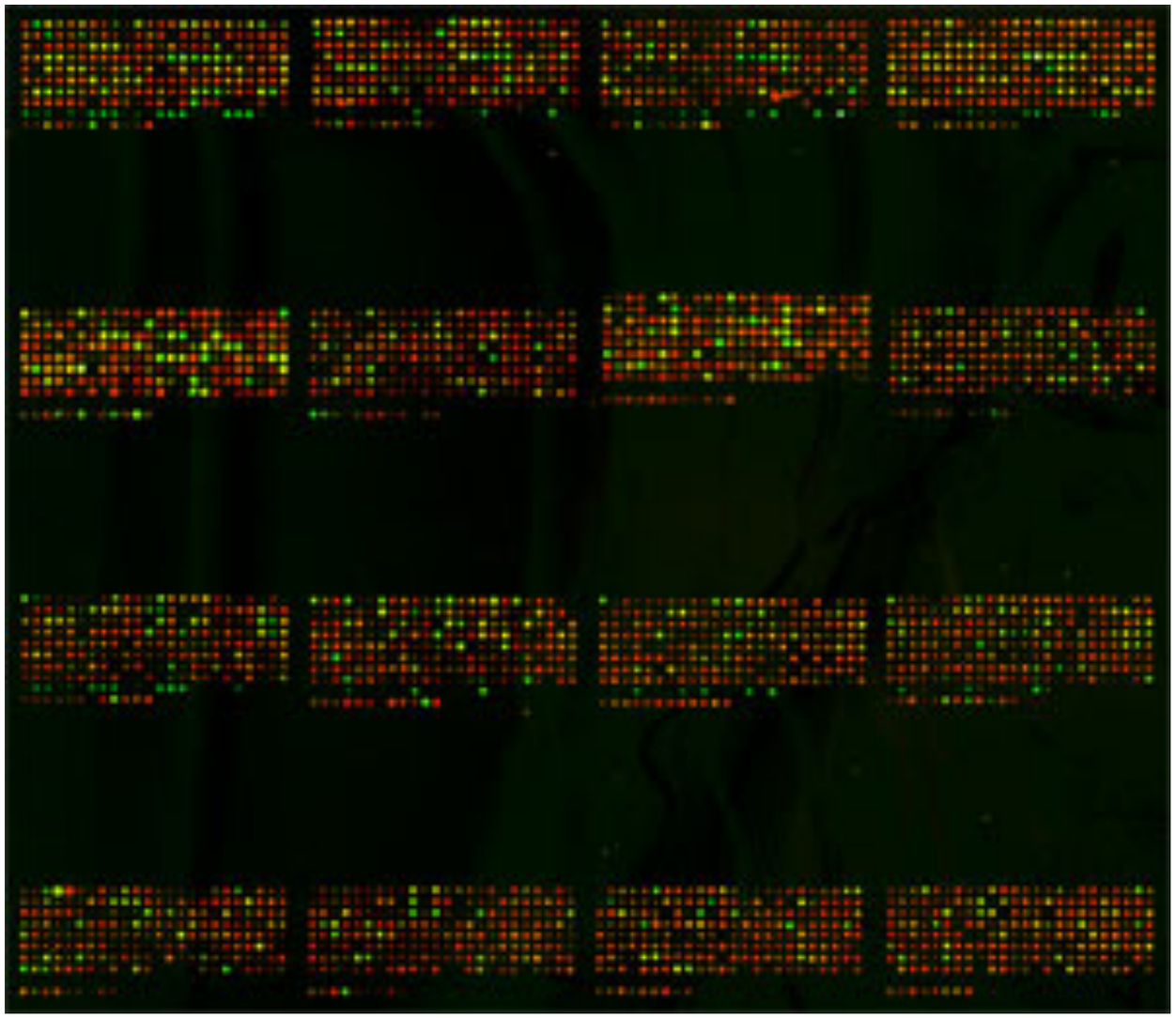
- Knowing which genes and proteins enables the development of **targeted treatments**



- 1st major Goal:
  Define ALL cancer genes!

Use A Cancer Genomics Approach

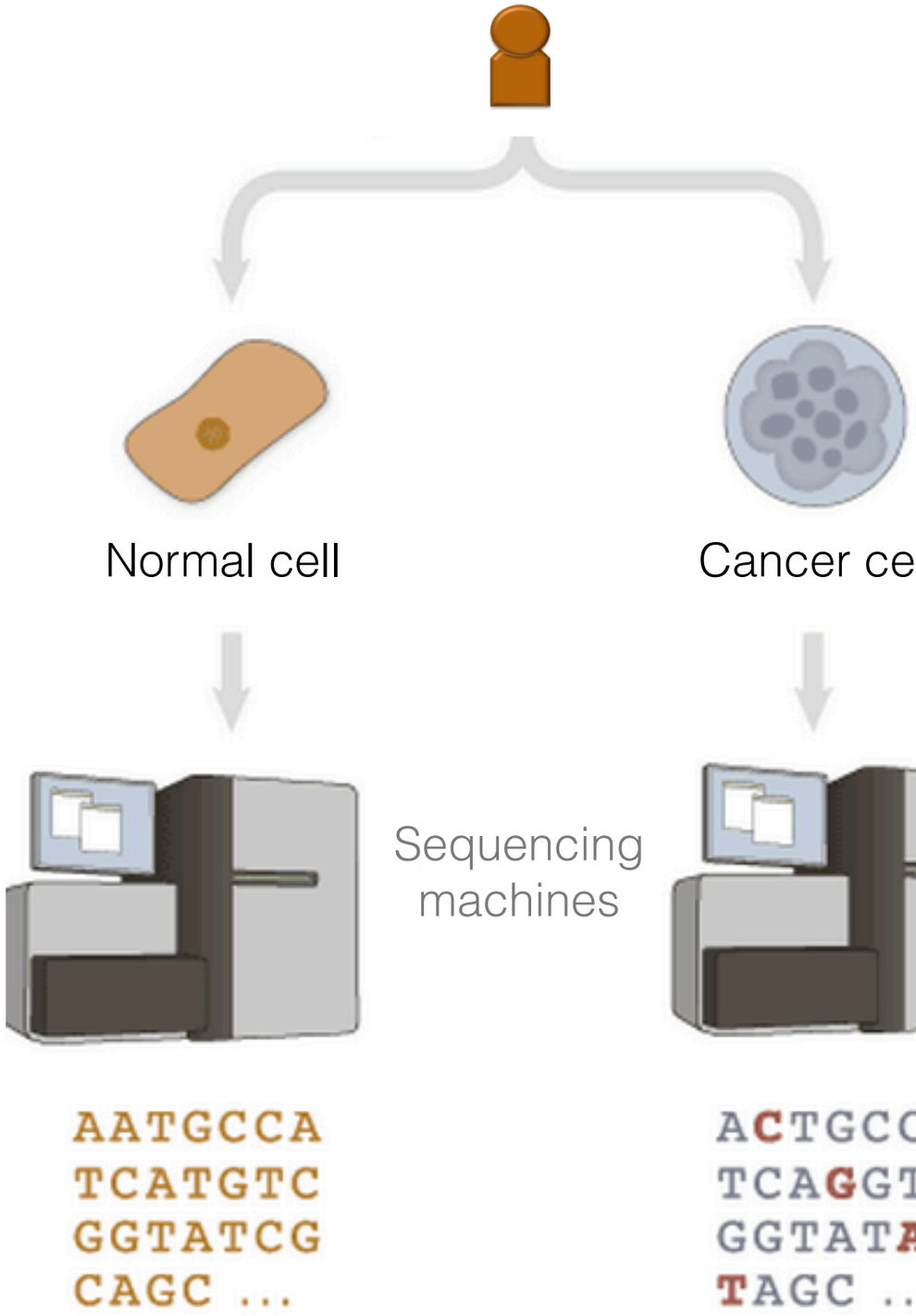
Arrays



Parallel Sequencing

ACTCAGCCCCAGCGGAGGTGAAGGACGTCCTTCCCCAGGAGCCGGTGAGA
AGCGCAGTCGGGGGCACGGGGATGAGCTCAGGGGCCTCTAGAAAGATGTA
GCTGGGACCTCGGGAAGCCCTGGCCTCCAGGTAGTCTCAGGAGAGCTACT
CAGGGTCGGGCTTGGGGAGAGGAGGAGCGGGGGTGAGGCCAGCAGCAGGG
GACTGGACCTGGGAAGGGCTGGGCAGCAGAGACGACCCGACCCGCTAGAA
GGTGGGGTGGGGAGAGCATGTGGACTAGGAGCTAAGCCACAGCAGGACCC
CCACGAGTTGTCACTGTCATTTATCGAGCACCTACTGGGTGTCCCCAGTG
TCCTCAGATCTCCATAACTGGGAAGCCAGGGGCAGCGACACGGTAGCTAG
CCGTCGATTGGAGAACTTTAAAATGAGGACTGAATTAGCTCATAAATGGA
AAACGGCGCTTAAATGTGAGGTTAGAGCTTAGAATGTGAAGGGAGAATGA
GGAATGCGAGACTGGGACTGAGATGGAACCGGCGGTGGGGAGGGGGAGGG
GGTGTGGAATTTGAACCCCGGGAGAGAAAGATGGAATTTTGGCTATGGAG
GCCGACCTGGGGATGGGGAAATAAGAGAAGACCAGGAGGGAGTTAAATAG
GGAATGGGTTGGGGGCGGCTTGGTAACTGTTTGTGCTGGGATTAGGCTGT
TGCAGATAATGGAGCAAGGCTTGGAAGGCTAACCTGGGGTGGGGCCGGGT
TGGGGTCGGGCTGGGGGCGGGAGGAGTCCTCACTGGCGGTTGATTGACAG
TTTCTCCTTCCCCAGACTGGCCAATCACAGGCAGGAAGATGAAGGTTCTG
TGGGCTGCCCCGACCCGCTAGAAGGTGGGGTGGGGAGAGCATGTGGACTA
GGAGCTAAGCCACAGCAGGACCCCCACGAGTTGTCACTGTCATTTATCGA
GCACCTACTGGGTGTCCCCAGTGTCCTCAGATCTCCATAACTGGGAAGCC
AGGGGCAGCGAC

Finding Cancer Associated Mutations



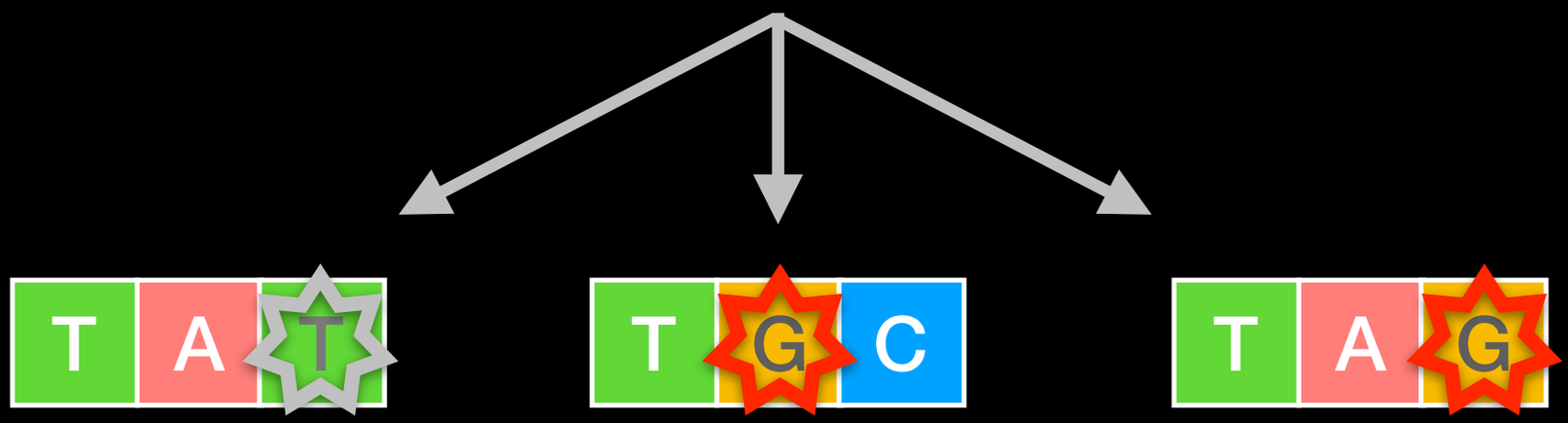
Identify all mutations specific to tumor cells

Filter out silent mutations

Mutations detected:

Point mutations

Original (Tyrosine)



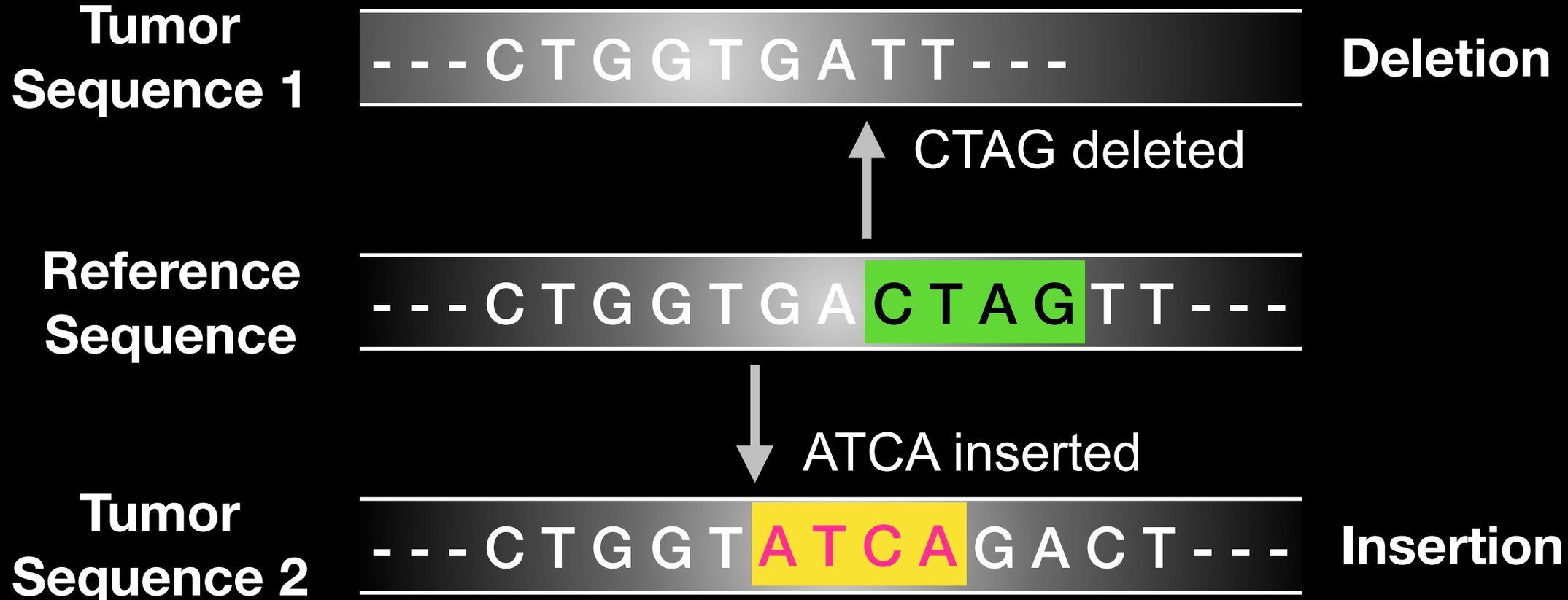
Silent
(Tyrosine)

Missense
(Cystine)

Nonsense
(STOP)

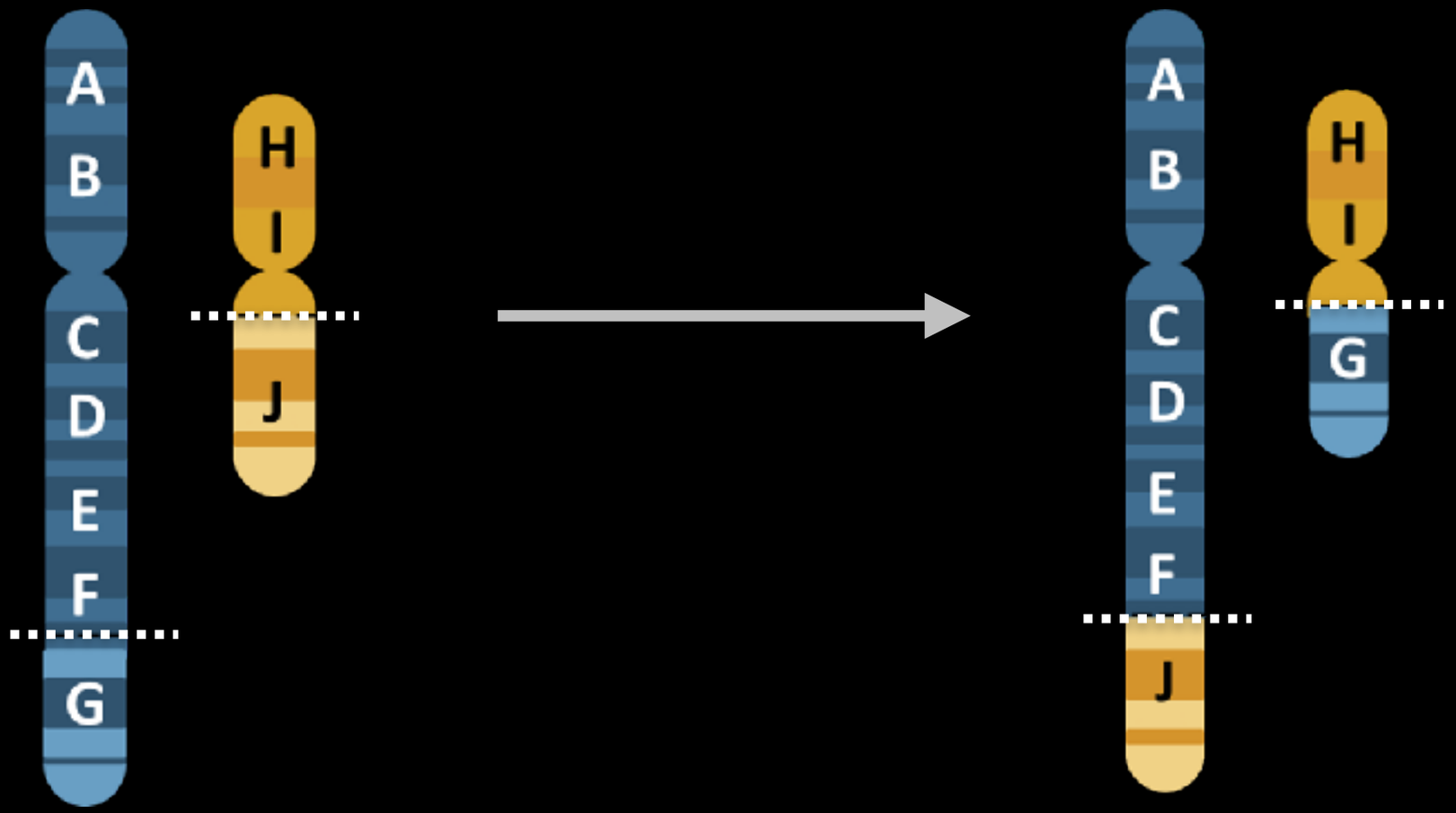
Mutations detected:

Indels



Mutations detected:

Translocations



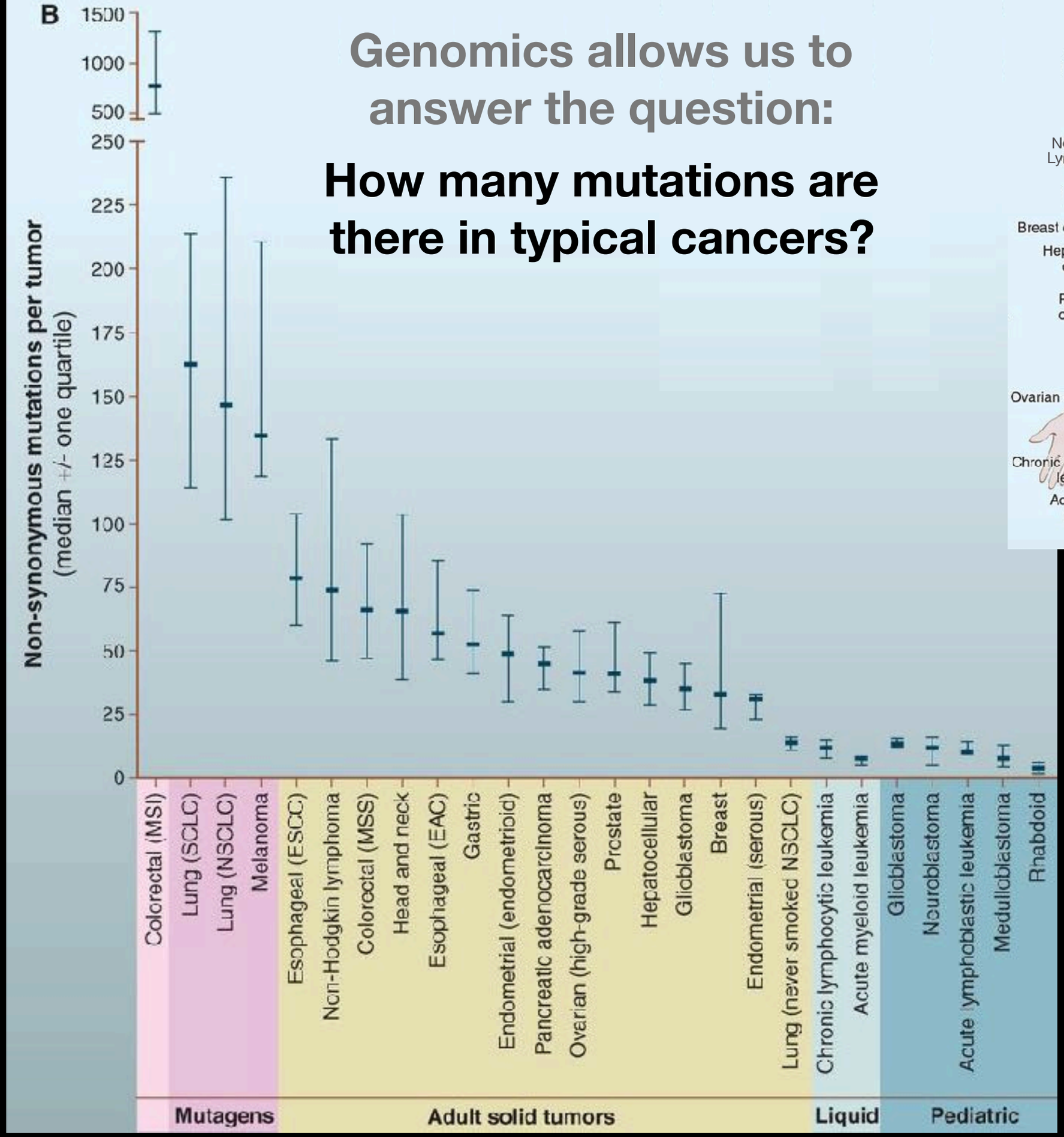
What can go wrong in cancer genomes?

