Project Statius

Prediction of individualized therapeutic vulnerabilities in cancer from genomic profiles

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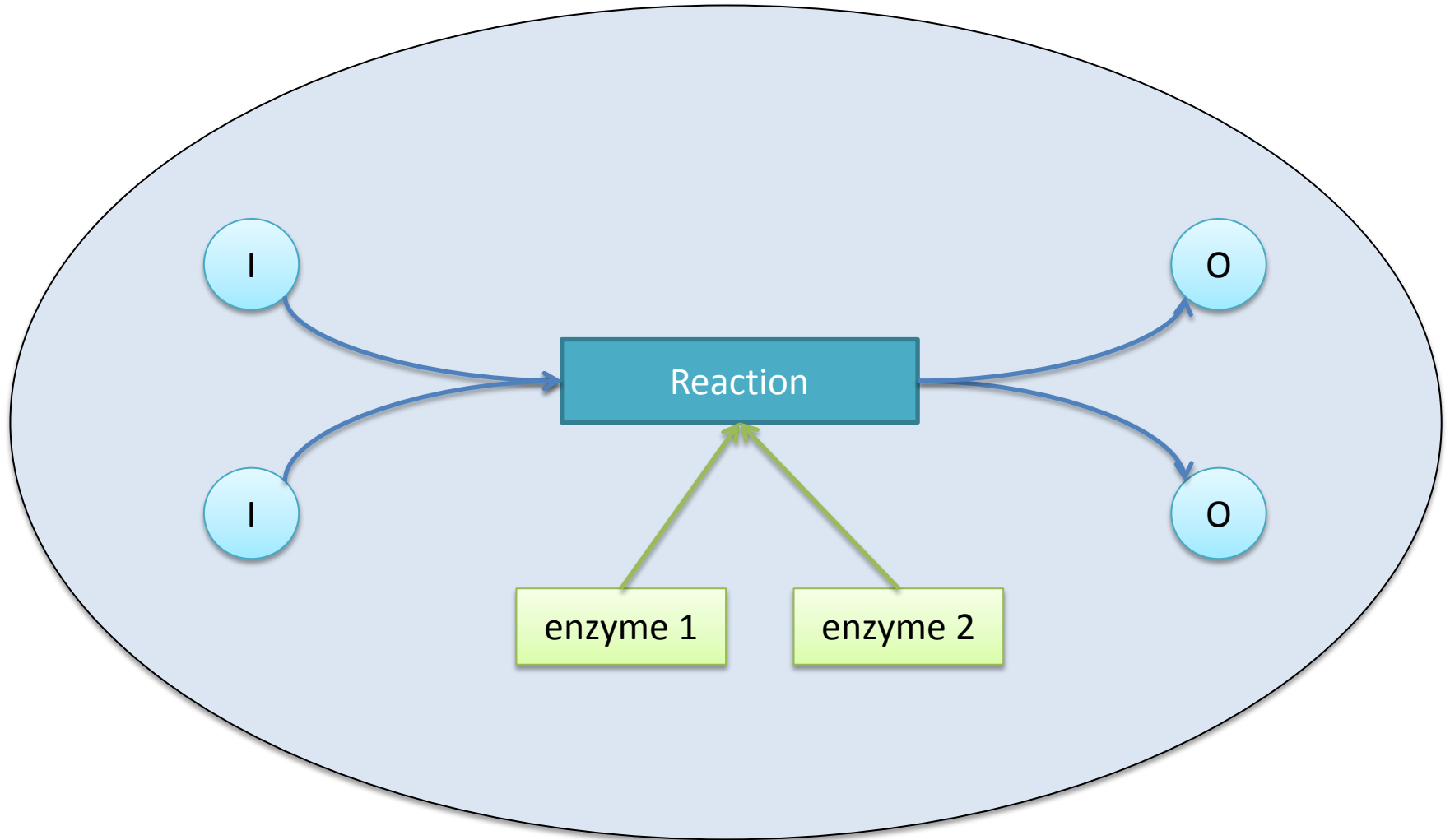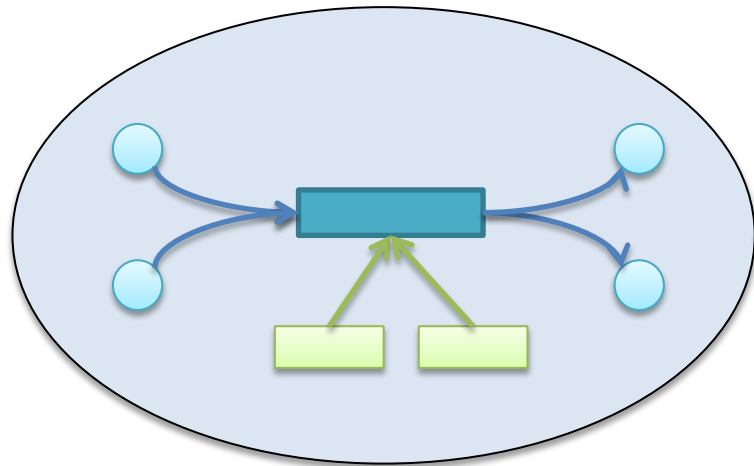
Memorial Sloan-Kettering
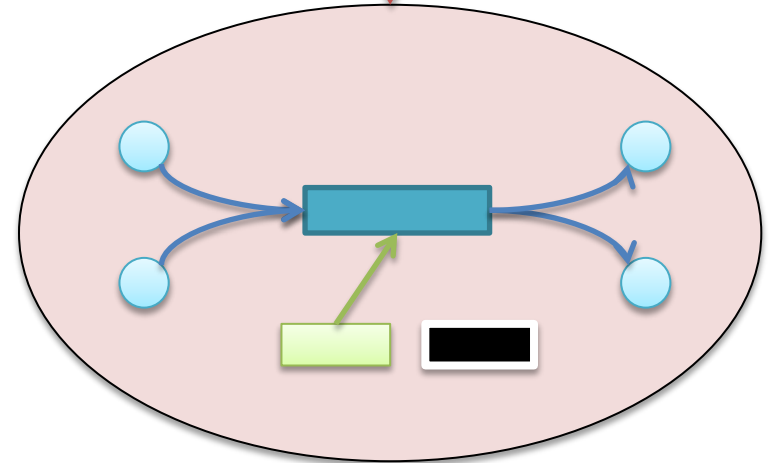Cancer Center

