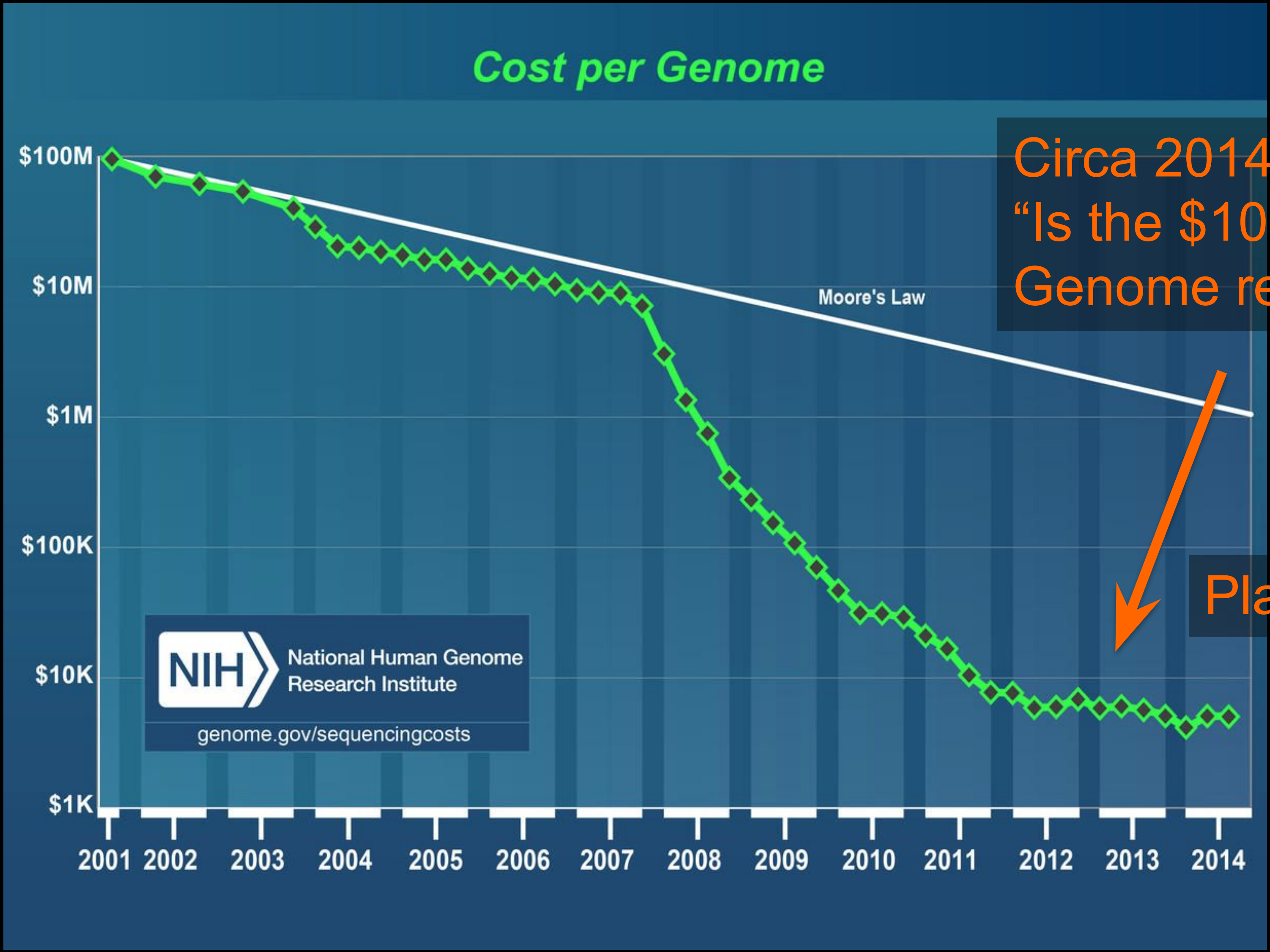
Unmasking All Forms of Cancer:

Toward Integrated Maps of All Tumor Subtypes

Distinguished Lecture in Causal Discovery
Center for Causal Discovery
(U. Pitt, Carnegie Mellon, Pitt. SCC, Yale)
University of Pittsburgh, PA. *Feb 16, 2017*

Josh Stuart, Professor
Baskin Engineering Endowed Chair
UC Santa Cruz

THE -$1 GENOME IS HERE

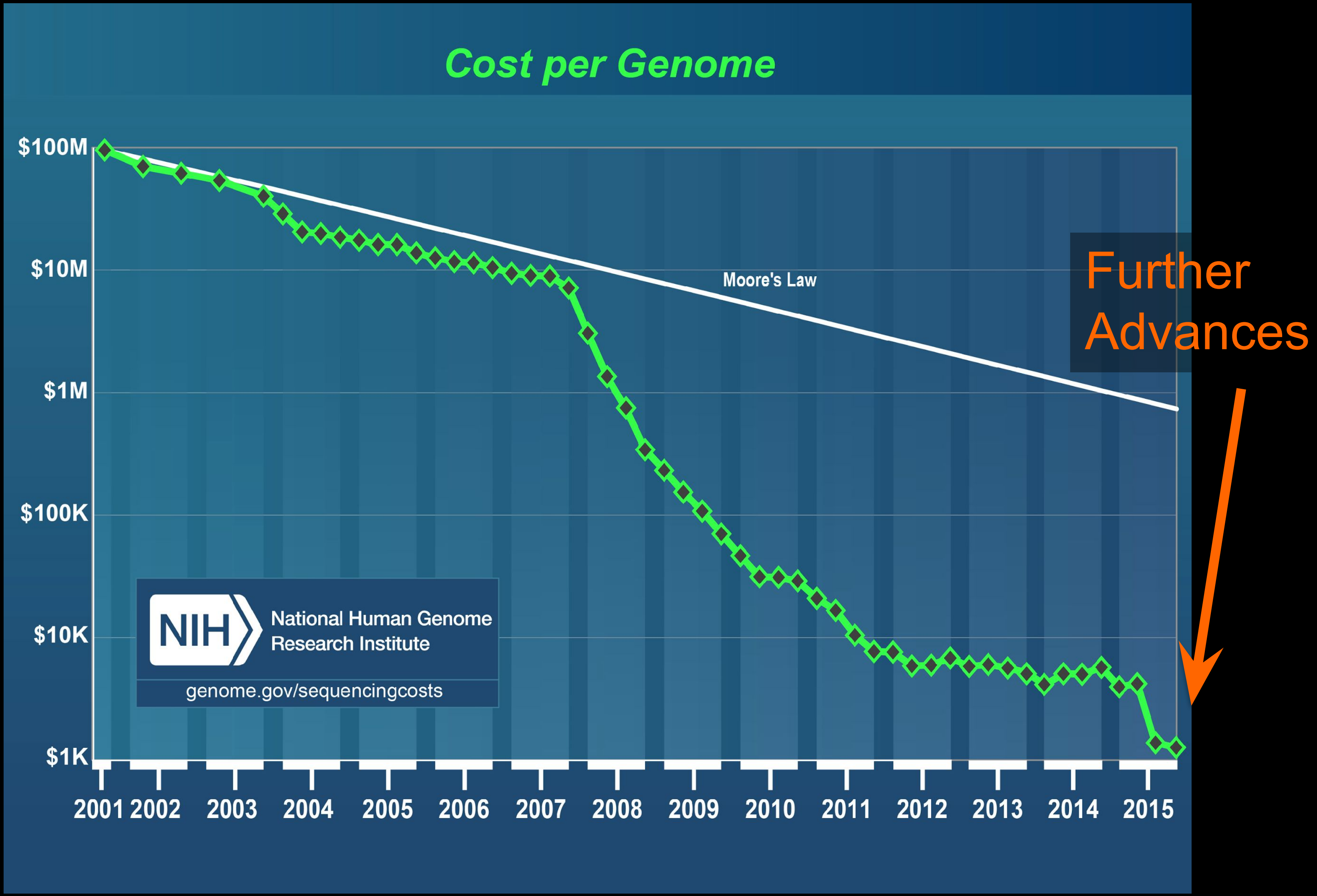


Circa 2014
“Is the $1000
Genome real?”

Plateau?

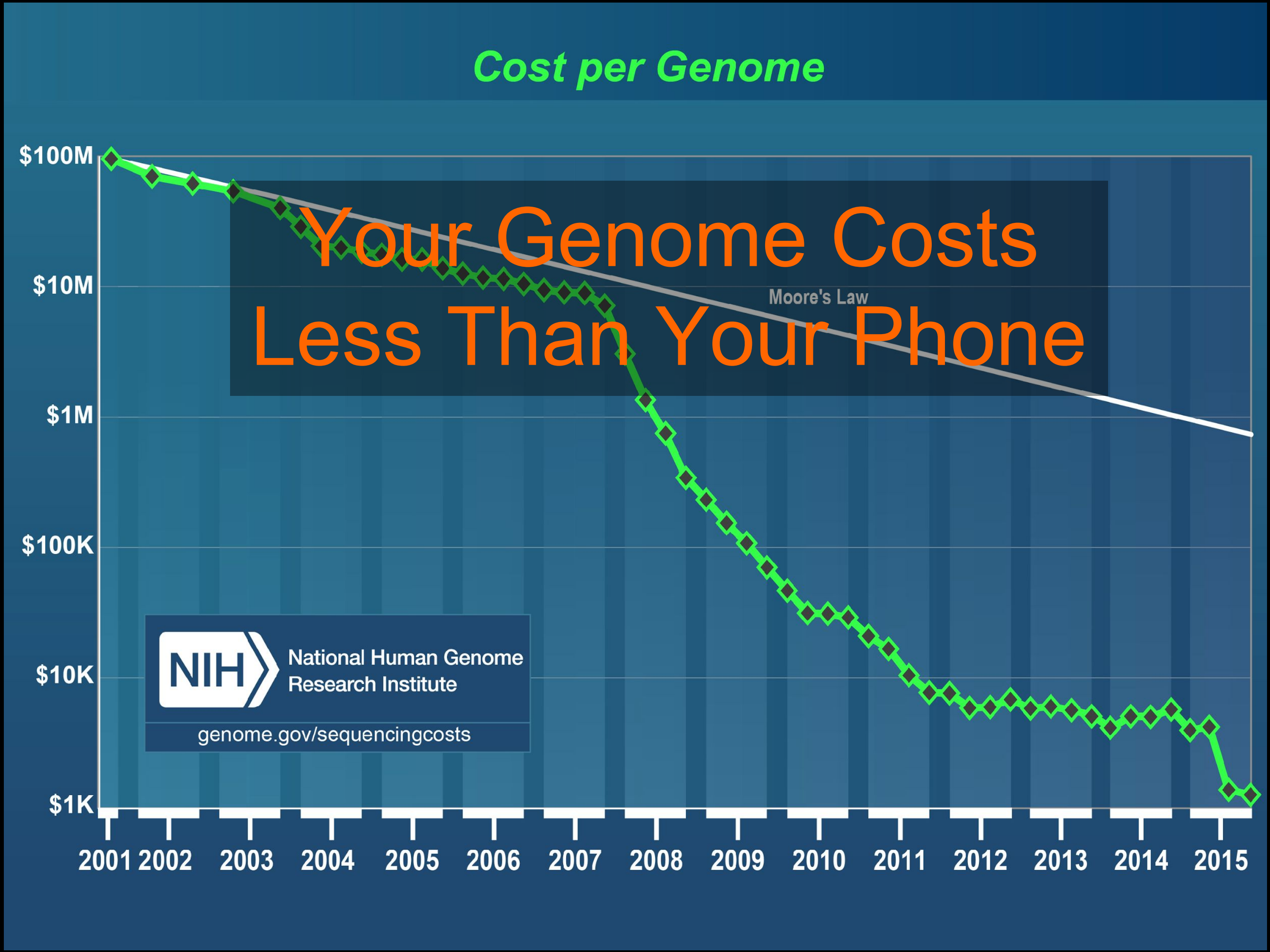
Sources: NIH: www.genome.gov/sequencingcosts; UC San Diego, 1/14/14: Illumina breaks genome cost barrier

THE -$1 GENOME IS HERE



Sources: NIH: www.genome.gov/sequencingcosts; UC San Diego, 1/14/14: Illumina breaks genome cost barrier

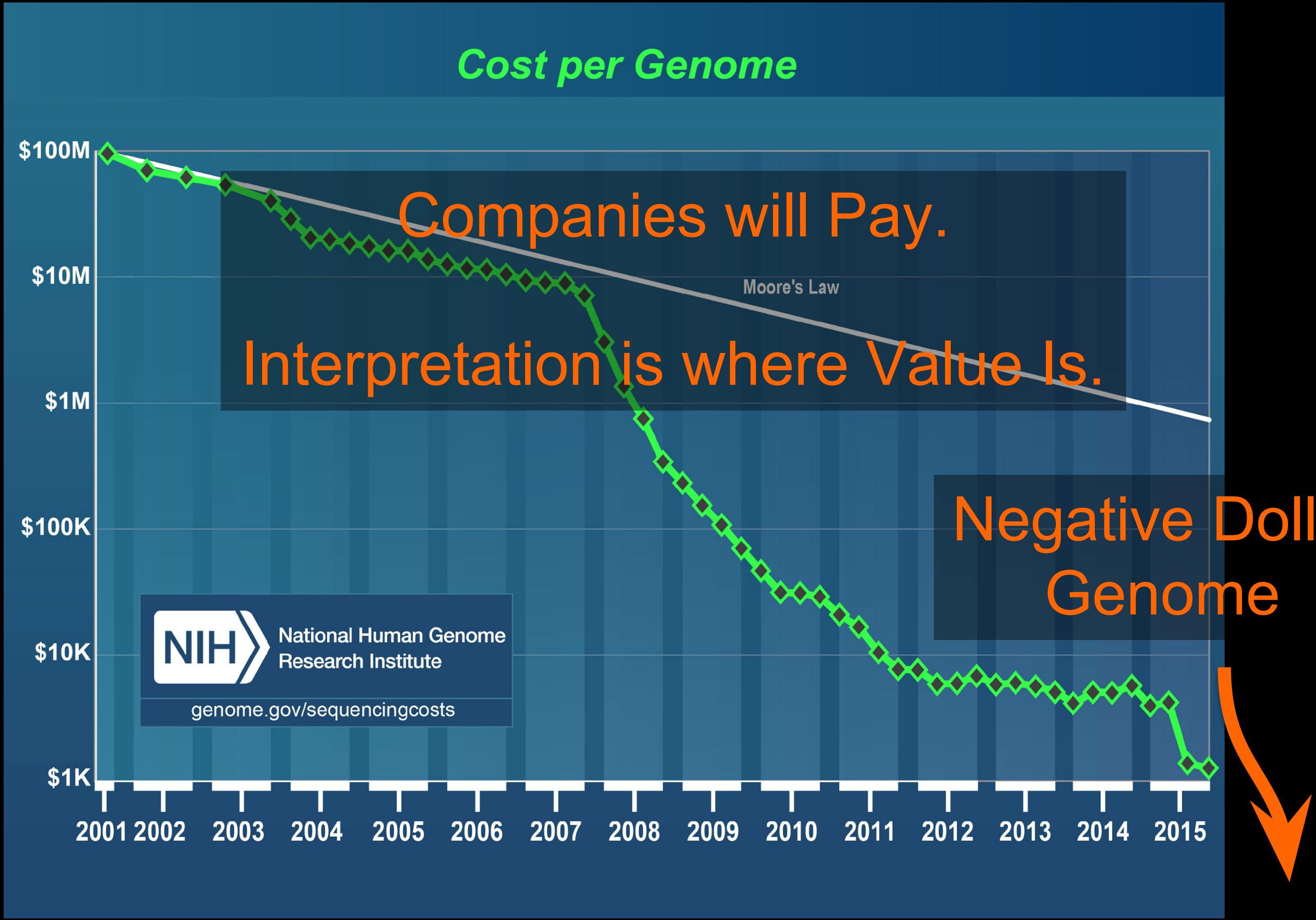
THE -$1 GENOME IS HERE



Your Genome Costs
Less Than Your Phone

Sources: NIH: www.genome.gov/sequencingcosts; UC San Diego, 1/14/14: Illumina breaks genome cost barrier

THE -$1 GENOME IS HERE



Companies will Pay.

Interpretation is where Value Is.

Negative Dollar Genome

Sources: NIH: www.genome.gov/sequencingcosts; UC San Diego, 1/14/14: Illumina breaks genome cost barrier

Price: $0.40

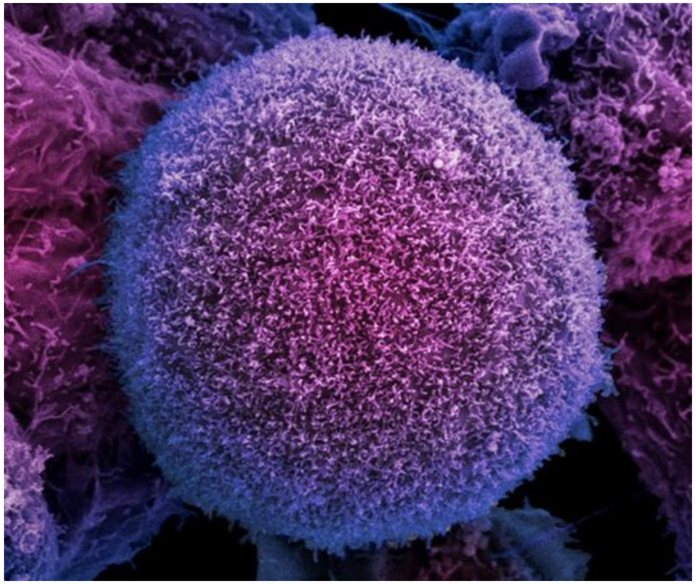
David Haussler
UC Santa Cruz Genomics Institute

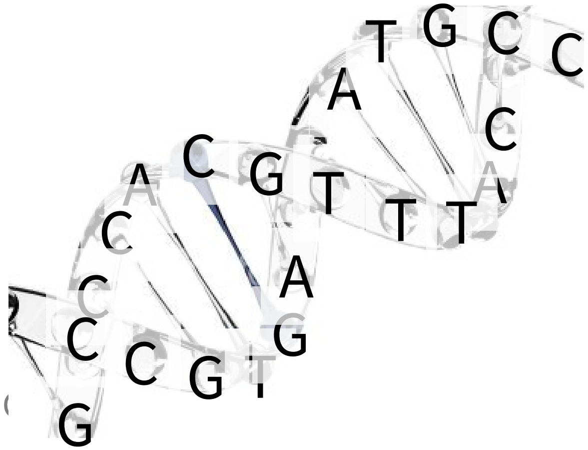
THE POTENTIAL FOR DNA AND COMPUTING TO TRANSFORM MEDICINE IS NOT BEING REALIZED

Opportunities to save lives are lost every day

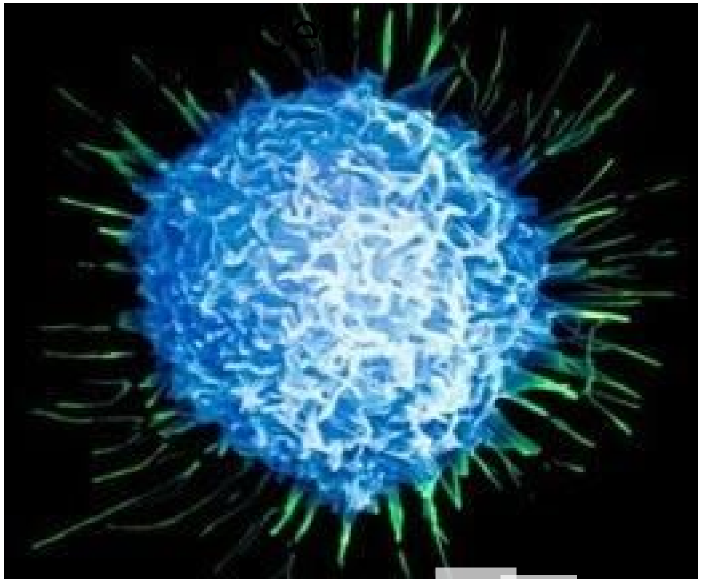
CANCER GENOMICS:
A VIEW INSIDE TUMOR CELLS

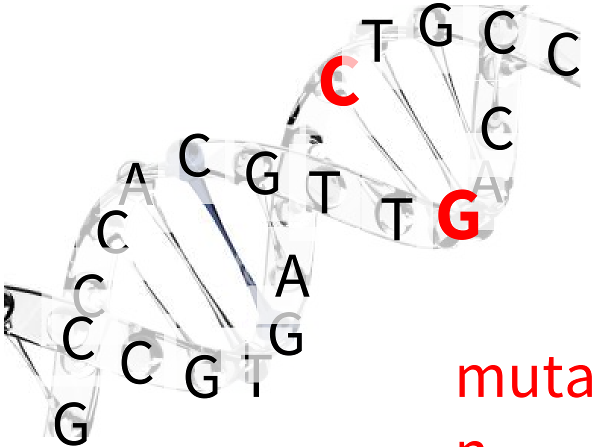
Normal Cell





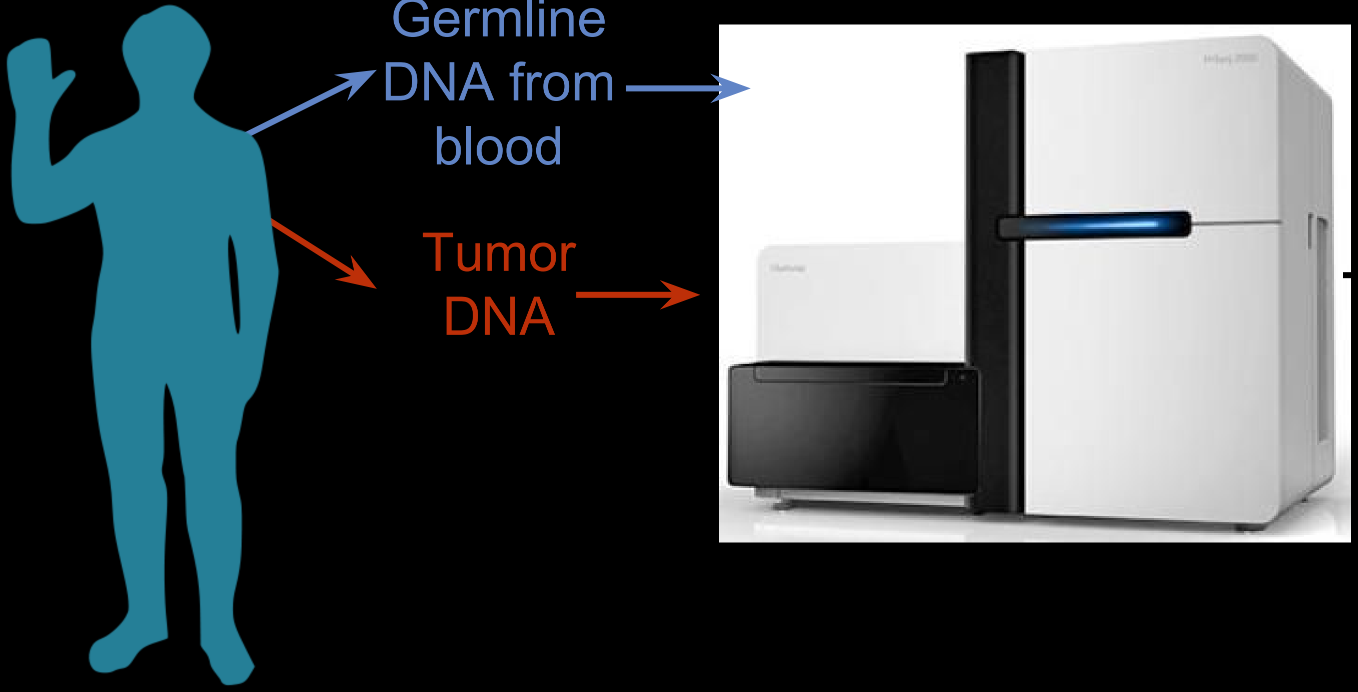
Tumor





mutation

SEQUENCE THE CANCER GENOME

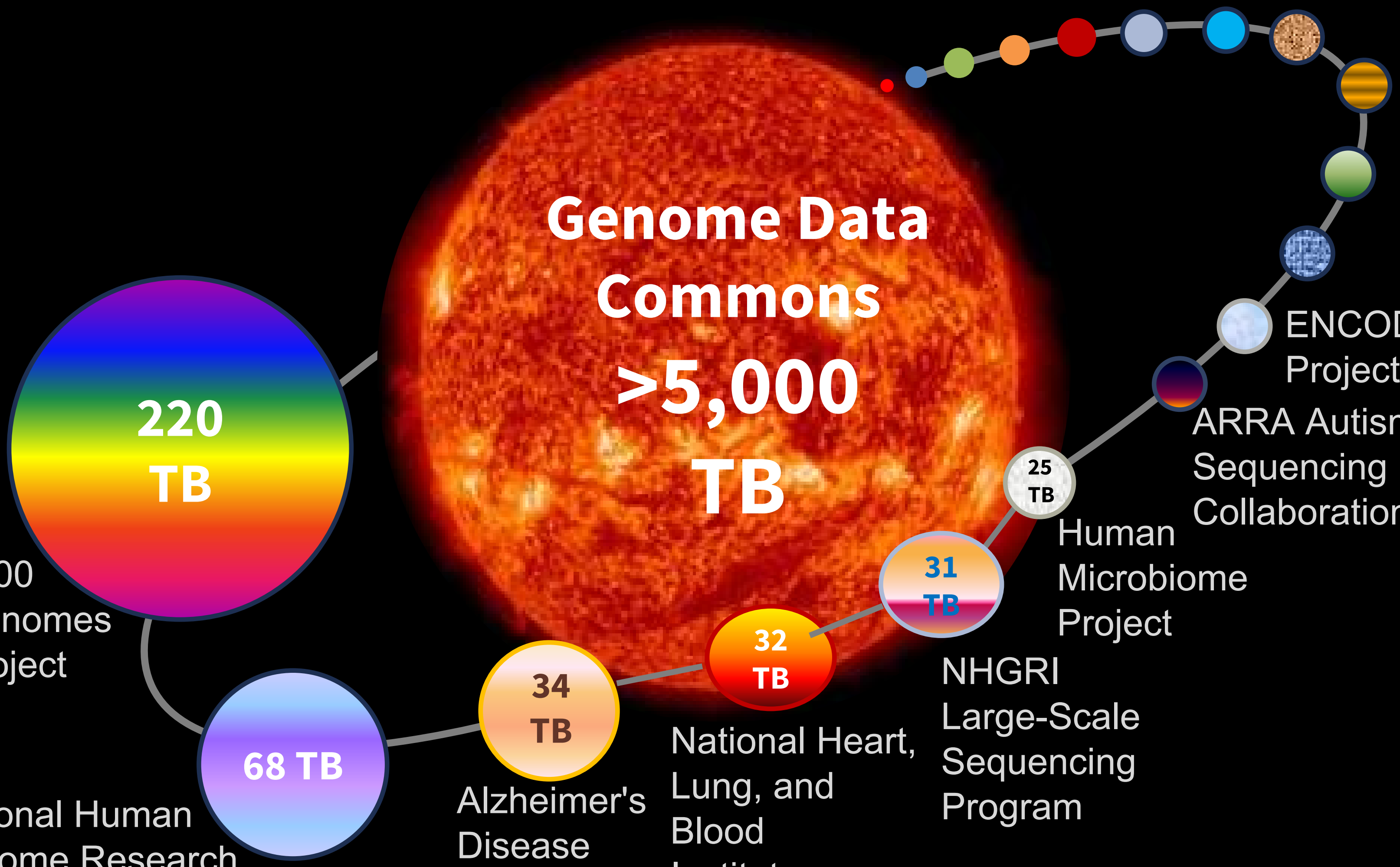


Germline DNA from blood

Tumor DNA

Billions of short DNA reads

Cancer Data Revolution



Genome Data Commons

>5,000 TB

220 TB

1000 Genomes Project

68 TB

National Human Genome Research Institute

34 TB

Alzheimer's Disease Sequencing Project

32 TB

National Heart, Lung, and Blood Institute

31 TB

NHGRI Large-Scale Sequencing Program

25 TB

Human Microbiome Project

ARRA Autism Sequencing Collaboration

ENCODE Project

Sequenced Cancer. Now What?

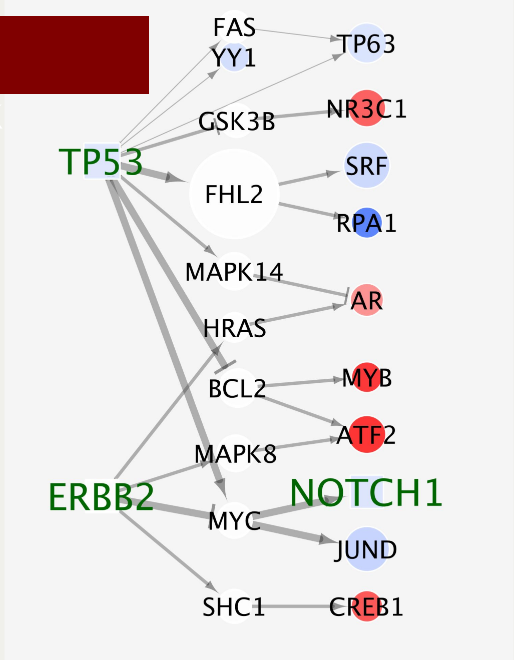
Sequenced Cancer. Now What?

- Interpret DNA changes w/ functional information
- Transcriptome key to state read-out
- Connect-the-dots with pathway inference

PERSONALIZED NETWORKS FOR TARGETING

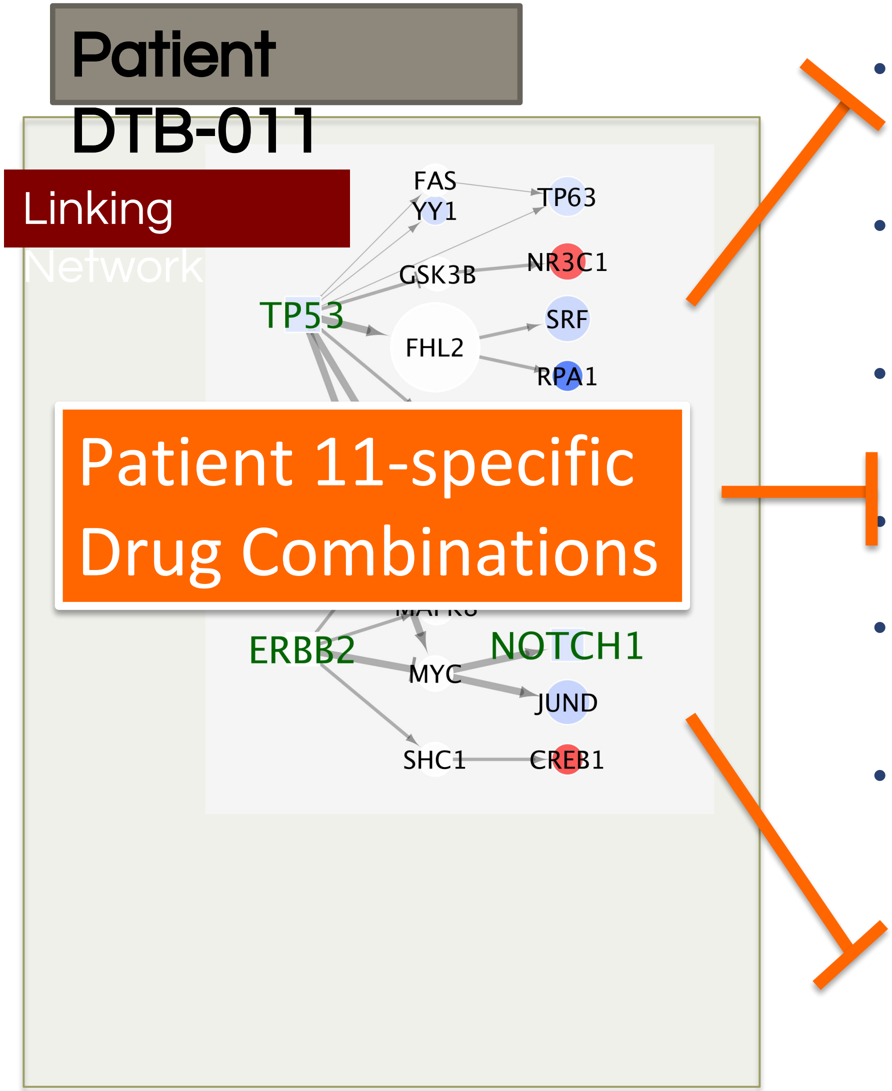
Patient DTB-011

Linking Network



- BCL2 – B-cell lympoma related
    - Blocks apoptosis of cells.
    - Targeting in PCa (Zielinski *Cancer J* 2013)
- GSK38 – glycogen synthase kinase 3
    - inhibitors reduce PCa growth (Darrington *Int J Cancer* 2012).
- MAPK8 (aka JUN Kinase)
    - siRNA induces apoptosis in PCa (Parra *Int J Mol Med* 2012)
- MAPK14 (aka p38)
    - Inhibitors may promote mets
- HRAS
    - Synthetic lethal w/ JNK (above) (Zhu *Genes Cancer* 2010)
- SHC1 – Src homolog
    - ERK and TGFB signaling

PERSONALIZED NETWORKS FOR TARGETING



Patient DTB-011

Linking Network

Patient 11-specific Drug Combinations

- BCL2 – B-cell lympoma related
  - Blocks apoptosis of cells.
  - Targeting in PCa (Zielinski *Cancer J* 2013)
- GSK38 – glycogen synthase kinase 3
  - inhibitors reduce PCa growth (Darrington *Int J Cancer* 2012).
- MAPK8 (aka JUN Kinase)
  - siRNA induces apoptosis in PCa (Parra *Int J Mol Med* 2012)
- MAPK14 (aka p38)
  - Inhibitors may promote mets
- HRAS
  - Synthetic lethal w/ JNK (above) (Zhu *Genes Cancer* 2010)
- SHC1 – Src homolog
  - ERK and TGFB signaling

Outline:
Interpreting A Cancer Genome (N-of-1)

- Identify the closest known *form*

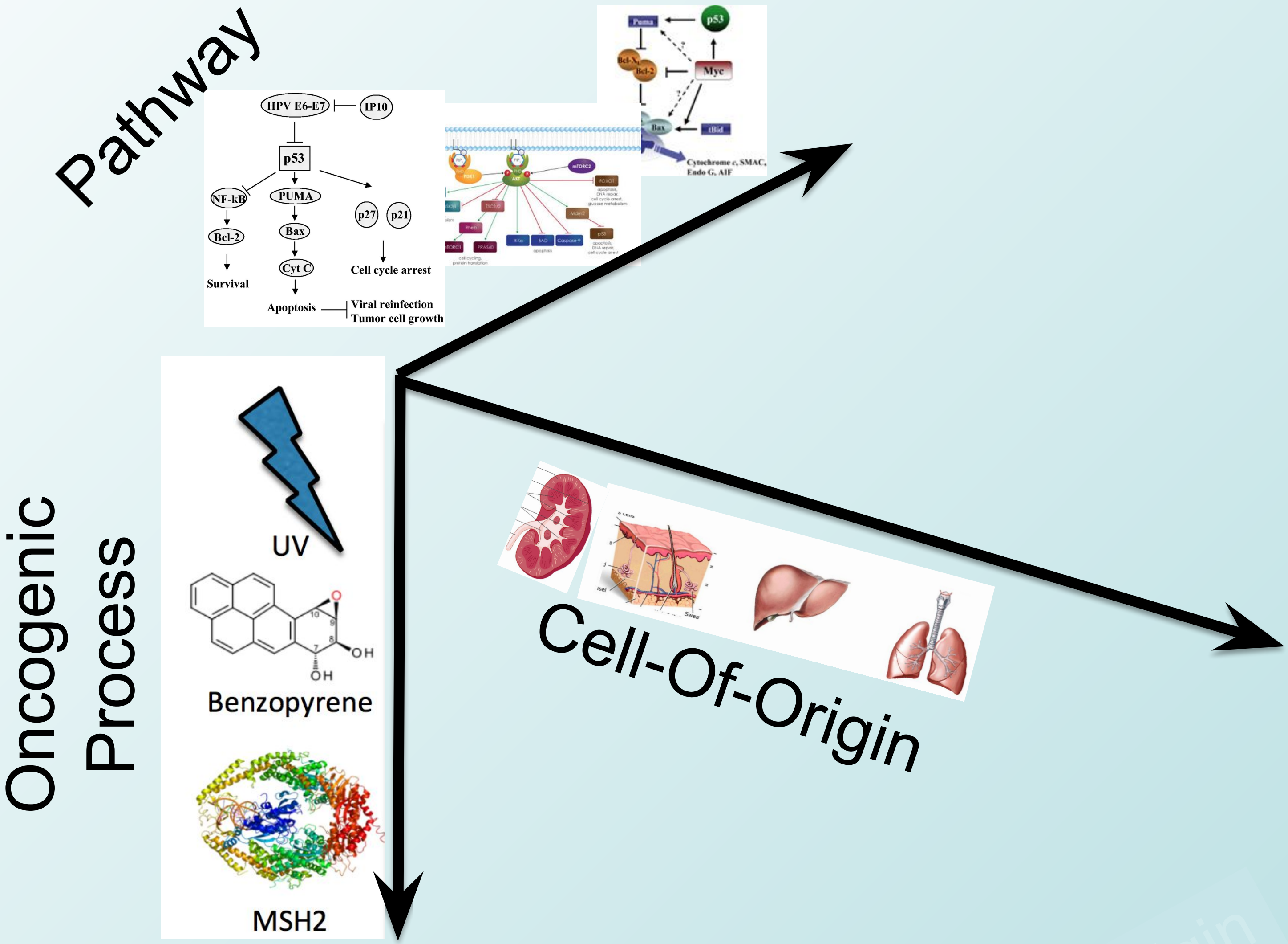
- Tailor the pathway model to fit an individual tumor's unique combination of events

Outline:
Interpreting A Cancer Genome (N-of-1)

- Identify the closest known *form*

- Tailor the pathway model to fit an individual tumor's unique combination of events

Identify all the forms of cancer?



Pathway

Oncogenic Process

UV

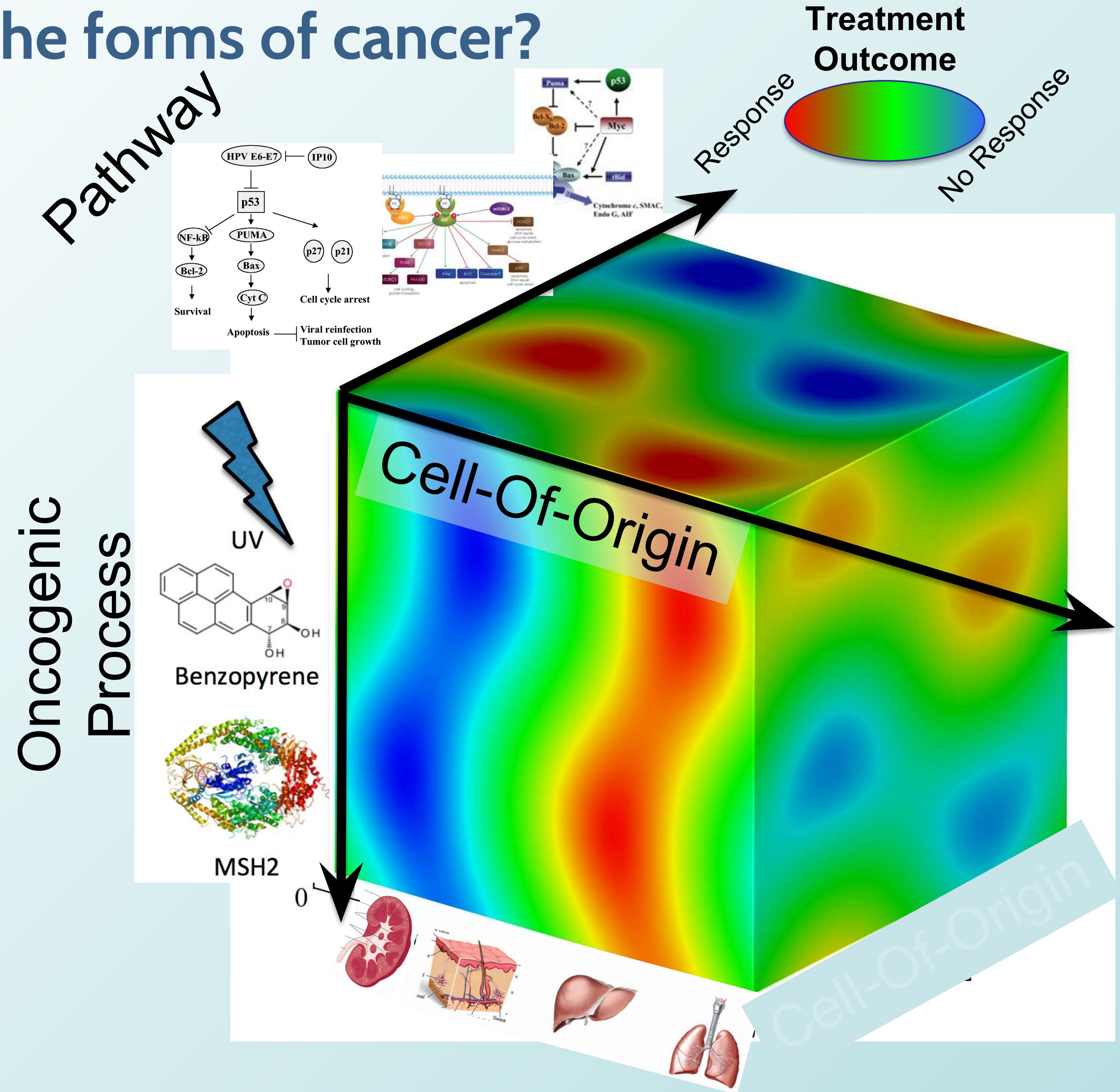
Benzopyrene

MSH2

Cell-Of-Origin

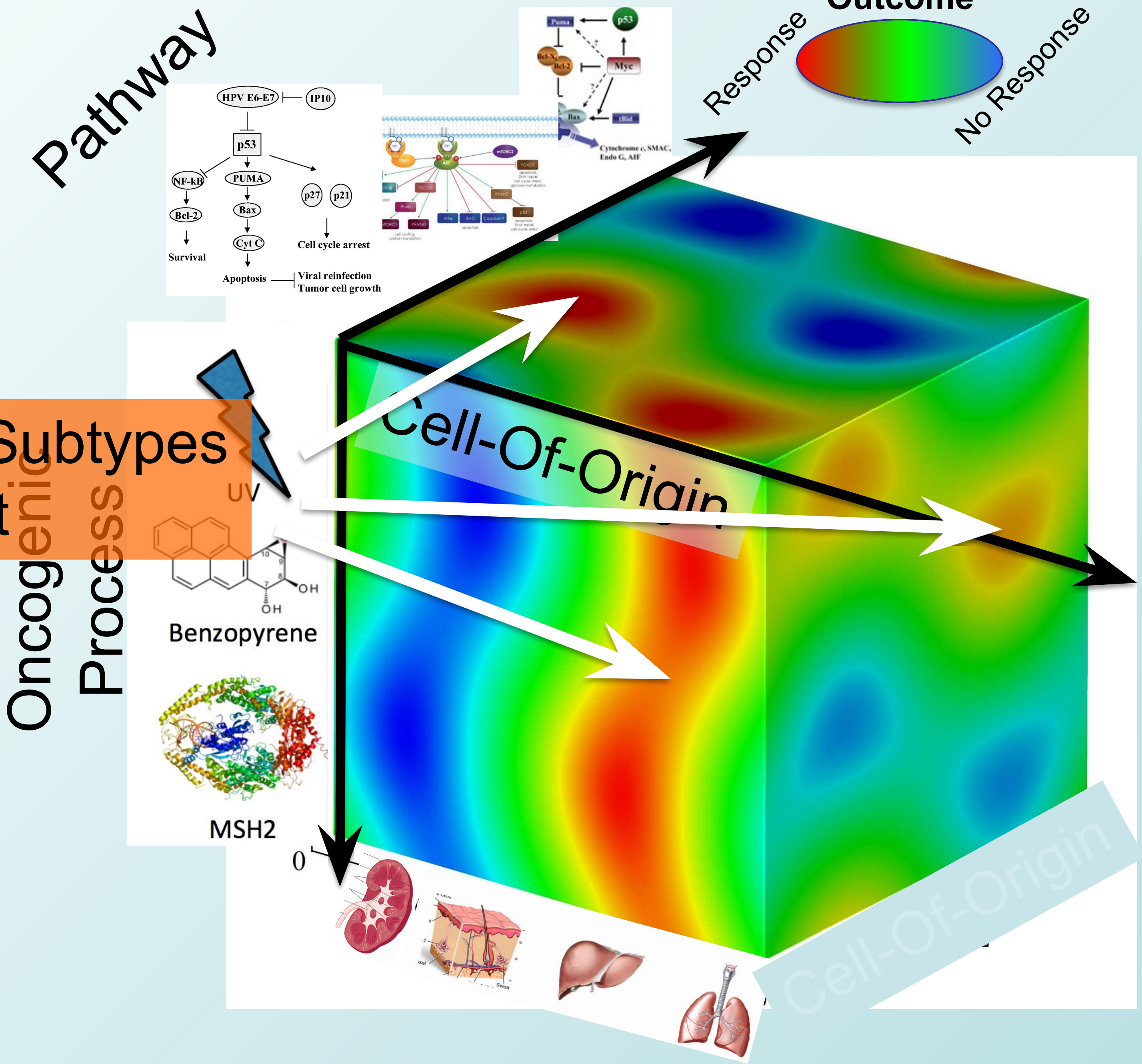
Cell-Of-Origin

Identify all the forms of cancer?



Identify all the forms of cancer?

