

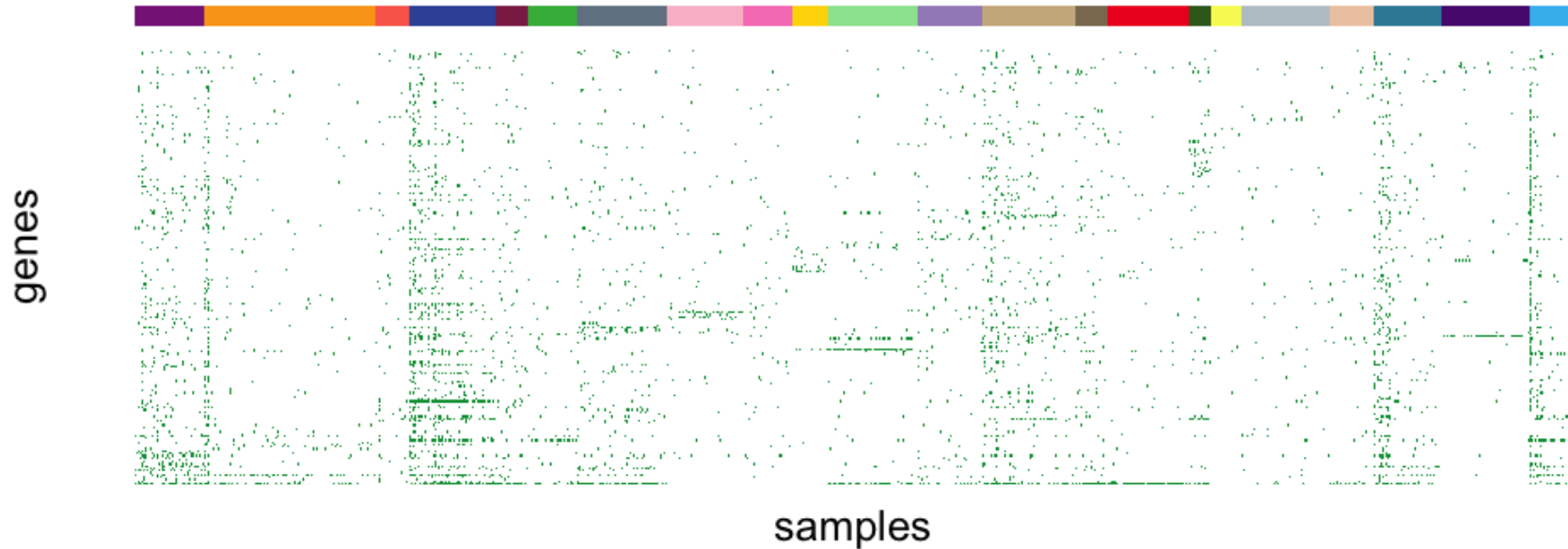
# Mutational interactions define novel cancer subgroups

## Can they inform precision oncology?

Jack Kuipers, ETH Zürich  
4th June 2019

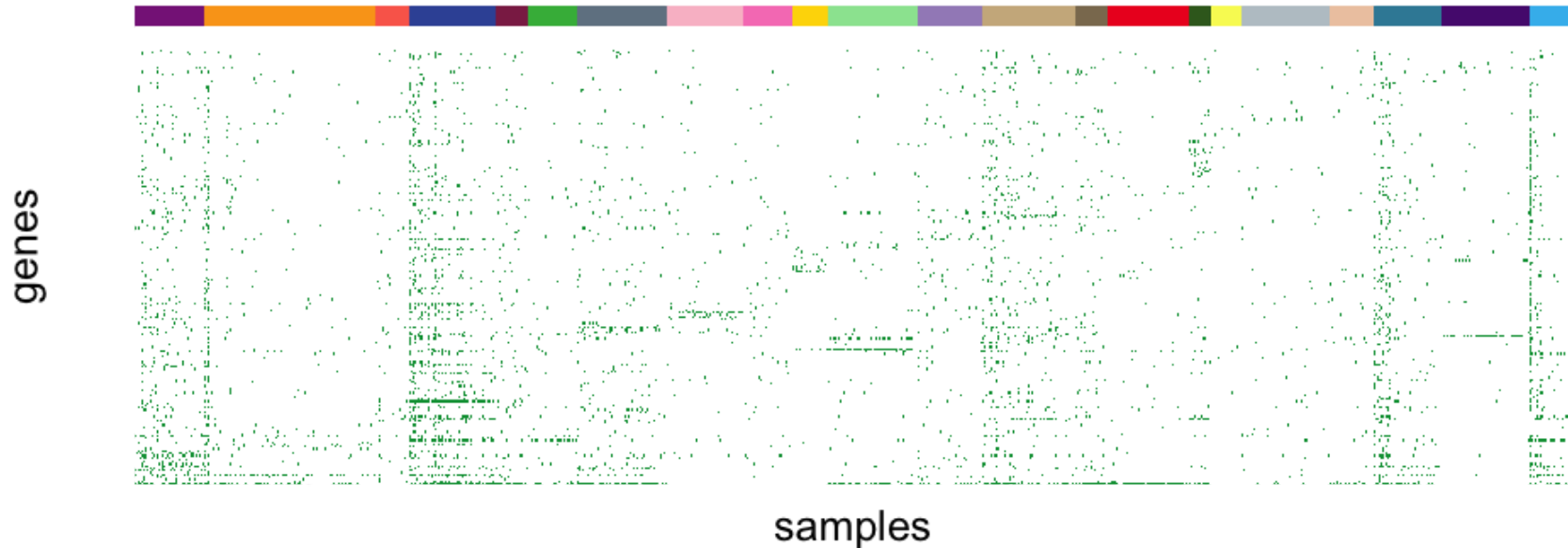
Thomas Thurnherr, Giusi Moffa, Polina Suter, Jonas Behr  
Ryan Goosen, Gerhard Christofori & Niko Beerenwinkel

# TCGA mutations



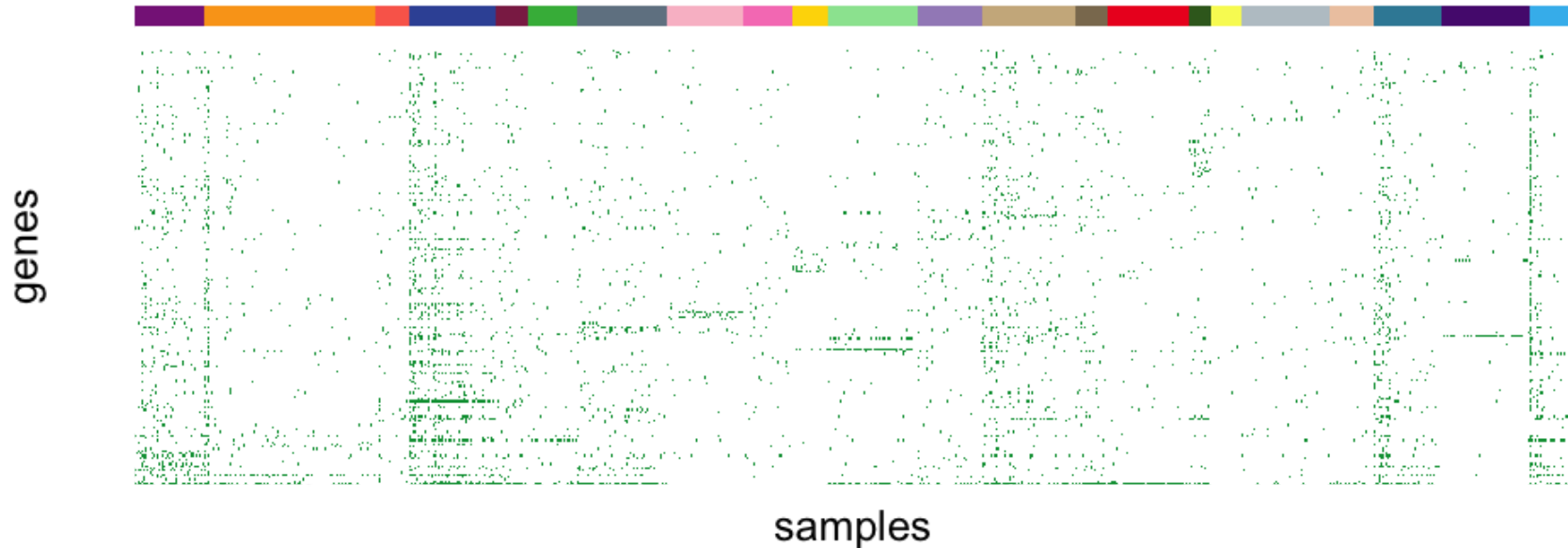
- characterize mutation patterns within and across cancer types
  - correlations and interactions
  - generative model

