Bioinformatics for (clinical) interpretation of cancer genomics

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> *Trained as engineer (~2004)*
> *PhD in Medicine (HC-UB – cardiology department) (~2009)*
> *Master in **bioinformatics** & molecular biology (~2013)*

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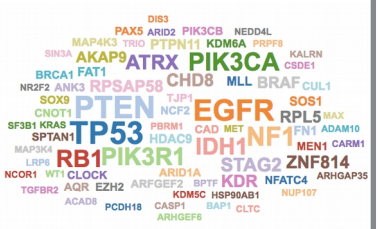
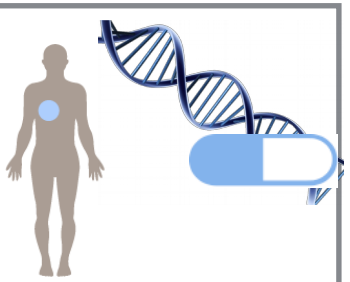
(Bioinformatics) study of tumor genomes

Understanding mutational processes



Finding drivers of cancer



Precision cancer medicine

Bioinformatics enables testing hypotheses at an **unprecedent scale** by using computational methods across **large datasets**

(Bioinformatics) study of tumor genomes

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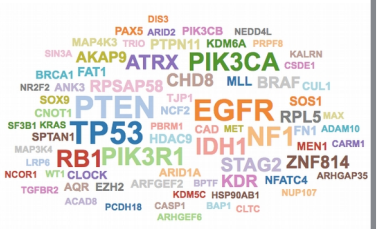

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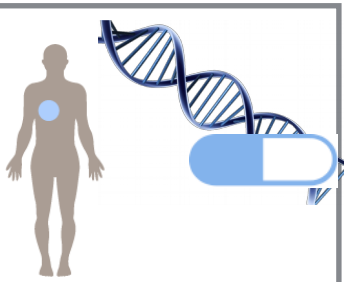

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findings in one supports the other!

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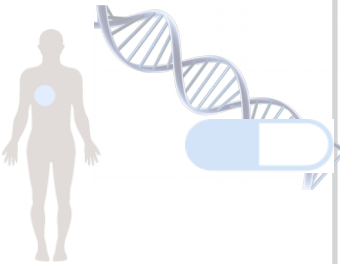

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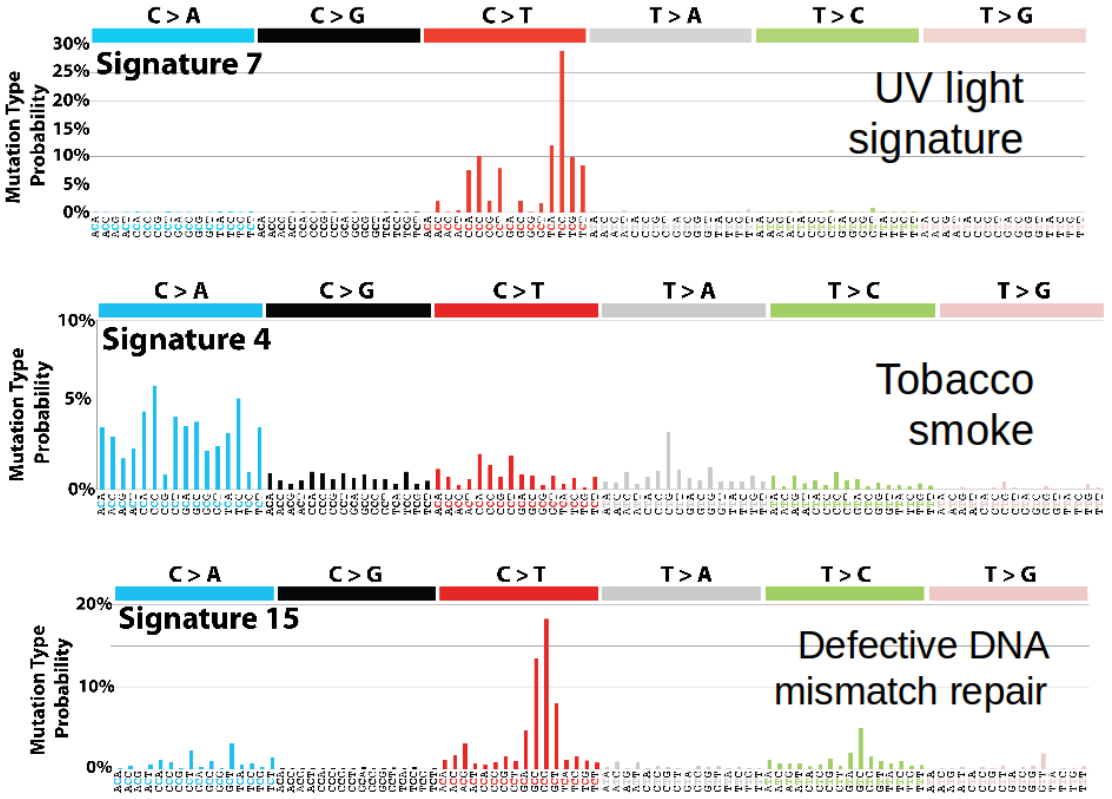
Marc Rosenthal

