Topic 05
drug repurposing for cancer cell lines

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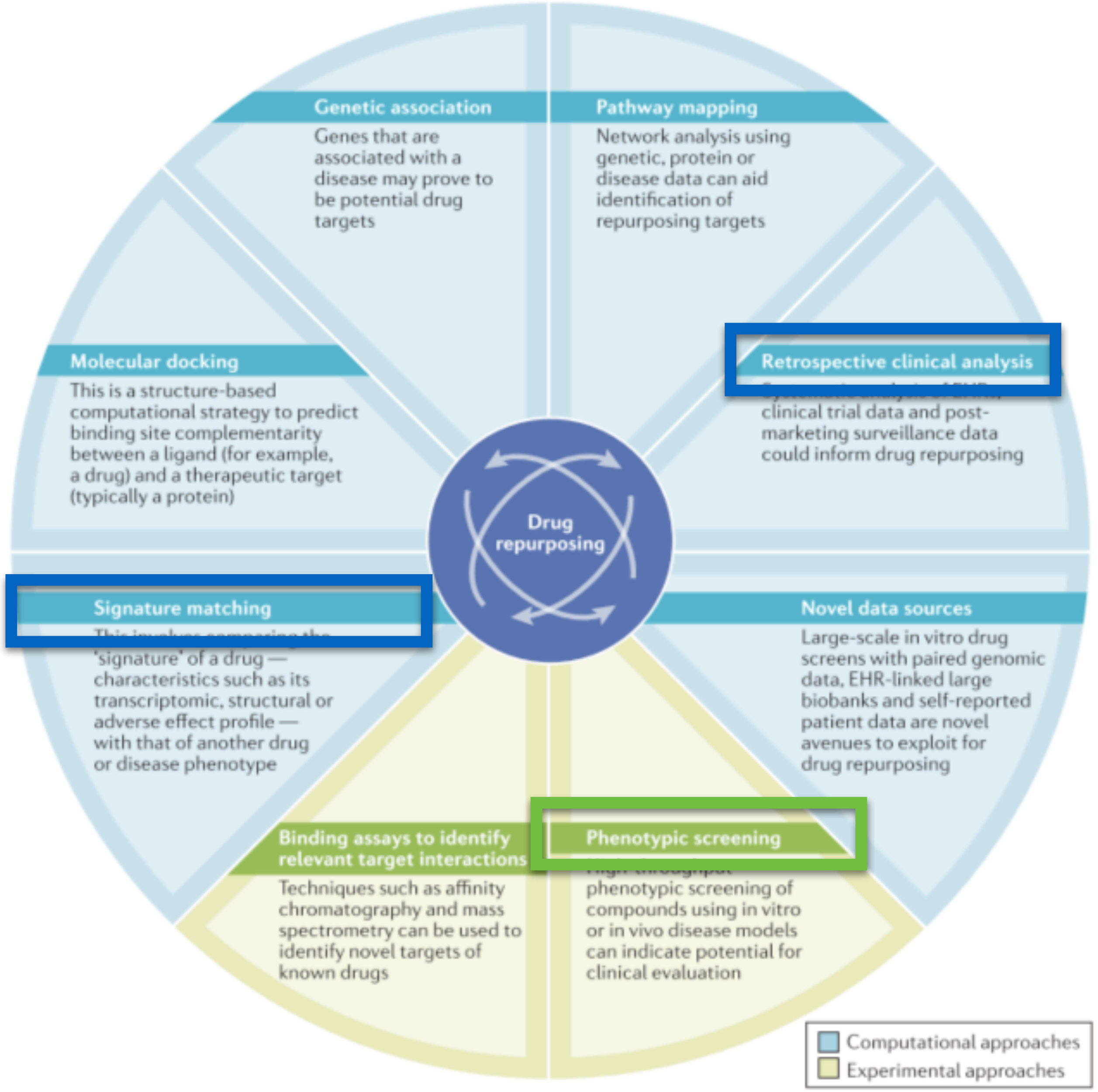
Strategies for drug repurposing