# TCGA mutations



- characterize mutation patterns within and across cancer types
  - correlations and interactions
  - generative model
- cluster patient samples by mutation profiles
  - survival prediction
  - precision treatment?

# TCGA data



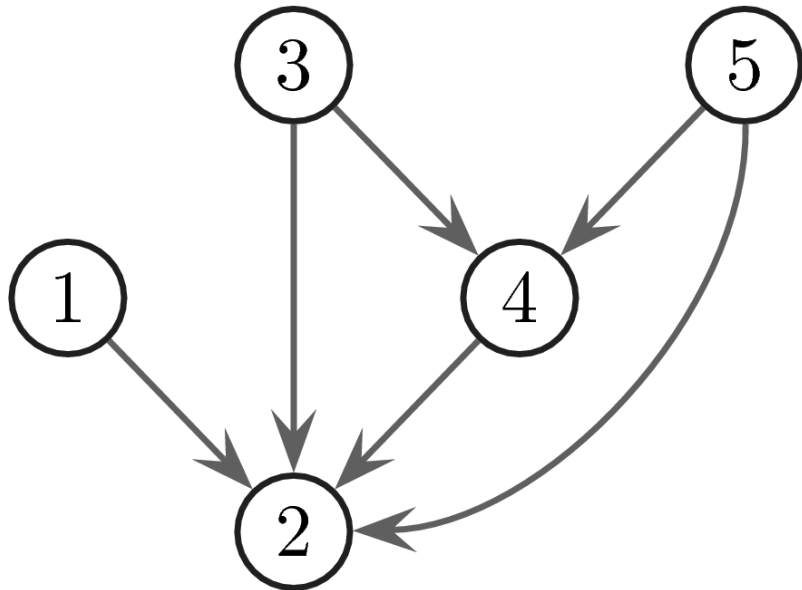
- characterize mutation patterns within and across cancer types
  - correlations and interactions
  - generative model
- 22 cancer types [with more than 100 samples](#)
  - 8198 patients
- 16 most significantly mutated genes per cancer type [MutSig2CV](#)
  - 201 genes

# Bayesian networks

Underlying structure comprised of DAGs

Directed Acyclic Graphs

- random variable on each node  
regressed on parents
- edges encode conditional dependencies

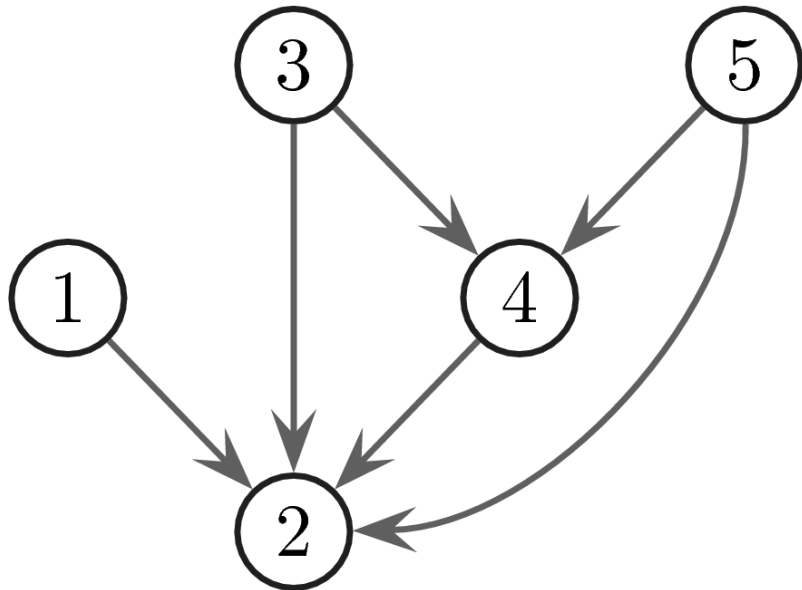


# Bayesian networks

Underlying structure comprised of DAGs

Directed Acyclic Graphs

- random variable on each node  
regressed on parents
- edges encode conditional dependencies



DAGs can be:

- generated recursively

Robinson, 1970, 1973

|    |                   |
|----|-------------------|
| 1  | 1                 |
| 2  | 3                 |
| 3  | 25                |
| 4  | 543               |
| 5  | 29281             |
|    | ...               |
| 21 | $\approx 10^{80}$ |

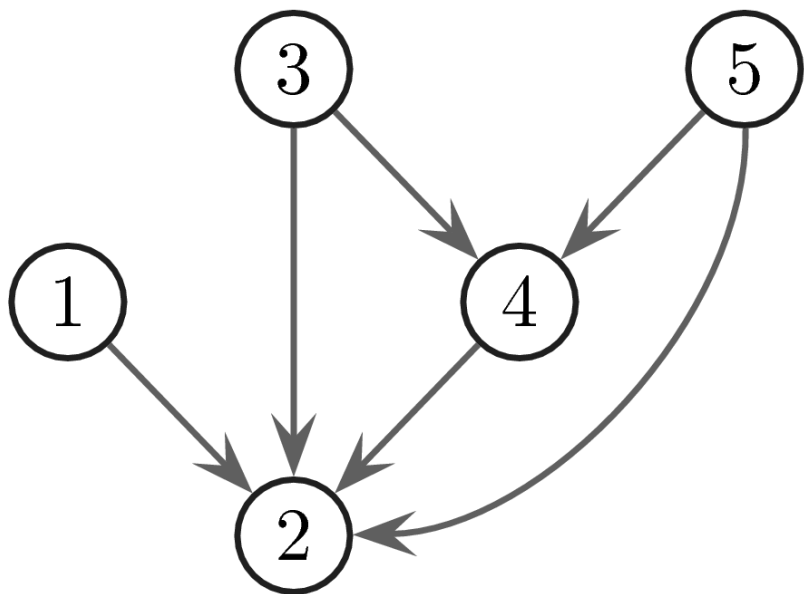
- sampled uniformly

Kuipers and Moffa, Stats Comp 2015

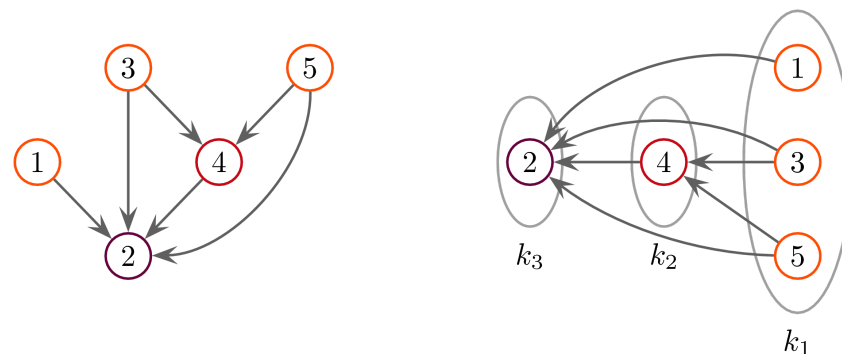
# Partition MCMC

Underlying structure comprised of DAGs

- random variable on each node  
regressed on parents
- edges encode conditional dependencies