**TCGA Annual Scientific Symposium
May 12, 2014**

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Normal cell
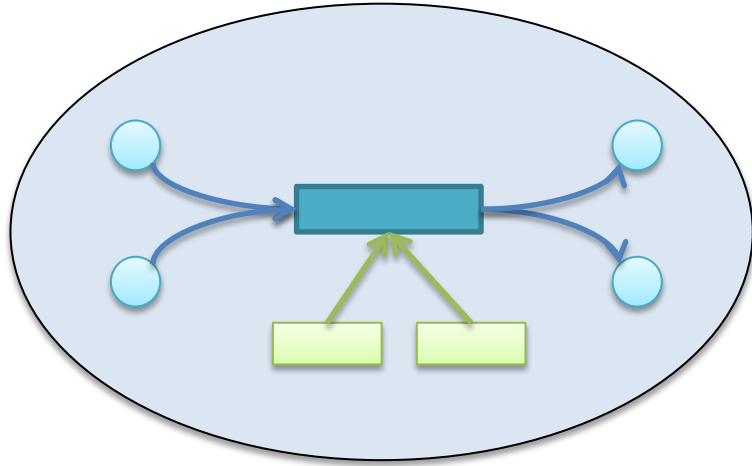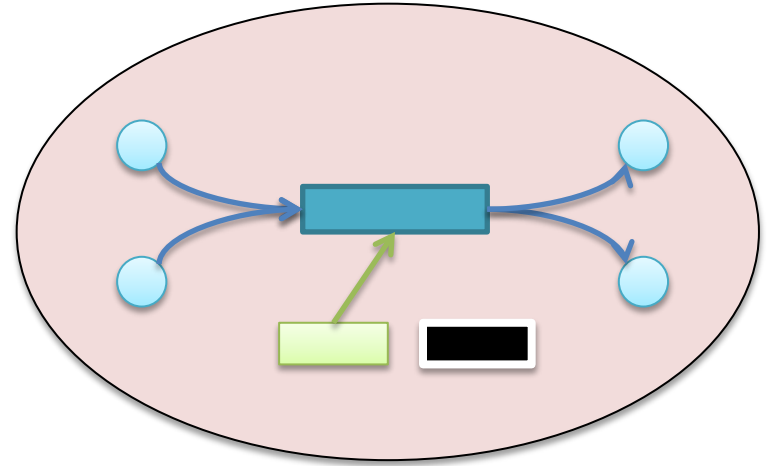
Normal cell