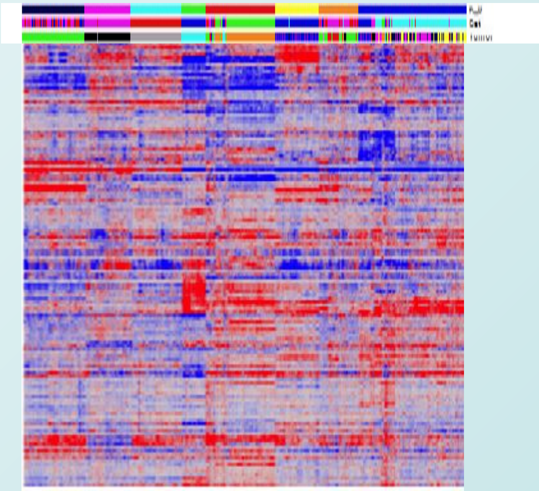
Responsive Subtypes To Treatment



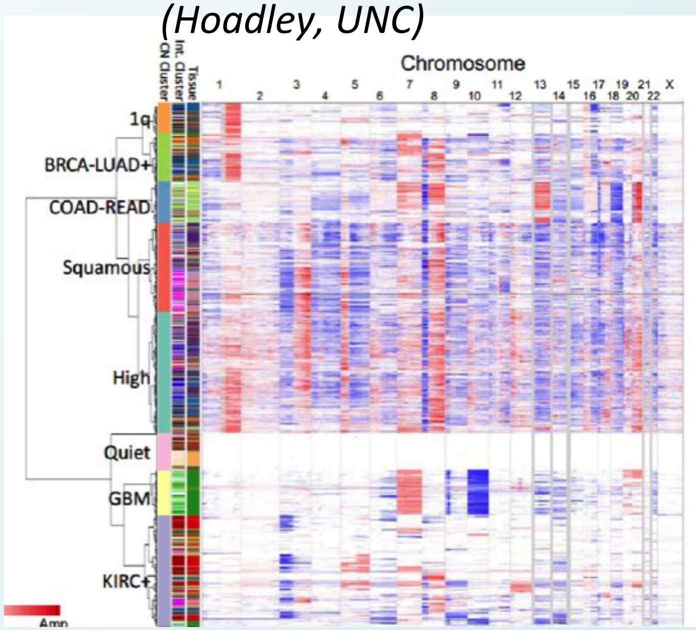
6 Data Platforms – Subtypes from each

mRNA
(Hoadley, UNC)

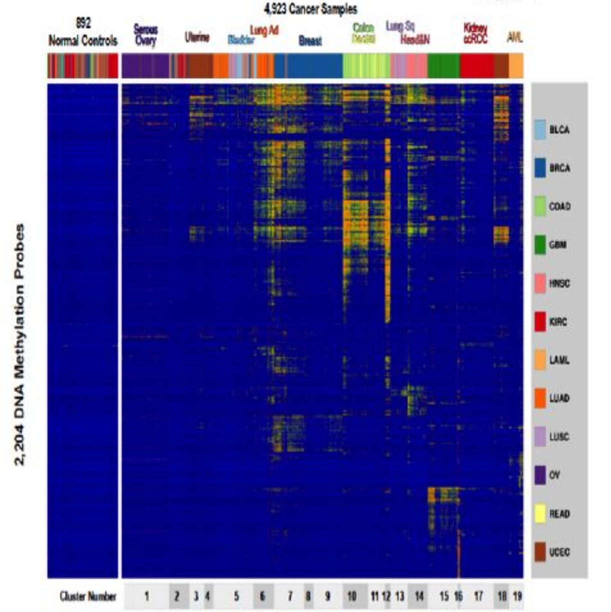
microRNA
(Robertson, UBC)



Protein
(Akbani, MDACC)



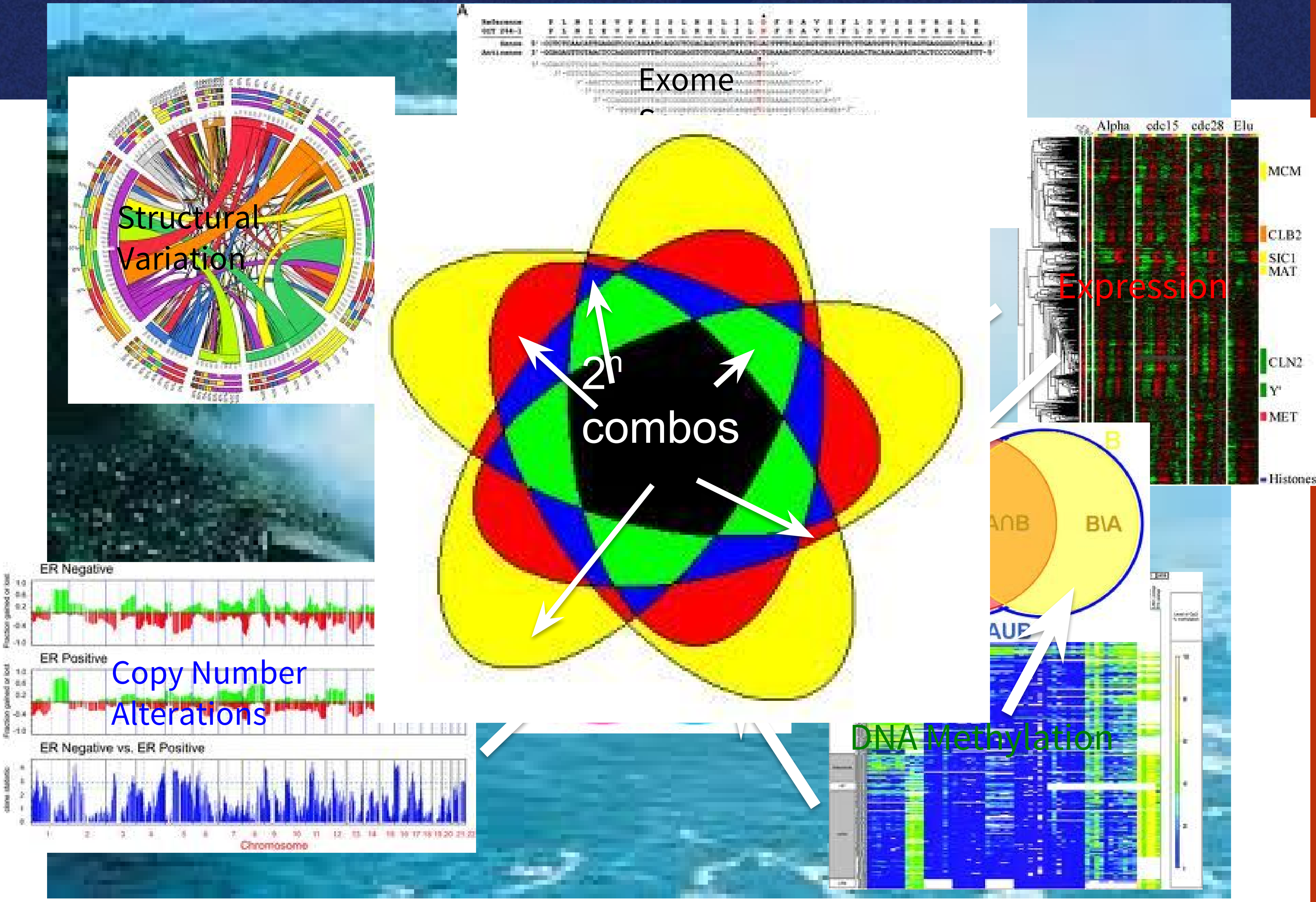
DNA Copy Number
(Cherniack, Broad)



DNA Methylation
(Shen, USC)

Exome-Mutations
(not used)
(Uzunangelov, UCSC)

MULTIPLE TYPES OF GENOMICS DATA



Structural Variation

Exome

Expression

2^n combos

Copy Number Alterations

DNA Methylation

FLOOD OF DATA ANALYSIS CHALLENGES

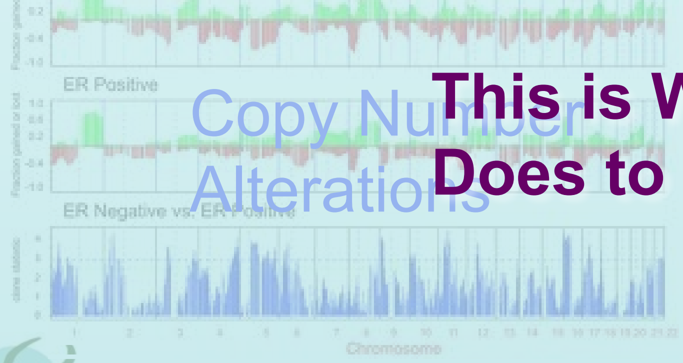
Genomics, Functional Genomics, Metabolomics, Epigenomics =

Exome

ces

Multiple, Possibly Conflicting Signals

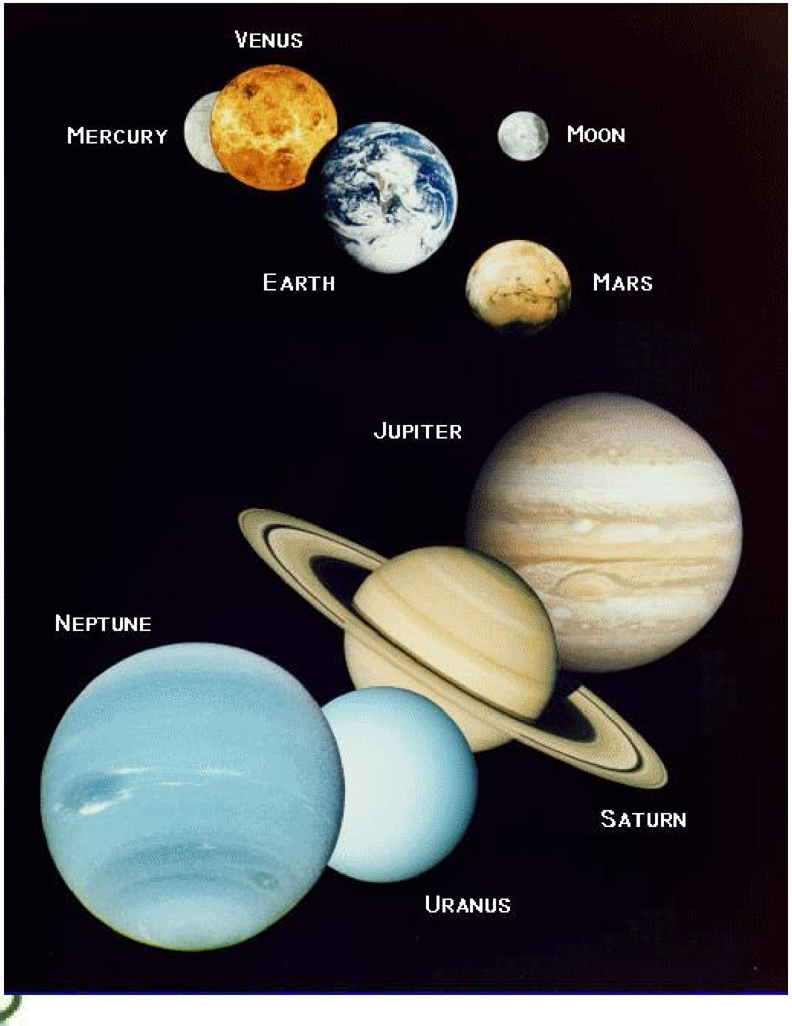
Expression



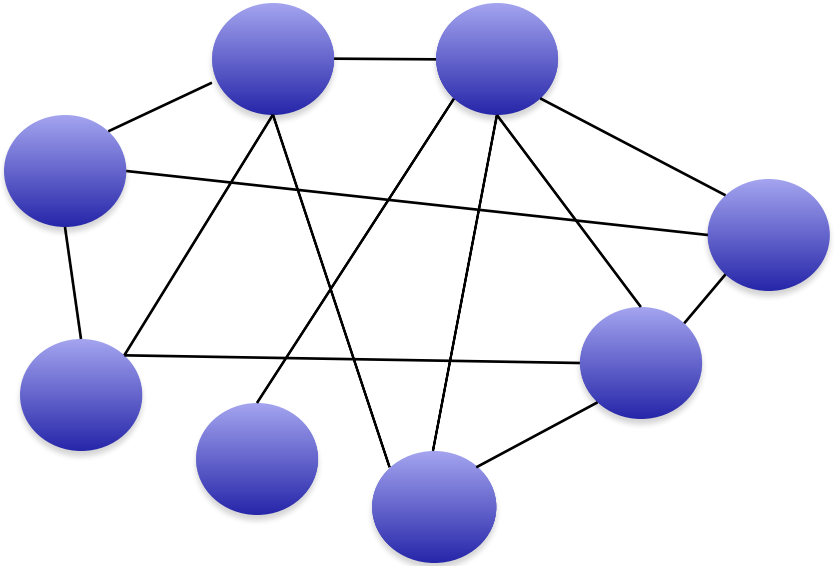
Copy Number Alterations

This is What it Does to You →

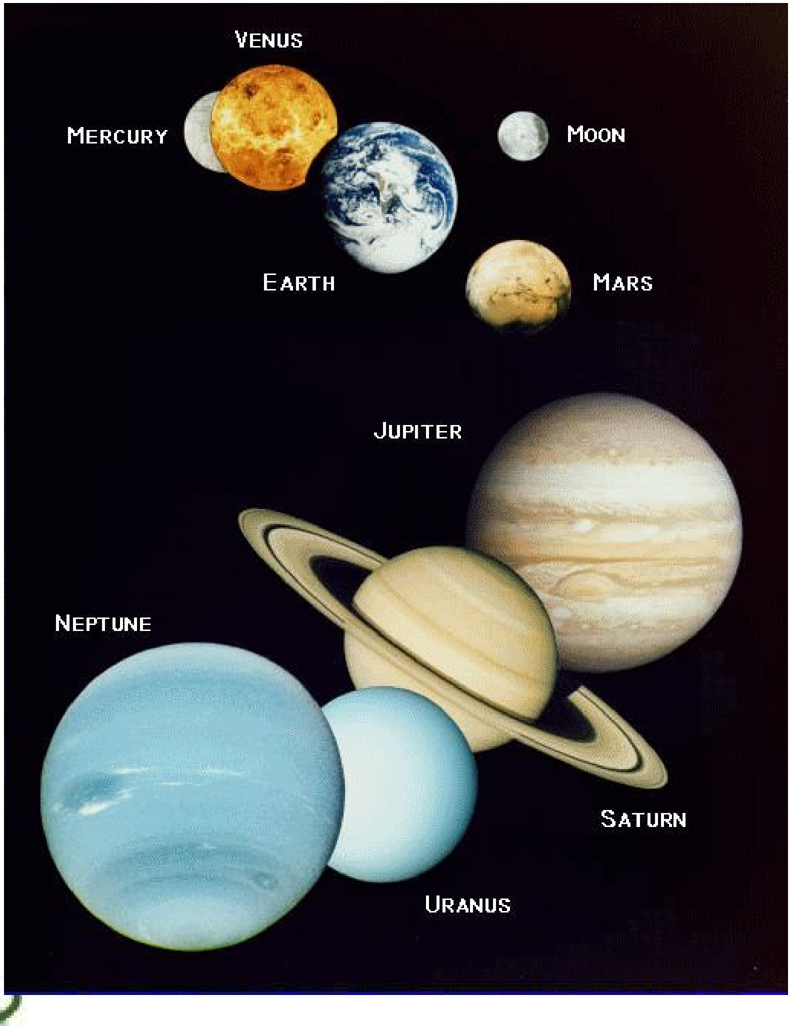
WHAT GUIDES DO WE HAVE TO INFER THE LAWS GOVERNING INTERPLAY OF CELLULAR SYSTEMS?



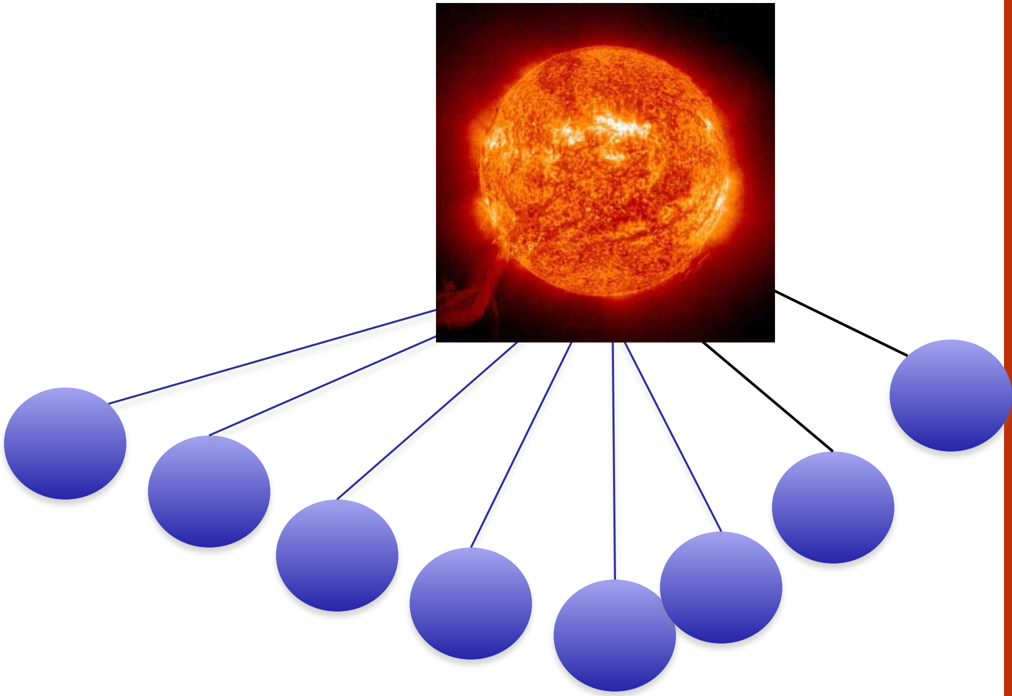
Relationships of the motions confusing!



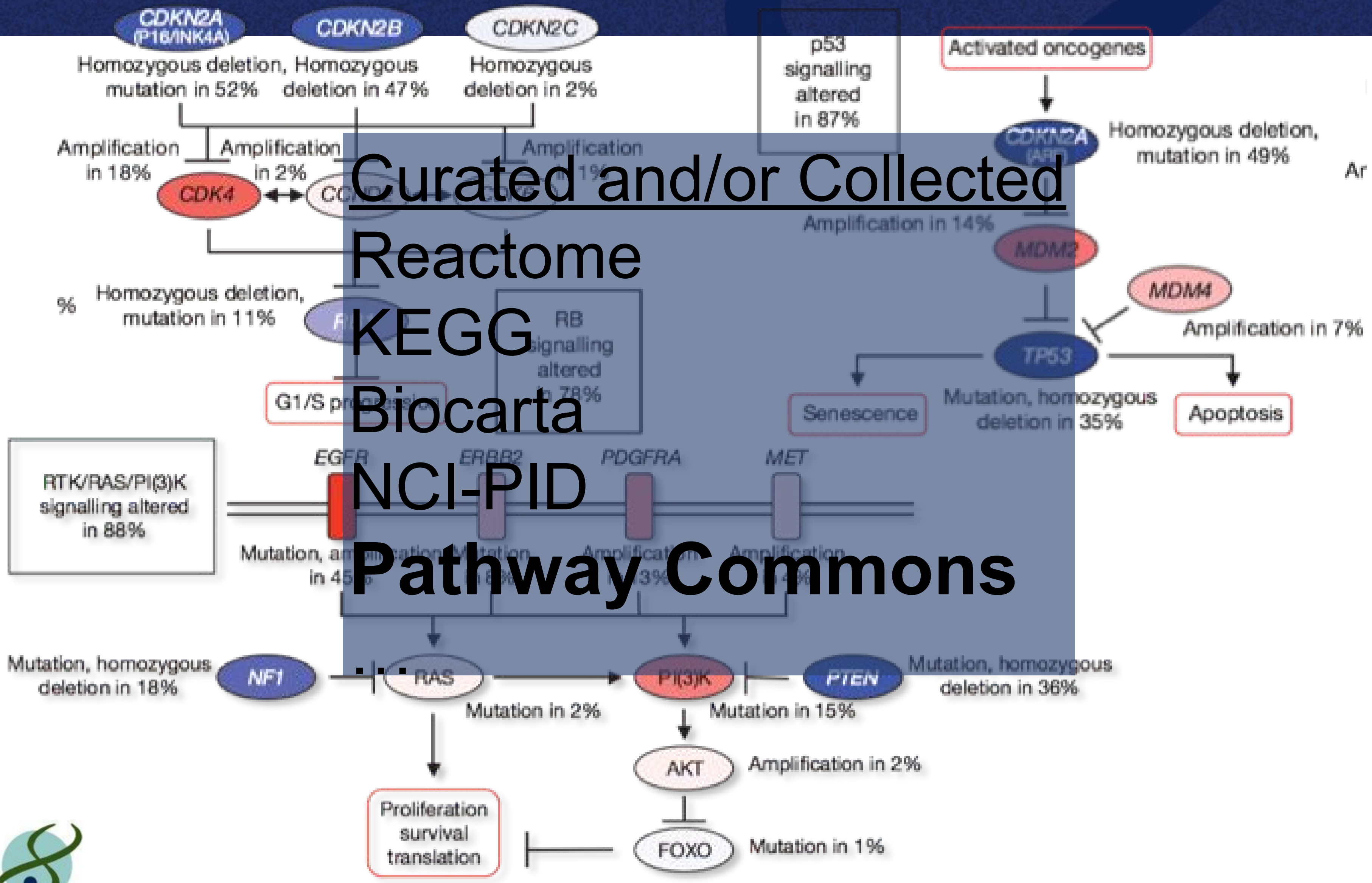
WHAT GUIDES DO WE HAVE TO INFER THE LAWS GOVERNING INTERPLAY OF CELLULAR SYSTEMS?



Model = Simpler Explanation



CYC FOR MOLECULAR BIOLOGY:
GENE CIRCUITRY NOW AVAILABLE.



<u>Curated and/or Collected</u>

Reactome

KEGG

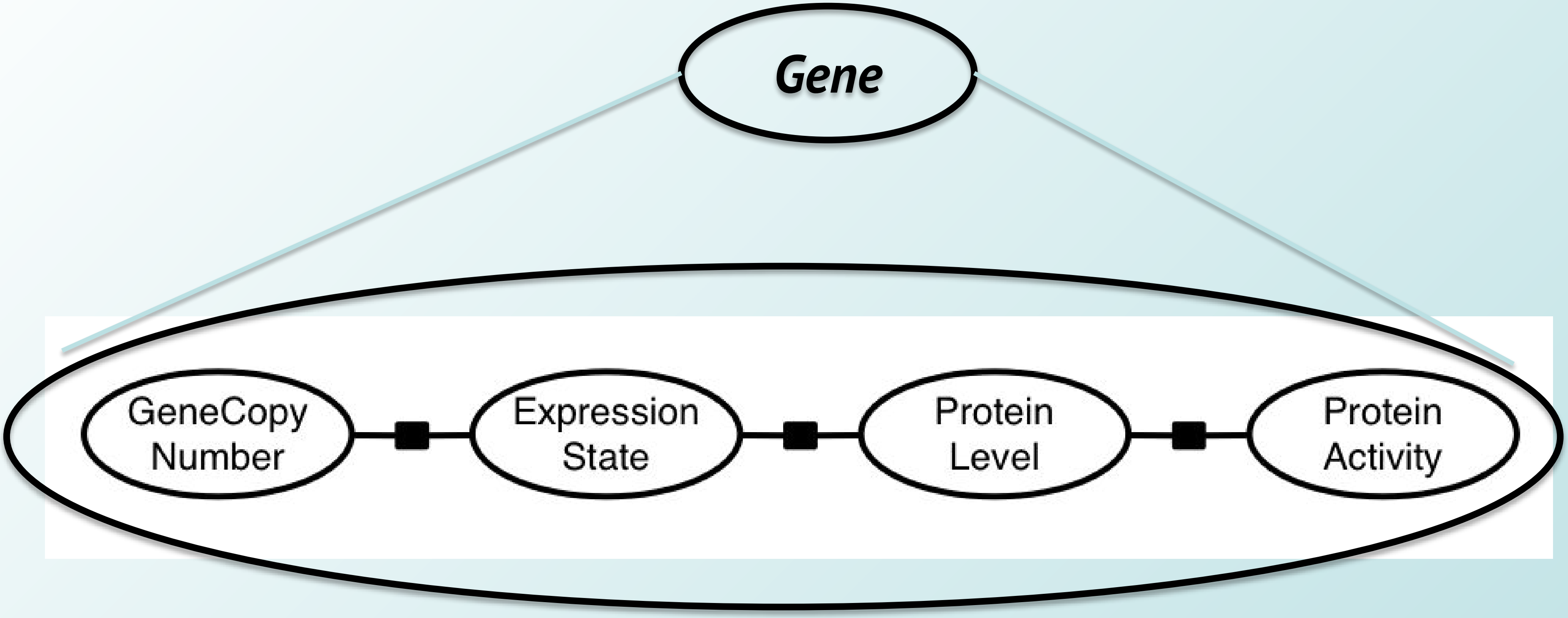
Biocarta

NCI-PID

Pathway Commons

…

Pathway Recognition Algorithm Using Data Integration on Genomic Models (PARADIGM)



○ Variable

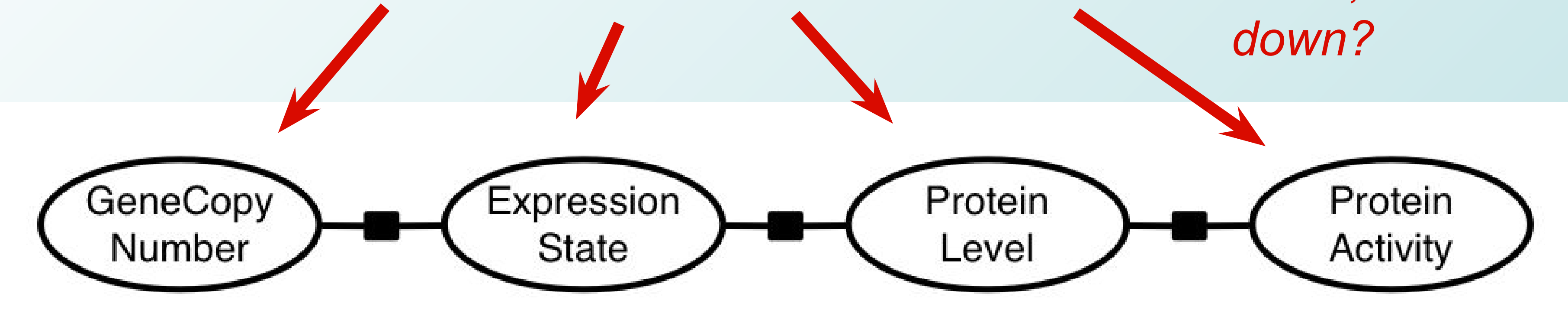
■ Factor - interaction term

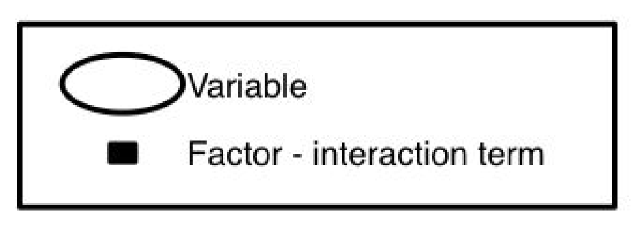
Charlie Vaske, Steve Benz

PARADIGM
Gene Model to Integrate Data

relative to non-cancer,
is this sample:
up,
same,
down?

3-state discrete variables



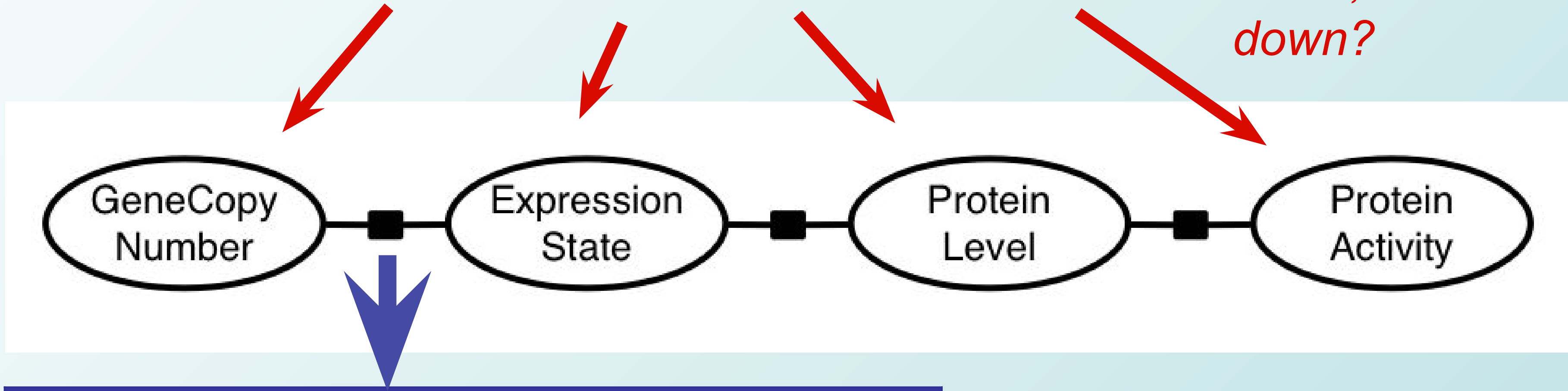


Charlie Vaske, Steve Benz

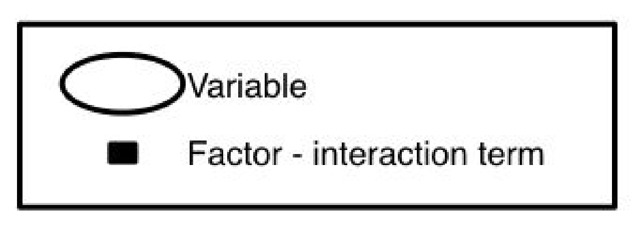
PARADIGM Gene-level Model

relative to non-cancer,
is this sample:
up,
same,
down?

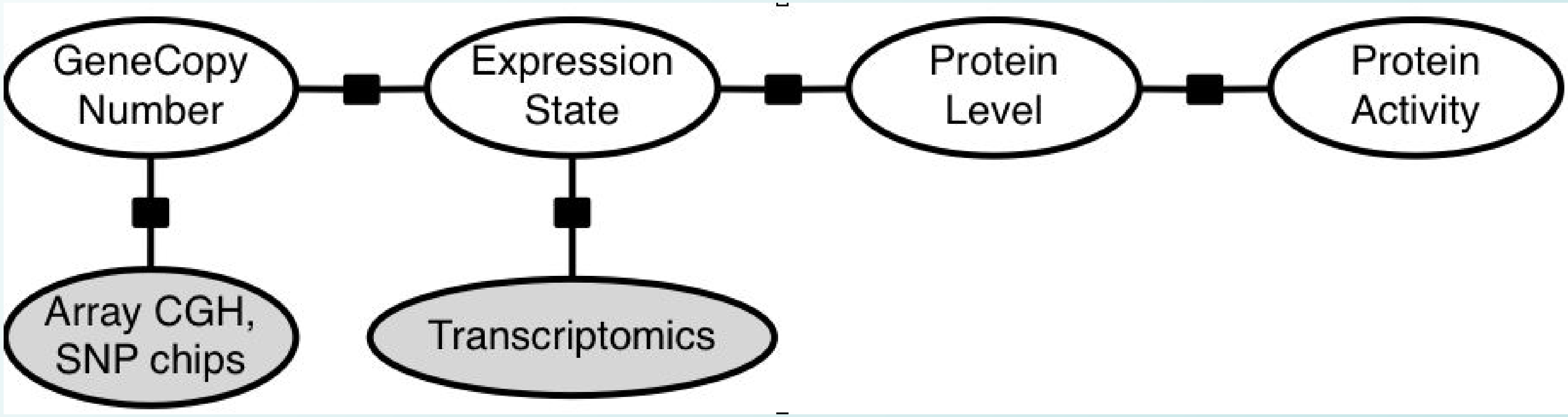
3-state discrete variables

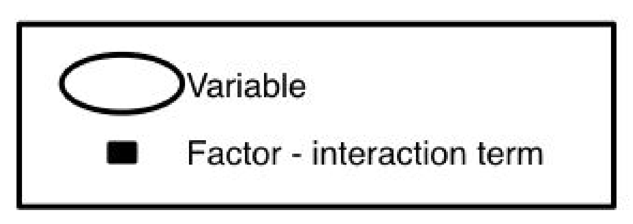


CNA \ Exp	Down	Same	Up
Down	0.90	0.09	0.01
Same	0.05	0.90	0.05
Up	0.01	0.09	0.90



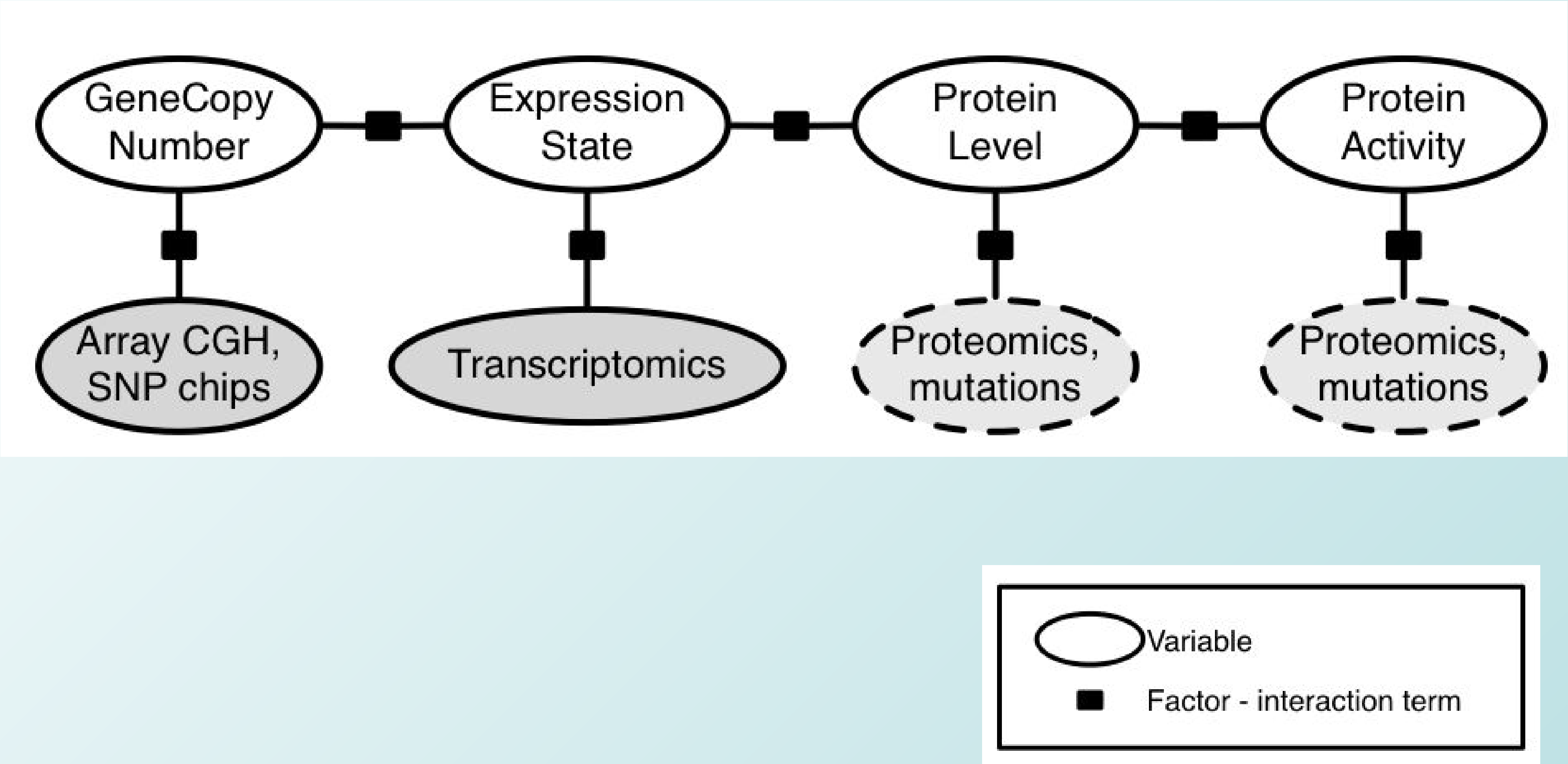
PARADIGM Gene Model to Integrate Data





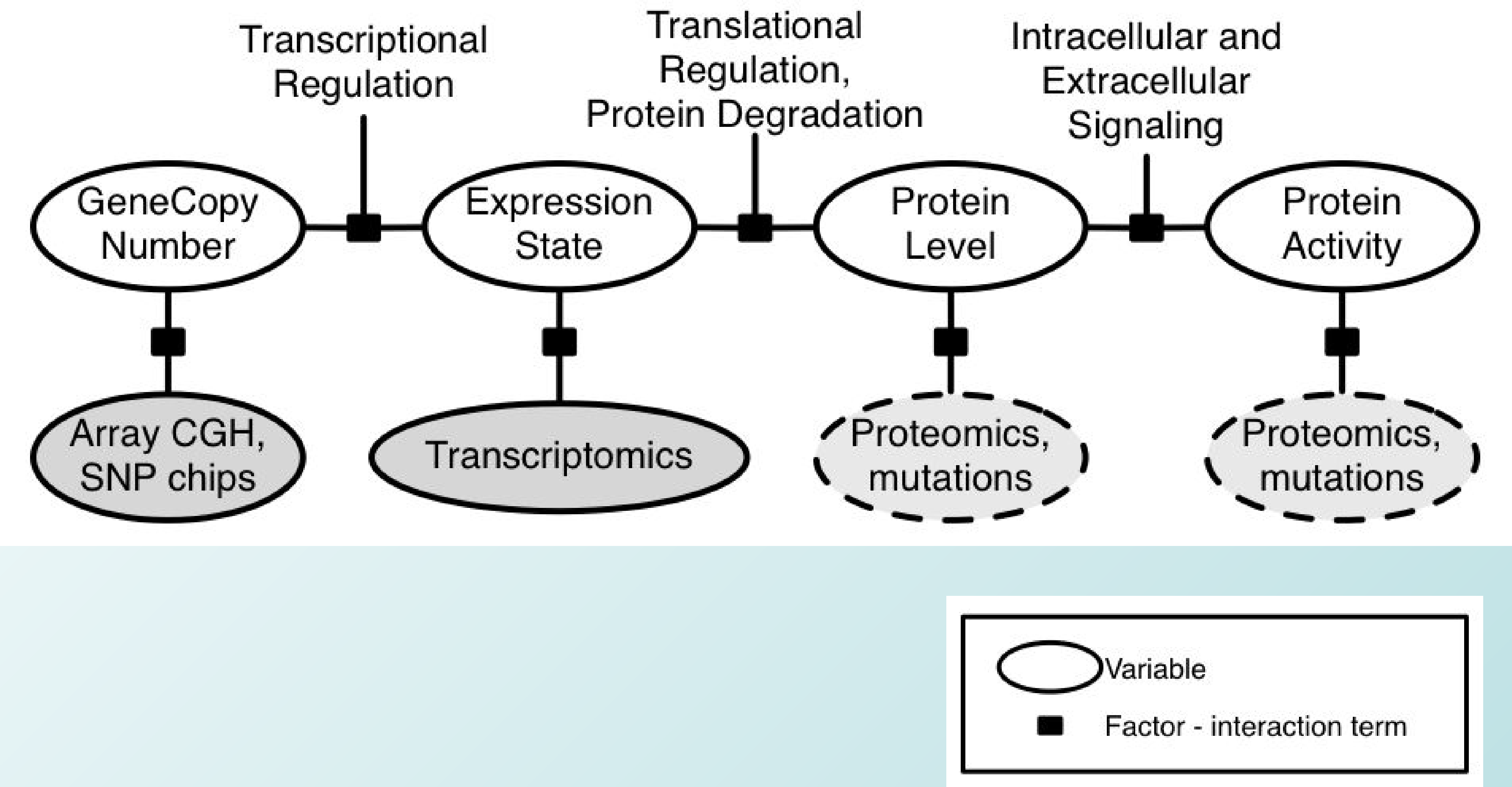
Charlie Vaske, Steve Benz

PARADIGM Gene Model to Integrate Data



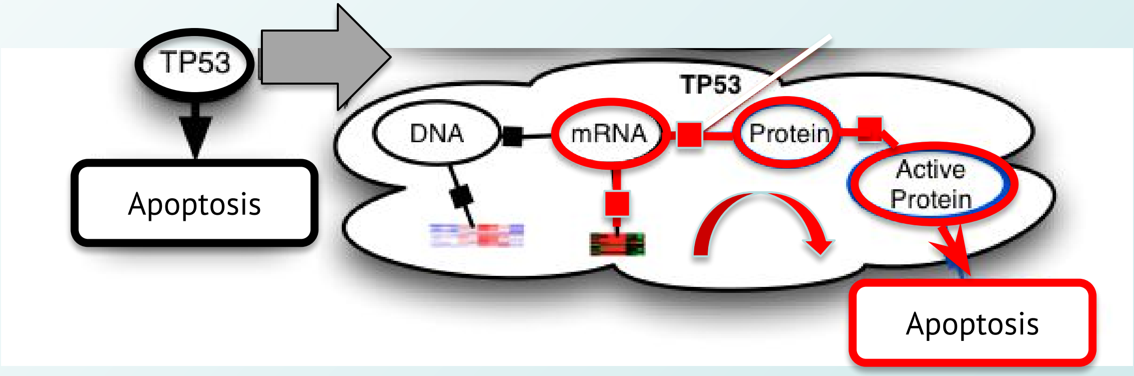
Charlie Vaske, Steve Benz

PARDIGM Gene Model to Integrate Data



Charlie Vaske, Steve Benz

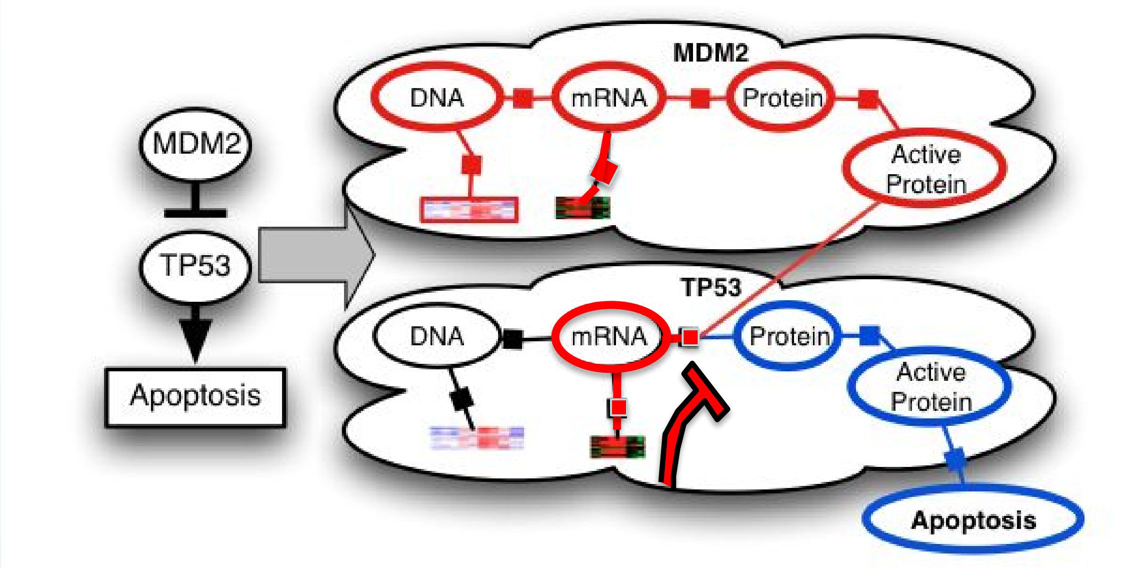
Interactions Matter



- Given information about the expression of TP53 alone
- Reasoning predicts apoptosis is in tact in these cells.

Charlie Vaske, Steve Benz

Interactions Matter



- Given the interaction and data about MDM2.
- apoptosis inference reversed

Quantitative Output

Log likelihood Ratio:

log odds of state and data

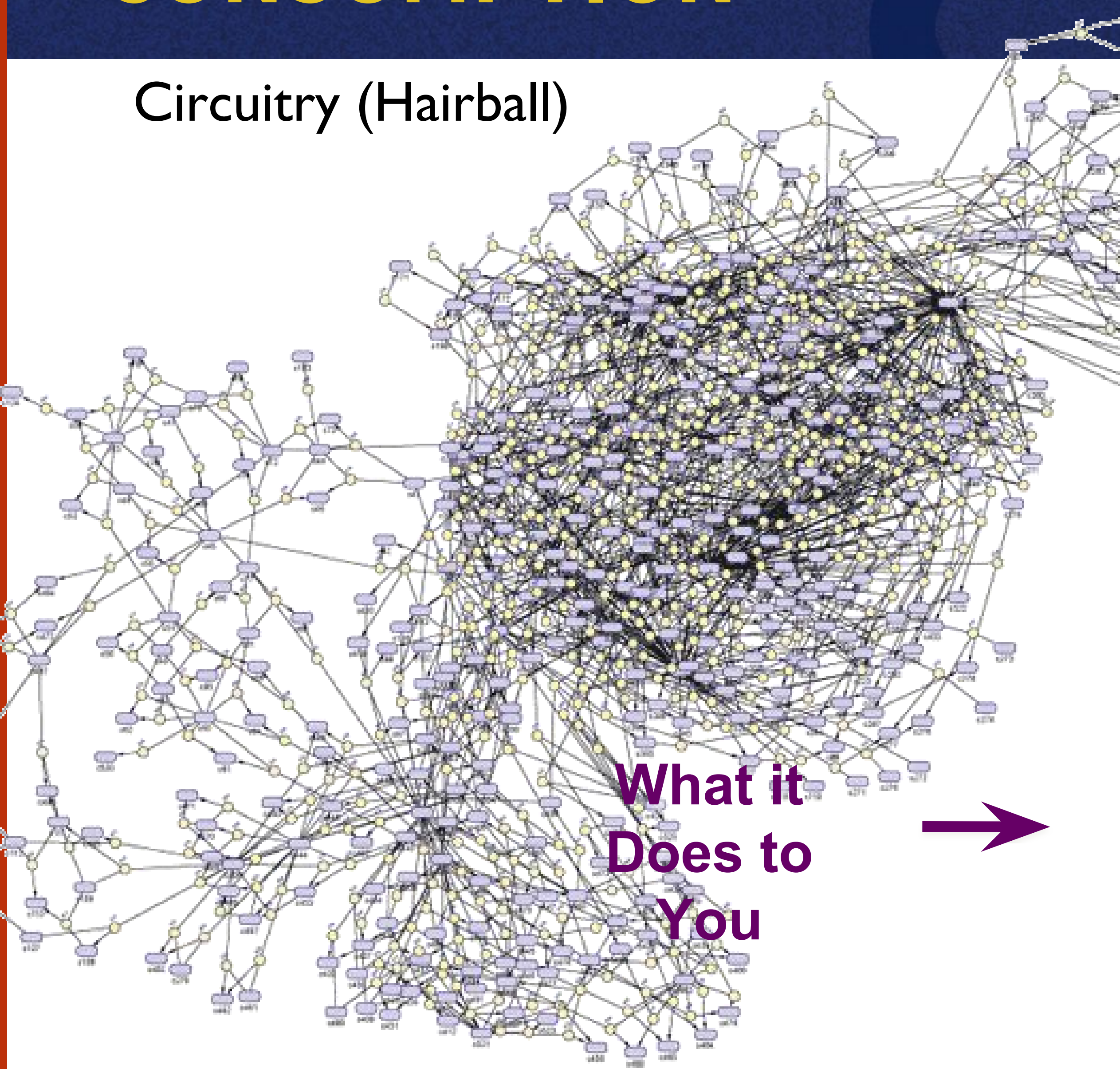
prior log odds

$$\log\frac{P(Data \mid Apoptosis = active, \Phi)}{P(Data \mid Apoptosis \neq active, \Phi)} = \log\frac{P(Data, Apoptosis = active \mid \Phi)}{P(Data, Apoptosis \neq active \mid \Phi)} - \log\frac{P(Apoptosis = active \mid \Phi)}{P(Apoptosis \neq active \mid \Phi)}$$

Charlie Vaske, Steve Benz

CELL CIRCUITRY – BAD FOR HUMAN CONSUMPTION

Circuitry (Hairball)



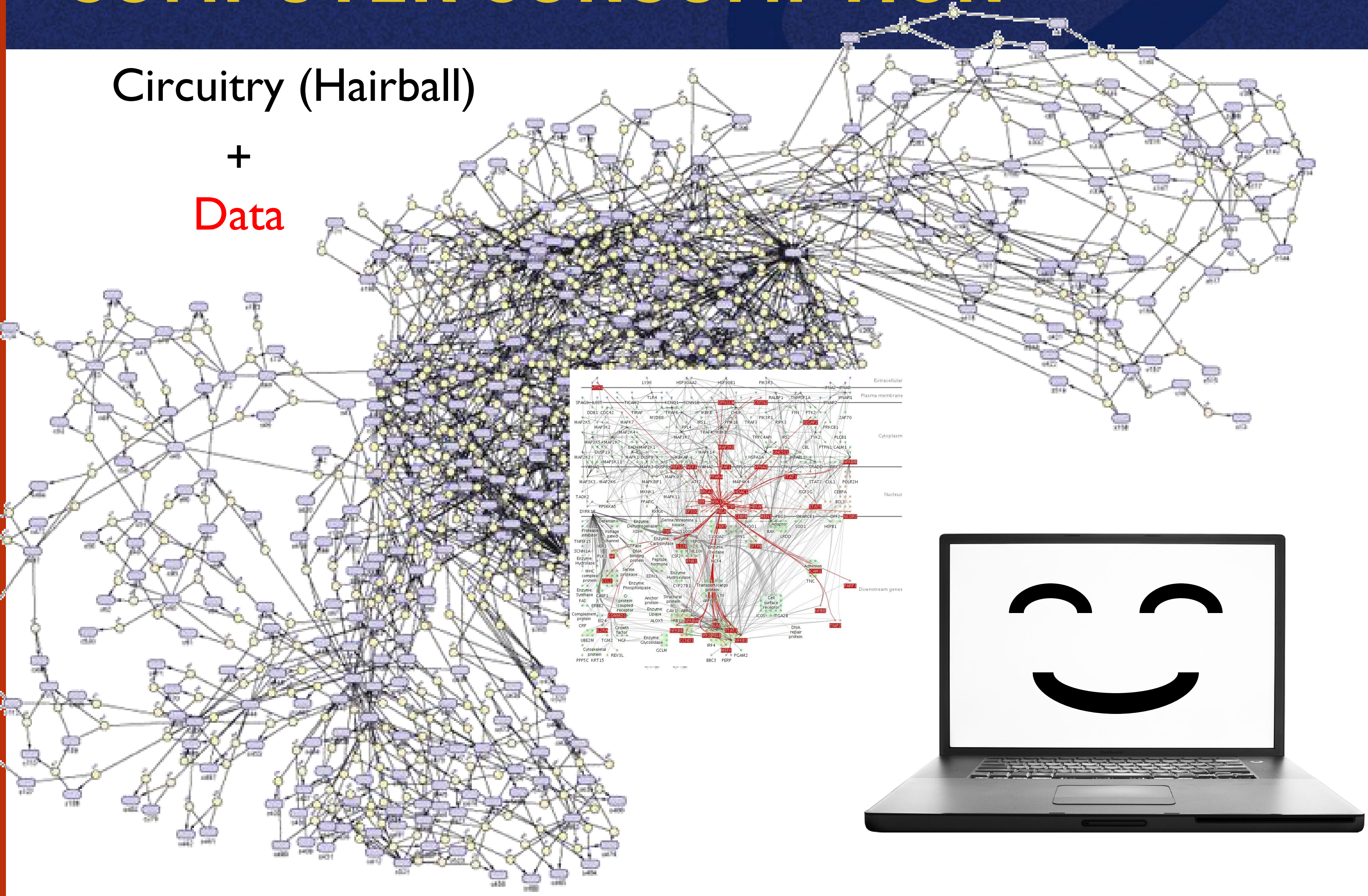
What it Does to You →

CELL CIRCUITRY – GREAT FOR COMPUTER CONSUMPTION

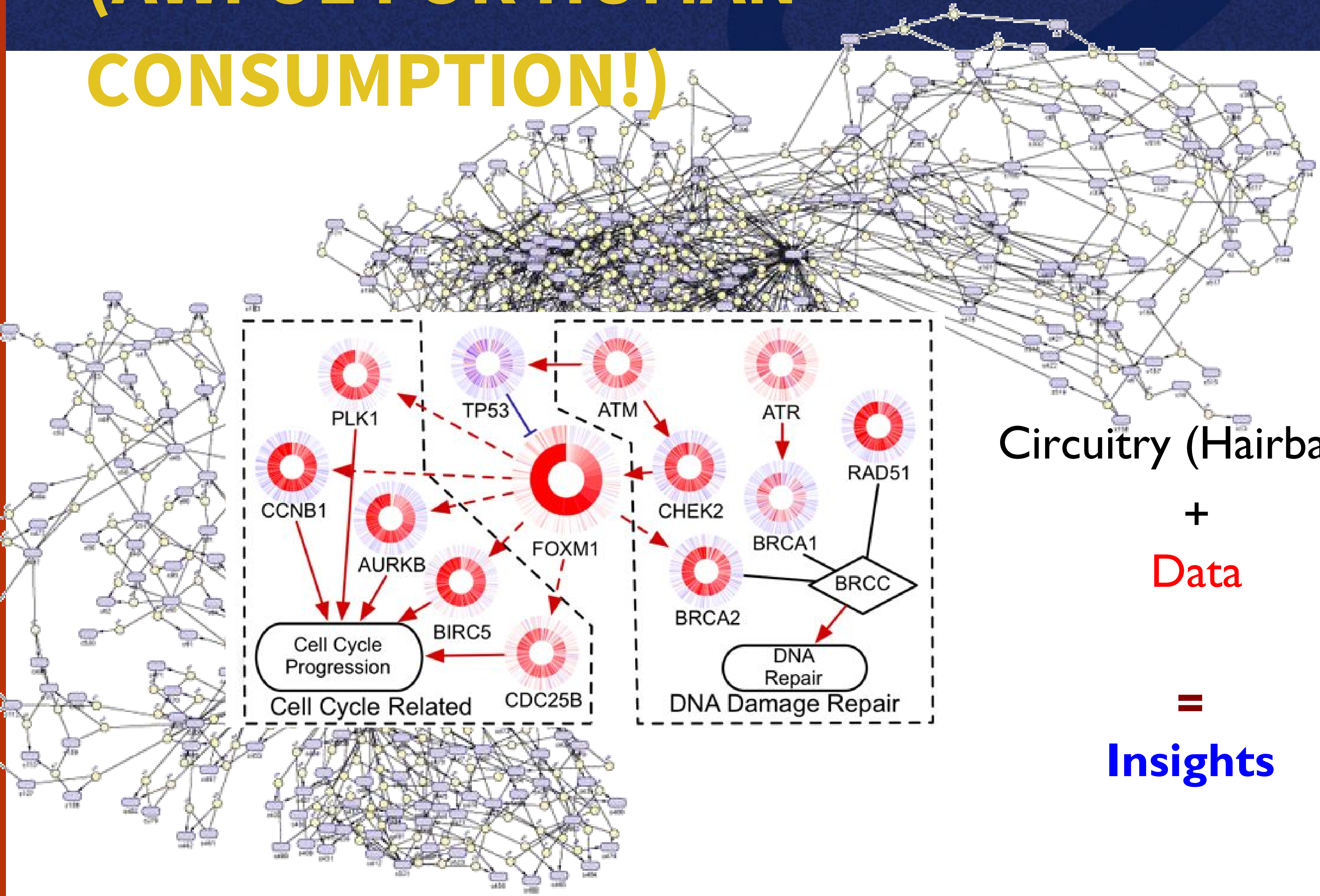
Circuitry (Hairball)

+

Data



COMPUTING! (AWFUL FOR HUMAN CONSUMPTION!)



