Double Trouble: Understanding Sex Differences in Synthetic Lethal interactions in Human Cancers

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Synthetic Lethality has Been Around for Some Time

- (1922) American geneticist Calvin Bridges was crossing fruit flies (*Drosophila melanogaster*) and observed certain genes were lethal only in combination
- (1946) Years later, a colleague of Bridges observed the same phenomena in a different species of fruit fly, *Drosophila pseudoobscura*, and coined the term 'synthetic lethality'

Synthetic = Combining

[1] Nijman, 2011

The Combined Inactivation of Two Genes Can Lead to Synthetic Lethal Interactions

- Synthetic lethal interactions describe the relationship between two genes whose coupled inactivation, but not their individual inactivation, causes cell death or reduces cell viability

- Inactivation: Preventing or disabling normal function of a gene (e.g mutation)

[2] Lee et al., 2018

Researchers Harness Synthetic Lethal Interactions in a Variety of Biological Applications

To gain insight into gene function

- In *Saccharomyces cerevisiae* (baker's yeast), the mapping of synthetic lethal interactions has reached a genome-wide scale and these networks of interaction are a rich source for the functional annotation of genes

[3] Nijman, 2011; Shen and Ideker, 2018

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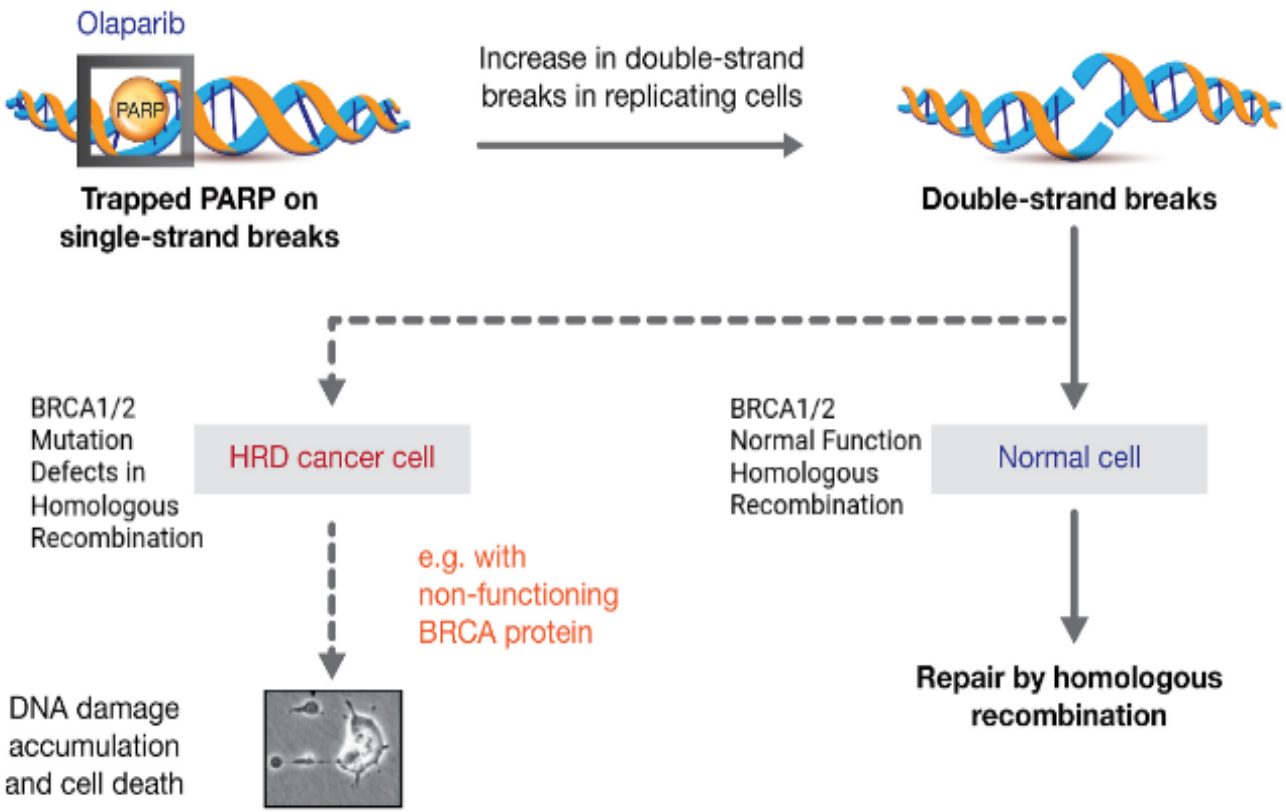
To uncover new opportunities for precision oncology

