

# Precision medicine: Panacea or false dawn?

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Wellcome Trust Sanger Institute



# Disclosure Information

ESMO Meeting 2014

Peter Campbell

**I have the following financial relationships to disclose:**

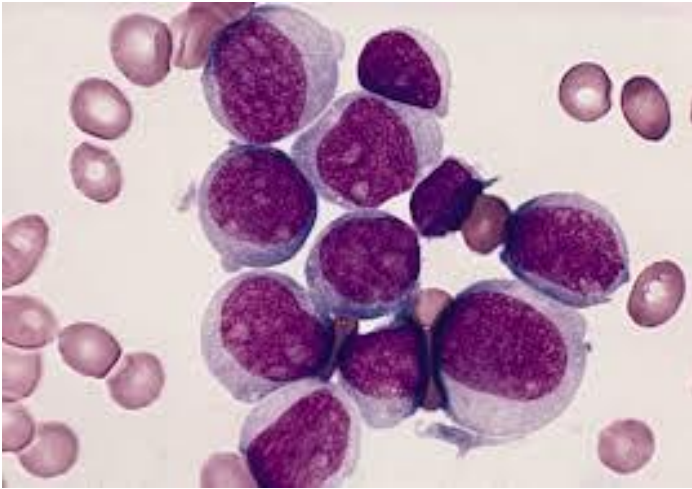
**Consultant for 14M Genomics Ltd**

**Stockholder in 14M Genomics Ltd**

***- and -***

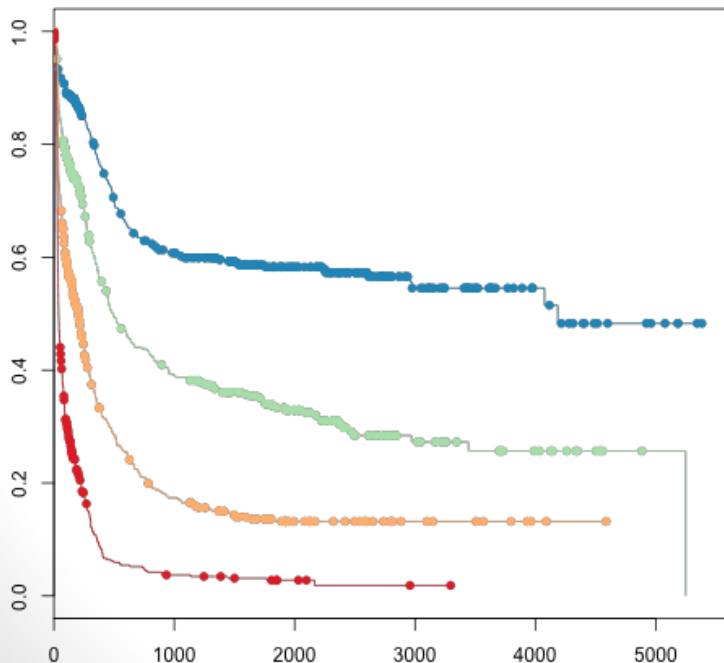
**I will not discuss off label use and/or investigational use in my presentation.**

# Acute myeloid leukaemia



Accurate prognosis enables:

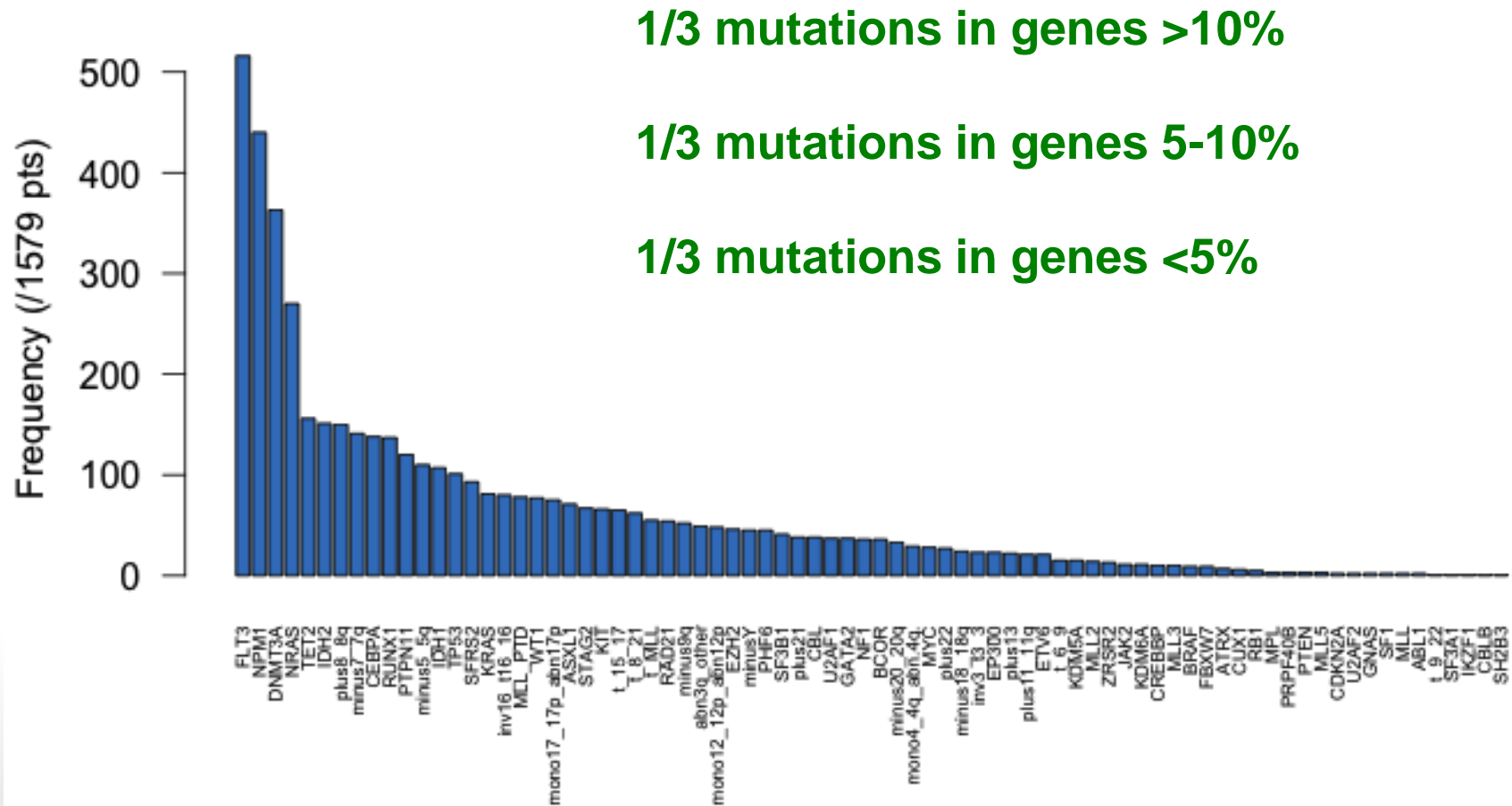
- Stratification of treatment esp bone marrow transplant
- More informed, personalised patient discussions
- Design of risk-adapted clinical trials



