Precision medicine: Panacea or false dawn?

Peter Campbell,
Wellcome Trust Sanger Institute

Disclosure Information

ESMO Meeting 2014

Peter Campbell

I have the following financial relationships to disclose:

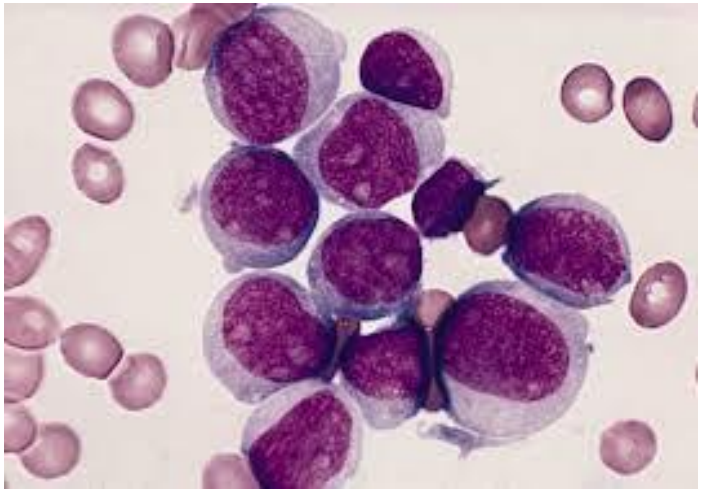
Consultant for 14M Genomics Ltd

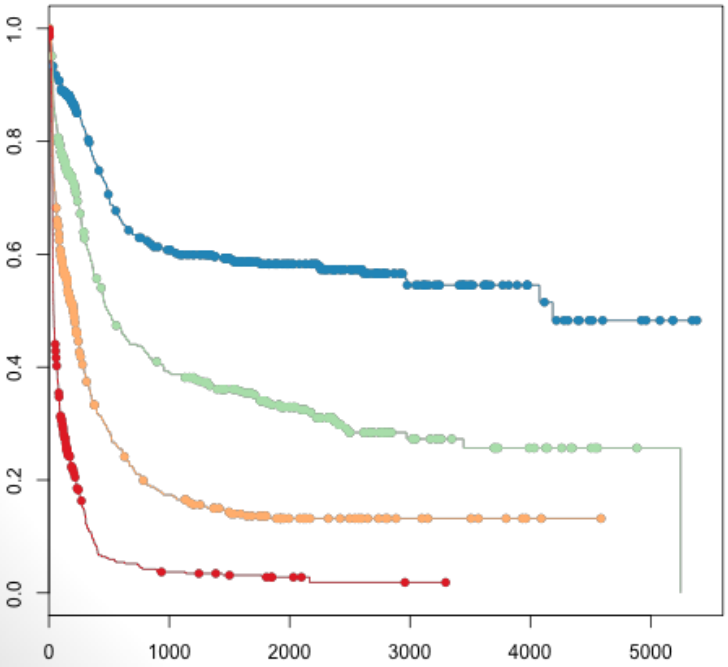
Stockholder in 14M Genomics Ltd

- and -

I will not discuss off label use and/or investigational use in my presentation.

Acute myeloid leukaemia





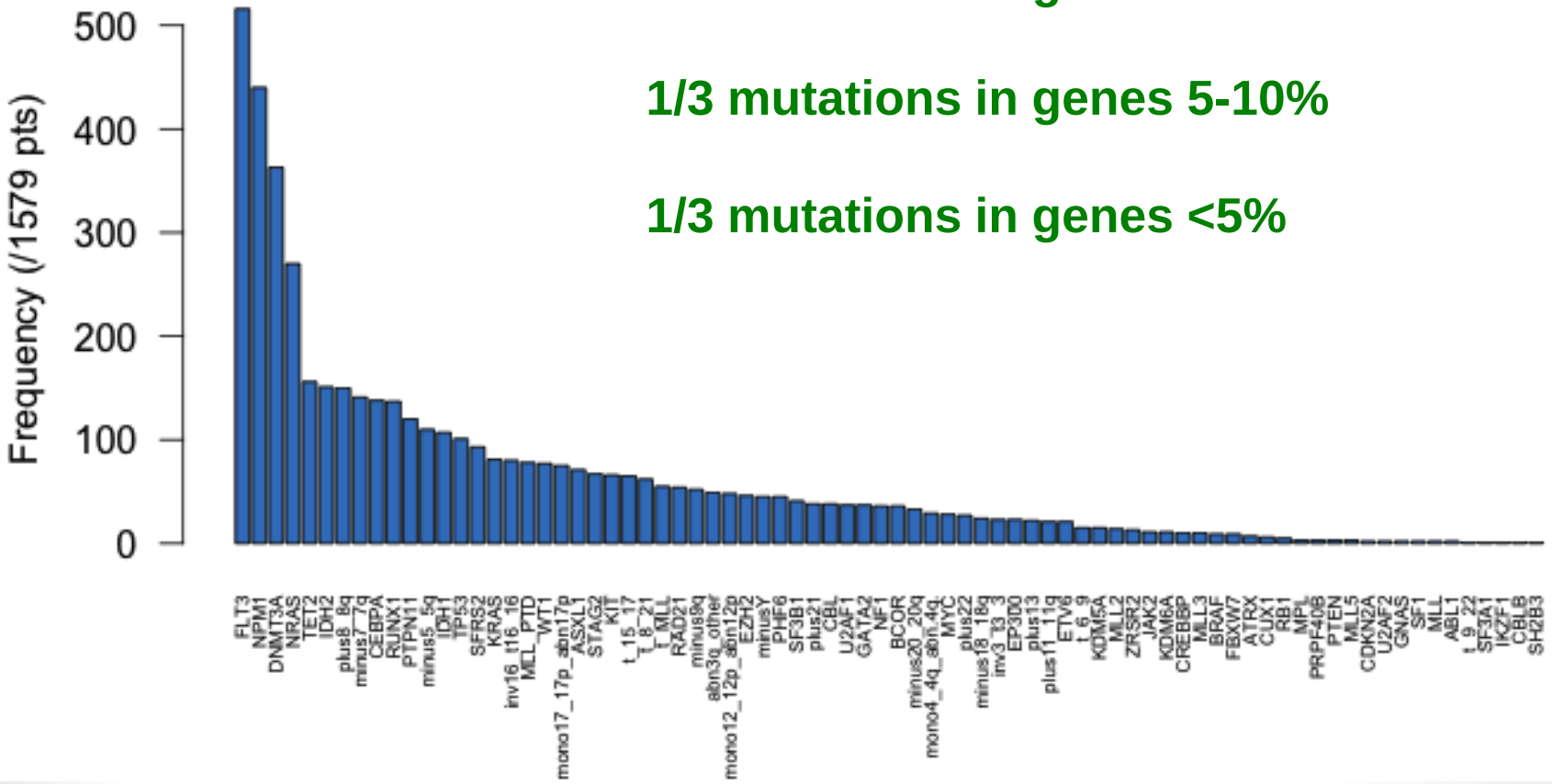
Accurate prognosis enables:

- Stratification of treatment esp bone marrow transplant
- More informed, personalised patient discussions
- Design of risk-adapted clinical trials

AML data set

- 1579 patients with AML
- Enrolled in three trials performed through the German-Austrian AML Study Group
- Long-term clinical outcome data available
- Sequenced for 110 genes involved in AML pathogenesis
- Triaged variants into:
  - Known drivers
  - Possible oncogenic
  - Variants of unknown significance (not considered here)