Circuitry (Hairball)

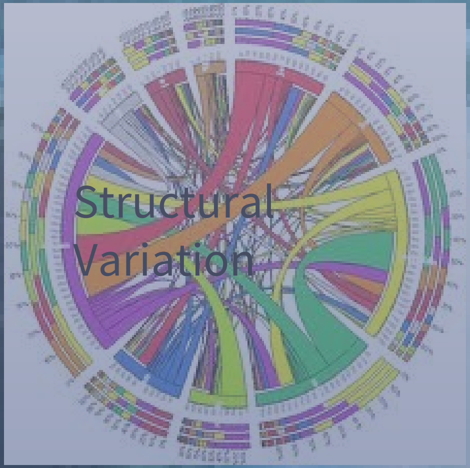
+

Data

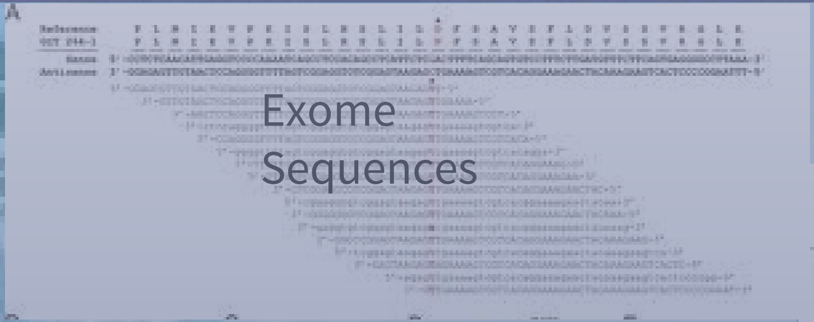
=

Insights

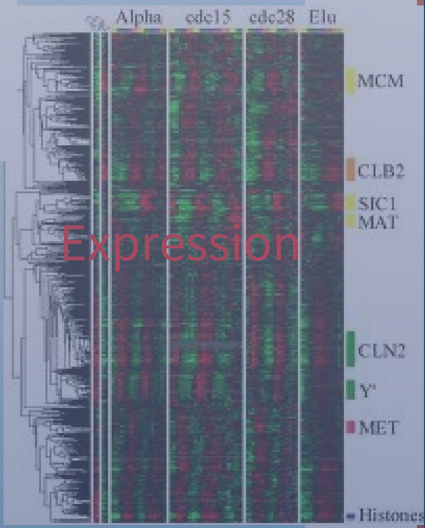
INTEGRATED MAP TO RULE THEM ALL



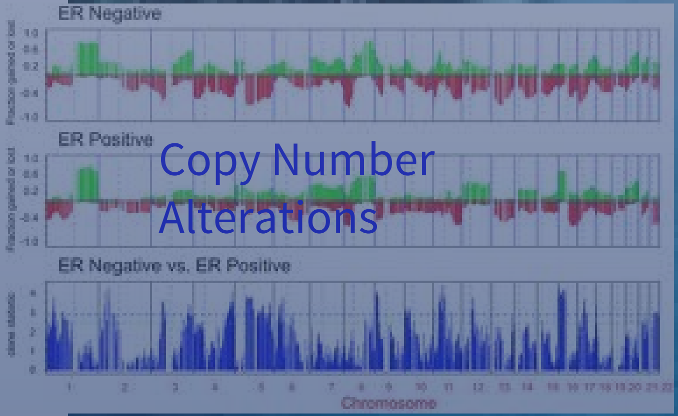
Structural Variation



Exome Sequences



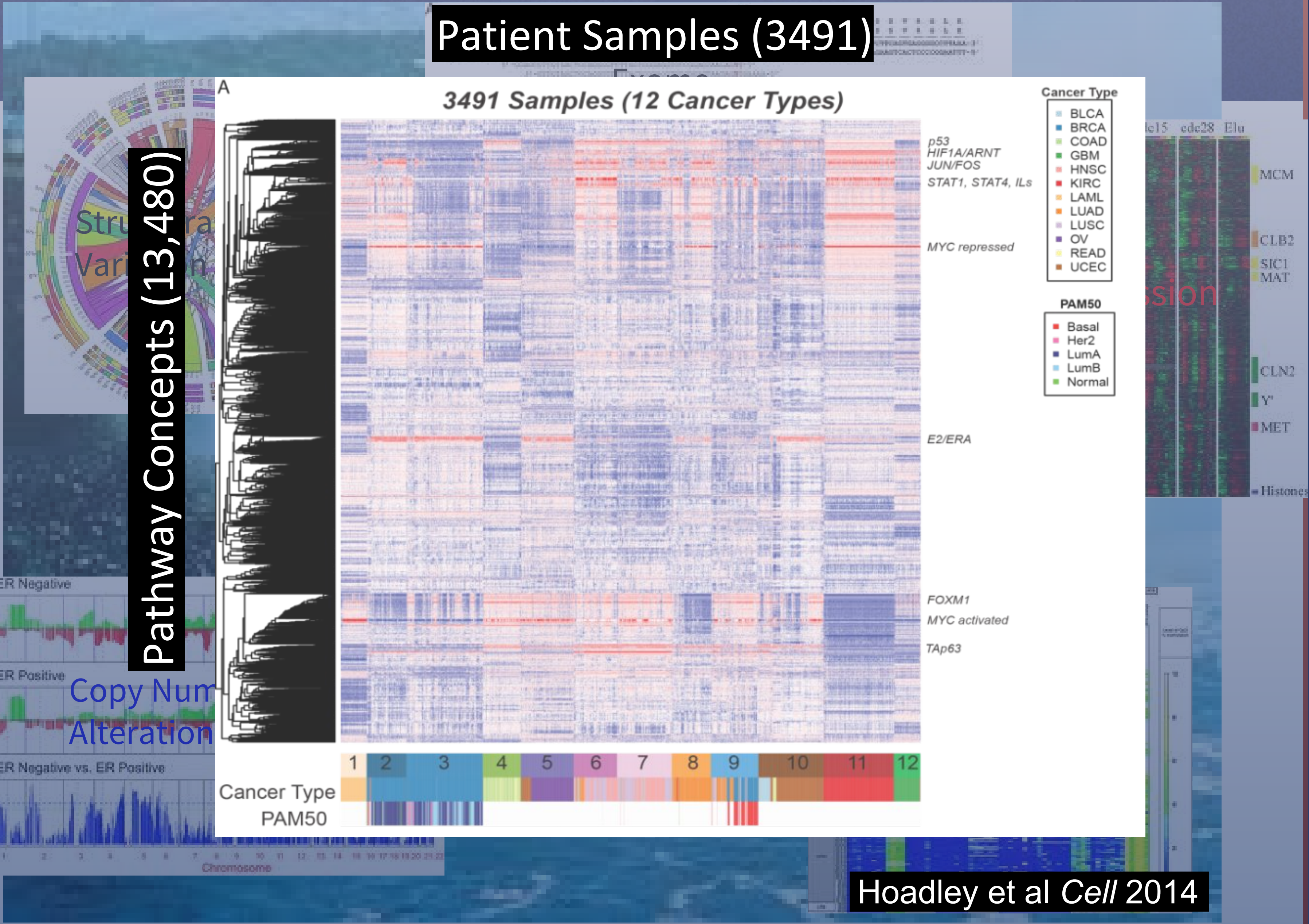
Expression



Copy Number Alterations

DNA Methylation

INTEGRATED MAP TO RULE THEM ALL

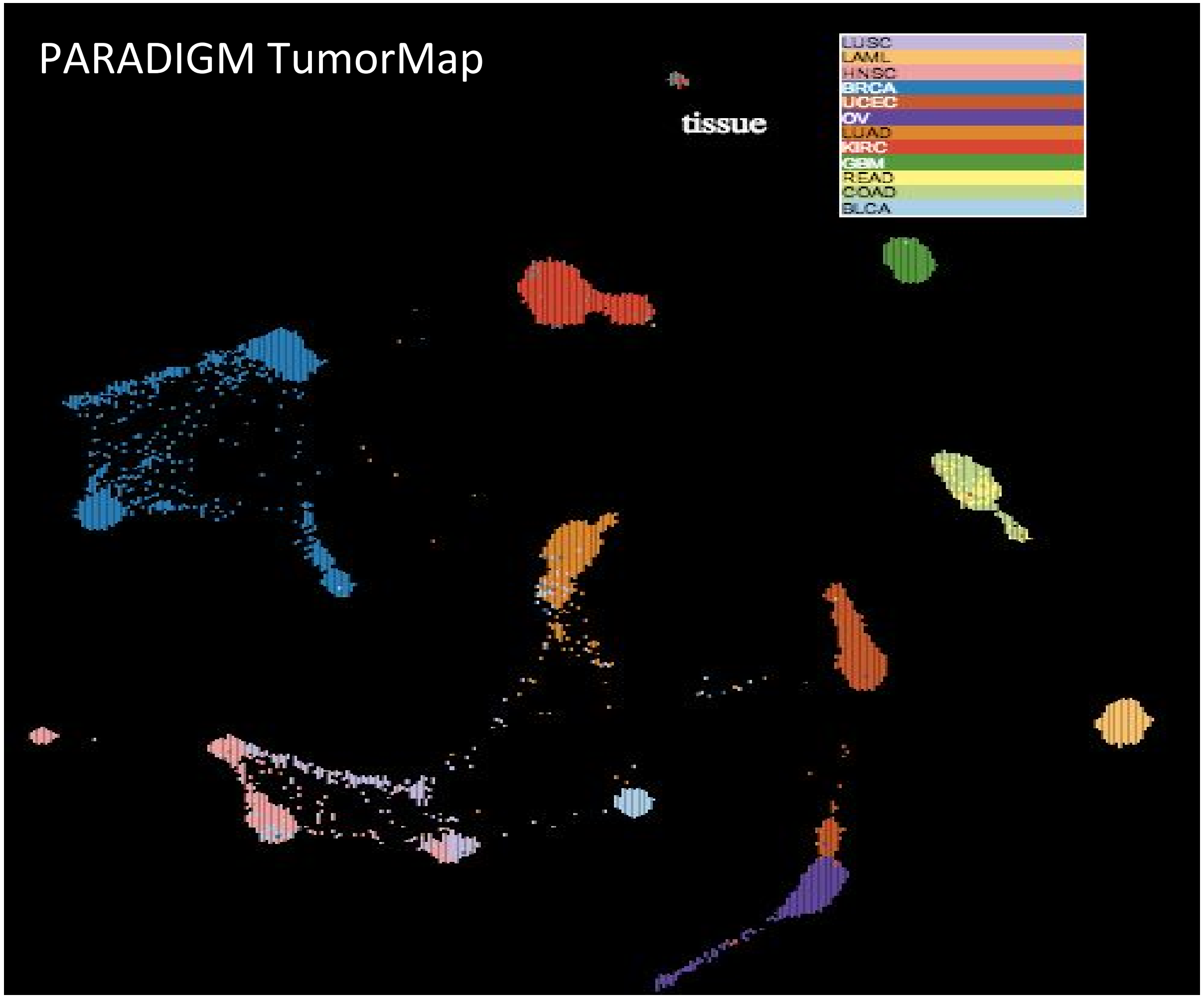


Patient Samples (3491)

Pathway Concepts (13,480)

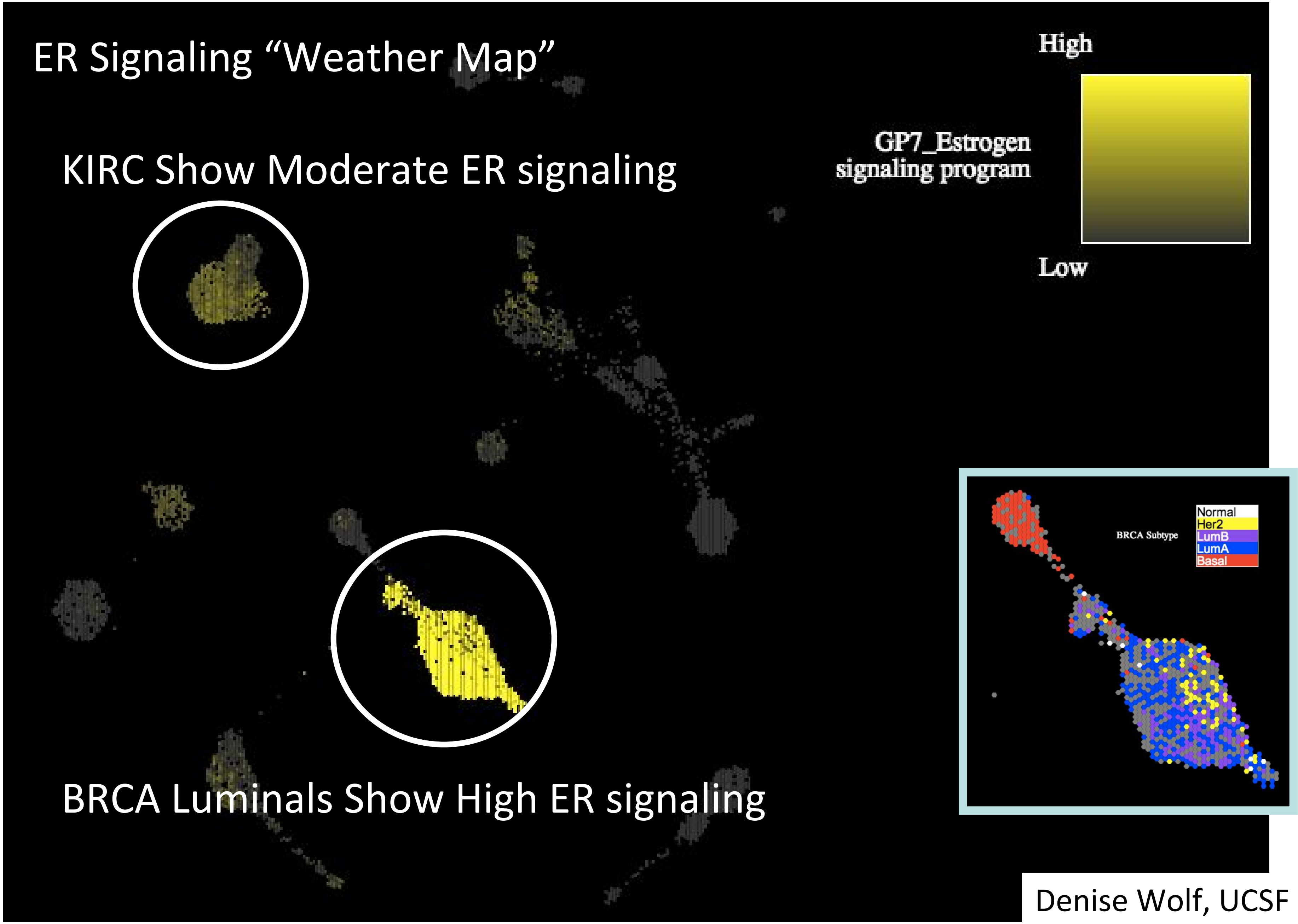
Hoadley et al *Cell* 2014

UCSC TUMORMAP: BROWSER FOR CANCER SAMPLES



- ~90% of samples cluster with their tissue

Viewing Gene Programs on the TumorMap



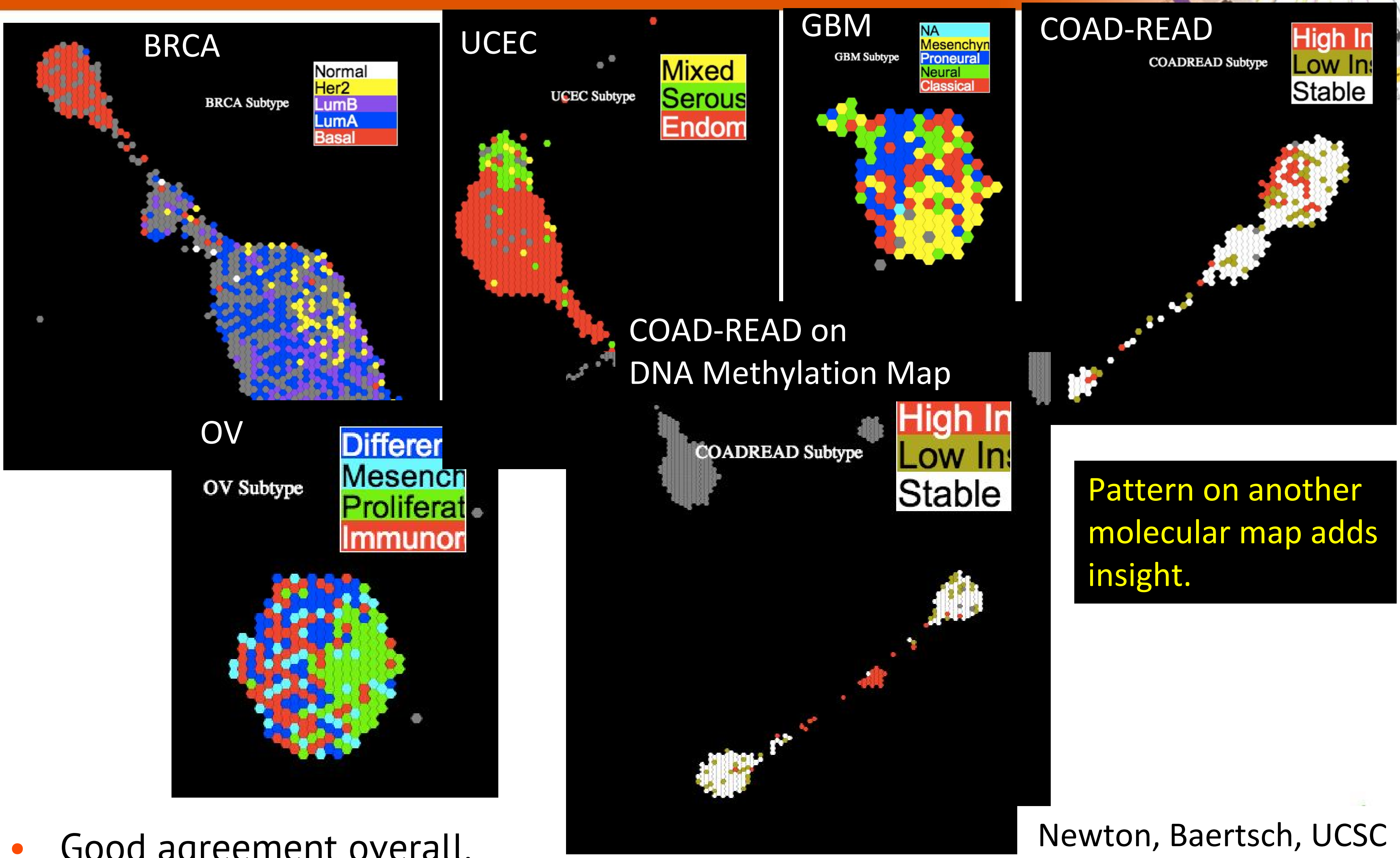
ER Signaling “Weather Map”

KIRC Show Moderate ER signaling

BRCA Luminals Show High ER signaling

Denise Wolf, UCSF

Are disease-specific AWG subtypes recapped in TumorMap?

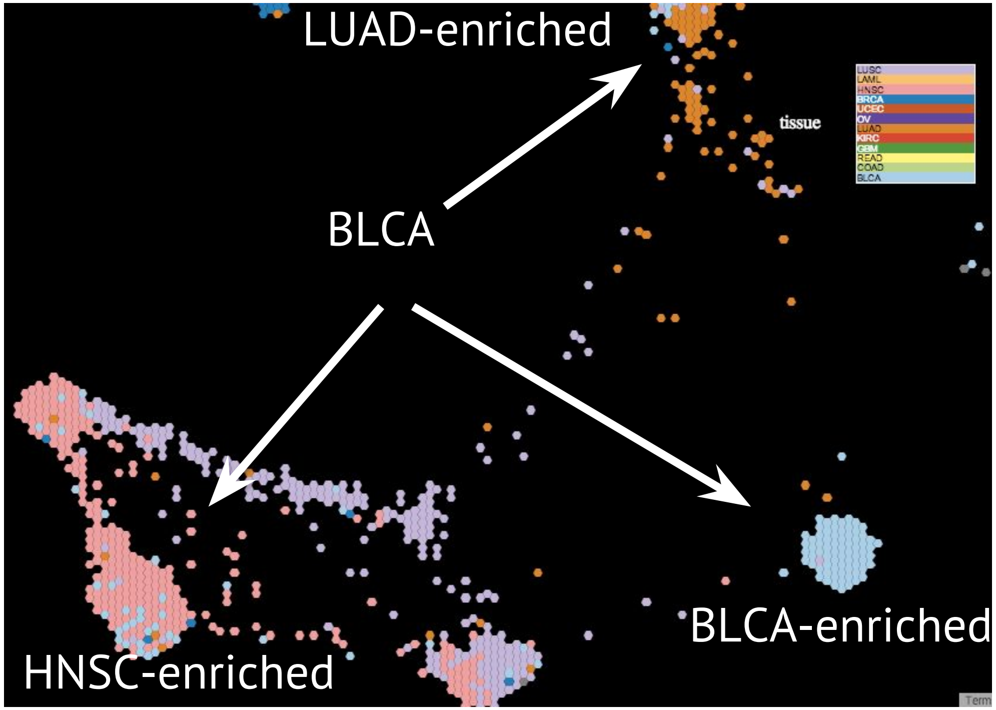


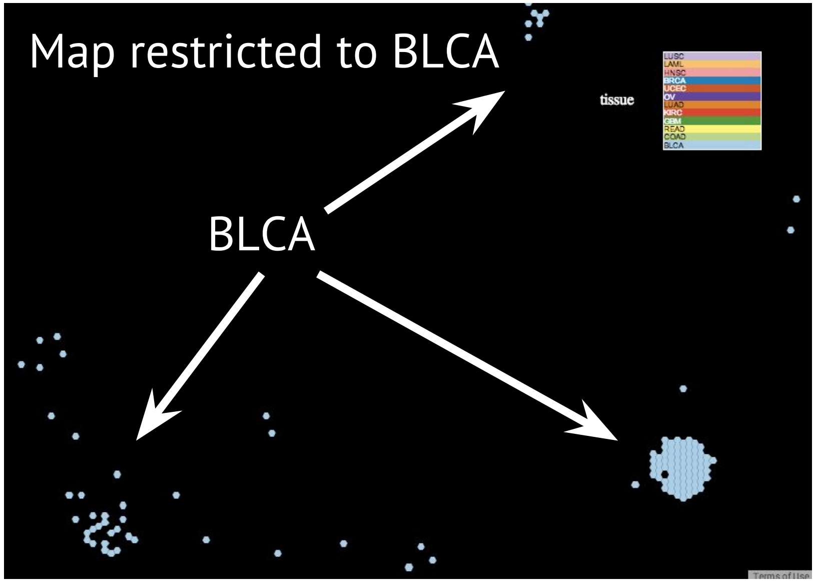
Pattern on another molecular map adds insight.

Newton, Baertsch, UCSC

- Good agreement overall.

BLCA DIVERGENCE ON TUMORMAP

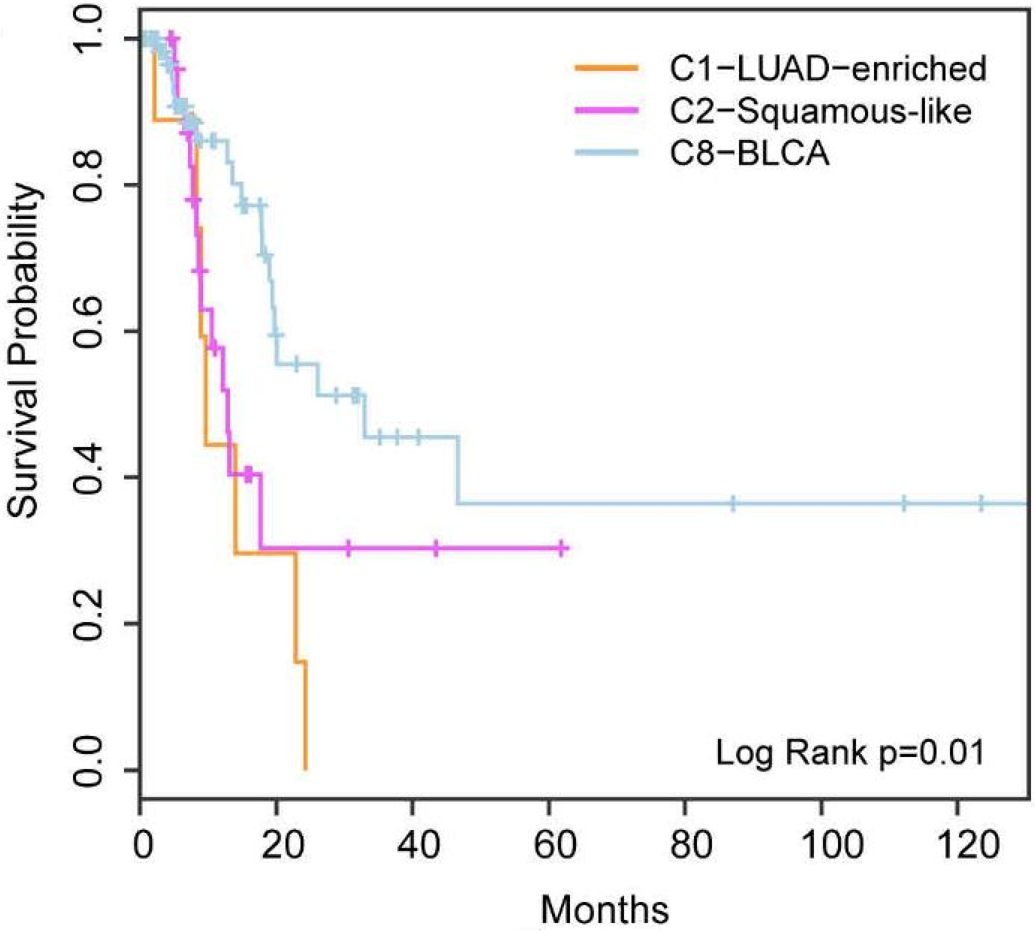




- BLCA diverge into bladder-enriched, squamous, and LUAD-enriched islands

Hoadley, Cell, Aug

INTEGRATED SUBTYPING OF BLCA DISTINGUISHES PATIENT OUTCOMES

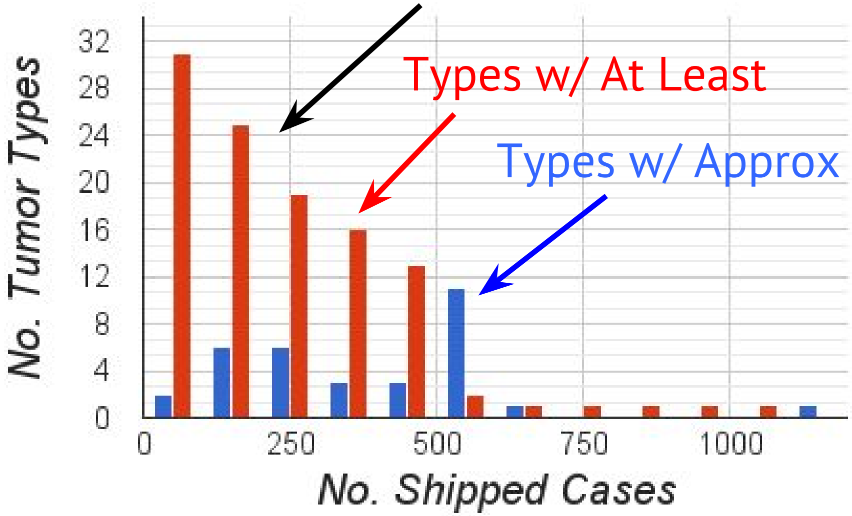


- COCA clusters distinguish different survival classes for BLCA

Hoadley, Cell, Aug

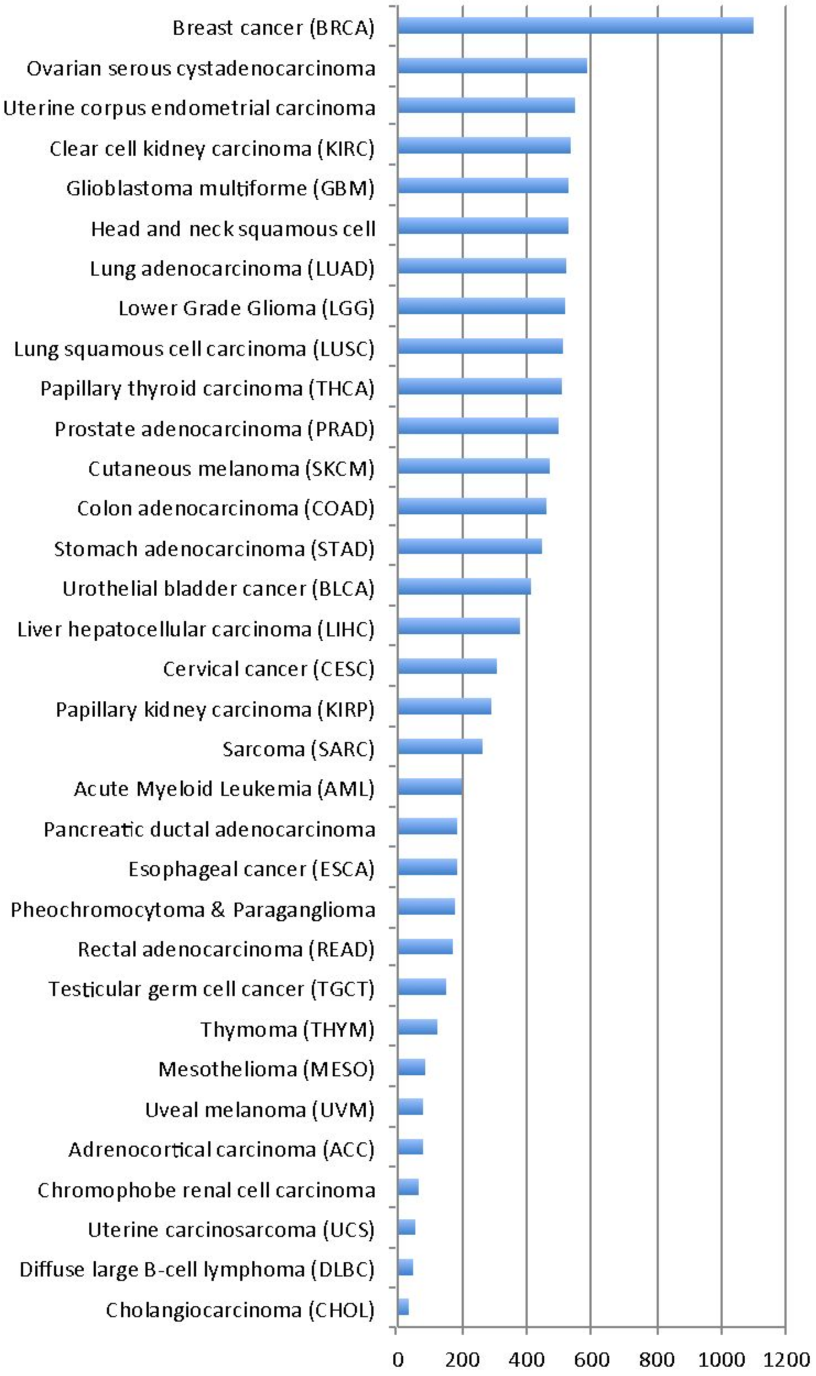
PanCan-33: PanCanAtlas

- **33 Tumor Types**
- 11,053 Total Cases
- Latest Publication Restrictions Lift in December, 2015 (e.g. testicular)
- Average cases: 335
- Median cases: 308
- BRCA most cases: 1100
- CHOL least cases: 36

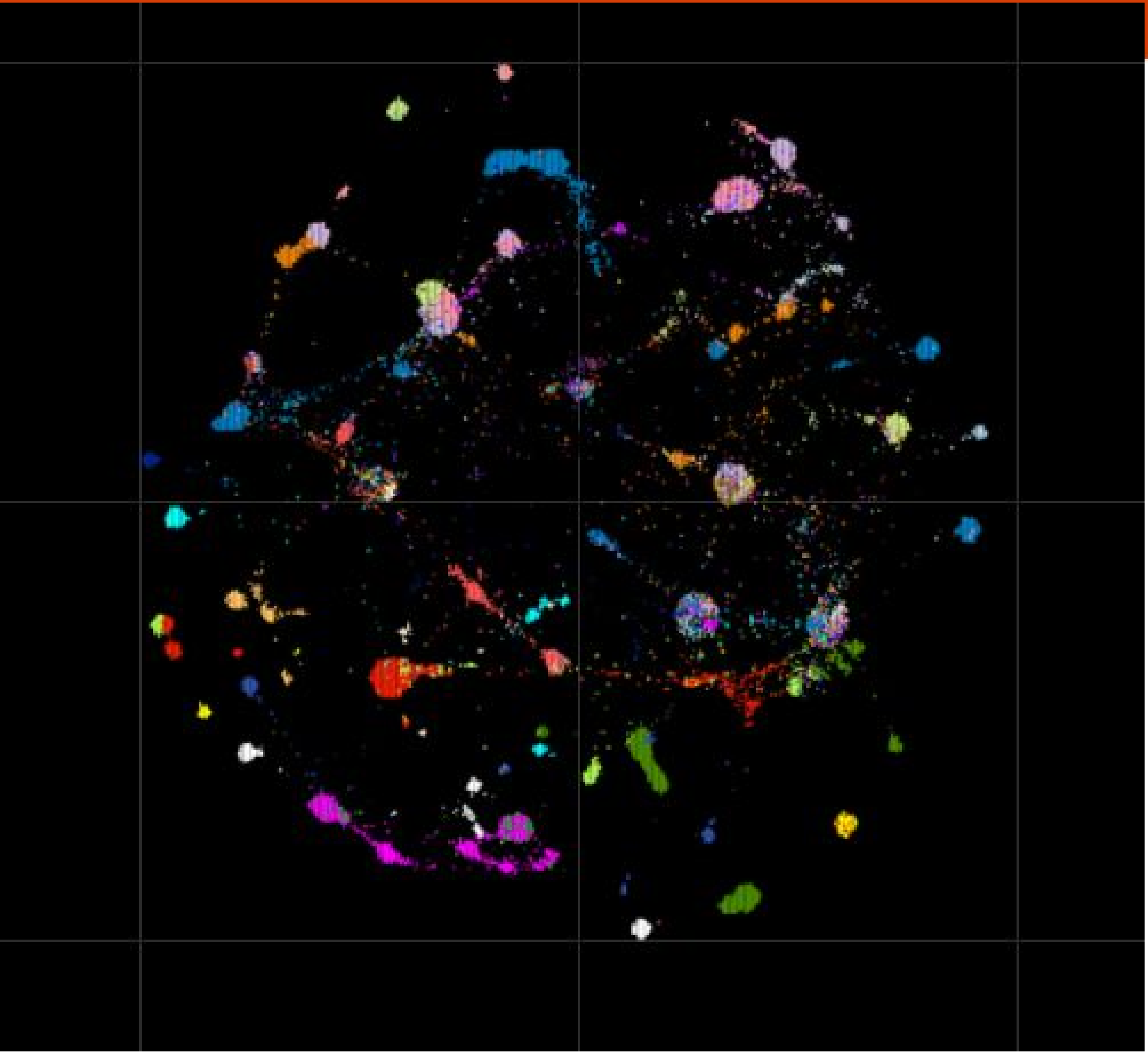

20 Types w/ >= 200 cases

Types w/ At Least

Types w/ Approx



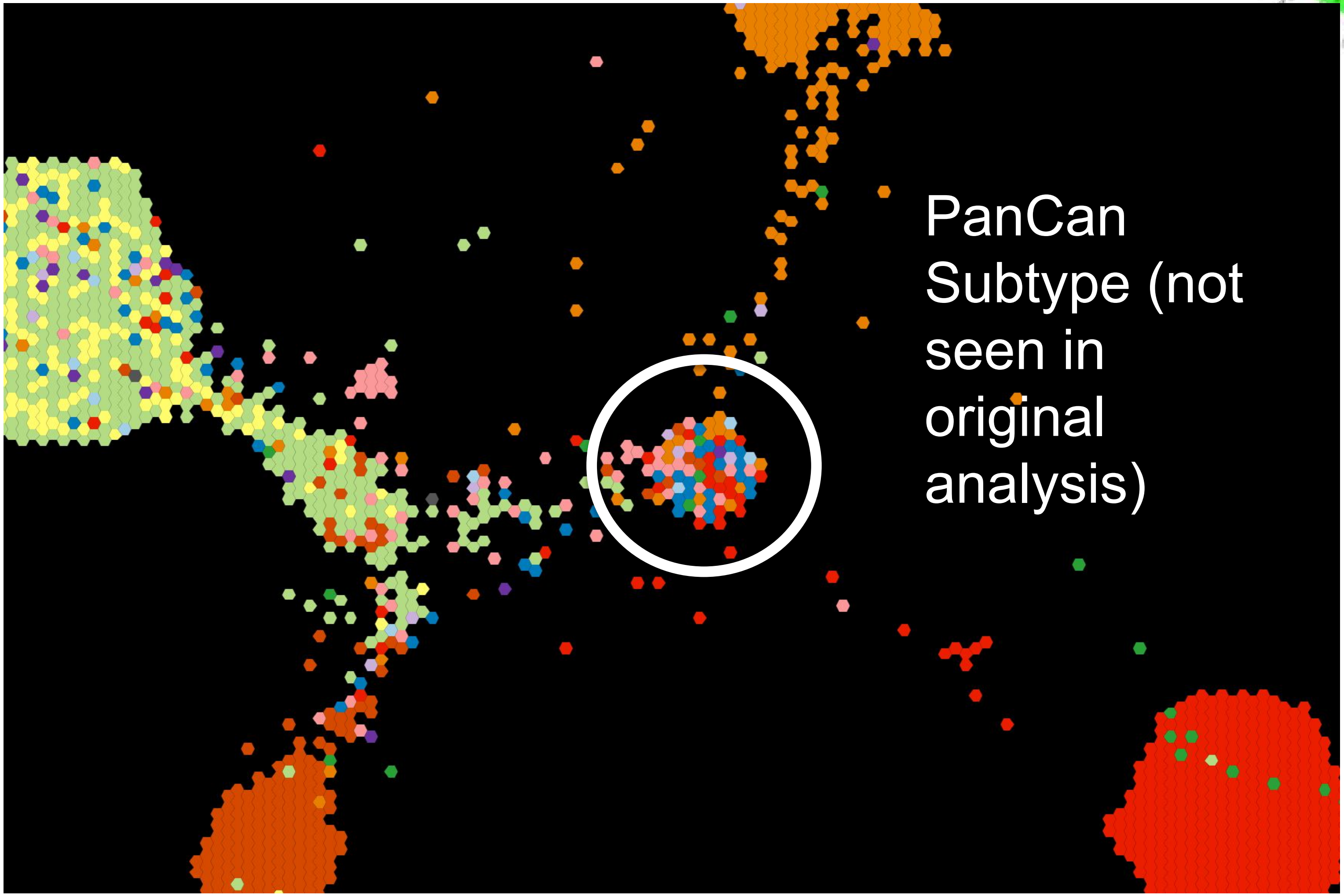
PanCan-33 TumorMap



Colors show Tissue of origin.

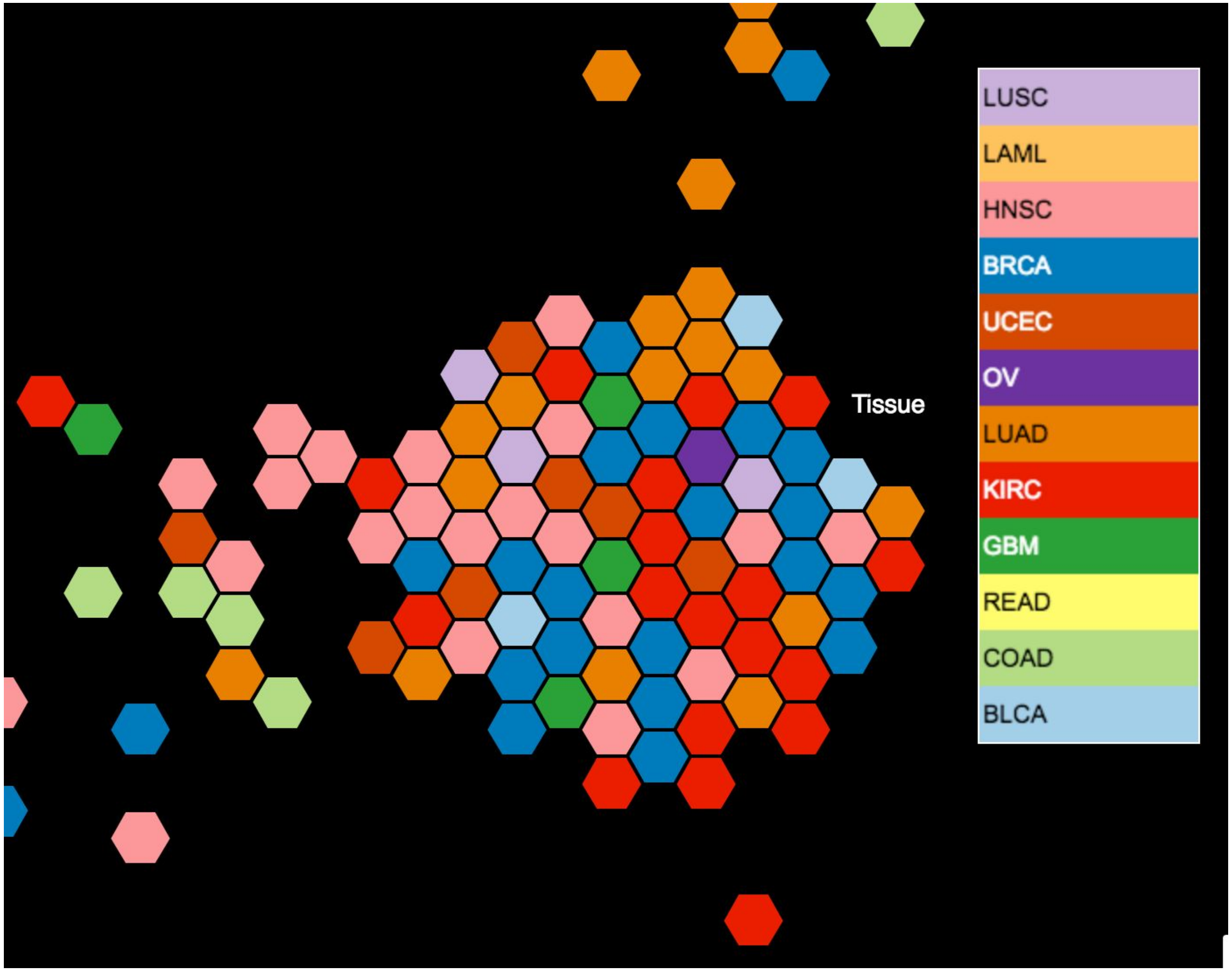
Newton, Baertsch, UCSC

Integrated map reveals pancan subtypes



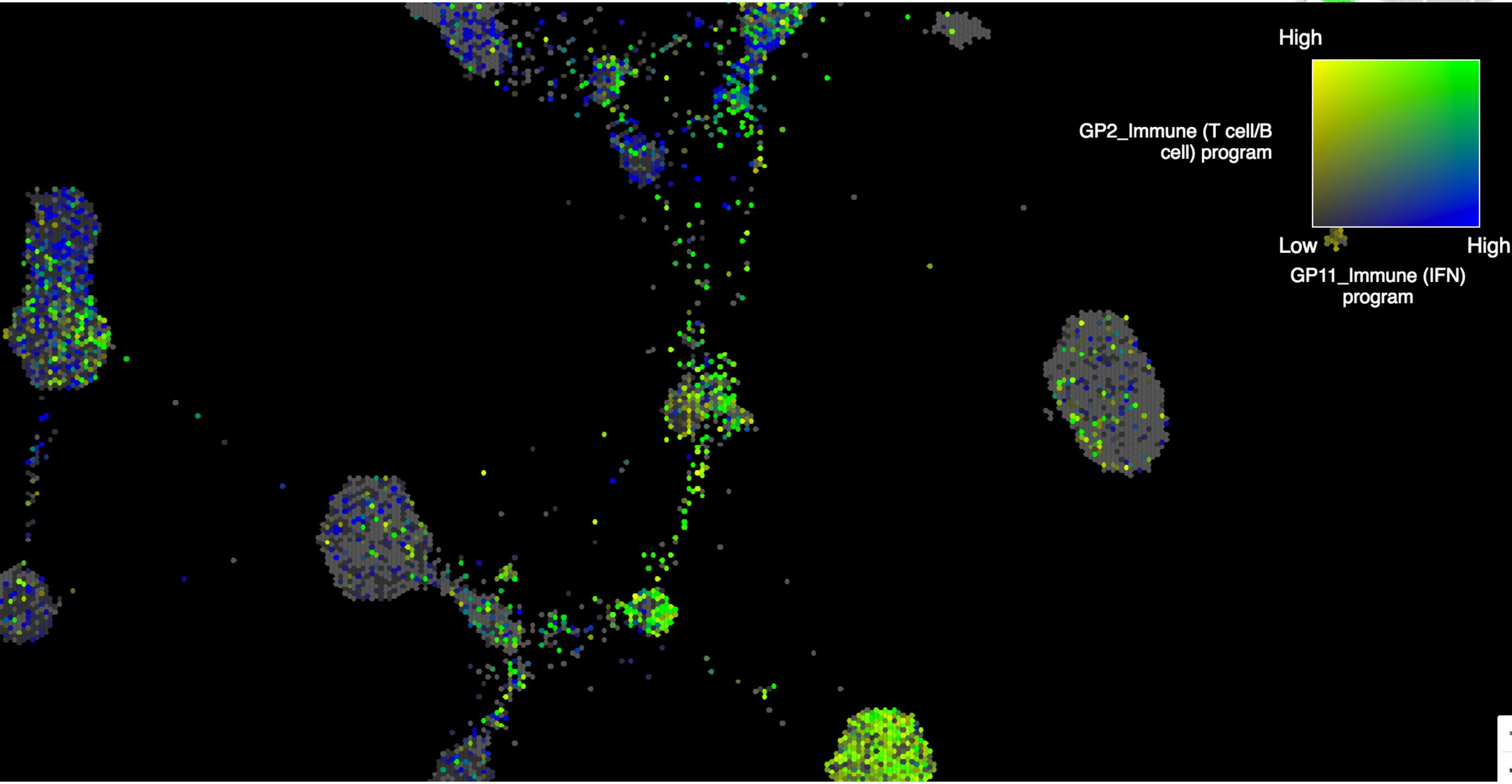
PanCan Subtype (not seen in original analysis)

Integrated map reveals new subtypes

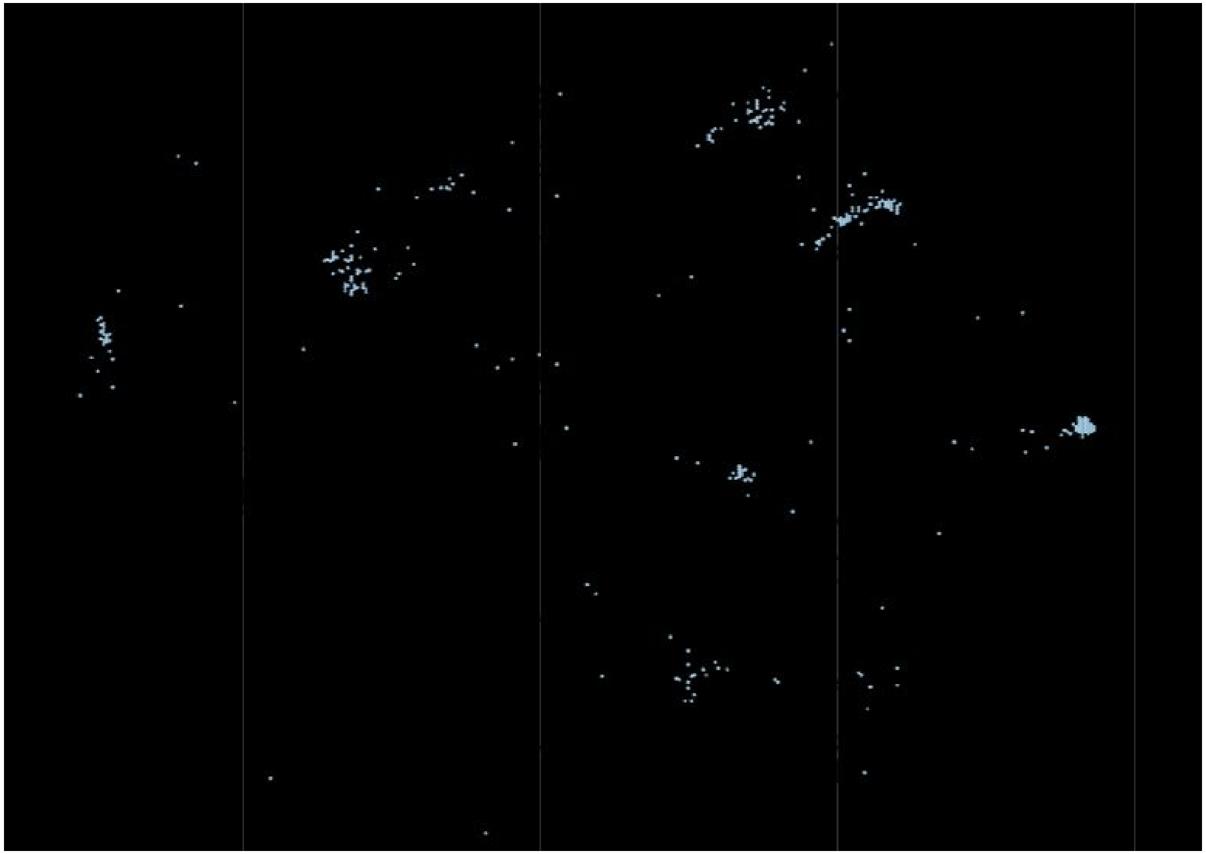


What characterizes these tumors?