Genetic association
Genes that are associated with a disease may prove to be potential drug targets

Pathway mapping
Network analysis using genetic, protein or disease data can aid identification of repurposing targets

Molecular docking
This is a structure-based computational strategy to predict binding site complementarity between a ligand (for example, a drug) and a therapeutic target (typically a protein)

Retrospective clinical analysis
clinical trial data and post-marketing surveillance data could inform drug repurposing

Drug repurposing

Signature matching
'signature' of a drug — characteristics such as its transcriptomic, structural or adverse effect profile — with that of another drug or disease phenotype

Novel data sources
Large-scale in vitro drug screens with paired genomic data, EHR-linked large biobanks and self-reported patient data are novel avenues to exploit for drug repurposing

Binding assays to identify relevant target interactions
Techniques such as affinity chromatography and mass spectrometry can be used to identify novel targets of known drugs

Phenotypic screening
phenotypic screening of compounds using in vitro or in vivo disease models can indicate potential for clinical evaluation

🟦 Computational approaches
🟨 Experimental approaches

[Pushpakom et al., Nature Reviews Drug Discovery]

- Experimental/computational strategies for pre-screening of drug
    - **matching signature profiles**: which genes are affected by a specific drug? does this correspond to genes differentially expressed in a specific disease?
    - **using clinical data** based electronic health records
    - **phenotypic screens** using large libraries of celllines and molecules