The long tail of cancer genes

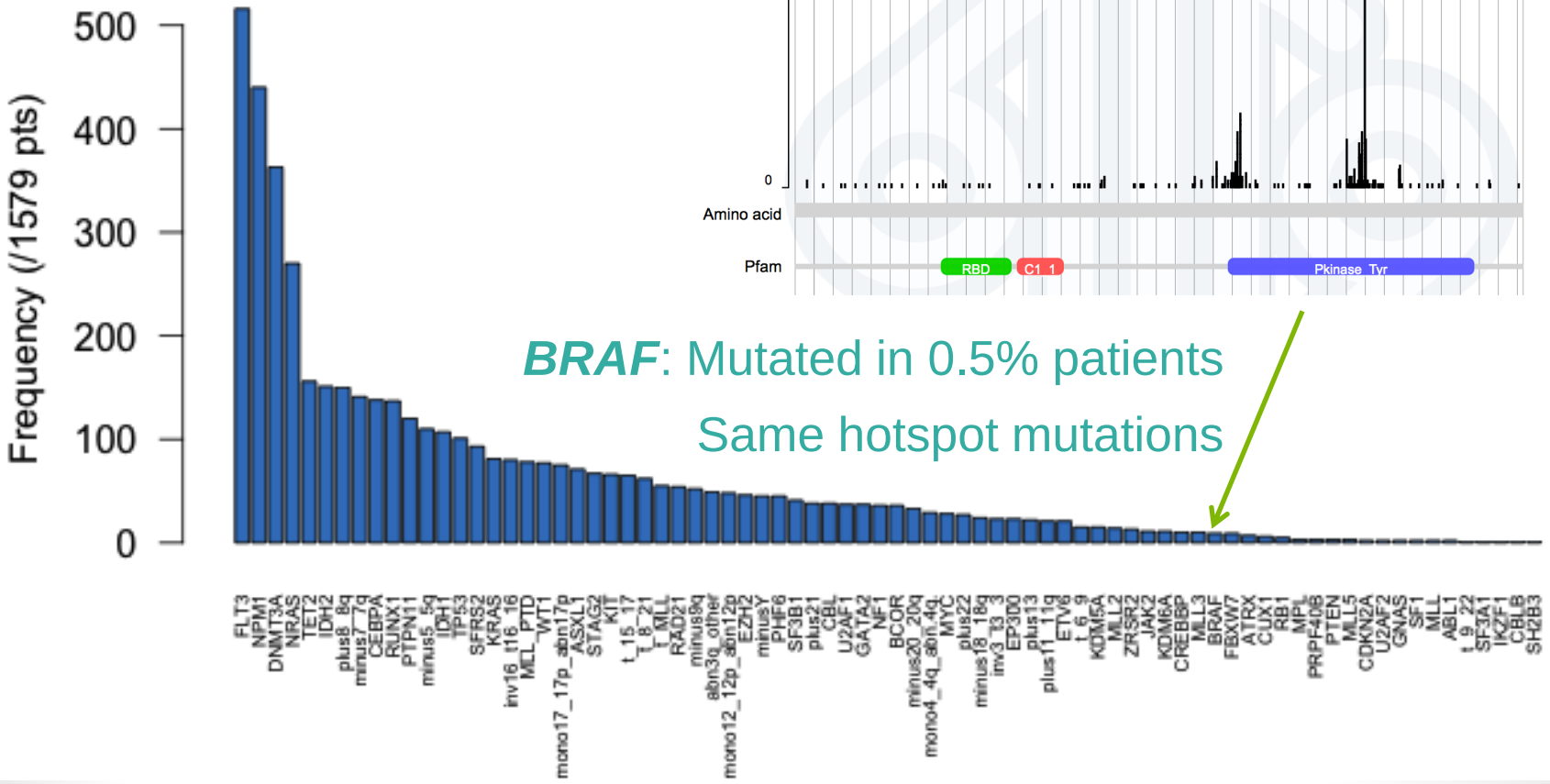


1/3 mutations in genes >10%

1/3 mutations in genes 5-10%

1/3 mutations in genes <5%

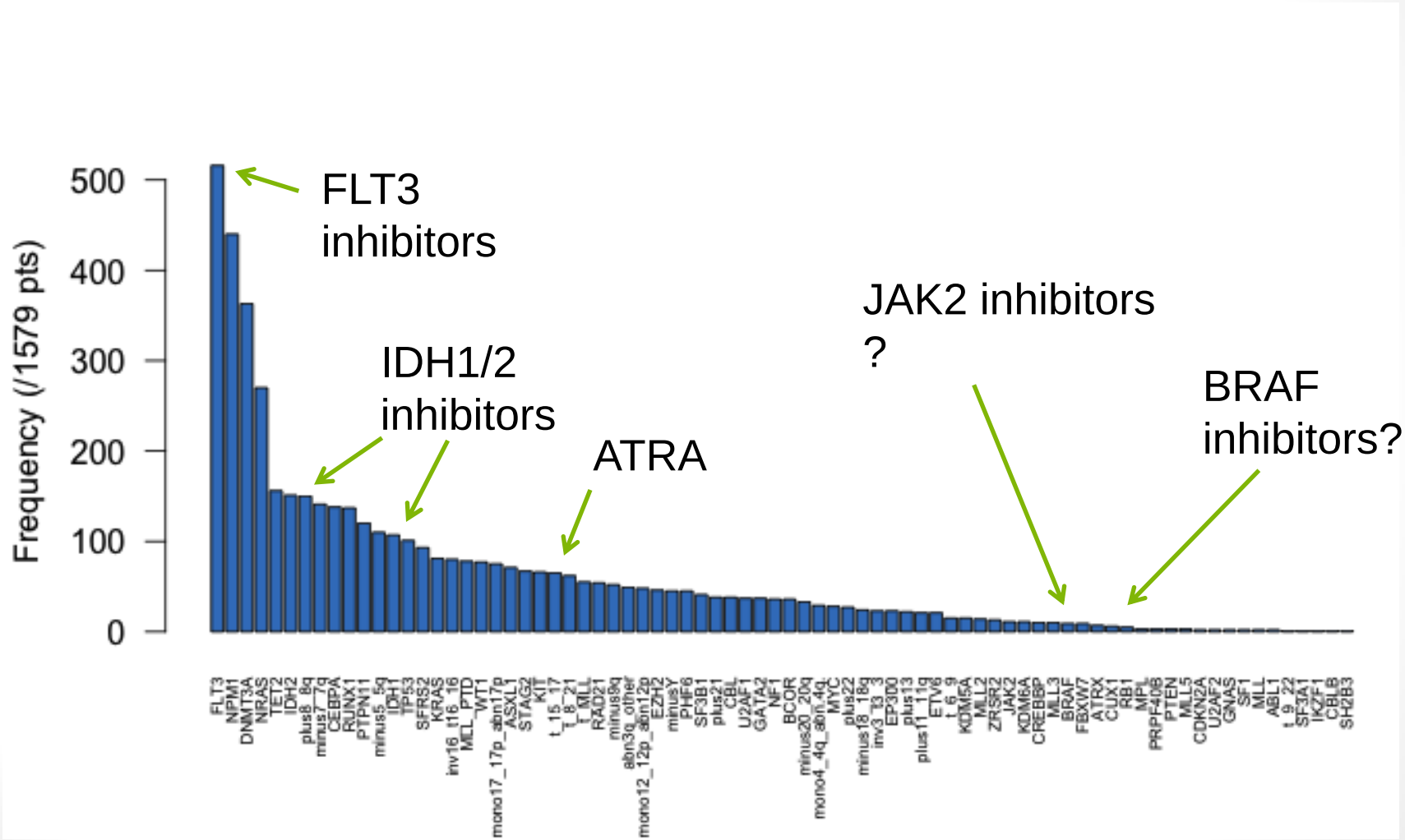
The long tail of cancer genes



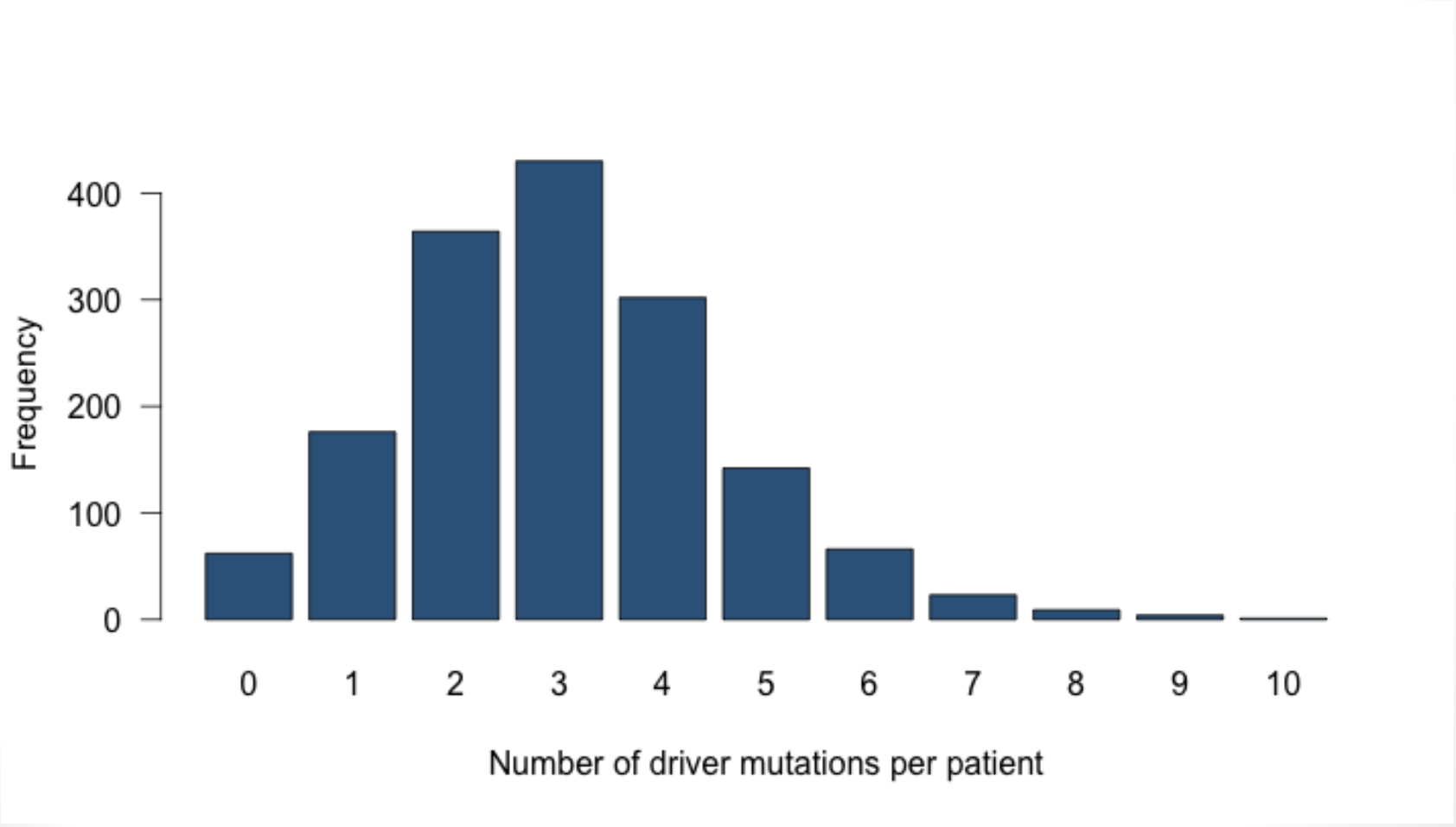
BRAF: Mutated in 0.5% patients

Same hotspot mutations

Personalised treatment

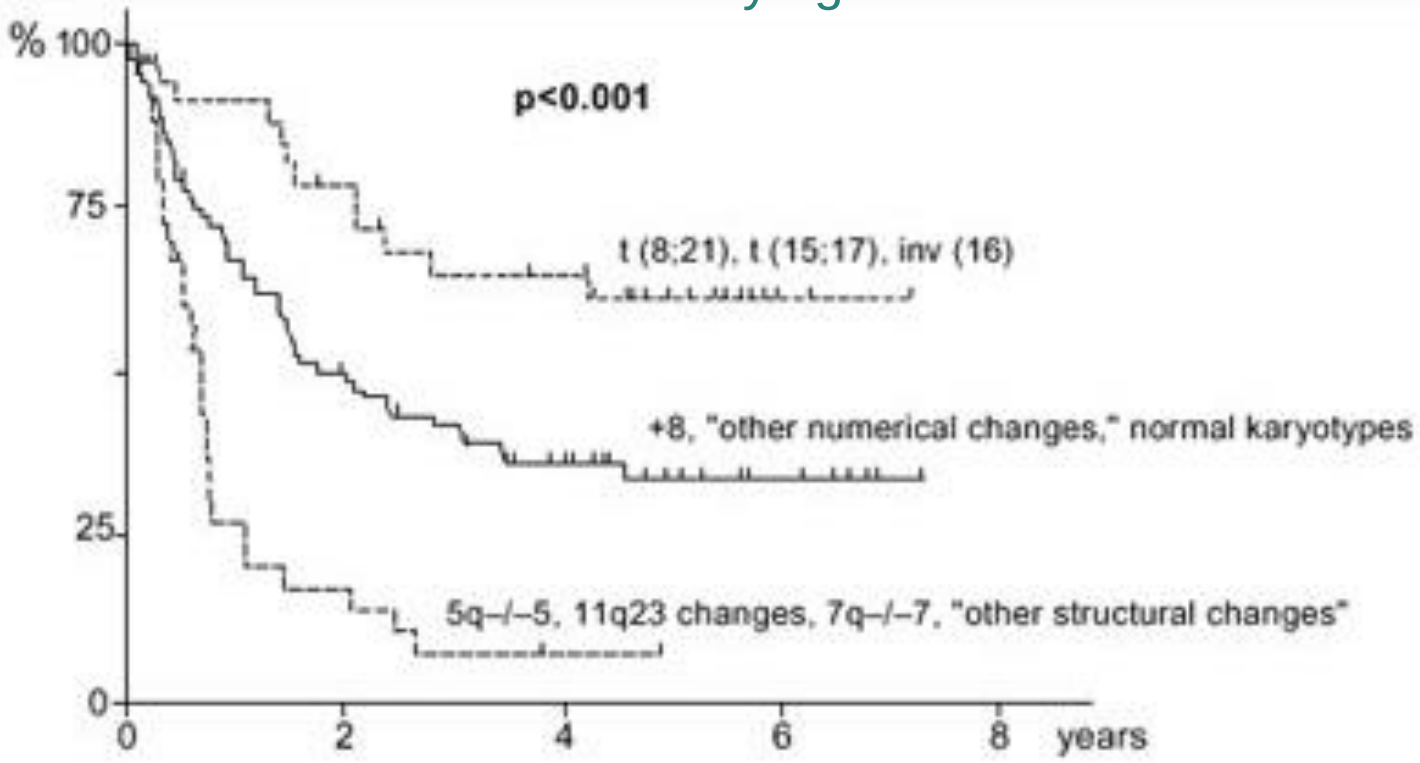


Number of mutations per patient



Using genomics to predict outcome