Identifying patterns in the mutations observed across cancer cohorts provides knowledge about the biology of the (tumor) cell
(e.g. ***mutational processes****)*

Processes occurring ~at the whole **genome scale**:

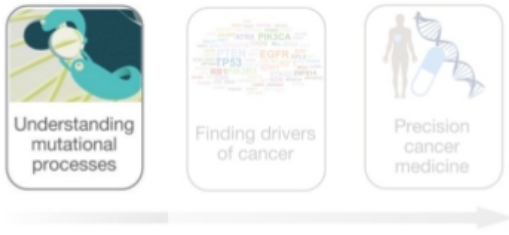


COSMIC website

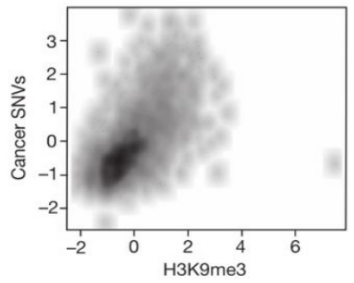
Tumor mutation signatures

Obtained by de-convoluting **unique, distinct patterns** of mutations across tumor cohorts

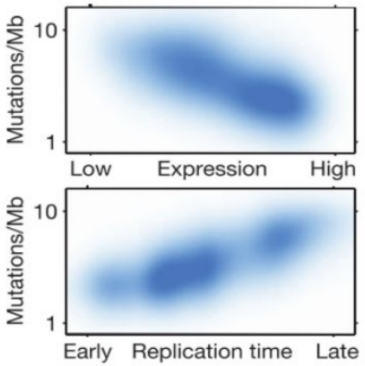
They are associated to specific **biological processes/ environmental "aggressions"** acting through the **~entire genome**



Processes constrained at the **megabase scale:**



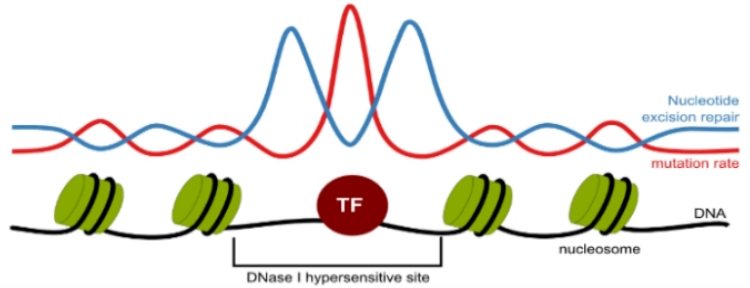
Schuster-Böckler & Lehner. *Nature*. 2012



Lawrence *et al. Nature*. 2013

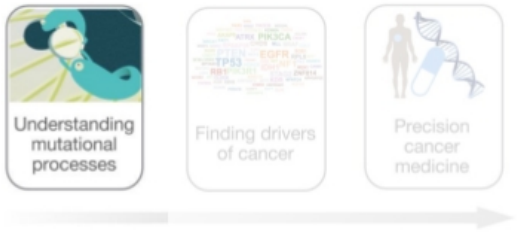
More mutations in regions with **closed-chromatin** conformations and **late-replicated** regions