Cancerogenesis

Cancer cell

- **Cancerogenesis**
  - Many factors
  - Genomic Instability
    - **Homozygous Deletions**
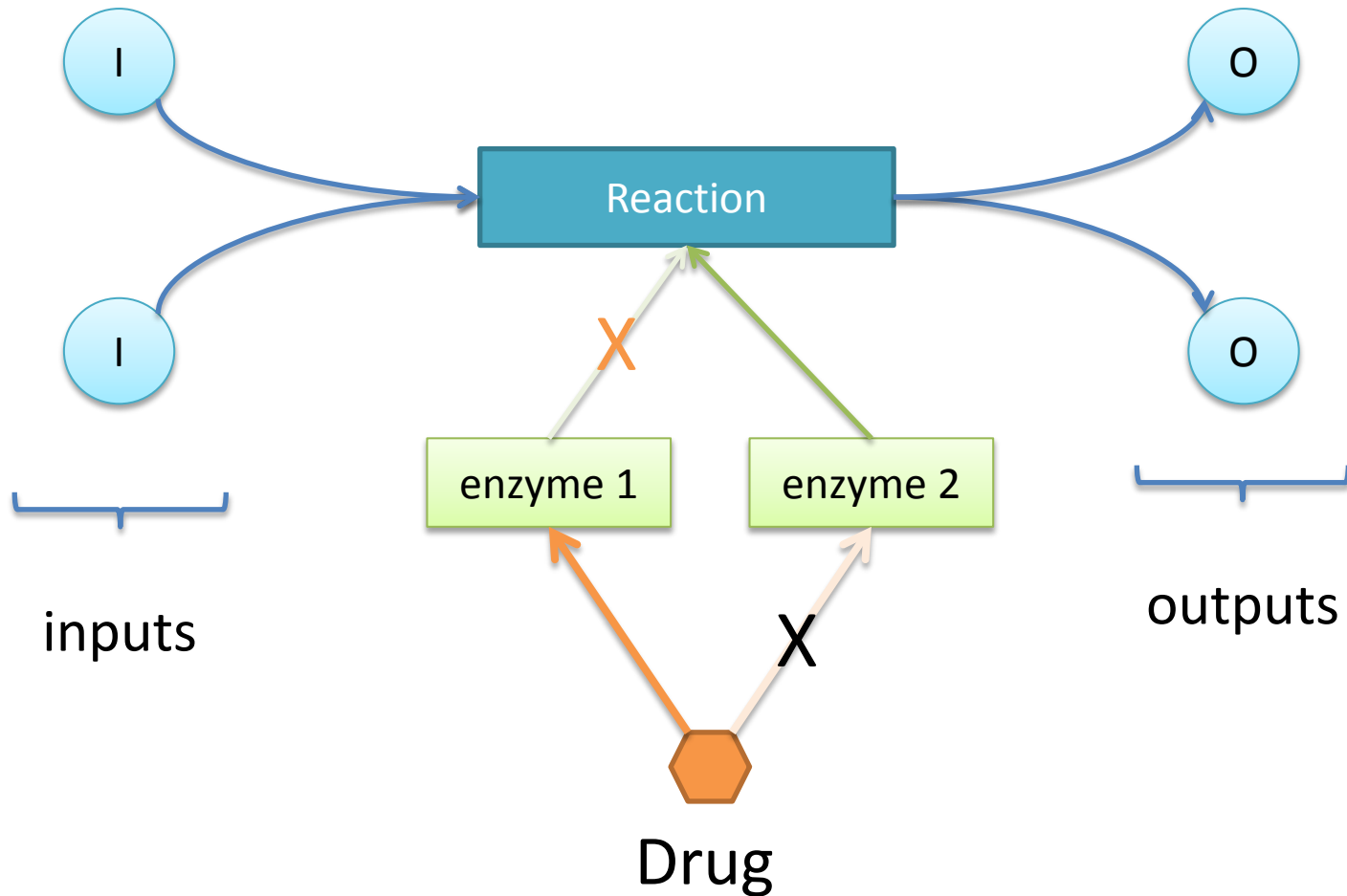   - **One of the enzymes is lost by chance**