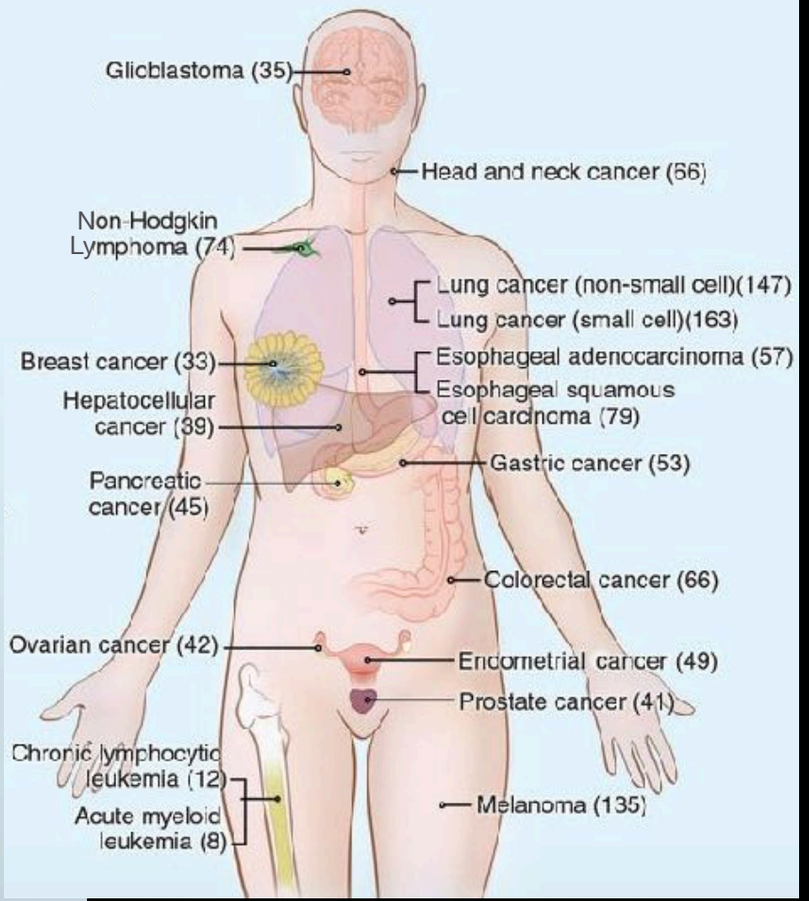
Type of change	Some common technology to study changes
DNA mutations	WGS, WXS
DNA structural variations	WGS
Copy number variation (CNV)	CGH array, SNP array, WGS
DNA methylation	Methylation array, RRBS, WGBS
mRNA expression changes	mRNA expression array, RNA-seq
miRNA expression changes	miRNA expression array, miRNA-seq
Protein expression	Protein arrays, mass spectrometry

WGS = whole genome sequencing, WXS = whole exome sequencing
RRBS = reduced representation bisulfite sequencing, WGBS = whole genome bisulfite sequencing

Genomics allows us to answer the question:

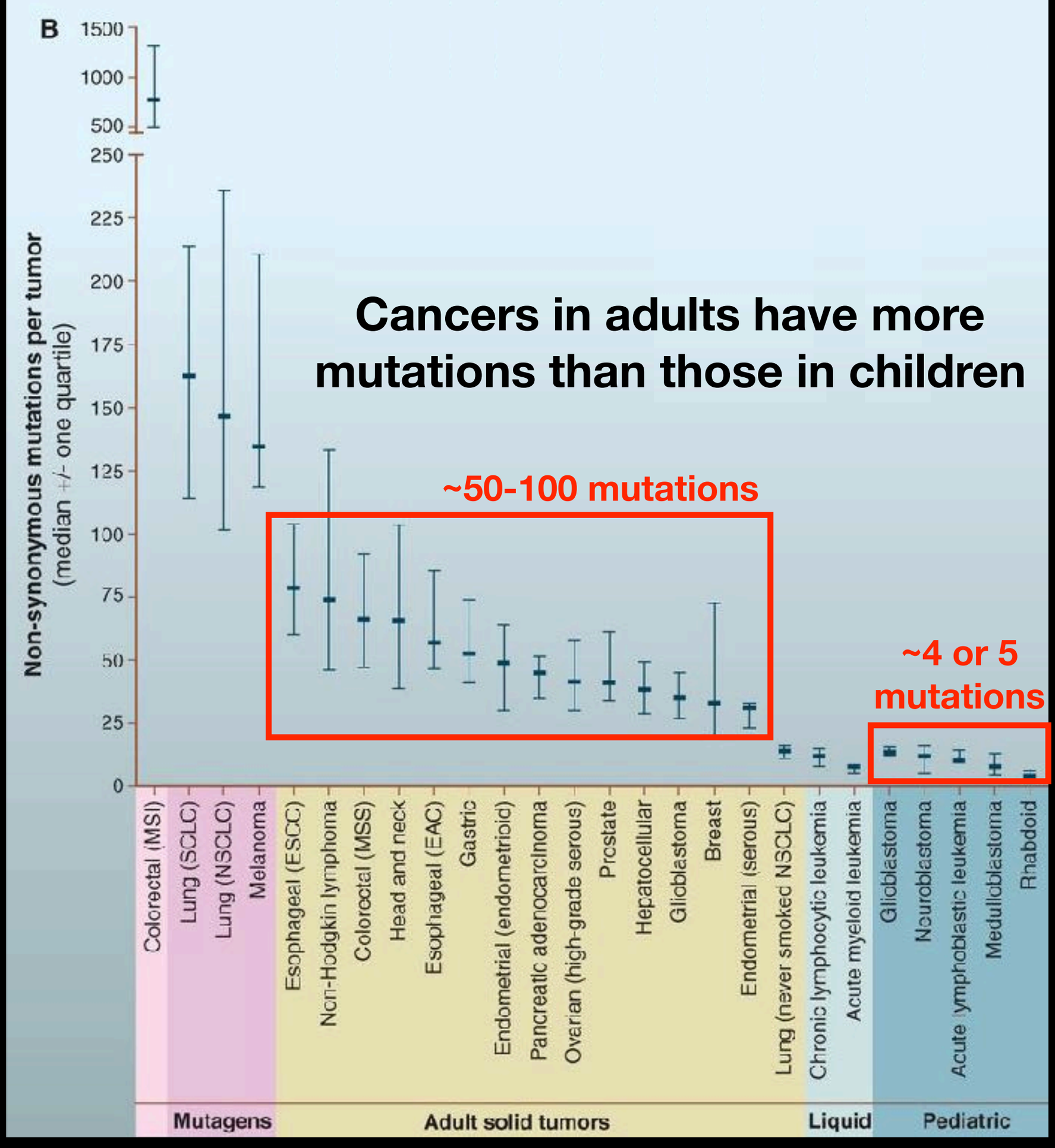
How many mutations are there in typical cancers?



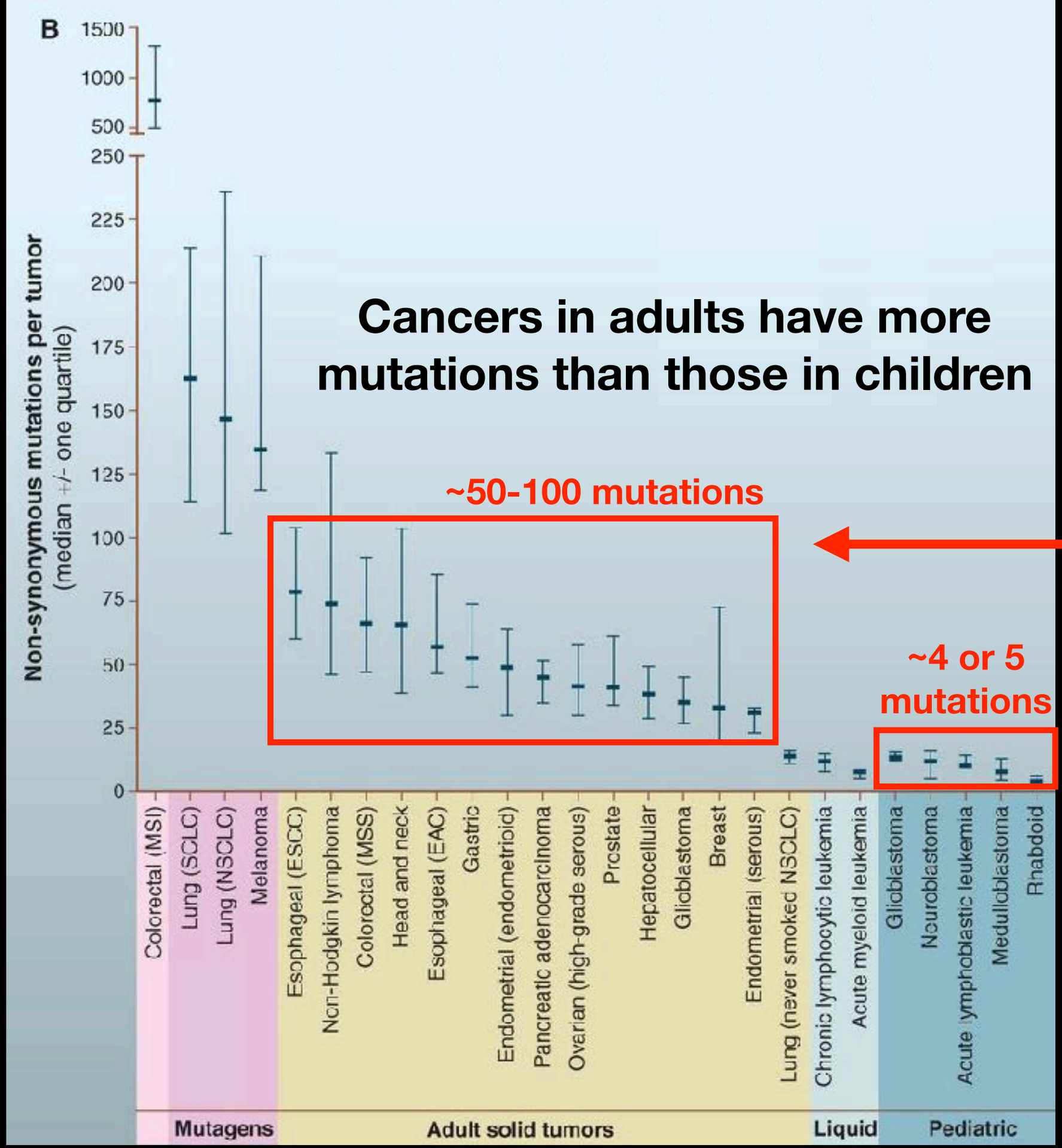


Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

Vogelstein et al. Science (2013)

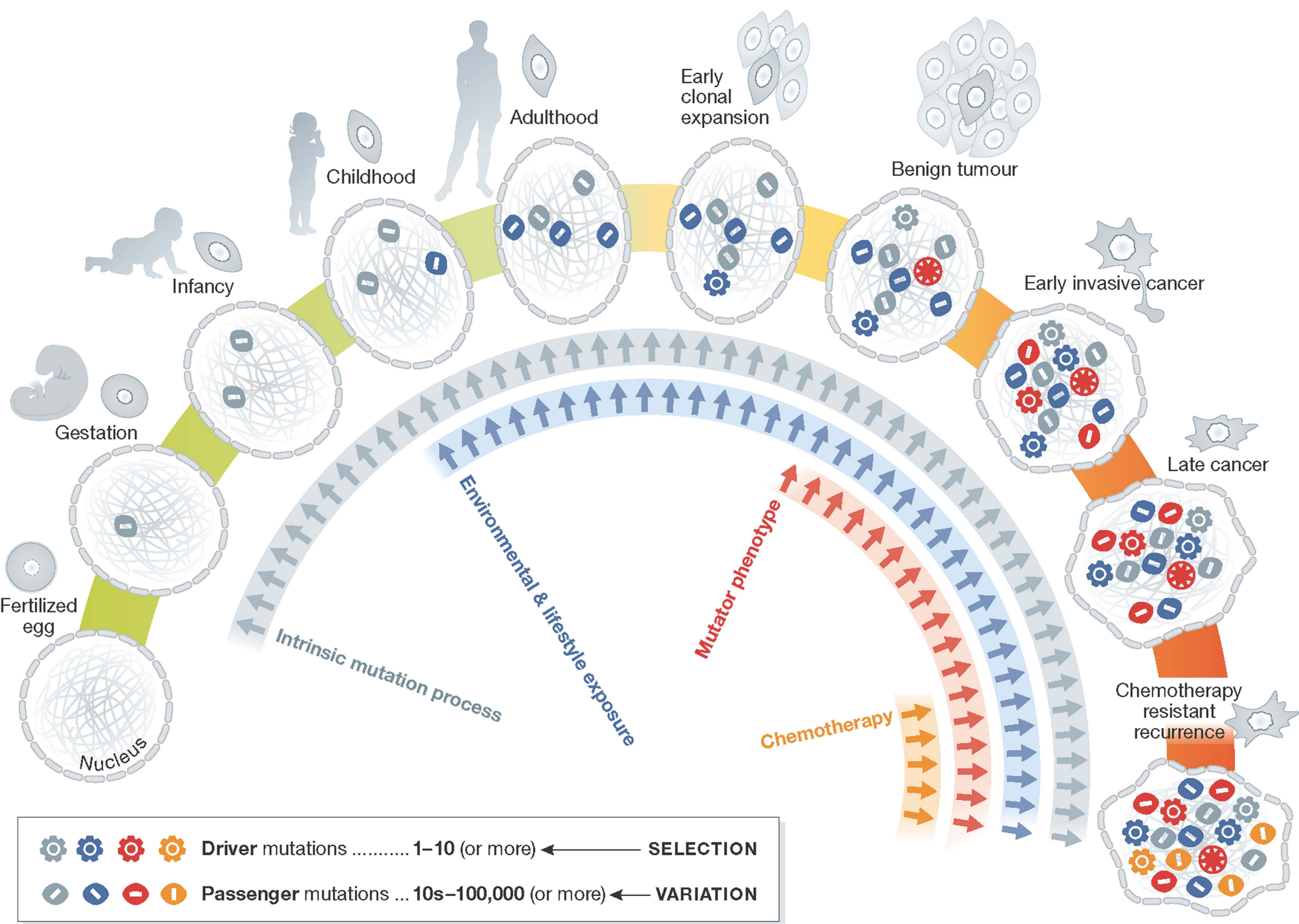


Vogelstein et al.
Science (2013)

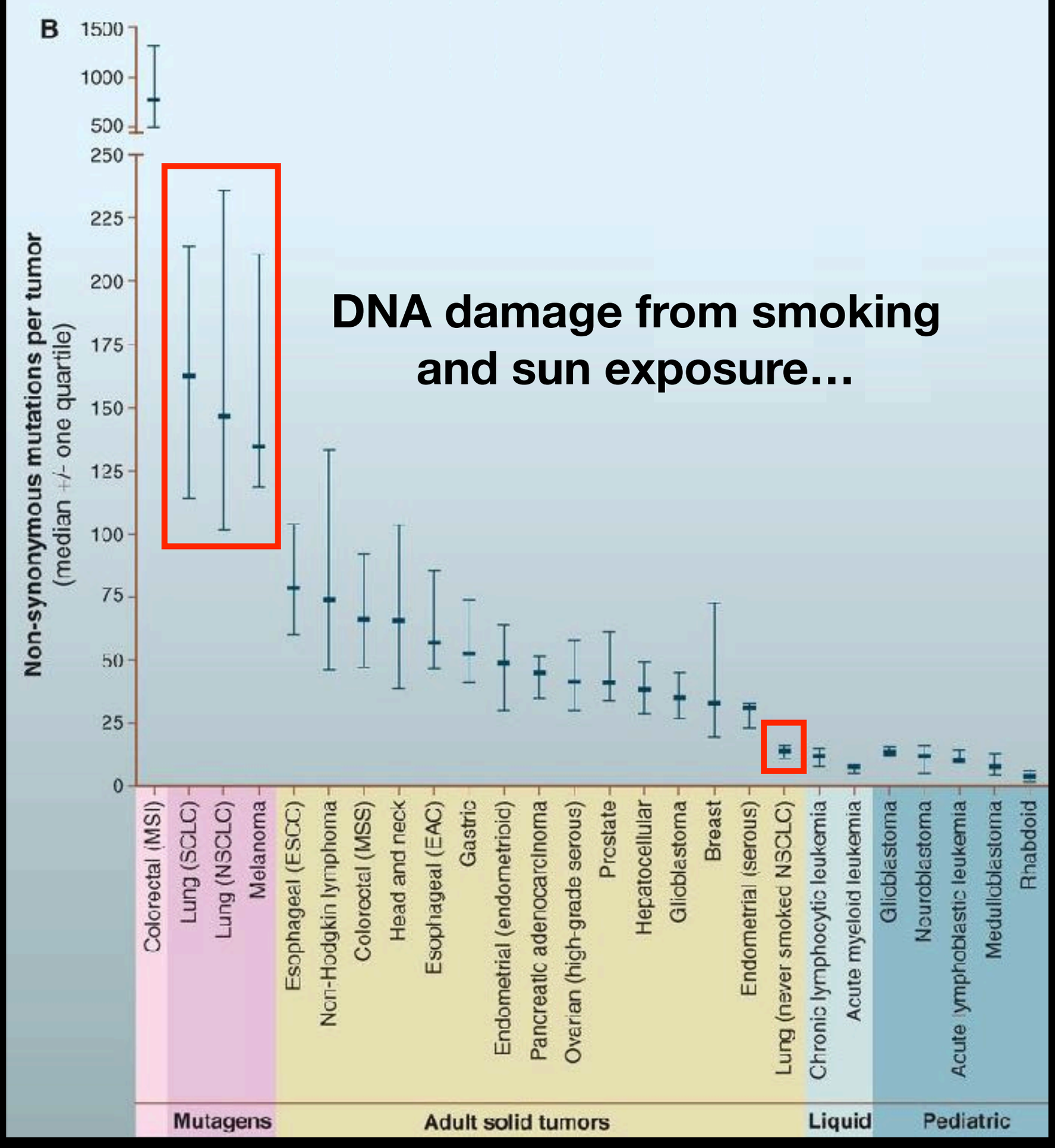


Most of these mutations are likely "passenger" mutations

Vogelstein et al. Science (2013)