Rearrange DAG as ordered partition



Build MCMC on space of partitions

- join or break elements
- swap nodes between them

Unbiased sampling

Kuipers and Moffa, JASA 2017

# Larger Bayesian network inference

Speed up inference for large DAGs by filtering parents [arXiv:1803.07859](https://arxiv.org/abs/1803.07859)

- filter with independence tests

[PC algorithm, Spirtes, Glymour and Scheines, 2000](#)

- allow one additional parent
- MCMC search and score

## Example

- 20 nodes
- 200 observations
- 80 repetitions
- 1.4 expected number of parents

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Speed up inference for large DAGs by filtering parents [arXiv:1803.07859](https://arxiv.org/abs/1803.07859)

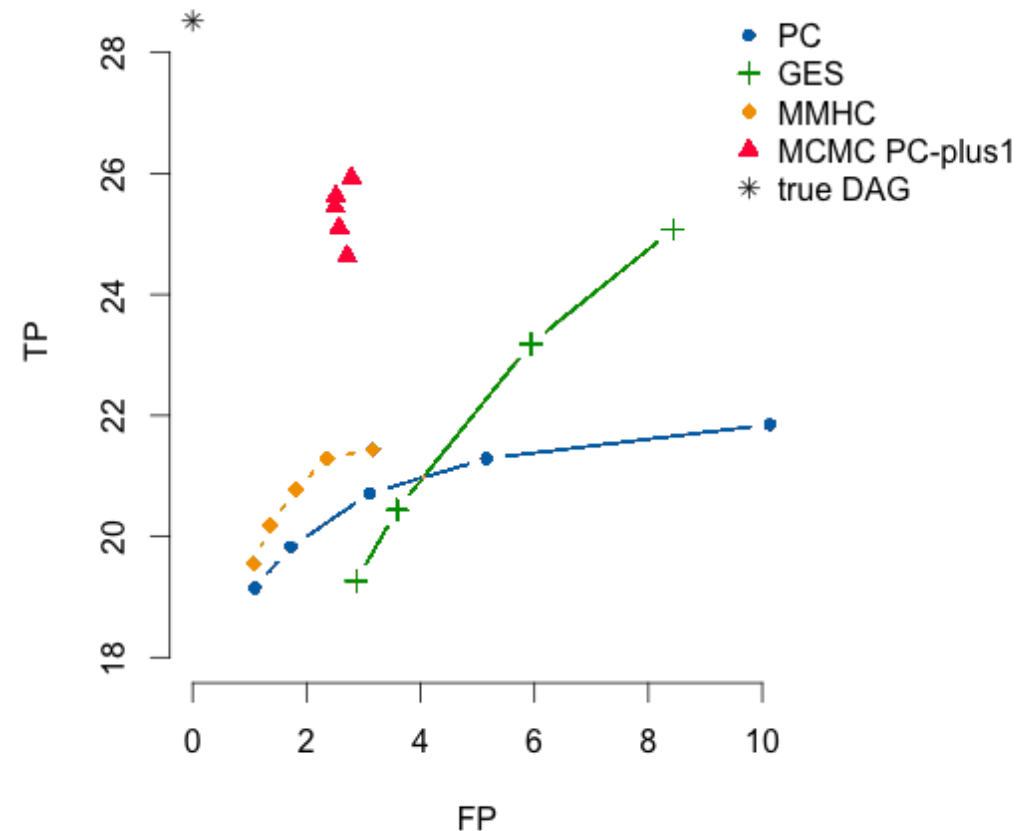
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## Example

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GES: Greedy equivalent search

[Chickering, JMLR 2002](#)

MMHC: Max-min hill climbing

[Tsmardinos, Brown and Aliferis, ML 2006](#)

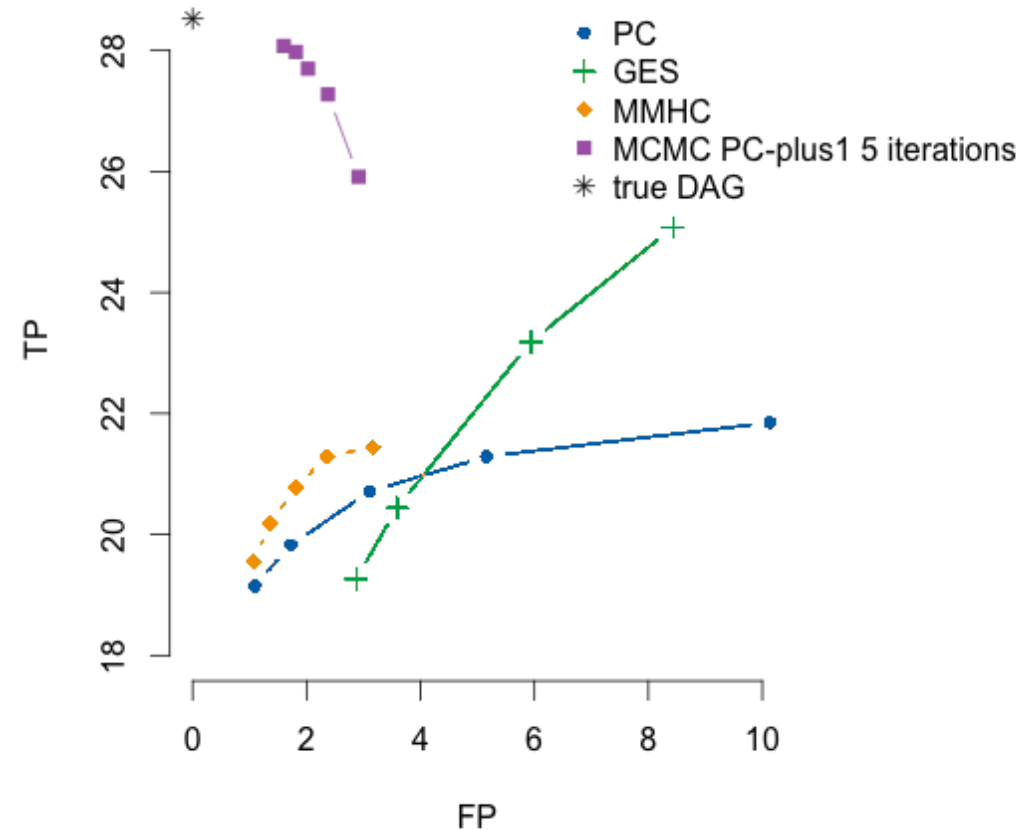
# Iterative improvement

Speed up inference for large DAGs by filtering parents [arXiv:1803.07859](https://arxiv.org/abs/1803.07859)

- filter with independence tests  
[PC algorithm, Spirtes, Glymour and Scheines, 2000](#)
- allow one additional parent
- iteratively improve search space