Cytogenetic risk stratification

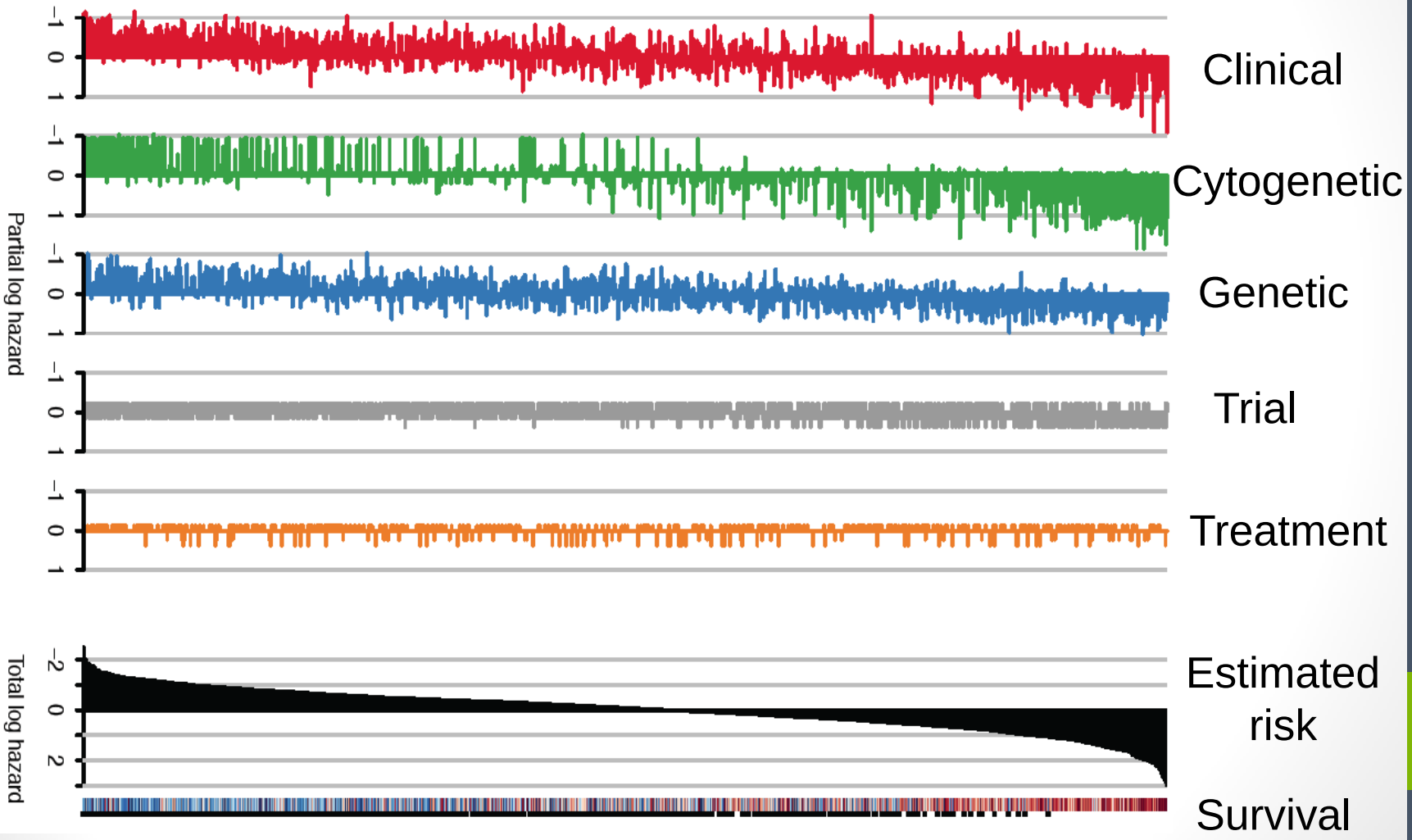


From Martin Tallman, Leukemia 1995

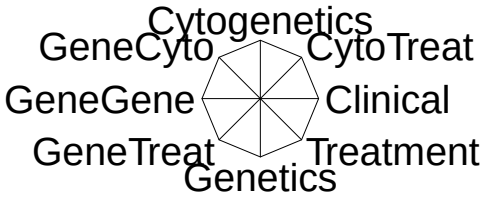
Prognostic variables in AML

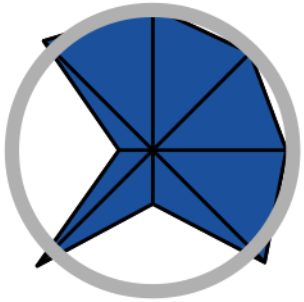
- Cytogenetics
  - For example, inv(16), t(15;17), monosomy 7 etc
- Point mutations
  - *TP53*, *NPM1*, *FLT3* etc
- Clinical variables
  - White cell count, age etc
- Gene-by-gene interactions?
- Gene-by-cytogenetic interactions?