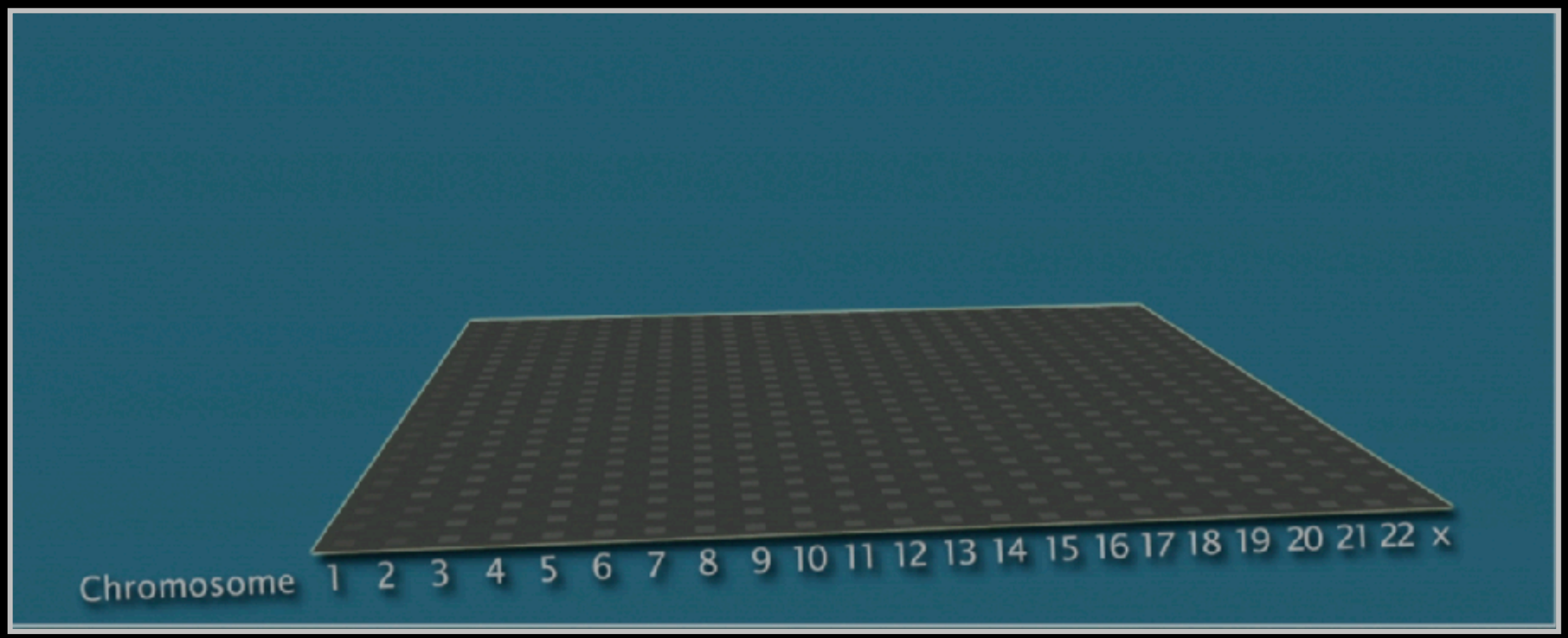
Mike Stratton. EMBO Molecular Medicine (2013)



DNA damage from smoking and sun exposure…

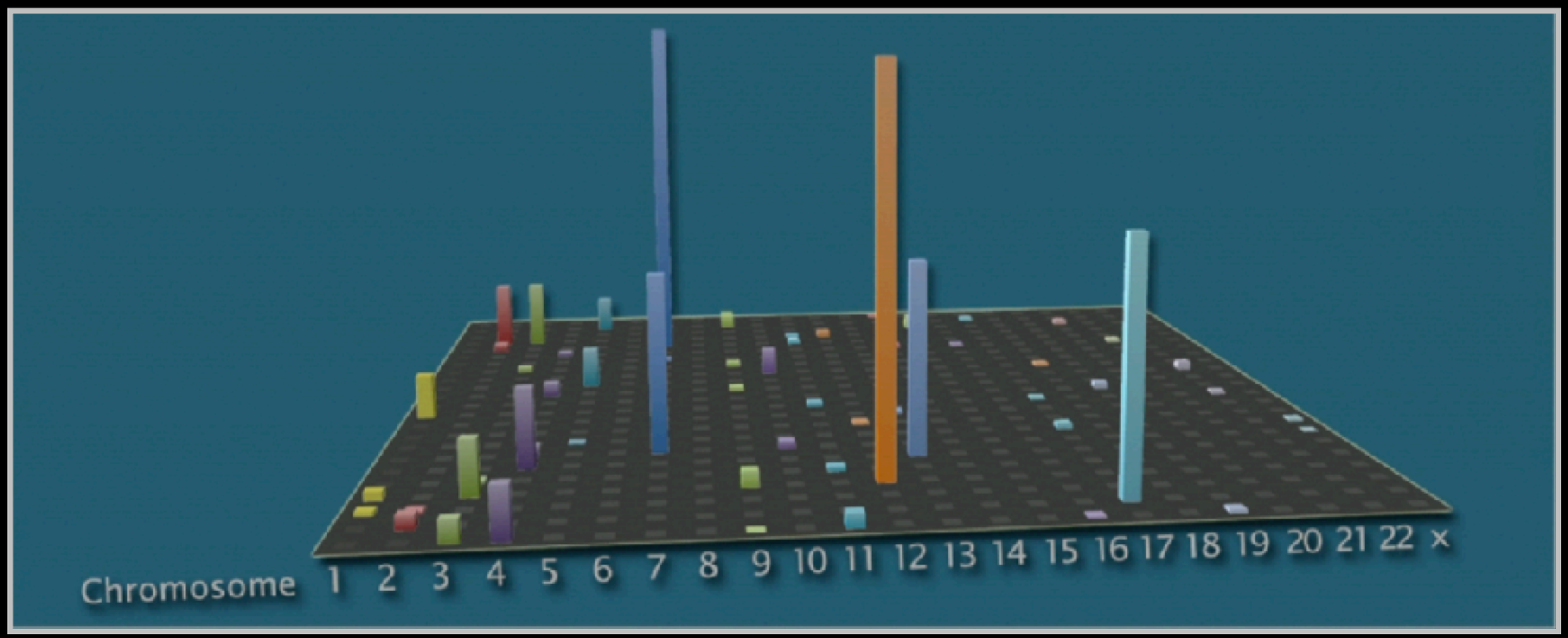
Vogelstein et al. Science (2013)

Genomic approaches can identify the genes most commonly mutated in cancer



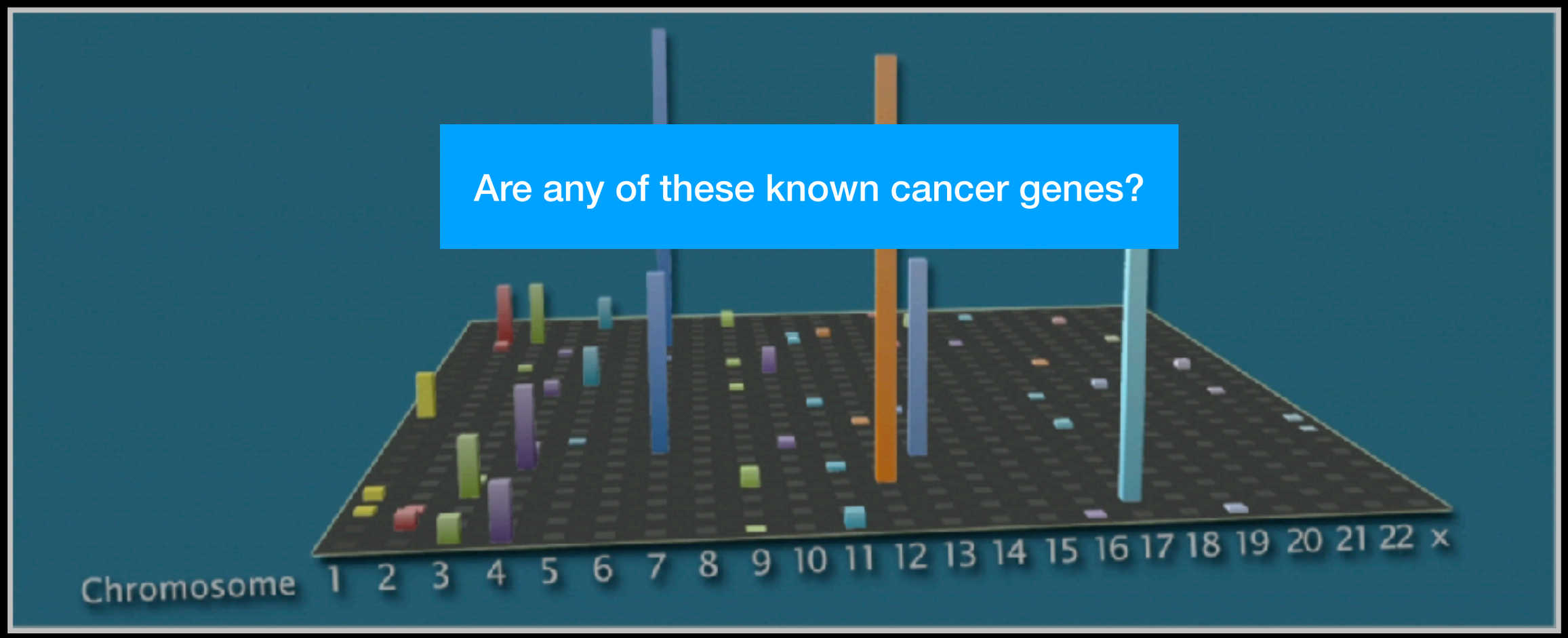
Arrange all genes in a matrix, ordered by chromosomes

Identifying genes most commonly mutated in cancer



Add all data together to see which genes are most often mutated

Identifying genes most commonly mutated in cancer



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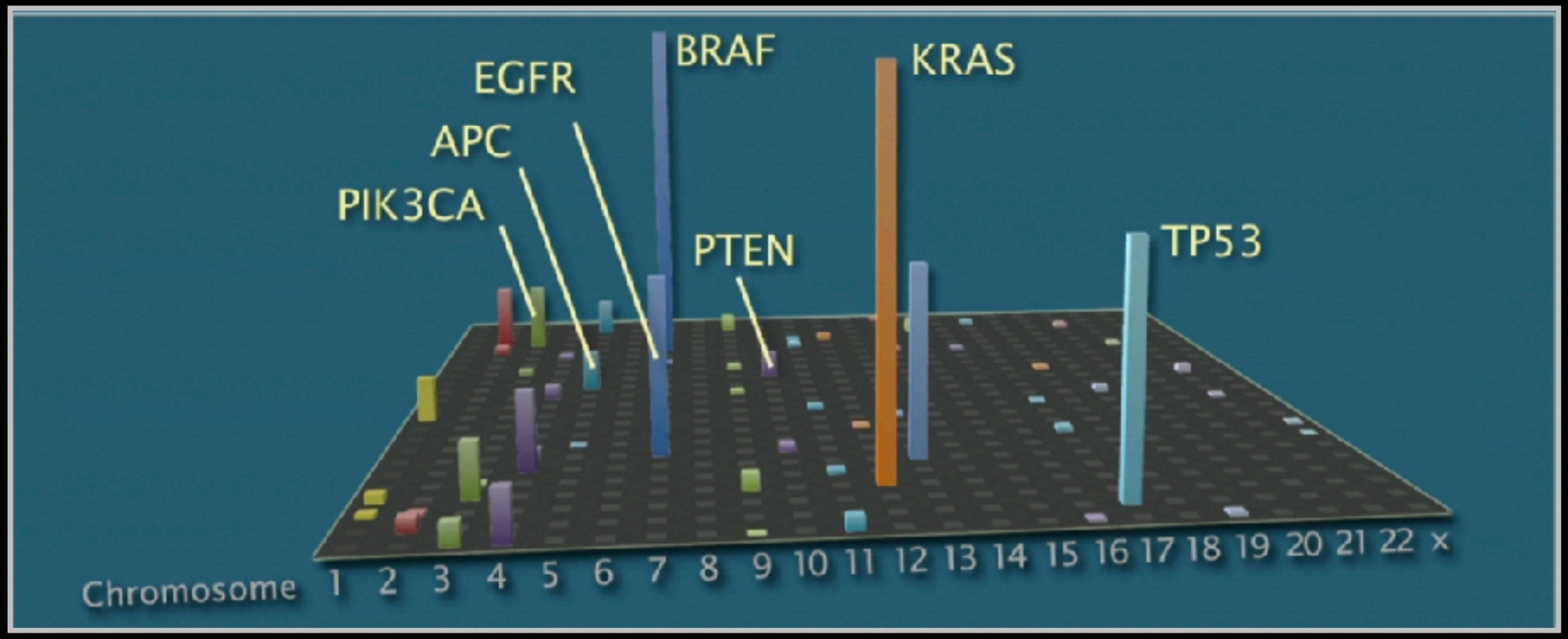
Identifying genes most commonly mutated in cancer



Many are famous porto-oncogenes, many others are new cancer genes!

Three Main Types of Cancer Genes:

- Oncogenes, such as **Ras**, normally function to accelerate cell division and growth. They can be mutated to act like stuck gas pedals.

- Tumor suppressor genes, such as **p53** normal act like breaks. Mutations can cause these breaks to fail.

- DNA repair genes, such as **BRCA1** & **2**, normally function to fix minor damage to DNA when it replicates. When these genes are mutated, DNA damage can accumulate and lead to cancer.

Functions of the 140 cancer genes

Current genomics approaches have identified ~140 cancer genes. Of which there are:

- ~60 Oncogenes (normally stimulate growth)
- ~80 Suppressor genes (normally inhibit growth)

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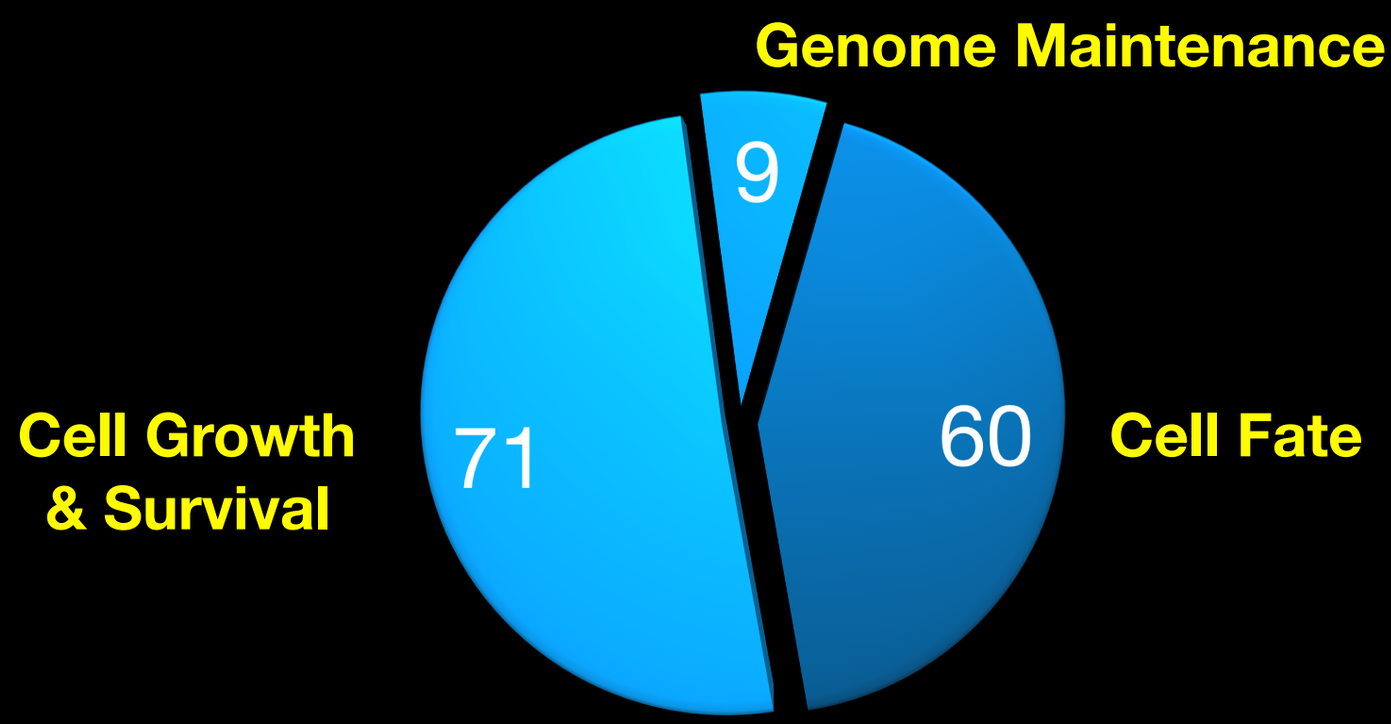
Three main categories



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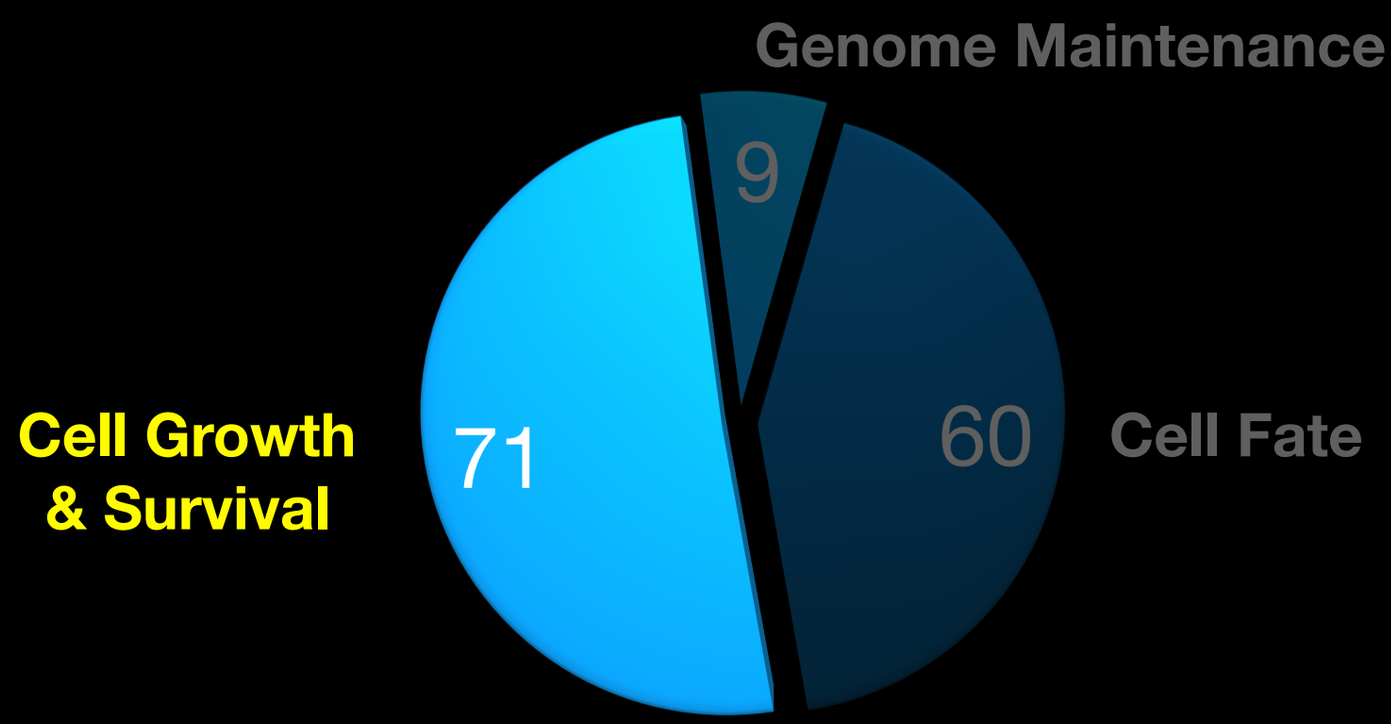
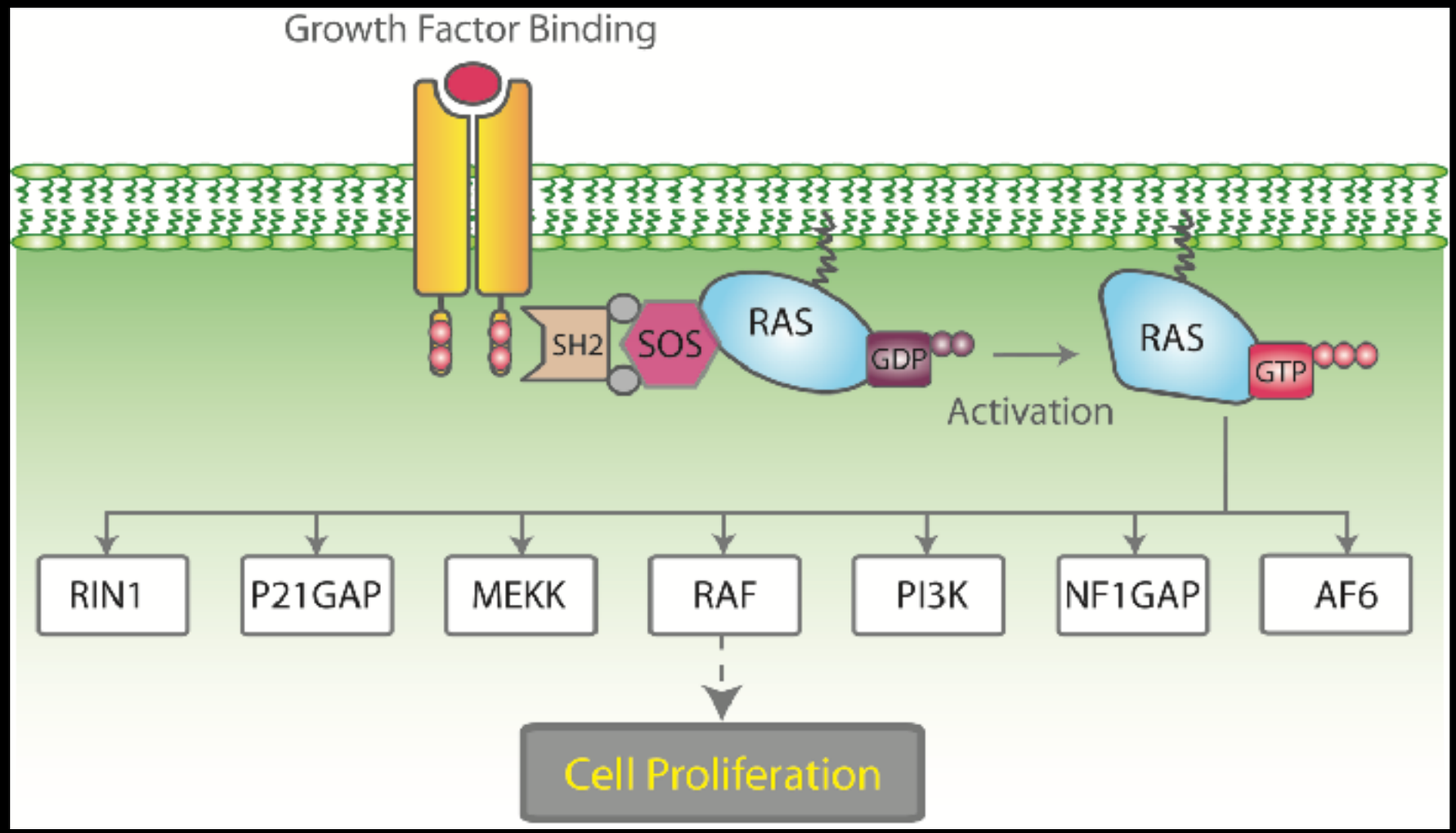