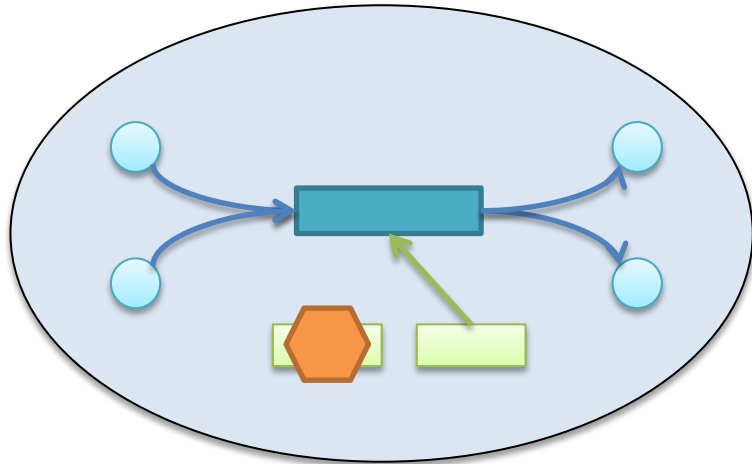Normal cell   Cancer cell

Both can catalyze the reaction!
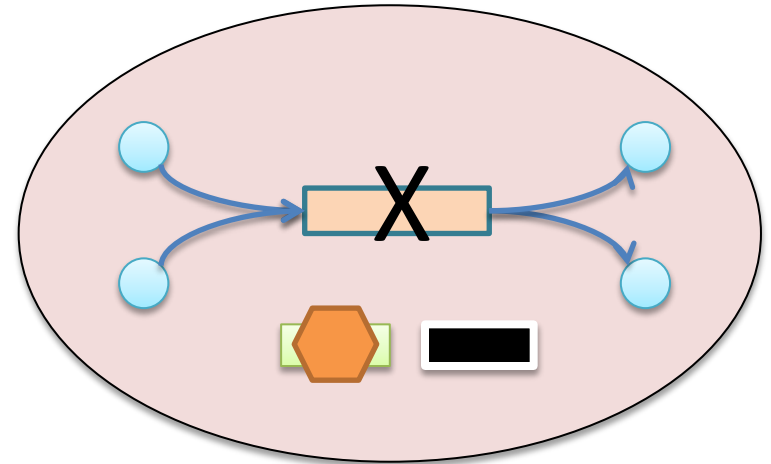
Targeted, selective drugs

Vulnerability

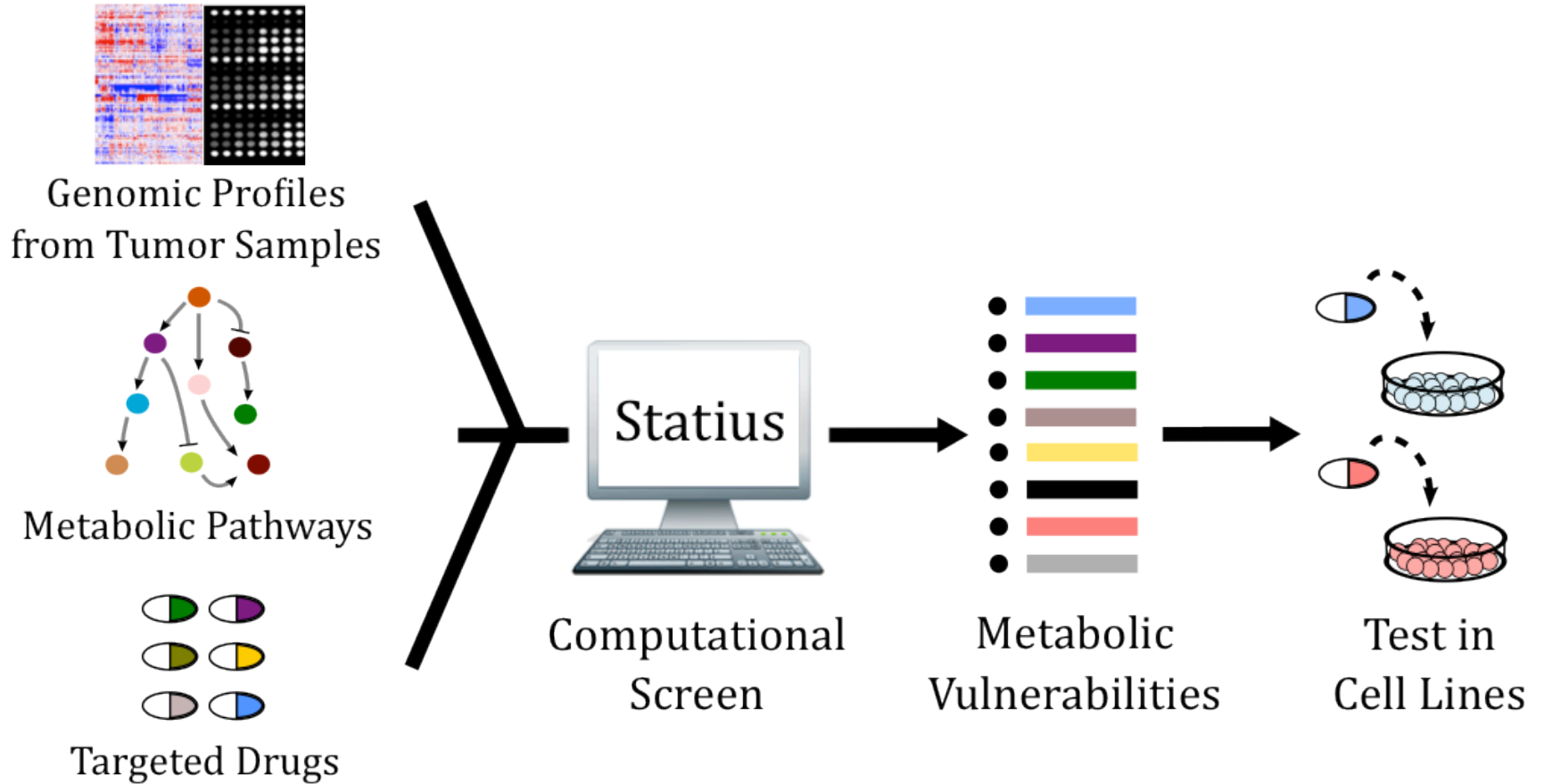
Normal cell

Cancer cell

Still can catalyze the reaction!