# AML data set

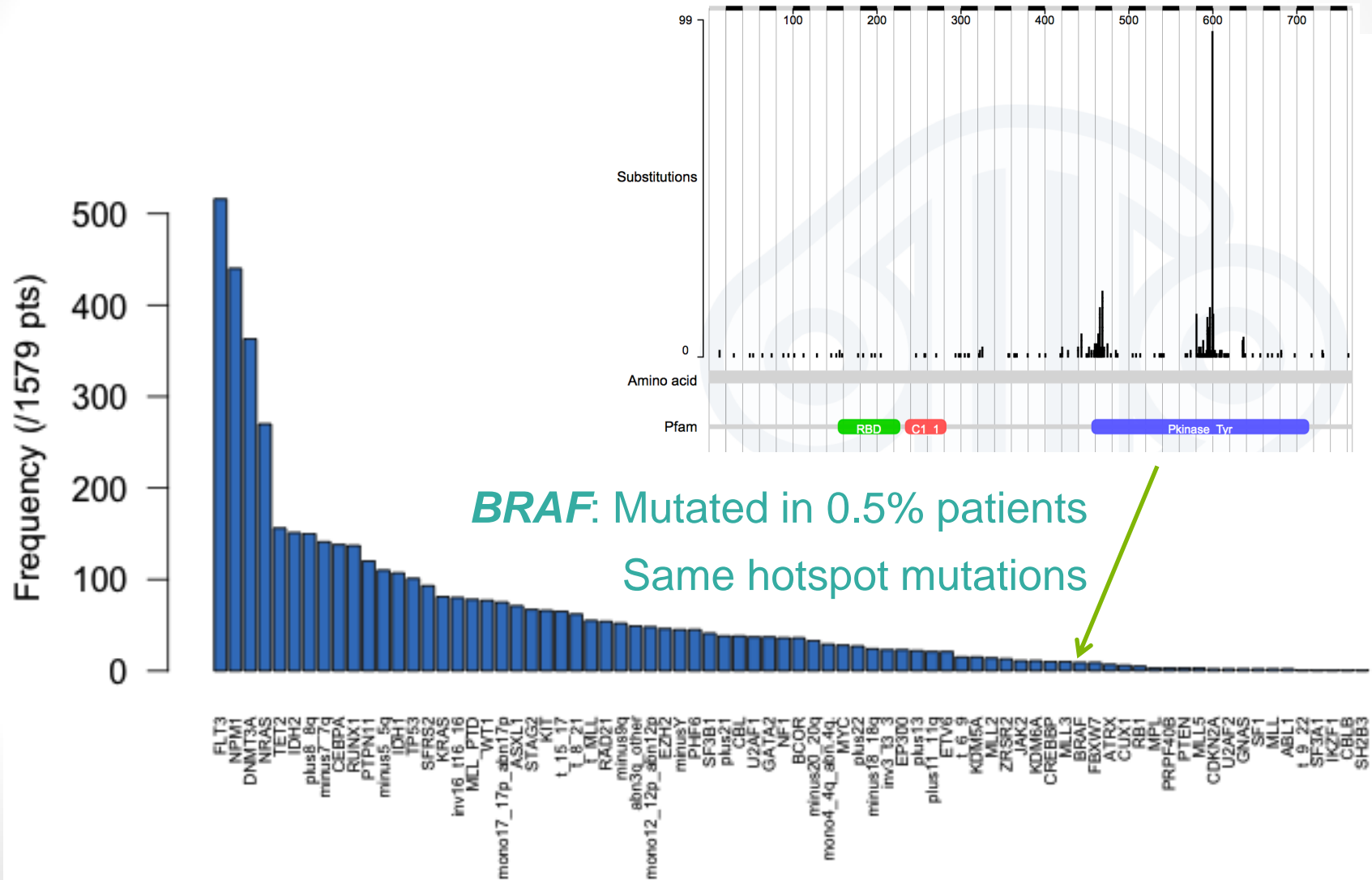
- 1579 patients with AML
- Enrolled in three trials performed through the German-Austrian AML Study Group
- Long-term clinical outcome data available
- Sequenced for 110 genes involved in AML pathogenesis
- Triaged variants into:
  - Known drivers
  - Possible oncogenic
  - Variants of unknown significance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