Personally tailored risk profile



Personalised predictions

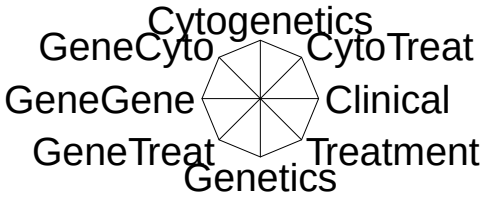


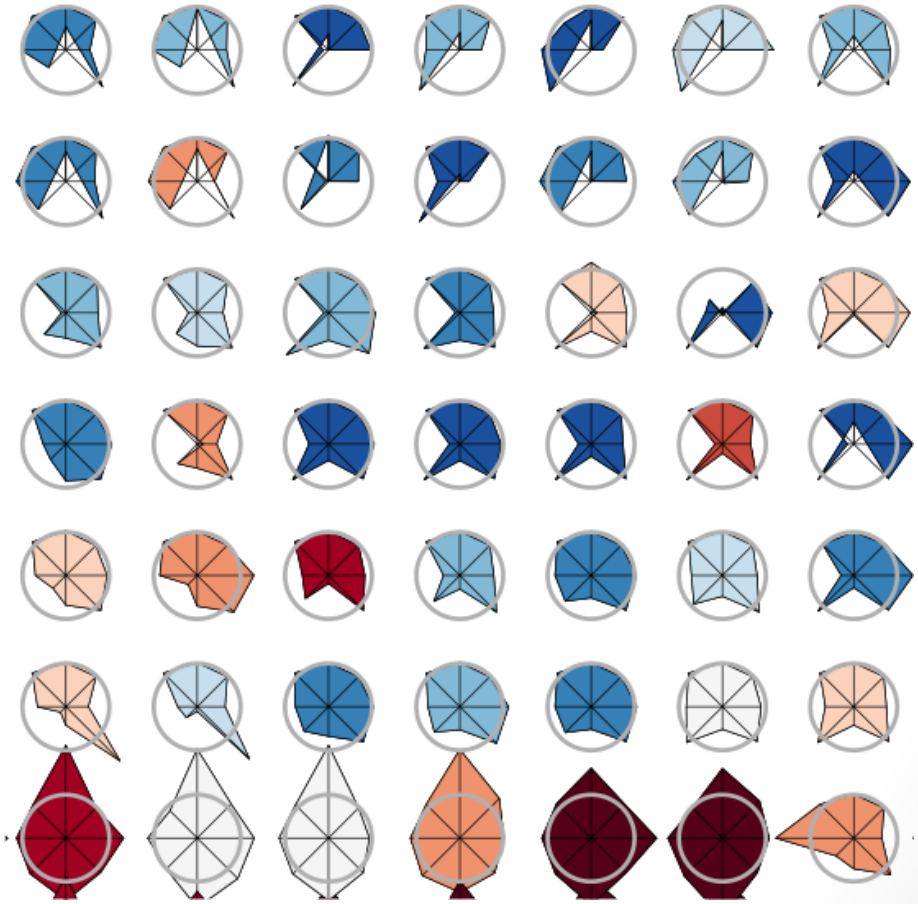


RED: short survival

BLUE: long survival

Personalised predictions

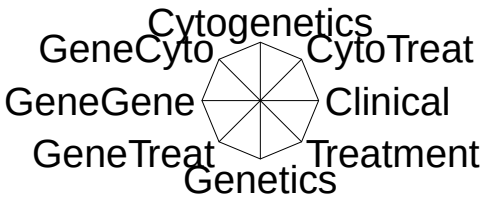


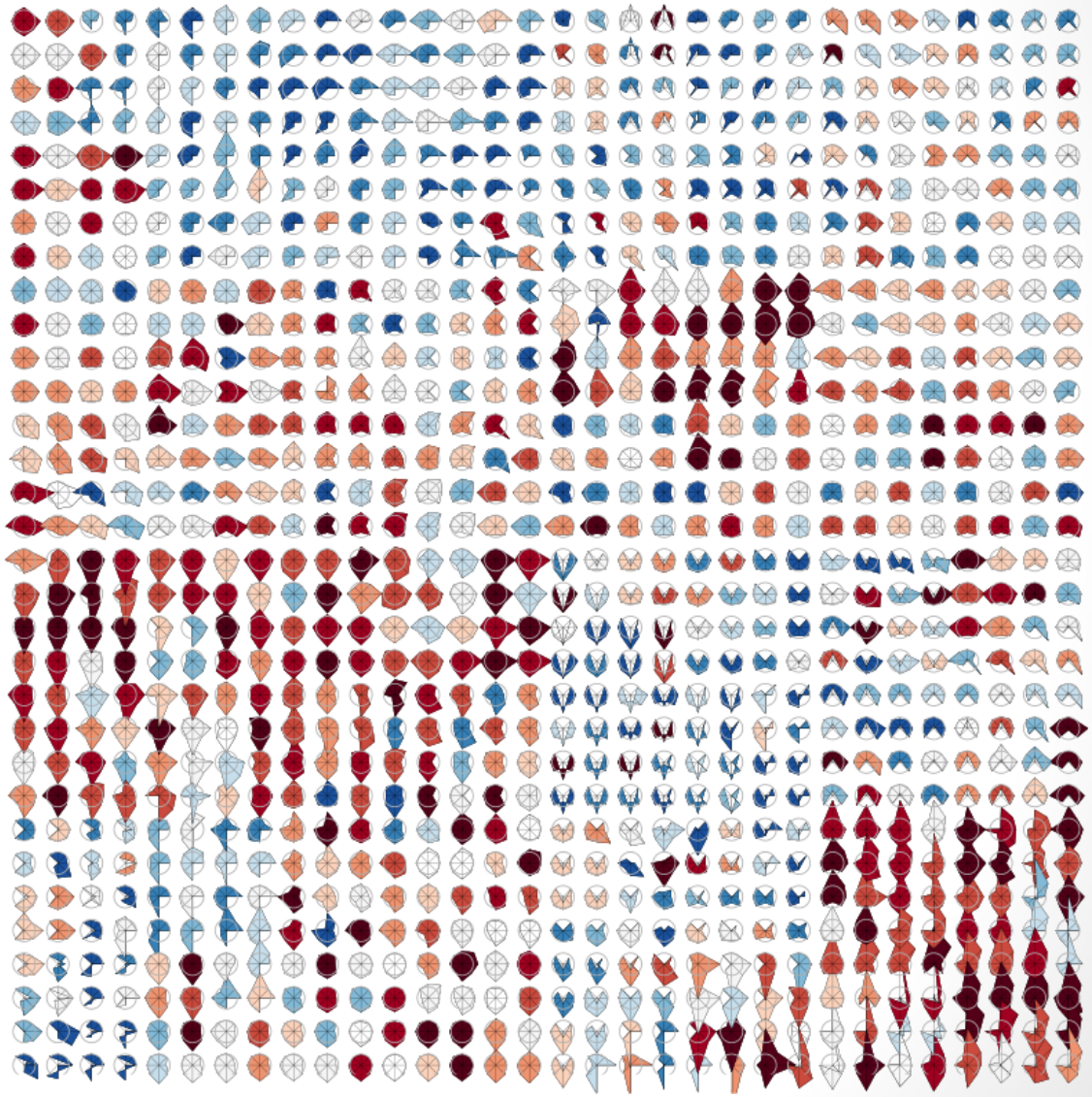


RED: short survival

BLUE: long survival

Personalised predictions

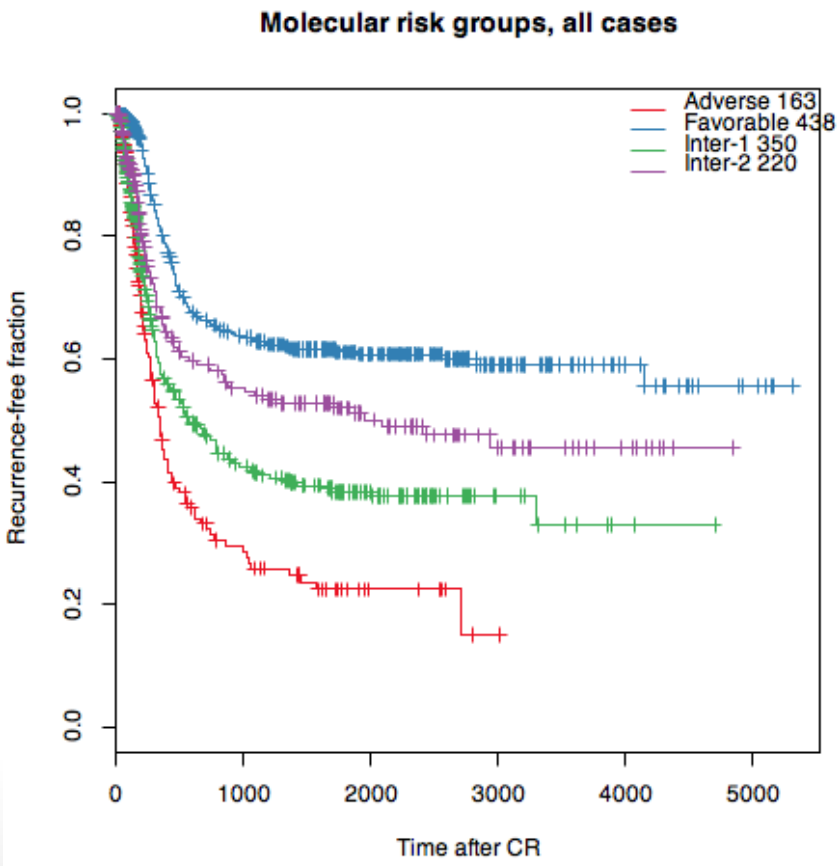




RED: short survival