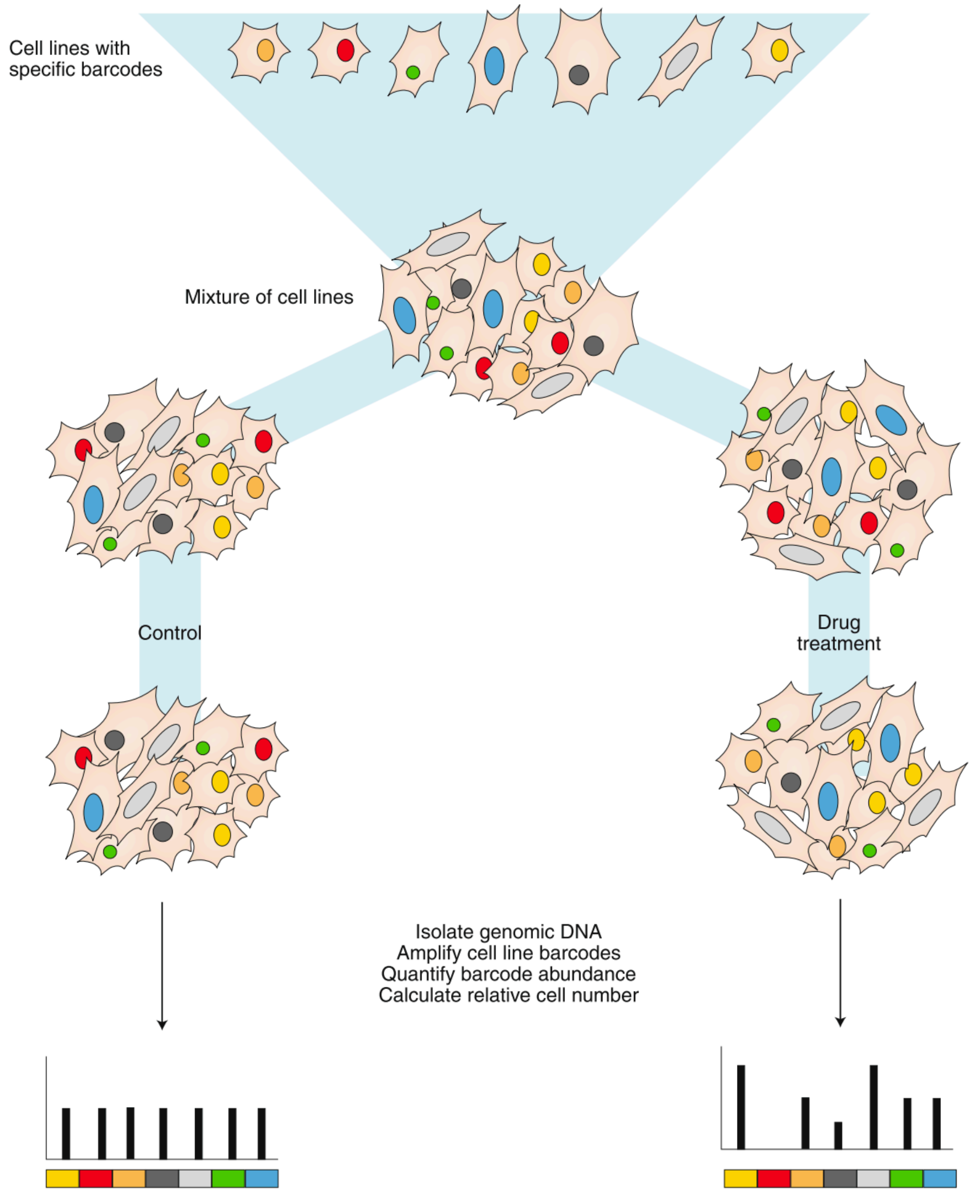
DepMap

- Large-scale screening effort by **Broad Institute** focussed on cancer cell lines
  - cell line expression profiles (RNA-seq)
  - Sensitivity to CRISPR/Cas9 gene knock-out
  - Genomic profiling of cell lines (single-nucleotide variation - SNV / copy-number variations - CNV)
  - Drug sensitivity (cell growth/survival - expression profiles)

[Boehm et al., Nature (2021)]

https://depmap.org

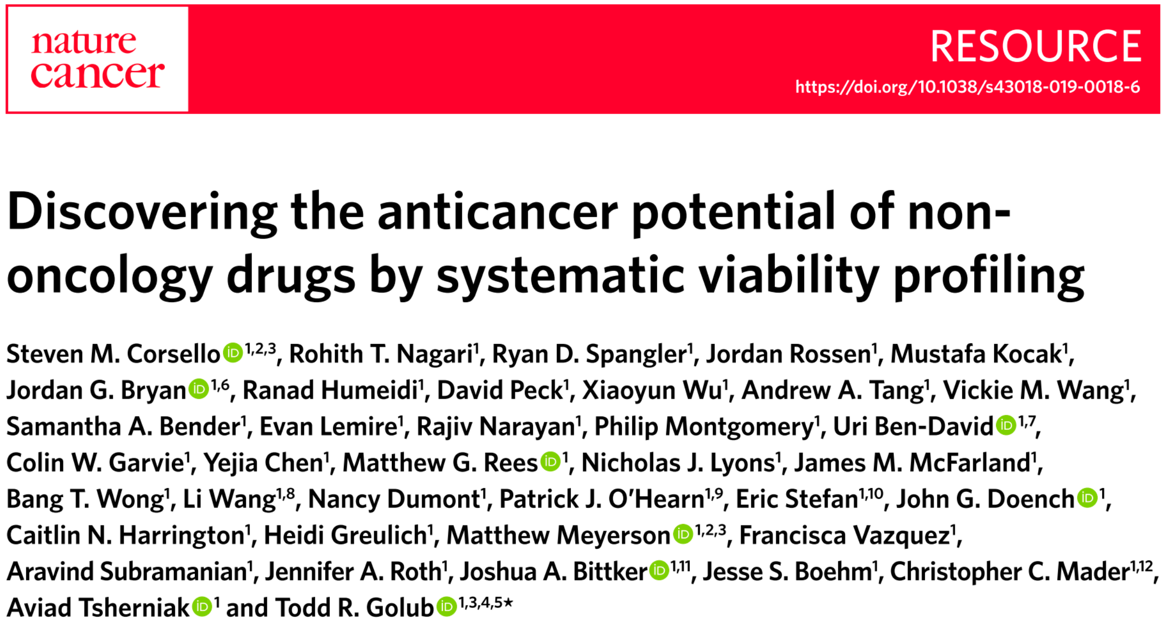
PRISM methodology for screening



[Yu et al., Nature Biotechnology (2016)]
[Beijersbergen, Nature Cancer (2020)]

- Plate based assay
- each cellline has a specific **barcode** → mixture of celllines
- each well corresponds to a specific drug/concentration/condition
- amount of barcode is determined through colored beads (imaging assay)
  - treatment condition
  - control condition
- Ratio of treatment vs control indicates the effect of the drug on a specific cell line!