# The long tail of cancer genes

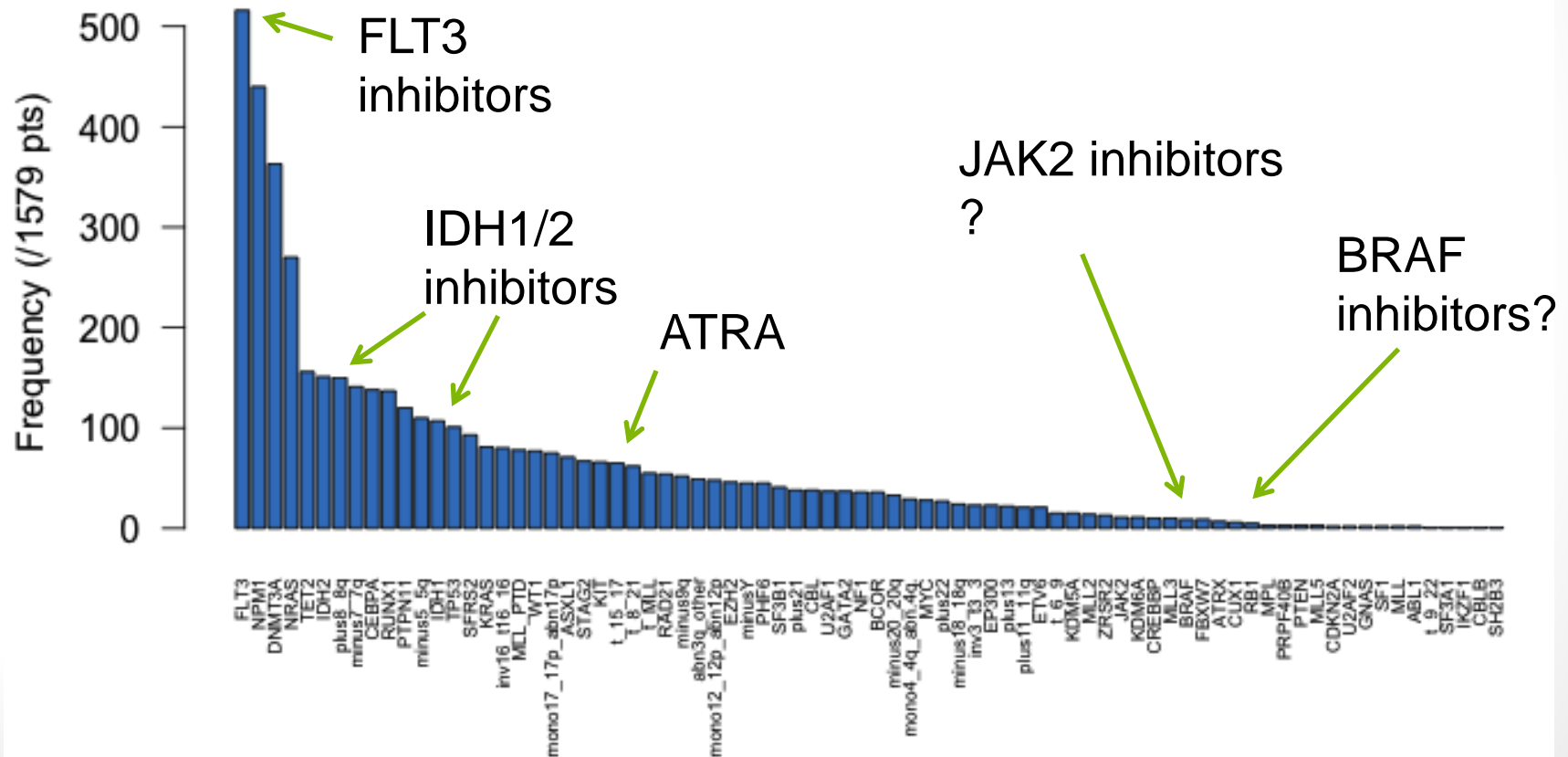




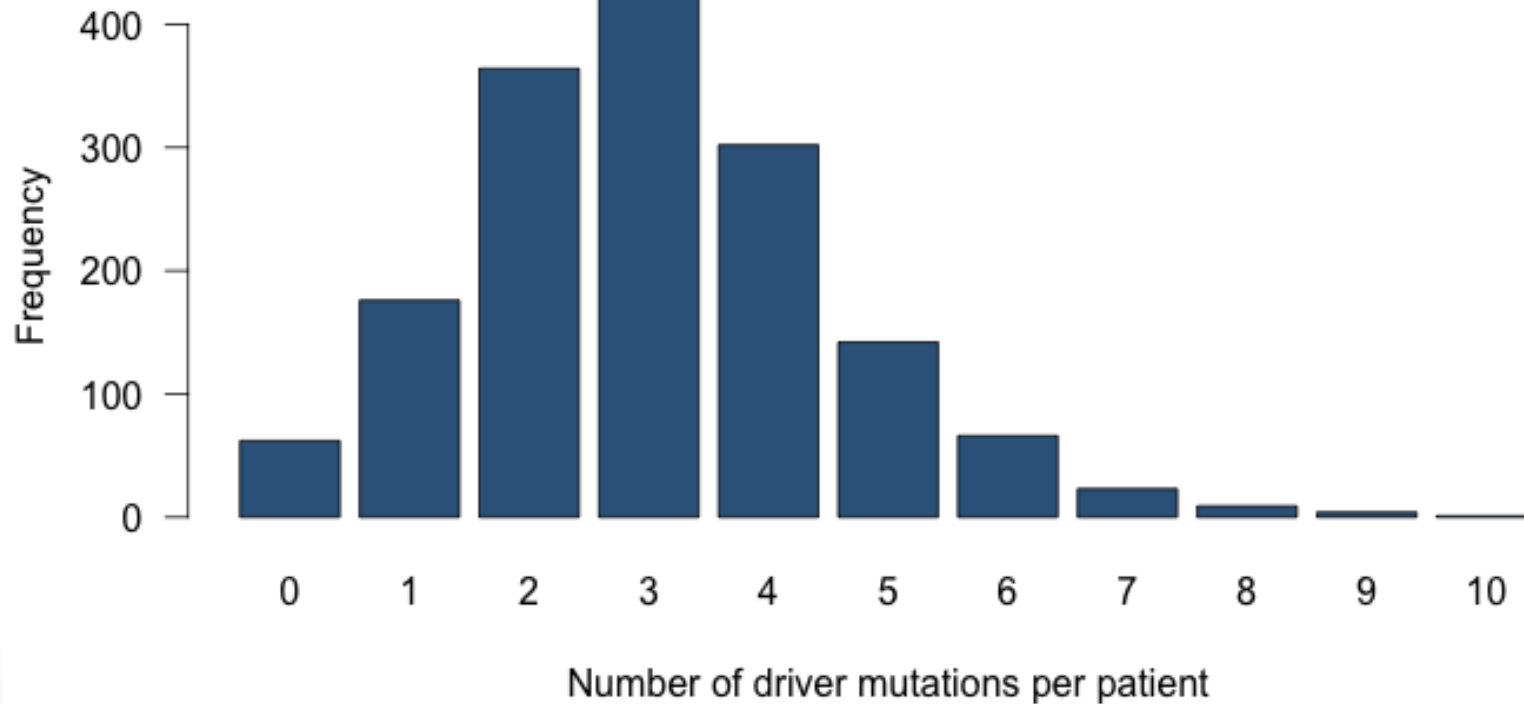
# The long tail of cancer genes



# Personalised treatment



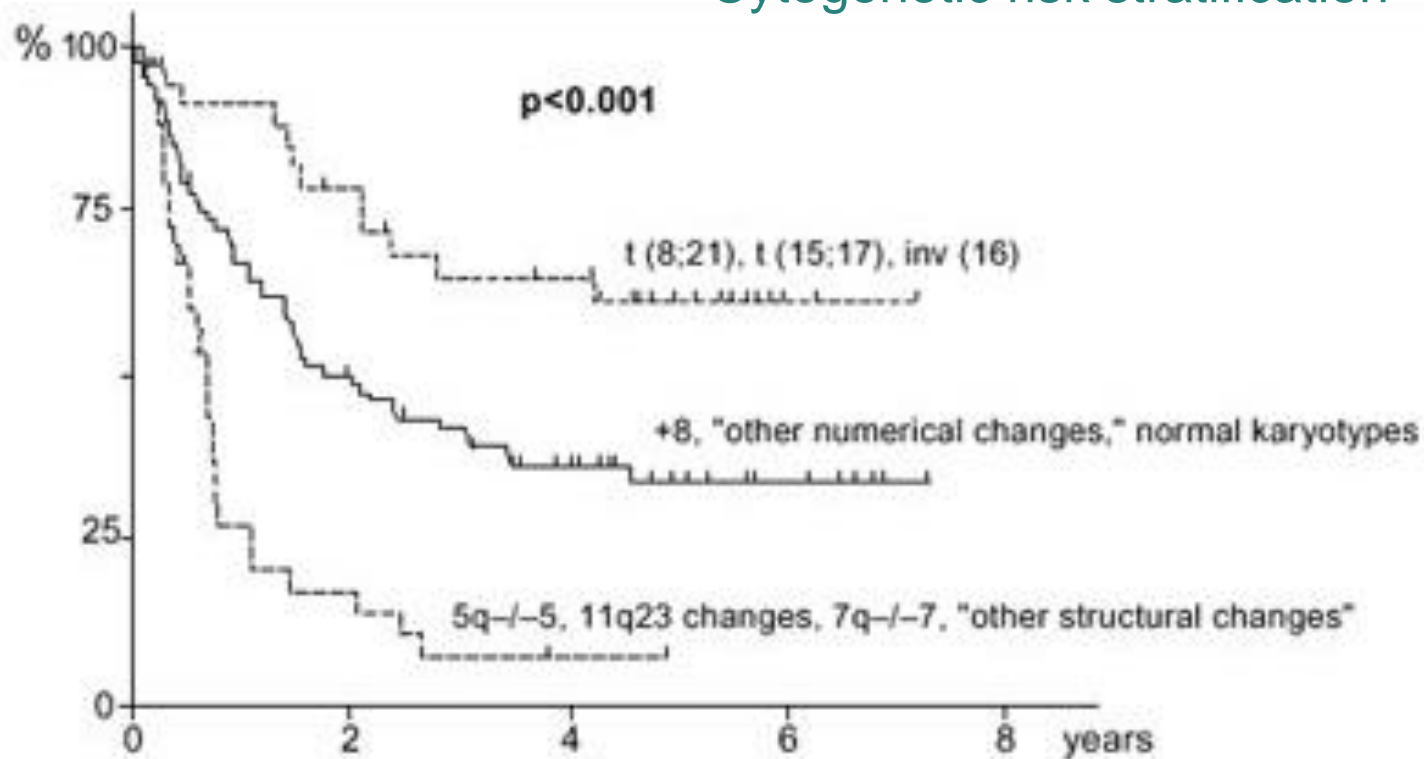
# Number of mutations per patient





# Using genomics to predict outcome

## Cytogenetic risk stratification

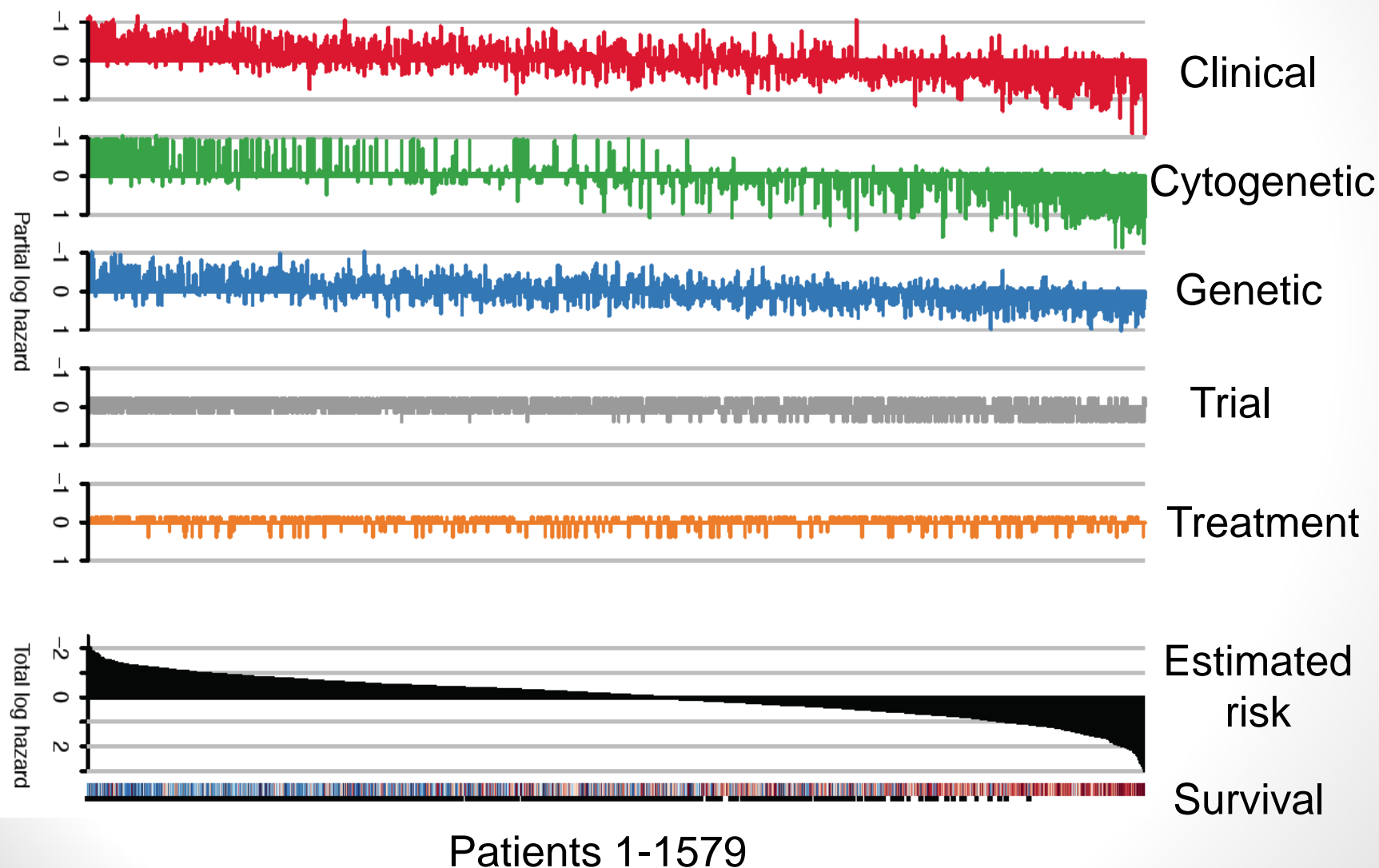