Cell growth and survival genes

Many participate in signaling pathways that promote cell proliferation (E.G. EGFR, Ras, BRAF, MEK etc.)



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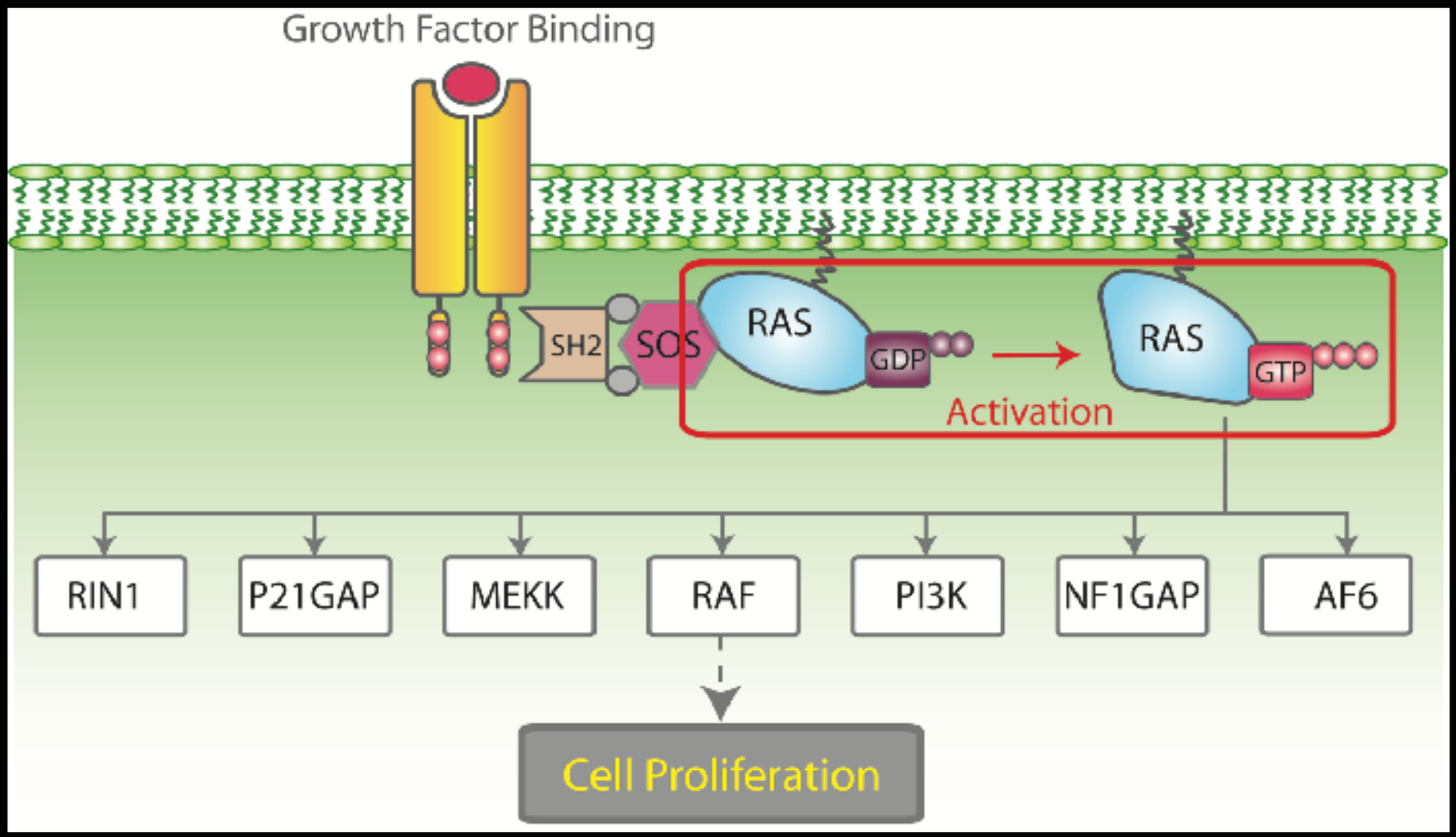
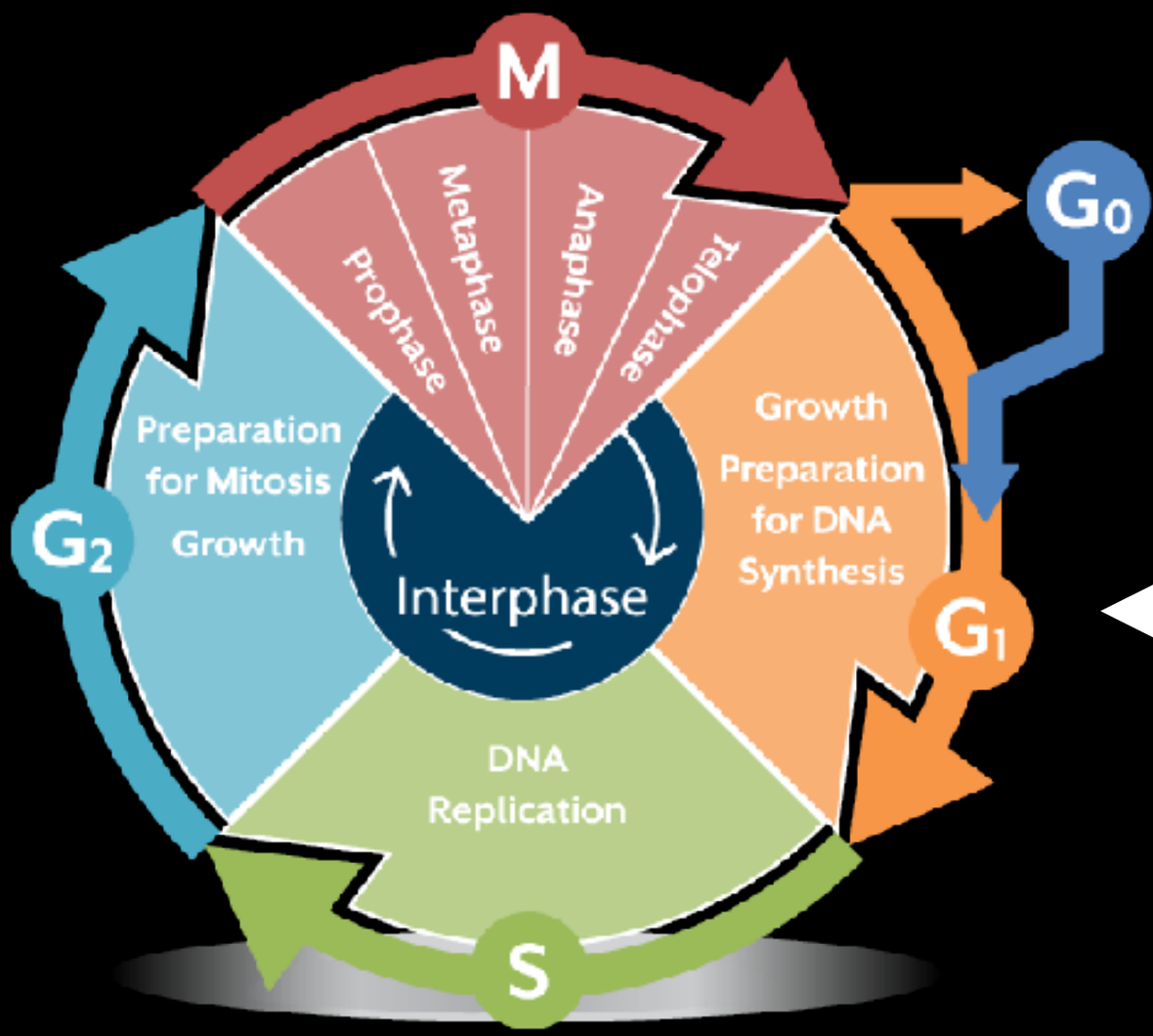


Regulators of Cell Cycle and Cell Death

Some **stimulate** the cell cycle

Some **inhibit** the cell cycle



Cyclin D1

CDK4

\+

Oncogenes

\-

P53

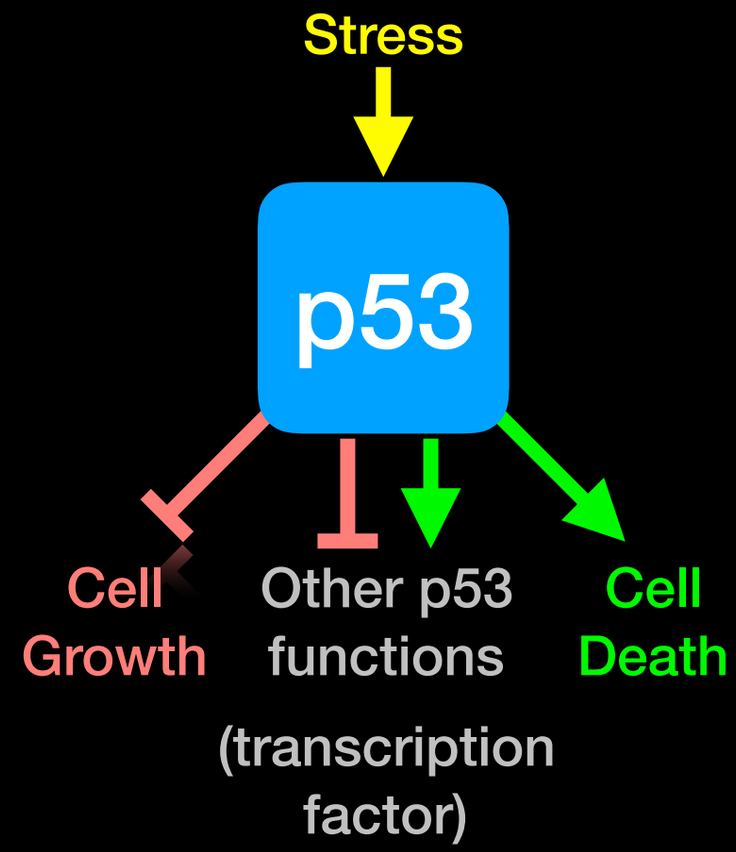
RB

Suppressor genes

p53 Regulates Cell Division

Probably the most famous cancer gene that is mutated in about half of all tumors. Often called the '*guardian of the genome*'

- p53 normally shuts down cell division when a cell is stressed (e.g. by DNA damage)
- When DNA is damaged, p53 activates genes that stop cell growth or trigger the cell to die.
- Thus, p53 guards against changes to cells that might lead to tumor formation.
- It appears necessary to inactivate p53 to develop many forms of cancer.



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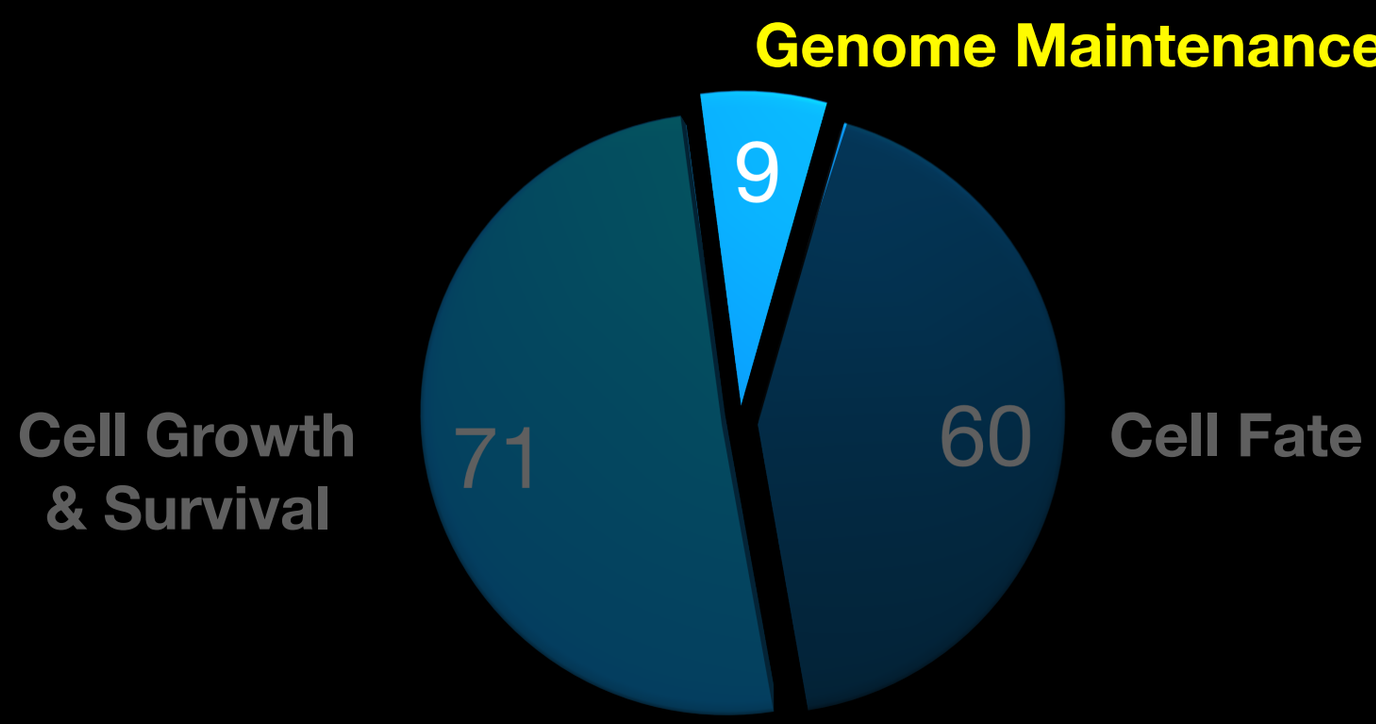

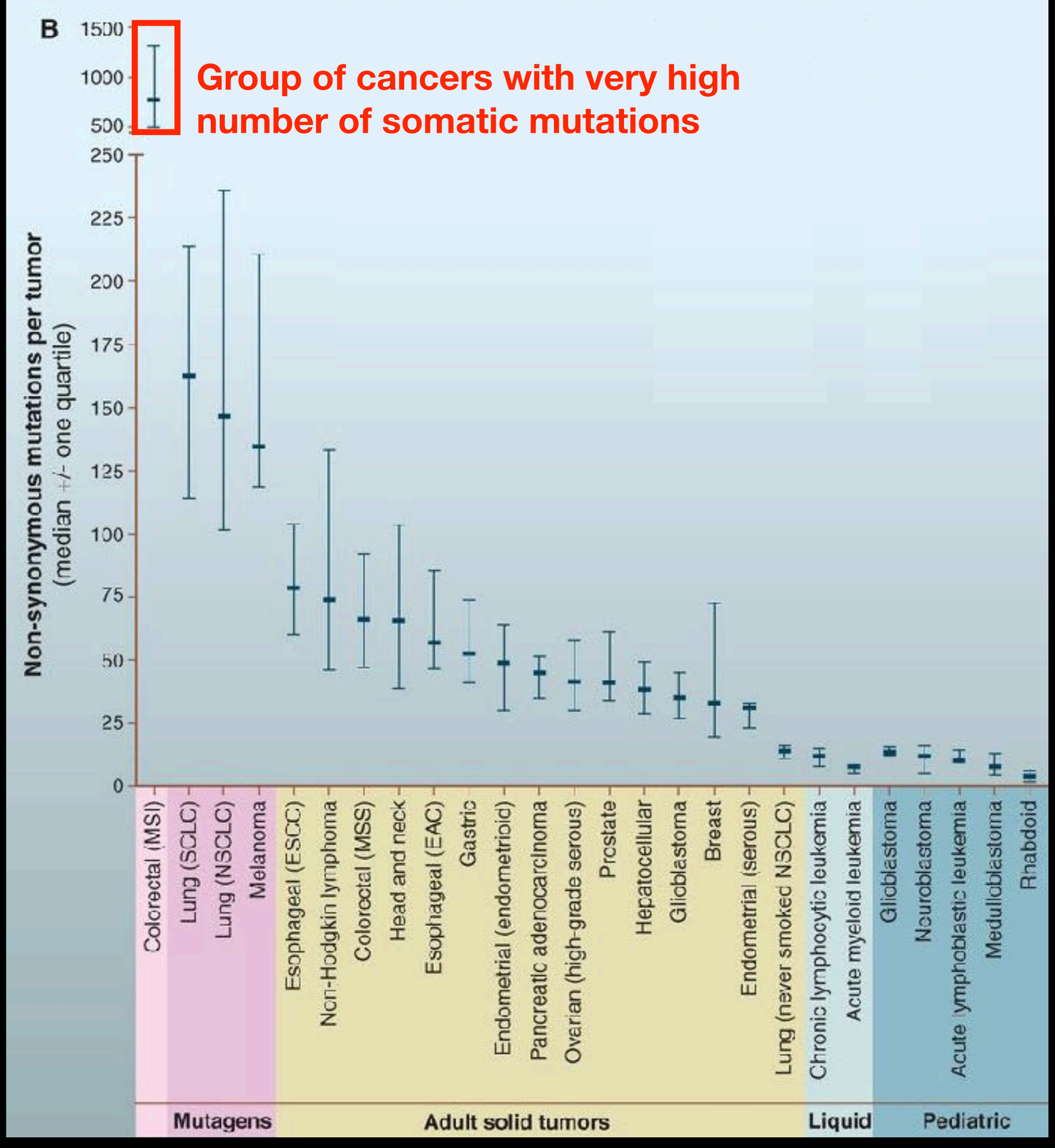

Linked to mutations in **DNA repair genes**.