## Example

- 20 nodes
- 200 observations
- 80 repetitions
- 1.4 expected number of parents



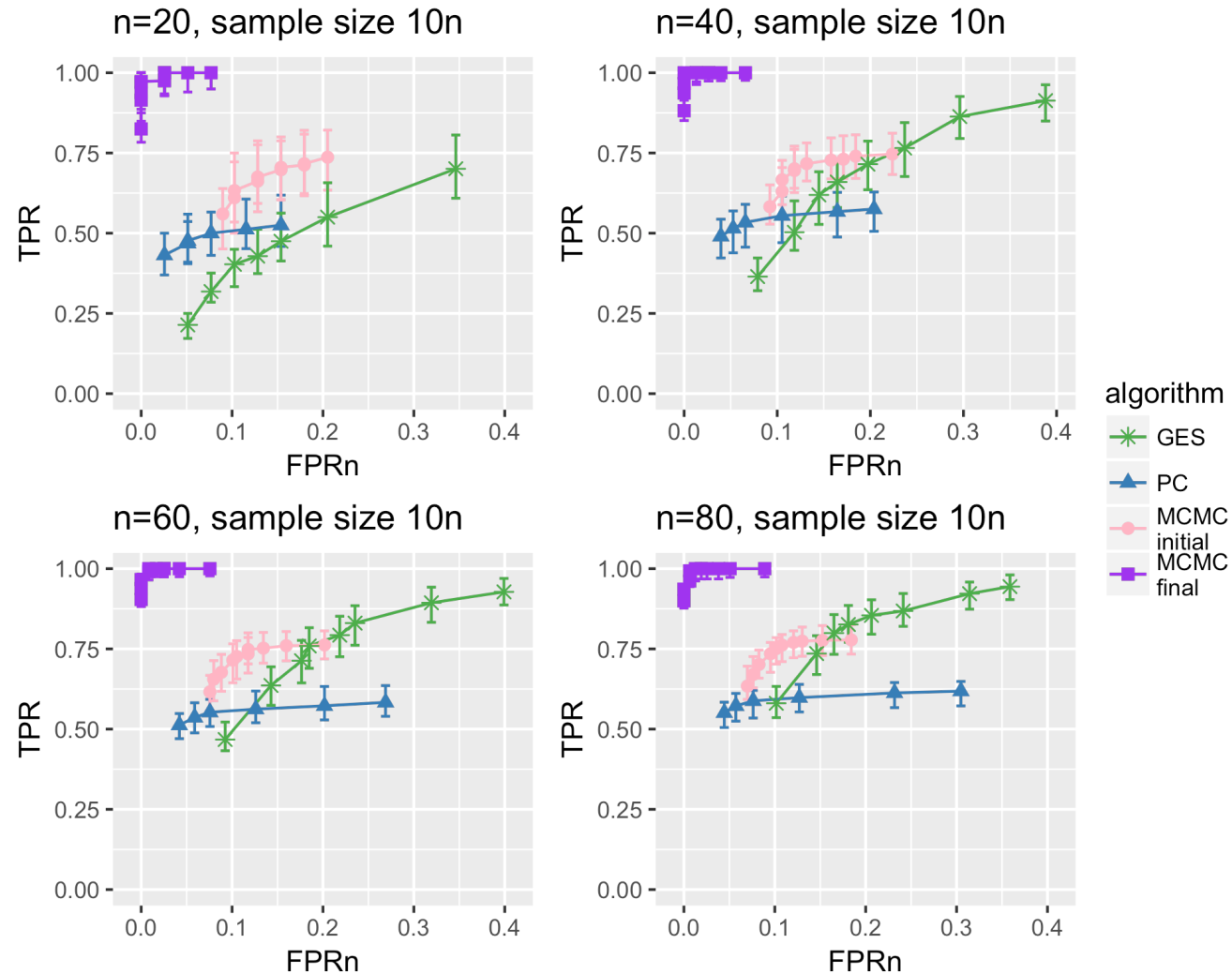
GES: Greedy equivalent search

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[Tsmardinos, Brown and Aliferis, ML 2006](#)

# Larger DAGs



# BDe score

Bayesian Dirichlet equivalent (BDe) score

Heckerman and Geiger, UAI 1995

Binary case for DAG  $G$

- node  $X$  with  $m$  parents  $Y$
- each state of  $Y$  has parameter  $\theta_Y$

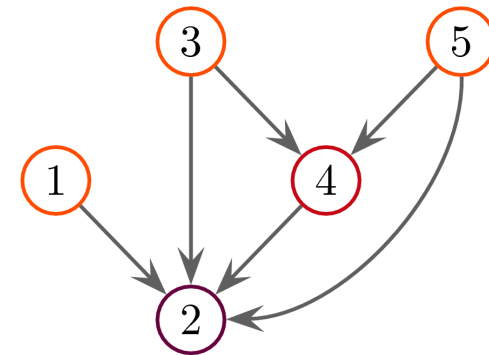
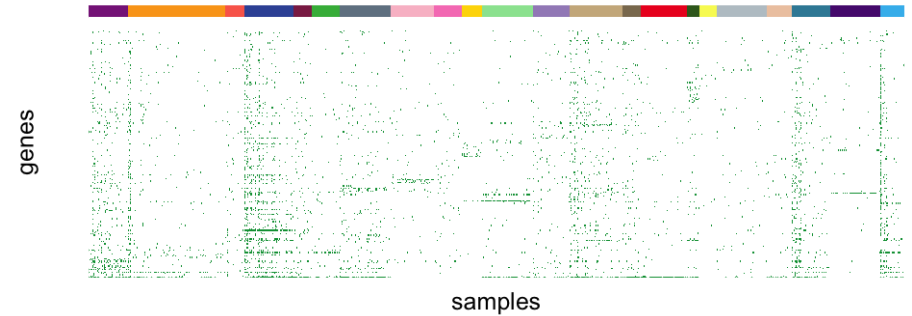
$$P(X = 1|Y) = \theta_Y$$