From Martin Tallman, Leukemia 1995

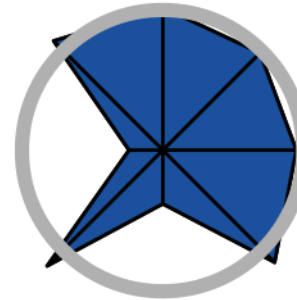
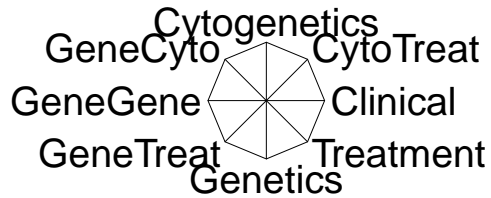
# Prognostic variables in AML

- 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



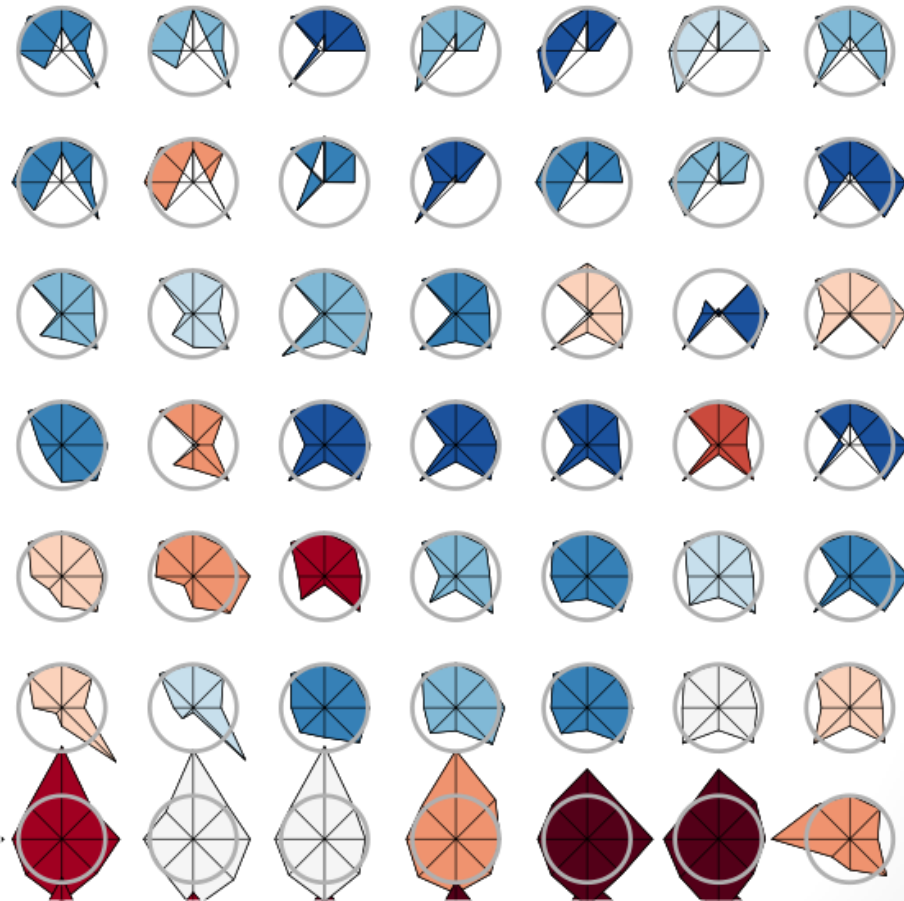
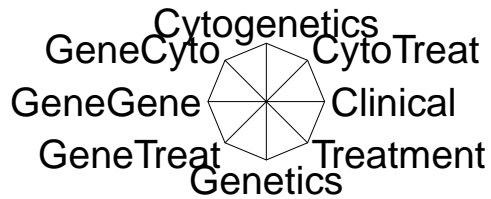
# Personalised predictions