Processes constrained to **(few) nucleotides** scale:

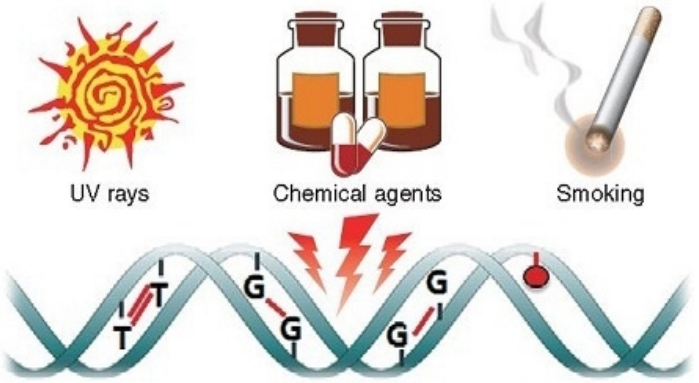


Sabarinathan et al. Nature 2016

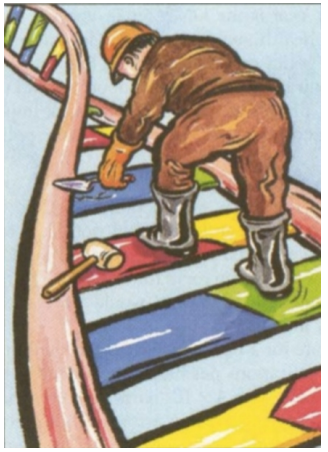
More mutations in **transcription factor binding sites** of melanocytes *(due to interference with NER proteins)*



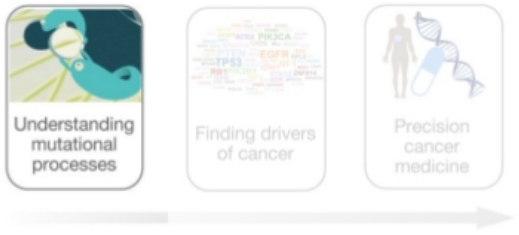
Bioinformatics analyses of large data sets has contributed to a better understanding on how the **mutagenic processes** vs. **mechanisms of DNA repair** shapes the landscape of (somatic) mutations in (tumor) cells



Mutagenic processes (intrinsic/extrinsic)



Mechanisms of DNA repair

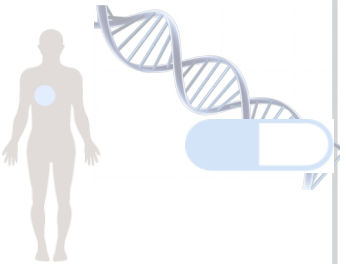


Adapted from Lopez-Bigas

(Bioinformatics) study of tumor genomes

Understanding mutational processes

Finding drivers of cancer



Precision cancer medicine

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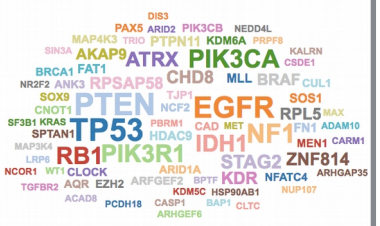

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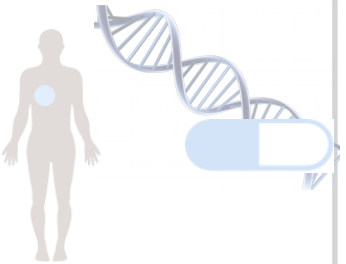

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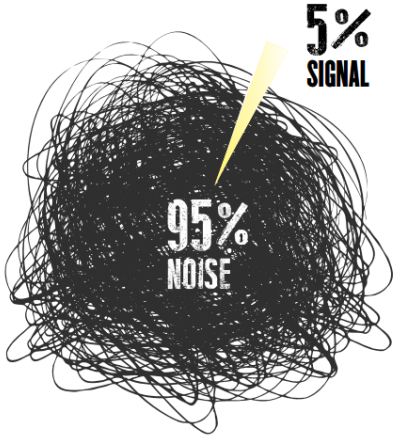