- An emerging strategy is to identify potential synthetic lethal interactions between tumor suppressor genes and other genes that can be simultaneously disrupted leading to cancer cell death (e.g. Olaparib was the first drug to work via a synthetic lethal mechanism)

[3] Nijman, 2011; Shen and Ideker, 2018

Four FDA Approved Anti-Cancer Drugs Work via a Synthetic Lethal Mechanism

- Olaparib, Niraparib, Rucaparib, Talazoparib are Poly [ADP-ribose] polymerase 1/2 (PARP1/2) inhibitors



[4] Figure From O'Connor, 2015

Synthetic Lethality can also Help Explain Factors Related to the Tissue-Specificity of Cancer

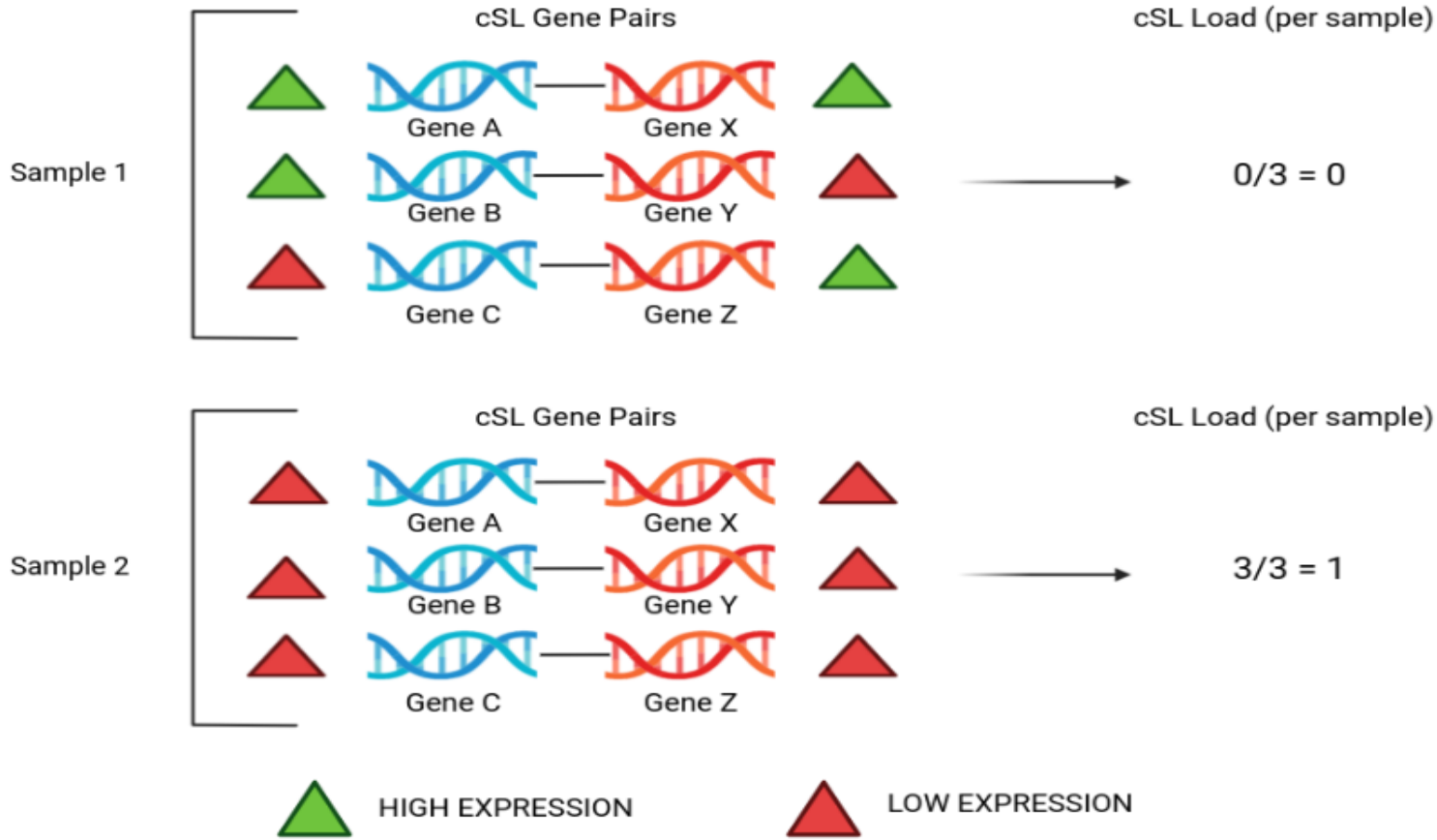
Tissue Specificity: Cancers which manifest in different human tissues have different molecular, phenotypic, and epidemiological characteristics. Some aspects of this phenomena are;