Vogelstein et al. Science (2013)

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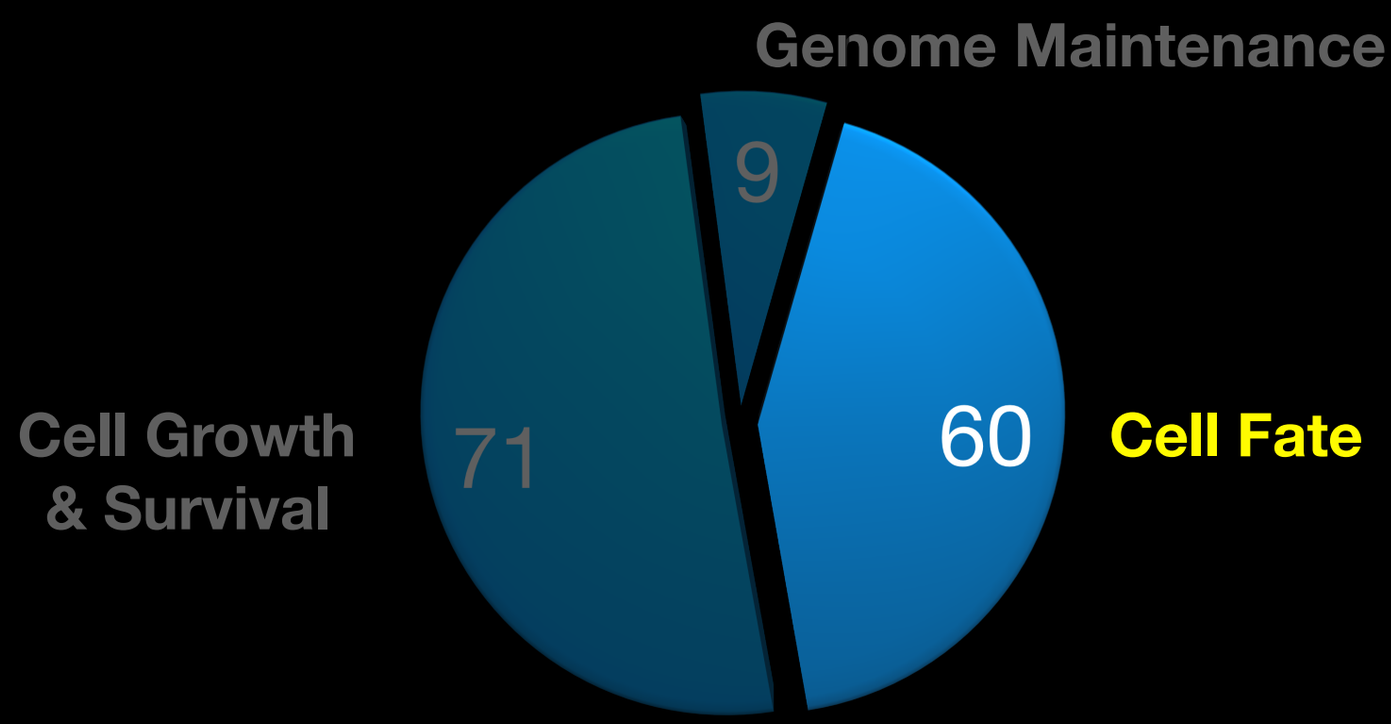
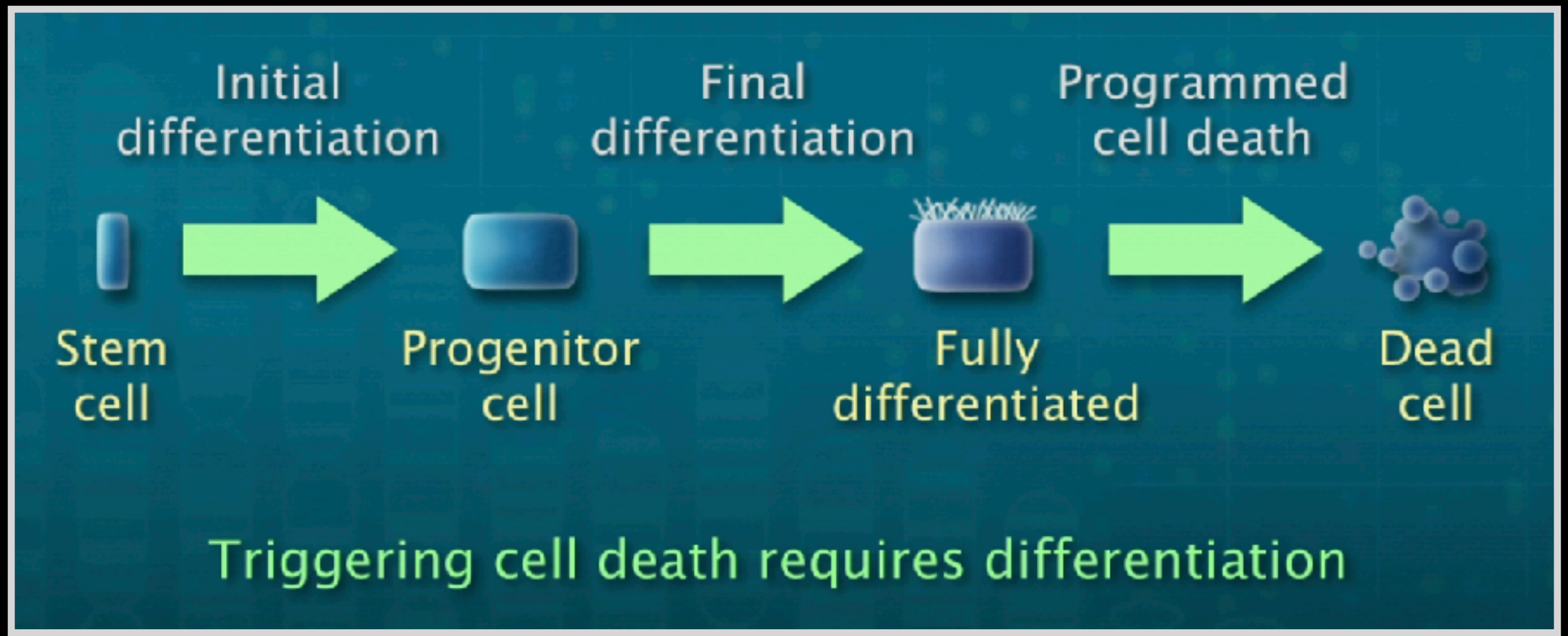


How Can Mutations in Cell Fate Genes Cause Cancer?



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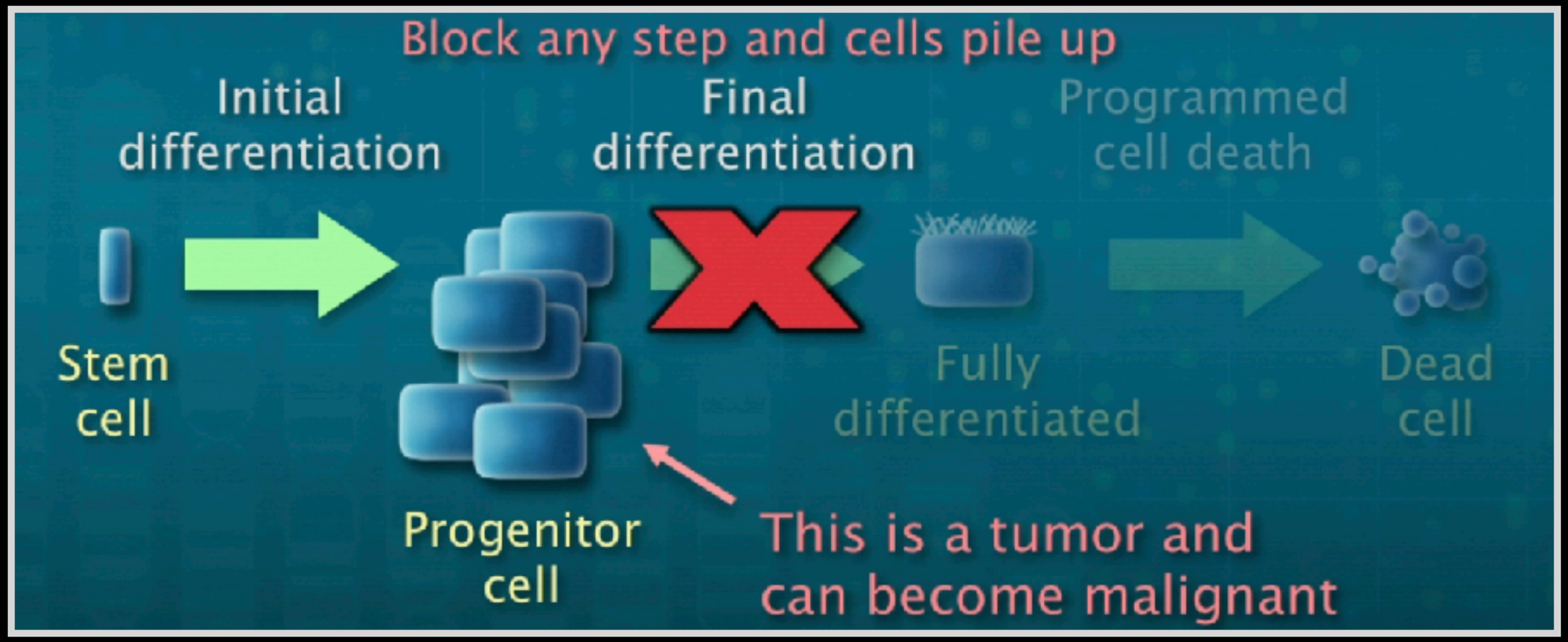


Disrupting the normal processes of differentiation and maturation of the intestinal epithelial cells can lead to cancer.

http://molecularmovies.com/movies/kellermcgill_clonalconveyorbelt.mov

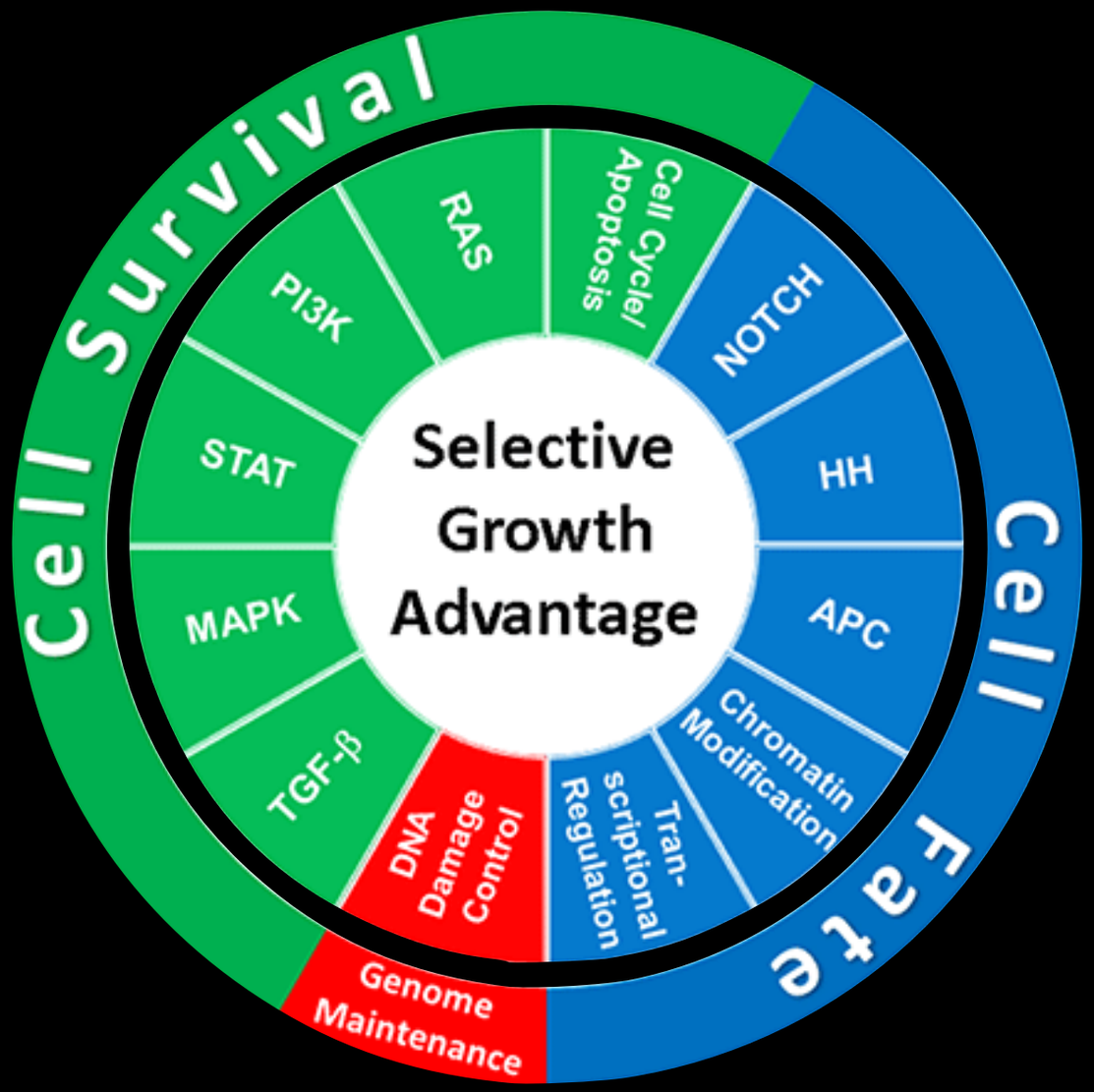
Do We Need 140 Drugs for the 140 Cancer Genes?

Or can we simplify the problem?

Further Simplifying The Problem

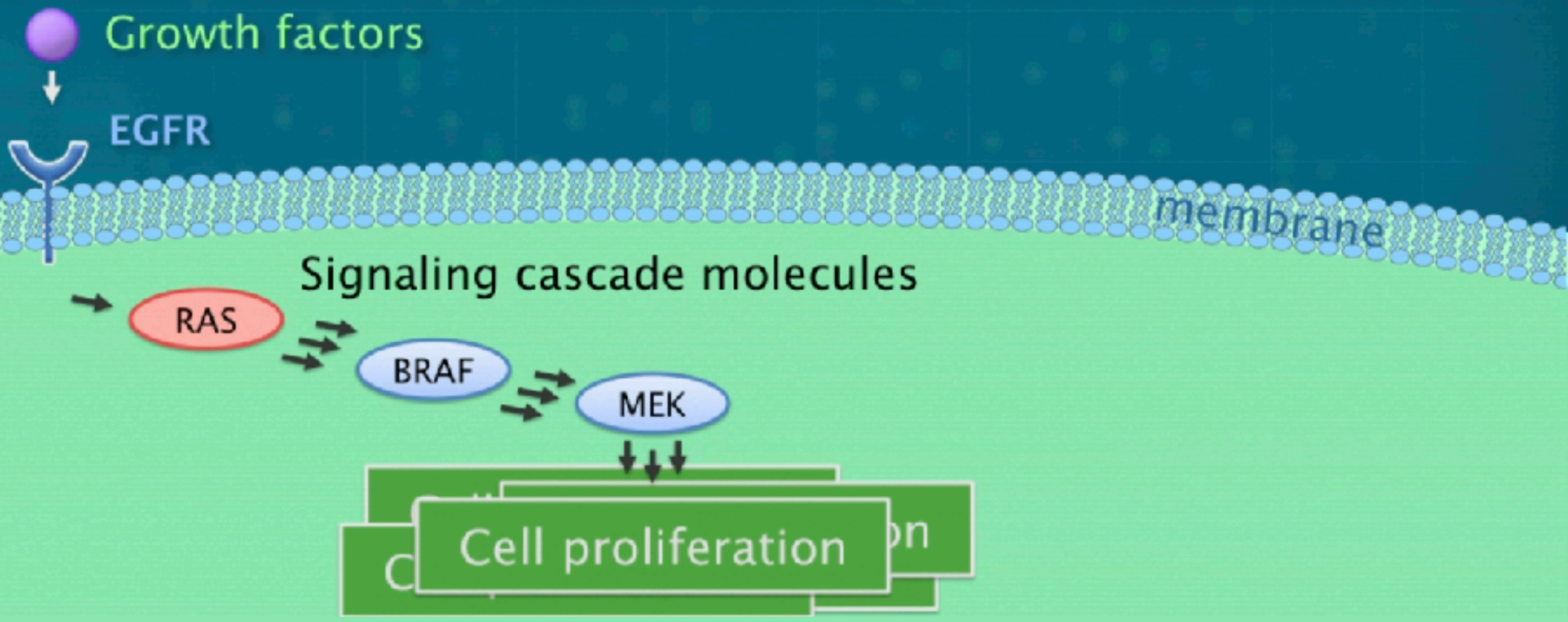
The known driver genes can be classified into one or more <u>major pathways</u> (middle ring) that confer a selective growth advantage.

These pathways can themselves be further organized into three core cellular processes (outer ring).



Vogelstein et al. Science (2013)

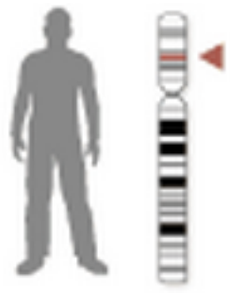
Drugs That Block the Last Step of a Pathway May Be Sufficient



Perhaps drugging the last step in the pathway may be sufficient especially if we do not yet have a Ras directed chemotherapy?