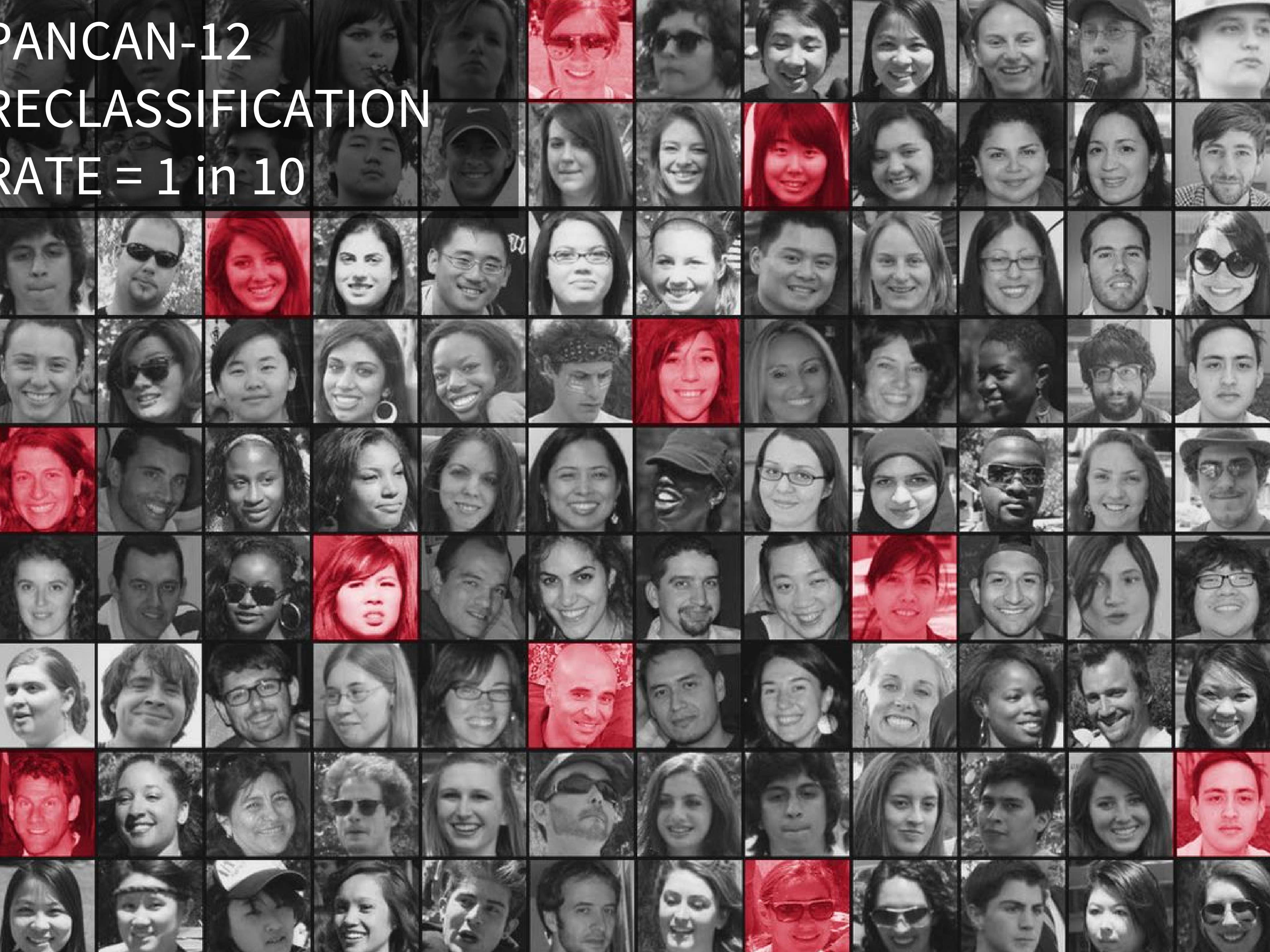
Enriched for t/B and IFN immune (D. Wolf's) programs



BLCA divergence in Pan-Can-33



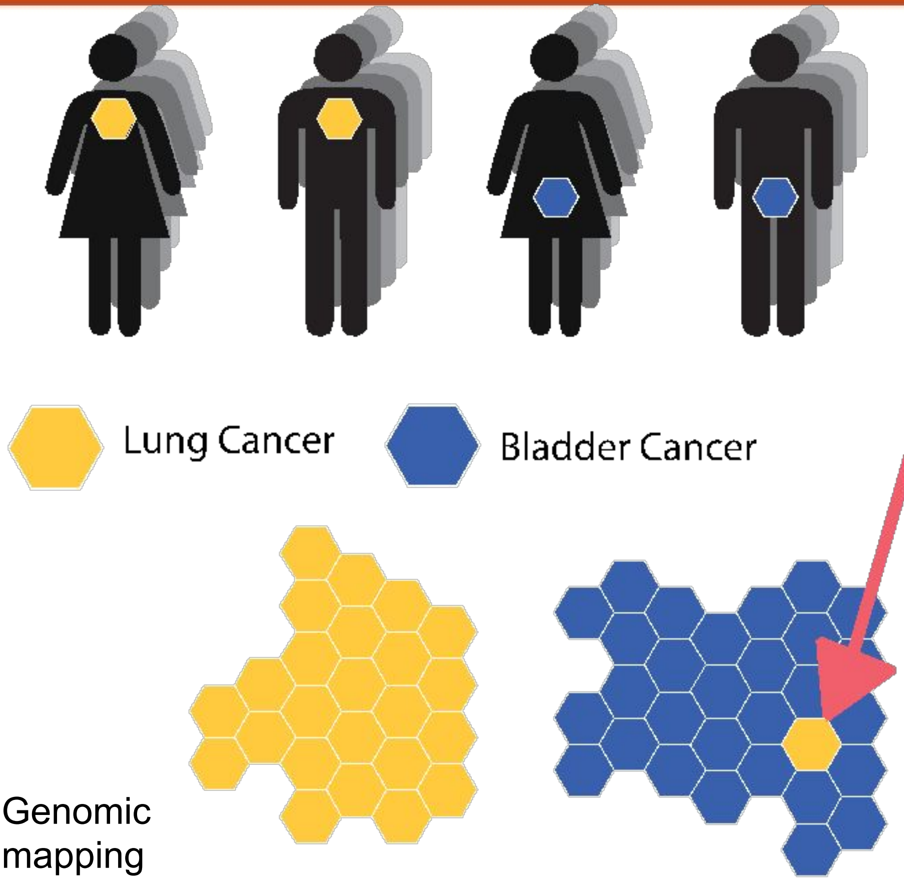
- BLCA diverge into several more subtypes



PANCAN-12
RECLASSIFICATION
RATE = 1 in 10

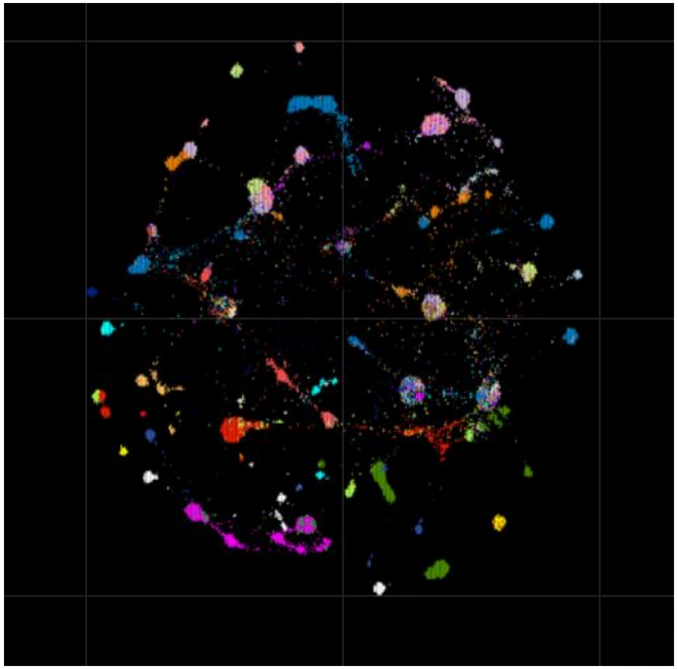
PANCAN-33 RECLASSIFICATION RATE = 1 in 5

PANCAN FOR N=1 PATIENTS

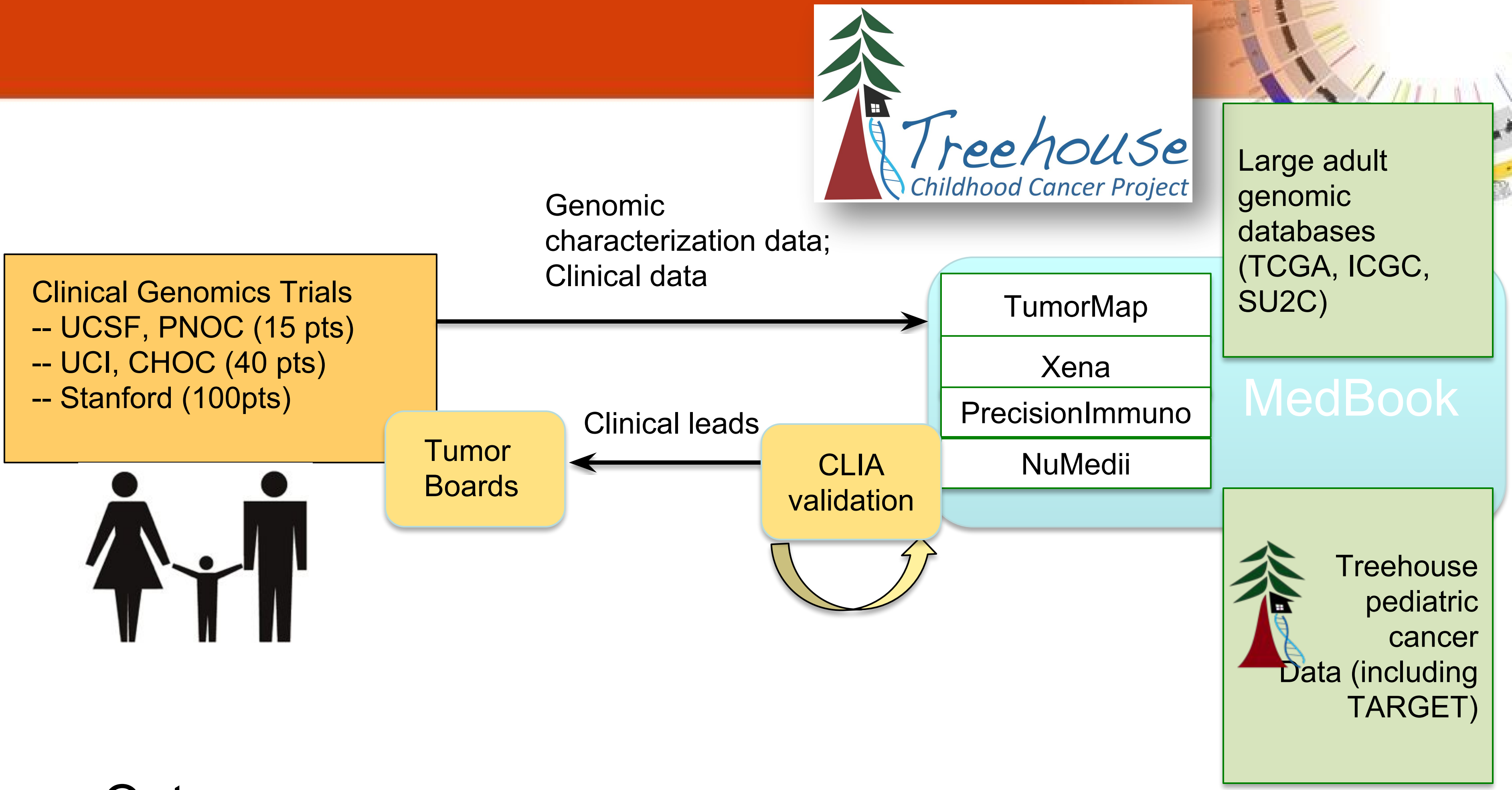


Genomic mapping

PanCan-33 Map:



CALIFORNIA KIDS CANCER COMPARISON



Clinical Genomics Trials
-- UCSF, PNOC (15 pts)
-- UCI, CHOC (40 pts)
-- Stanford (100pts)

Genomic characterization data; Clinical data

TumorMap

Xena

PrecisionImmuno

NuMedii

MedBook

Large adult genomic databases (TCGA, ICGC, SU2C)

Treehouse pediatric cancer Data (including TARGET)

Clinical leads

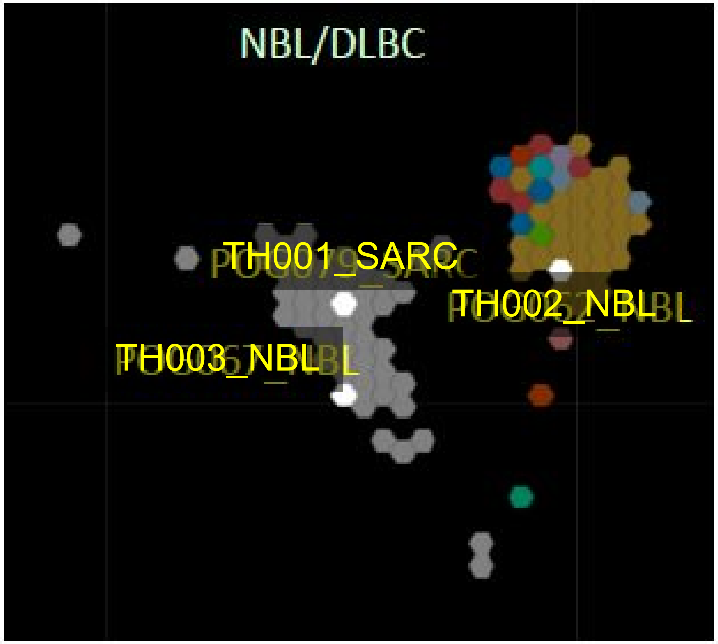
CLIA validation

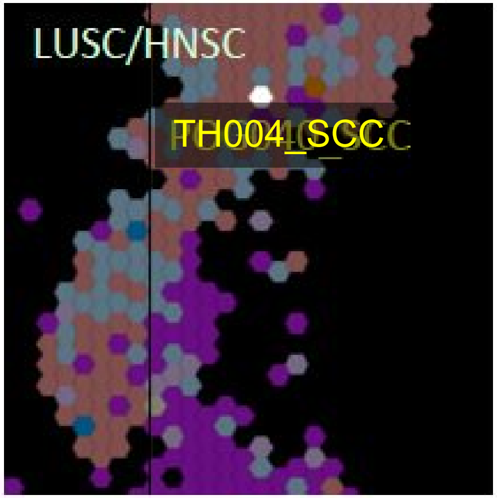
Tumor Boards

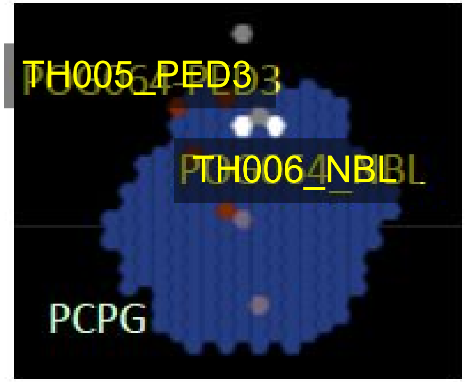
- Outcome measures:
  - New clinical leads
  - New evidence for clinical leads
  - New/refined molecular diagnoses

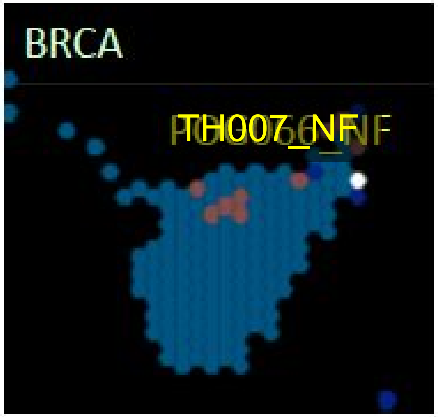
The Cancer Genome Atlas

WHERE DO Childhood Samples MAP?





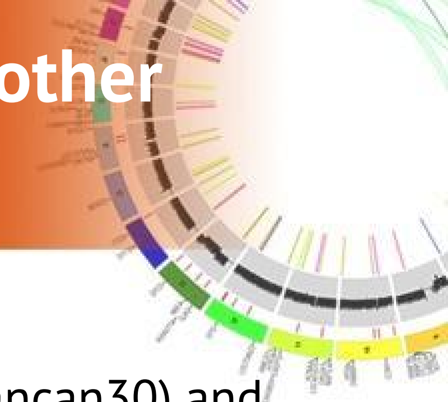




Olena Morozova
Yulia Newton

The

Analysis of POG samples in the context of other cancers

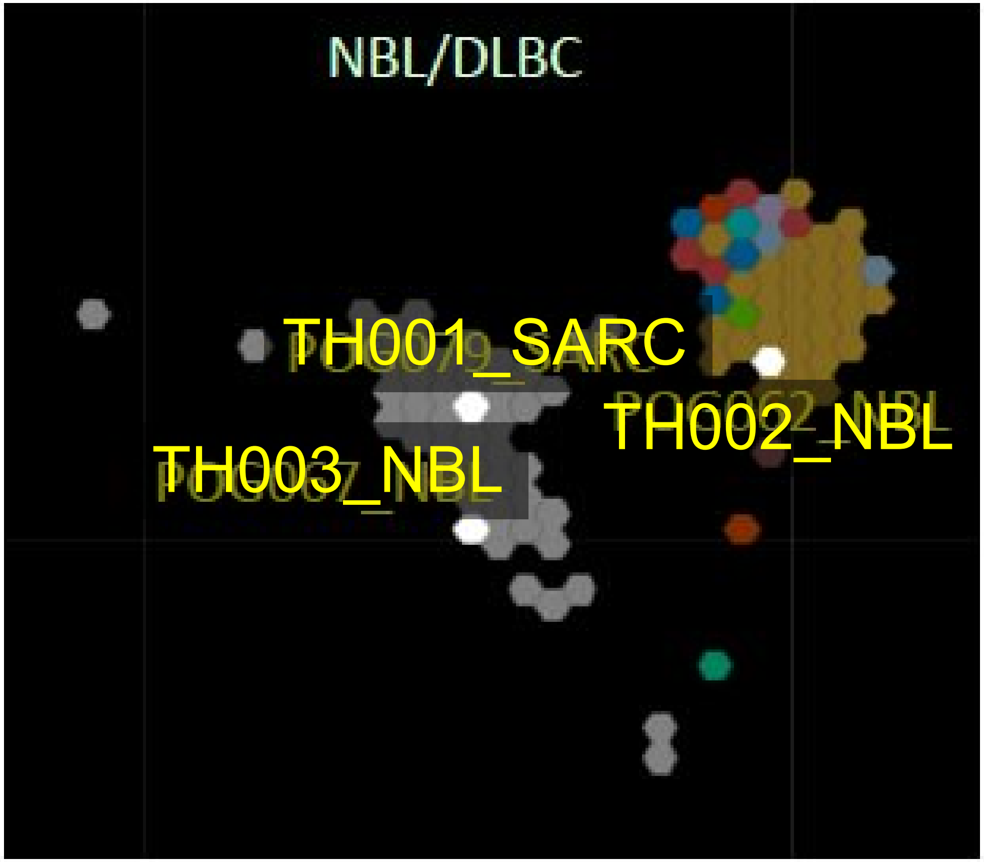


- TH005-PED3
  - Clusters with Pheochromocytoma and Paraganglioma (pancan30) and with Neuroblastoma (pancan14)
- TH002_NBL
  - Clusters with Lymphoid Neoplasm Diffuse Large B-cell Lymphoma (pancan30) and with Neuroblastoma (pancan14)
- TH004_SCC
  - Clusters with Head and Neck Squamous Cell Carcinoma
- TH006_NBL
  - Clusters with Pheochromocytoma and Paraganglioma (pancan30) and with Neuroblastoma (pancan14)
- TH007_NF
  - Clusters with Breast Invasive Carcinoma
- TH003_NBL
  - Clusters with Neuroblastoma
- **TH001_SARC**
  - Clusters with Neuroblastoma ALK fusion tumors

Olena Morozova
Yulia Newton

WHERE DO Childhood Samples MAP?

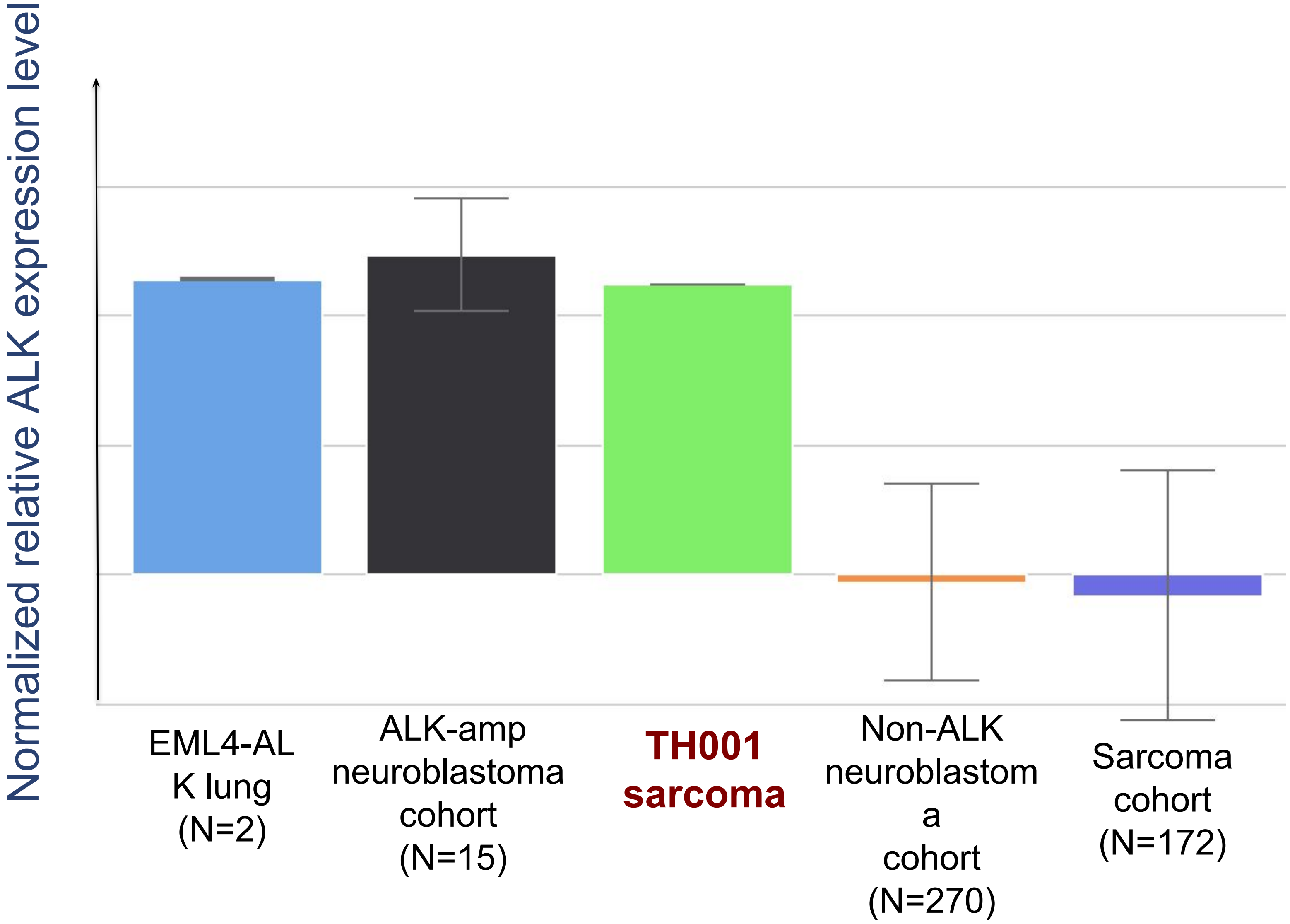
Observation:
TH001 pediatric sarcoma groups with neuroblastoma ALK-mutant samples.



Olena Morozova
Yulia Newton

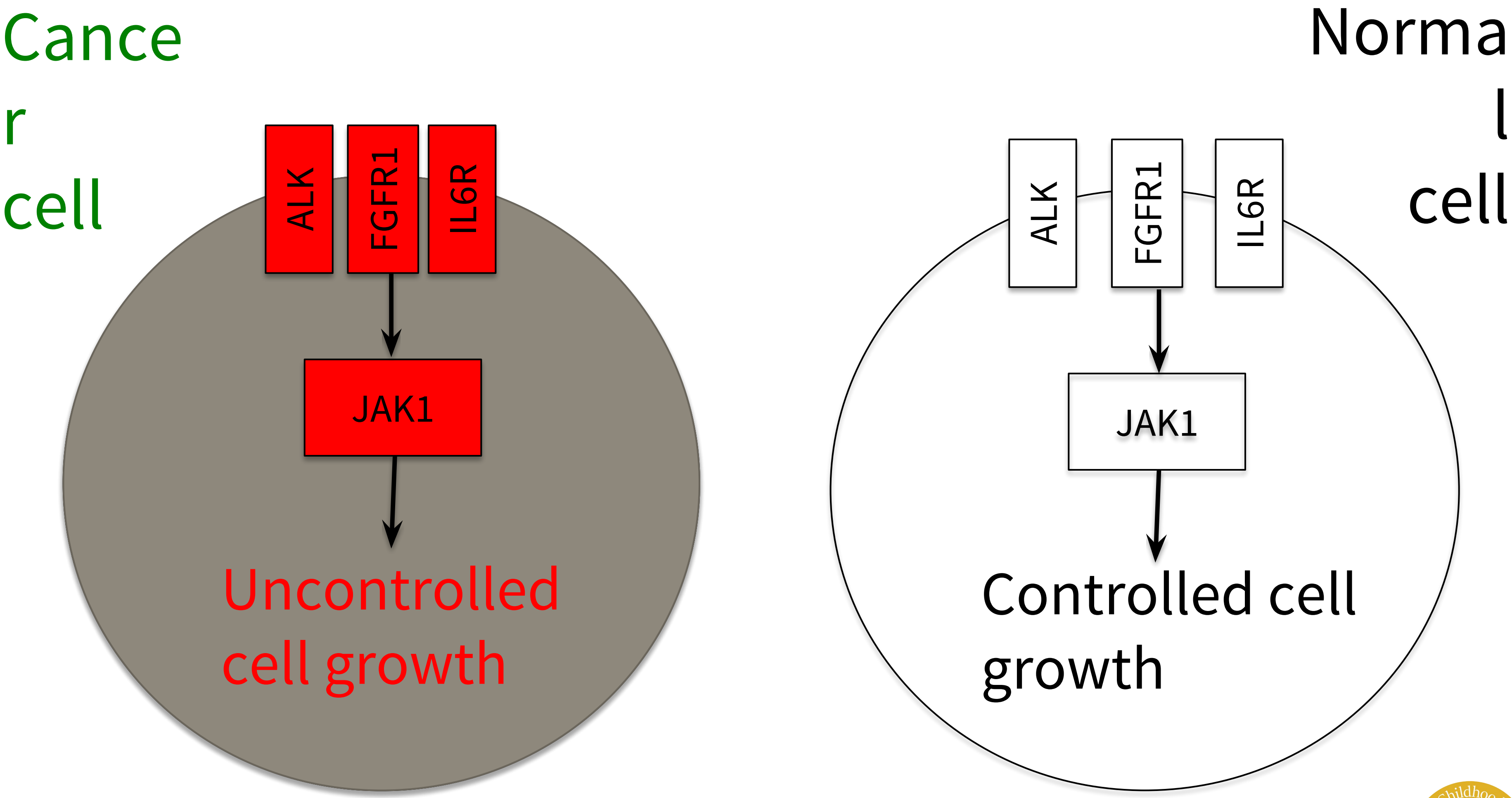
The

ALK POTENTIAL TARGET FOR PATIENT 1 BASED ON PAN-CANCER ANALYSIS



Xena.ucsc.edu

TWO NEW TREATMENTS FOR PATIENT 1



Cancer cell

ALK

FGFR1

IL6R

JAK1

Uncontrolled cell growth

Normal cell

ALK

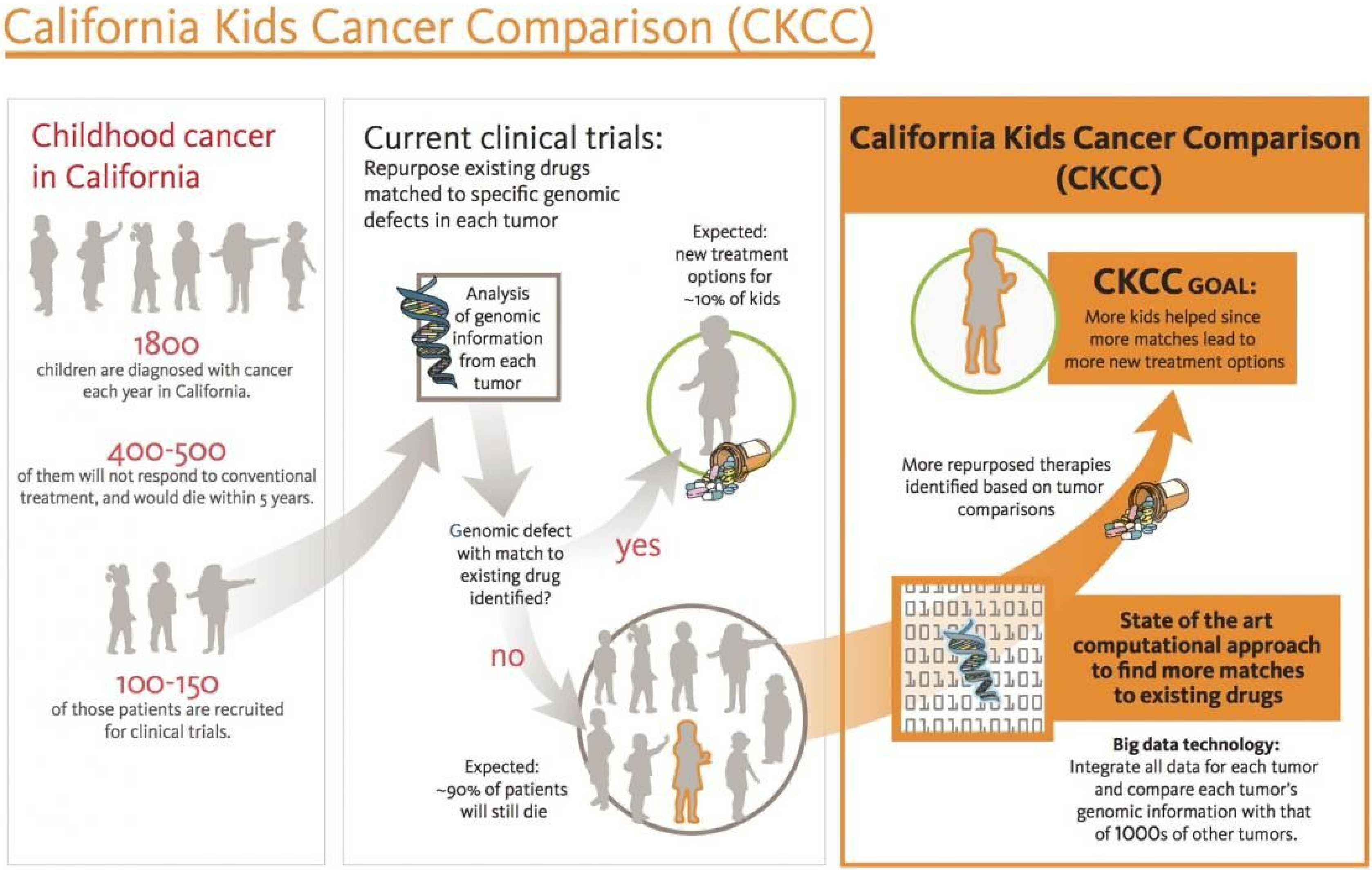
FGFR1

IL6R

JAK1

Controlled cell growth

BECAUSE OF PATIENT 1…



California Kids Cancer Comparison (CKCC)

Childhood cancer in California

1800
children are diagnosed with cancer each year in California.

400-500
of them will not respond to conventional treatment, and would die within 5 years.

100-150
of those patients are recruited for clinical trials.

Current clinical trials:

Repurpose existing drugs matched to specific genomic defects in each tumor

Analysis of genomic information from each tumor

Genomic defect with match to existing drug identified?

Expected: new treatment options for ~10% of kids

Expected: ~90% of patients will still die

California Kids Cancer Comparison (CKCC)

CKCC GOAL:
More kids helped since more matches lead to more new treatment options

More repurposed therapies identified based on tumor comparisons

State of the art computational approach to find more matches to existing drugs

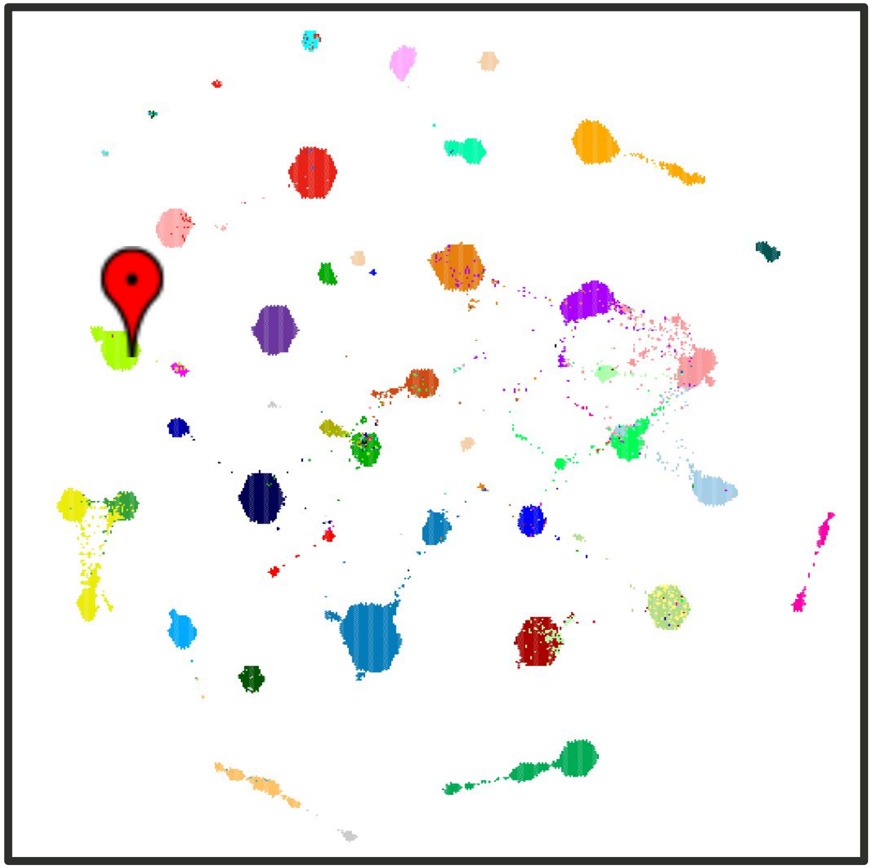
Big data technology:
Integrate all data for each tumor and compare each tumor's genomic information with that of 1000s of other tumors.

WHAT WE ARE DOING NOW: MOLECULAR DETECTIVES

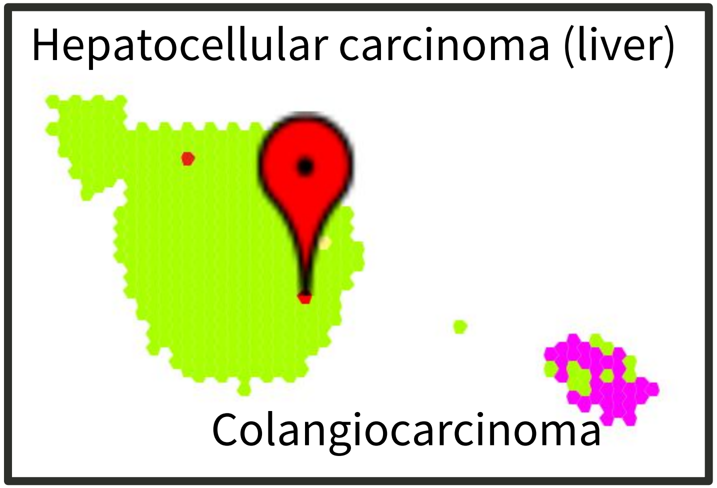
- Current cases of children with cancer
- TH008: 2-year-old diagnosed with Stage 4 Hepatoblastoma (liver cancer)
- Underwent two chemo protocols and two surgeries
- In need of new treatment options
- Foundation Medicine test revealed CTNNB1G34V mutation

TH008 IS MORE SIMILAR TO ADULT LIVER TUMORS THAN EXPECTED

Bird’s eye view (tumors colored by disease)



Zoom in on the patient (tumors colored by disease)



TH008 IS SIMILAR TO A SUBTYPE OF ADULT LIVER CANCER WITH TREATMENT OPTIONS

Target	Drug	Availability
Aurora kinases	Pazopanib	Clinical trial
IGF1R	Metformin	Off-label
ABCC2	Simvastatin plus chemo	Clinical trial
JAK/STAT	Ruxolitinib	Off-label

Turns out trial of pazopanib is opening up at Stanford and so treating oncologist chose this option

Outline:
Interpreting A Cancer Genome (N-of-1)

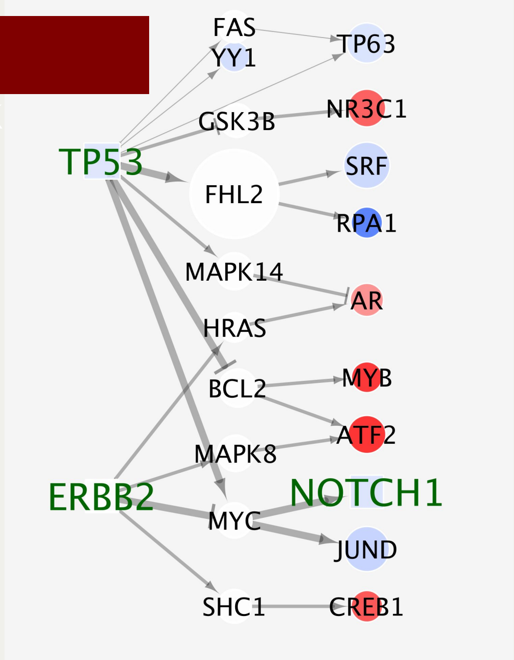
- Identify the closest known *form*

- Tailor the pathway model to fit an individual tumor’s unique combination of events

PERSONALIZED NETWORKS FOR TARGETING

Patient DTB-011

Linking Network

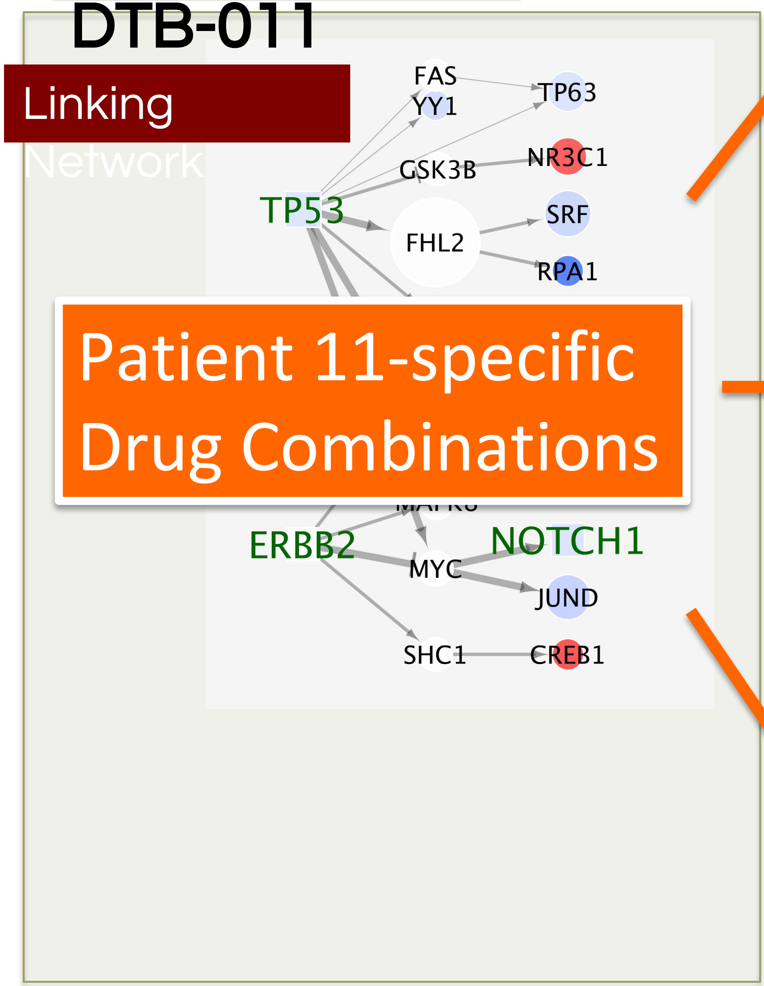


- BCL2 – B-cell lympoma related
  - Blocks apoptosis of cells.
  - Targeting in PCa (Zielinski *Cancer J* 2013)
- GSK38 – glycogen synthase kinase 3
  - inhibitors reduce PCa growth (Darrington *Int J Cancer* 2012).
- MAPK8 (aka JUN Kinase)
  - siRNA induces apoptosis in PCa (Parra *Int J Mol Med* 2012)
- MAPK14 (aka p38)
  - Inhibitors may promote mets
- HRAS
  - Synthetic lethal w/ JNK (above) (Zhu *Genes Cancer* 2010)
- SHC1 – Src homolog
  - ERK and TGFB signaling

PERSONALIZED NETWORKS FOR TARGETING

Patient DTB-011

Linking Network



Patient 11-specific Drug Combinations

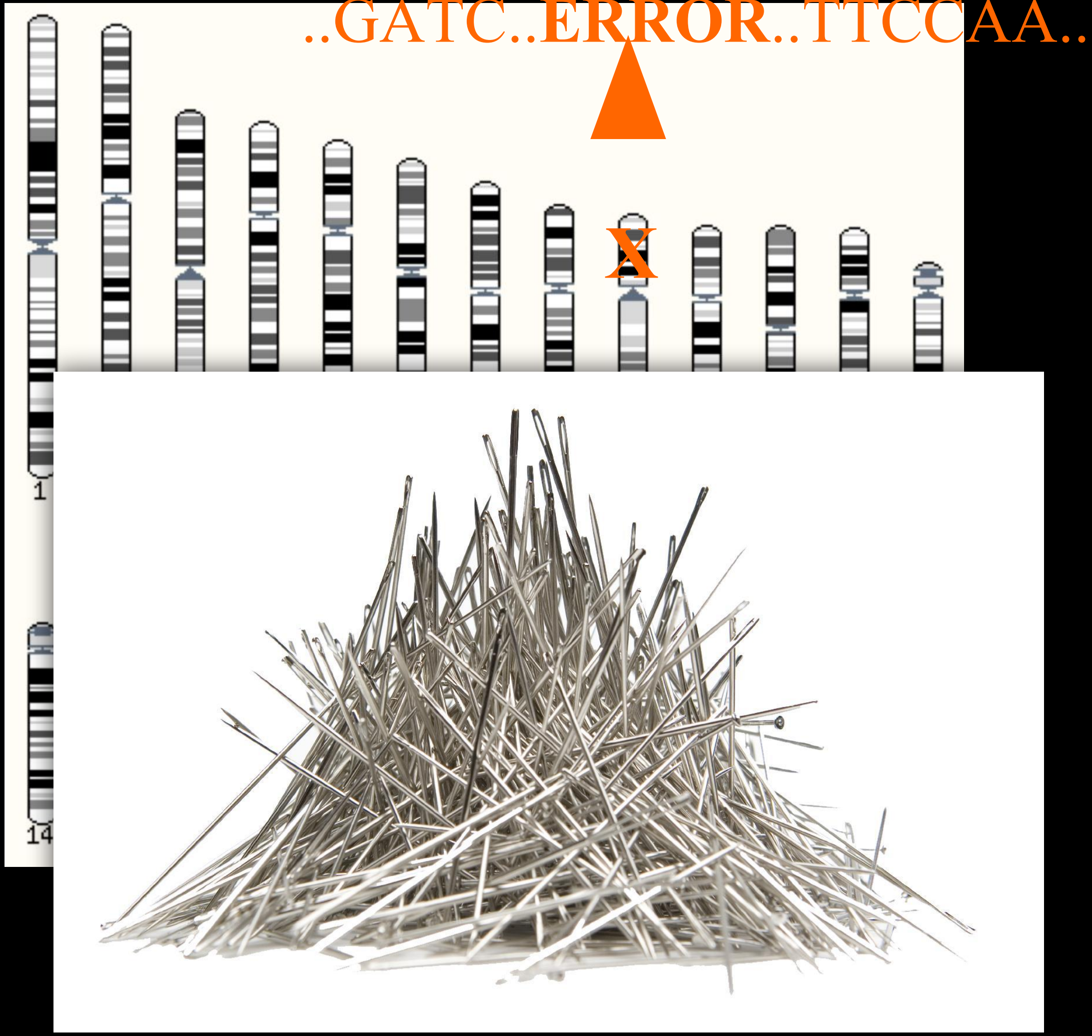
- BCL2 – B-cell lympoma related
  - Blocks apoptosis of cells.
  - Targeting in PCa (Zielinski *Cancer J* 2013)
- GSK38 – glycogen synthase kinase 3
  - inhibitors reduce PCa growth (Darrington *Int J Cancer* 2012).
- MAPK8 (aka JUN Kinase)
  - siRNA induces apoptosis in PCa (Parra *Int J Mol Med* 2012)
- MAPK14 (aka p38)
  - Inhibitors may promote mets
- HRAS
  - Synthetic lethal w/ JNK (above) (Zhu *Genes Cancer* 2010)
- SHC1 – Src homolog
  - ERK and TGFB signaling

ASIDE: WHAT ARE THE IMPORTANT “EVENTS” IN A TUMOR?