Large-scale screening



nature cancer

RESOURCE

https://doi.org/10.1038/s43018-019-0018-6

Discovering the anticancer potential of non-oncology drugs by systematic viability profiling

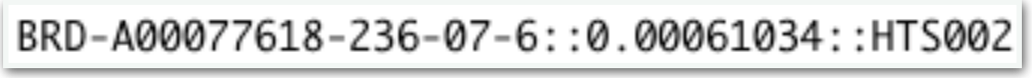
Steven M. Corsello[1,2,3], Rohith T. Nagari[1], Ryan D. Spangler[1], Jordan Rossen[1], Mustafa Kocak[1], Jordan G. Bryan[1,6], Ranad Humeidi[1], David Peck[1], Xiaoyun Wu[1], Andrew A. Tang[1], Vickie M. Wang[1], Samantha A. Bender[1], Evan Lemire[1], Rajiv Narayan[1], Philip Montgomery[1], Uri Ben-David[1,7], Colin W. Garvie[1], Yejia Chen[1], Matthew G. Rees[1], Nicholas J. Lyons[1], James M. McFarland[1], Bang T. Wong[1], Li Wang[1,8], Nancy Dumont[1], Patrick J. O'Hearn[1,9], Eric Stefan[1,10], John G. Doench[1], Caitlin N. Harrington[1], Heidi Greulich[1], Matthew Meyerson[1,2,3], Francisca Vazquez[1], Aravind Subramanian[1], Jennifer A. Roth[1], Joshua A. Bittker[1,11], Jesse S. Boehm[1], Christopher C. Mader[1,12], Aviad Tsherniak[1] and Todd R. Golub[1,3,4,5]*

February 2020

- 4518 drugs tested on 578 human cell lines
    - 77% are non-oncological drugs
    - 21% targeted oncology agents
    - 2% chemotherapeutics
- 2 stage screening strategy
    - first stage: single-dose screening → 1448 positive drugs
    - second stage: 1448 drugs were rescreened with various doses

Structure of the data

Drug ID::concentration::screen



```
BRD-A00077618-236-07-6::0.00061034::HTS002
```

