

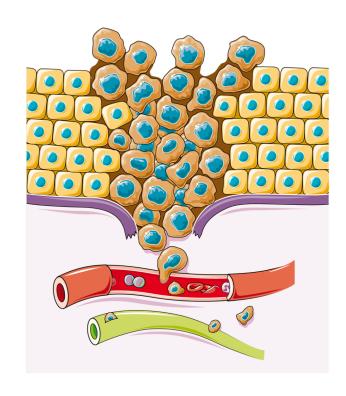
Analysis of Cancer Dependency Maps

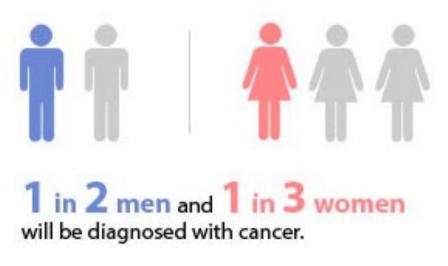
Antoine Bichat
Artificial intelligence & Health
June 29, 2022



WHAT IS CANCER?

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body



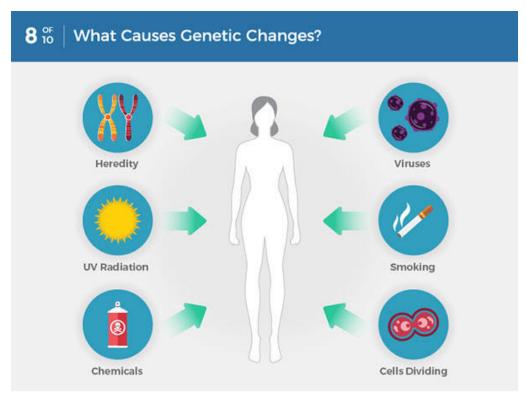


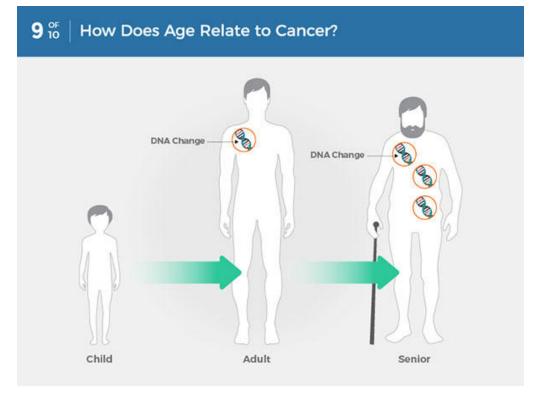
Cancer Treatment Centers of America



WHAT CAUSES CANCER?

Cancer is a genetic disease, caused by changes to genes that control the way our cells function, especially how they grow and divide

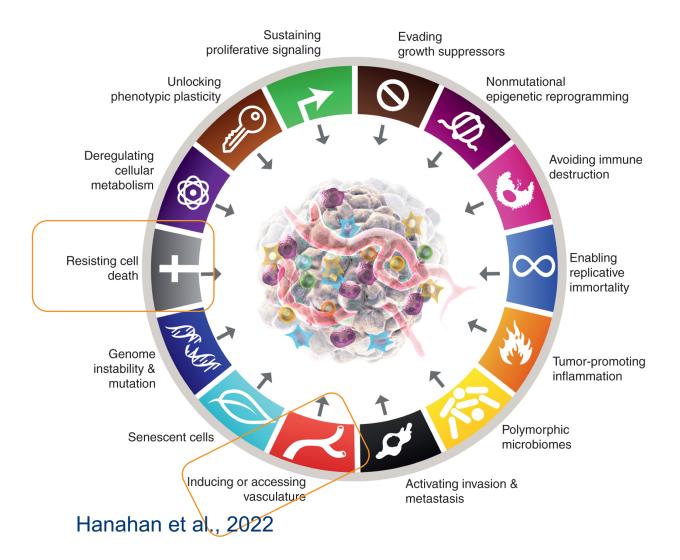








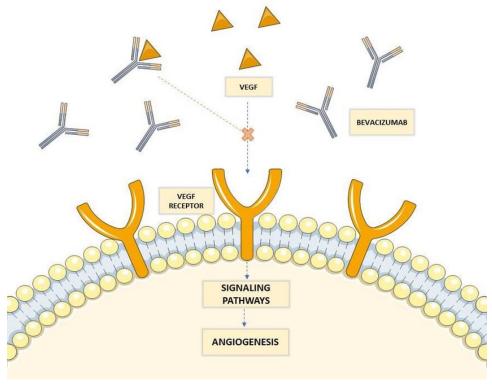
CANCER HALLMARKS





TARGETED THERAPIES

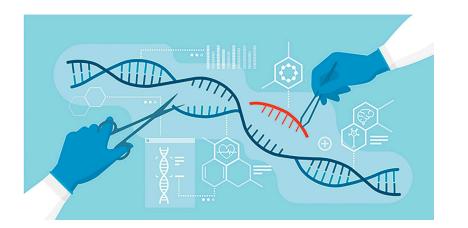
- Counter essential survival mechanisms of cancers
- e.g. Bevacizumab
 - binds to VEGF (Vascular Endothelial Growth Factor)
 - prevents angiogenesis



Kotoski et al., 2018



CRISPR SCREENS



CRISPR-Cas9 technology can edit any part genome



This could be use to remove genes (silencing)