- beta prior on  $\theta$  with hyperparameter

$$\alpha = \beta = \frac{\chi}{2^m}$$

BDe metric is marginal likelihood  $P(D|G)$

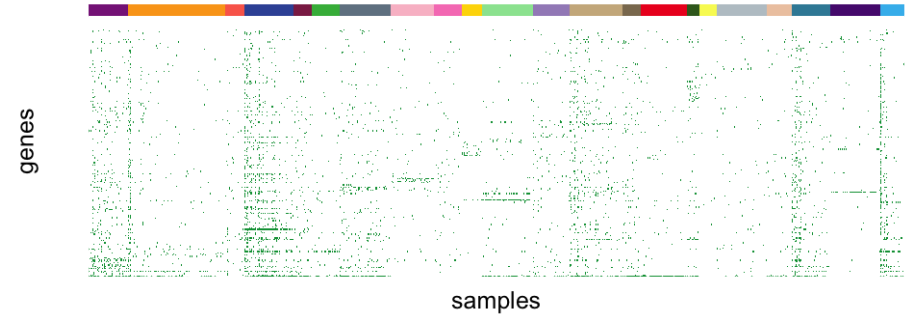
BDe score is posterior  $P(G|D)$



# TCGA graph sampling

For each cancer type

- sampled 100 DAGs from posterior
- edge prior from STRING



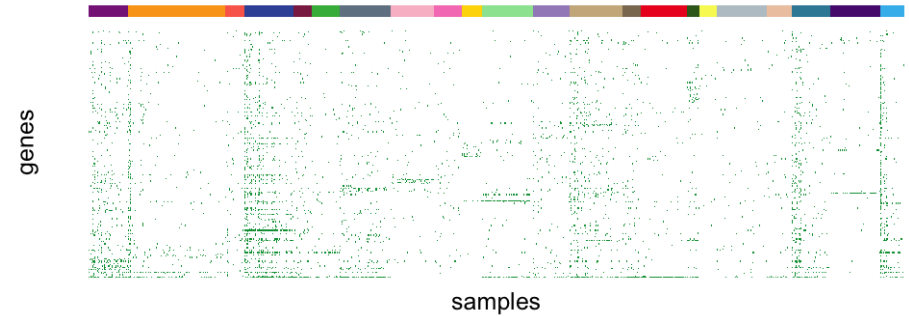
# TCGA graph sampling

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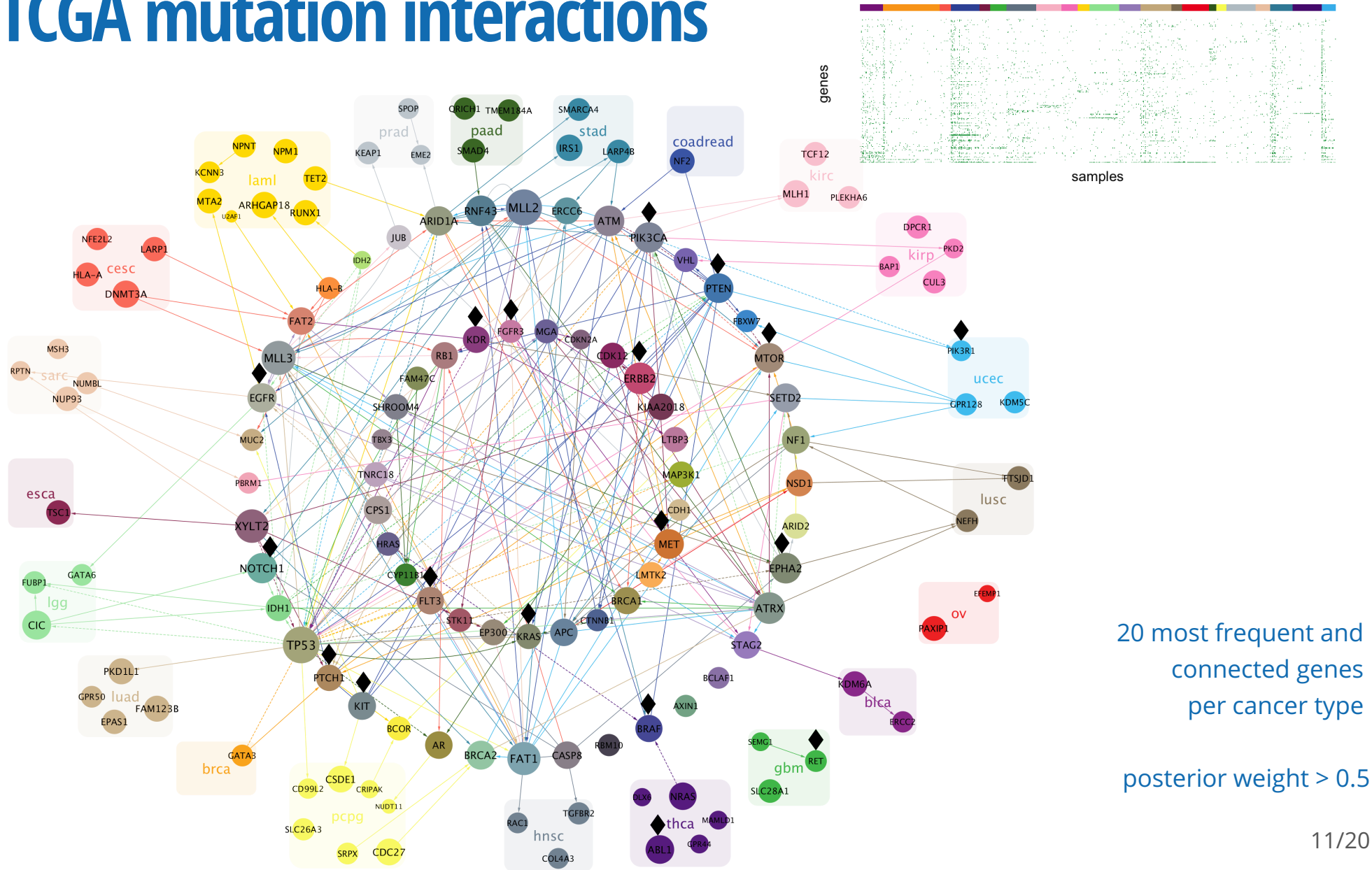
- sampled 100 DAGs from posterior
- edge prior from STRING

To visualise networks:

- Select edges
  - posterior weight  $> 0.5$
- Select 20 most frequent and connected genes
  - frequency  $\times$  edges
- Extract subnetwork
  - colour edges by cancer type
  - overlay



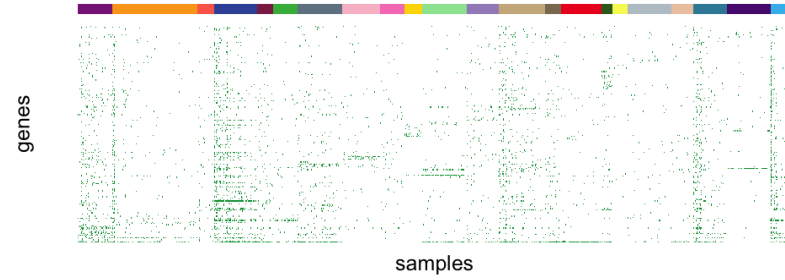
# TCGA mutation interactions



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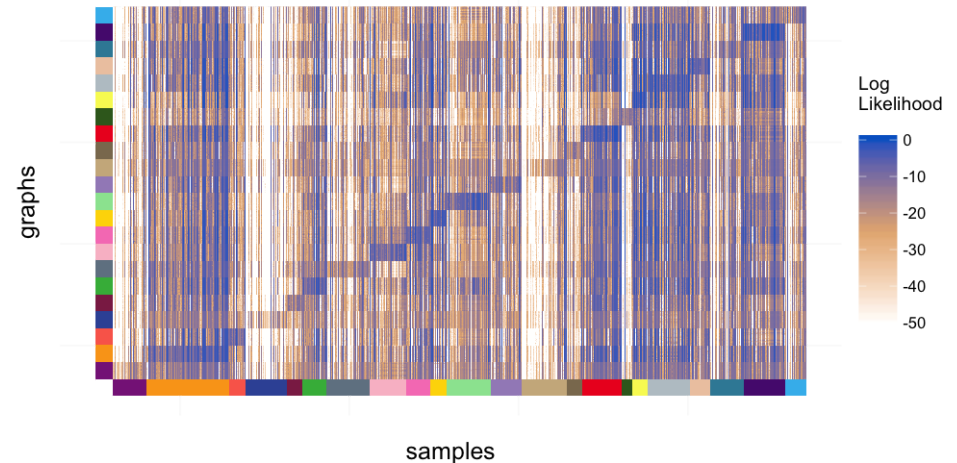
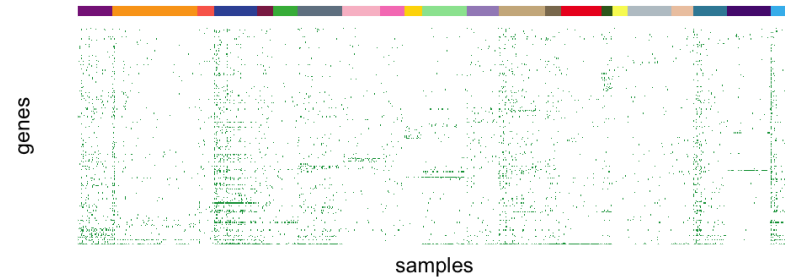
To visualise heterogeneity:

- Fit each patient sample to each graph

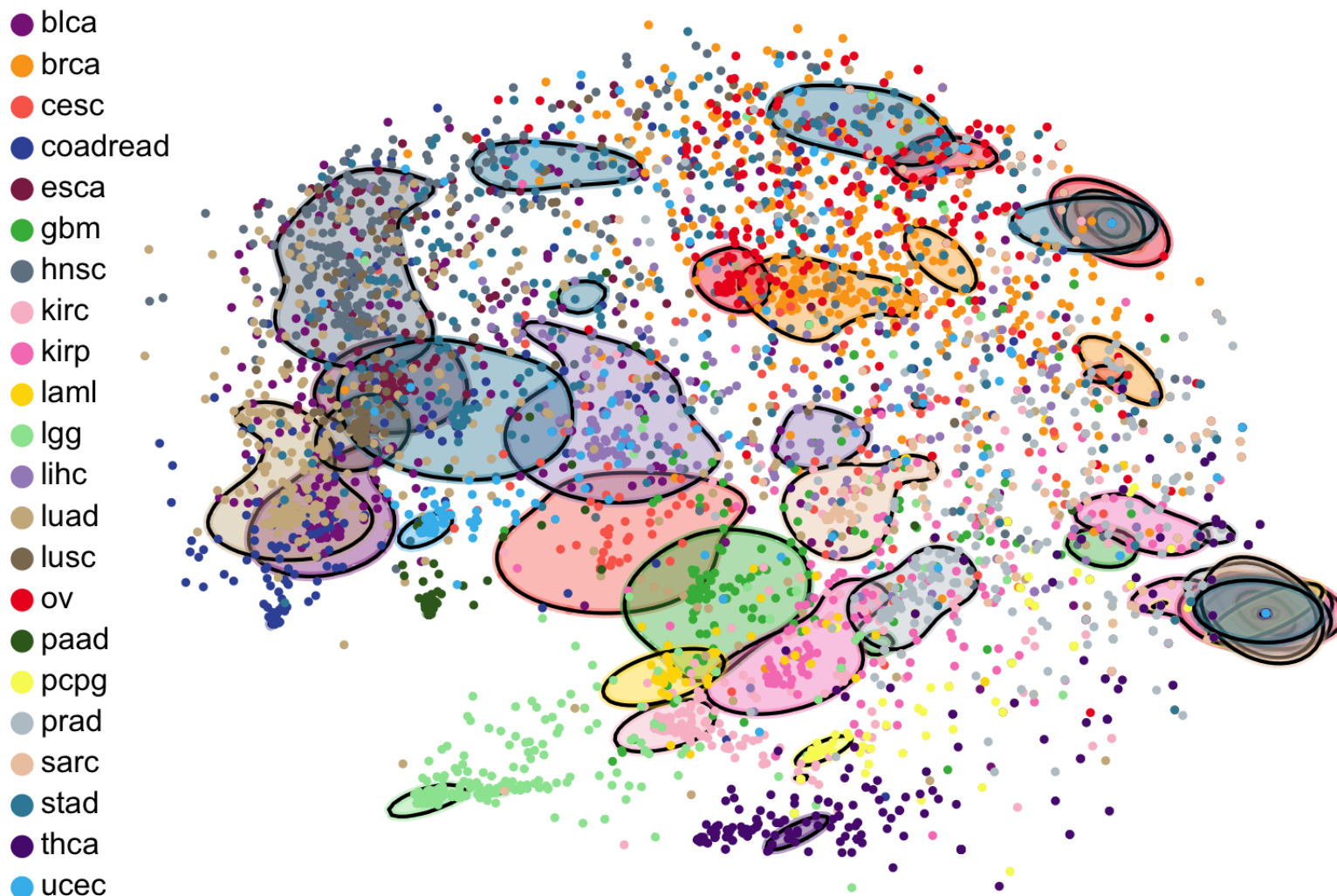
$$P(D_i|G_j, \bar{\theta}_j)$$

using posterior means  $\bar{\theta}$

- Calculate Jensen-Shannon divergence between columns
  - distance between patient samples
  - project to 2D



# Inter-patient heterogeneity



# EM MAP mixture model clustering

Weight patient samples into  $k$  groups

- compute MAP relative sizes  $\tau$
- learn MAP DAG  $G, \theta$  for each
- reweight patient samples

$$\propto \tau_j P(D_i | G_j, \bar{\theta}_j)$$

- repeat till convergence

Latent  $Z$  indicates which graph model each patient sample derives from

$$D_i | (Z_i = j) \sim (G_j, \theta_j)$$

$$P(Z_i = j) = \tau_j$$

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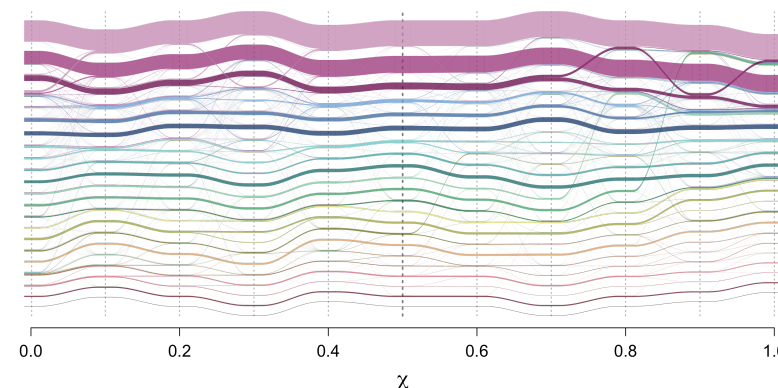
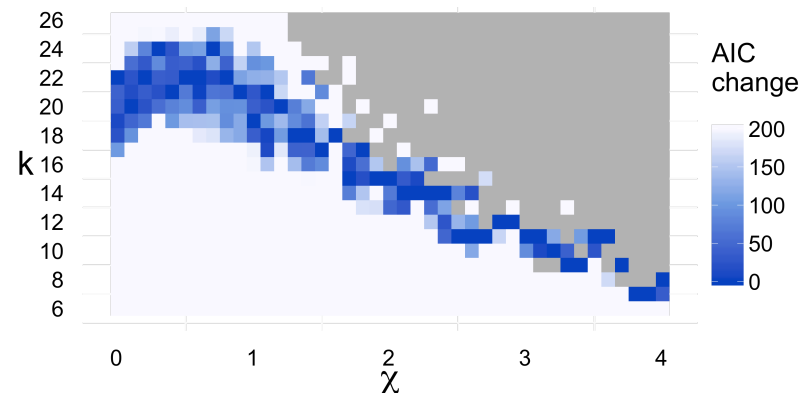
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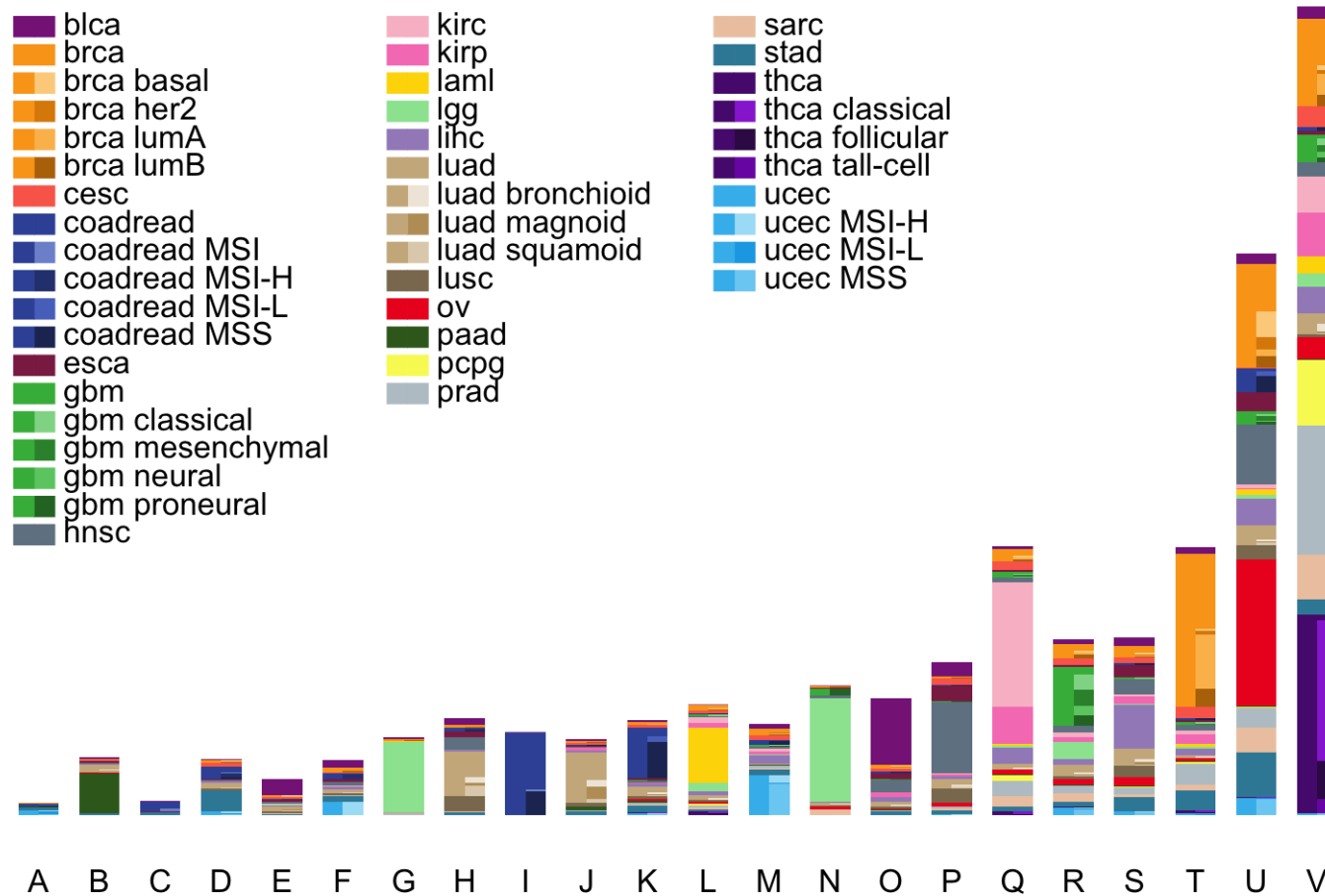
$$P(Z_i = j) = \tau_j$$

