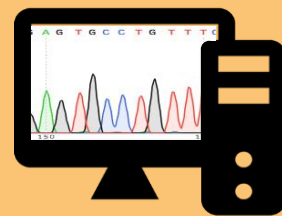


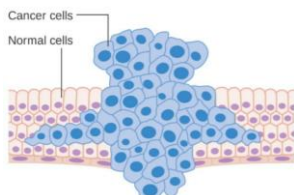
What can we learn from cancer genomes?



1 Introduction to cancer genomics

What is cancer?

Cancer is a group of diseases characterized by the **abnormal growth and spread of cells**.



Most cancers are caused by genetic alterations that can be:

- Inherited → germline
- Acquired during life → somatic

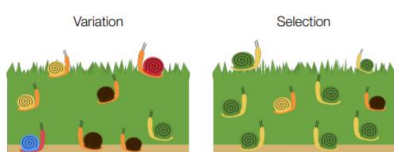
Most cancers are driven by somatic mutations.

Can Darwin teach us something about cancer?

YES!

Cancer evolves as a Darwinian evolutionary process.

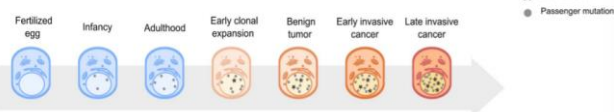
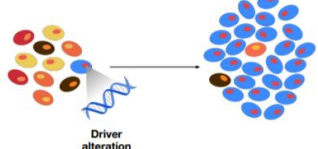
Here snails and cells behave the same way.
The more adapted, the more chances of survival.



IMPORTANT

Cancer drivers are the genomic alterations that confer selective advantage to the cell.

Driver genes are those that carry driver mutations.

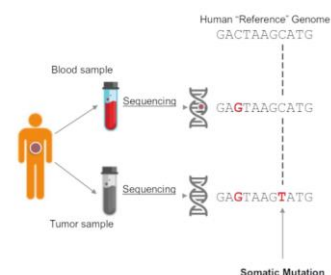


Reference 1

2 Identification of cancer drivers

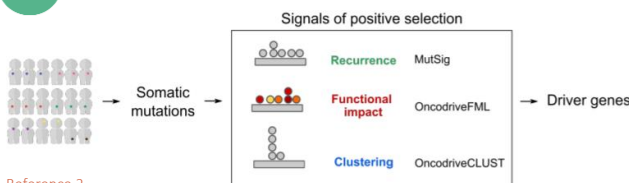
HOW DO WE IDENTIFY CANCER DRIVERS?

Sequencing tumour samples to identify cancer somatic mutations.



The main problem is that **tumours genomes have thousands of somatic mutations** and only an **average on 4.6 of them are drivers**.

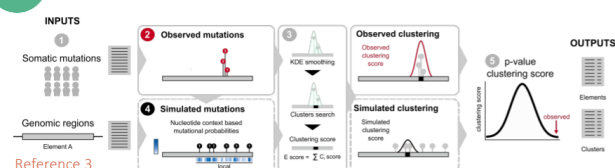
1 Signals of positive selection



Reference 2

Driver genes can be detected through **signals of positive selection** (special patterns in the distribution of mutations that appear as a result of tumorigenesis → **selective advantage**). These signals are **complementary** (not all driver genes have the 3 signals). To identify them we test **whether what we observe is expected to occur by chance** (neutral evolution).

2 A method in depth: Oncodrive CLUSTL



Reference 3

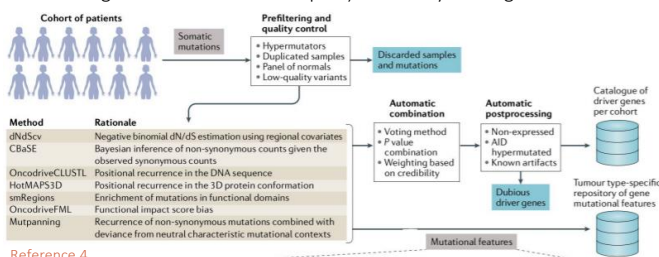
OncodriveCLUSTL is a sequence-based clustering method that **identifies drivers in protein-coding regions**.

3 The pipeline: IntOGen + boostDM

Since the signals are complementary, the idea would be to merge all these methods.

IntOGen: One method to rule them all

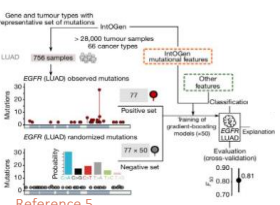
Using sequences of patients from different projects, **IntOGen uses 7 methods** (2 based on recurrence, 3 based on clustering and some of the remaining based on functional impact) to identify driver genes.



Reference 4

BUT... not all mutations in driver genes are driver mutations!

They are detected by **boostDM**, a machine learning algorithm that can predict driver mutations in human cancers.



Reference 5

PERSPECTIVES

The number of sequencings of different cancers will increase, which will allow the identification of driver mutations in less common cancers.

3 Clinical application: Cancer Genome Interpreter

Cancer Genome Interpreter is a very useful algorithm to clinics because it facilitates the **interpretation of mutations of an specific patient**. Doctors can introduce the tumour mutations that the patients have and the Cancer Genome Interpreter **identifies which ones are drivers or passengers**. This knowledge allows to choose **the most effective therapy** to each patient (personalized therapy).

ALTERATIONS

PRESCRIPTIONS

Biomarkers

Biactivities

Show entries with

mutations described as biomarkers for the selected tumor type

mutations described as biomarkers for a different tumor type

mutations in genes described as biomarkers with a different annotated change

mutations in genes described as biomarkers upon other alteration types

Sample id	Observed alteration	Drugs	Effect	Tumor type	Level of evidence	Reference	Tumor match	Biomarker match
corred_01	BRAF V600E	Cetuximab, Panitumumab	Resistant	COREAD	Late trials	PMID: 20619739 PBL		
corred_01	BRAF V600E	Vemurafenib	Resistant	COREAD	Early trials	PMID: 26287891		
corred_01	BRAF V600E	Irinotecan + Cetuximab + Vemurafenib	Responsive	COREAD	Guidelines	NCIN guidelines		
corred_01	BRAF V600E	Panitumumab + Dabrafenib + Trametinib	Responsive	COREAD	Early trials	ASCO 2015 label 103...		
corred_01	BRAF V600E	Panitumumab + Dabrafenib + Alpelisib	Responsive	COREAD	Early trials	PMID: 26362009		
corred_02	APC R1450* + G	Tyrosine inhibitor	Responsive	COREAD	Pre-clinical	PMID: 22460713 PBL		
corred_05	RNF43 A169T	Perceptase inhibitor	Responsive	COREAD	Case report	ENA 2015 label CAS...		

Reference 6

REFERENCES

- Ref 1. Adapted from Stratton et al., Nature 2009
 Ref 2. Tamborero et al., Sci. Rep. 2013; Porta-Pardo et al., Nat. Methods 2017
 Ref 3. Arnedo-Pac et al., Bioinformatics 2019
 Ref 4. Martinez-Jimenez et al., Nat Rev Cancer 2020
 Ref 5. Muñoz et al., Nature 2021
 Ref 6. Tamborero et al., Genome Medicine 2018