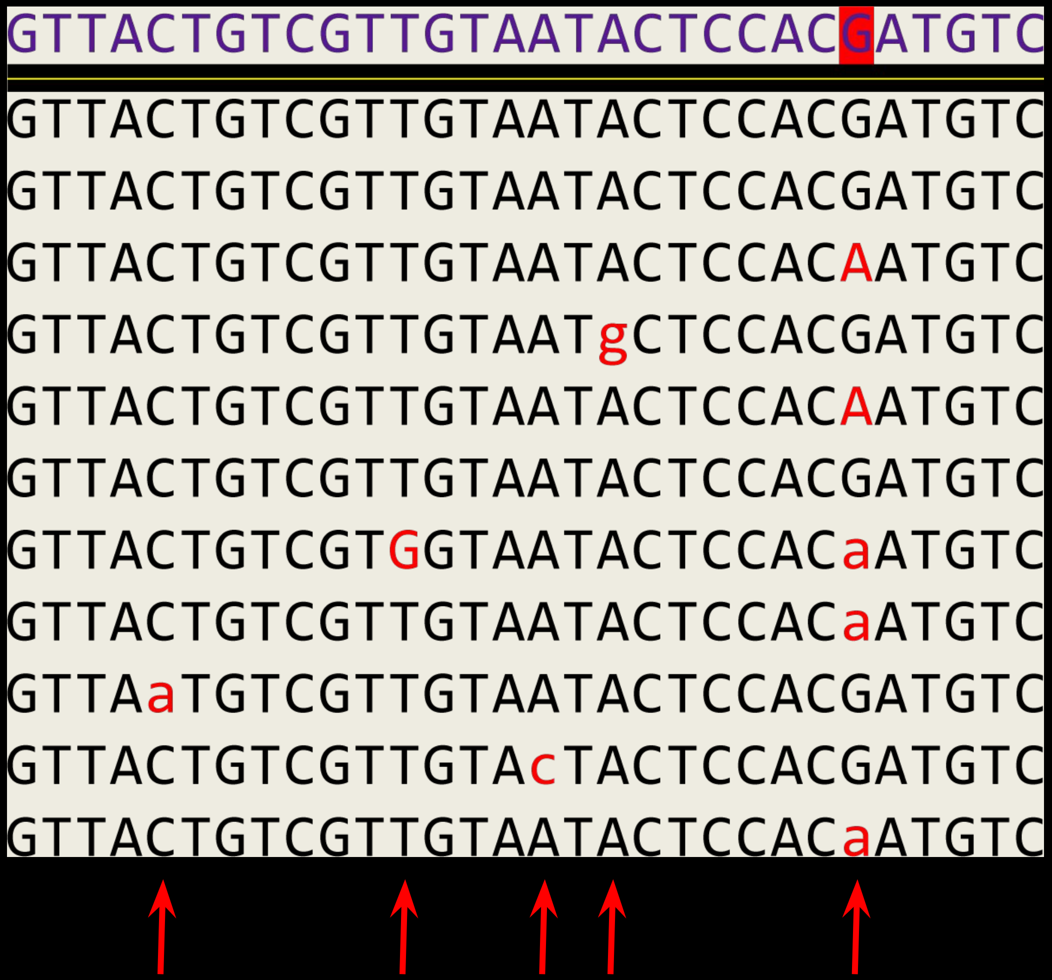
- Lots of Copy number, point mutations
- Which are *passengers*? Which *drivers*?
- What does data reveal about essential signaling?
- Aside: Just *identifying* variants is hard!

A needle in a human genome ~~haystack~~ needlestack

- A human genome has **23** chromosomes.
- **6 billion** individual DNA basepairs per genome.
- A **single basepair** error can be a disease mutation.



Distinguish True Variation from Artifact



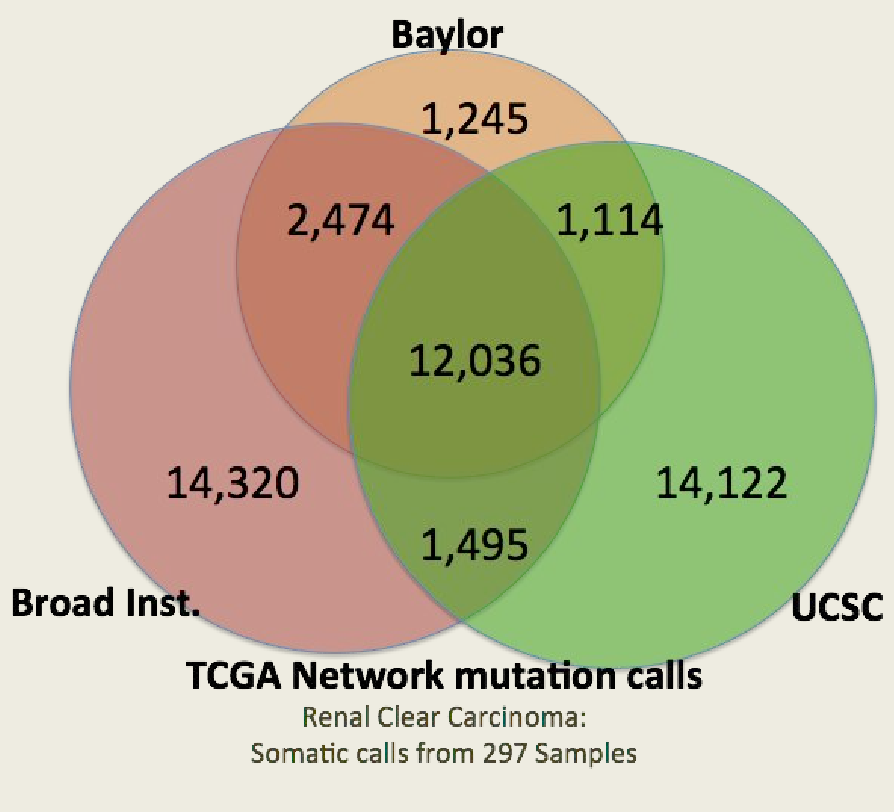
```
GTTACTGTCGTTGTAATACTCCACGATGTC

GTTACTGTCGTTGTAATACTCCACGATGTC
GTTACTGTCGTTGTAATACTCCACGATGTC
GTTACTGTCGTTGTAATACTCCACAATGTC
GTTACTGTCGTTGTAATgCTCCACGATGTC
GTTACTGTCGTTGTAATACTCCACAATGTC
GTTACTGTCGTTGTAATACTCCACGATGTC
GTTACTGTCGTGGTAATACTCCACaATGTC
GTTACTGTCGTTGTAATACTCCACaATGTC
GTTAaTGTCGTTGTAATACTCCACGATGTC
GTTACTGTCGTTGTAcTACTCCACGATGTC
GTTACTGTCGTTGTAATACTCCACaATGTC
```

sequencing errors

SNV

Mutation Callers Give Different Answers …

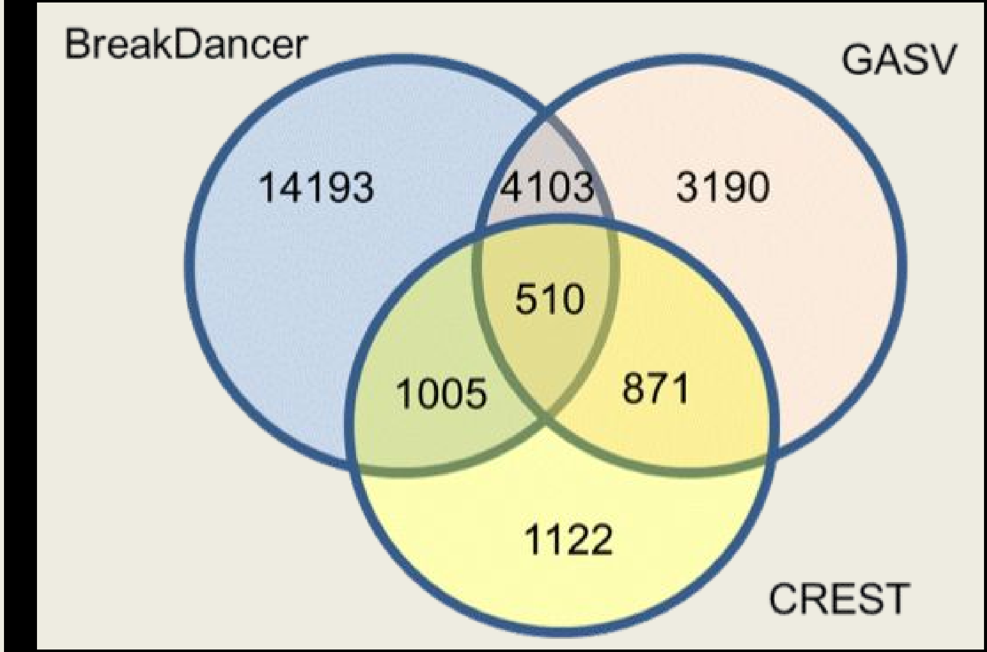
SNVs



TCGA Network mutation calls

Renal Clear Carcinoma:
Somatic calls from 297 Samples

SVs



DREAM for the best method(s)

Crowd-source for best mutation detectors.

Define dataset and goal.

Put out incentives (talks, papers, $$)

Collaboration: OICR, TCGA, UCSC, SAGE

Results of DREAM-SMC

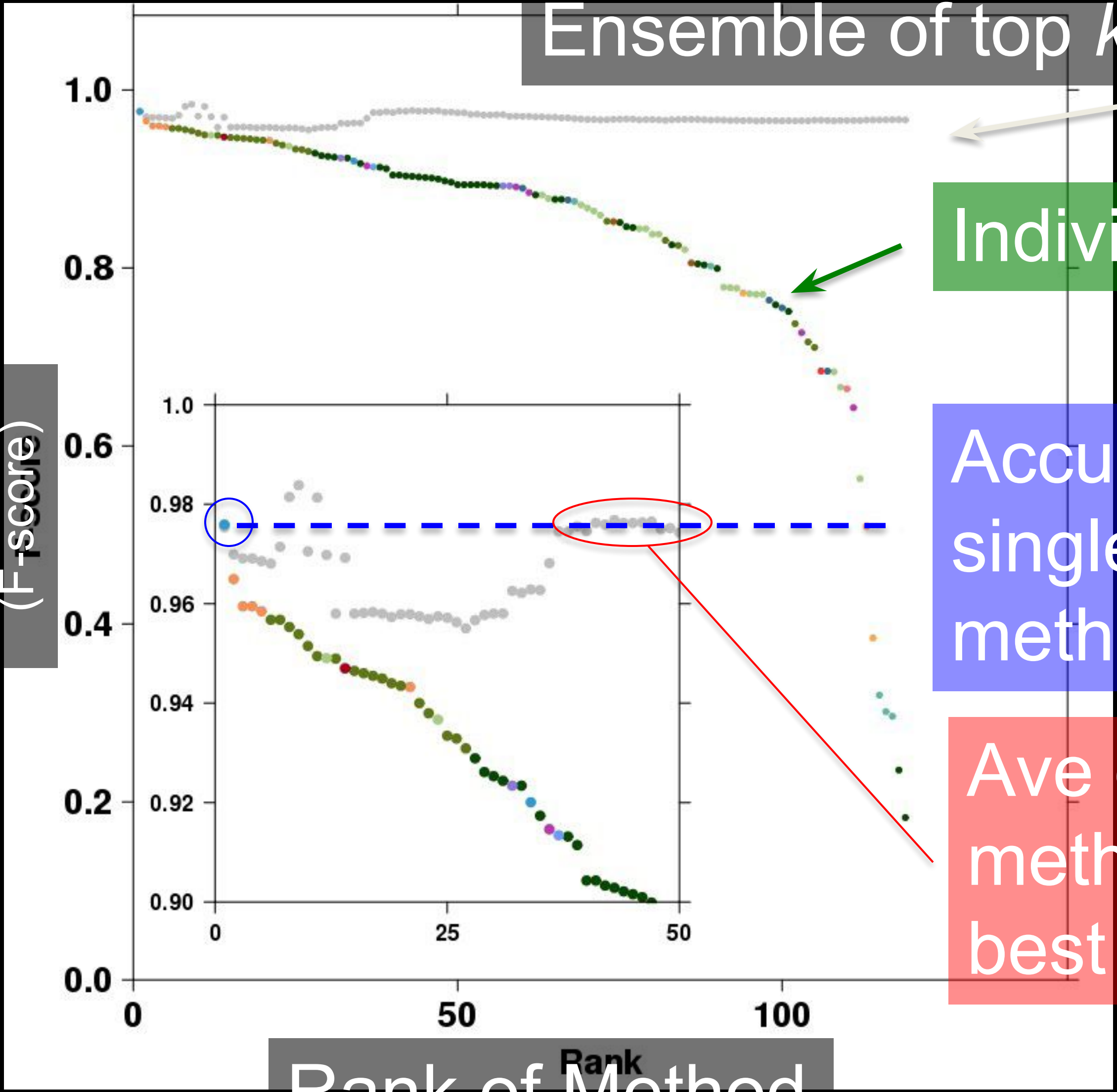
Participation At Closing Time:

- 345 contestants
- 948 entries on 4 *in silico* genomes

On-going post-challenge submissions (*living benchmark*)

Key insights into simulating cancer genomes (BamSurgeon)

Wisdom of the Crowds for DREAM-SMC



Ensemble of top *k* methods

Individual methods

Accuracy of single best method

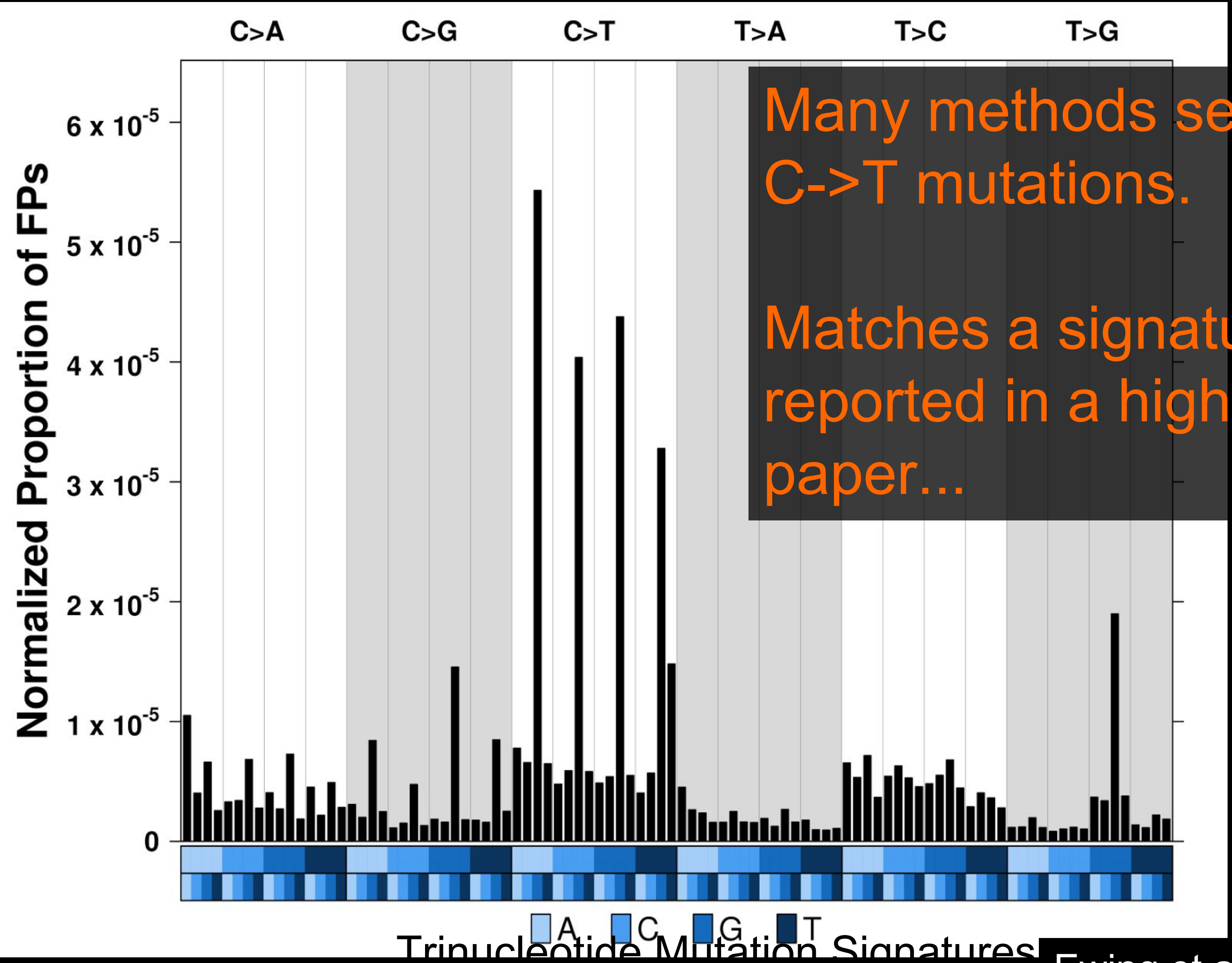
Ave of all methods matches best single

Accuracy (F-score)

Rank of Method

Ewing et al. *Nat Meth* 2014

Negative Results Reveal False-Positive Signature



Many methods see “ghost” C->T mutations.

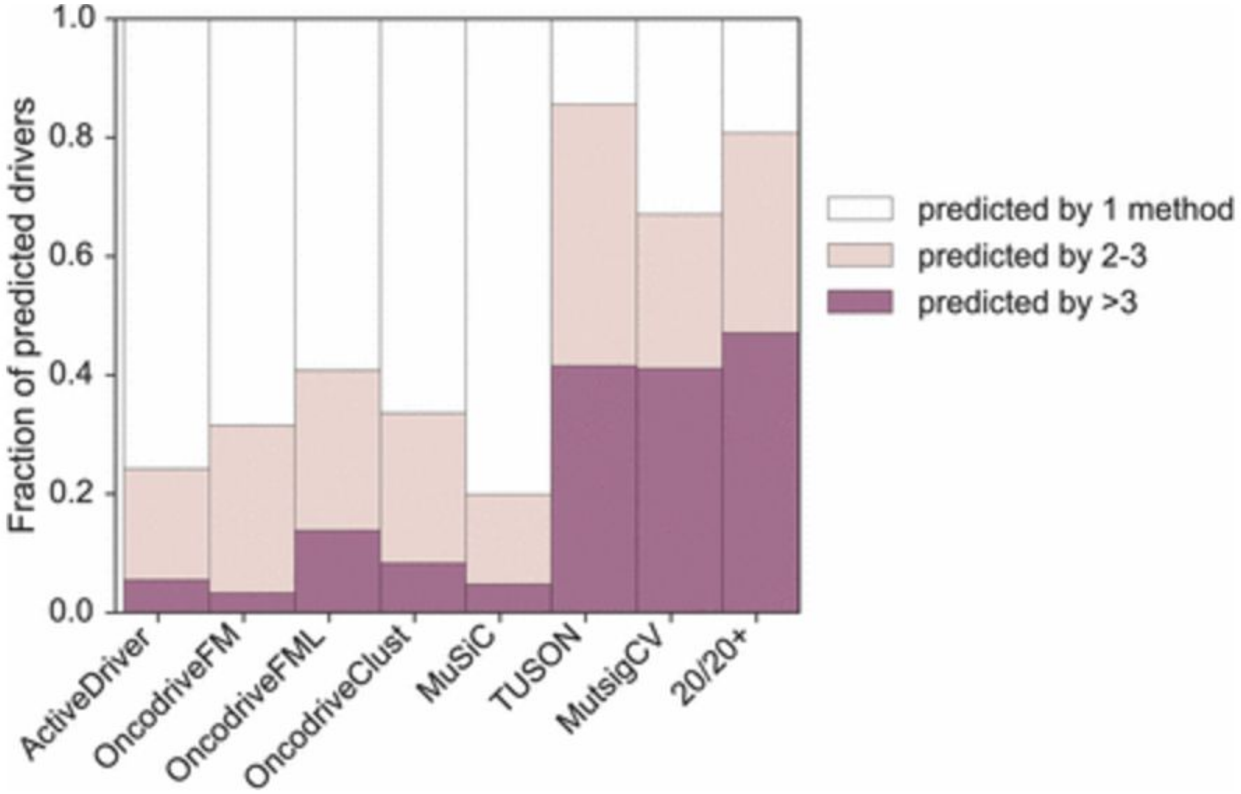
Matches a signature reported in a high-profile paper...

Ewing et al. *Nat Meth* 2014

ASIDE: WHAT ARE THE IMPORTANT "EVENTS" IN A TUMOR?

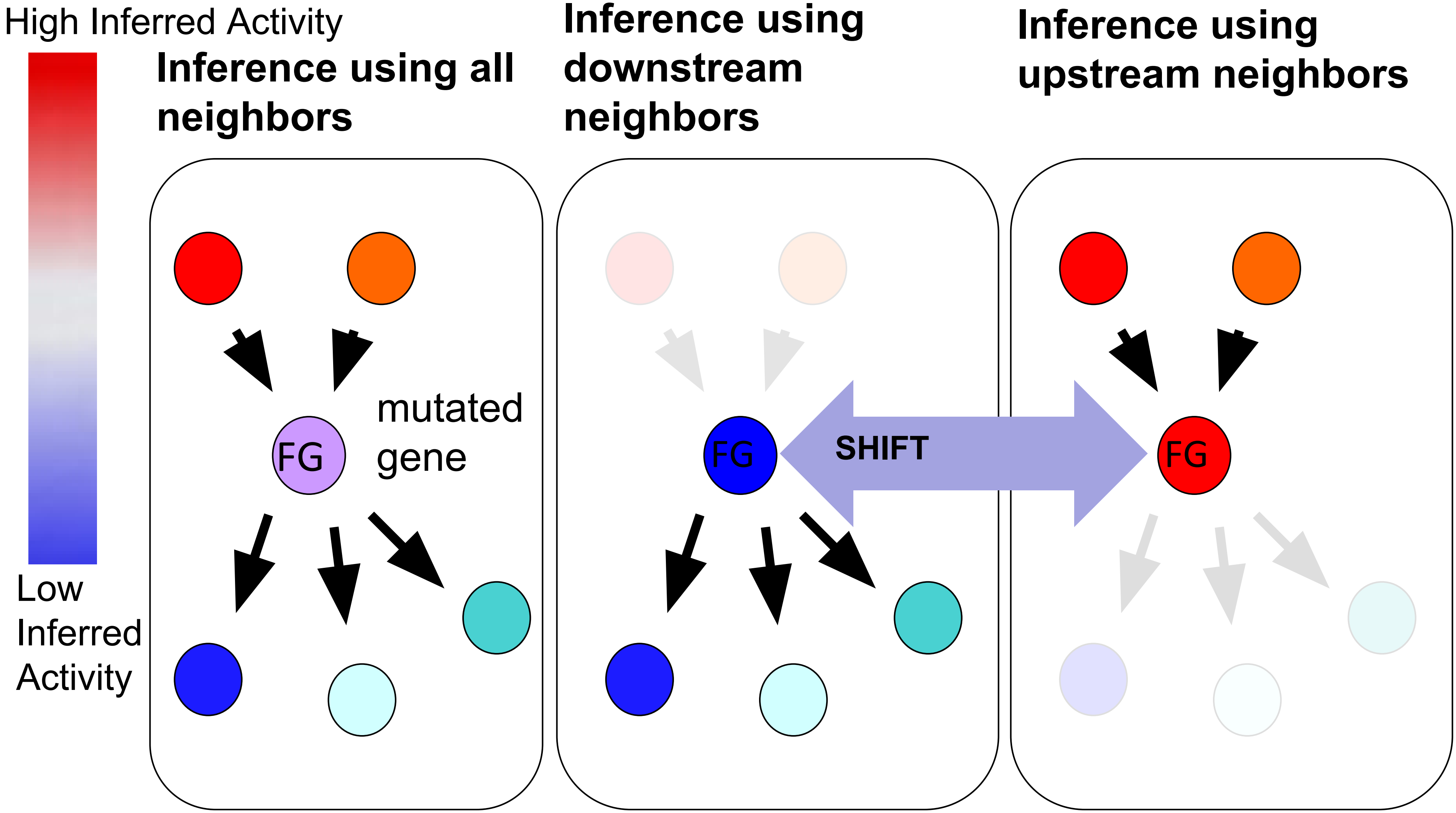
- No current consensus on how to interpret variants.

- There are many algorithms and boutique bakeoffs



Tokheim et al PNAS 2016

PATHWAY REASONING



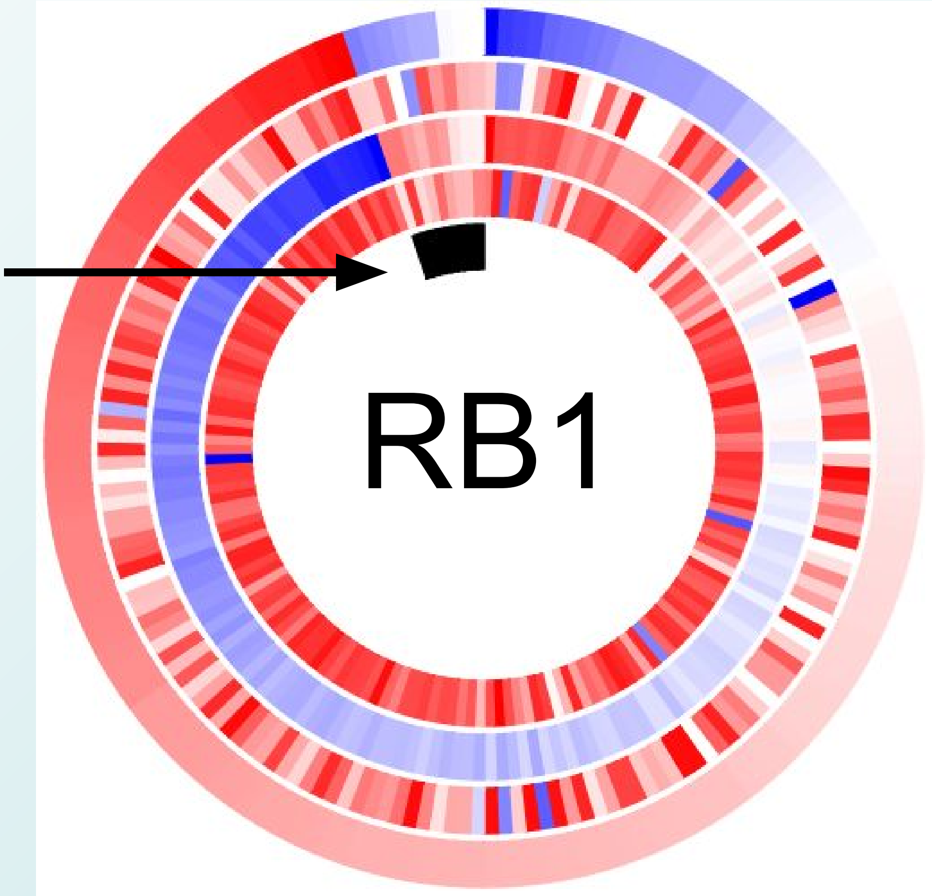
Inference using all neighbors

Inference using downstream neighbors

Inference using upstream neighbors

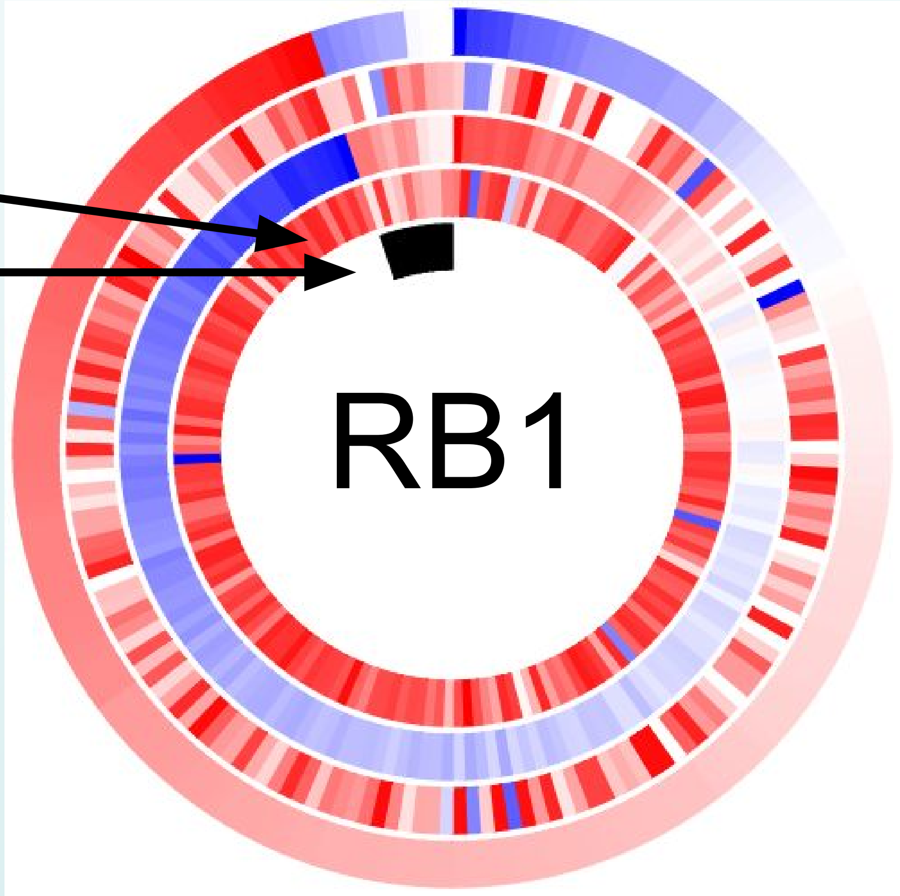
Sam Ng, *Bioinformatics* 2012

RB1 LOF (GBM)



RB1 Mutation

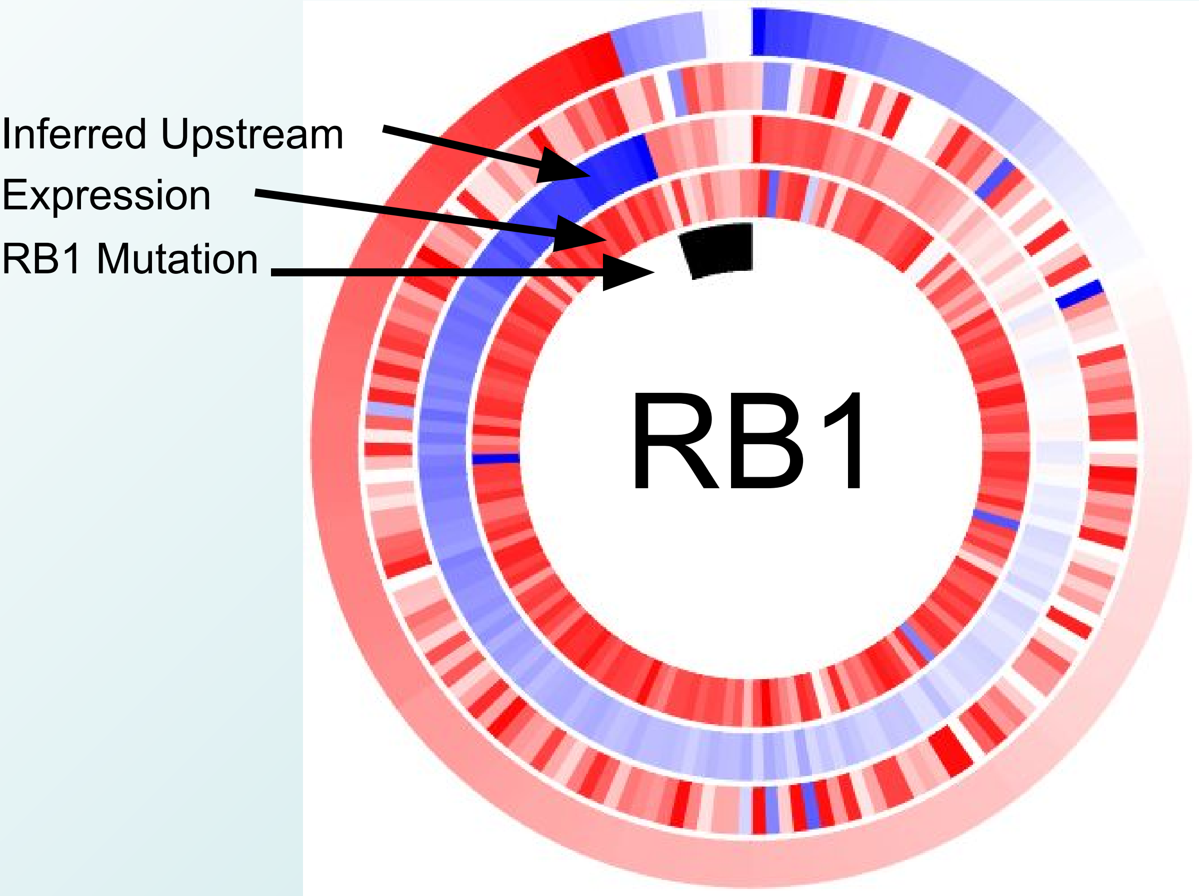
RB1 LOF (GBM)



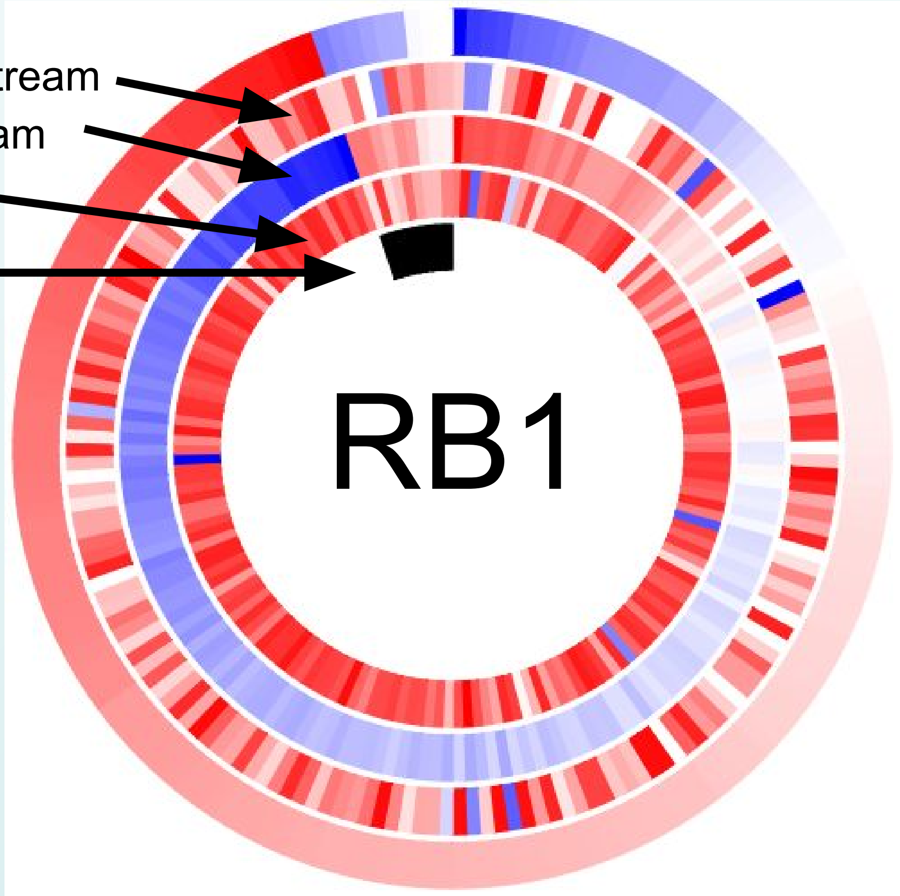
Expression

RB1 Mutation

RB1 LOF (GBM)



RB1 LOF (GBM)



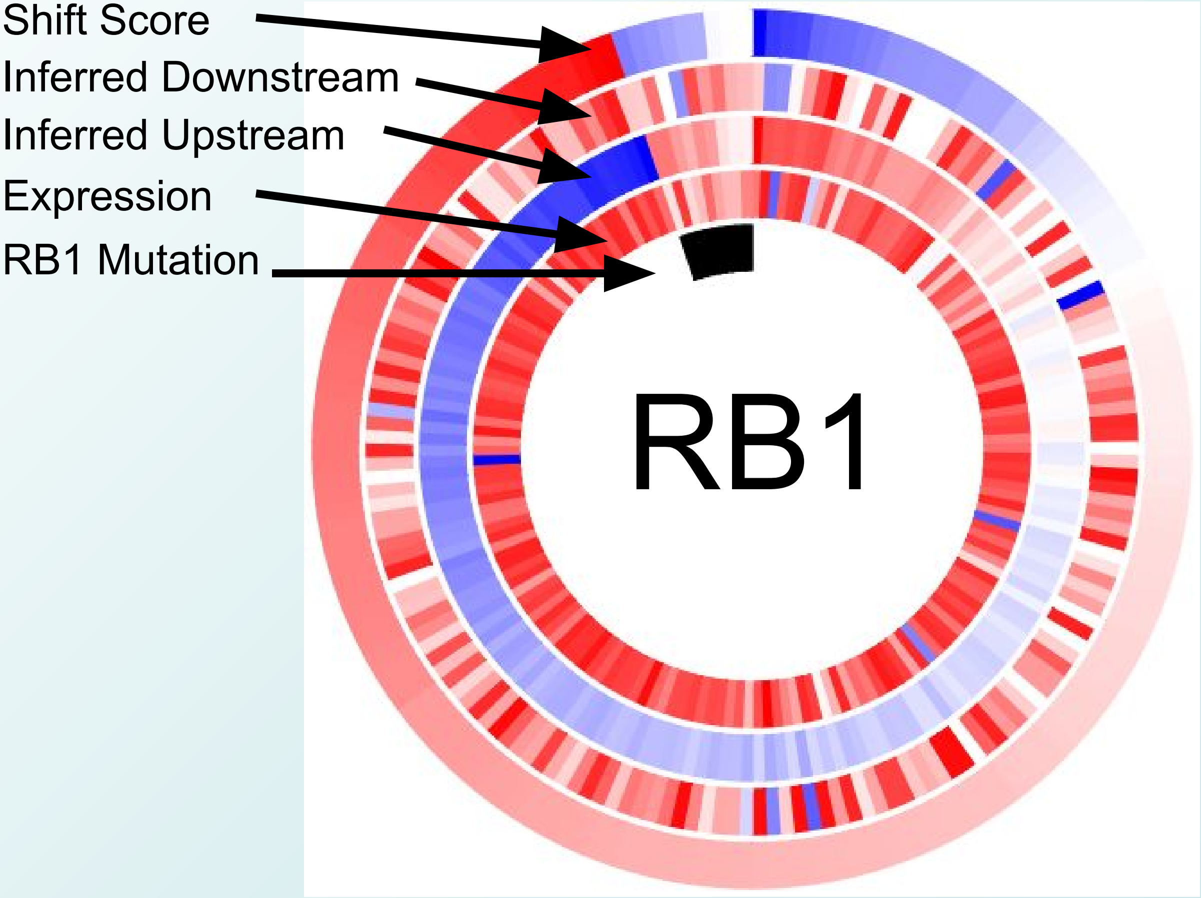
Inferred Downstream

Inferred Upstream

Expression

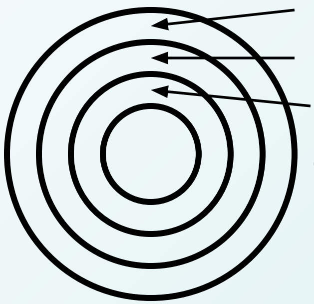
RB1 Mutation

RB1 LOF (GBM)


Shift Score
Inferred Downstream
Inferred Upstream
Expression
RB1 Mutation
RB1

RB1 LOF (GBM)

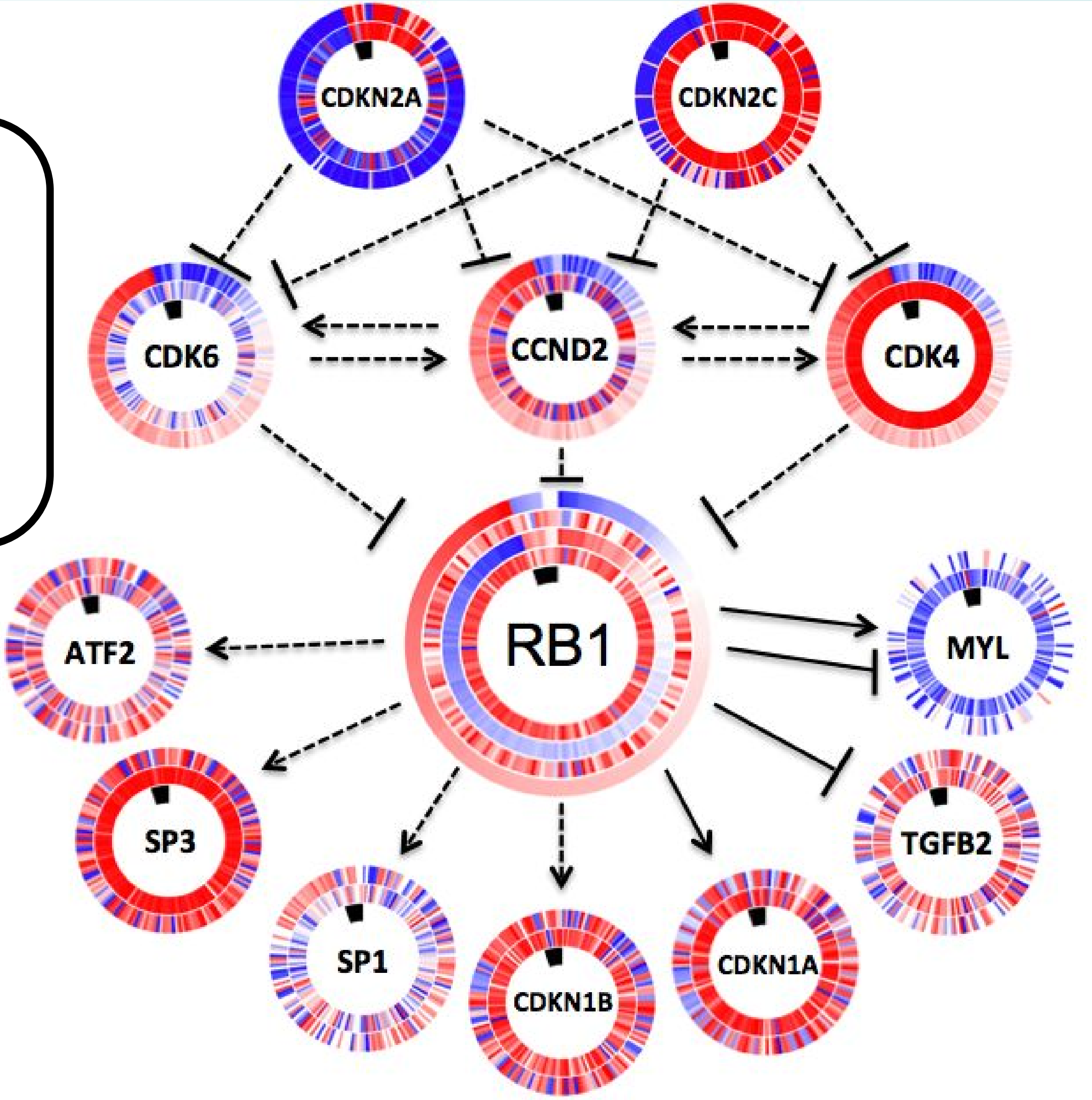
Upstream and Downstream Genes



PARADIGM

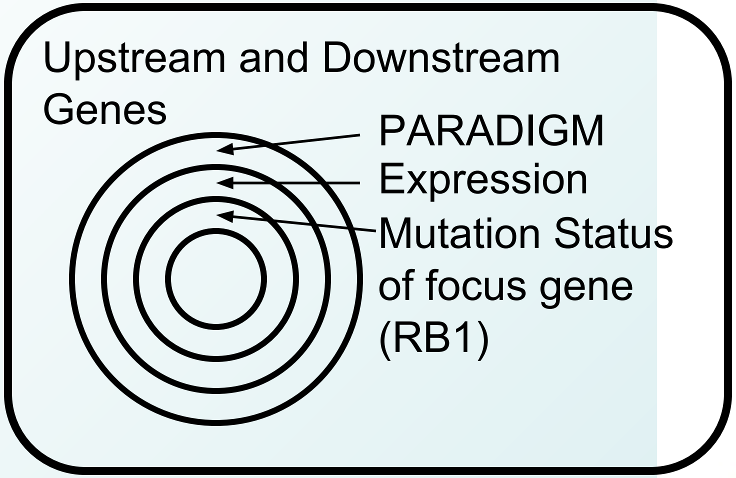
Expression

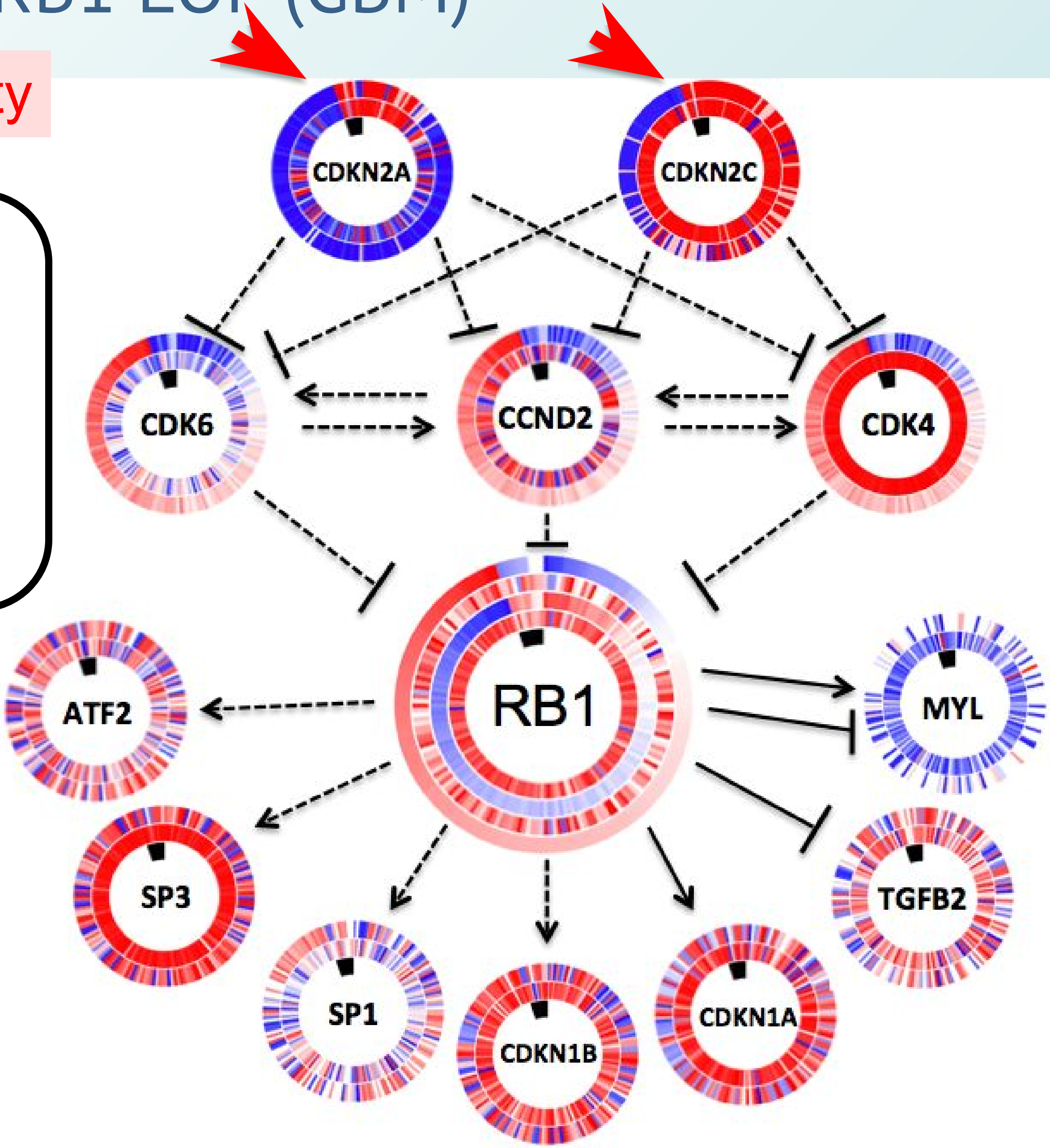
Mutation Status of focus gene (RB1)