Start with no edges [parameter learning](#)



- find 22 clusters for  $\chi = 0.5$

# Graphical clustering



- alternative stratification?

# Survival analysis

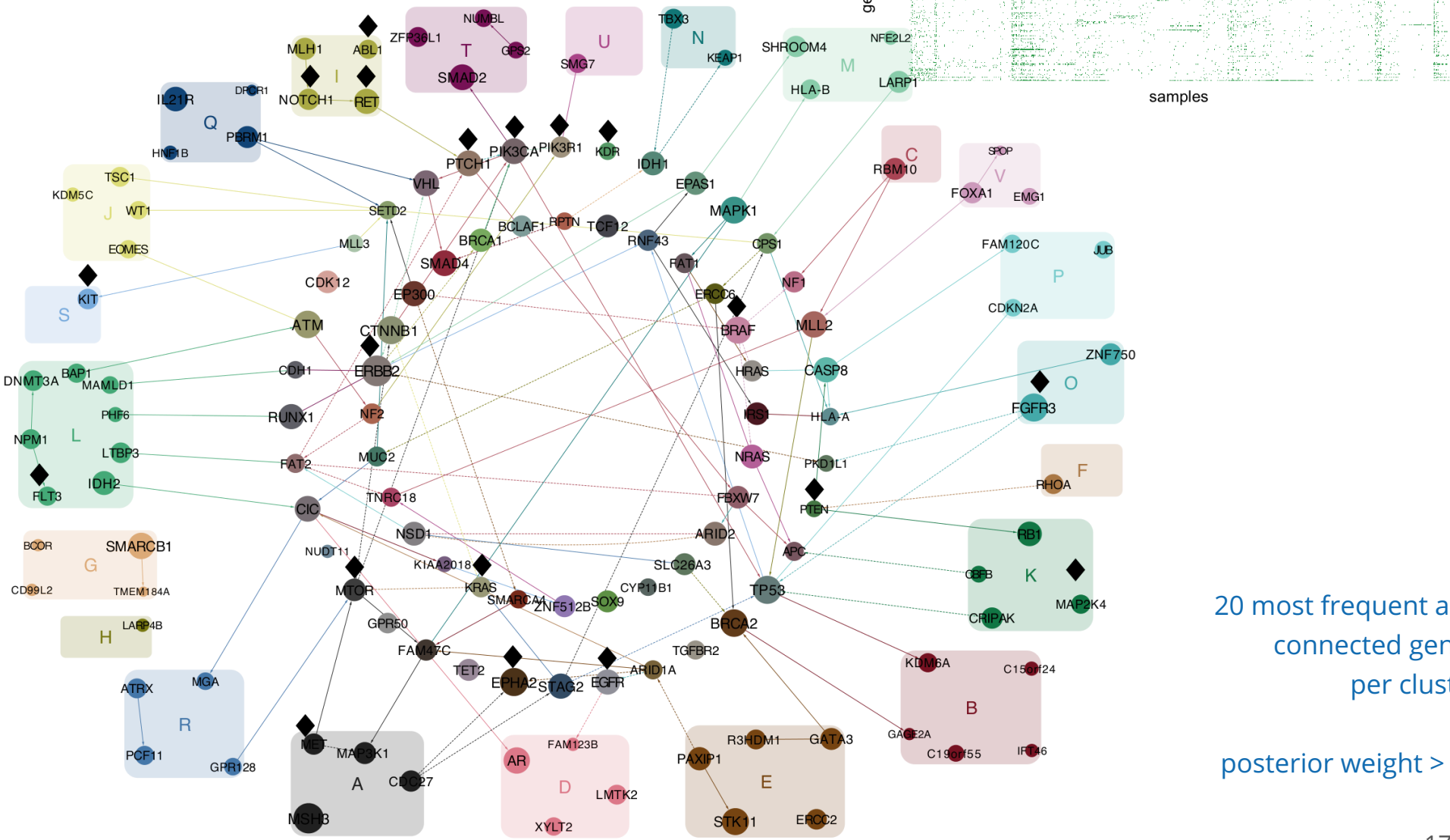
Check if clusters based on mutational profiles are a significant survival predictor

- above age, stage and cancer type

| METHOD                                            | UNCORRECTED LR | CORRECTED LR | P-VALUE              |
|---------------------------------------------------|----------------|--------------|----------------------|
| Hierarchical clustering (Hamming distance)        | 11.4           | 5.7          | 0.95                 |
| Non-negative matrix factorisation                 | 104.7          | 12.7         | 0.23                 |
| K-means                                           | 172.0          | 29.8         | $1.5 \times 10^{-5}$ |
| Gaussian mixture model (Mclust)                   | 205.6          | 33.1         | $1.4 \times 10^{-6}$ |
| Bernoulli mixture model (no edges, $\chi = 0$ )   | 240.9          | 34.0         | $7.5 \times 10^{-7}$ |
| Bernoulli mixture model (no edges, $\chi = 0.5$ ) | 242.4          | 35.7         | $2.1 \times 10^{-7}$ |
| Graphical clustering (edges, $\chi = 0.5$ )       | 253.0          | 37.0         | $7.6 \times 10^{-8}$ |