RED: short survival

BLUE: long survival

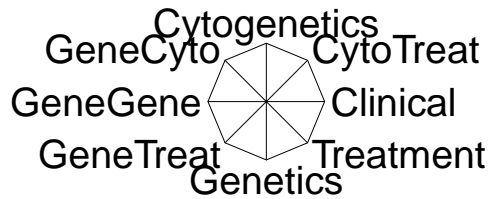
# Personalised predictions



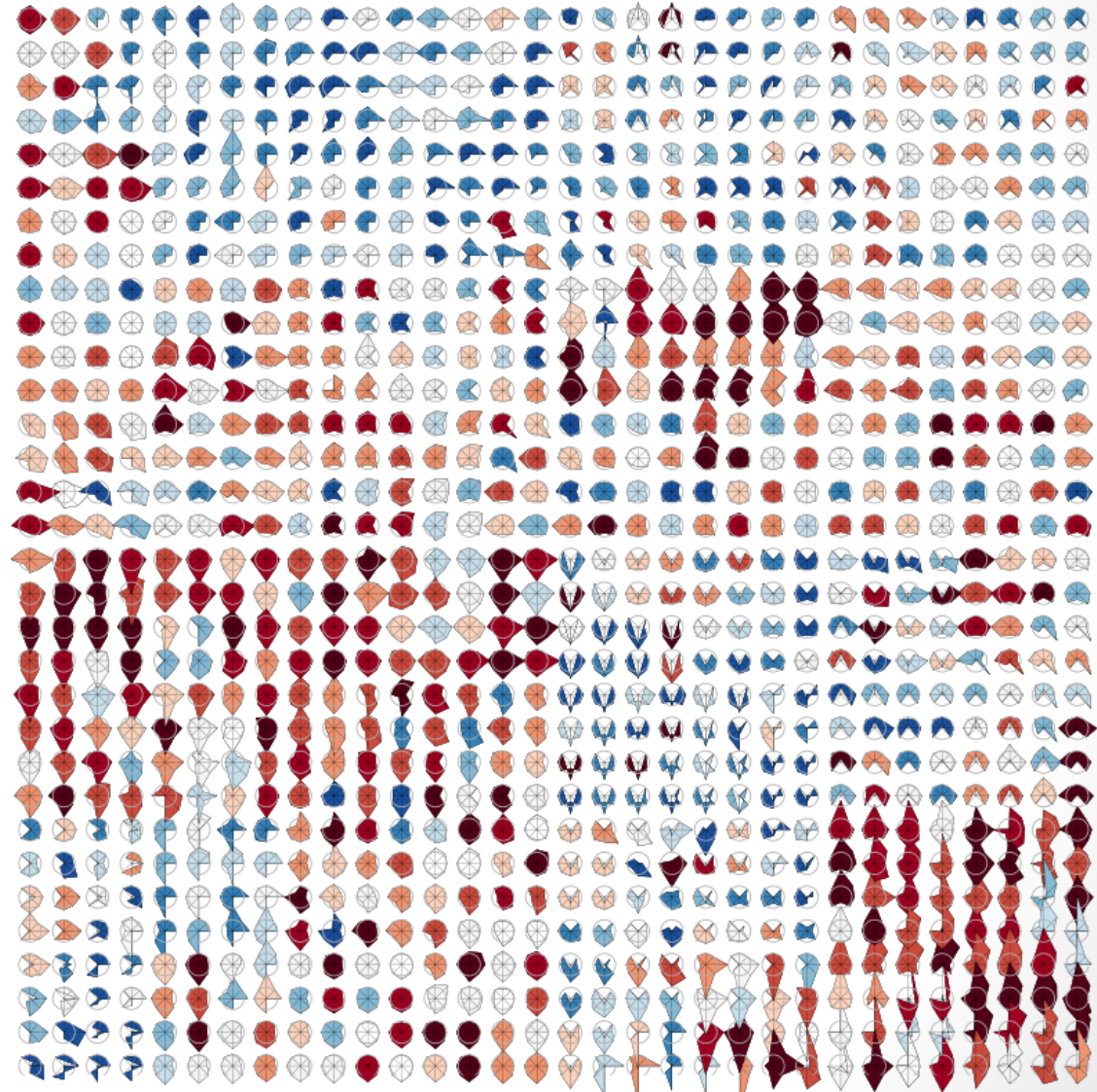
RED: short survival

BLUE: long survival

# Personalised predictions



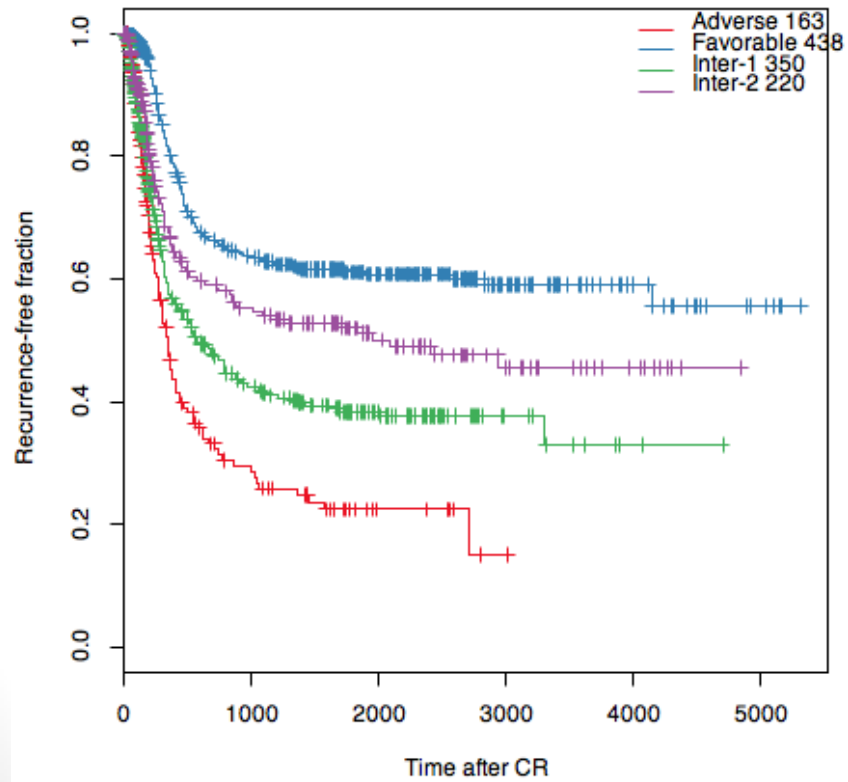
RED: short survival  
BLUE: long survival