1. Variation in lifetime cancer risk
2. Variation in cancer onset age
3. Variation in the genes driving the cancer across tissue types

The literature has only reported the **number of lifetime stem cell divisions** and the **abnormal levels of CpG island DNA methylation** to be factors able to explain the variance in lifetime cancer risk across tissues (aside from well known global and cancer-specific factors)

Quantifying cSL Load in Normal Human Tissue

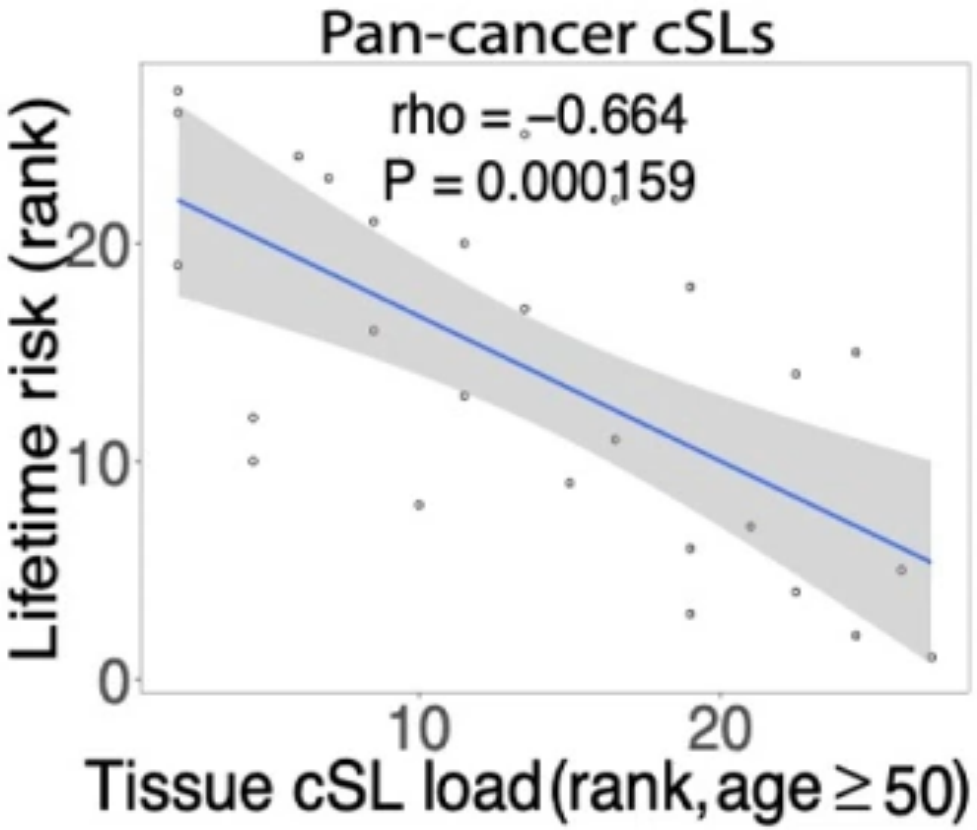
cSL Load: Quantitatively captures the level of cancer synthetic lethal (cSL) gene pair co-inactivation based on gene expression data from normal human tissues