cell line ID

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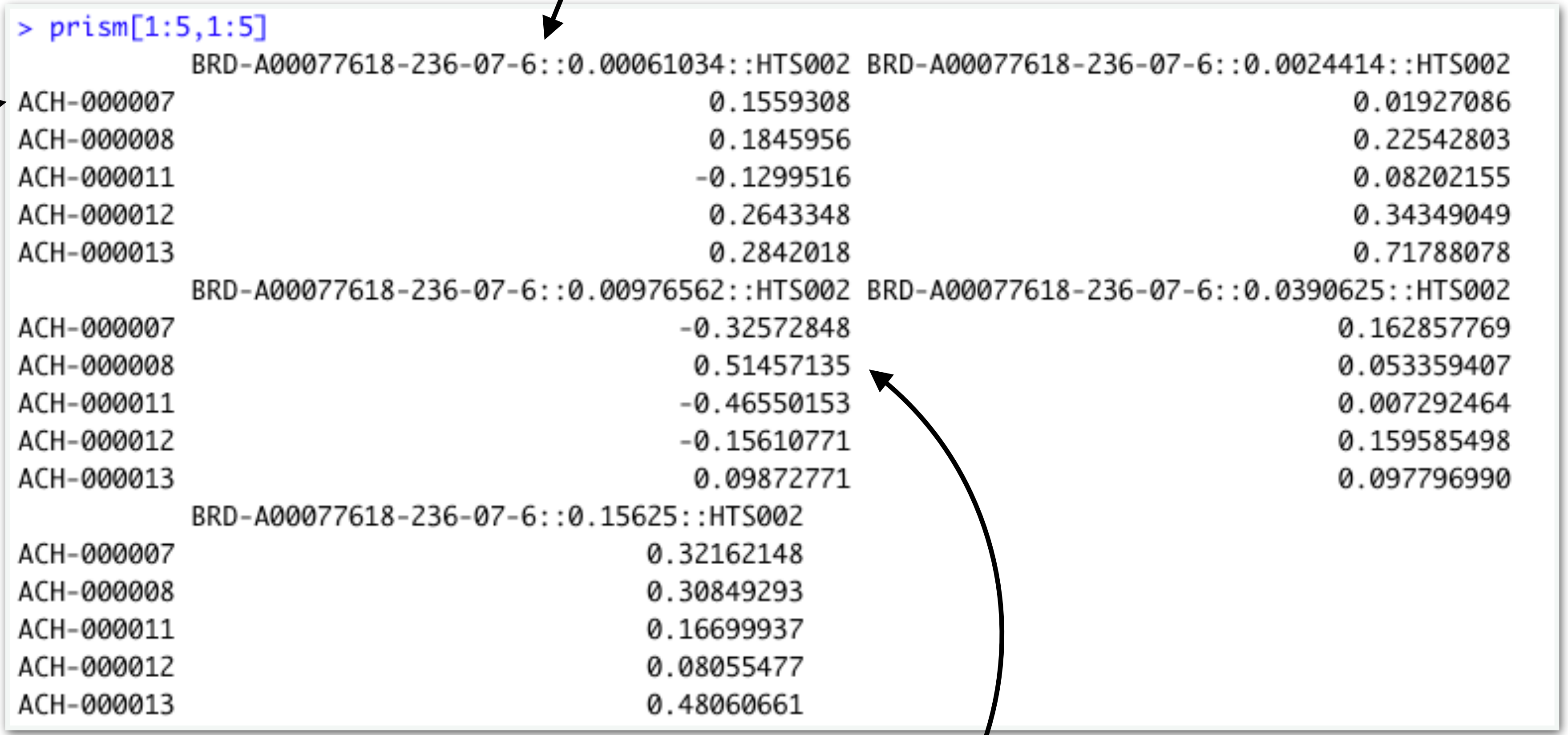
ACH-000007
```



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ACH-000008                                  0.1845956                                0.22542803
ACH-000011                                 -0.1299516                                0.08202155
ACH-000012                                  0.2643348                                0.34349049
ACH-000013                                  0.2842018                                0.71788078
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ACH-000011                                -0.46550153                               0.007292464
ACH-000012                                -0.15610771                               0.159585498
ACH-000013                                 0.09872771                               0.097796990
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ACH-000011                              0.16699937
ACH-000012                              0.08055477
ACH-000013                              0.48060661
```

```
0.51457135
```

https://depmap.org/repurposing/

signal: log(treatment/control)
check exact protocol!

Complementary dataset

- ACHILLES Project (part of DepMap)
- CRISPR/Cas9 gene knock-out screen on cancer cell lines
    - 18,119 genes
    - 808 cell lines
- Can be used to investigate the relationship between drug and genetic sensitivity!