One can see how cell survive without a particular gene



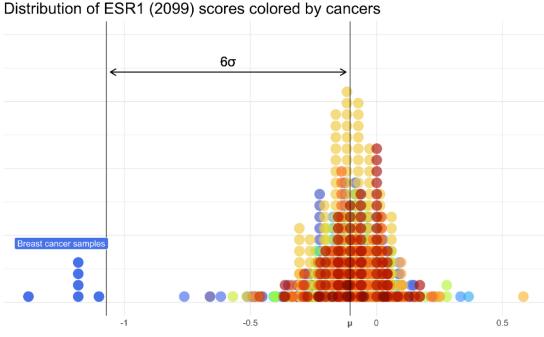
DEPMAP DATA



■ All of 20'000 gens were silencied one by one in 800 cell lines (CCLE)

A viability/dependency score is associated with each experiment

A more negative score implies a more essential gene for the cell line

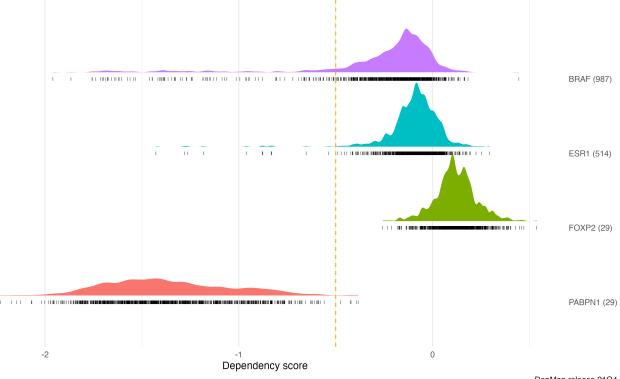




SELECTIVE DEPENDENCIES

We want to find genes that are essential in a specific group of cell lines (e.g. an indication)

with left tail



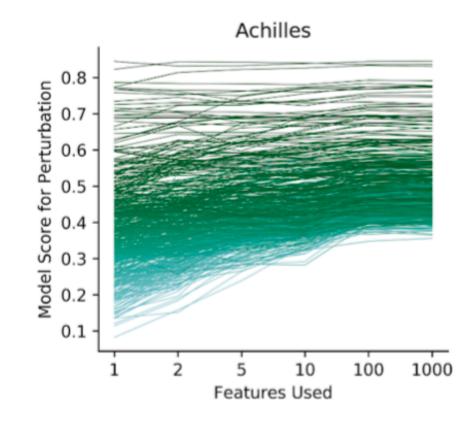
DepMap release 21Q4



PREDICTING DEPENDENCY

Dependency ~ all genes expression

- Random forest with recursive features elimitation:
 - Fit a RF model on the top 1000 features
 - Select the top 100 most important features
 - Fit a RF model on these 100 features
 - ...
 - Select the top 5 most important features



Dempster et al., 2020



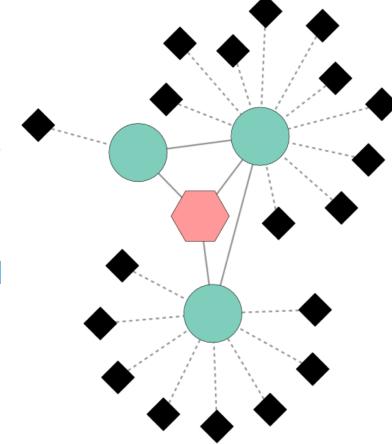
DRUG REPURPOSING

Identify potential target as selective essential gene

Identify significant neighbours of this gene in a PPI

Find drugs that targets these neighbours





- Target gene
- Proxy-target gene
- Drug



LIMITATIONS

CRISPR silencings could fail or have offtarget effects

Some oncogenic mechanisms are not available in cell lines (angiogenesis)

DepMap failed to retrieve targets from most used oncodrugs

Best selling oncodrugs				
Drug	Molecule	Indication*	Target	Essentiality**
Opdivo	Nivolumab	Melanoma	PDCD1	
Lenalidomide	Revlimid	Myeloma	CRBN	
Herceptin	Trastuzumab	Breast cancer	ERBB2	
Avastin	Bevacizumab	Colorectal cancer	VEGFA	
Rituxan	Rituximab	Non– Hodgkin's Lymphoma	MS4A1	
Ibrance	Palbociclib	Breast cancer	CDK4	
Xtandi	Enzalutamide	Prostate cancer	AR	

*First indication given by DrugBank.

**Probability of dependency in indication versus others.

← Low dependency

High dependency ⇒

^{*} EEDVIE





www.servier.com

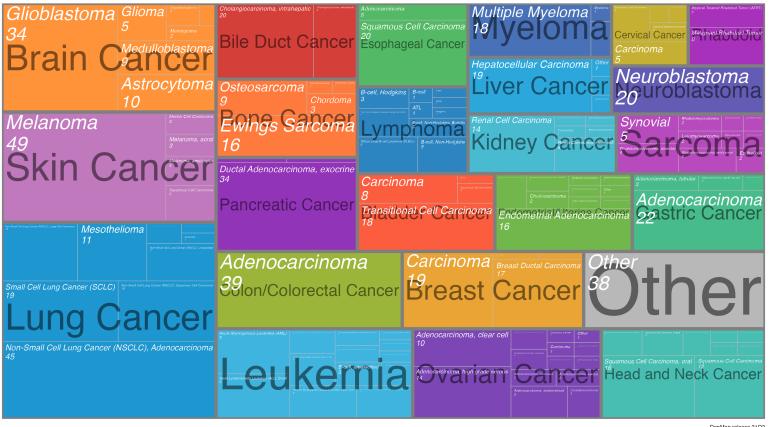
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CELL LINES IN CCLE

Among the 1814 samples of CCLE, 859 are screened by Achilles



DepMap release 21Q2



DEPENDENCY SCORE AND PROBABILITY

Relationship between gene scores and probabilities