Examples of targeted drug therapies

Targeted Cancer Therapy



Cancer-causing mutations with drug treatment available

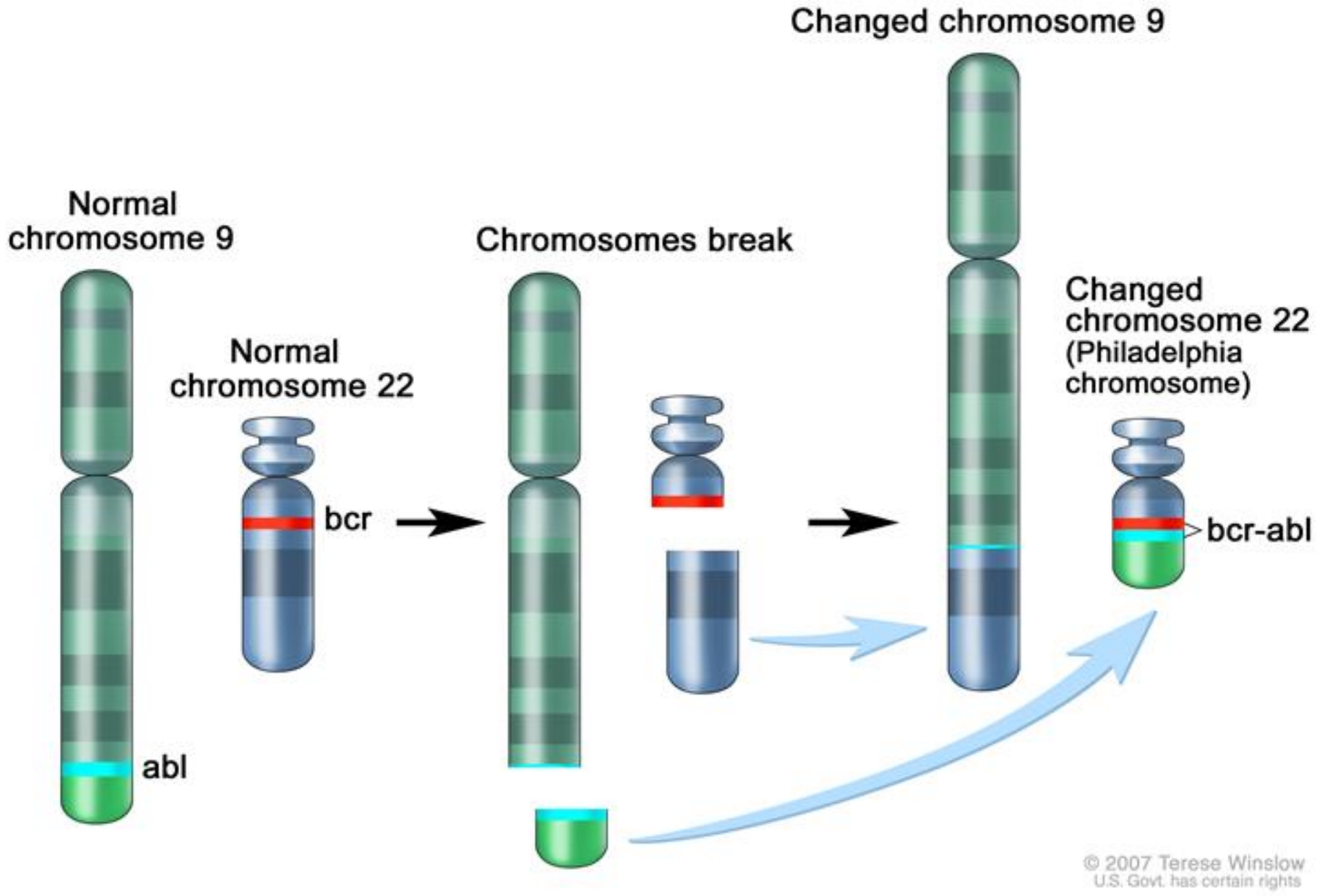
Mutation with no drug available

Cancer drug

Radiation and chemotherapy

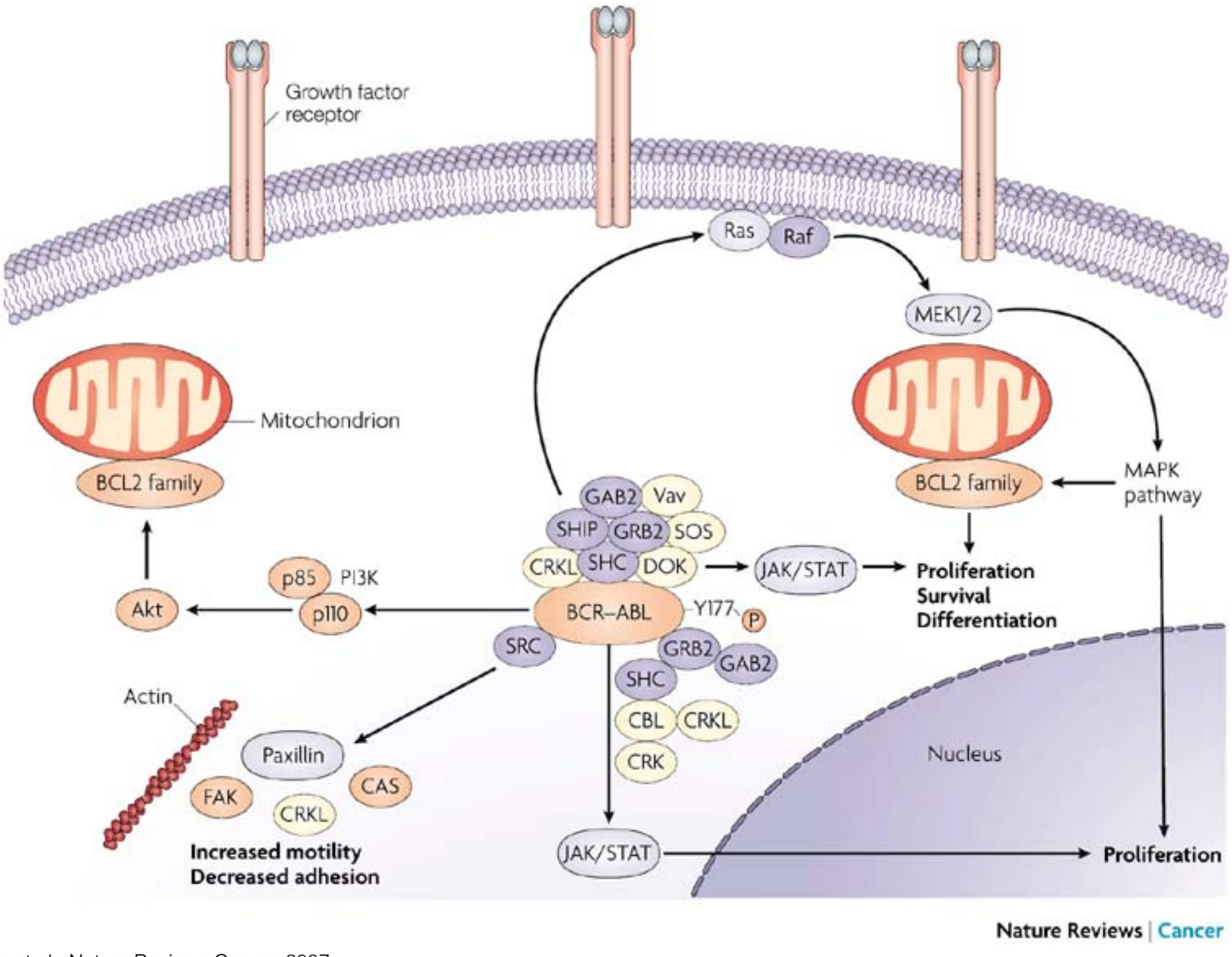
Schema adapted from NY times

BCR-ABL fusion cause Chronic Myelogenous Leukemia (CML)



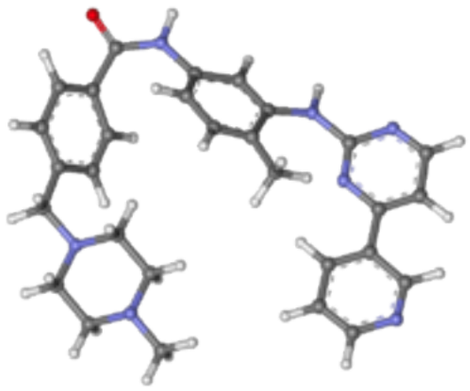
1985

BCR-ABL: constitutive active ABL kinase activity

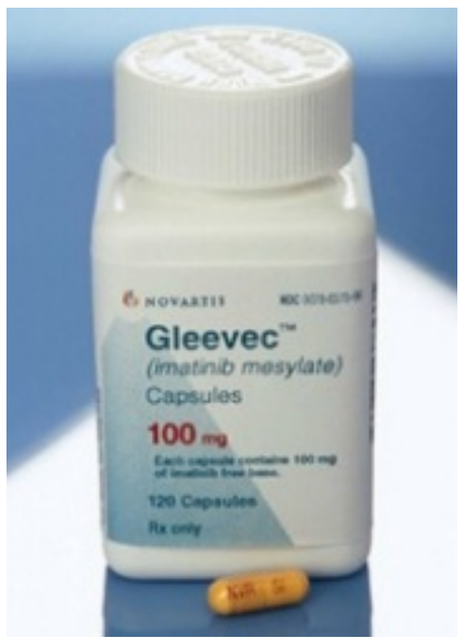


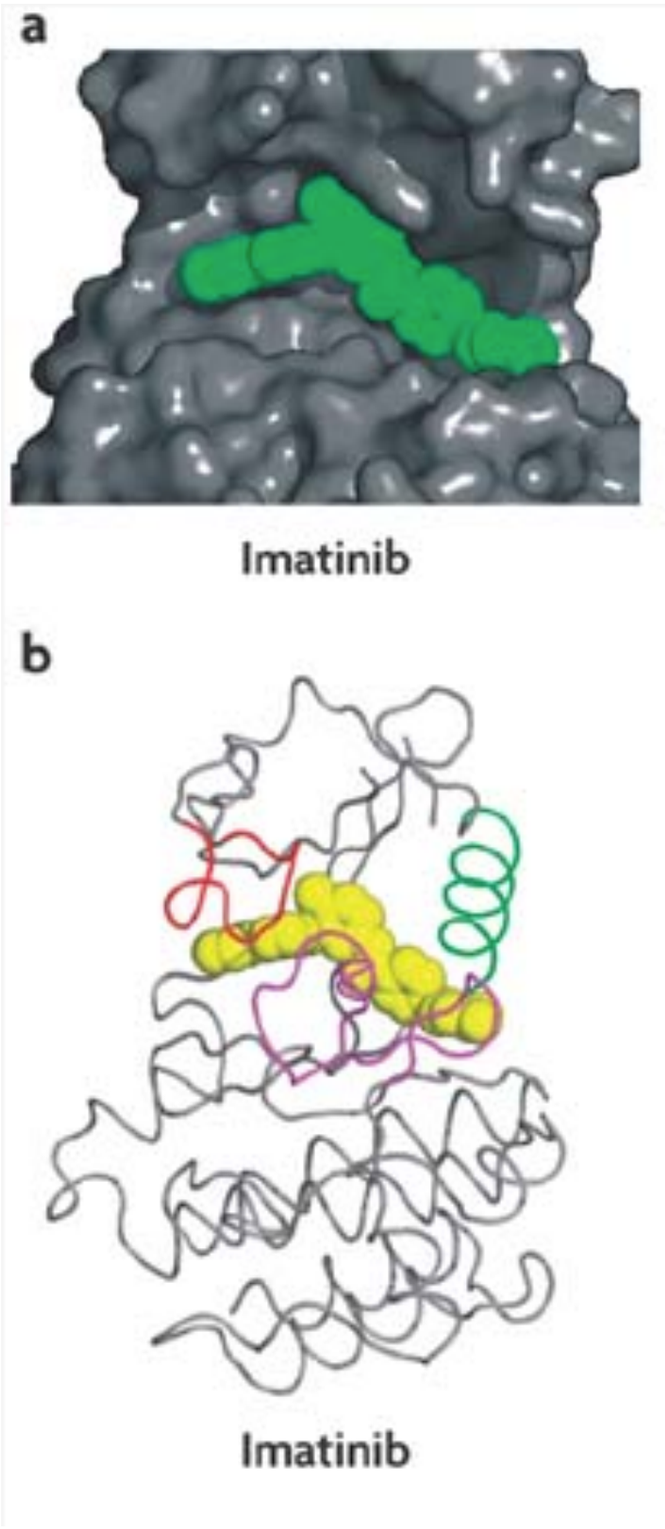
Weisberg et al., Nature Reviews Cancer 2007

Imatinib inhibits tyrosine-kinase activity of ABL

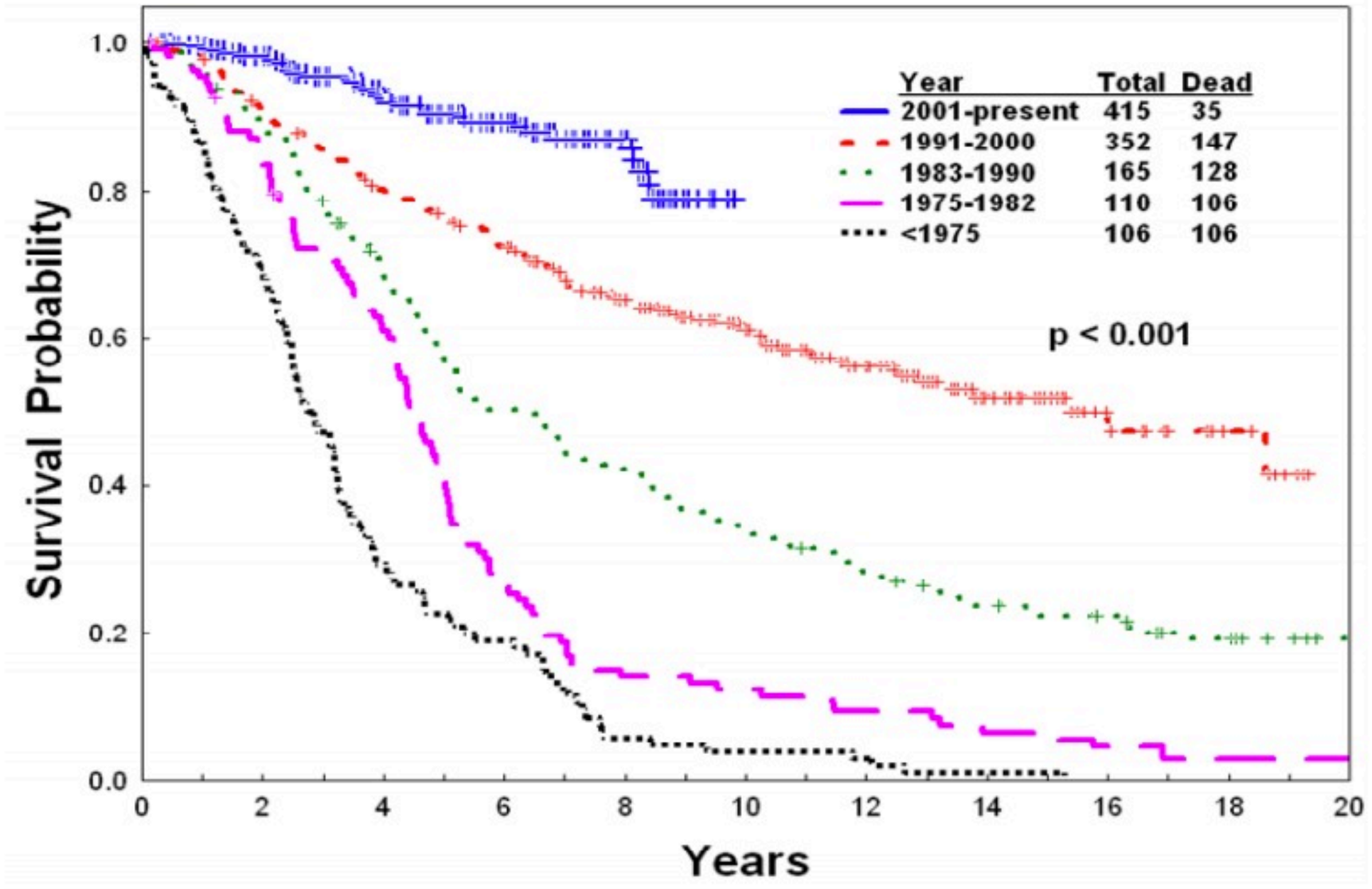


Imatinib



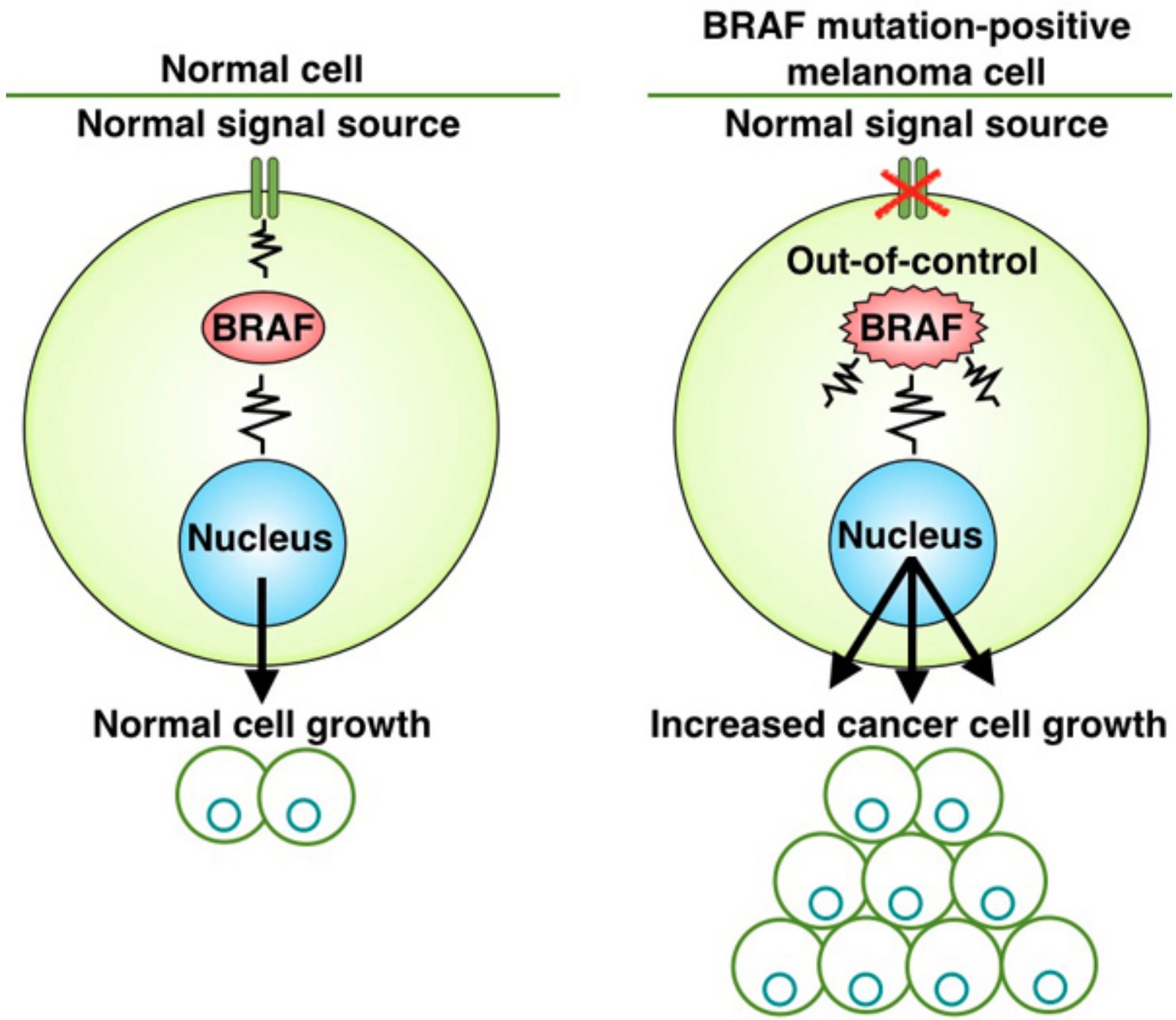


Dramatically improved long term survival rates (95.2%) since the introduction of Gleevec in 2001