# Risk reclassification

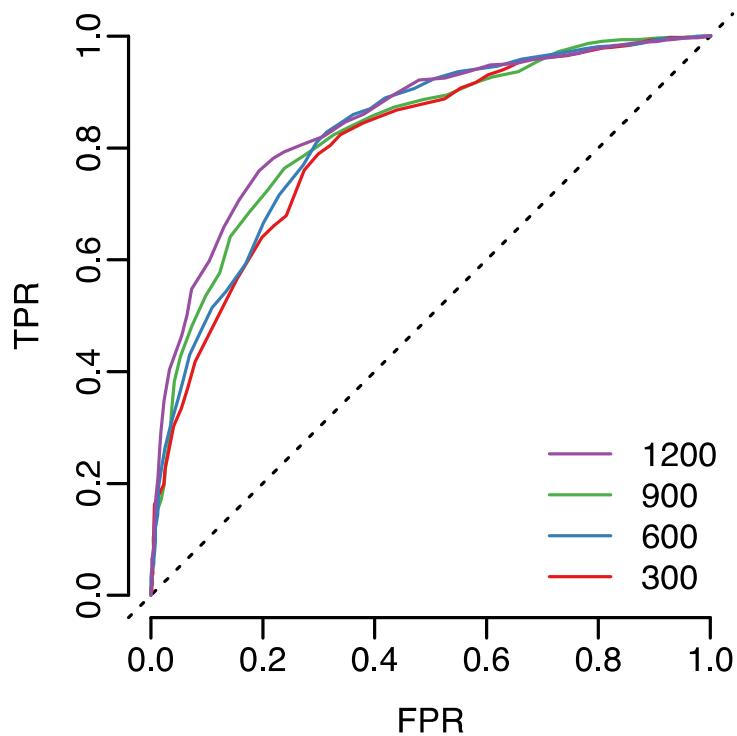
Molecular risk groups, all cases



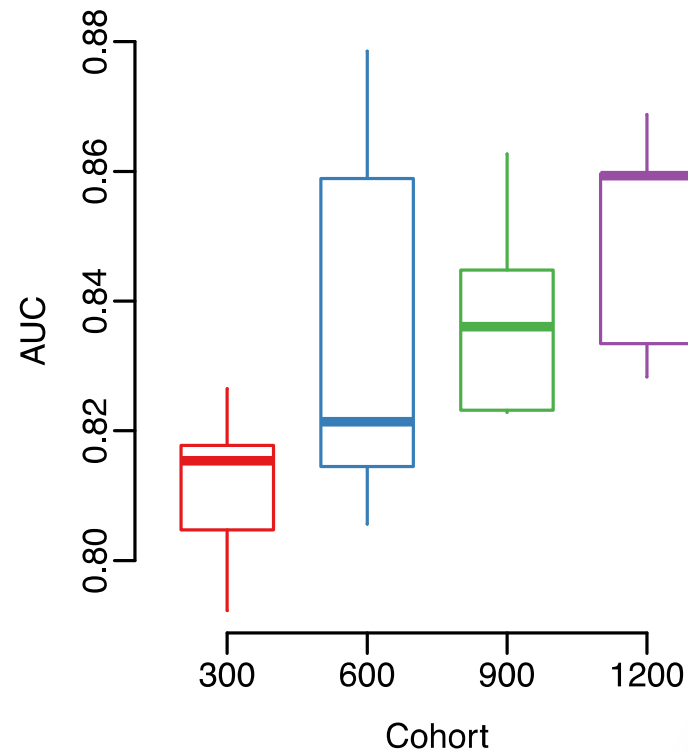
# How important is sample size?