Most of the tumor mutations are a **consequence** of the tumorigenic processes, while only a minority are **causing** the disease

(Bioinformatics) study of tumor genomes

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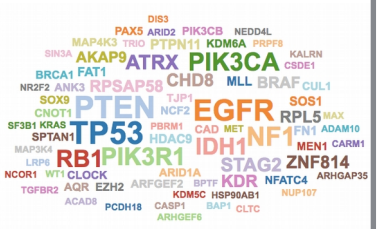

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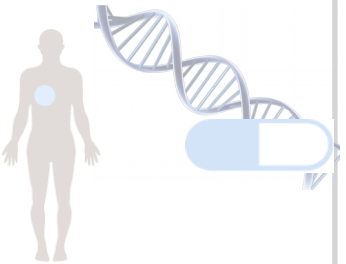

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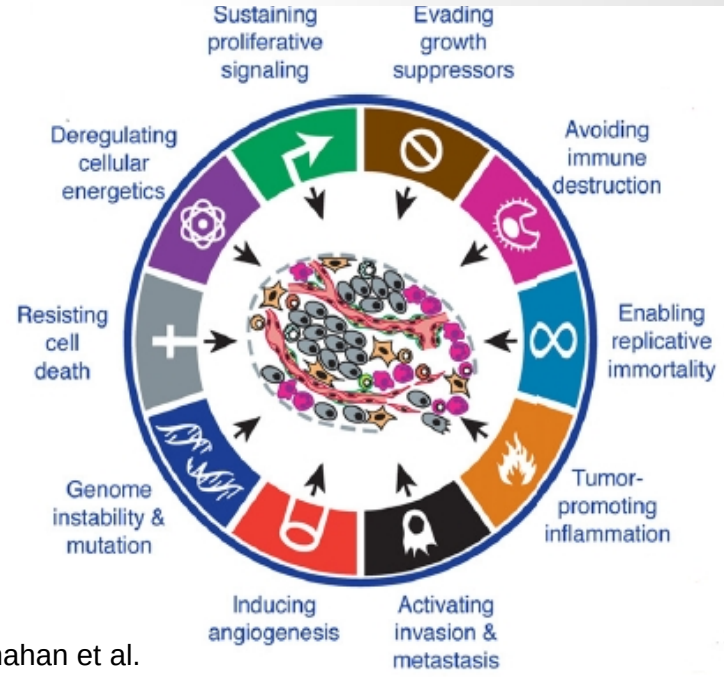
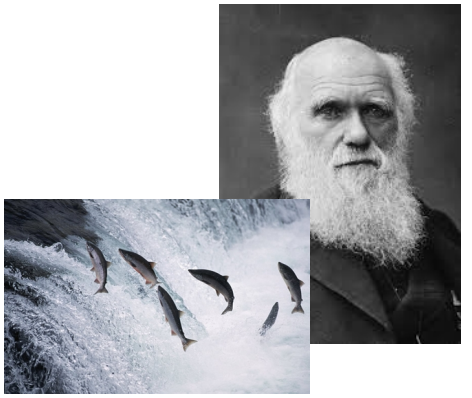


Hanahan et al.

How <u>bionformatic</u> analyses can support the identification of molecular alterations that **<u>drive</u>** the cancer hallmarks **?**

(vs passengers)

Cancer is an evolutionary process



Mutations are fixed during rounds of clonal expansion **if** they confer a **selective advantage** to the tumor cells (*~Darwinian process*)

Bioinfo analyses aim to detect the **signals of positive selection** in the mutations that occur in **driver genes** → i.e. those mutations that deviate from a **random* distribution**

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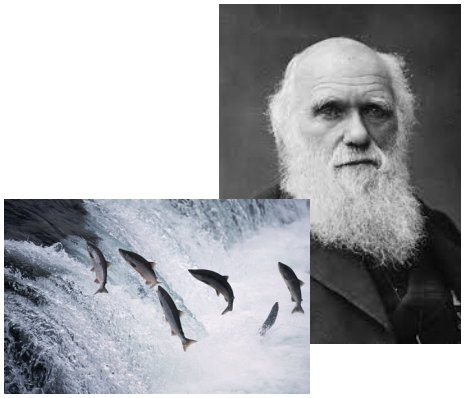