RB1 LOF (GBM)

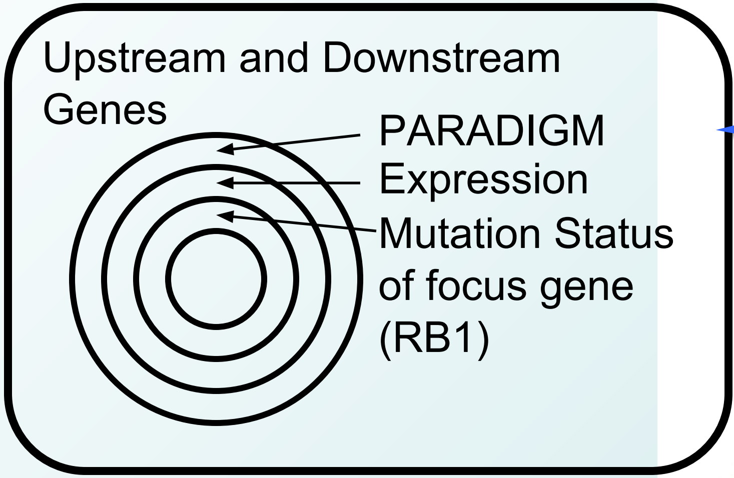
High Activator Activity





RB1 LOF (GBM)

Low Inhibitor Activity

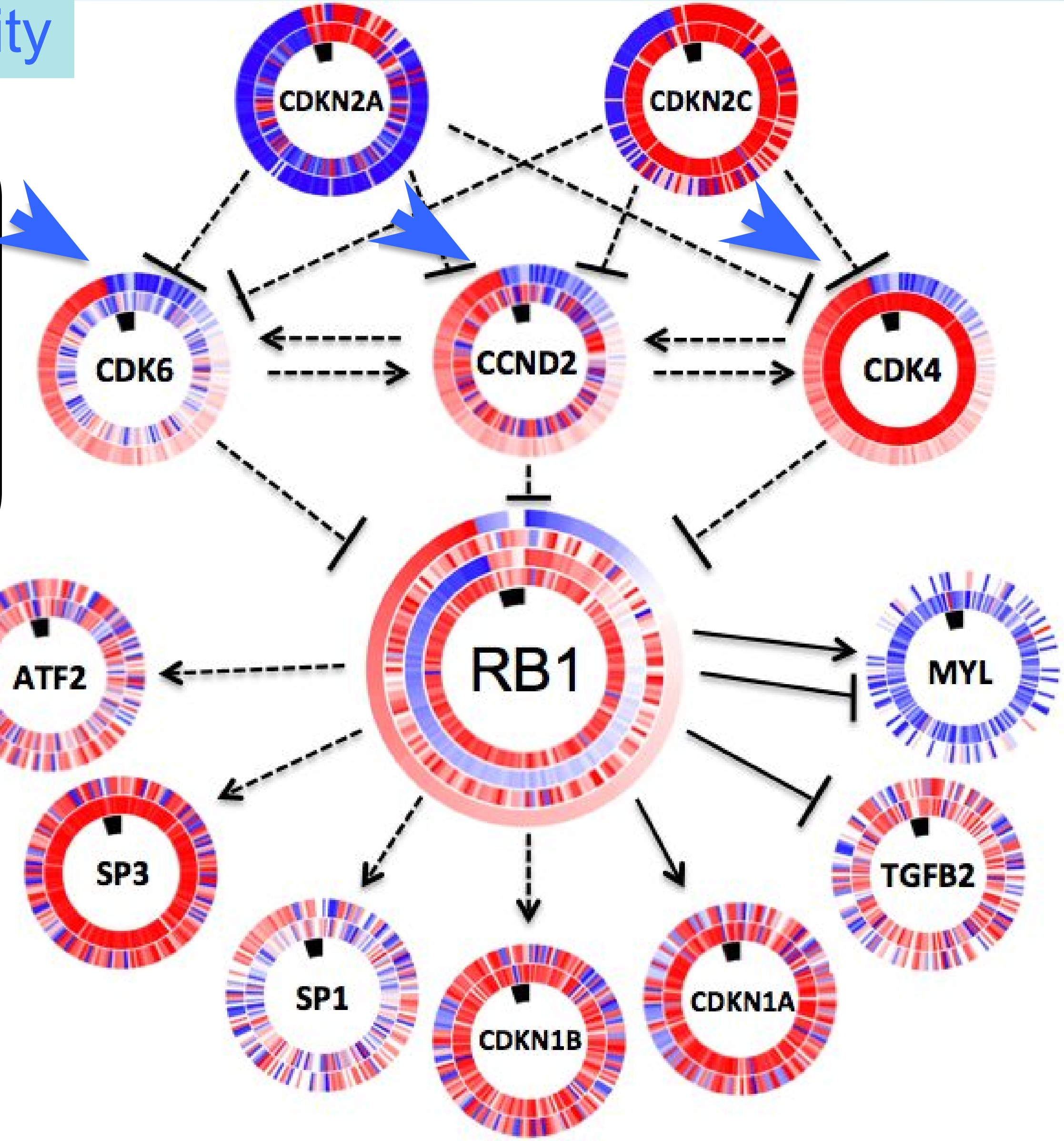


Upstream and Downstream Genes

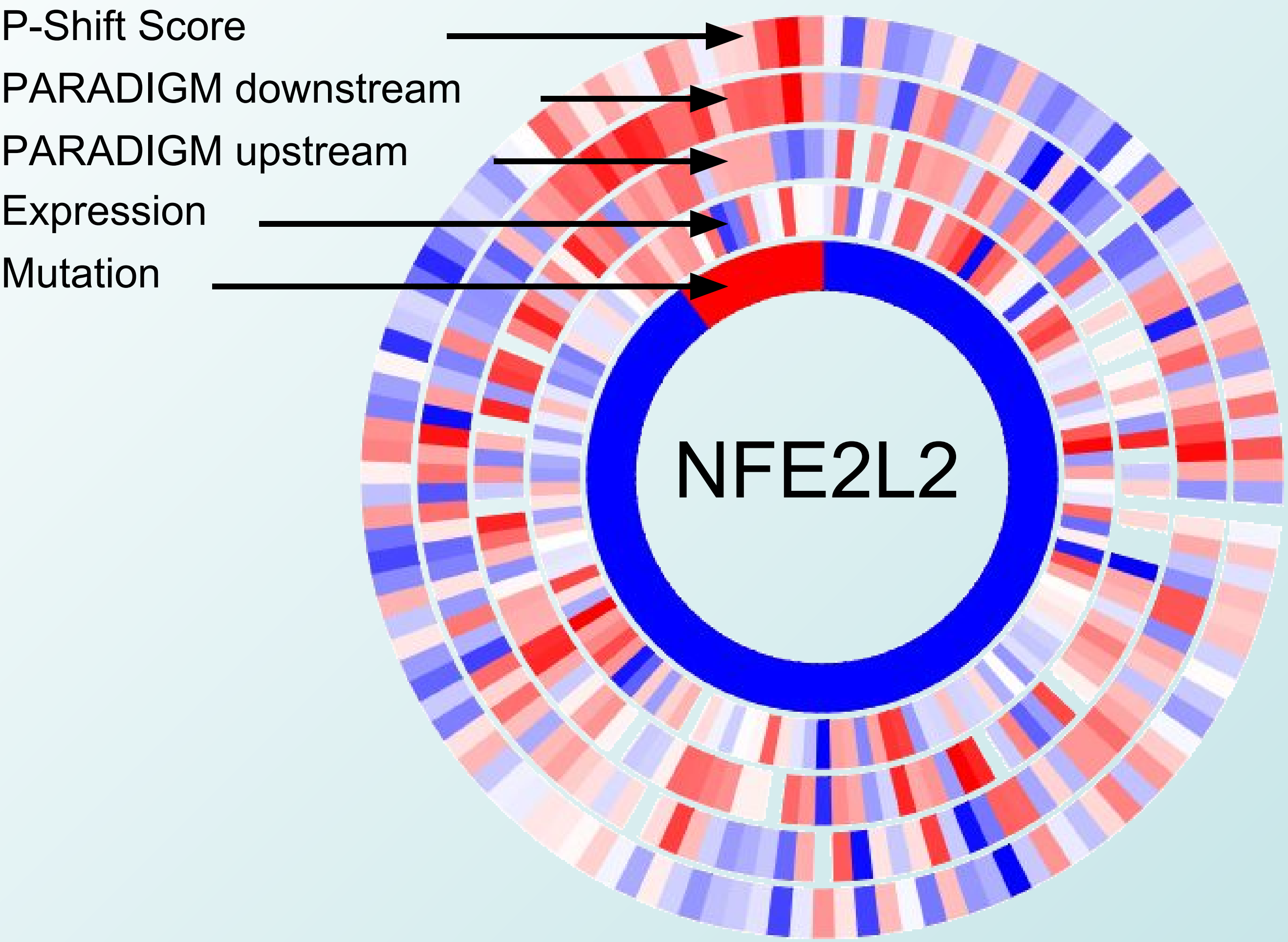
PARADIGM

Expression

Mutation Status of focus gene (RB1)

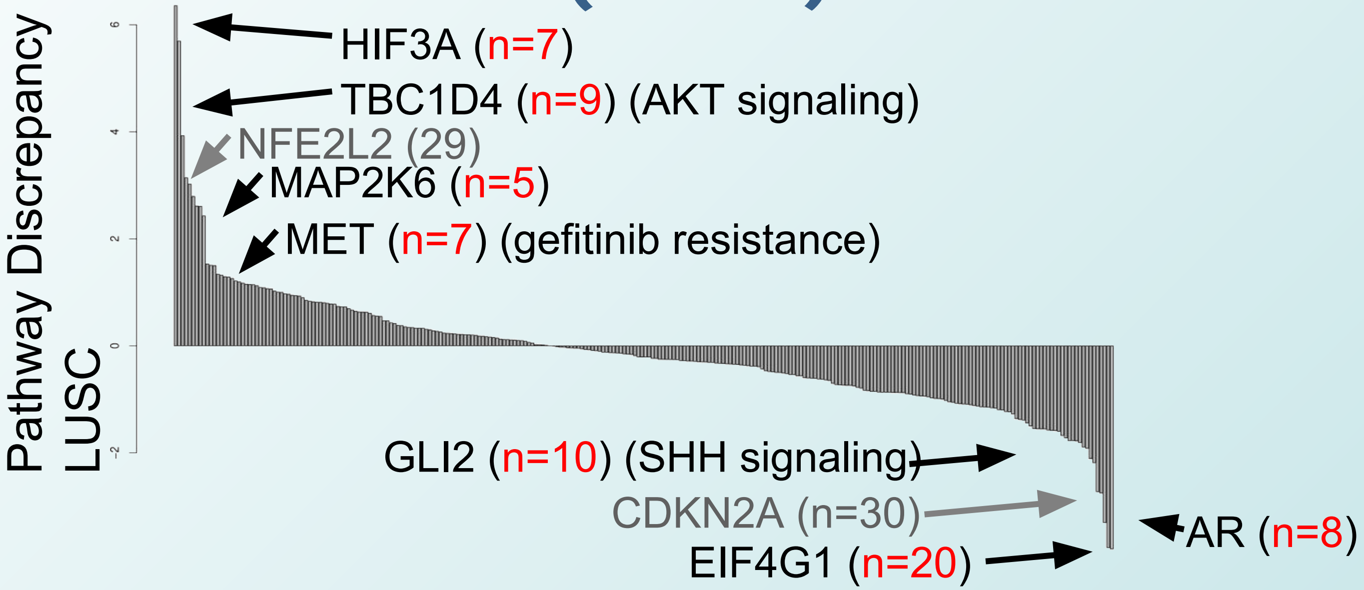


Gain-of-Function (LUSC)



Sam Ng

PARADIGM-Shift gives orthogonal view of the importance of mutations (LUSC)



- Enables probing into infrequent events
- Can detect non-coding mutation impact (pseudo FPs)
- Can detect presence of pathway compensation for those seemingly functional mutations (pseudo FPs)
- Extend beyond mutations
- Limited to genes w/ pathway representation

Sam Ng

PERSONALIZED NETWORKS FOR TARGETING

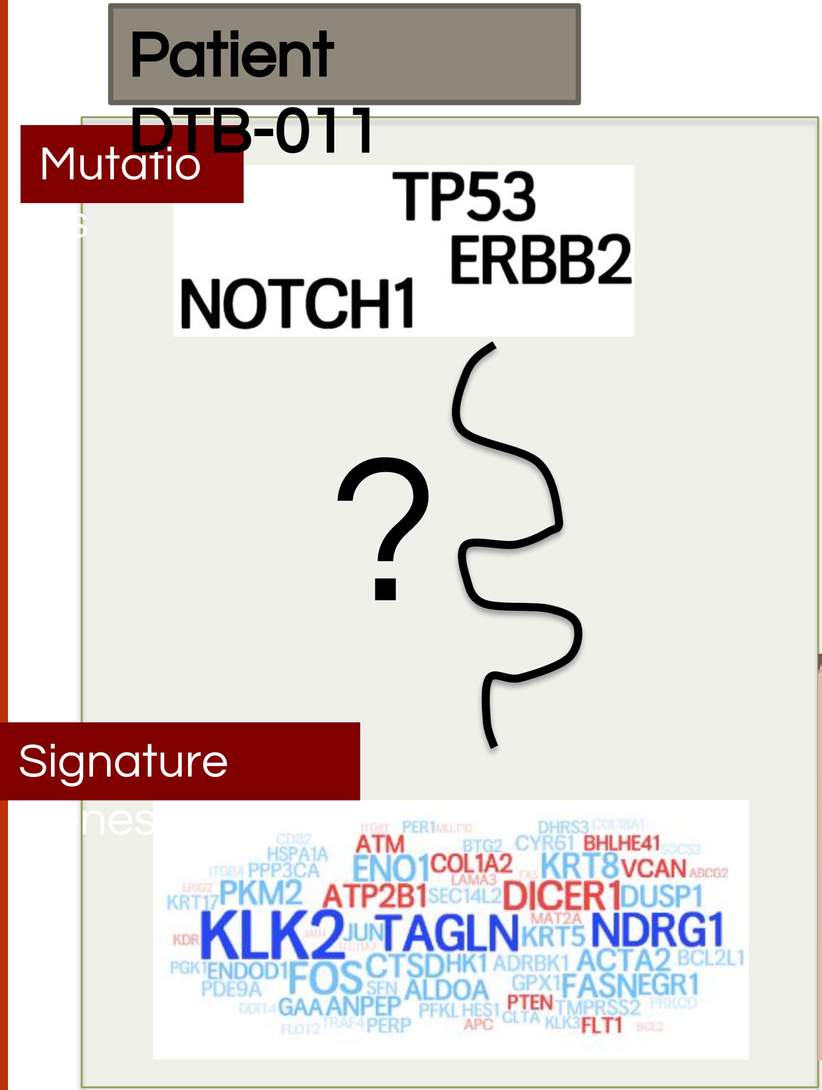
Patient DTB-011

Mutatio
s

Signature
nes

- RNA-seq data informs a set of genes are significantly up- and another down-regulated.
- Match profile with a known cancer subtype to obtain robustness of transcripome classification

PERSONALIZED NETWORKS FOR TARGETING

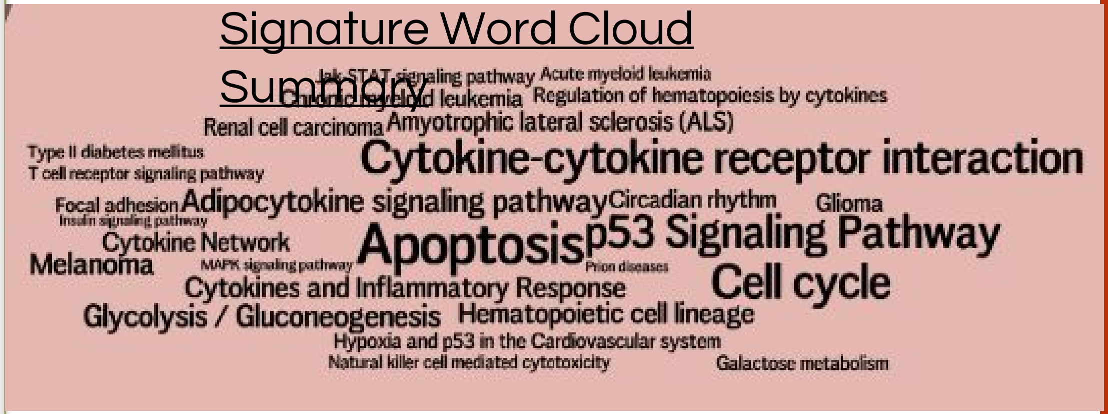


Patient DTB-011

Mutatio
s

Signature
nes

- Link mutations to transcriptional changes with heat-diffusion on networks (e.g. PPI or curated).



Signature Word Cloud Summary

PERSONALIZED NETWORKS FOR TARGETING

Patient DTB-011

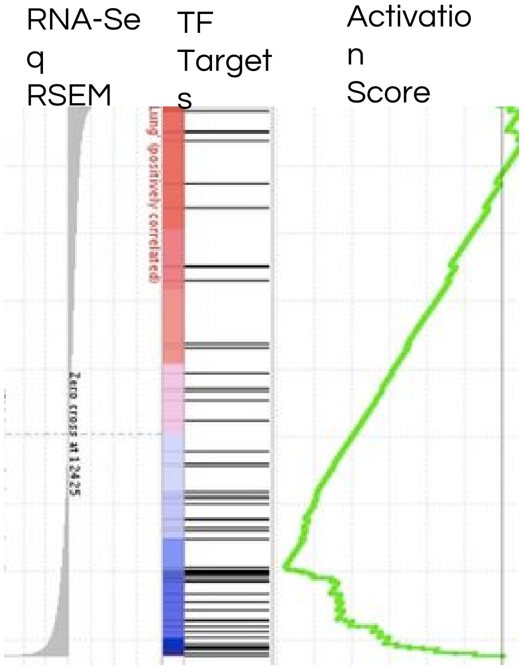
Mutations

TP53
ERBB2
NOTCH1

Signature
nes

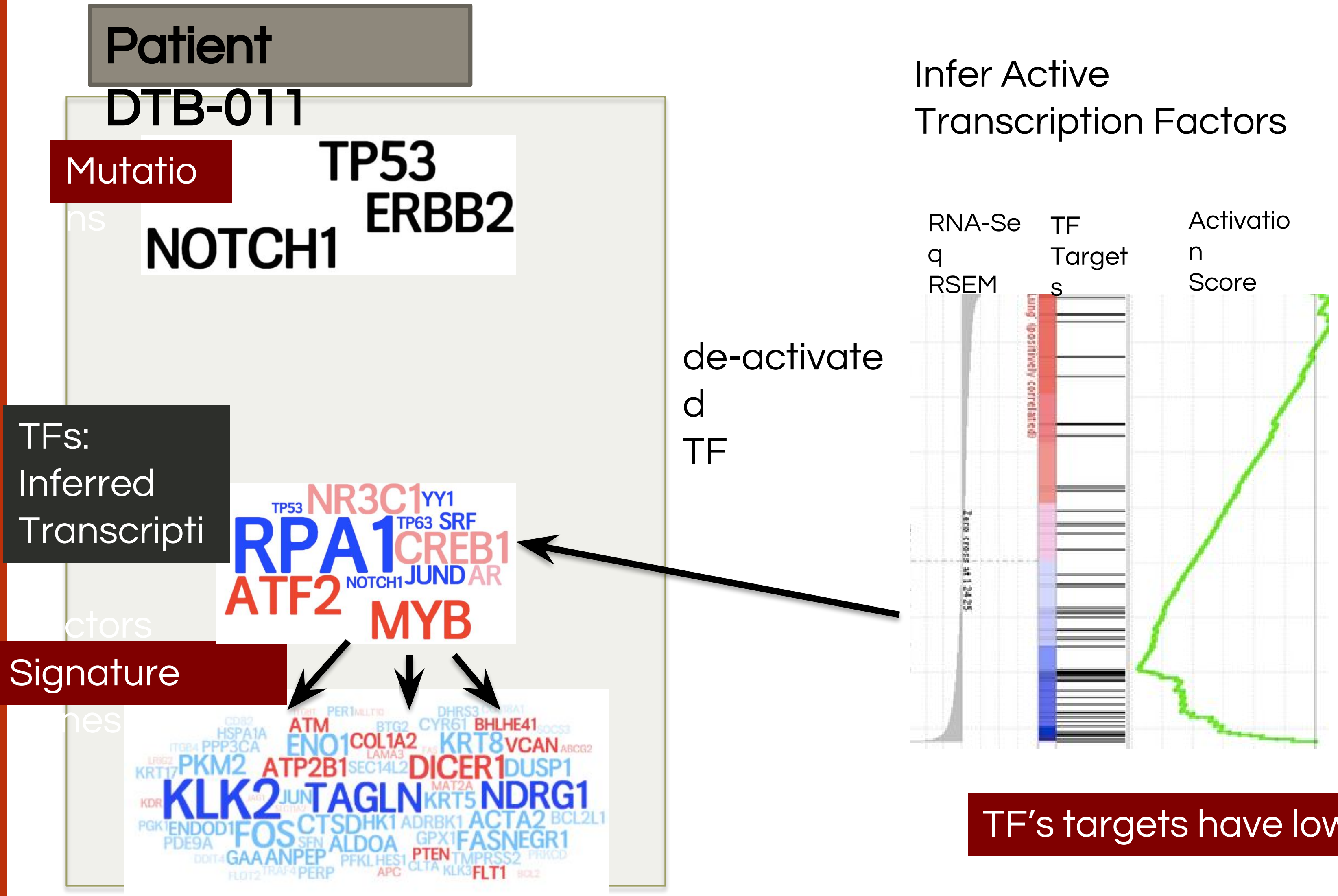
MARINa

Infer Active Transcription Factors



See Master Regulator Analysis (Califano Lab)

PERSONALIZED NETWORKS FOR TARGETING



Patient
DTB-011

Mutatio
ns

TFs:
Inferred
Transcripti
ctors

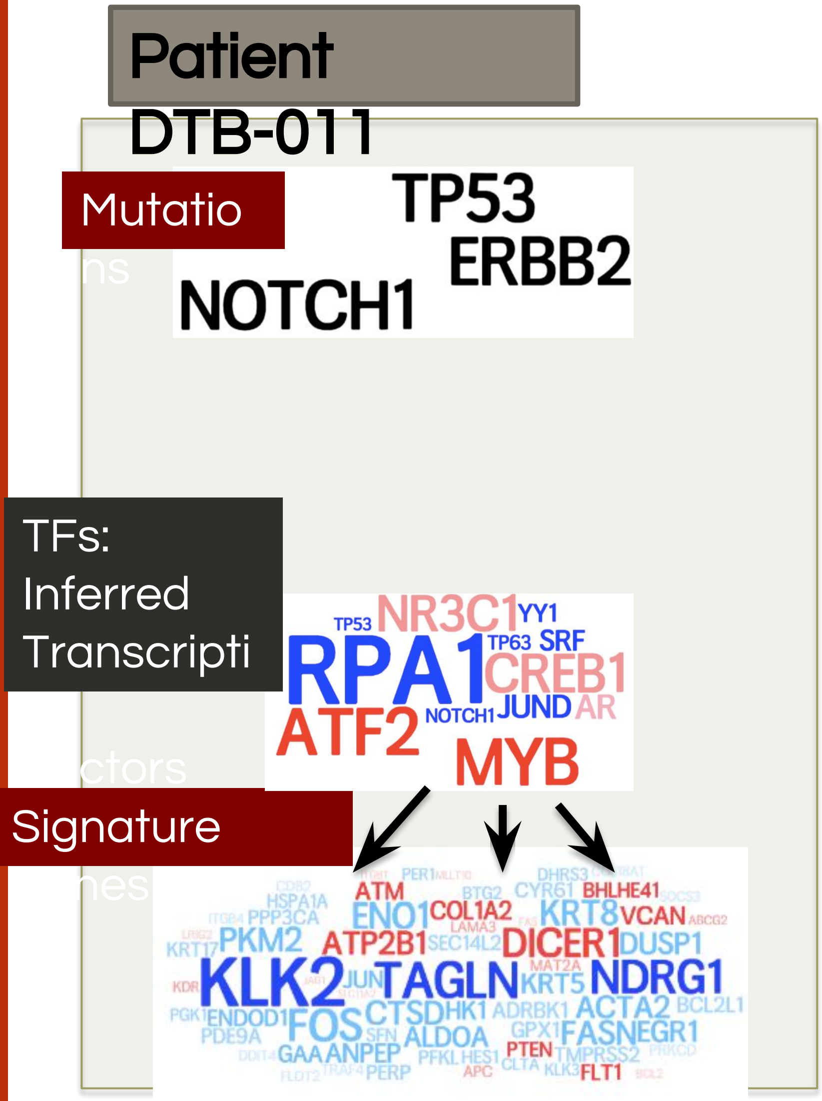
Signature
nes

de-activated
TF

Infer Active
Transcription Factors

TF's targets have low

TIEDIE: LINKING MUTATIONS TO SIGNATURES



Patient DTB-011

Mutations

TFs: Inferred Transcripti

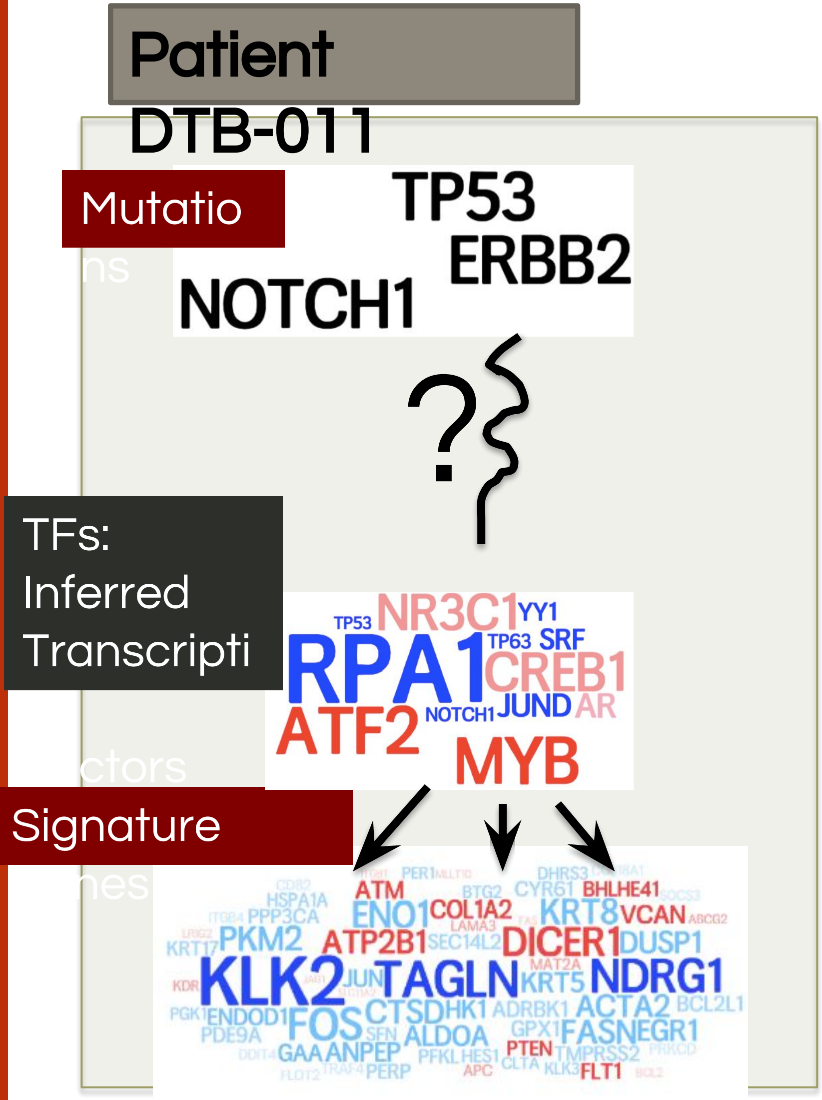
ctors

Signature

nes

- Still need connections between mutations and inferred TFs

PERSONALIZED NETWORKS FOR TARGETING



Patient DTB-011

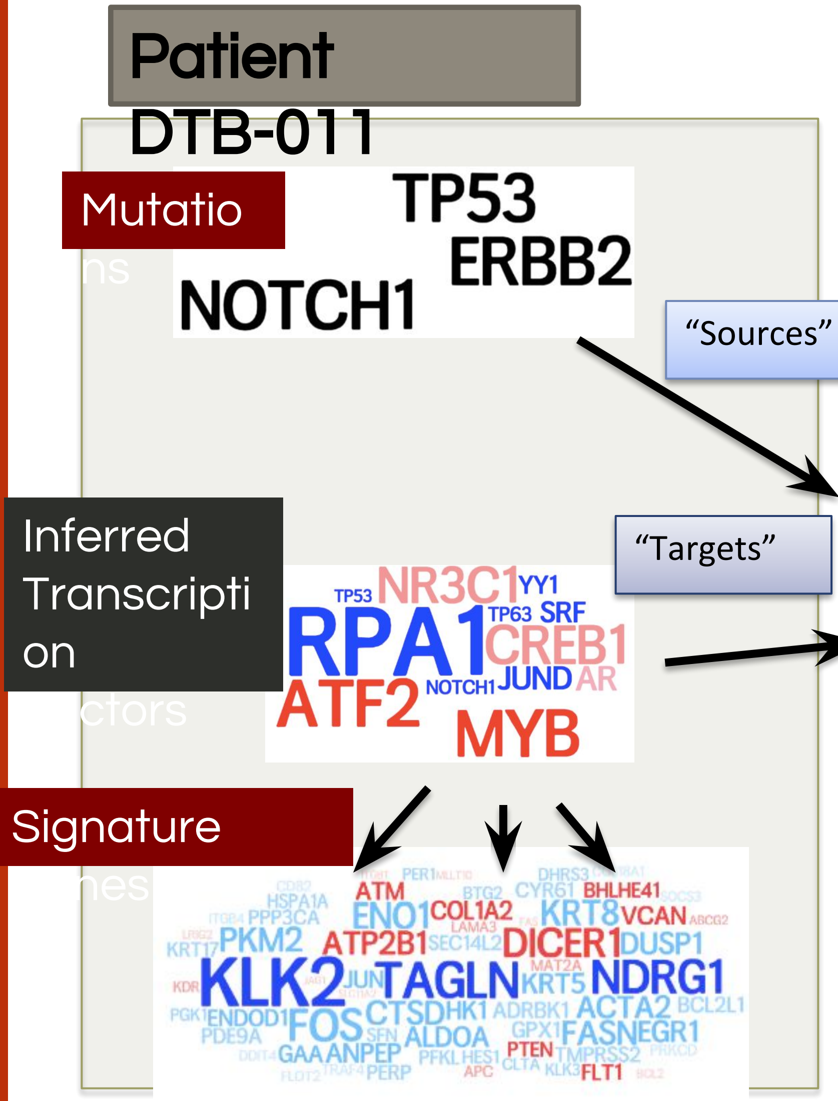
Mutatio ns

TFs: Inferred Transcripti ctors

Signature nes

- Still need connections between mutations and inferred TFs

PERSONALIZED NETWORKS FOR TARGETING



Patient DTB-011

Mutatio ns

Inferred Transcripti on ctors

Signature nes

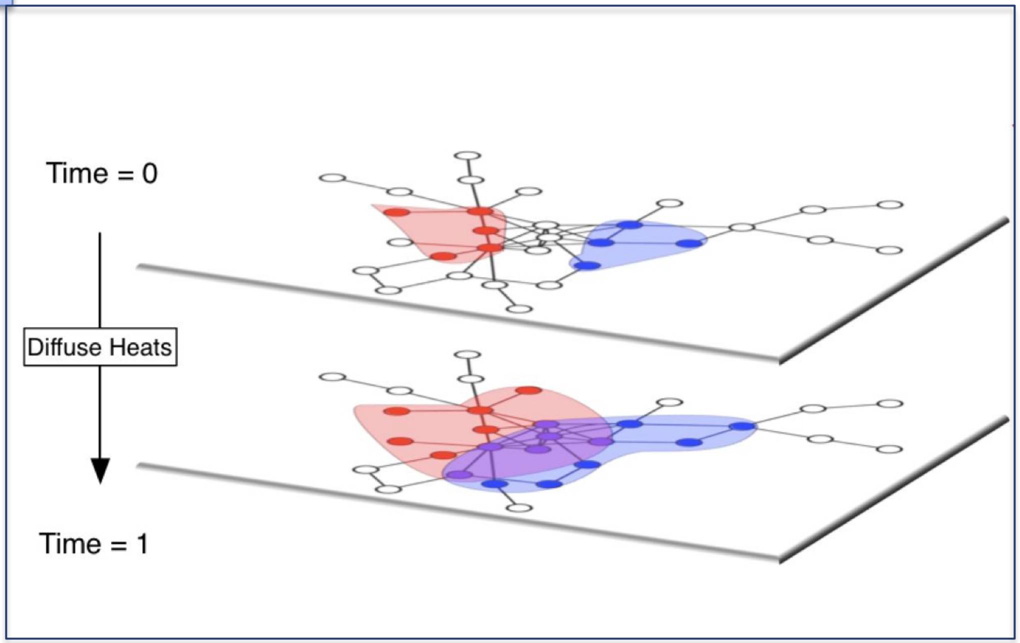
"Sources"

"Targets"

Linking Network

Background Network

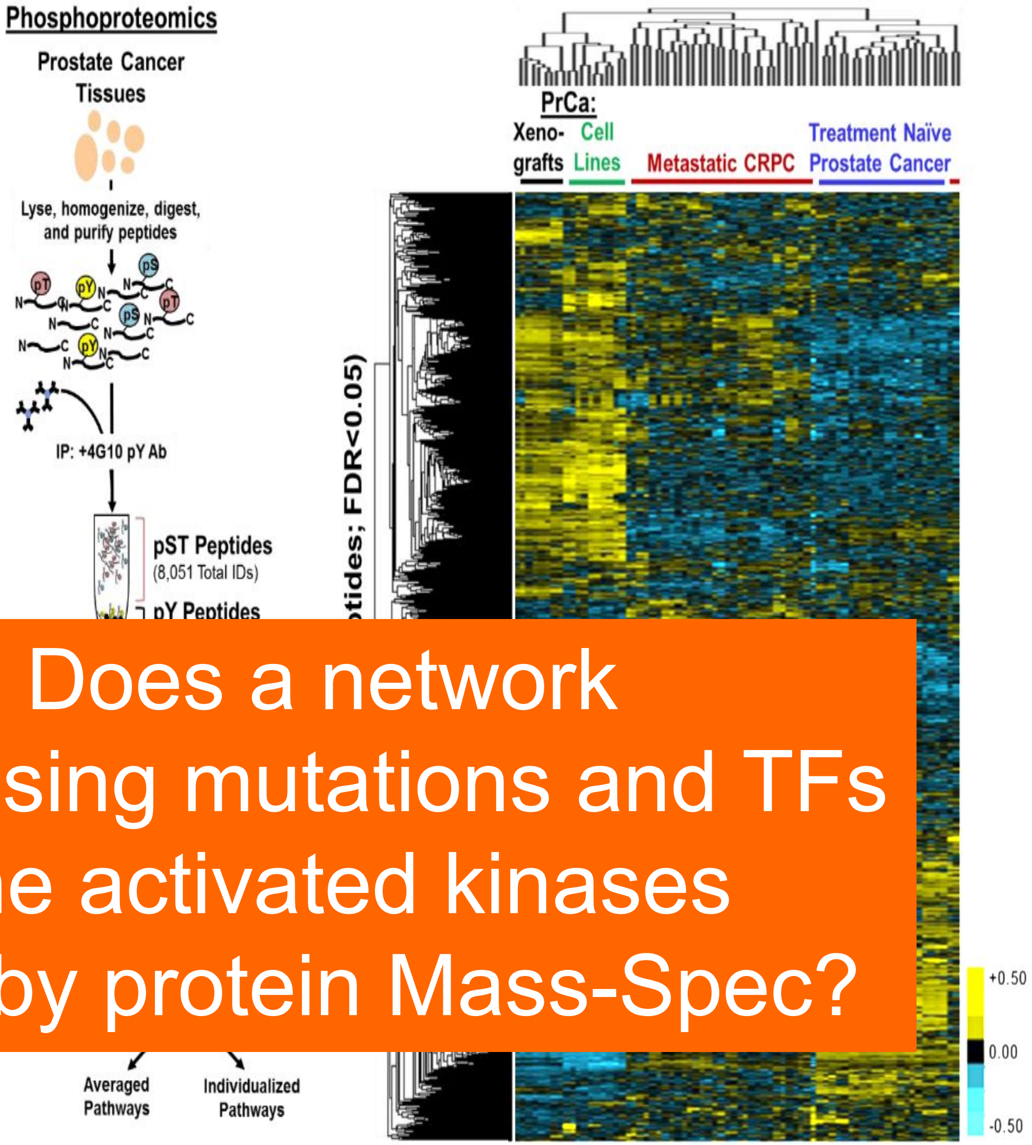
Heat diffusion approaches



e.g. Bader 2010, Vandin 2012, Paull 2013, Hofree 2013)

Characterizing Protein Signaling Changes in Mets with Phosphoproteomics

- Mets show a distinct phosphorylation pattern, when compared with treatment-naive samples.
- In total, **8,051** peptides were



Question: Does a network solution using mutations and TFs Include the activated kinases detected by protein Mass-Spec?

Drake, Paull et al *Cell 2016*

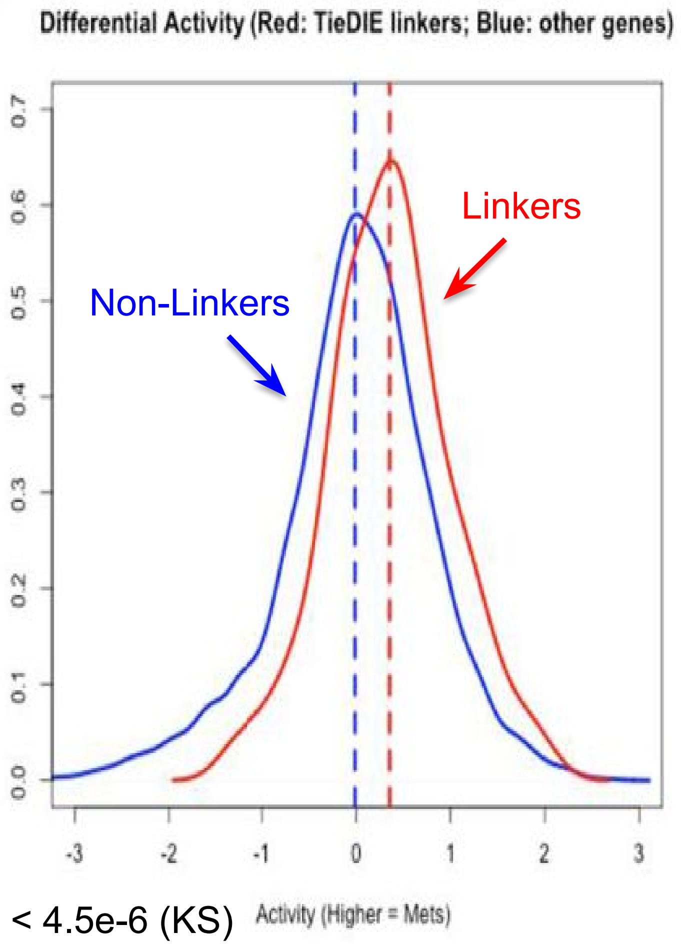
TieDIE Networks Embed Activated Proteins

Are Linkers More Activated?

Drake, Paull et al *Cell 2016*

TieDIE Networks Embed Activated Proteins

Are Linkers More Activated?

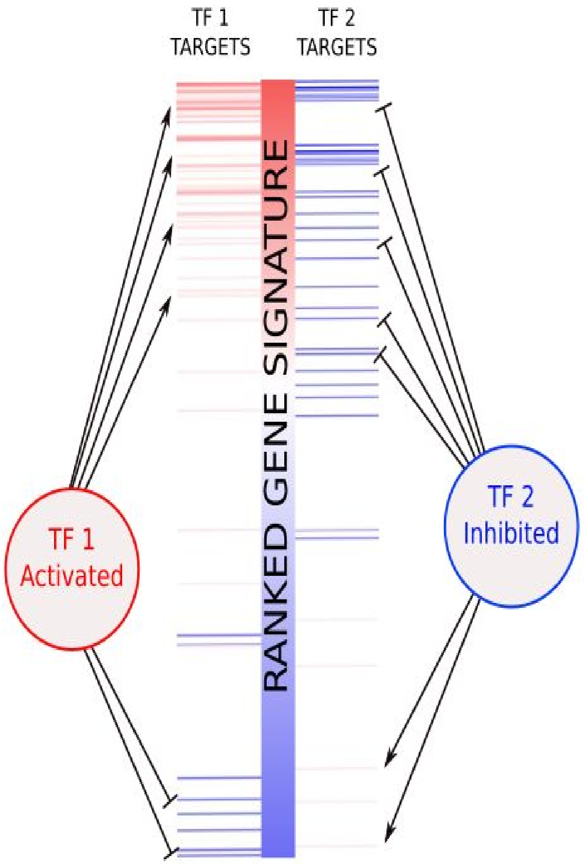


p < 4.5e-6 (KS)

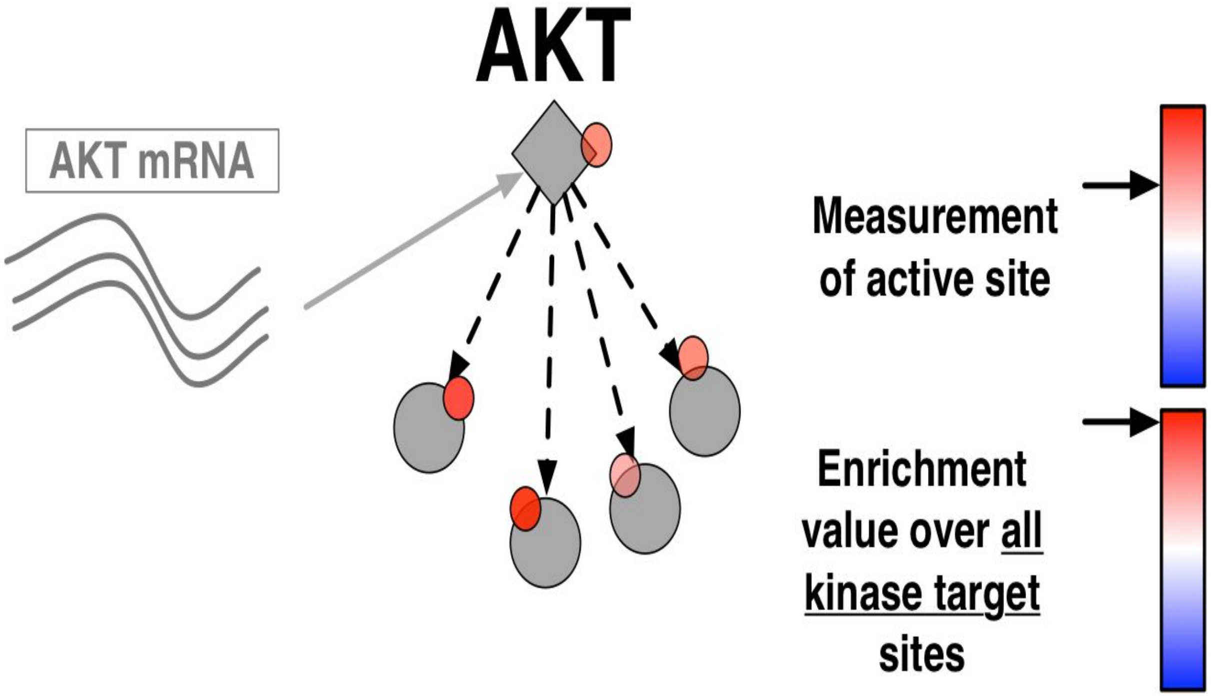
Drake, Paull et al *Cell 2016*

Master Regulator Analysis (MRA) on ***Phosphoproteomic*** data

Classic MRA: target gene expression -> protein activity
Proteomic MRA: kinase target phosphorylation -> protein activity



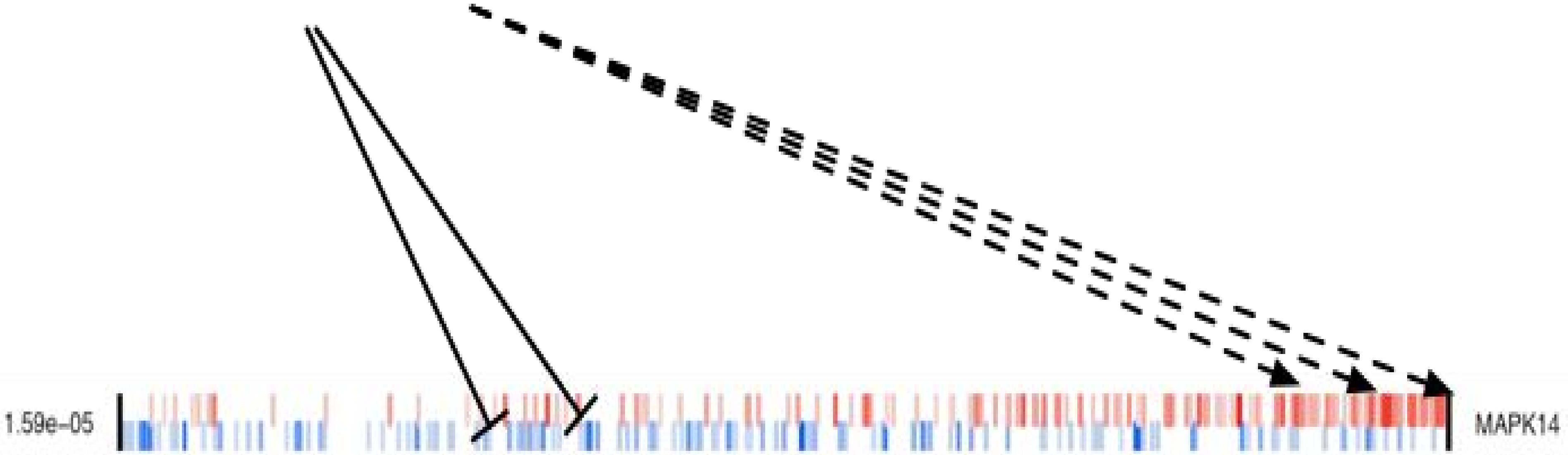
*Chen et al., Califano 2014



Drake, Paull et al *Cell 2016*

Master Regulator Analysis on ***Phosphoproteomic*** data

MAPK14, PRKDC, CDK1, AKT1, SRC, PRKAA2….