- Likelihood ratio (LR) from Cox proportional hazard regression including cluster assignment
- number of clusters fixed to 22

# TCGA cluster graphs



20 most frequent and  
connected genes  
per cluster

posterior weight > 0.5

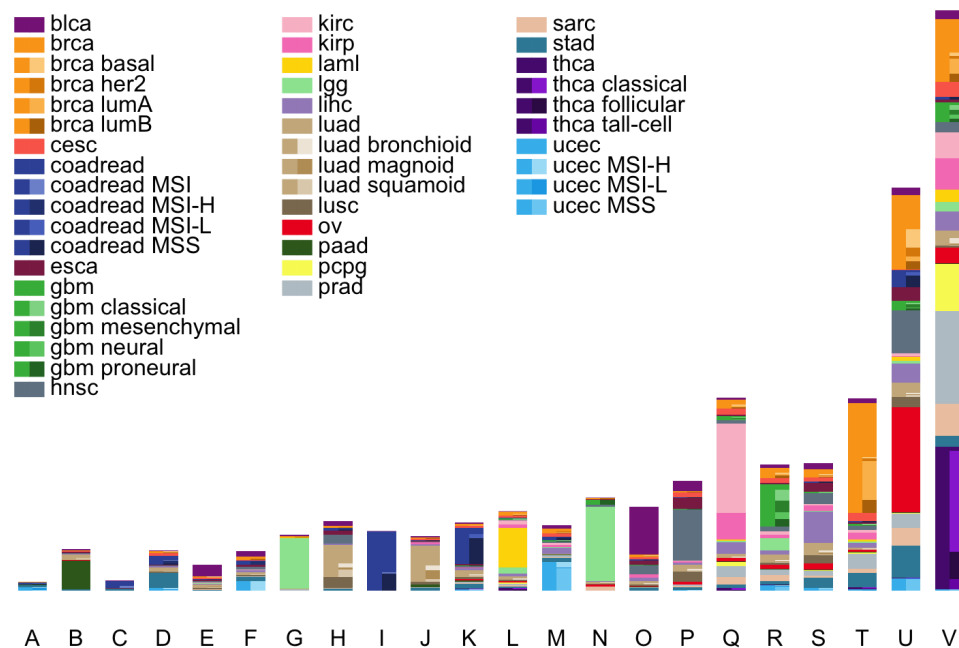
# Towards precision oncology?

Can cluster mutation profiles

- recapitulate a lot of clinical information

Want to integrate clinical covariates

- cluster conditionally



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Want to integrate clinical covariates

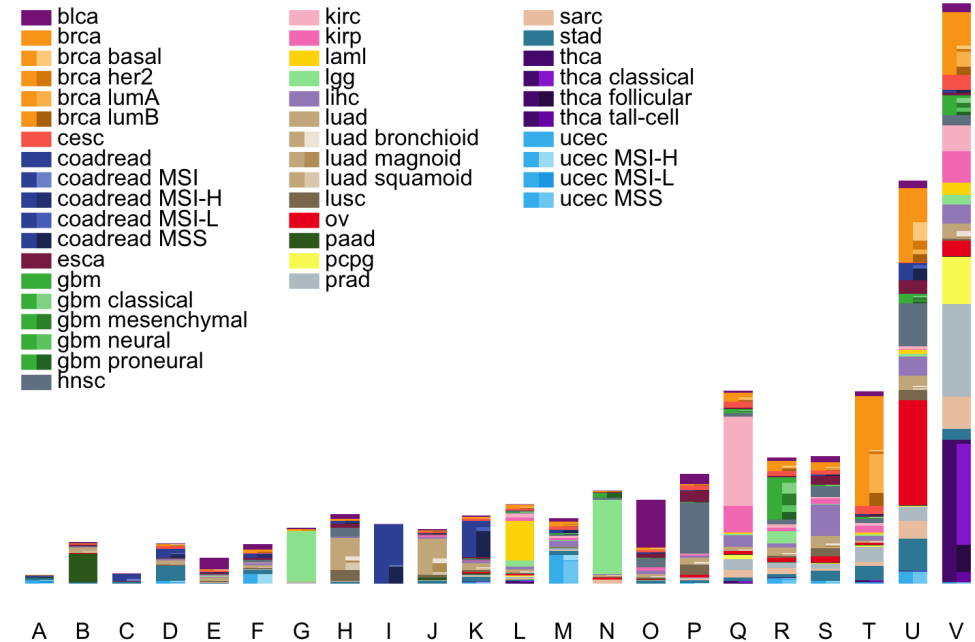
- cluster conditionally

Want to link to drug response

- cell line data [GDSC](#)

Want to integrate further data

- expression
- copy number aberrations
- methylation



# Tumour progression

Tumours are heterogeneous

- complex clonal structure

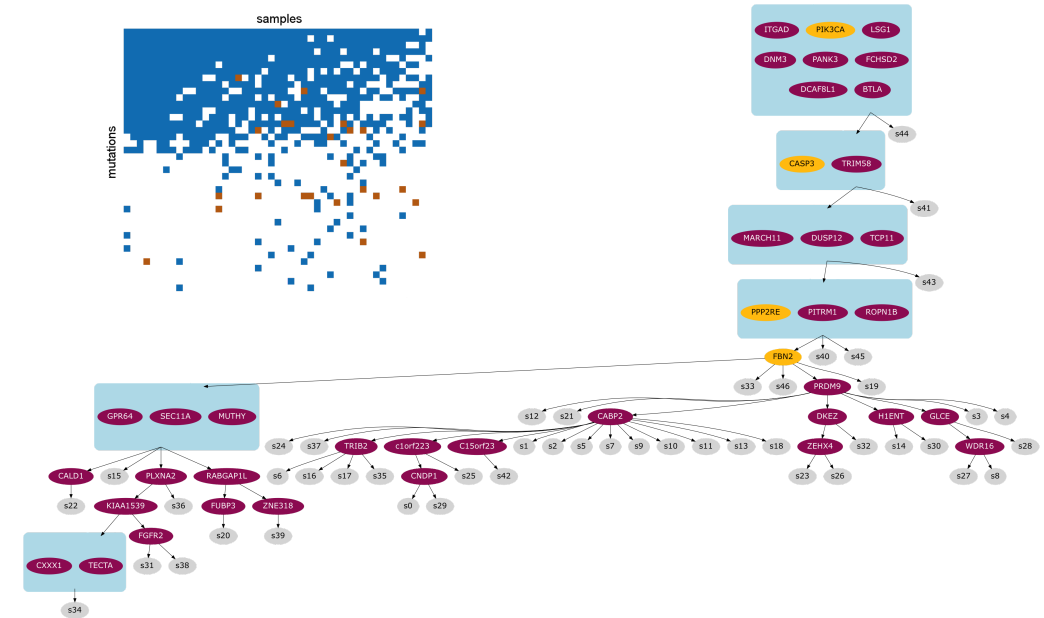
They evolve

- over time
- under treatment

Mutation profiles were a single snapshot!

Should account for

- clonal structure
- tumour progression



Data [Wang ... Navin, Nature 2014](#)

Inference [Jahn, Kuipers and Beerenwinkel, GB 2016](#)

# Summary

Can use partitions to sample DAGs [JASA 2017](#)

Extend to larger networks [arXiv:1803.07859](#)

Applied to pancancer mutations [NC 2018](#)

- supervised cancer type networks
- unsupervised clustering

## Outlook

- integrate clinical data?
- integrate other data modalities?
- tumour progression and heterogeneity?