BLUE: long survival

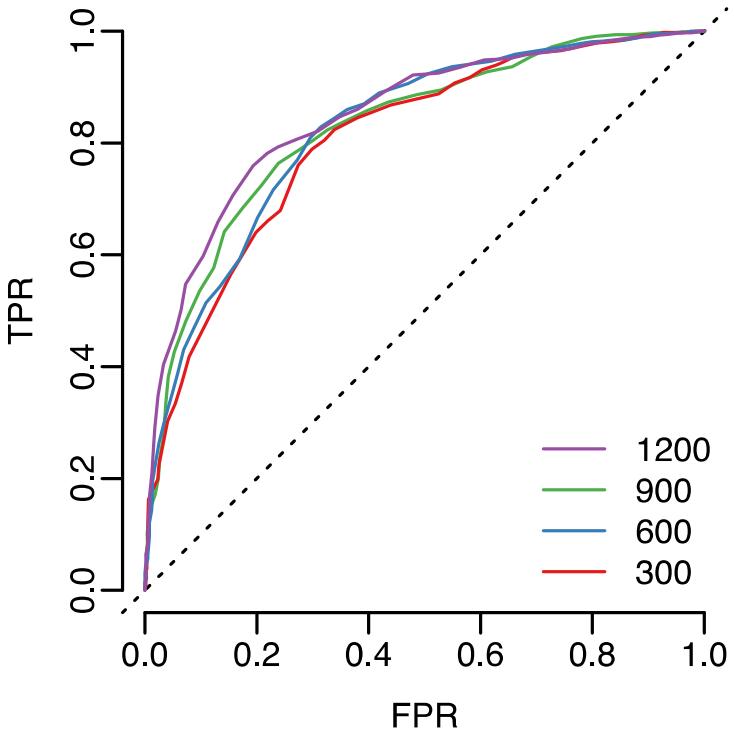
Risk reclassification



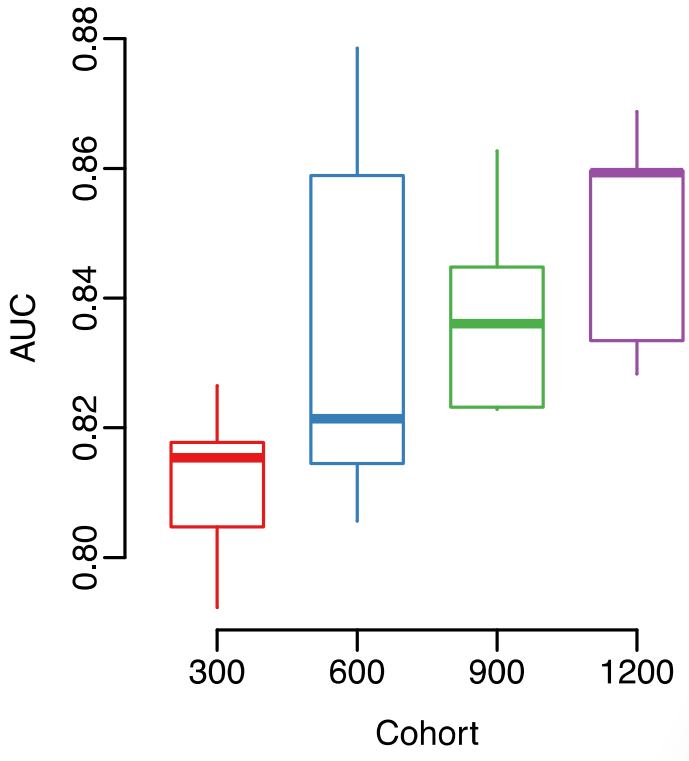
How important is sample size?

- Training sets of 300, 600, 900 & 1200 randomly selected patients from the cohort
- Validation set of 300 randomly selected, non-training patients
- Build prognostic models using LASSO stability selection (to minimise risk of over-fitting)
- Test predictive accuracy using ROC curves