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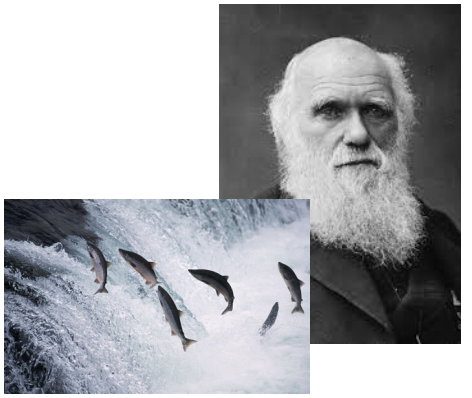

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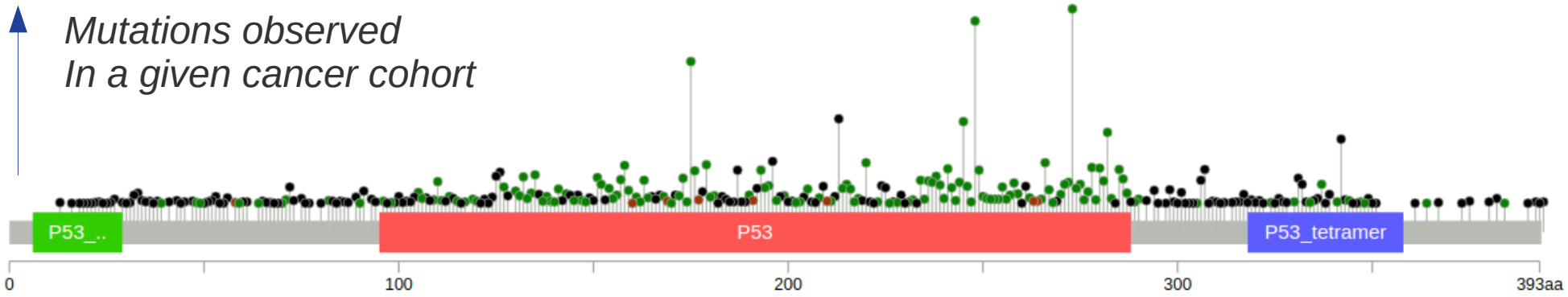
Based on the knowledge about the 'random pattern of mutations' in tumor cells

Hotspots: protein sites accumulating more somatic mutations than expected by the background processes

Hotspots point out mutated protein sites that are **positively selected** by **tumor cells** (of a given cancer type)