[5] Adapted From Cheng et al., 2021

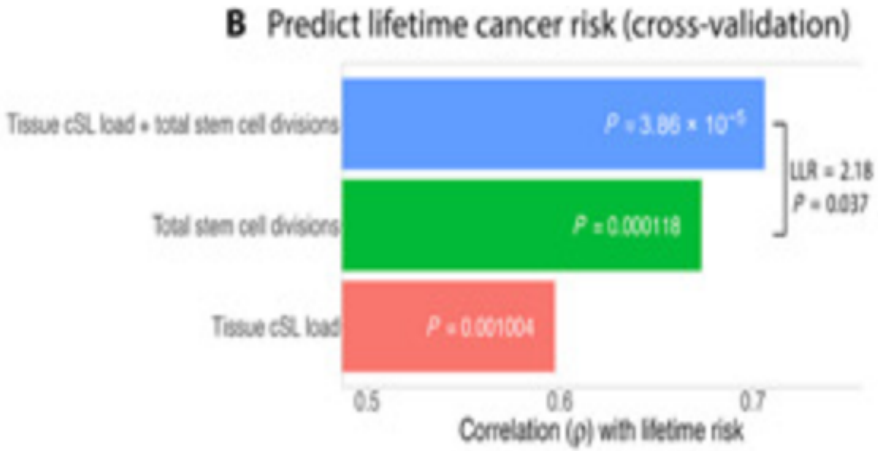
Tissue cSL Load in Normal Tissues is Negatively Correlated with Lifetime Cancer Risk

Tissue cSL Load: Median cSL load value across all samples of each tissue type

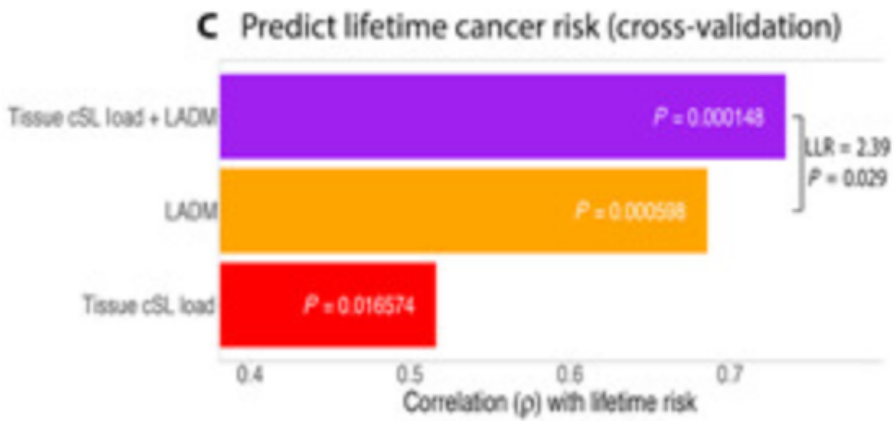


[5] Cheng et al., 2021

Synthetic Lethality Increases Predictive Power of Models Associated with Tissue Specificity