Cannot catalyze the reaction anymore!

- **Drug (⬡) selectively kills cancer cells**
  - Reduced toxicity

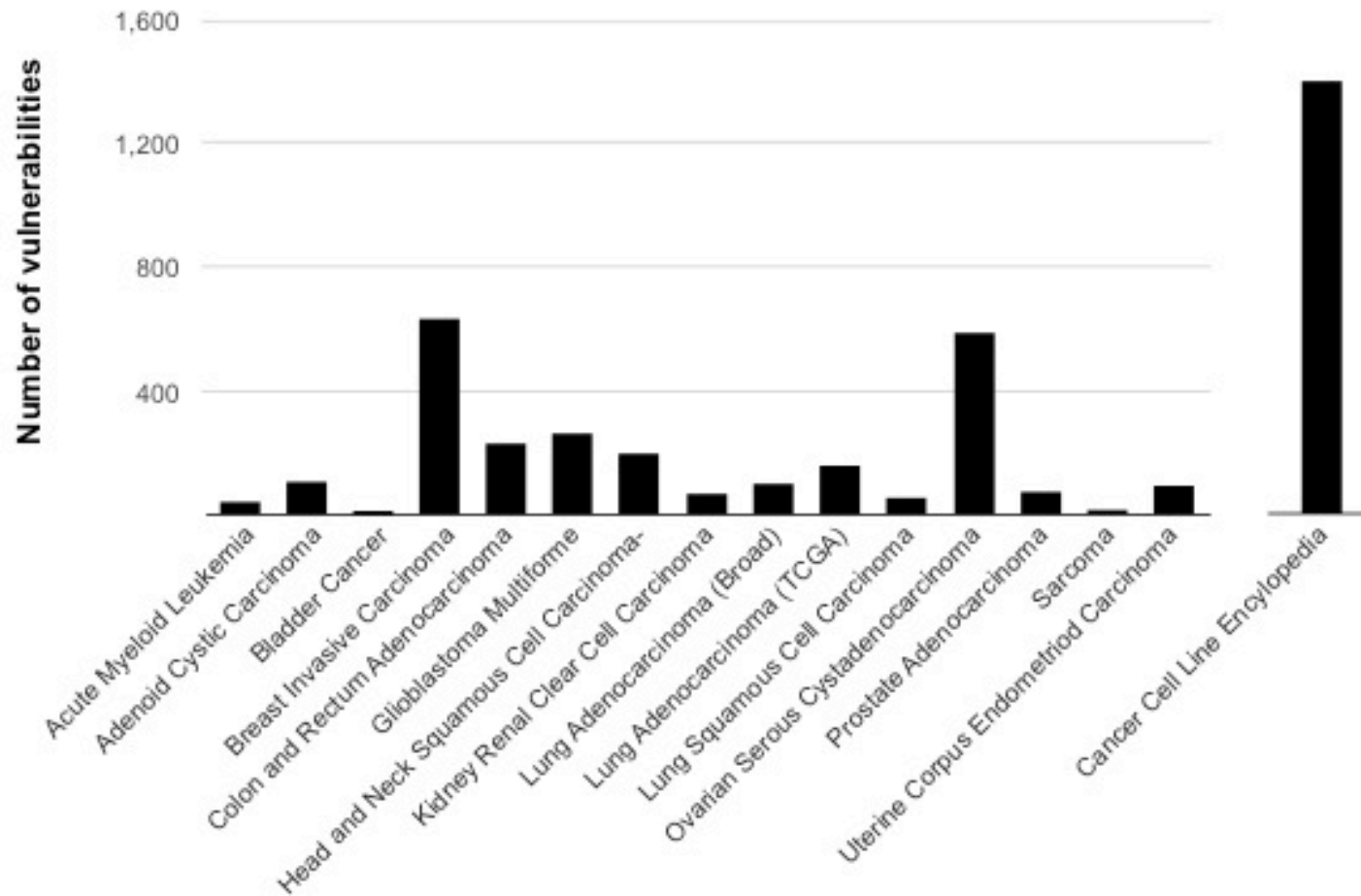# Systematic screen

Resources

- **Parallel pathways and metabolic isoenzymes**
  - Pathway Commons 2
    - HumanCyc
    - Reactome
  - KEGG Enzymes
- **Drugs**
  - PiHelper
    - DrugBank
    - KEGG Drugs
    - NCI Cancer drugs