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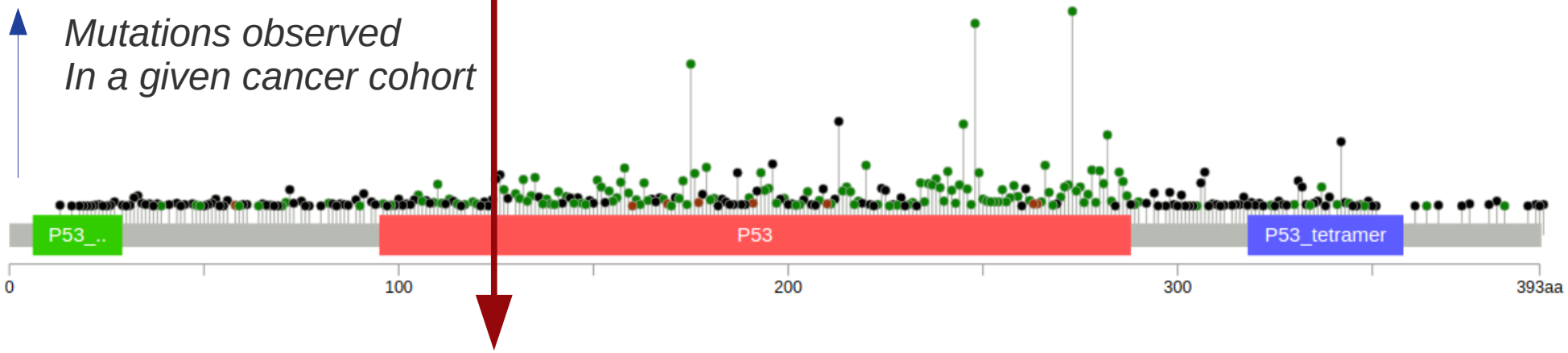
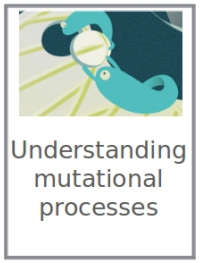
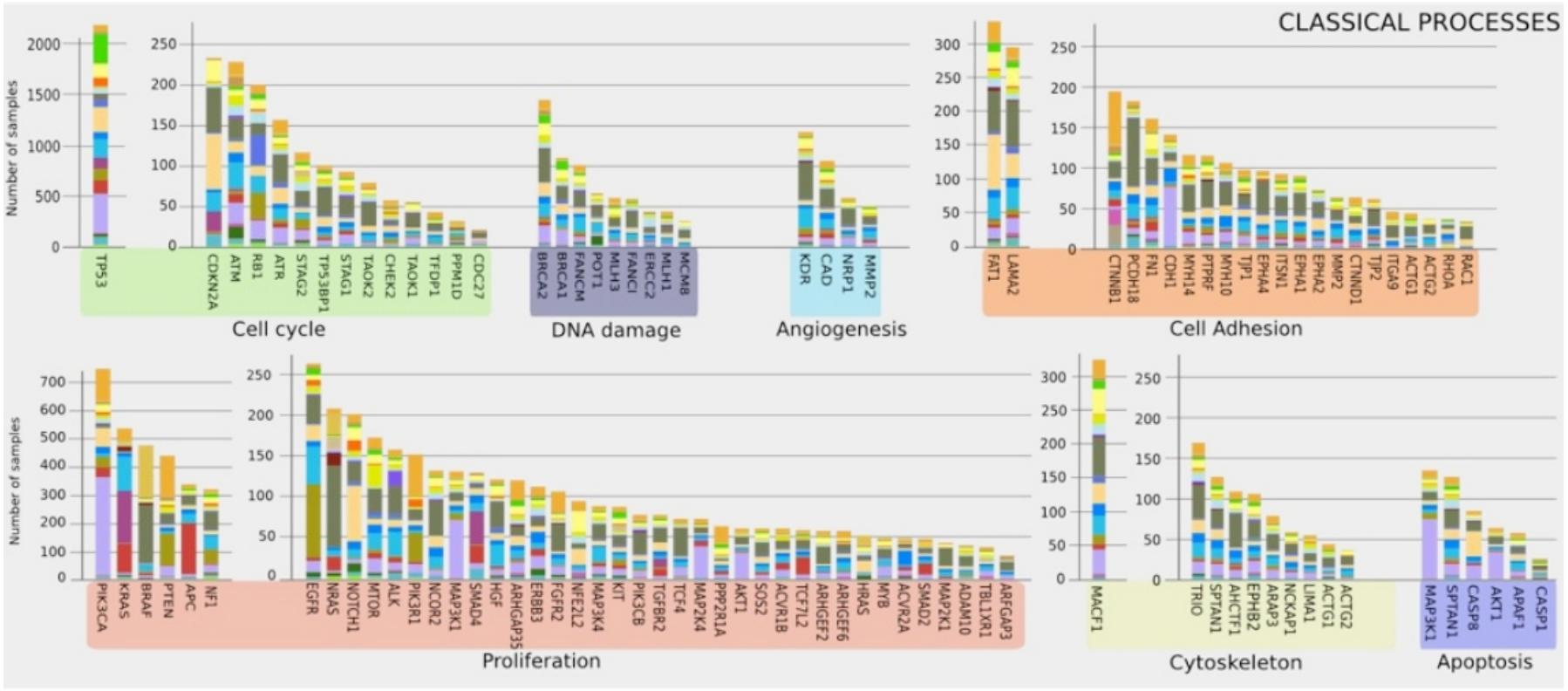