Stem Cell Divisions

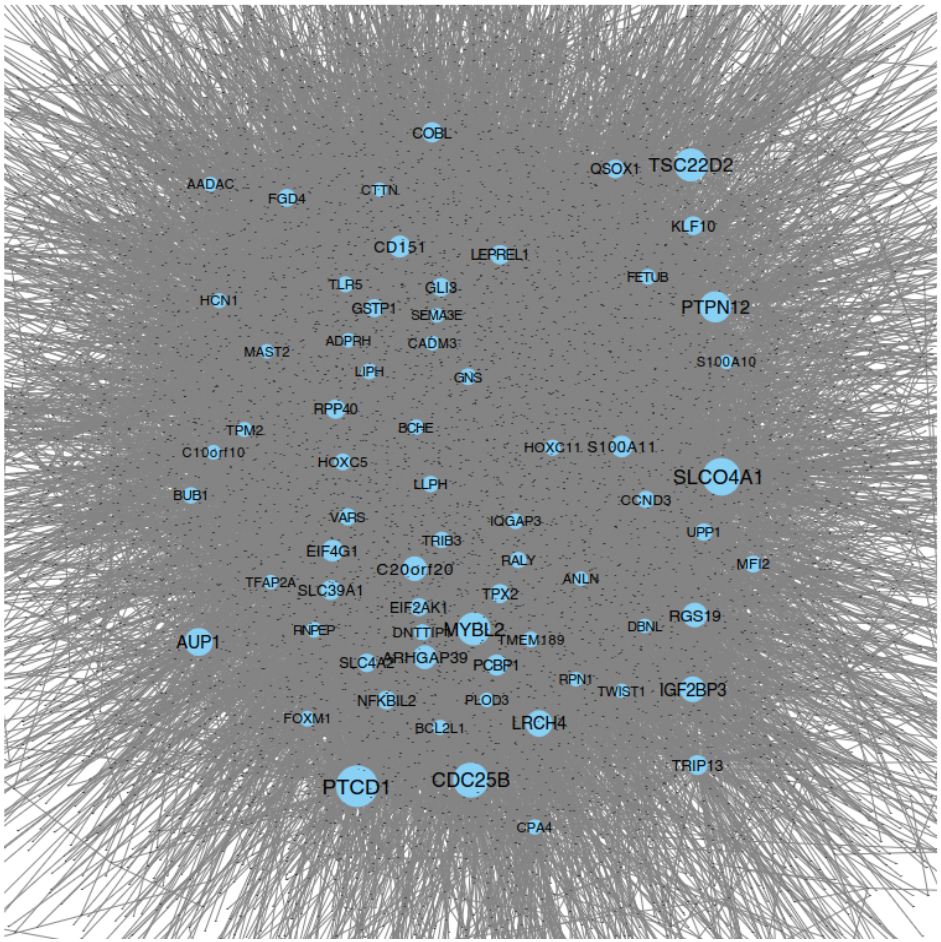


Methylation

[5] Cheng et al., 2021

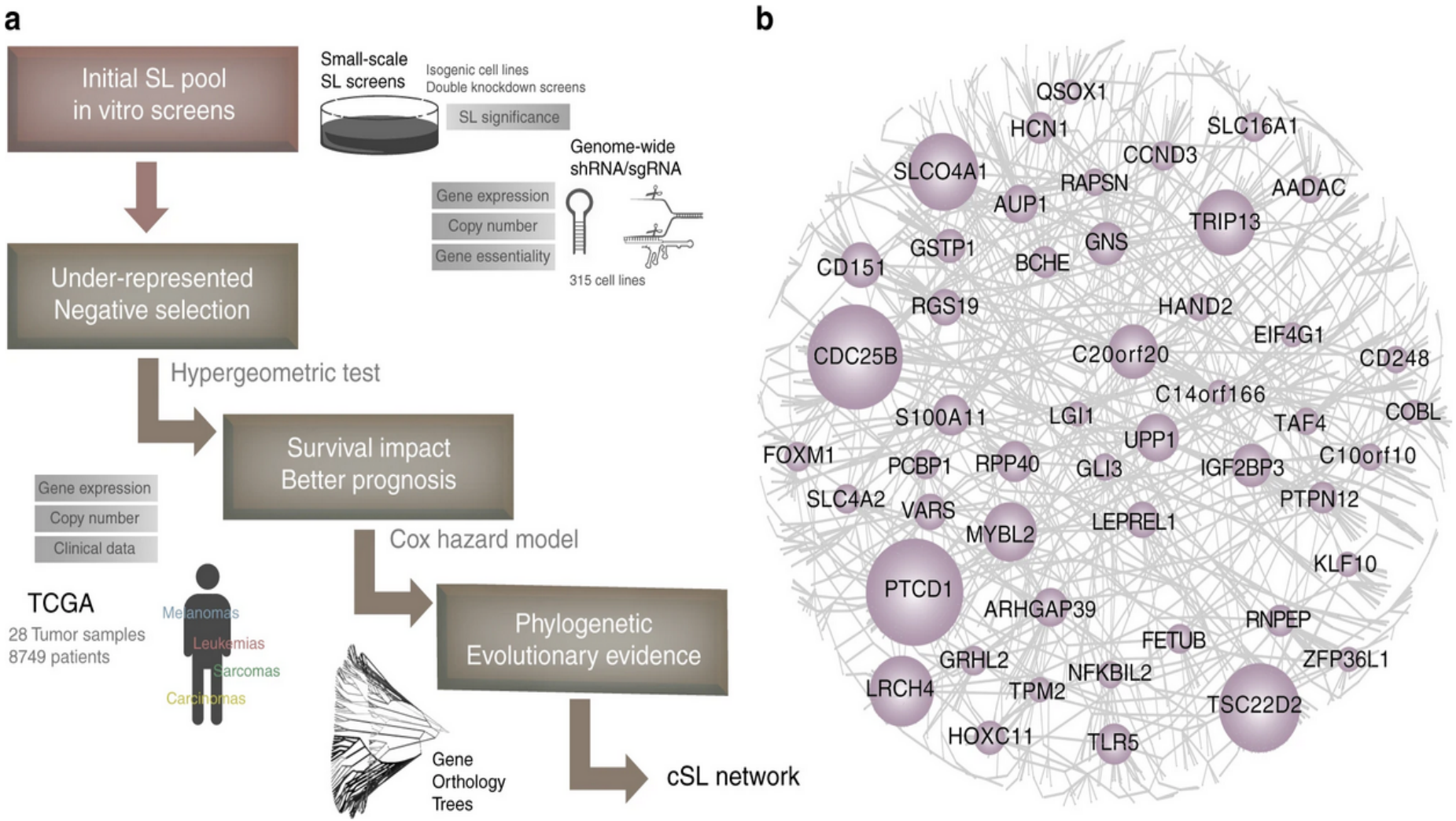
Where did the Data come From?