Predictive performance

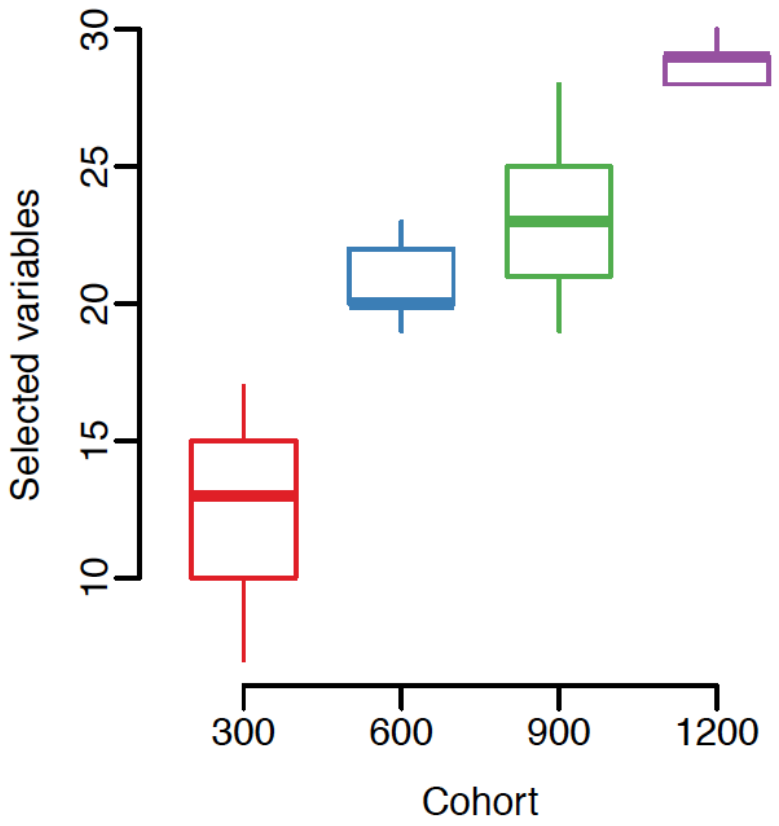


ROC curves

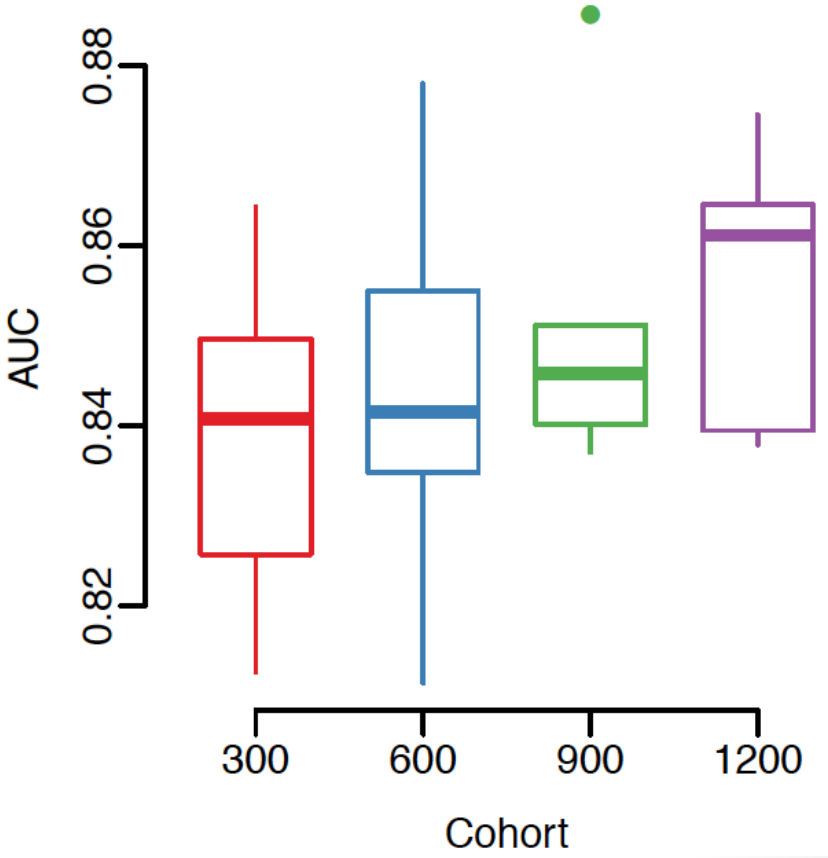


Area under ROC curve

More variables; better estimation

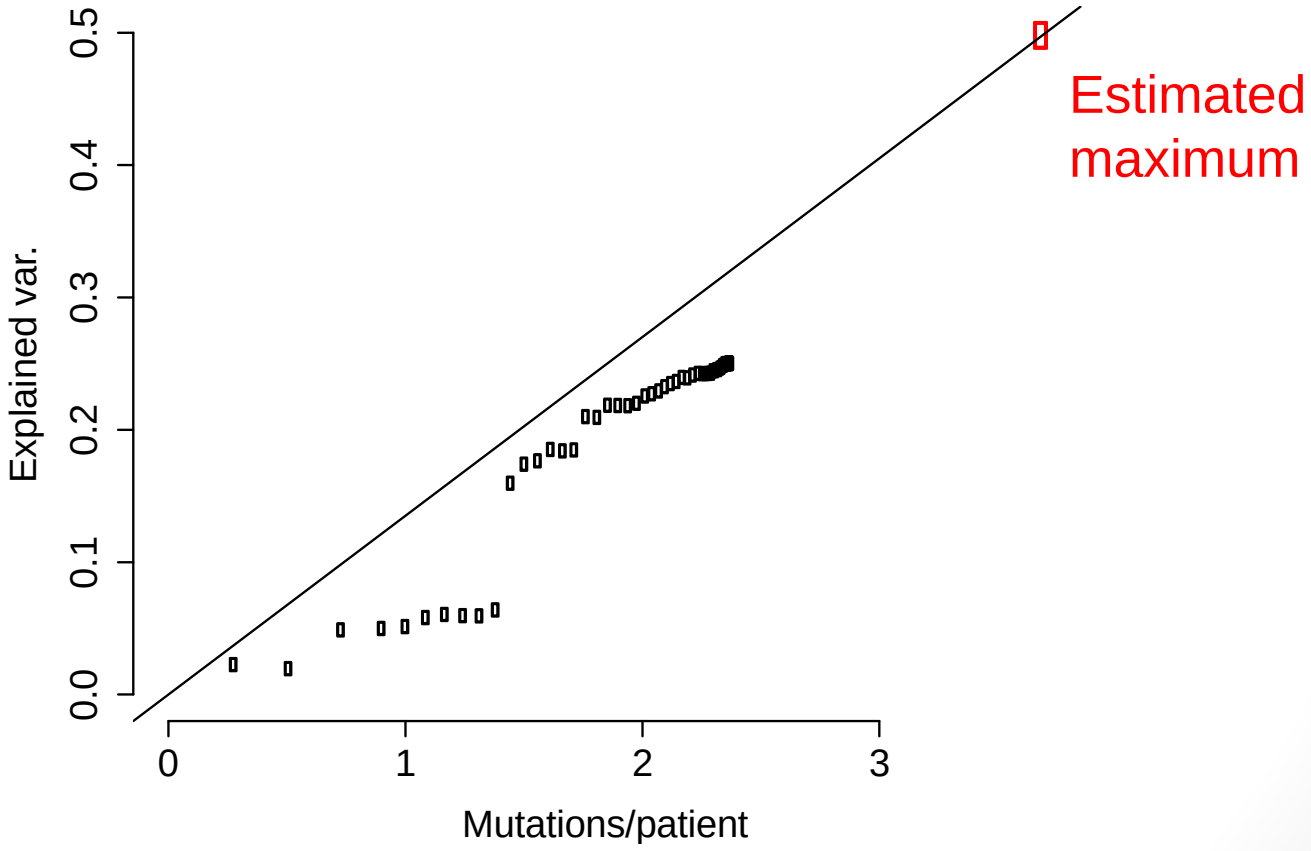


Number of selected variables



AUC with constant variable selection

How far can we improve?



Summary

- Cancer is a disease of the genome
- Complex genomic alterations in cancer
  - Long tail of cancer genes
  - Multiple driver mutations per patient
  - Considerable secondary structure
- Genomic changes drive biology and therefore clinical phenotype
  - Inter-patient heterogeneity of cancer genomes may partially explain heterogeneity of clinical outcomes
- Scope for genomics to inform clinical management of cancers

Personalised cancer medicine – Current state of play

- Meaningful gene-drug interactions available for only small minority of patients
- Very complex genomic landscape for most cancers
- Minimal large-scale data on clinical correlations of genomic features
- Interventional clinical trials under-powered to detect gene-drug interactions
- **Need to develop ethical, regulatory and logistic framework for sharing clinical – genomic data sets among collaborative groups**

Acknowledgements

Sanger Institute

Elli Papaemmanuil

Moritz Gerstung

Laura Mudie
Sarah O'Meara
Jonathan Hinton
Keiran Raine
David Jones
Adam Butler
Jon Teague