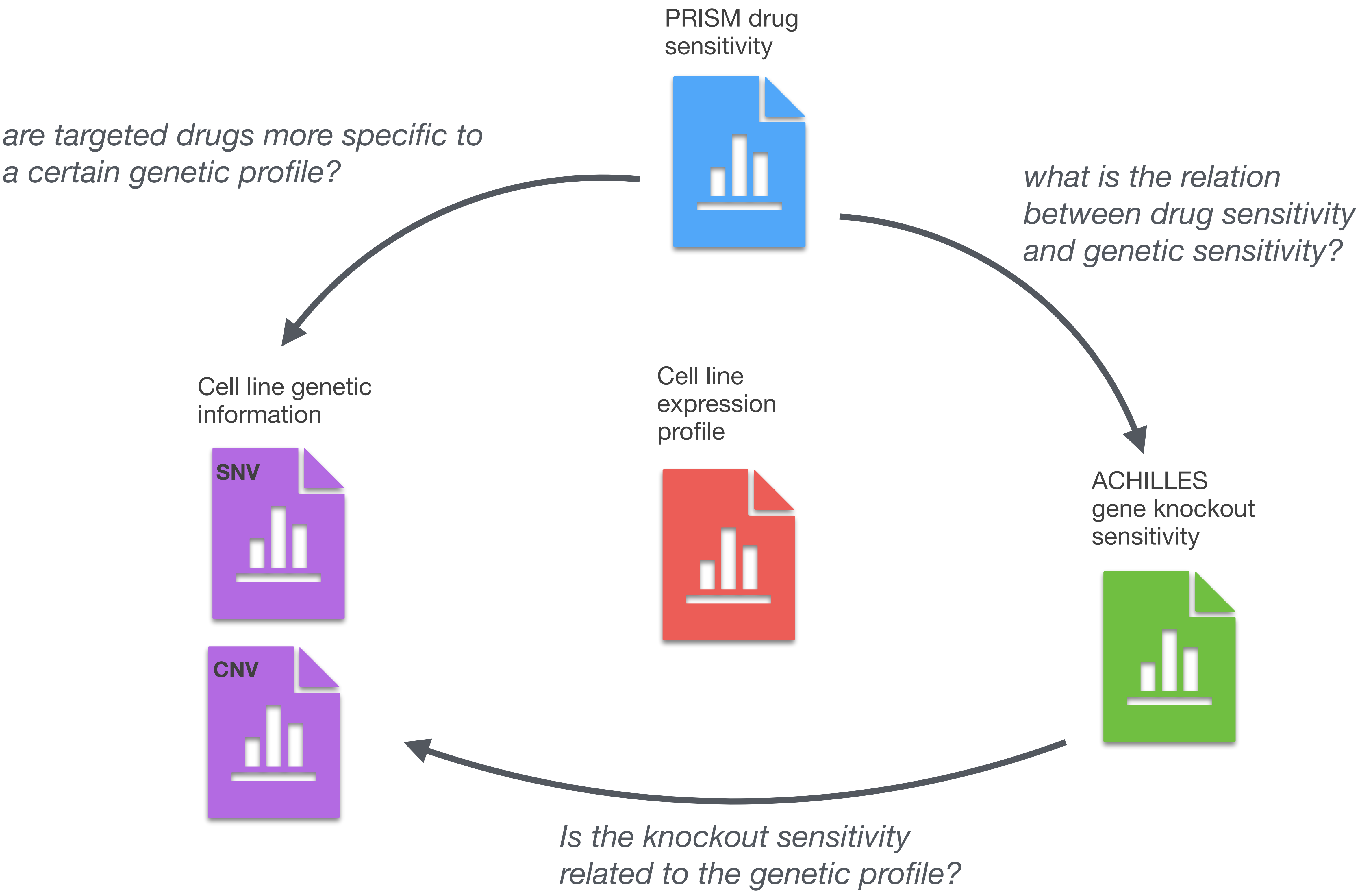
Datasets

- The datasets are available as **R objects** (see project description here https://github.com/datascience-mobi/01_DrugSensitivity_2021)
  - Drug sensitivity screen (PRISM dataset)
  - Gene knockout sensitivity screen (ACHILLES data)
  - Genetic data on the cell lines
    - SNV profiles
    - CNV profiles
  - Expression profiles of cell lines
  - Metadata on
    - cell lines
    - drugs

Biological questions

- Which are the non-oncological drugs that are efficient on cancer cell lines?
  - in general
  - for a set of tumor specific cell lines (lung tumor / skin / ...)
- How do drugs / cell lines cluster with respect to their sensitivity profiles?
- What are the most **predictive features**?
  - single-nucleotide polymorphisms / copy-number variations in cancer cell lines
  - gene expression profiles?
  - sensitivity to knock-down?
- Sub-projects: focus on cell lines for a specific tumor type

Biological questions



PRISM drug sensitivity

are targeted drugs more specific to a certain genetic profile?

what is the relation between drug sensitivity and genetic sensitivity?