- **Genomic data**
  - cBioPortal
    - TCGA (Tumors)
    - CCLE (Cell lines)
    - Others (Tumors)
  - Expression patterns
    - TIGER
  - Essential genes
    - DEG

Number of vulnerabilities
(across 16 studies)

Vulnerable samples

Tumor Cell line ≈ 60 samples

Vulnerable sample

Tumors Cell Line

64 156 43

Testable
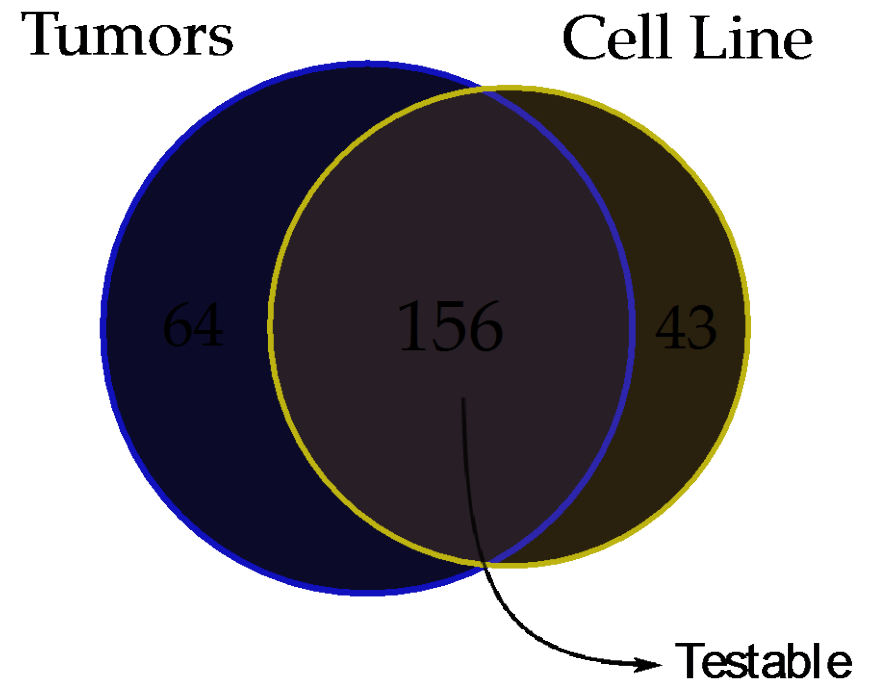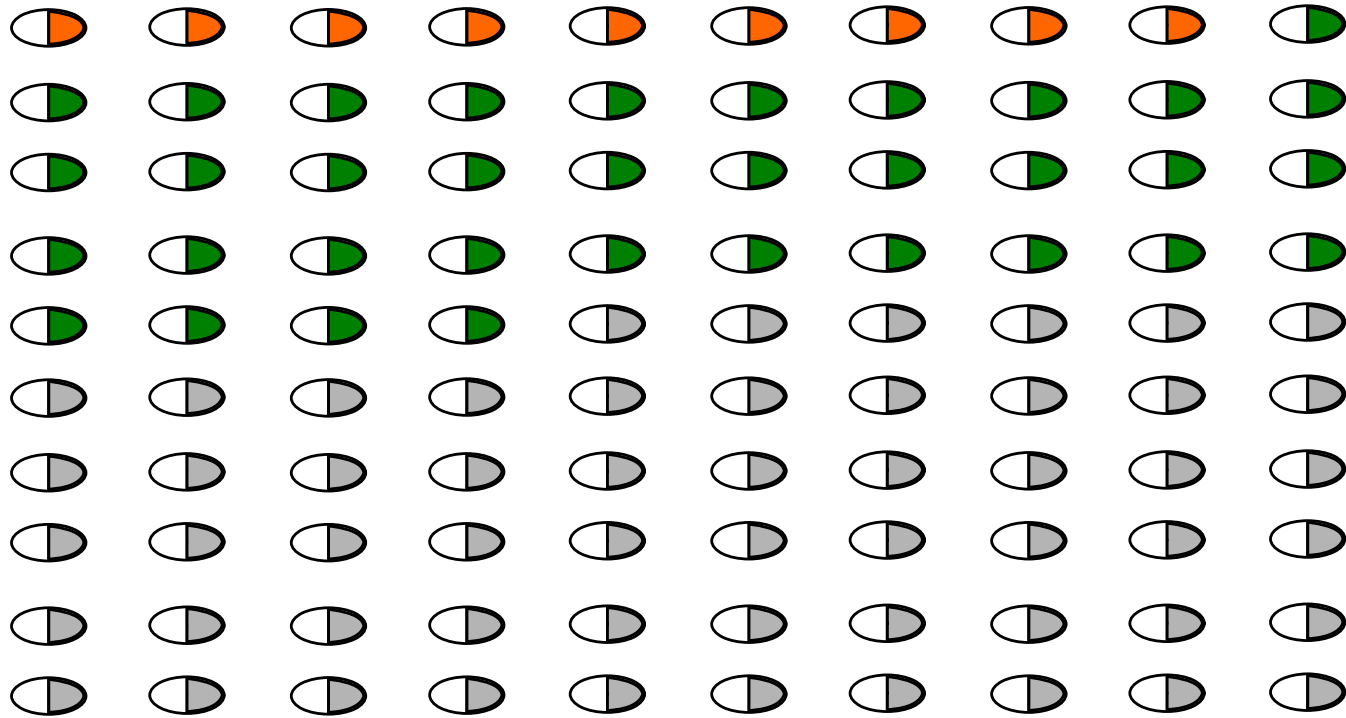
Deletion events that result
in a vulnerability