University of Ulm

Hartmut Dohner

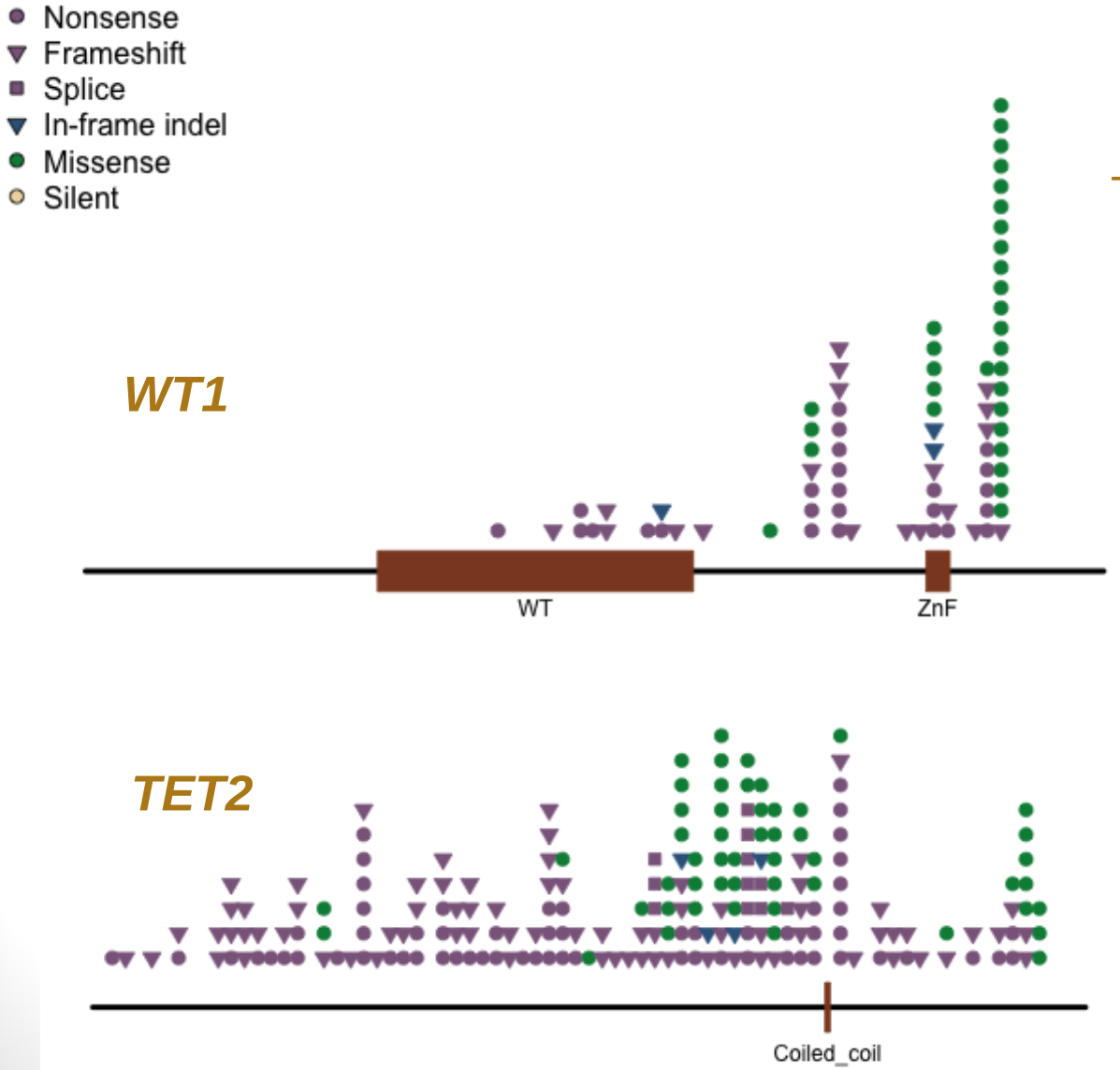
Lars Bullinger

Konnie Dohner

Richard Schlenk

wellcome trust

Distribution of mutations

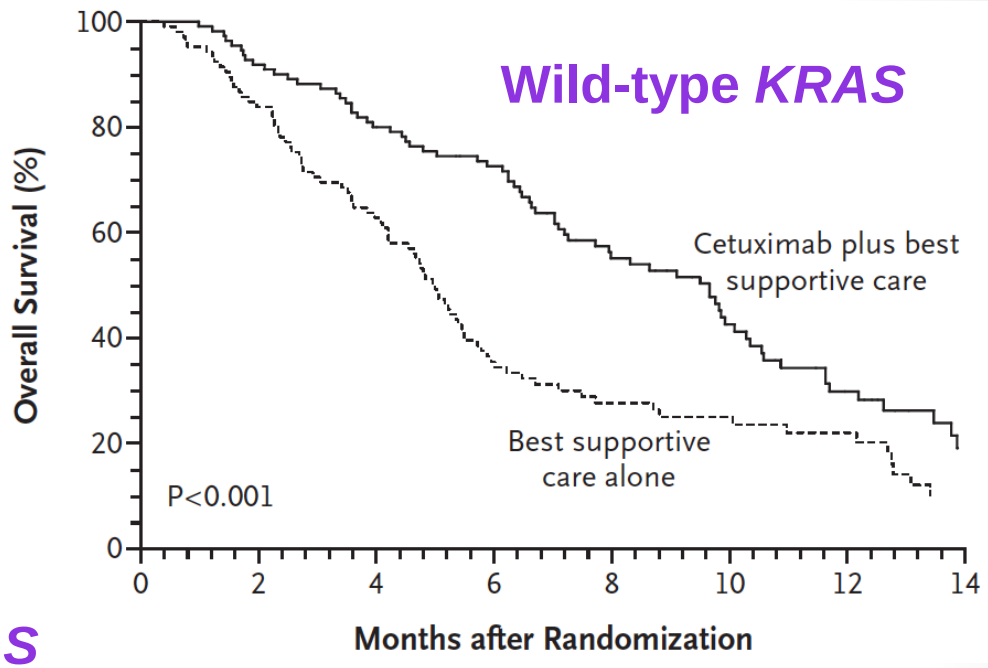


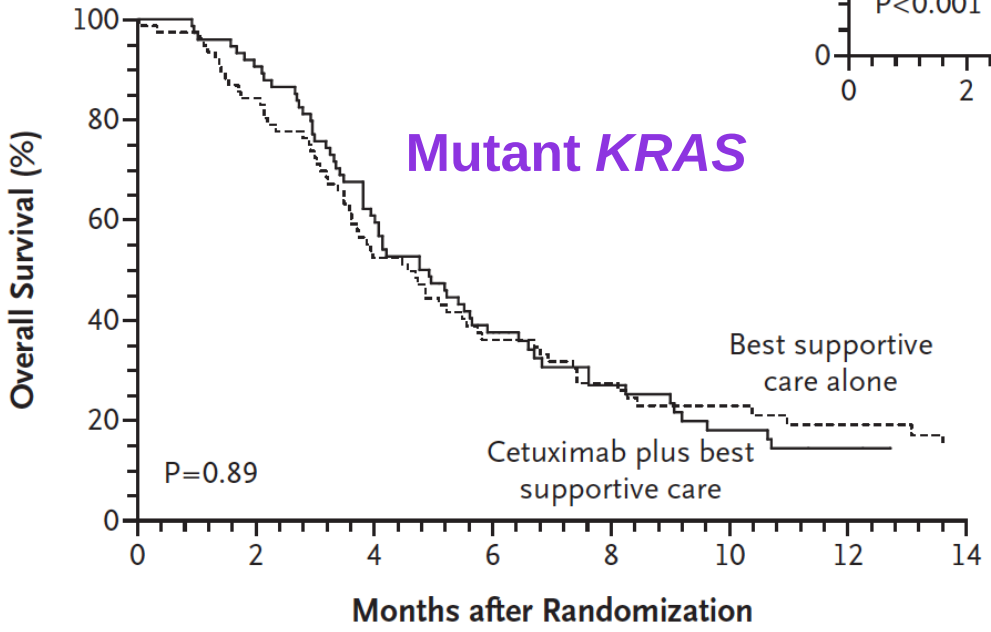
Test of uniform dist^{n} truncating muts