Cell line genetic information

Cell line expression profile

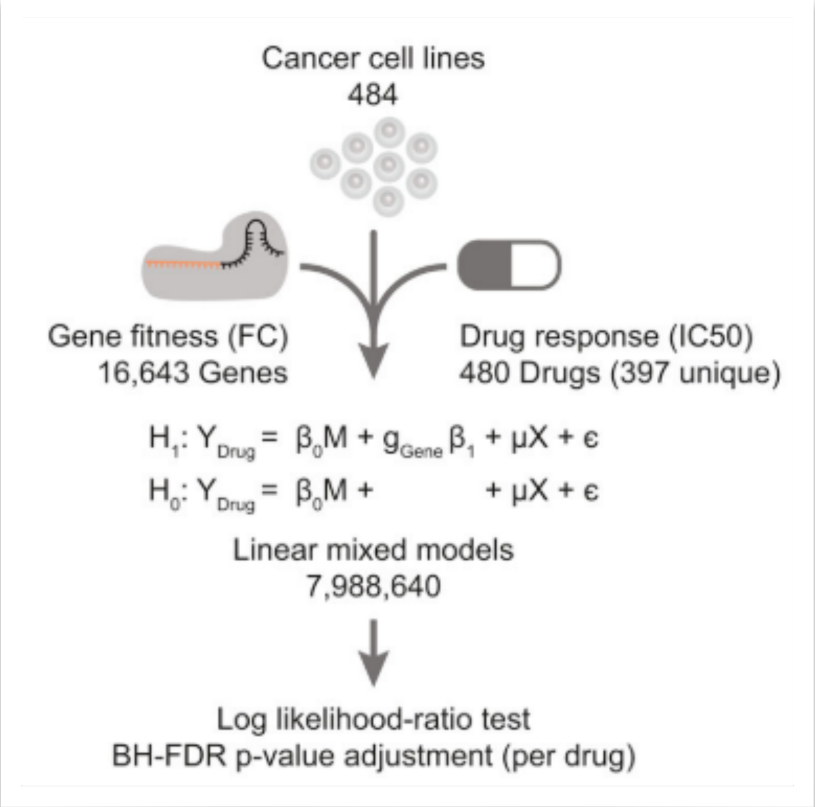
ACHILLES gene knockout sensitivity

Is the knockout sensitivity related to the genetic profile?

Relation drug sensitivity/gene sensitivity?

Drug mechanism-of-action discovery through the integration of pharmacological and CRISPR screens

Emanuel Gonçalves[1], Aldo Segura-Cabrera[2], Clare Pacini[1], Gabriele Picco[1], Fiona M Behan[1], Patricia Jaaks[1], Elizabeth A Coker[1], Donny van der Meer[1], Andrew Barthorpe[1], Howard Lightfoot[1], Tatiana Mironenko[1], Alexandra Beck[1], Laura Richardson[1], Wanjuan Yang[1], Ermira Lleshi[1], James Hall[1], Charlotte Tolley[1], Caitlin Hall[1], Iman Mali[1], Frances Thomas[1], James Morris[1], Andrew R Leach[2], James T Lynch[3], Ben Sidders[3], Claire Crafter[3], Francesco Iorio[1,4], Stephen Fawell[5] & Mathew J Garnett[1,*]



Cancer cell lines
484

Gene fitness (FC)
16,643 Genes

Drug response (IC50)
480 Drugs (397 unique)

$H_1: Y_{Drug} = \beta_0 M + g_{Gene} \beta_1 + \mu X + \varepsilon$

$H_0: Y_{Drug} = \beta_0 M + \qquad \mu X + \varepsilon$

Linear mixed models
7,988,640

Log likelihood-ratio test
BH-FDR p-value adjustment (per drug)

- How does drug sensitivity relate to knock-out sensitivity?

First steps

- Download the datasets
- Open them in R
- Perform some descriptive statistics!
    - plots
    - summary statistics
    - ...
- **Get an impression for the data!**
- More advanced users:
    - ggplot2
    - tidyverse