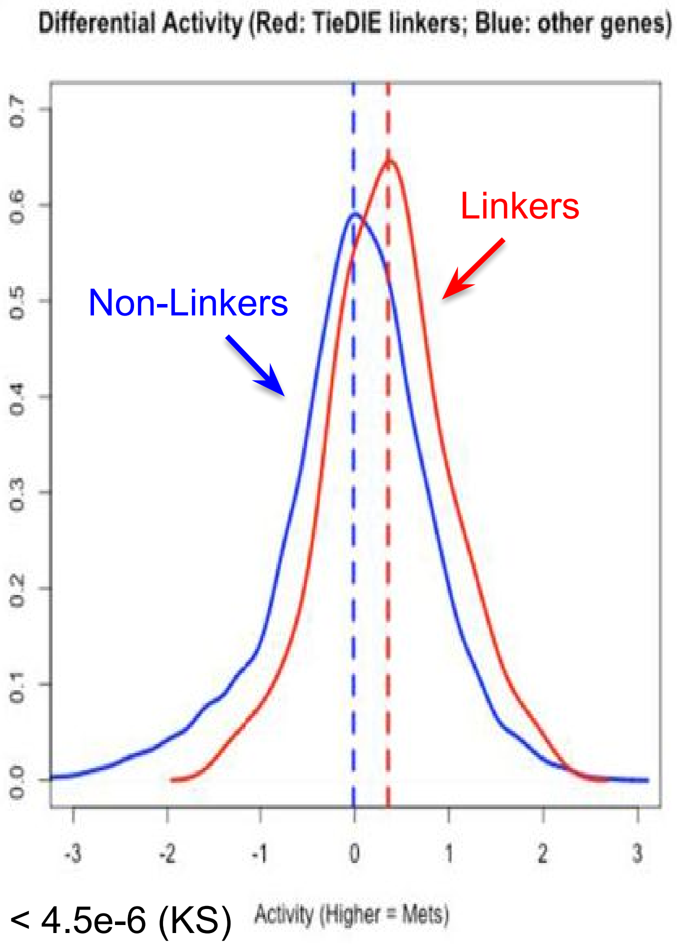
*Plot made with VIPER Bioconductor R package

```
source("https://bioconductor.org/biocLite.R")
biocLite("viper")
```

Drake, Paull et al *Cell 2016*

TieDIE Networks Embed Activated Proteins

Are Linkers More Activated?



Differential Activity (Red: TieDIE linkers; Blue: other genes)

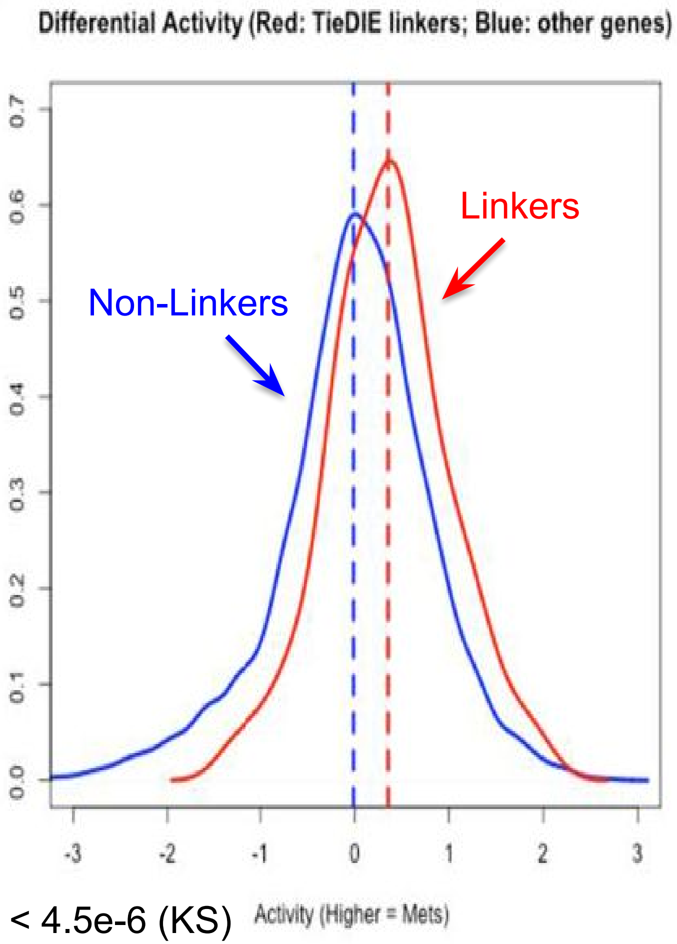
$p < 4.5e-6$ (KS)

Are ~Active TFs *near* ~Active Kinases?

Drake, Paull et al *Cell 2016*

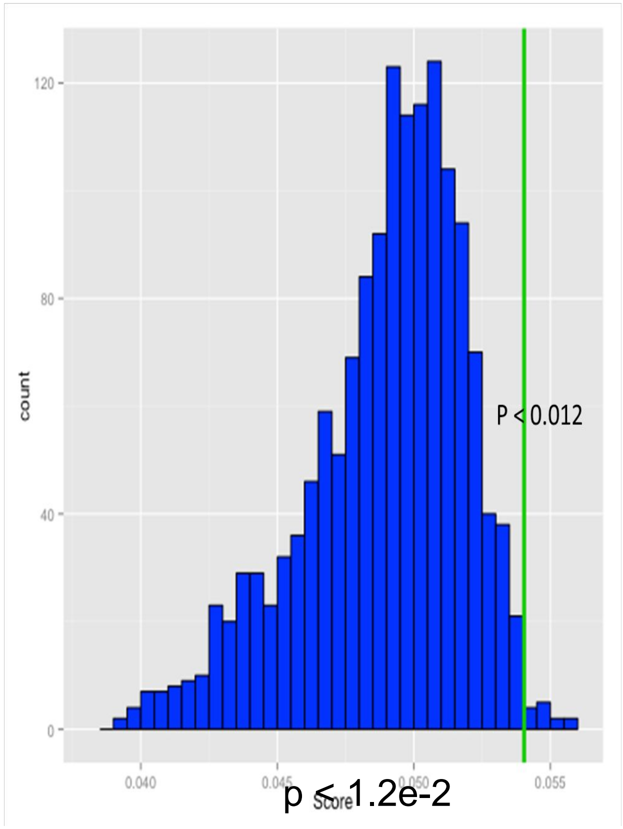
TieDIE Networks Embed Activated Proteins

Are Linkers More Activated?



p < 4.5e-6 (KS)

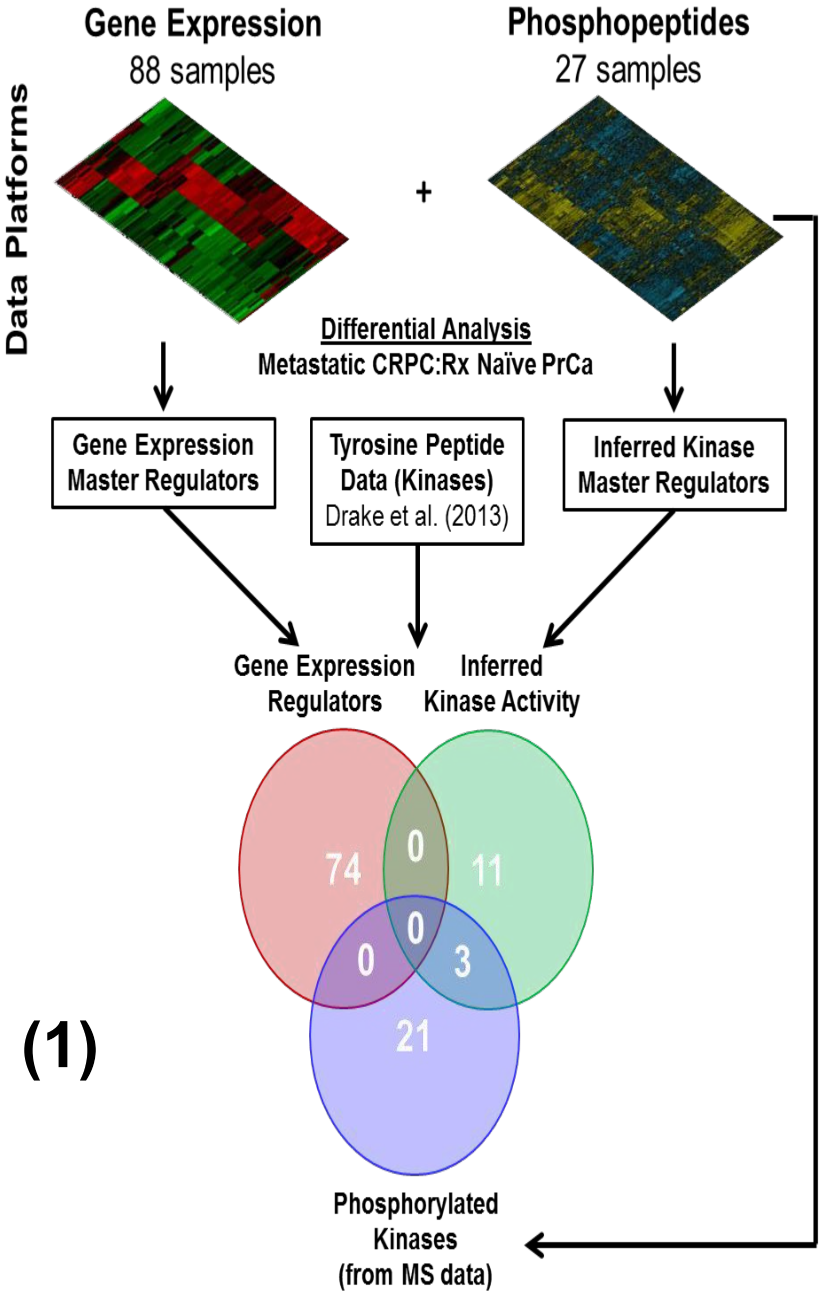
Are ~Active TFs *near* ~Active Kinases?



p < 1.2e-2

Drake, Paull et al *Cell 2016*

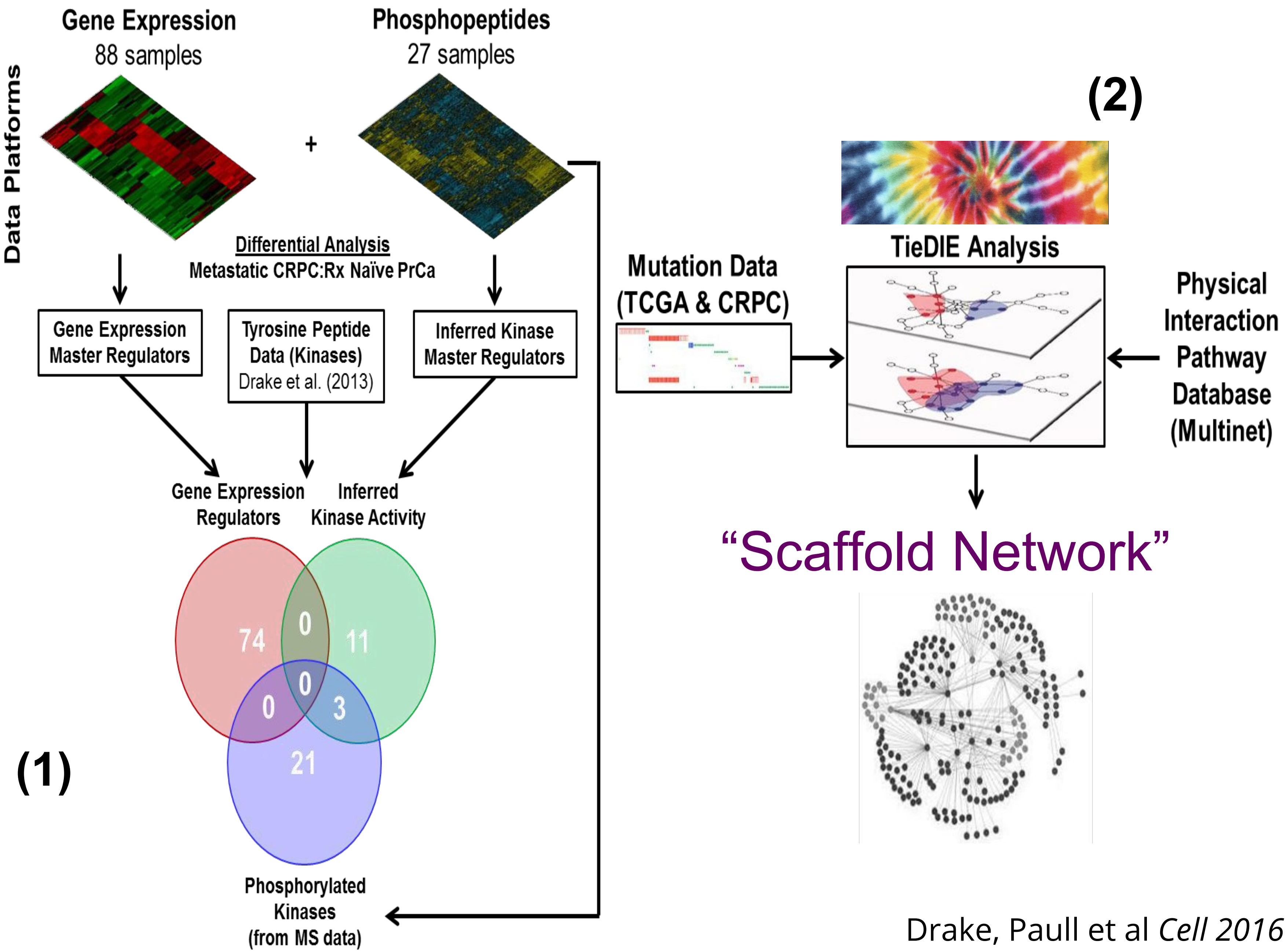
Scaffold network for CRPC from eclectic data



(1)

Drake, Paull et al *Cell 2016*

Scaffold network for metastatic prostate from diverse data



Data Platforms

Gene Expression
88 samples

+

Phosphopeptides
27 samples

Differential Analysis
Metastatic CRPC:Rx Naïve PrCa

Gene Expression Master Regulators

Tyrosine Peptide Data (Kinases)
Drake et al. (2013)

Inferred Kinase Master Regulators

Gene Expression Regulators

Inferred Kinase Activity

Phosphorylated Kinases
(from MS data)

(1)

(2)

Mutation Data
(TCGA & CRPC)

TieDIE Analysis

Physical Interaction Pathway Database (Multinet)

"Scaffold Network"

Drake, Paull et al *Cell 2016*

PERSONALIZED NETWORKS FOR TARGETING

Patient DTB-011

Linking Network

Mutations

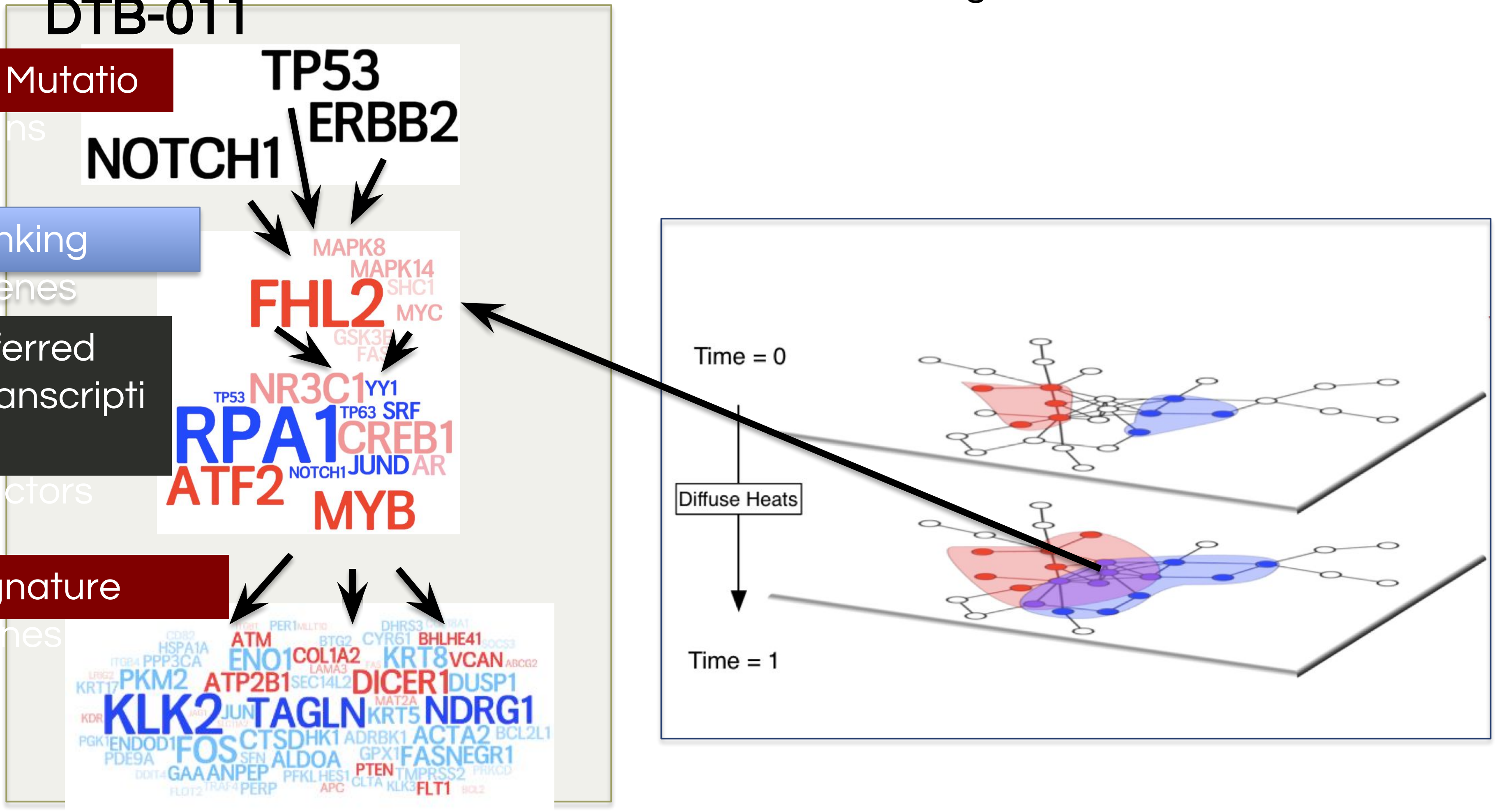
Linking Genes

Inferred Transcription

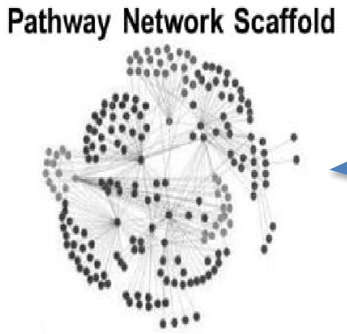
ctors

Signature

nes



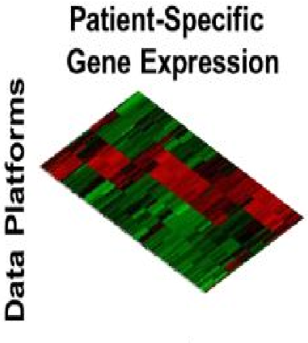
N-of-1 Patient-specific Network Approach Overview



TieDIE[1]

Patient-Specific Mutations

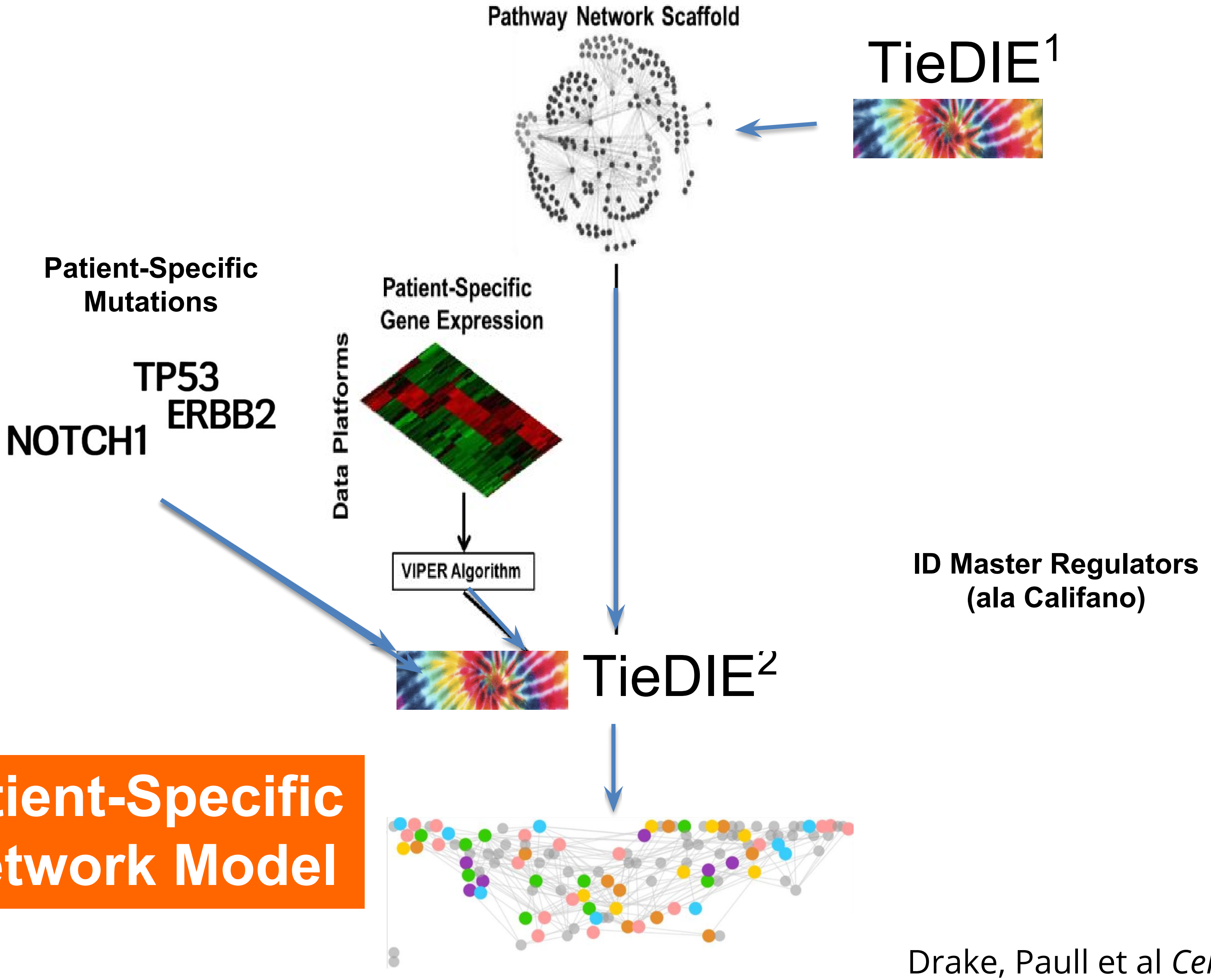
TP53
ERBB2
NOTCH1



Justin Drake (Witte Lab, UCLA), Evan Paull

Drake, Paull et al *Cell* 2016

N-of-1 Patient-specific Network Approach Overview



Pathway Network Scaffold

TieDIE[1]

Patient-Specific Mutations

TP53

ERBB2

NOTCH1

Patient-Specific Gene Expression

Data Platforms

VIPER Algorithm

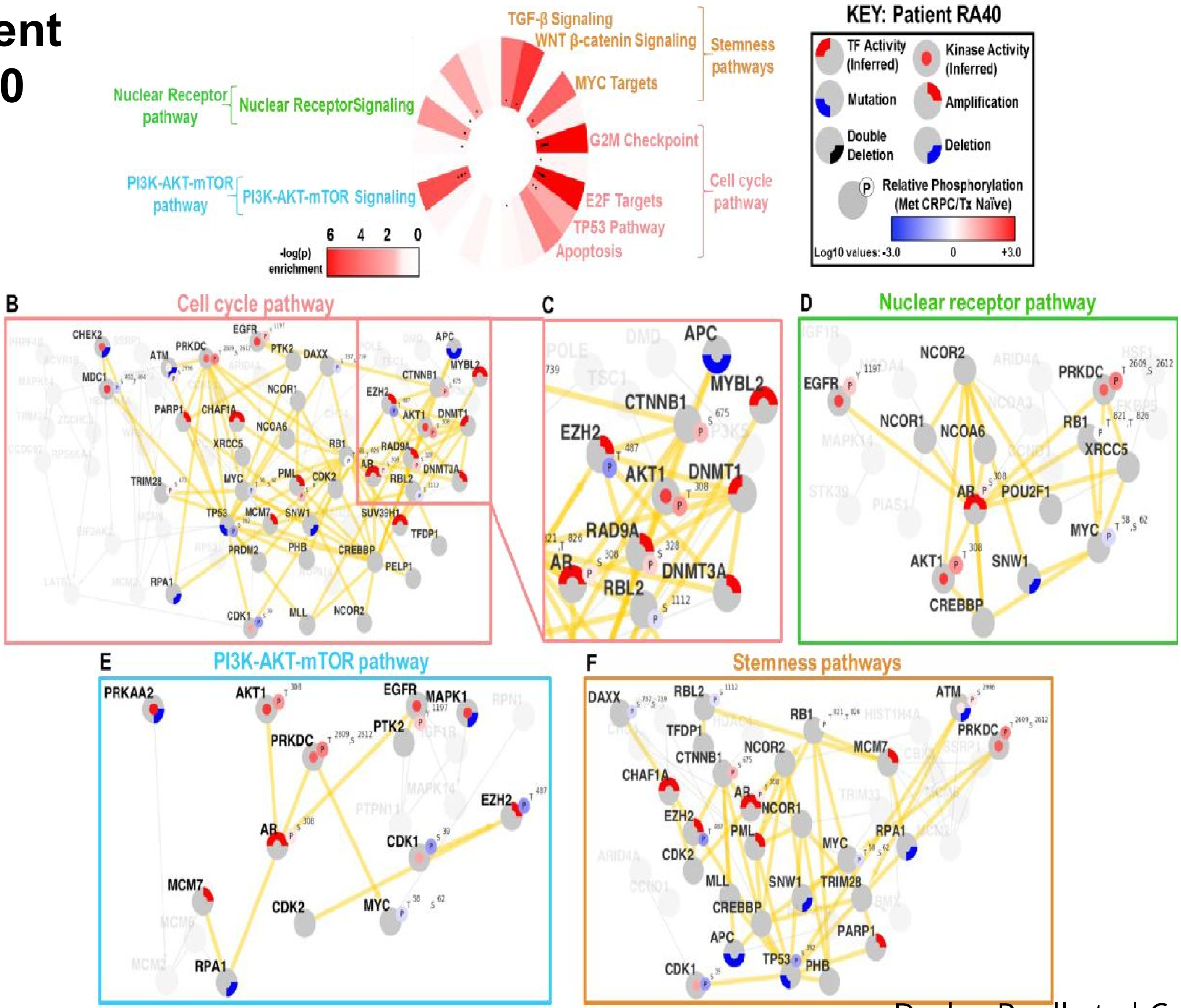
ID Master Regulators (ala Califano)

TieDIE[2]

Patient-Specific Network Model

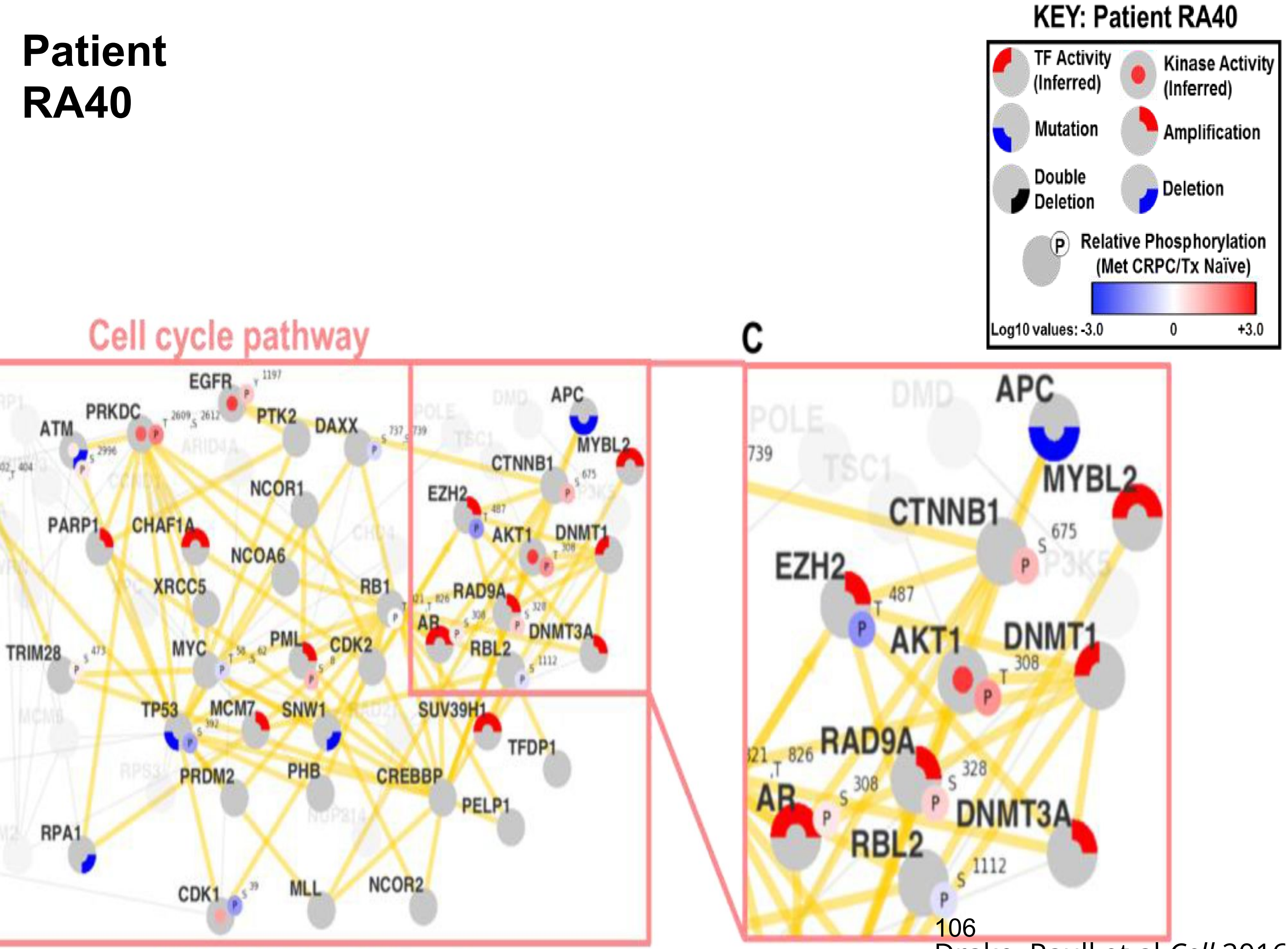
Drake, Paull et al *Cell* 2016

Patient RA40



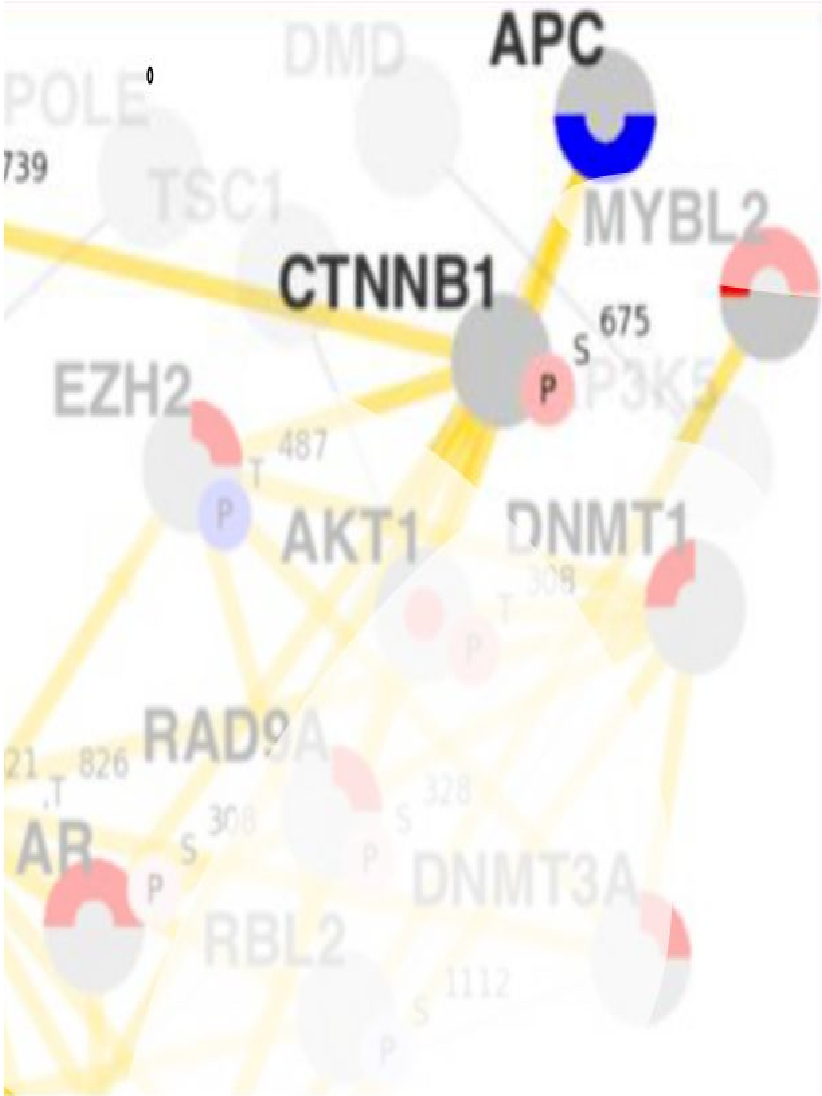
Drake, Paull et al *Cell* 2016

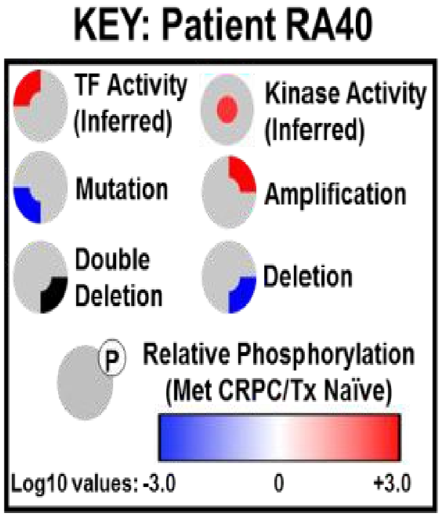
Patient RA40



Drake, Paull et al *Cell* 2016

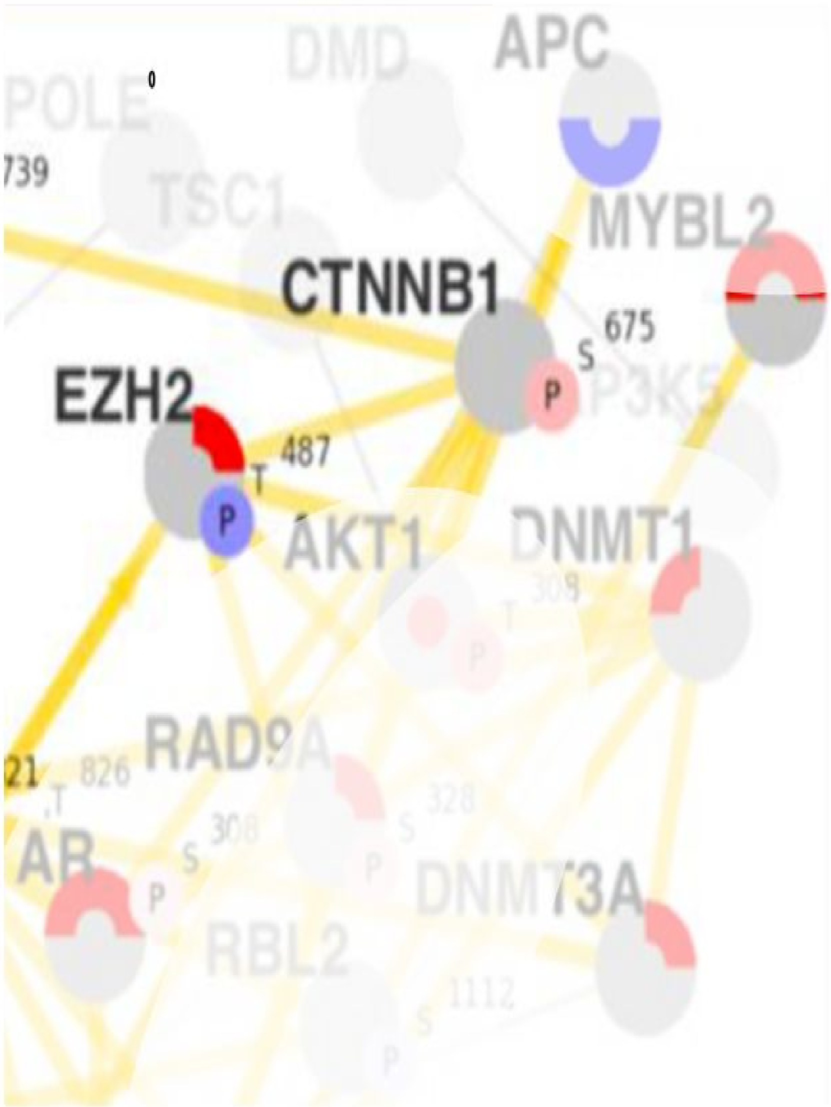
Patient RA40

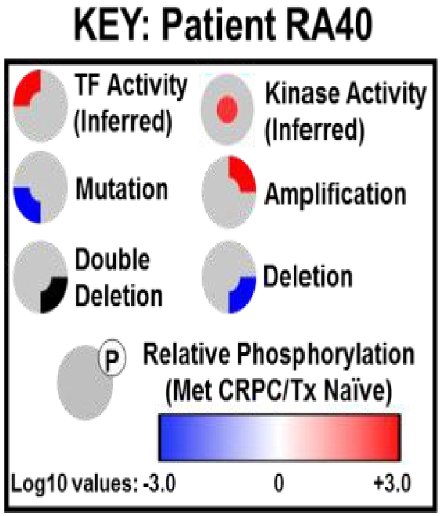




Drake, Paull et al *Cell* 2016

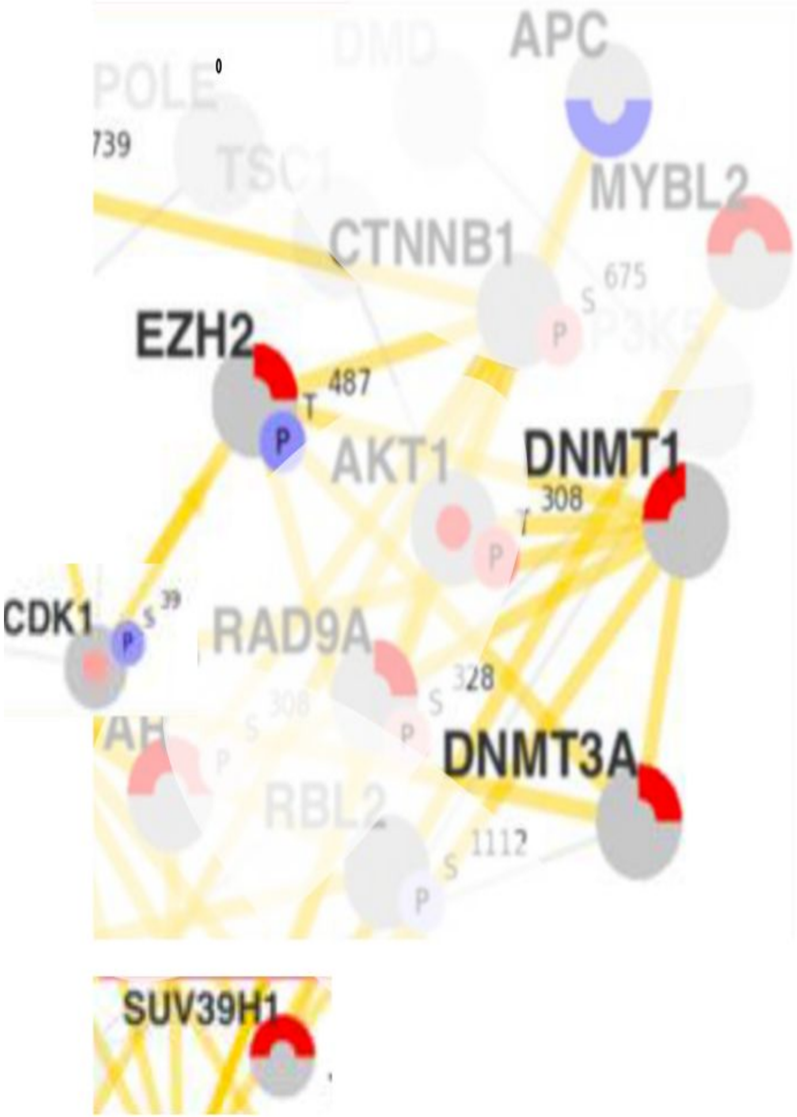
Patient RA40

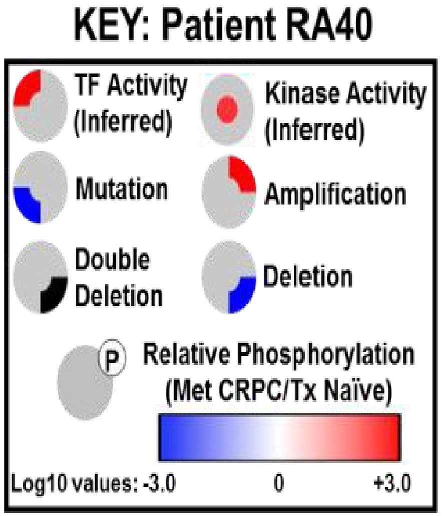




Drake, Paull et al *Cell* 2016

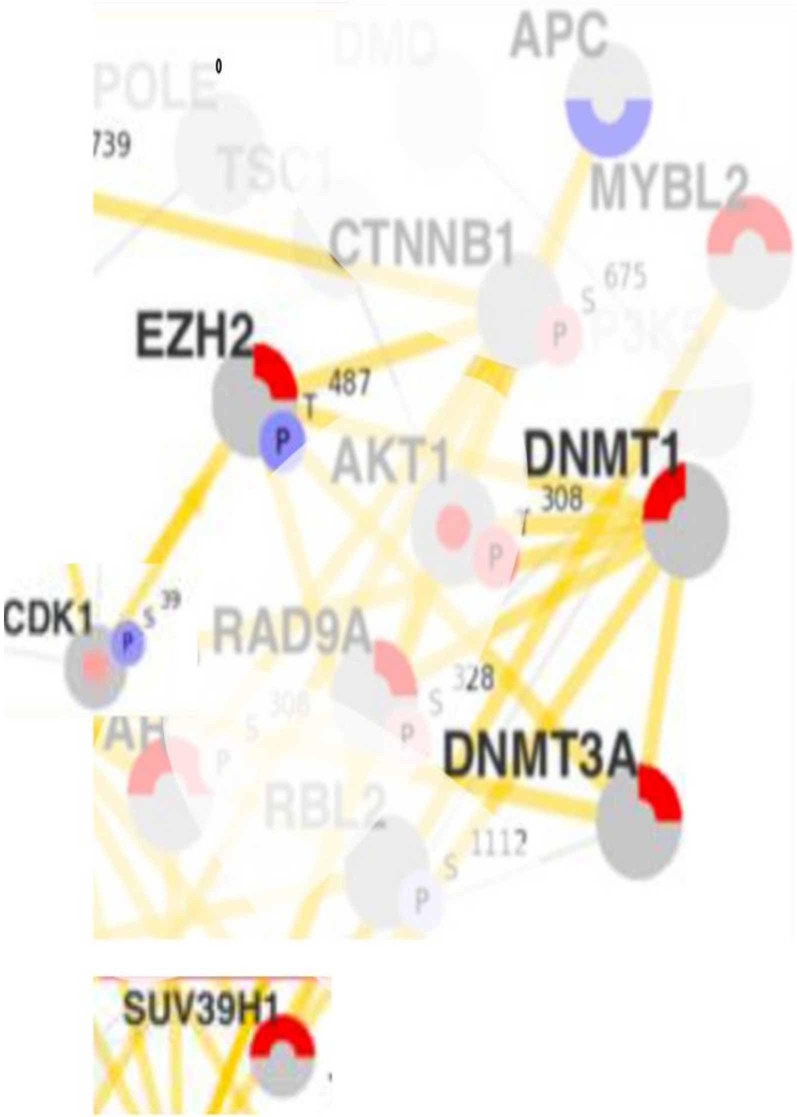
Patient RA40

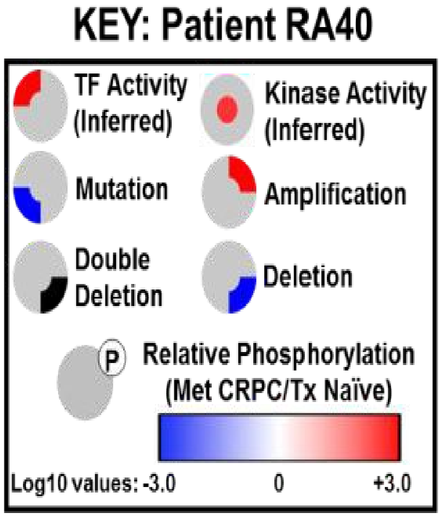




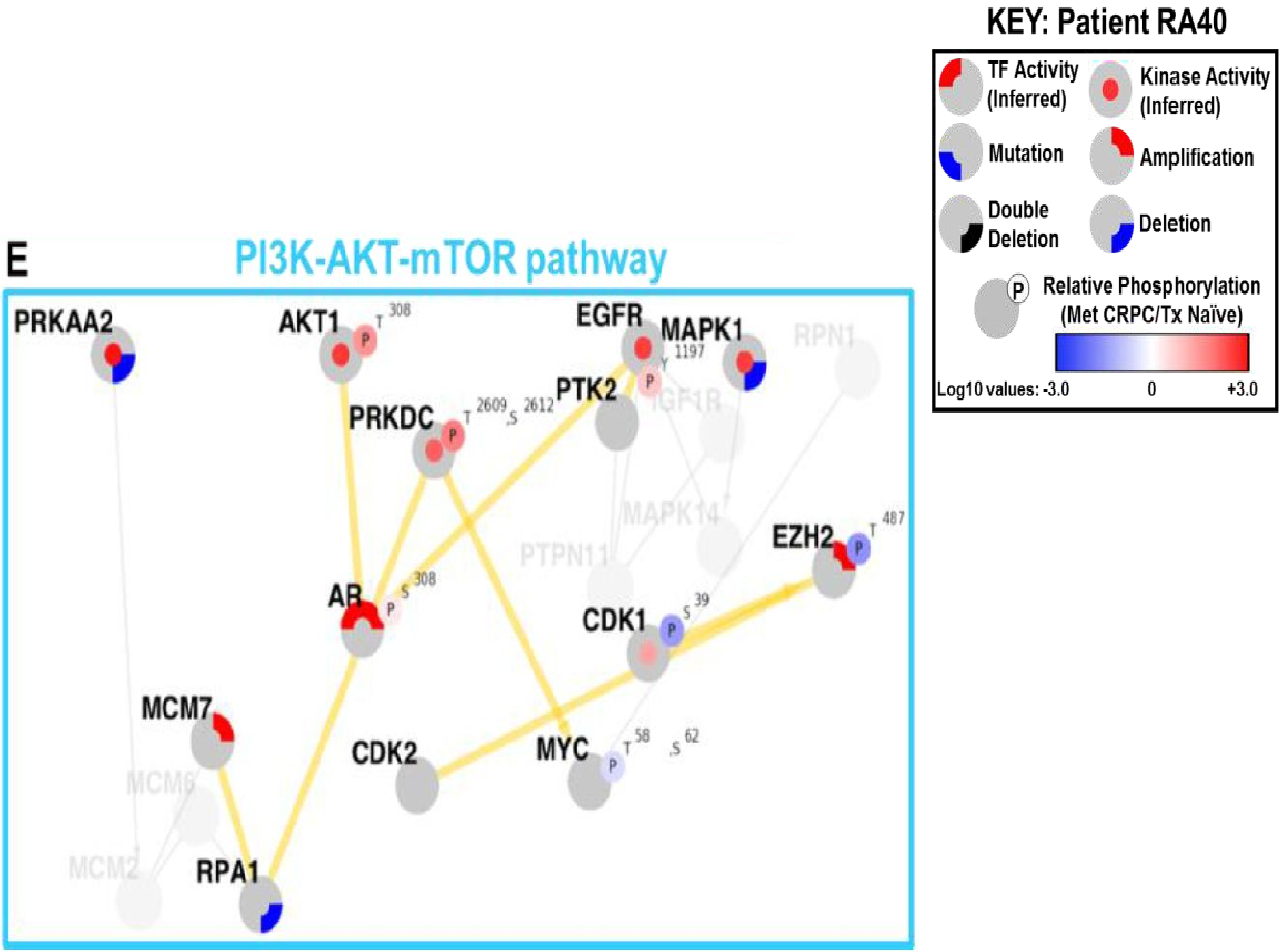
Drake, Paull et al *Cell* 2016

Patient RA40



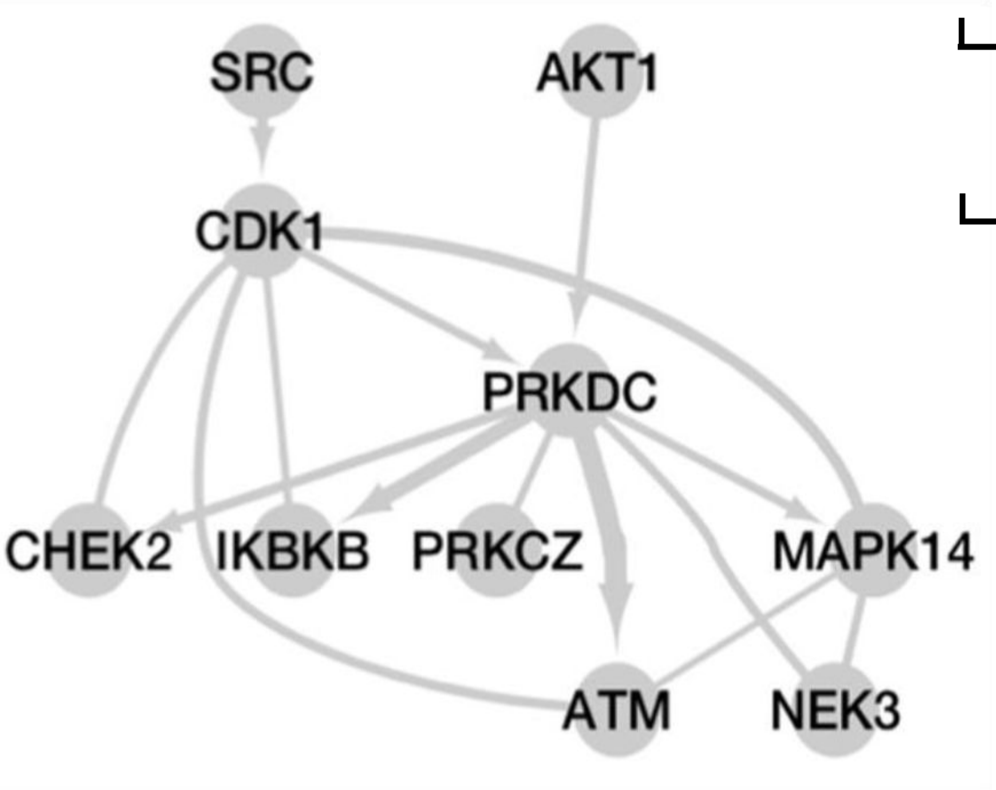


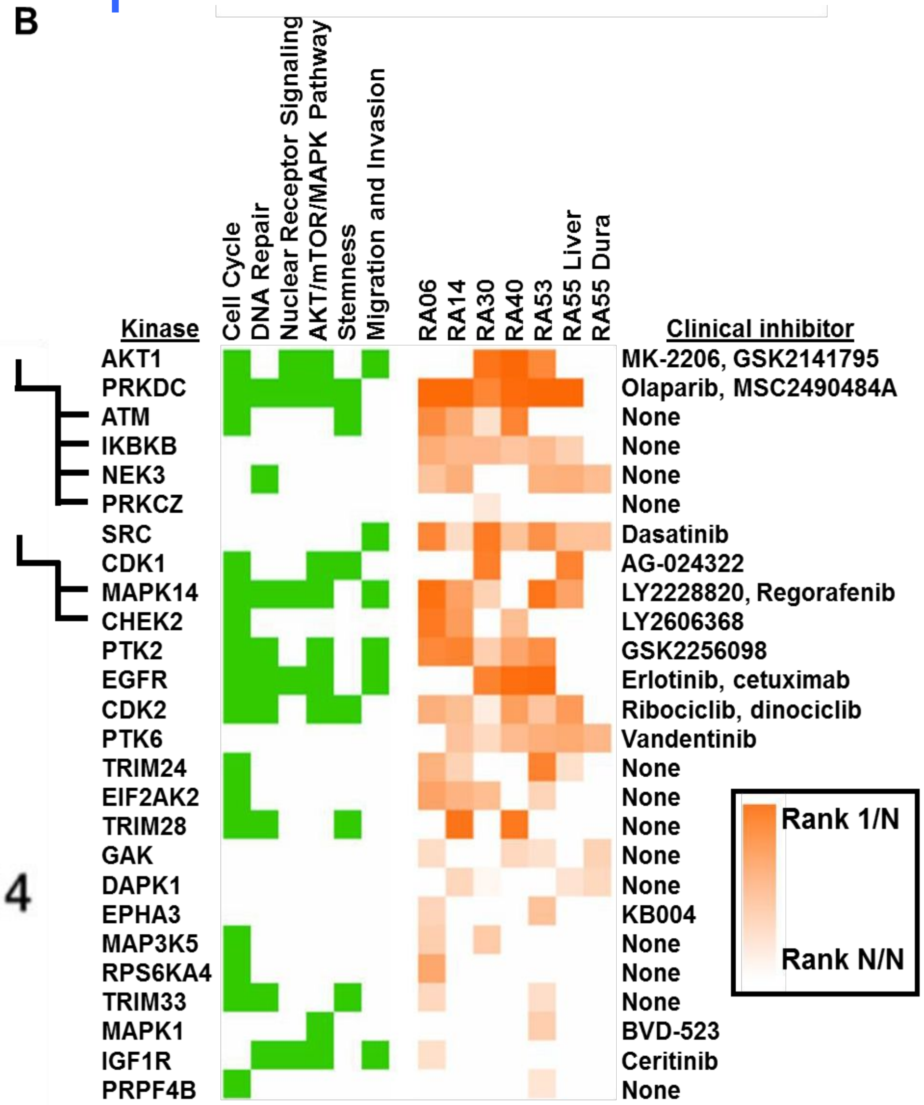
Drake, Paull et al *Cell* 2016



Drake, Paull et al *Cell* 2016

Network-based selection of targets and target combinations for individual patients