A recently published reference set of genome-wide cSLs common to many cancer types was utilized



[2] Lee et al., 2018

Building Pan-Cancer Synthetic Lethality Networks



[2] Lee et al., 2018

There is Variability in Synthetic Lethal Interactions Depending on Cancer Type

Pan-Cancer Analysis: Analysis of multiple types of cancer simultaneously, aims to identify commonalities shared across different types
Cancer-Specific Analysis: Analysis of individual cancer types to better understand the variation within a specific cancer type

- Pan-cancer analyses may overlook cancer-specific differences
- Availability of datasets for all cancer types varies, this may limit statistical power of pan-cancer analyses

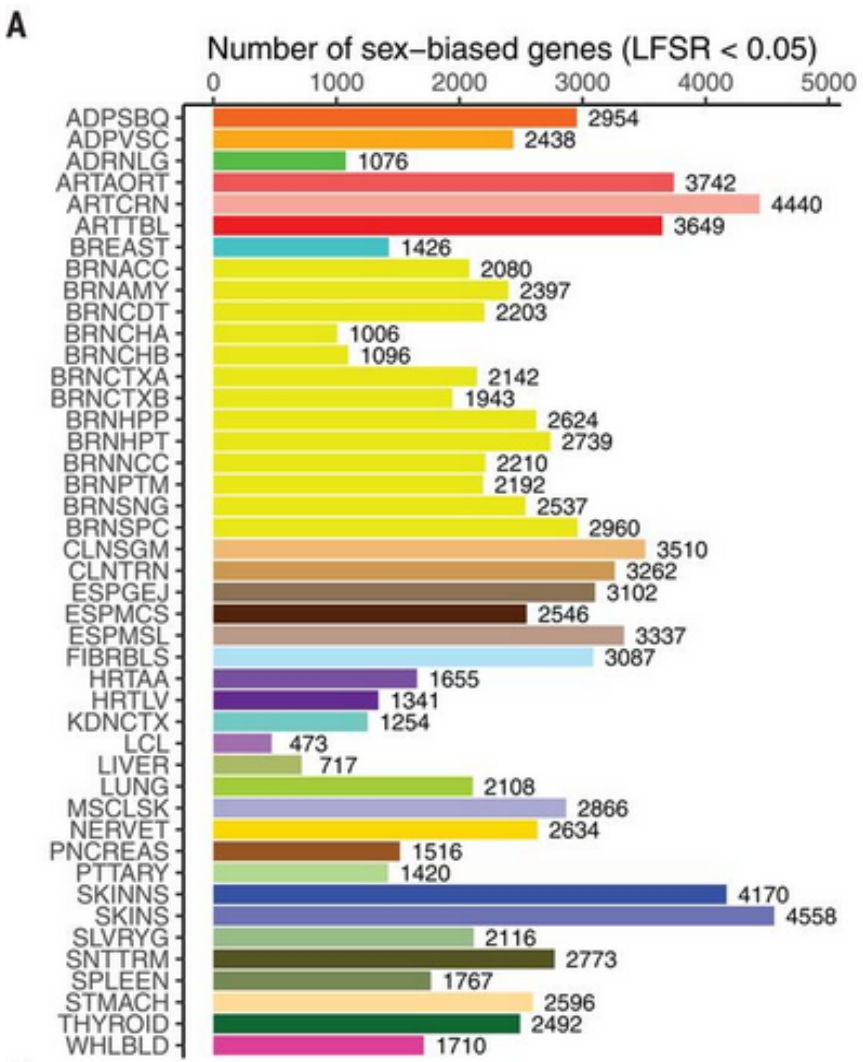
Sex Differences Add an Additional Layer of Complexity

Human sex differences are mainly caused by;

1. Gonadal hormone secretions
2. Genes located on the sex chromosomes (X and Y)

This leads to differences in the frequency of certain cancer types and the efficacy of treatments in males and females

Sex Differences Add an Additional Layer of Complexity



[6] Oliva et al., 2020

The Objective

Can we build sex-specific synthetic lethality networks for various cancer types?

More specifically, we are trying to elucidate the differences in synthetic lethal interactions between males and females using a network based approach.