Drugs of interest

Experimental drug   FDA-approved drug   Cancer drug

≈ 41 therapeutic vulnerabilities

There are many others (~200 of them)

Gene-set Statistics 470 gene-sets, 866 possible alterations

#	Gene-set & Deletion		Description	Number of hits	Details
1	**Gene** / EXTL3 (HomDel) / EXTL2 (Drugs: 2)	**Annotation**	**glucuronyl-galactosyl-proteoglycan 4-alpha-N-acetylglucosaminyltransferase** *UDP-N-acetyl-D-glucosamine + beta-D-glucuronosyl-(1->3)-beta-D-galactosyl-(1->3)-beta-D-galactosyl-(1->4)-beta-D-xylosyl-proteoglycan = UDP + alpha-N-acetyl-D-glucosaminyl-(1->4)-beta-D-glucuronosyl-(1->3)-beta-D-galactosyl-(1->3)-beta-D-galactosyl-(1->4)-beta-D-xylosyl-proteoglycan*	**Total:** 164 / **Cell-Line:** 47 / **Other:** 117	Details / PiHelper
2	**Gene** / PAPSS1 (Drugs: 2) / PAPSS2 (HomDel)	**Annotation**	**adenylyl-sulfate kinase** *ATP + adenylyl sulfate = ADP + 3'-phosphoadenylyl sulfate*	**Total:** 136 / **Cell-Line:** 18 / **Other:** 118	Details / PiHelper
3	**Gene** / GOT2 (Drugs: 1) / GOT1 (Drugs: 1) / GOT1L1 (HomDel)	**Annotation**	**aspartate degradation II** *L-aspartate + 2-oxoglutarate ↔ oxaloacetate + L-glutamate*	**Total:** 80 / **Cell-Line:** 27 / **Other:** 53	Details / PiHelper
4	**Gene** / TYRP1 (HomDel) / CAT (E/G) (Drugs: 1)	**Annotation**	**ethanol degradation IV** *ethanol + hydrogen peroxide → acetaldehyde + 2 H2O*	**Total:** 79 / **Cell-Line:** 71 / **Other:** 8	Details / PiHelper

http://cbio.mskcc.org/cancergenomics/statius/

A list of vulnerabilities (Ovarian Cancer)

Sample	Description	Genes & Alterations	Details
TCGA-59-2372	**superoxide dismutase** *2 O2.- + 2 H+ = O2 + H2O2* **Hit Score:** 0/4 (☆ ☆ ☆ ☆)	**Gene** / **Annotation** SOD1 — E/G, Drugs: 1 SOD3 — TS/E SOD2 — E/G, HomDel	Details PiHelper
TCGA-09-0369	**formate---tetrahydrofolate ligase** *ATP + formate + tetrahydrofolate = ADP + phosphate + 10-formyltetrahydrofolate* **Hit Score:** 2/4 (★ ★ ☆ ☆)	**Gene** / **Annotation** MTHFD1 — Drugs: 2 MTHFD1L — N/E, HomDel	Details PiHelper
TCGA-24-2281	**putrescine degradation III** *4-acetamidobutanal + NAD+ + H2O → 4-acetamidobutanoate + NADH + 2 H+* **Hit Score:** 3/4 (★ ★ ★ ☆)	**Gene** / **Annotation** ALDH2 — Drugs: 5 ALDH3A2 — N/E, HomDel	Details PiHelper
TCGA-29-1698	**carnitine O-palmitoyltransferase** *palmitoyl-CoA + L-carnitine = CoA + L-palmitoylcarnitine* **Hit Score:** 2/4 (★ ★ ☆ ☆)	**Gene** / **Annotation** CPT1C — TS/E, Drugs: 2 CPT1B — N/E, HomDel CPT2 — Drugs: 2 CPT1A — E/G, TS/E, Drugs: 3	Details PiHelper
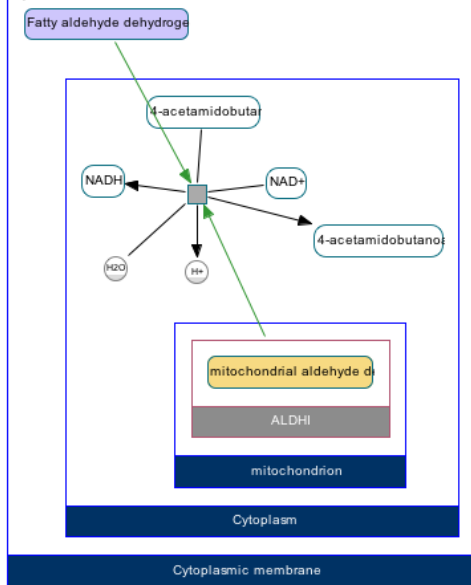
Vulnerability details