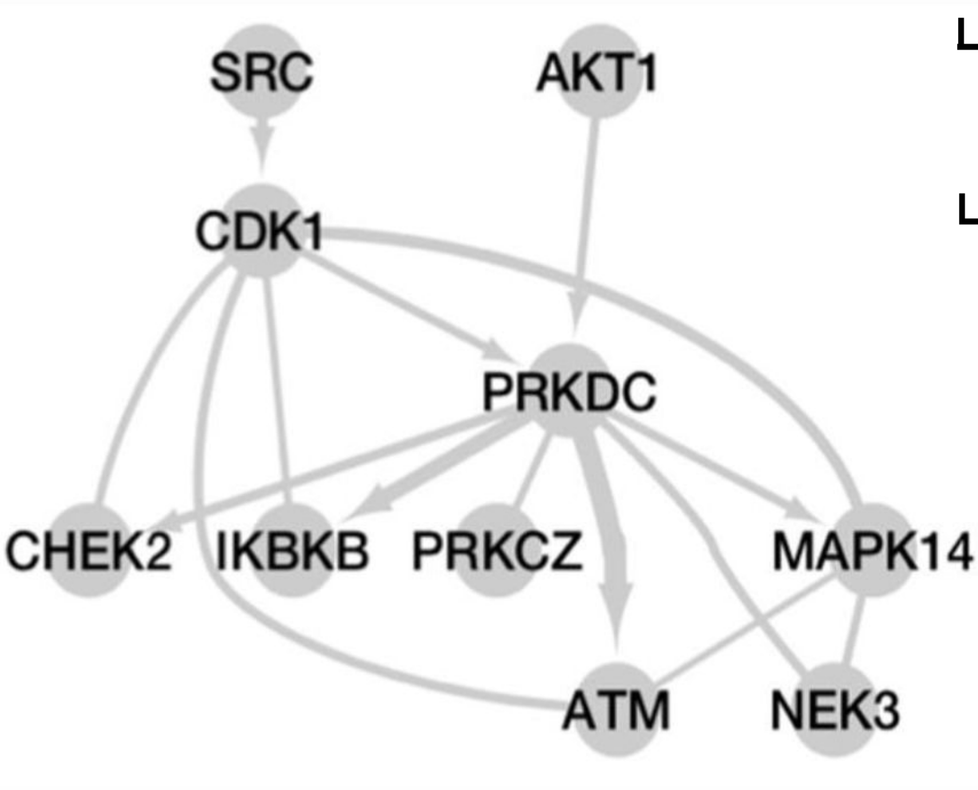


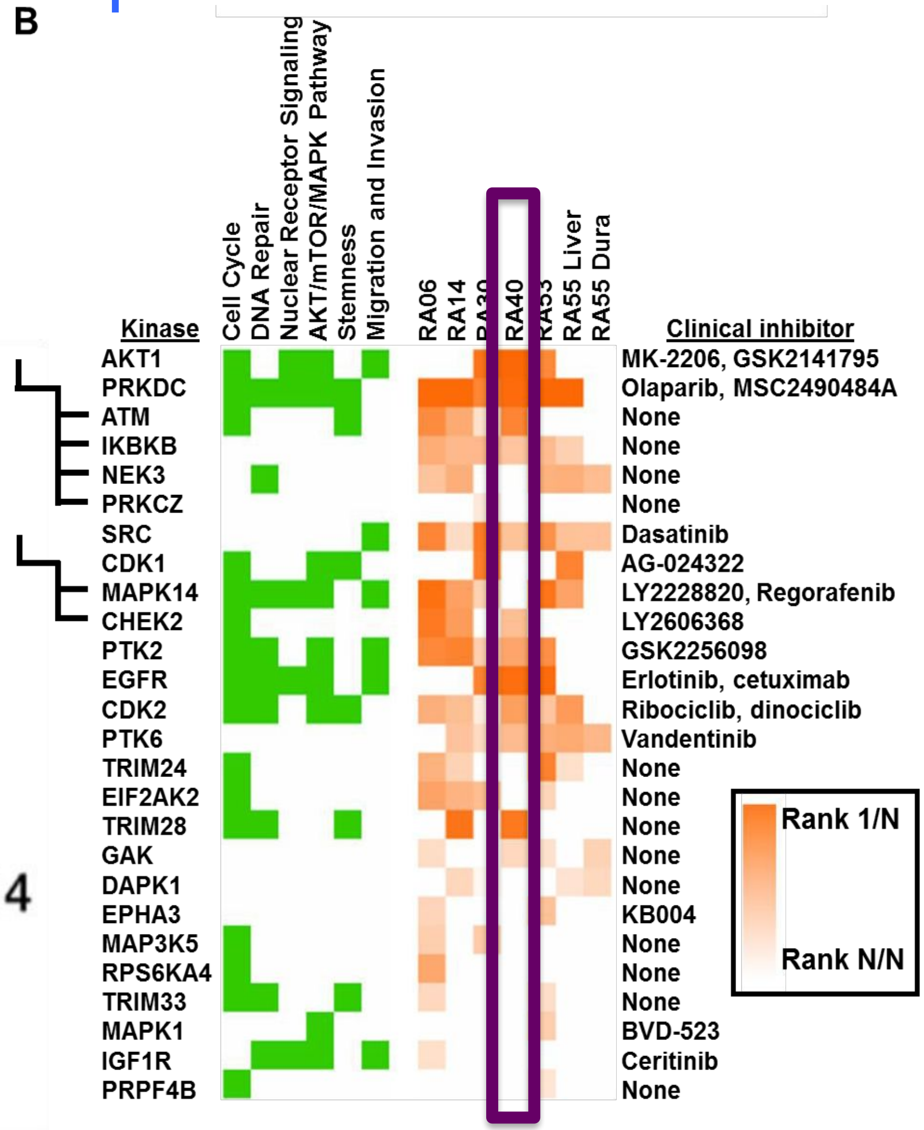
Kinase	Clinical inhibitor
AKT1	MK-2206, GSK2141795
PRKDC	Olaparib, MSC2490484A
ATM	None
IKBKB	None
NEK3	None
PRKCZ	None
SRC	Dasatinib
CDK1	AG-024322
MAPK14	LY2228820, Regorafenib
CHEK2	LY2606368
PTK2	GSK2256098
EGFR	Erlotinib, cetuximab
CDK2	Ribociclib, dinociclib
PTK6	Vandentinib
TRIM24	None
EIF2AK2	None
TRIM28	None
GAK	None
DAPK1	None
EPHA3	KB004
MAP3K5	None
RPS6KA4	None
TRIM33	None
MAPK1	BVD-523
IGF1R	Ceritinib
PRPF4B	None

Drake, Paull et al *Cell* 2016

Network-based selection of targets and target combinations for individual patients

Patient 40



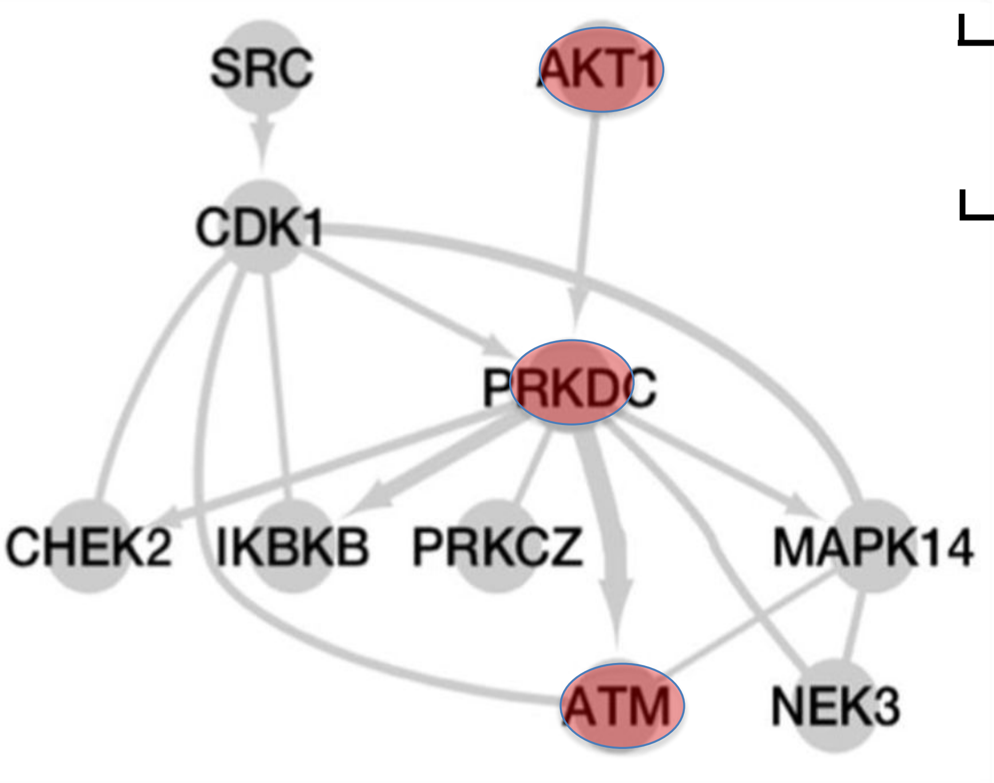


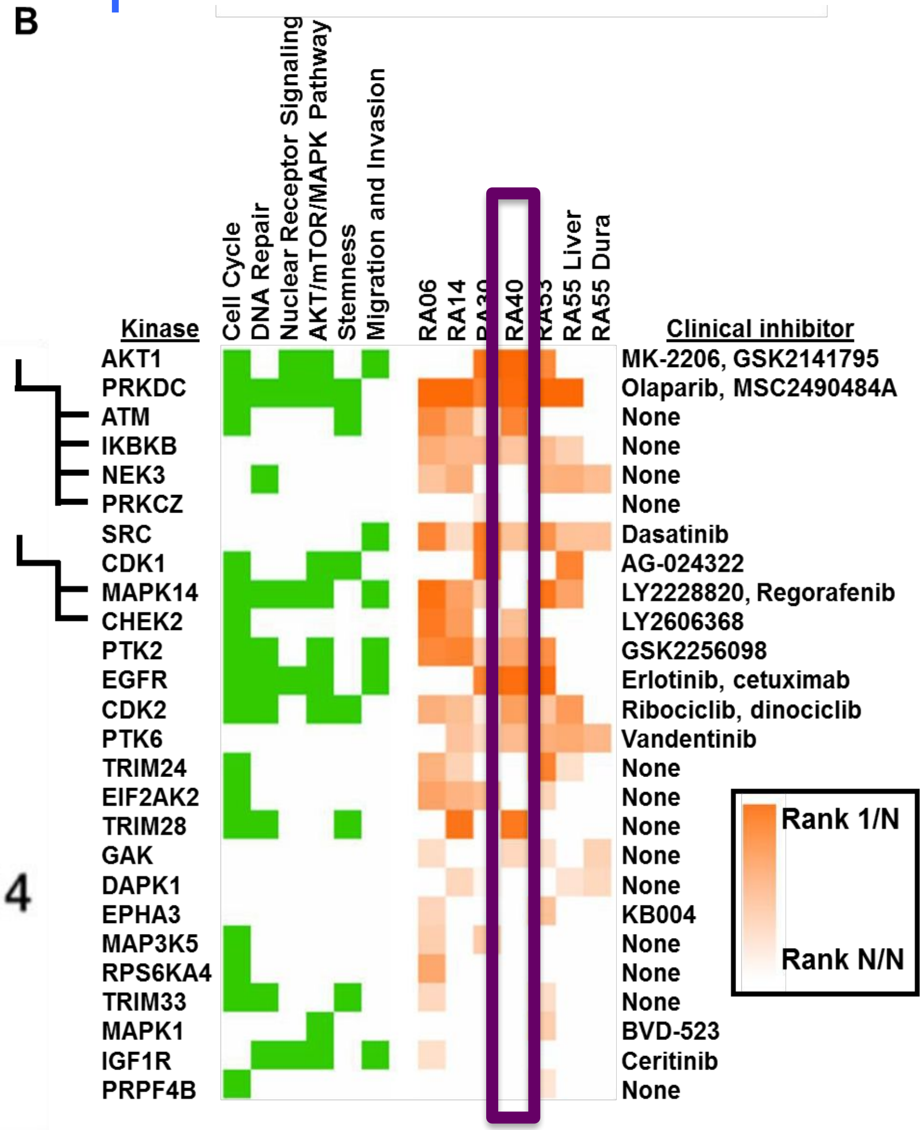
Kinase	Clinical inhibitor
AKT1	MK-2206, GSK2141795
PRKDC	Olaparib, MSC2490484A
ATM	None
IKBKB	None
NEK3	None
PRKCZ	None
SRC	Dasatinib
CDK1	AG-024322
MAPK14	LY2228820, Regorafenib
CHEK2	LY2606368
PTK2	GSK2256098
EGFR	Erlotinib, cetuximab
CDK2	Ribociclib, dinociclib
PTK6	Vandentinib
TRIM24	None
EIF2AK2	None
TRIM28	None
GAK	None
DAPK1	None
EPHA3	KB004
MAP3K5	None
RPS6KA4	None
TRIM33	None
MAPK1	BVD-523
IGF1R	Ceritinib
PRPF4B	None

Drake, Paull et al *Cell* 2016

Network-based selection of targets and target combinations for individual patients

Patient 40





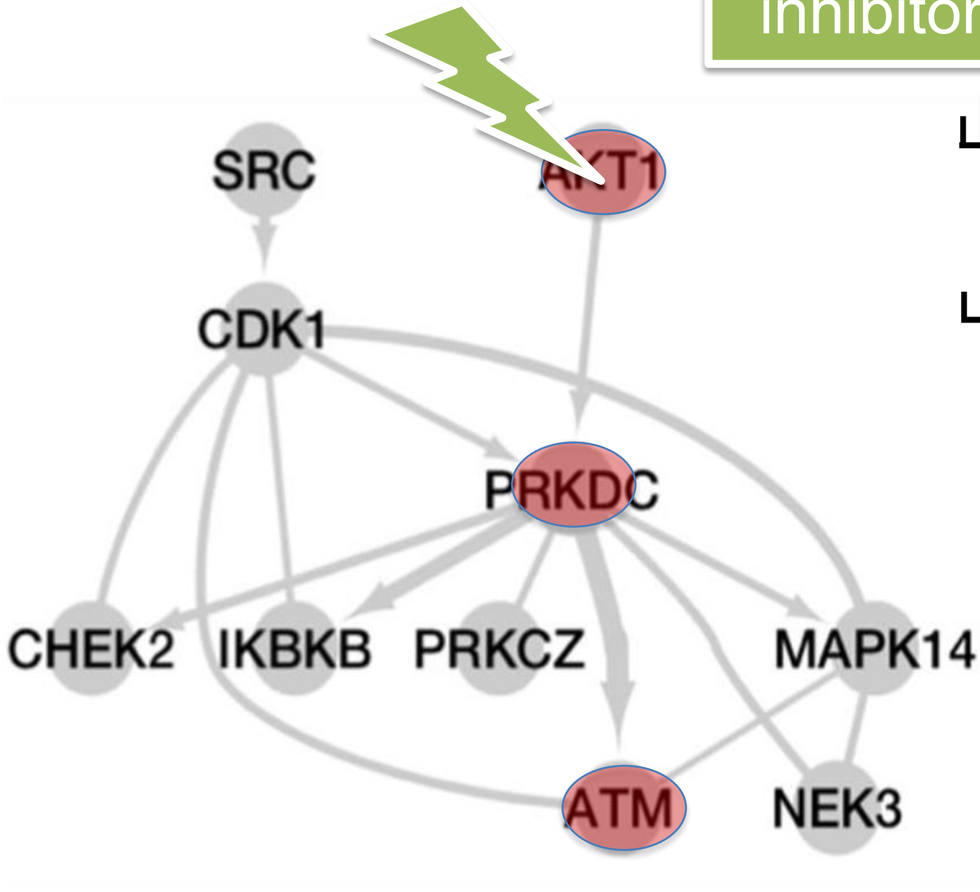
Kinase	Clinical inhibitor
AKT1	MK-2206, GSK2141795
PRKDC	Olaparib, MSC2490484A
ATM	None
IKBKB	None
NEK3	None
PRKCZ	None
SRC	Dasatinib
CDK1	AG-024322
MAPK14	LY2228820, Regorafenib
CHEK2	LY2606368
PTK2	GSK2256098
EGFR	Erlotinib, cetuximab
CDK2	Ribociclib, dinociclib
PTK6	Vandentinib
TRIM24	None
EIF2AK2	None
TRIM28	None
GAK	None
DAPK1	None
EPHA3	KB004
MAP3K5	None
RPS6KA4	None
TRIM33	None
MAPK1	BVD-523
IGF1R	Ceritinib
PRPF4B	None

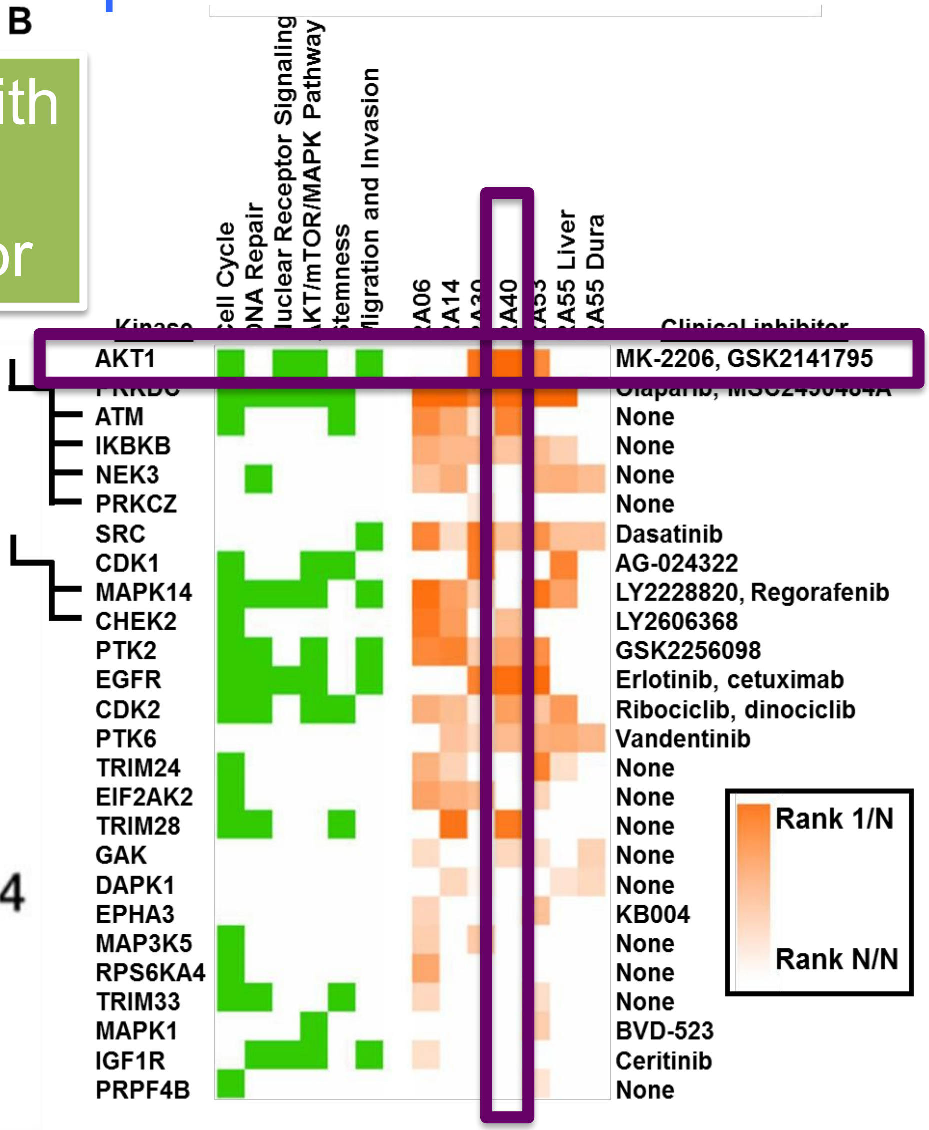
Drake, Paull et al *Cell* 2016

Network-based selection of targets and target combinations for individual patients

Patient 40

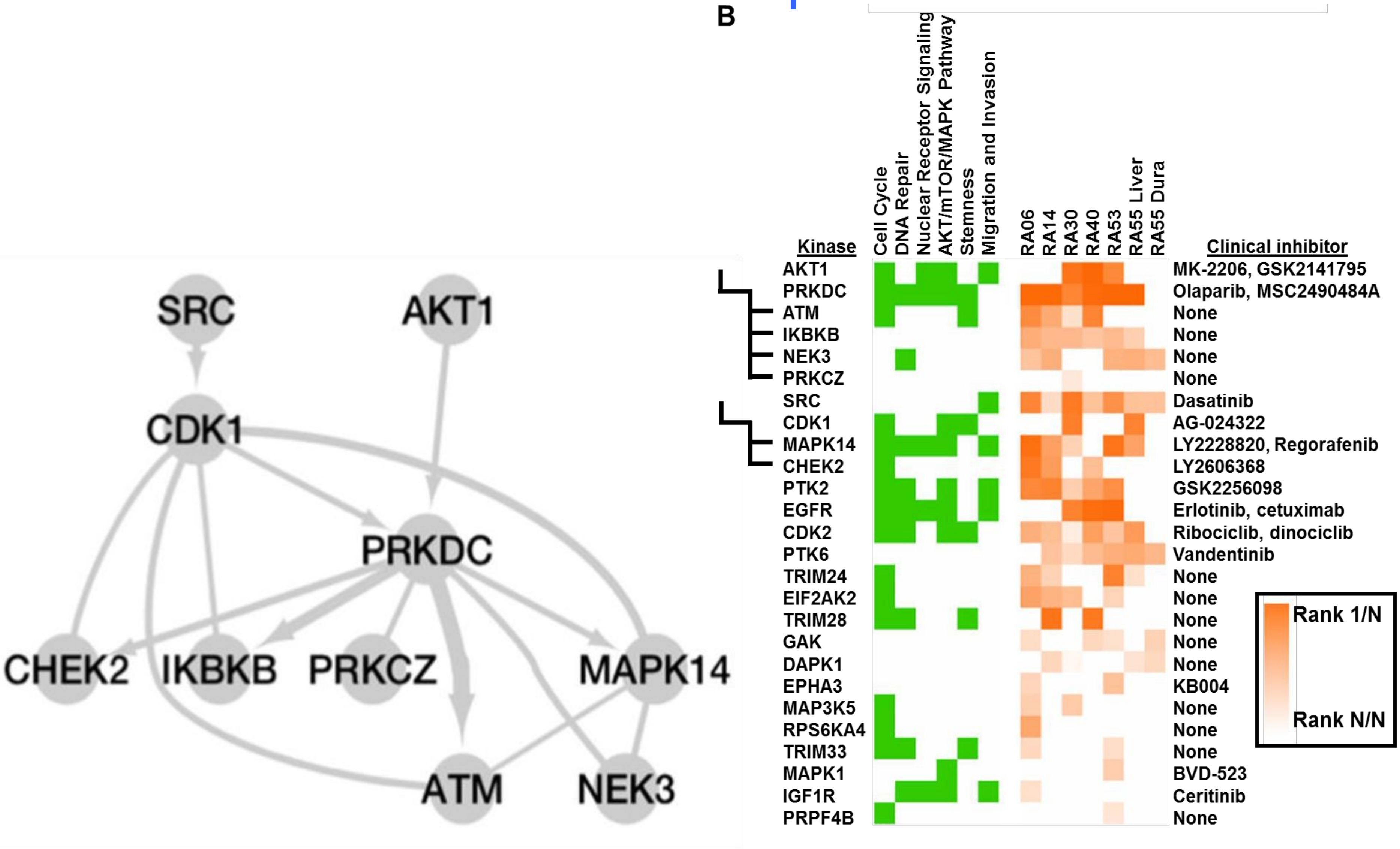
Treat with AKT1 inhibitor





Drake, Paull et al *Cell* 2016

Network-based selection of targets and target combinations for individual patients

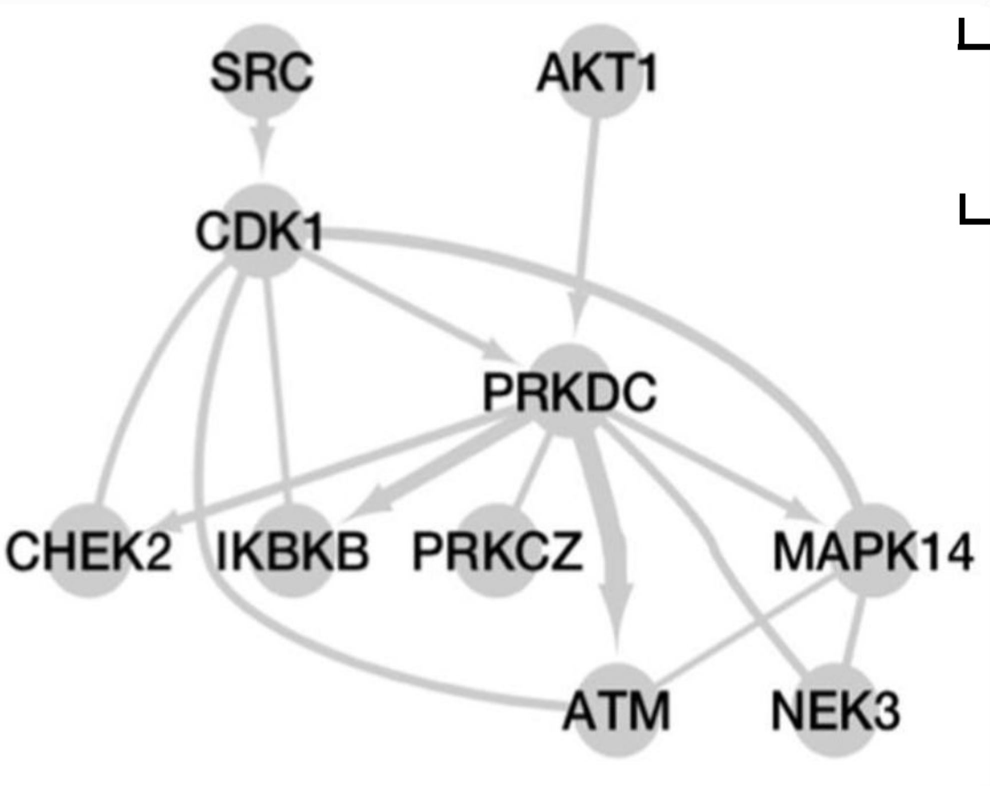


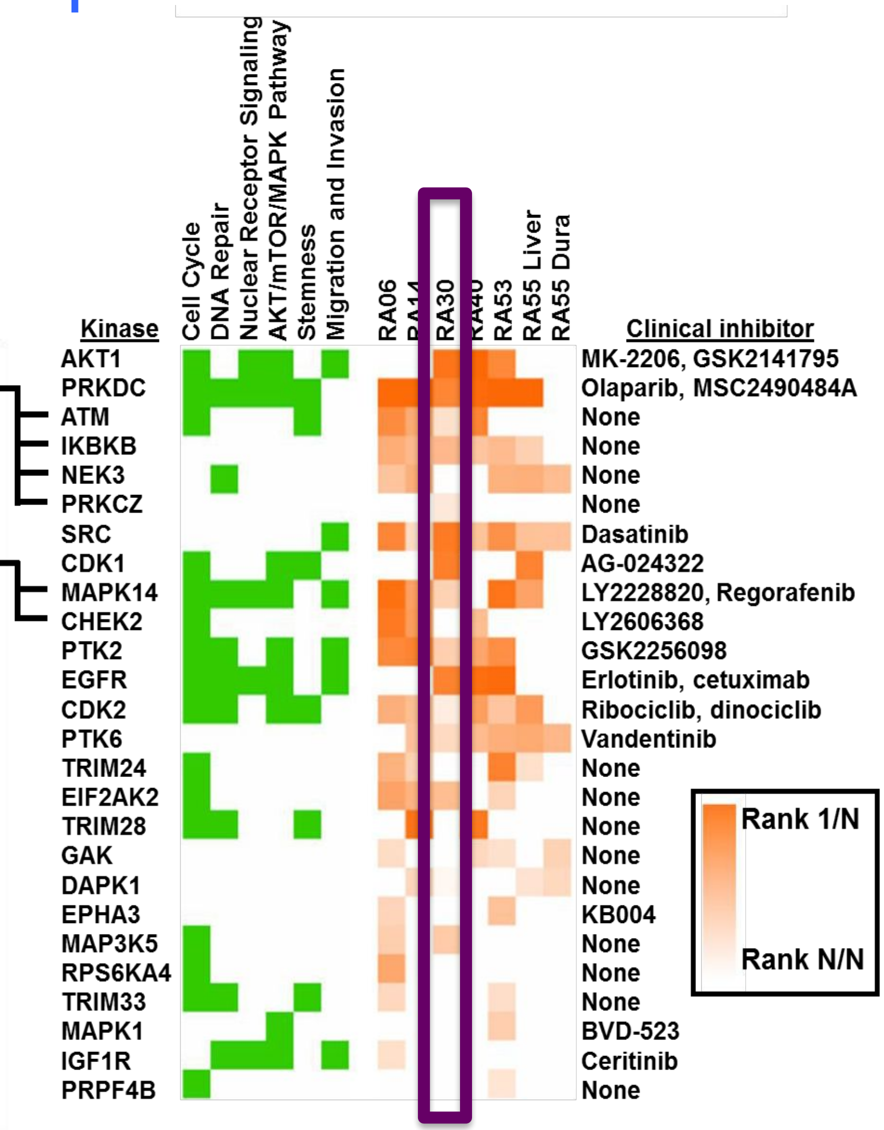
Kinase	Clinical inhibitor
AKT1	MK-2206, GSK2141795
PRKDC	Olaparib, MSC2490484A
ATM	None
IKBKB	None
NEK3	None
PRKCZ	None
SRC	Dasatinib
CDK1	AG-024322
MAPK14	LY2228820, Regorafenib
CHEK2	LY2606368
PTK2	GSK2256098
EGFR	Erlotinib, cetuximab
CDK2	Ribociclib, dinociclib
PTK6	Vandentinib
TRIM24	None
EIF2AK2	None
TRIM28	None
GAK	None
DAPK1	None
EPHA3	KB004
MAP3K5	None
RPS6KA4	None
TRIM33	None
MAPK1	BVD-523
IGF1R	Ceritinib
PRPF4B	None

Drake, Paull et al *Cell* 2016

Network-based selection of targets and target combinations for individual patients

Patient 30

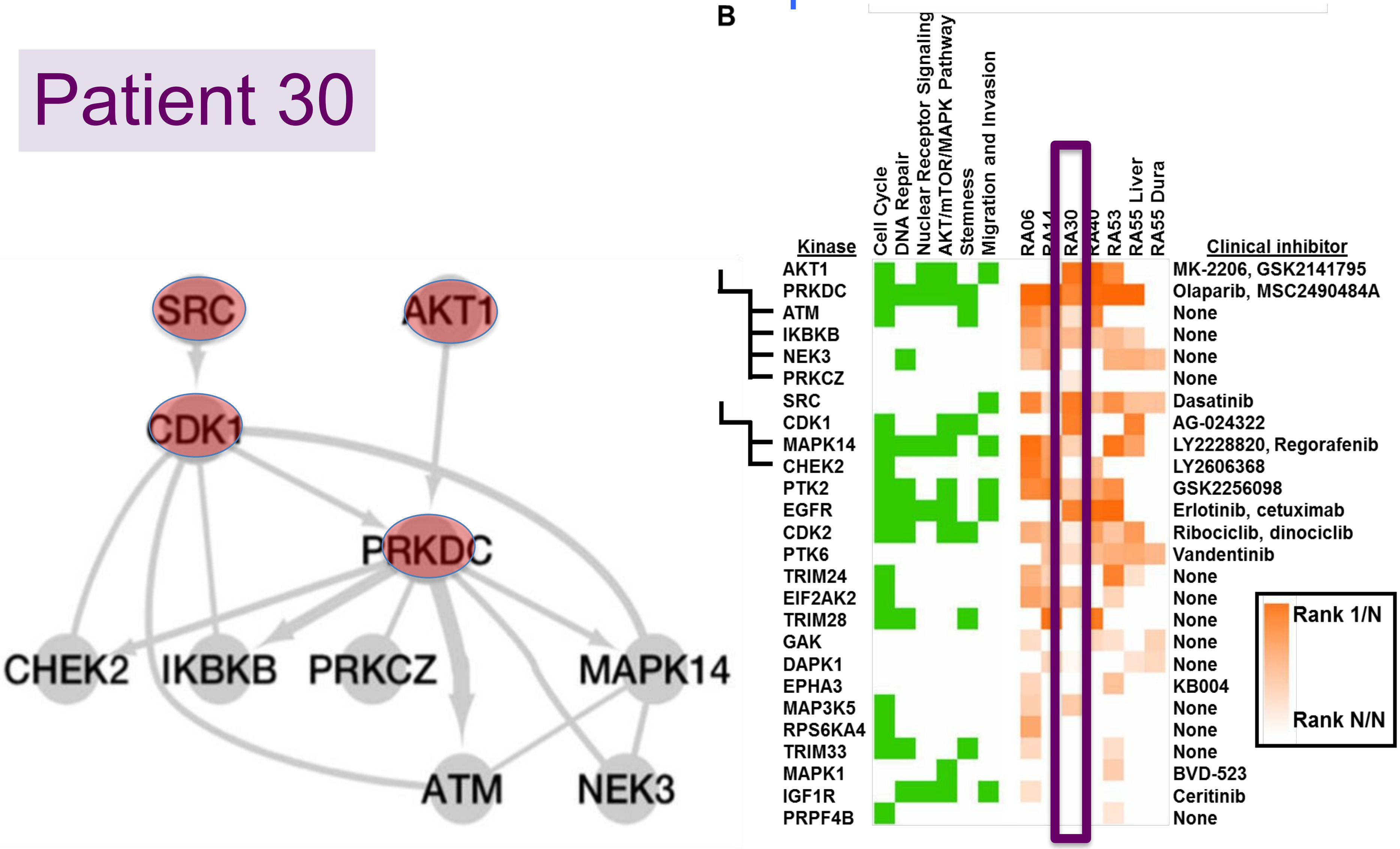




Drake, Paull et al *Cell* 2016

Network-based selection of targets and target combinations for individual patients

Patient 30



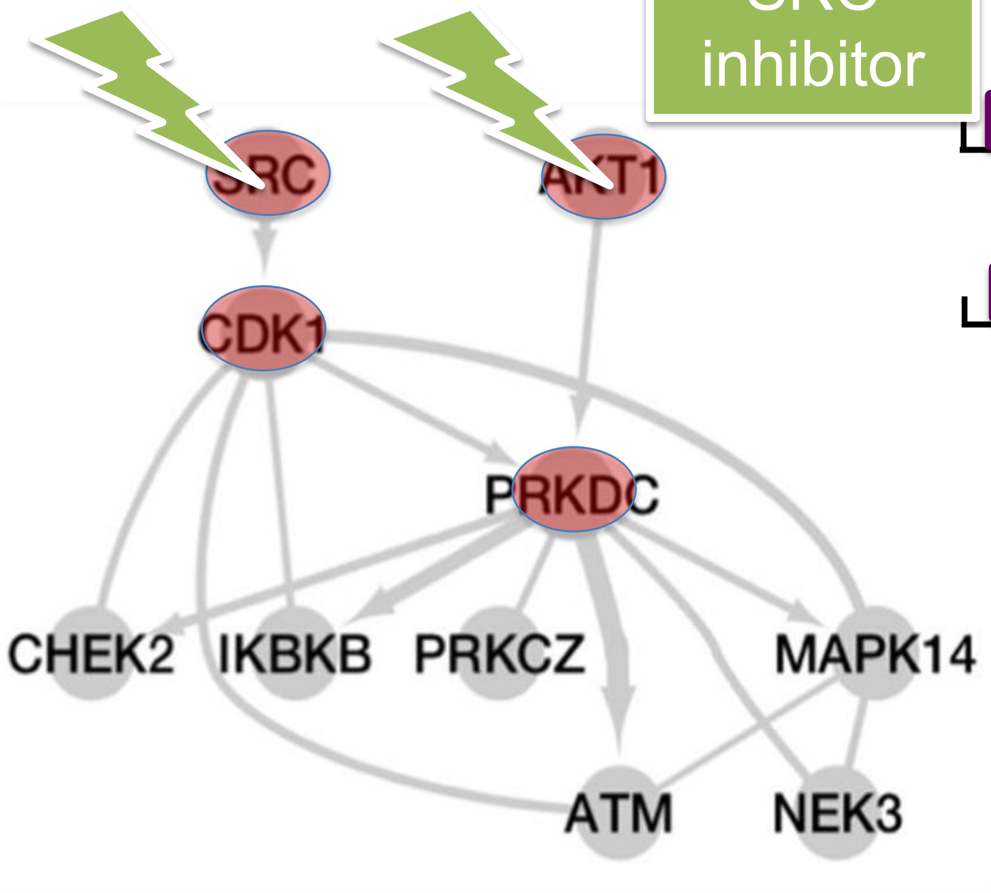
Kinase	Clinical inhibitor
AKT1	MK-2206, GSK2141795
PRKDC	Olaparib, MSC2490484A
ATM	None
IKBKB	None
NEK3	None
PRKCZ	None
SRC	Dasatinib
CDK1	AG-024322
MAPK14	LY2228820, Regorafenib
CHEK2	LY2606368
PTK2	GSK2256098
EGFR	Erlotinib, cetuximab
CDK2	Ribociclib, dinociclib
PTK6	Vandentinib
TRIM24	None
EIF2AK2	None
TRIM28	None
GAK	None
DAPK1	None
EPHA3	KB004
MAP3K5	None
RPS6KA4	None
TRIM33	None
MAPK1	BVD-523
IGF1R	Ceritinib
PRPF4B	None

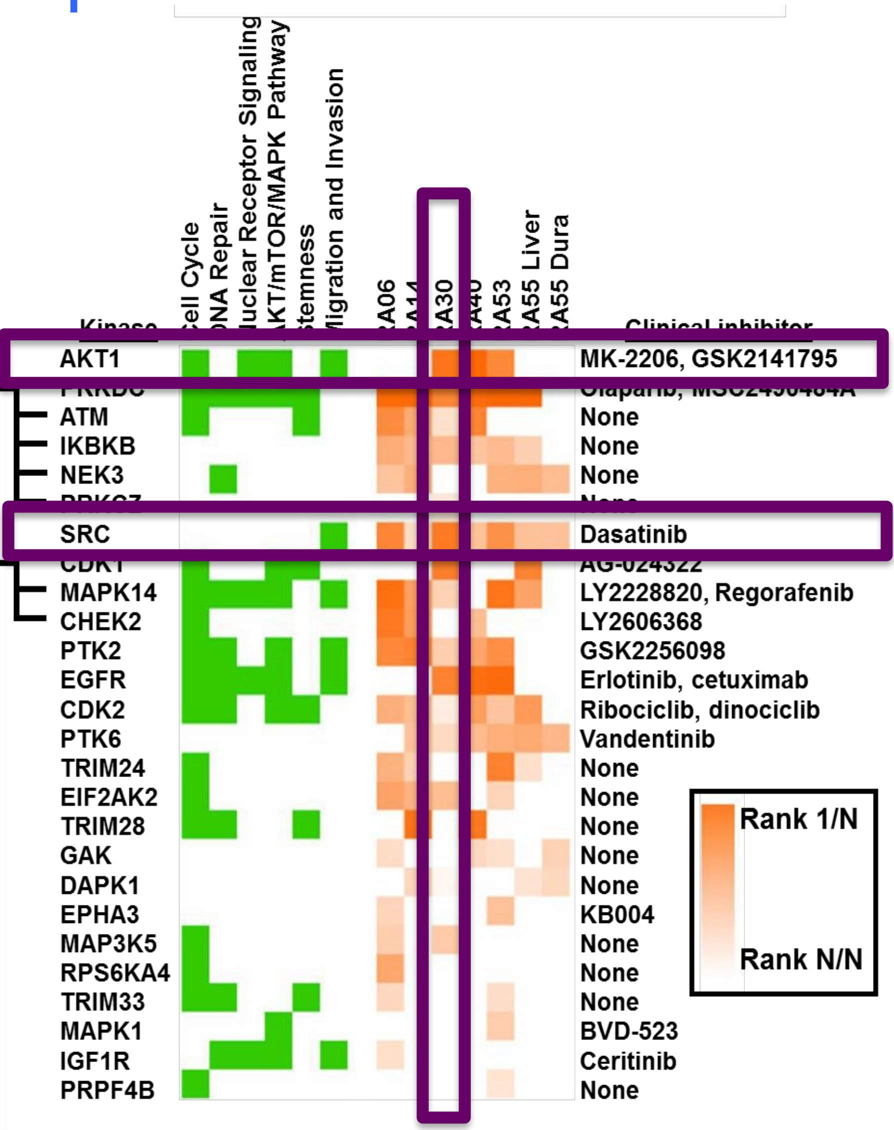
Drake, Paull et al *Cell* 2016

Network-based selection of targets and target combinations for individual patients

Patient 30

Treat with AKT1 & SRC inhibitor





Kinase	Clinical inhibitor
AKT1	MK-2206, GSK2141795
PRKDC	Olaparib, MSC2490484A
ATM	None
IKBKB	None
NEK3	None
PRKCZ	None
SRC	Dasatinib
CDK1	AG-024322
MAPK14	LY2228820, Regorafenib
CHEK2	LY2606368
PTK2	GSK2256098
EGFR	Erlotinib, cetuximab
CDK2	Ribociclib, dinociclib
PTK6	Vandentinib
TRIM24	None
EIF2AK2	None
TRIM28	None
GAK	None
DAPK1	None
EPHA3	KB004
MAP3K5	None
RPS6KA4	None
TRIM33	None
MAPK1	BVD-523
IGF1R	Ceritinib
PRPF4B	None

Drake, Paull et al *Cell* 2016

TAKE-HOME MESSAGES

- Pan-Cancer analysis reveals strong tissue-of-origin signals.
    - But ~10% reclassified associated w/ survival.

- Adult signatures can inform novel pan-cancer connections for treatment avenues in pediatric cancer

- Integration of proteomic data with other 'omics' data reveals signaling pathways in metastatic prostate cancer.

- Patient-specific hierarchy of clinically actionable pathways for therapy.

Future Directions

- Integrative methods for variant interpretation
- Pathway ID for sub-clones & stroma & immune, etc
- Formal causal models to reveal pathway “weaknesses”
- Single cell (e.g. cfDNA) pathway analysis for early detection

UCSC Integrative Genomics Group

Evan Paull

Vlado Uzunangelov

Kiley

Yulia Newton

David Haan

Artem Sokolov

James Durbin

Robert Baertsch

Chris Wong

Acknowledgments

David Haussler

UCSC Genome Browser Staff

- David Haussler
- Mark Diekins
- Melissa Cline
- Jorge Garcia
- Erich Weiler

Ted Goldstein

UCSC Medbook Team

- Ted Goldstein

UCSC Cancer Genomics

- Jing Zhu
- Sofie Salama
- Teresa Swatlowski
- Brian Craft

Jing

UCSC Tree House Project

- Olena Morozova
- Melissa Cline

Olena Morozova

UCSF / Buck Institute for A

Chris Benz,

- Chris Benz, Buck
- Christina Yau, Buck
- Denise Wolf, UCSF
- Laura van't Veer, UCSF
- Eric Collisson, UCSF

Collaborators

- Chuck Perou, UNC
- Katie Hoadley, UNC

Witte Lab

- Justin Drake, (now at Rutgers)
- Owen Witte, HHMI

ORACLE PCF LINCS

NSF Hitach

STAND UP TO CANCER

THE CANCER GENOME ATLAS