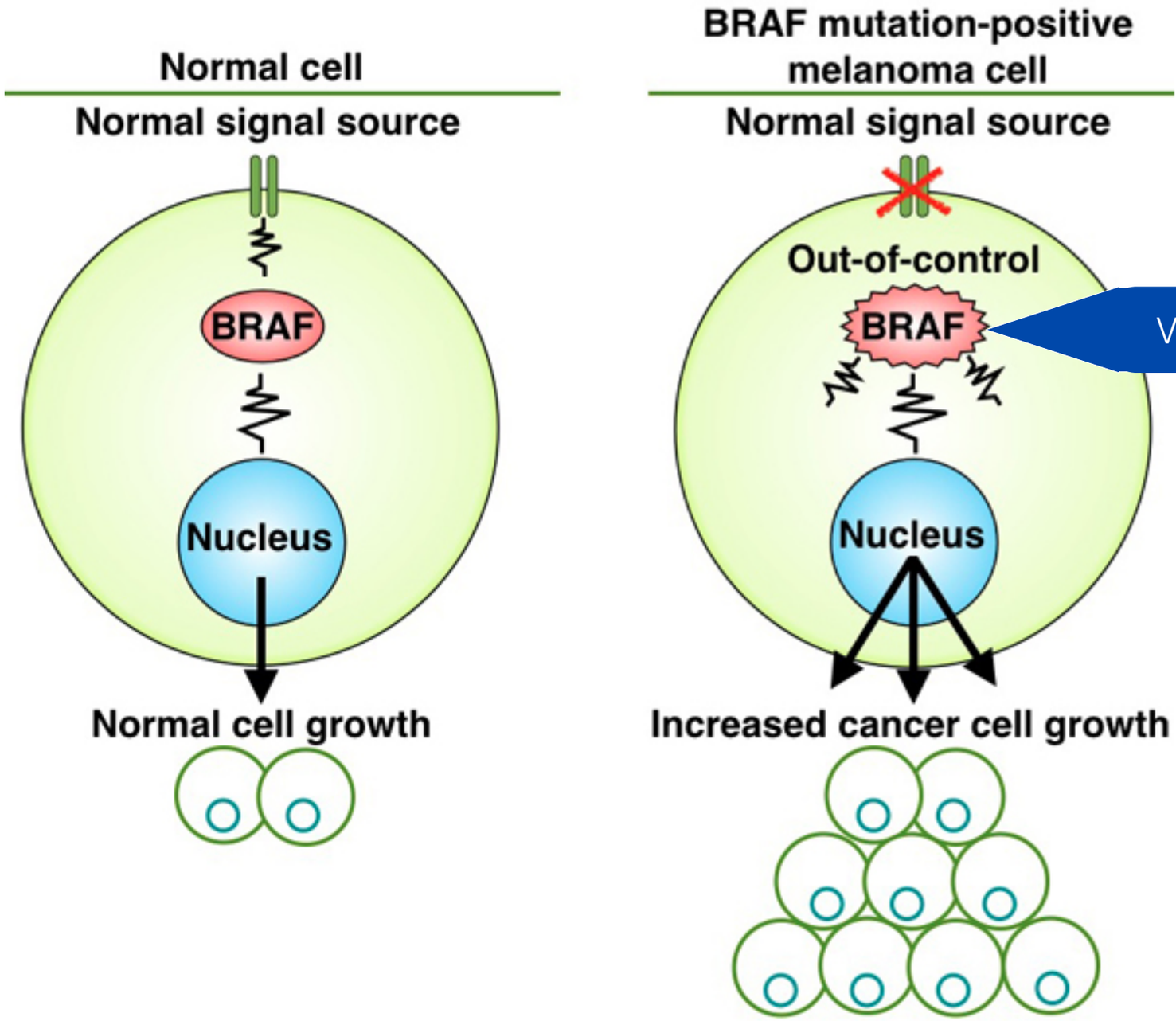


Kantarjian et al., Blood 2012

BRAF is frequently mutated in melanoma

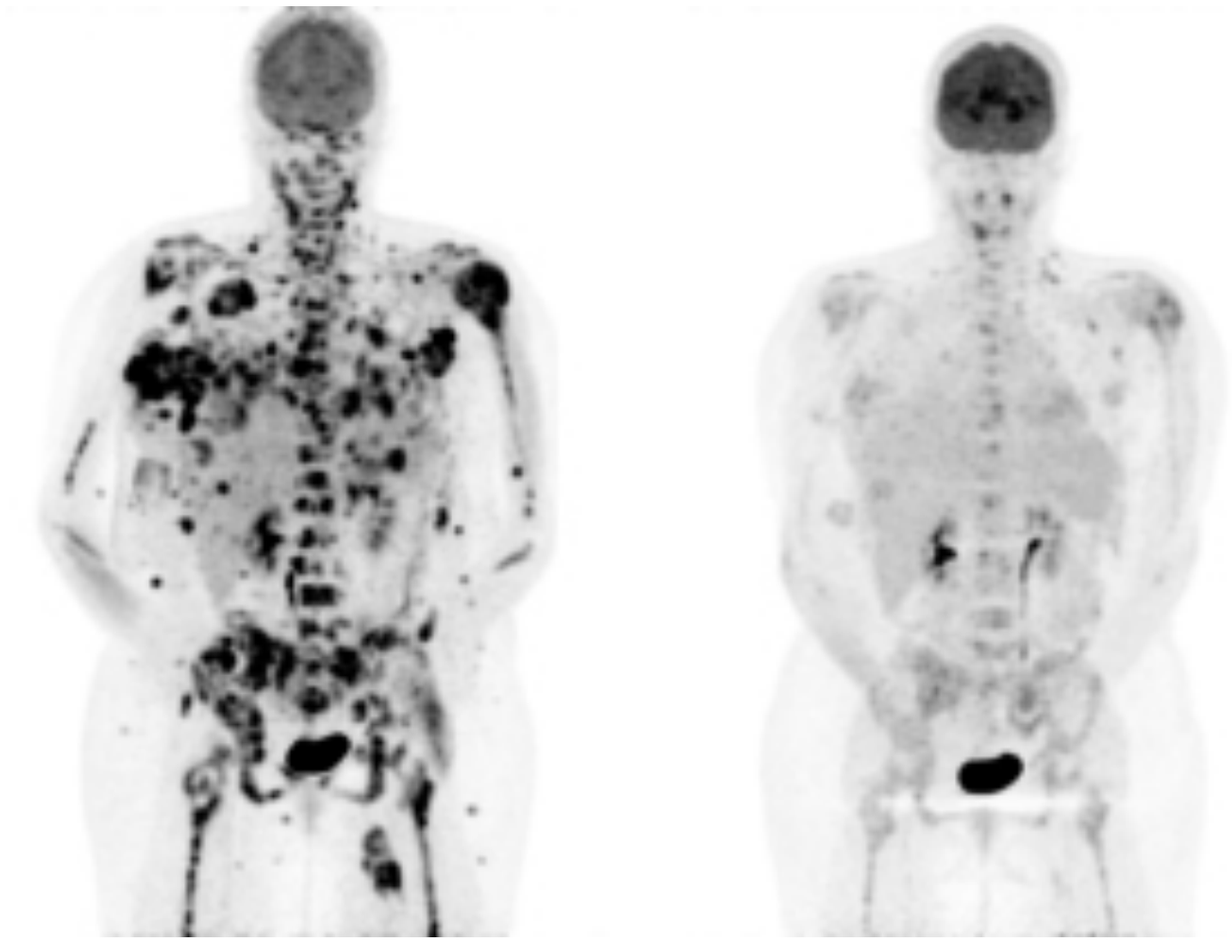


BRAF is frequently mutated in melanoma



2 setmanes
Vemurafenib

Vemurafenib



Personalized medicine / Precision medicine

Table 1. Anticancer Drugs Approved by the Food and Drug Administration (FDA) with Labeling Regarding Pharmacogenomic Biomarkers.*

Type of Biomarker and Associated Drug
Biomarker with pharmacokinetic effect
TPMT
Mercaptopurine
Thioguanine
UGT1A1
Irinotecan
Nilotinib
Biomarker with pharmacodynamic effect
EGFR
Cetuximab
Erlotinib
Gefitinib
Panitumumab
KRAS
Cetuximab
Panitumumab
ABL
Imatinib
Dasatinib
Nilotinib
C-Kit (*KIT*)
Imatinib
HER2/neu (*ERBB2*)
Lapatinib
Trastuzumab
Estrogen receptor
Tamoxifen

* Data are from the FDA's pharmacogenetics Web site (www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm). The biomarkers have been separated into pharmacokinetic effect (drug metabolism) and pharmacodynamic effect (drug target). Biomarkers for cytogenetic alterations have been excluded.

Anticancer drugs approved by the Food and Drug Administration with labeling regarding pharmacogenomic biomarkers

Wang L et al. N Engl J Med 2011;364:1144-1153.

Readings to find out more...

Leading Edge
Review

Cell

The Genetic Basis for Cancer Treatment Decisions

Janet E. Dancey,[1,2] Philippe L. Bedard,[3,4] Nicole Onetto,[1] and Thomas J. Hudson[1,5,6,*]
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[2]NCIC-Clinical Trials Group, Queen's University, Kingston, ON K7L 3N6, Canada
[3]Princess Margaret Hospital, Division of Medical Oncology and Hematology, University Health Network
[4]Department of Medicine
[5]Department of Medical Biophysics
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University of Toronto, Toronto, ON M5S 1A1, Canada
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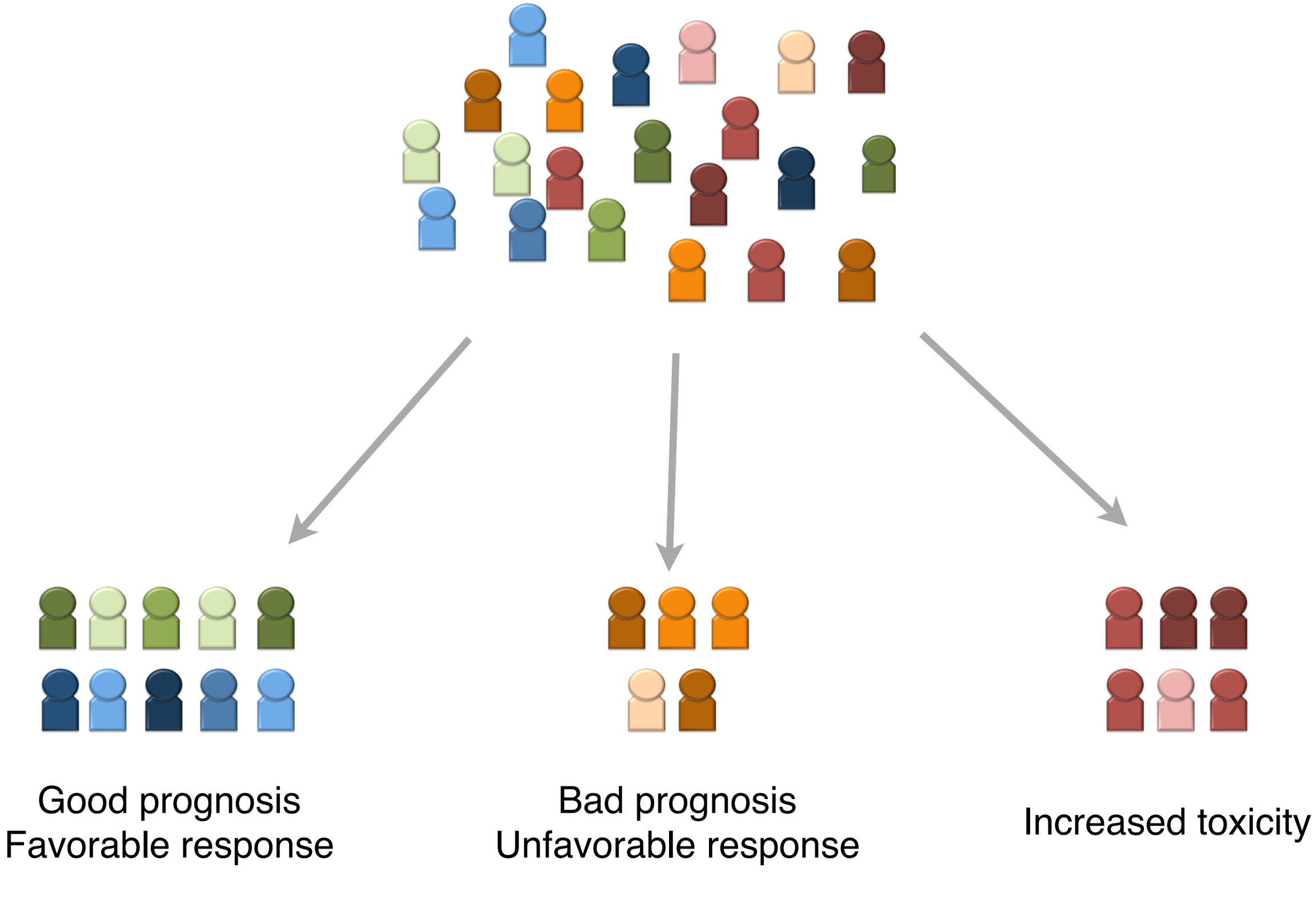
DOI 10.1016/j.cell.2012.01.014

Personalized cancer medicine is based on increased knowledge of the cancer mutation repertoire and availability of agents that target altered genes or pathways. Given advances in cancer genetics, technology, and therapeutics development, the timing is right to develop a clinical trial and research framework to move future clinical decisions from heuristic to evidence-based decisions. Although the challenges of integrating genomic testing into cancer treatment decision making are wide-ranging and complex, there is a scientific and ethical imperative to realize the benefits of personalized cancer medicine, given the overwhelming burden of cancer and the unprecedented opportunities for advancements in outcomes for patients.

Genetic and genomic approaches can identify a cancers molecular signature to usefully stratify tumors for treatment