Whether a specific protein site accumulates more mutations than ***expected by chance**** *is determined by the* ***mutational processes*** *in that* ***genomic region/cancer type***



*(*mutation count is 'only' an observation – hotspot is a statistical claim)*

Catalogs of cancer genes



Perez, Tamborero et al., Cancer Cell 2016

(Bioinformatics) study of tumor genomes

During last years, **bio**informatics analyses leveraged the large amount of available (molecular) cancer data to **provide/support** new insights about the mechanisms of the tumor cell, such as:

> mutational processes

> catalogs of driver genes

> gene mechanisms of action

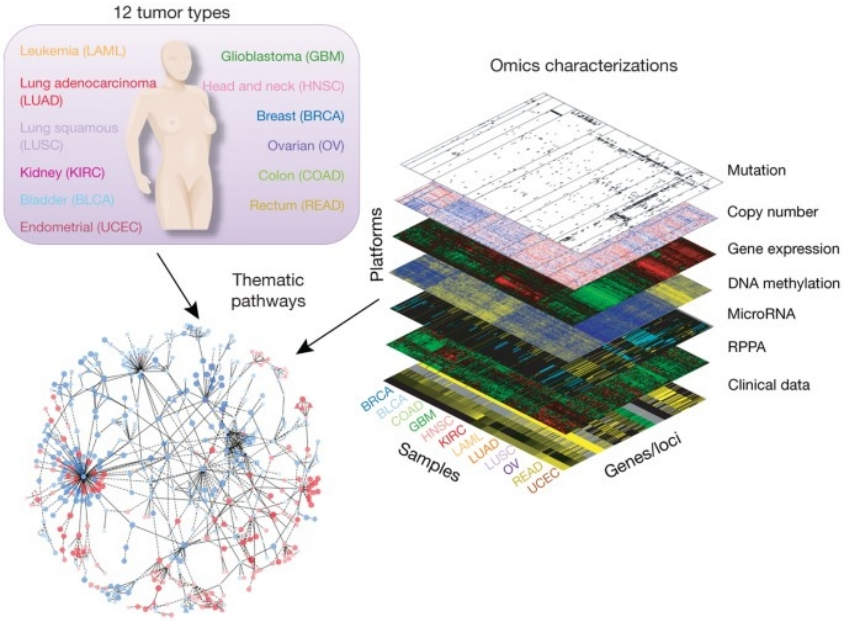
> molecular subtypes of cancer

> tumor evolution in time and space

> interactions with the TME

> identification of tumor vulnerabilities for drug interventions

> ...



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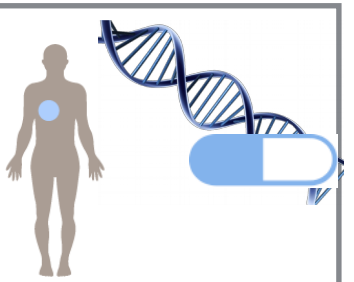

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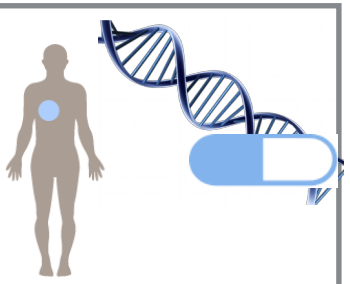

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Note that the objective here is not to generate new knowledge but to use the already available knowledge to inform a (prospective) n=1 clinical intervention

From cohorts to individual tumors

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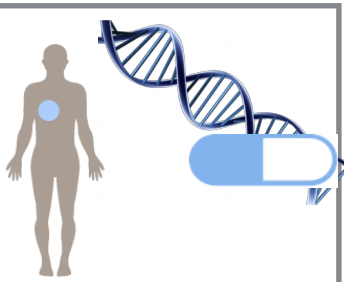

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Given the genomic alterations observed in a given patient's tumor:

- which ones are more likely to **drive** that tumor?

- which ones may be therapeutically **actionable**?