p<0.0001

p=0.1

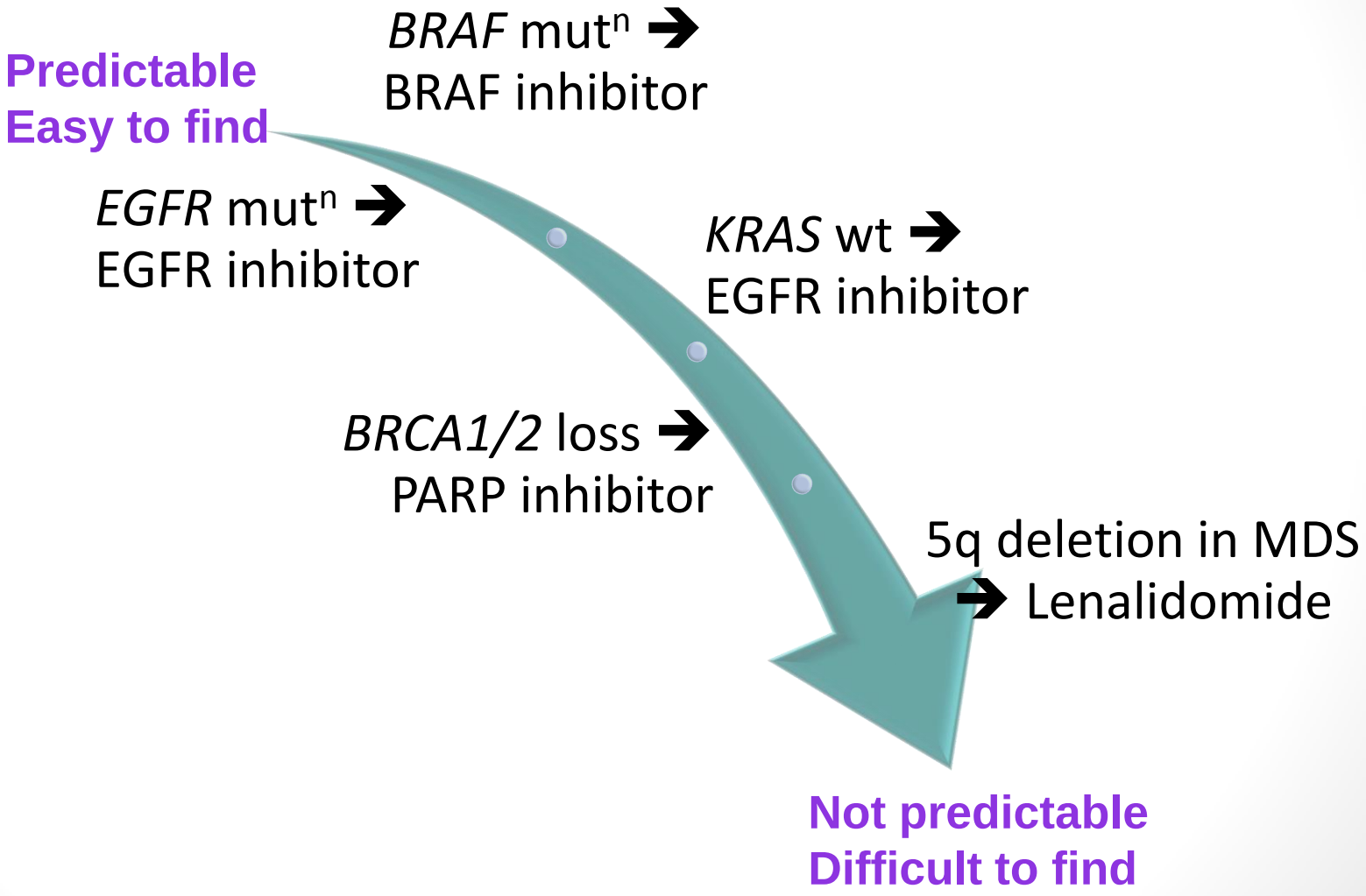
The gene-drug interaction





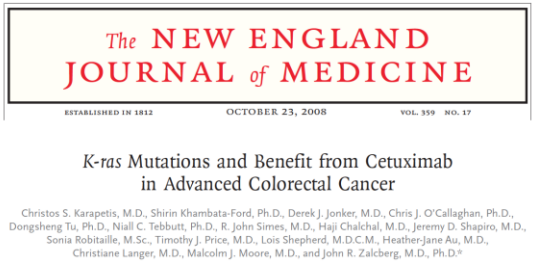
Karapetis *et al*, NEJM 2008

Known gene-drug interactions

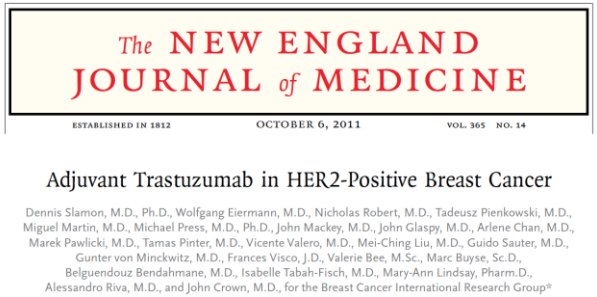


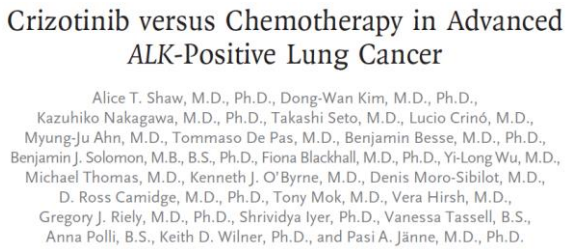
Discovery of gene-drug interactions

- Retrospective analysis of pivotal randomised trials

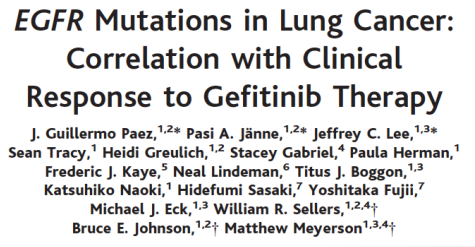


- Enrichment trials





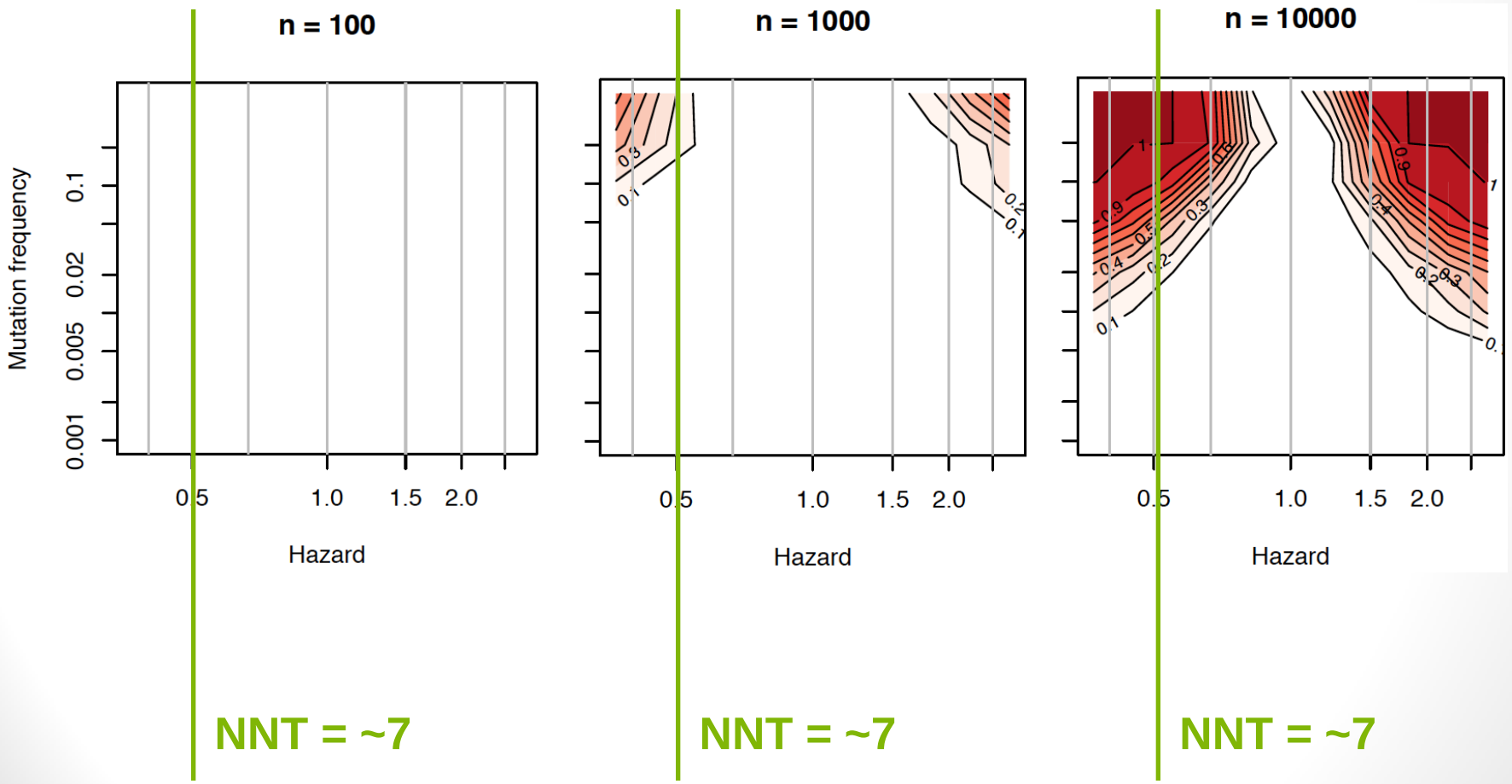
- Exceptional responder studies



Factors affecting statistical power

- Effect size
- Sample size
- Frequency of gene mutation in cohort
- Number of hypothesis tests
- Statistical methodology
- Correlated genomic / clinical features (multicollinearity)

Power


n = 100
n = 1000
n = 10000
Mutation frequency
0.001
0.005
0.02
0.1
0.5
1.0
1.5
2.0
Hazard
NNT = ~7
NNT = ~7
NNT = ~7

Number of driver mutations