Stratify tumors based on molecular patterns

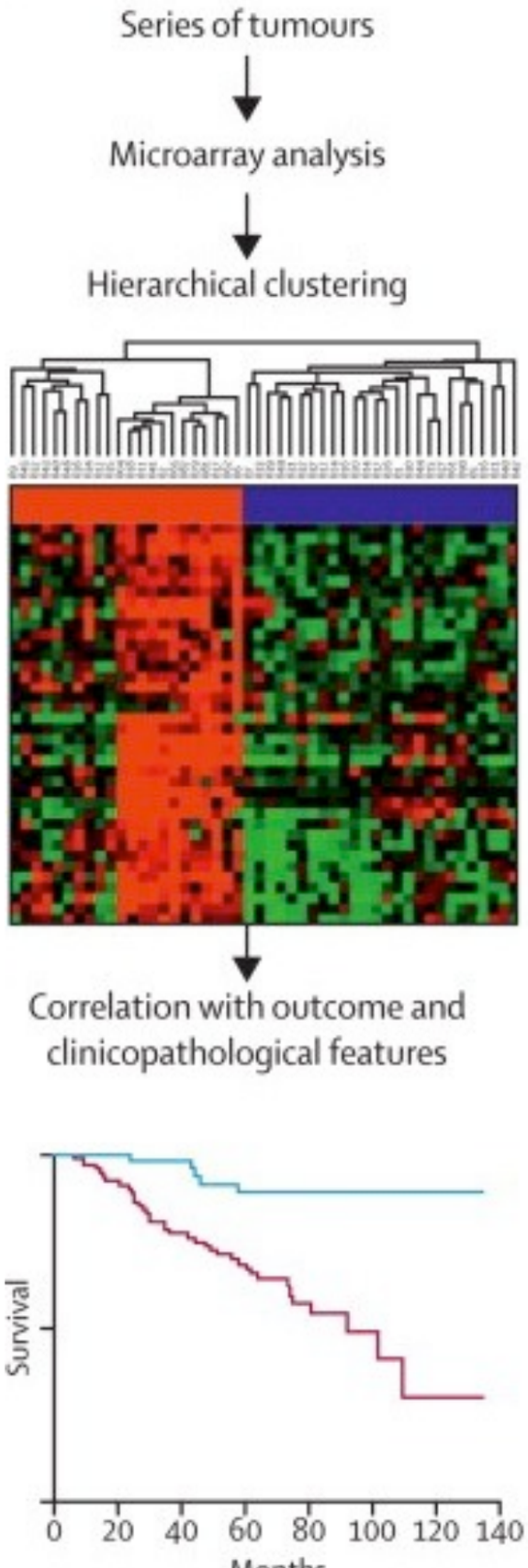


Good prognosis
Favorable response

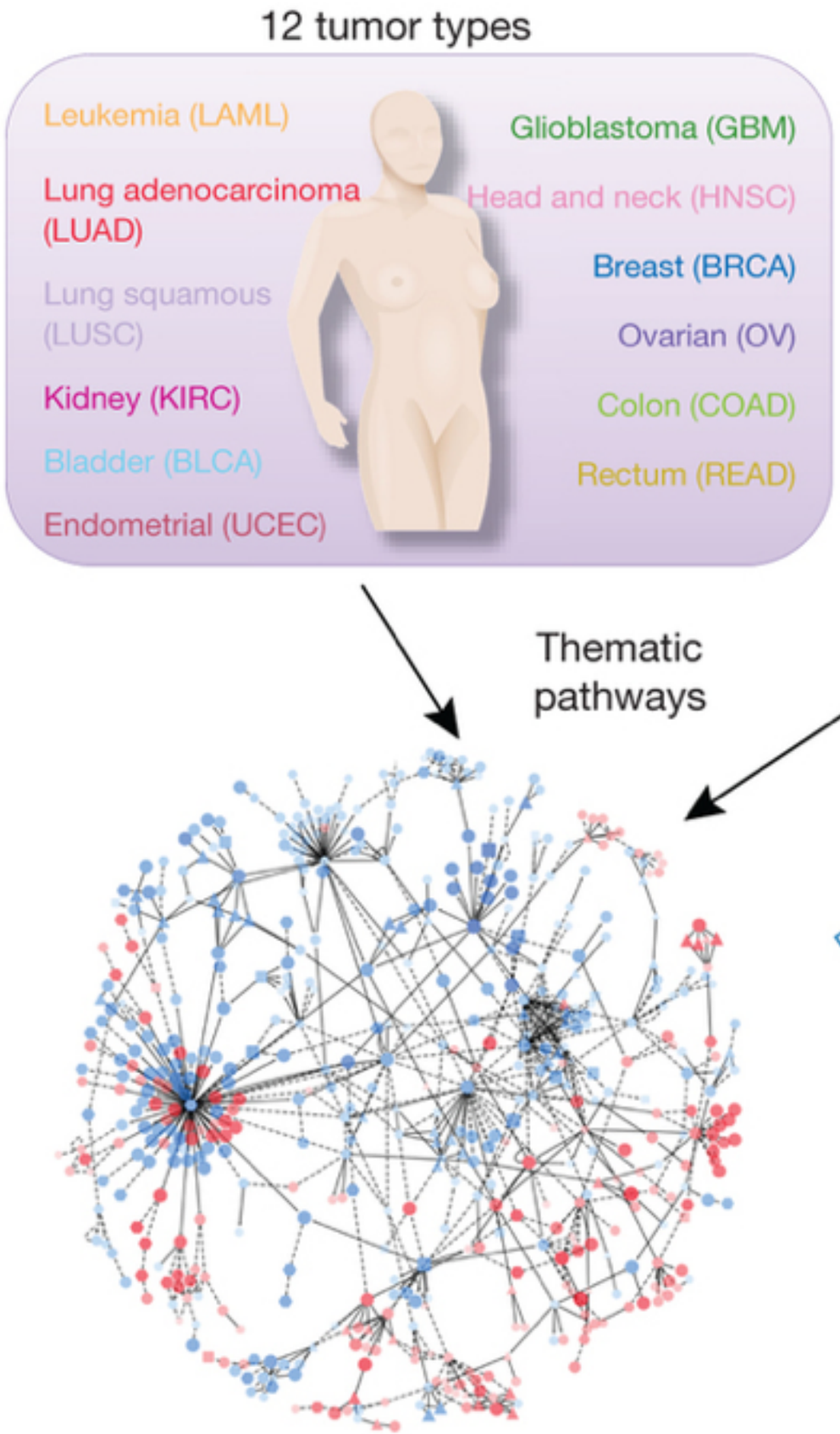
Bad prognosis
Unfavorable response

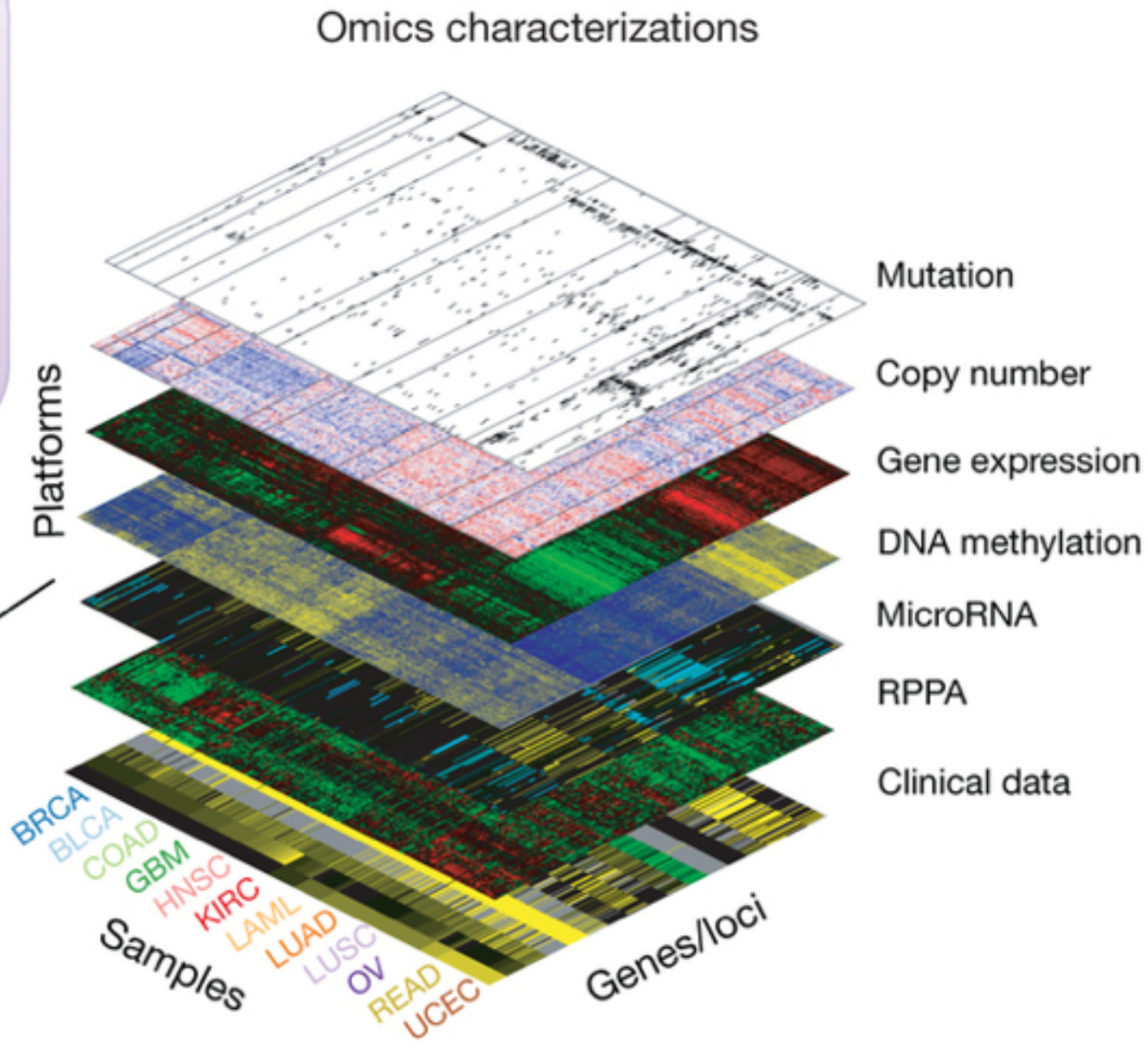
Increased toxicity

Stratify tumors based on molecular patterns

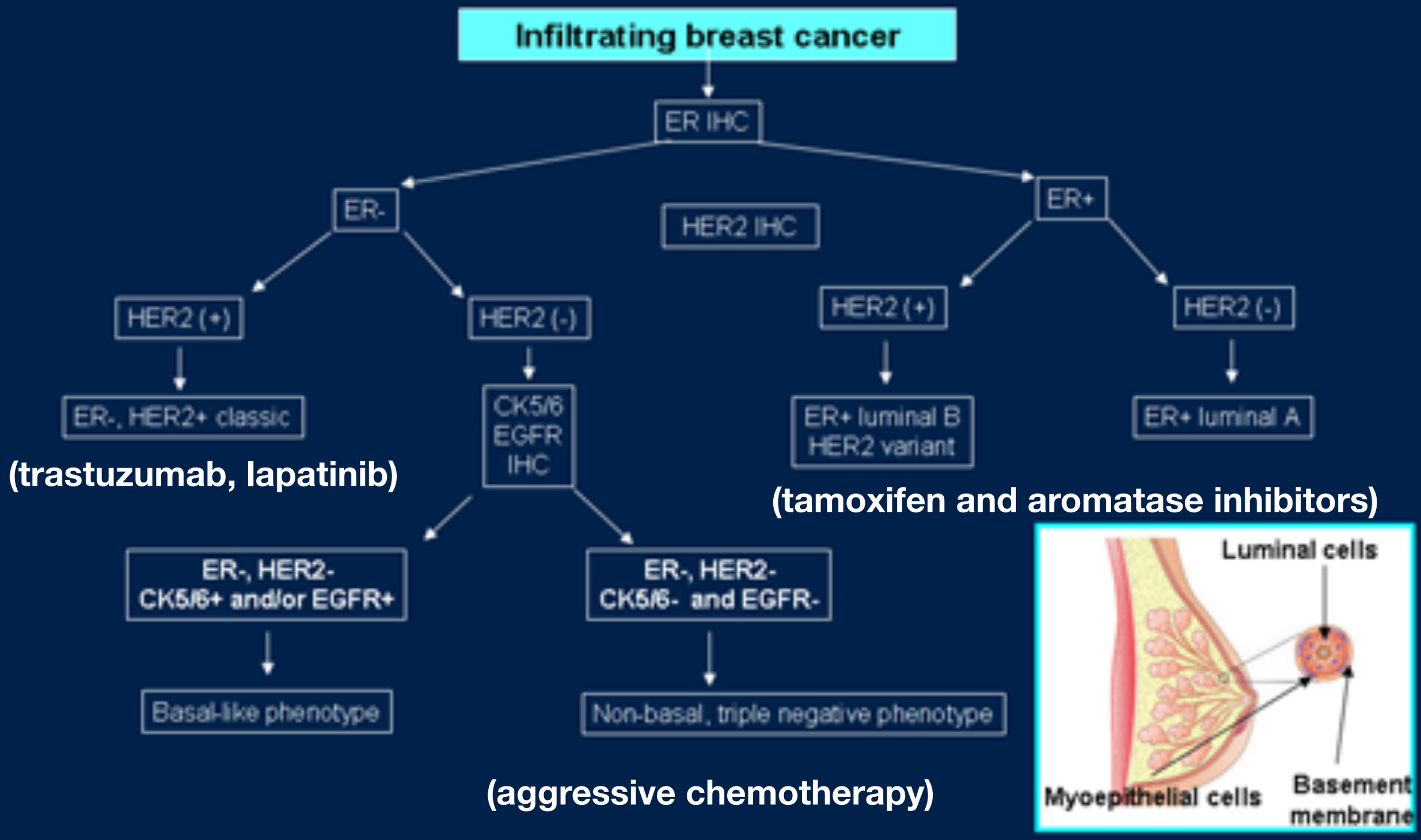


TCGA Pan-Cancer project





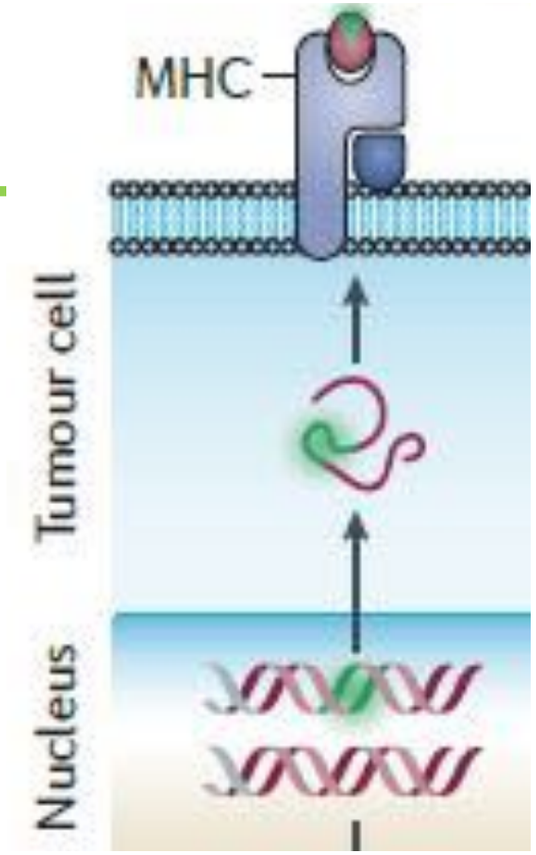
Classification of Breast Cancer



Cancer Immunotherapy

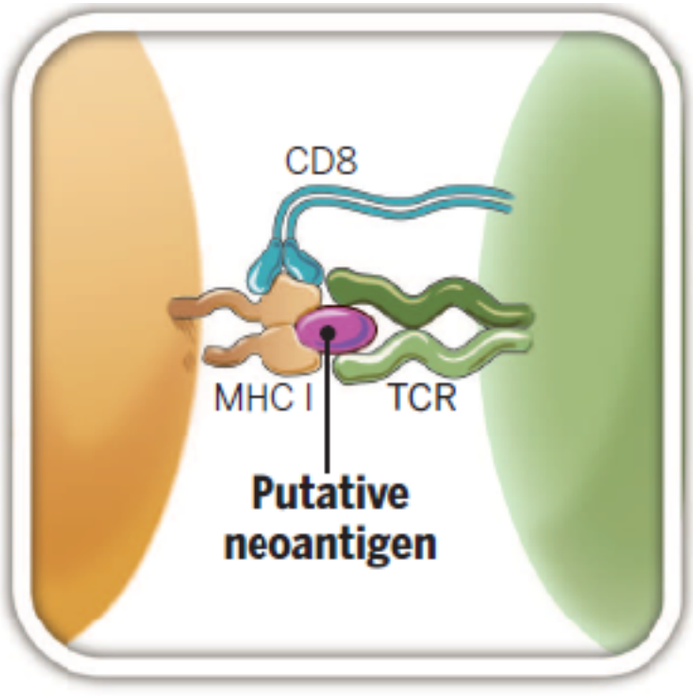
Neoepitopes (Neoantigens)

- Cancers genomes accumulate mutations
- Mutations in coding regions are translated in mutated protein sequences
- Mutated peptides can be presented as epitopes on MHC to T cells



Neoepitopes are presumably recognized by tumor-infiltrating lymphocytes **(TILs)**

Neoepitopes are highly tumor-specific!



Coulie et al, Nat Rev Cancer. 2014 Feb;14(2):135-46
Schumacher & Schreiber, Science. 2015 Apr 3;348(6230):69-74

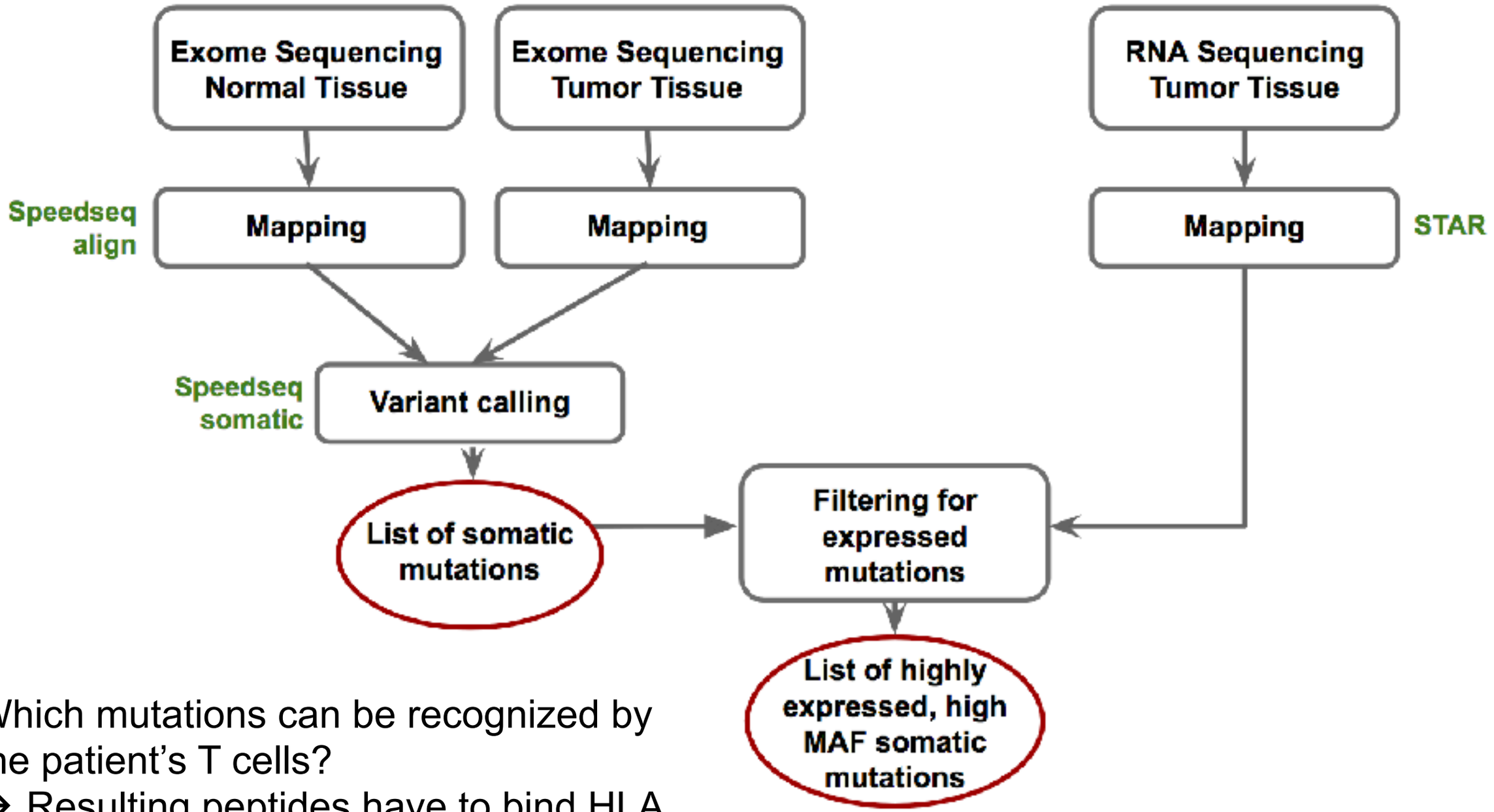
NCT

Cancer Immunotherapy

- Vaccination: Introduce or boost an immune response against a specific target (antigen)
- Cancer cells contain non-self antigens that *could* be recognized by T cells, but presence of cancer means this mechanism has failed, typically by the tumor suppressing immune responses
- Checkpoint blockade treatments: Block immune suppressive mechanisms to boost T cell immune responses against cancer cells.
- Problem: Checkpoint blockade is unspecific, and will also boost unwanted autoimmune responses
- Personalized Cancer Immunotherapy: Boost anti-tumor response with vaccine containing peptides corresponding to cancer mutations that can be recognized by T cells.

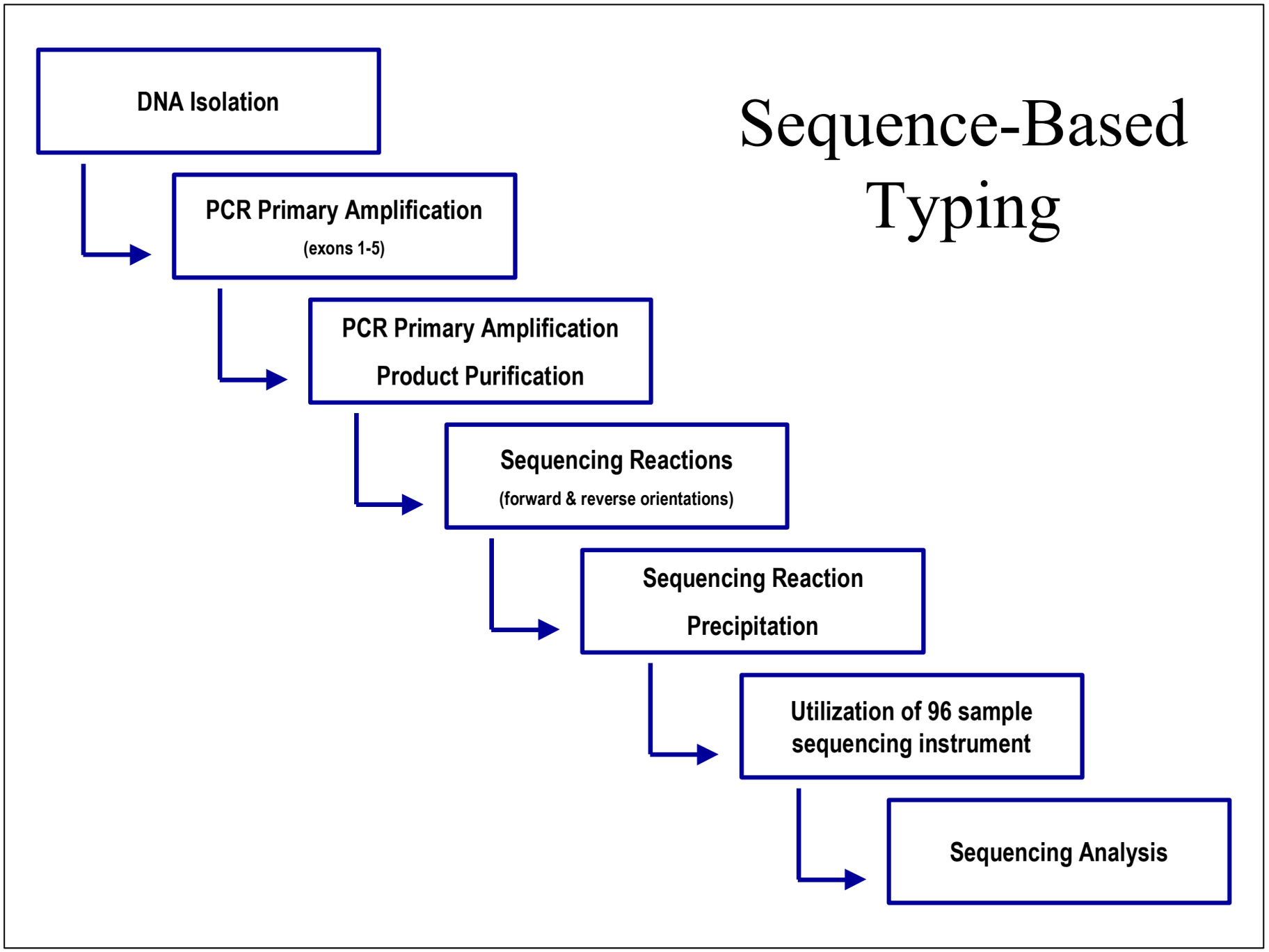
→ How can such a vaccine be designed?

DNA and RNA sequencing identifies tumor specific somatic mutations

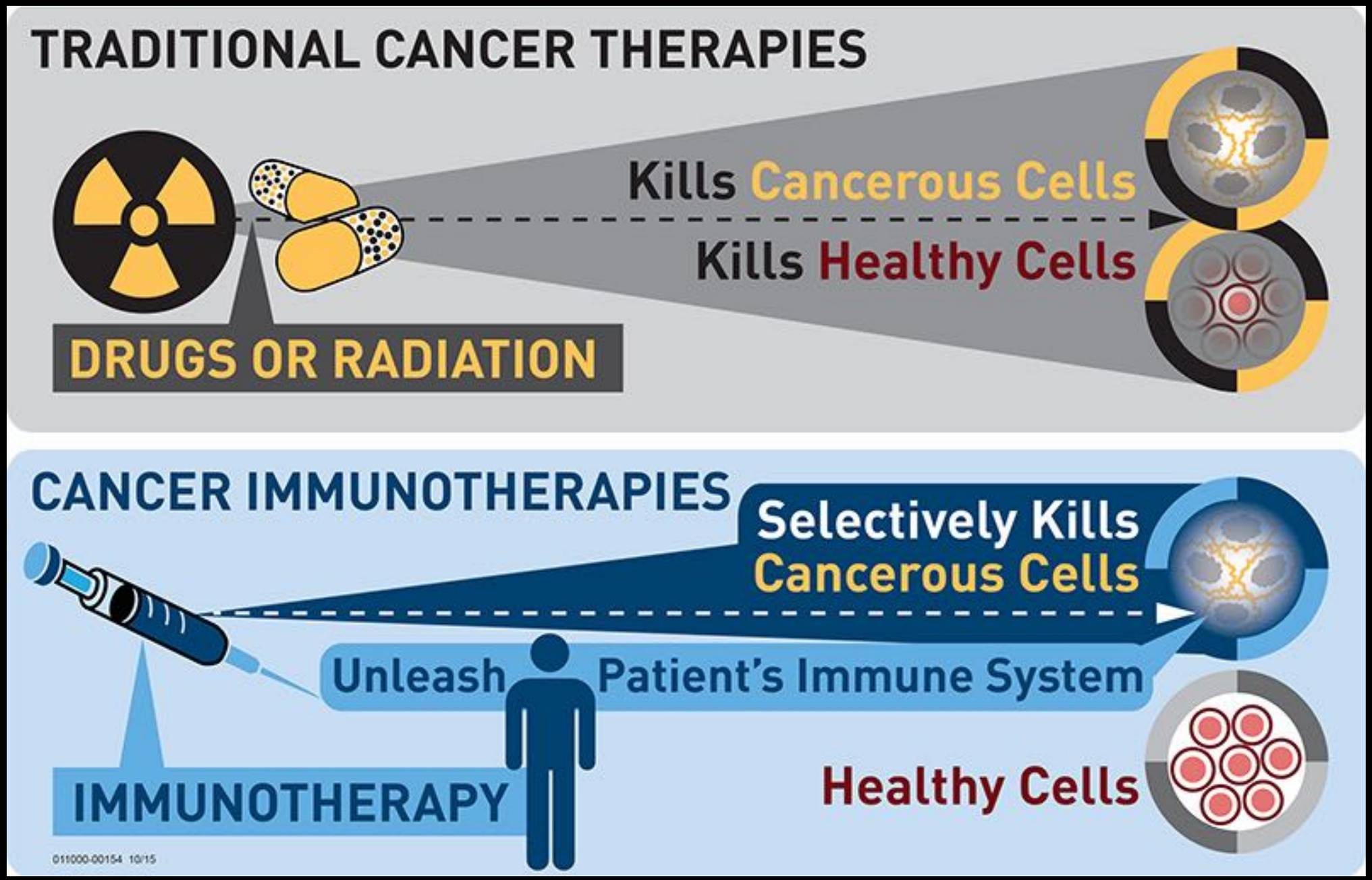


Which mutations can be recognized by the patient's T cells?
→ Resulting peptides have to bind HLA molecules of the patient

HLA Typing: Targeted sequencing of HLA locus



•http://www.ashi-hla.org/publicationfiles/ASHI_Quarterly/25_2_2001/highthrusbt3.htm


TRADITIONAL CANCER THERAPIES
Kills Cancerous Cells
Kills Healthy Cells
DRUGS OR RADIATION
CANCER IMMUNOTHERAPIES
Selectively Kills
Cancerous Cells
Unleash
Patient's Immune System
Healthy Cells
IMMUNOTHERAPY
011000-00154 10/15

Your Turn

Read and share your thoughts on the following class *Readings*

- Calling cancer's bluff with neoantigen vaccines
- Can genomics help detect early cancer and monitor treatment effectiveness?
- The increasing cost of cancer therapies

https://bioboot.github.io/bimm194_W18/readings/