- 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

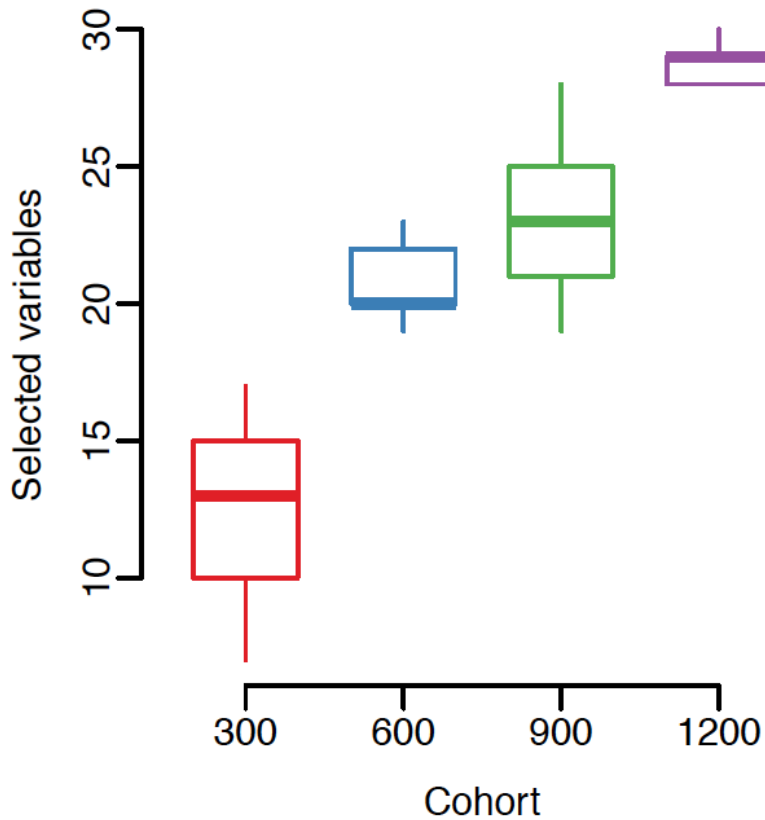


ROC curves

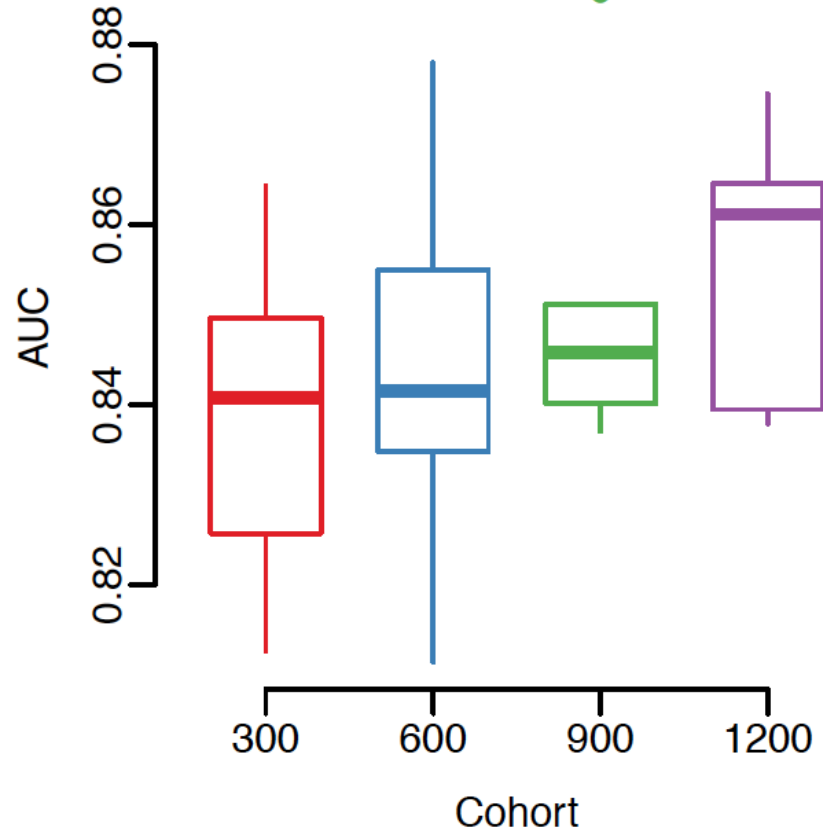


Area under ROC curve

# More variables; better estimation

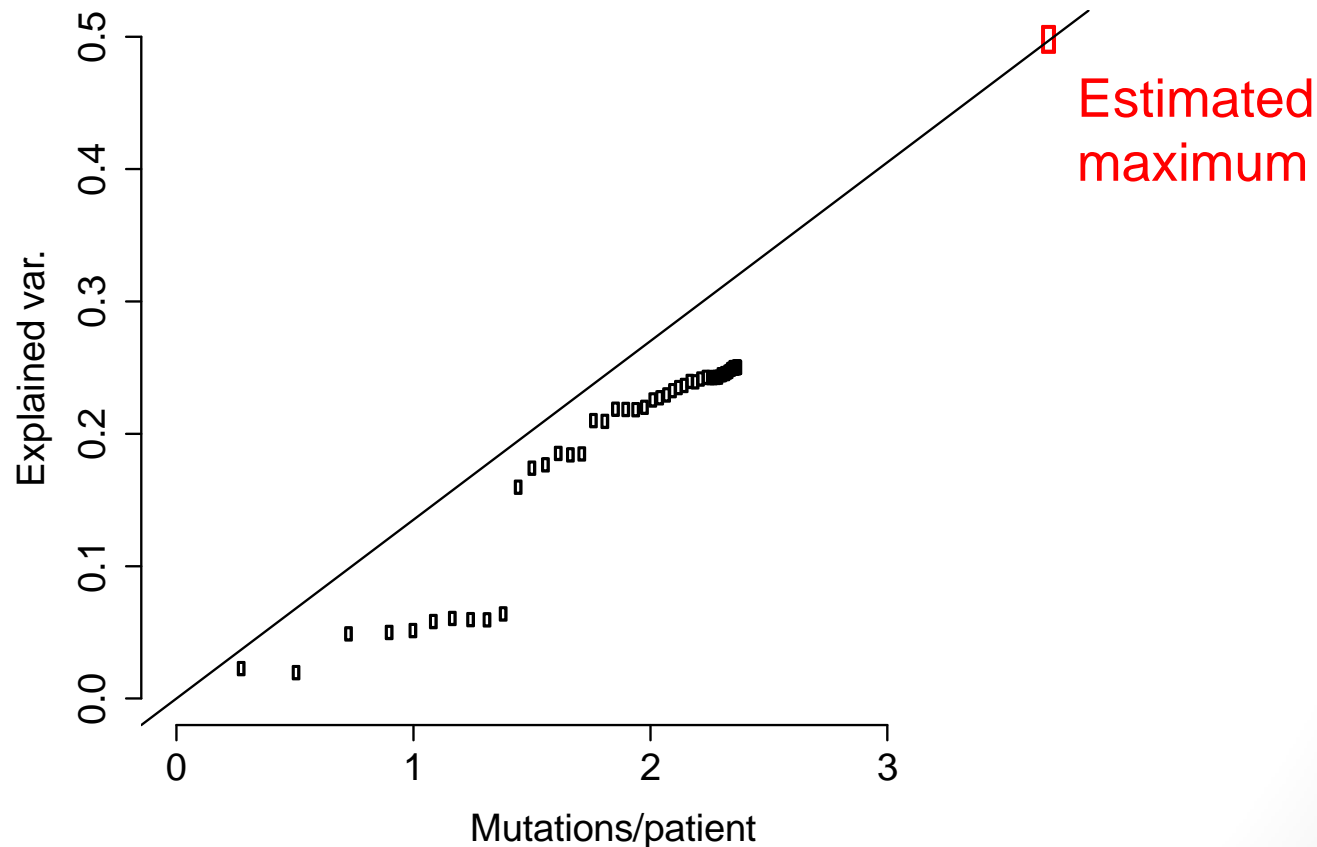


Number of selected variables



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

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Jon Teague

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Hartmut Dohner

Lars Bullinger

Konnie Dohner

Richard Schlenk

**wellcome**trust

# Distribution of mutations

- Nonsense
- ▼ Frameshift
- Splice
- ▼ In-frame indel
- Missense
- Silent

Test of uniform dist<sup>n</sup>  
truncating muts

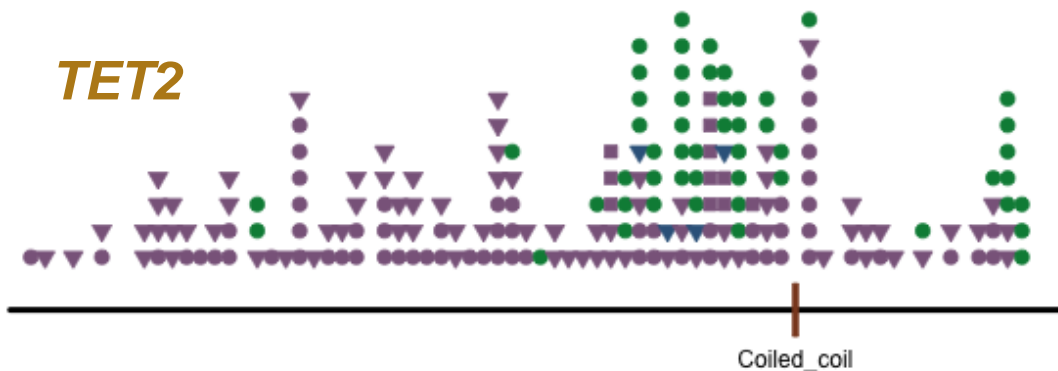
*WT1*

$p < 0.0001$

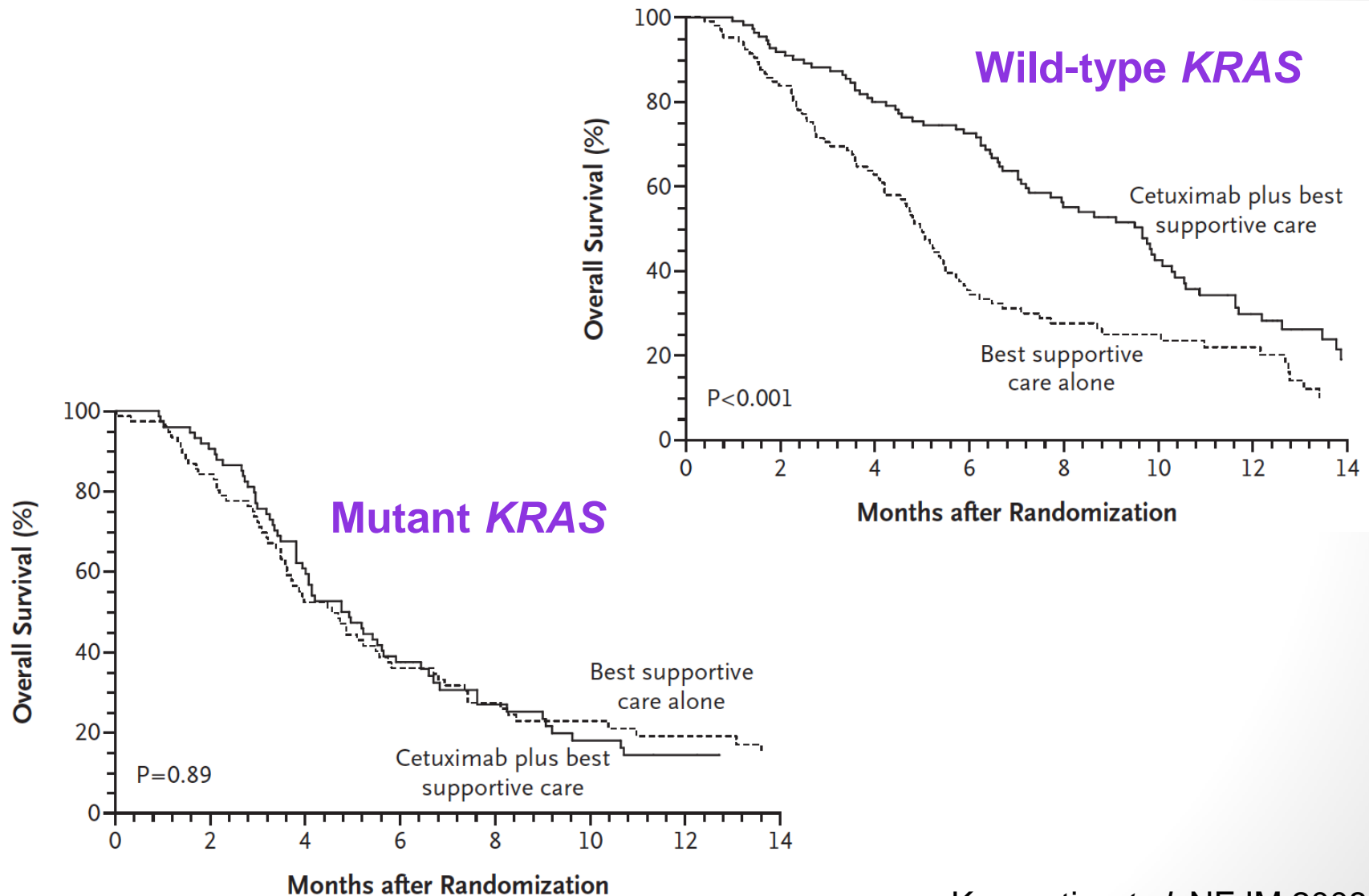


*TET2*

$p = 0.1$



# The gene-drug interaction



# Known gene-drug interactions

Predictable  
Easy to find

*BRAF* mut<sup>n</sup> →  
BRAF inhibitor

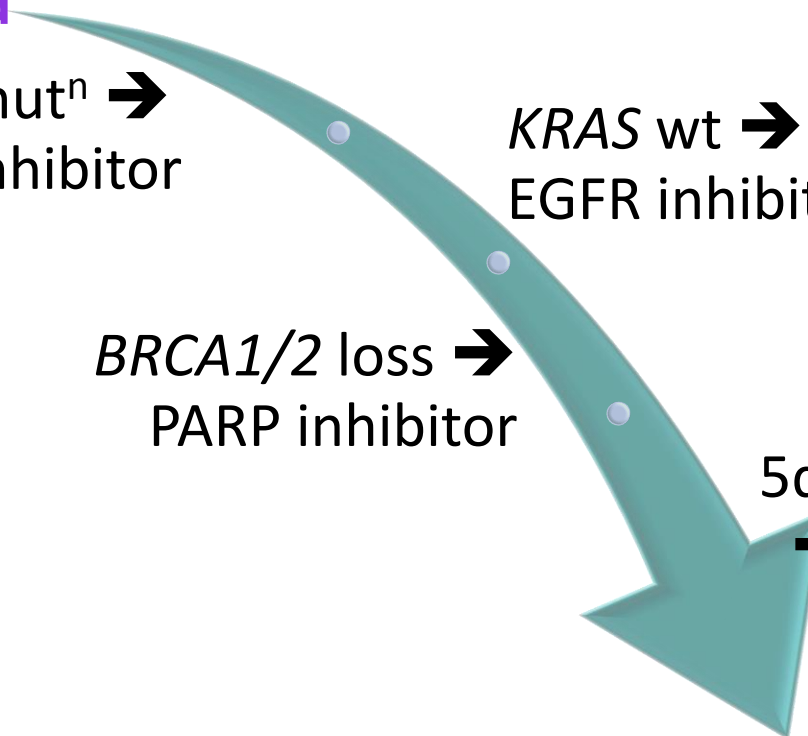
*EGFR* mut<sup>n</sup> →  
EGFR inhibitor

*KRAS* wt →  
EGFR inhibitor

*BRCA1/2* loss →  
PARP inhibitor

5q deletion in MDS  
→ Lenalidomide

Not predictable  
Difficult to find



# Discovery of gene-drug interactions

- Retrospective analysis of pivotal randomised trials



## K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

Christos S. Karapetis, M.D., Shirin Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Haji Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lois Shepherd, M.D.C.M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.\*

