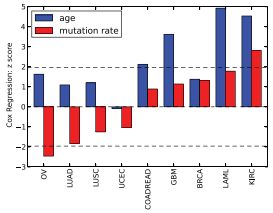
Attributing Genomic Events to Cancer

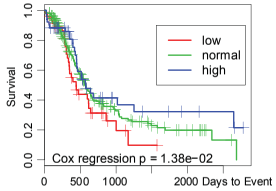
Problem	What events lead to cancer?
Intuition	Successful events are selected for in tumorigenesis.
Solution	Look for over-represented or mutually exclusive events.

Problem	What events differentiate people with cancer?
Intuition	Different types of patients should have different clinical and molecular phenotypes.
Solution	Stratify cohort, look for changes in phenotype.

Global Variables are Associated with Survival



Z-scores for age and mutation-rate association with patient survival assessed by Cox regression.



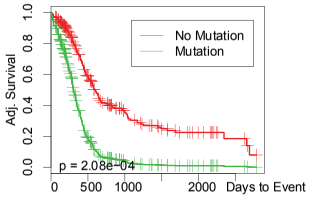
Patients stratified by mutation rate in the **Ovarian** cohort. Here low and high represent +/- 1 standard deviation from the mean.

Cox Proportional Hazards Model Adjusts Global Covariates

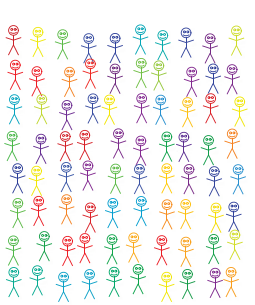
- Non-parametric survival function adjusted with parametric covariates
- Assumption of time-independence of covariates
- Assumes a proportional increase with increasing values of covariates (linear in log- space)

```
model = Surv(time, event) ~ covariates + interactions
```

	hazard ratio	p-value
pathway	3.10	0.0002
age	1.01	0.0740
rate	0.67	0.0033
pathway:age	0.99	0.7071
pathway:rate	0.71	0.6077

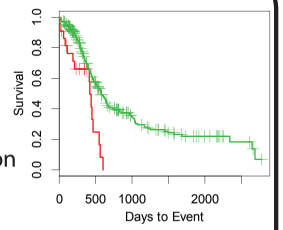


Associating Mutations with Survival

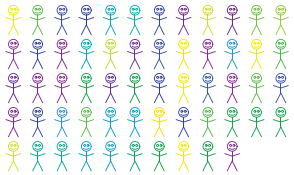


Mutated

Patient has mutation in pathway X?

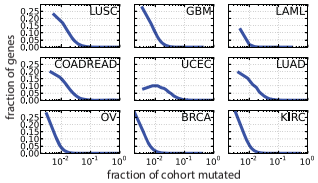


Not Mutated



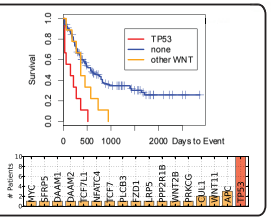
The Case for Pathways

Genetic mutations are sparse.

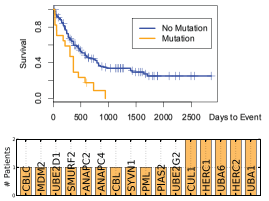


Collapsing onto pathways imprves power.

In the **LAML** dataset TP53 is mutated in 10 patients who are associated with poor survival. Expanding to the **WNT pathway** adds an additional 10 patients with a similar phenotype.



Often mutations are very sparse across the pathway but have a common effect. The **ubiquitin mediated proteolysis pathway** contains 138 genes, in **LAML** 19 of those contain mutations covering 20 patients. While this pathway is definately not under selection, taken together these patients have poor prognosis.



Many Pathways have Survival Associations

Sometimes mutations are very sparse across the pathway but have a common effect.

Conclusion

Selectivity is useful for finding genes that cause cancer, but we are also interested in markers for cancer progression and treatment success.
Integration of sparse genetic events over networks and pathways boosts our power to uncover novel targets.
Finding **associations** with clinical phenotypes allows for annotation of new genes and pathways.