Some samples are more vulnerable than the others

- If a homozygously-deleted gene is also under-expressed in the same sample
  - Secondary evidence
- If one or more suggested drugs are FDA-approved
  - Easier access to drugs (commercially available)
- If one or more suggested drugs are cancer drugs
  - Easier to translate to clinics
- If the target-protein is not `essential`
  - Loss of this gene does not cause lethality
  - Minimizing side-effects

Outlook
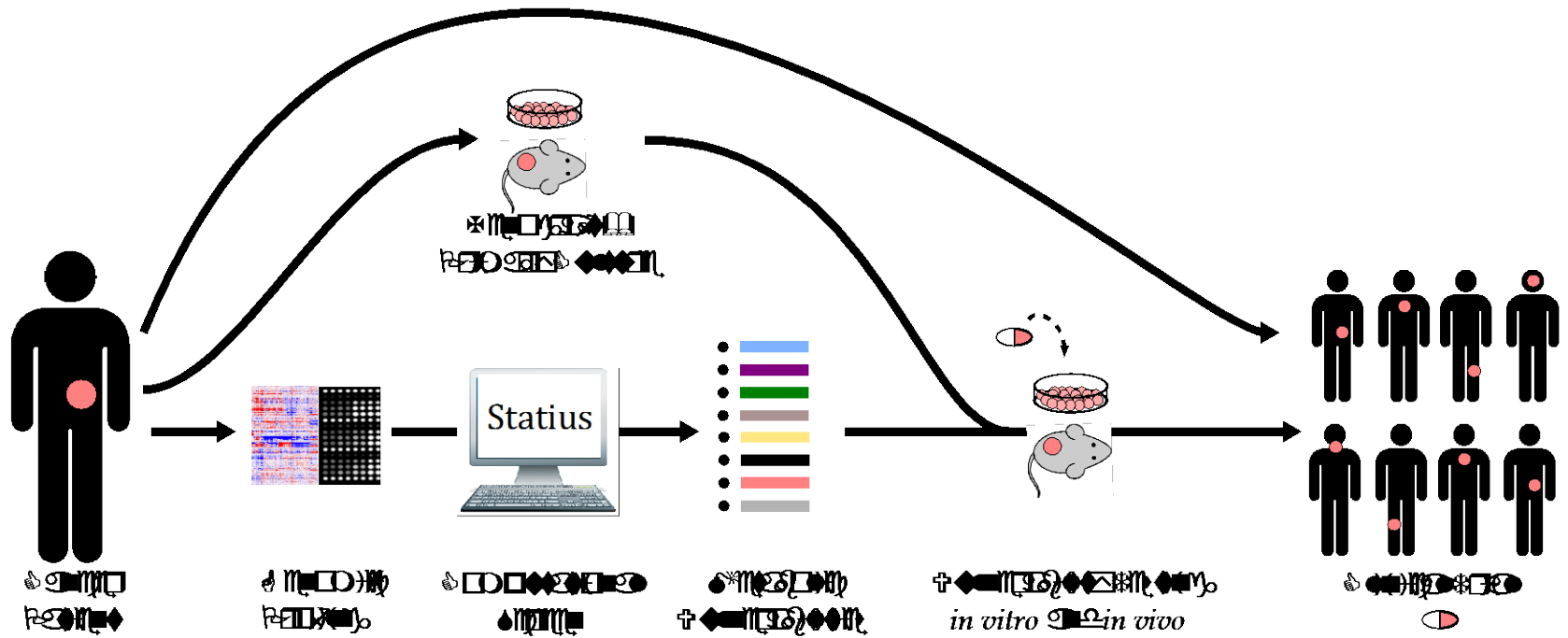
Thank you!

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Prediction of individualized therapeutic vulnerabilities in cancer from genomic profiles

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(Poster #2)

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