- Enrichment trials



## Adjuvant Trastuzumab in HER2-Positive Breast Cancer

Dennis Slamon, M.D., Ph.D., Wolfgang Eiermann, M.D., Nicholas Robert, M.D., Tadeusz Pienkowski, M.D., Miguel Martin, M.D., Michael Press, M.D., Ph.D., John Mackey, M.D., John Glaspy, M.D., Arlene Chan, M.D., Marek Pawlicki, M.D., Tamas Pinter, M.D., Vicente Valero, M.D., Mei-Ching Liu, M.D., Guido Sauter, M.D., Gunter von Minckwitz, M.D., Frances Visco, J.D., Valerie Bee, M.Sc., Marc Buyse, Sc.D., Belguendouz Bendahmane, M.D., Isabelle Tabah-Fisch, M.D., Mary-Ann Lindsay, Pharm.D., Alessandro Riva, M.D., and John Crown, M.D., for the Breast Cancer International Research Group\*

## Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D., Tommaso De Pas, M.D., Benjamin Besse, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Fiona Blackhall, M.D., Ph.D., Yi-Long Wu, M.D., Michael Thomas, M.D., Kenneth J. O'Byrne, M.D., Denis Moro-Sibilot, M.D., D. Ross Camidge, M.D., Ph.D., Tony Mok, M.D., Vera Hirsh, M.D., Gregory J. Riely, M.D., Ph.D., Shrividya Iyer, Ph.D., Vanessa Tassell, B.S., Anna Polli, B.S., Keith D. Wilner, Ph.D., and Pasi A. Jänne, M.D., Ph.D.

- Exceptional responder studies

## Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Hasserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

## EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

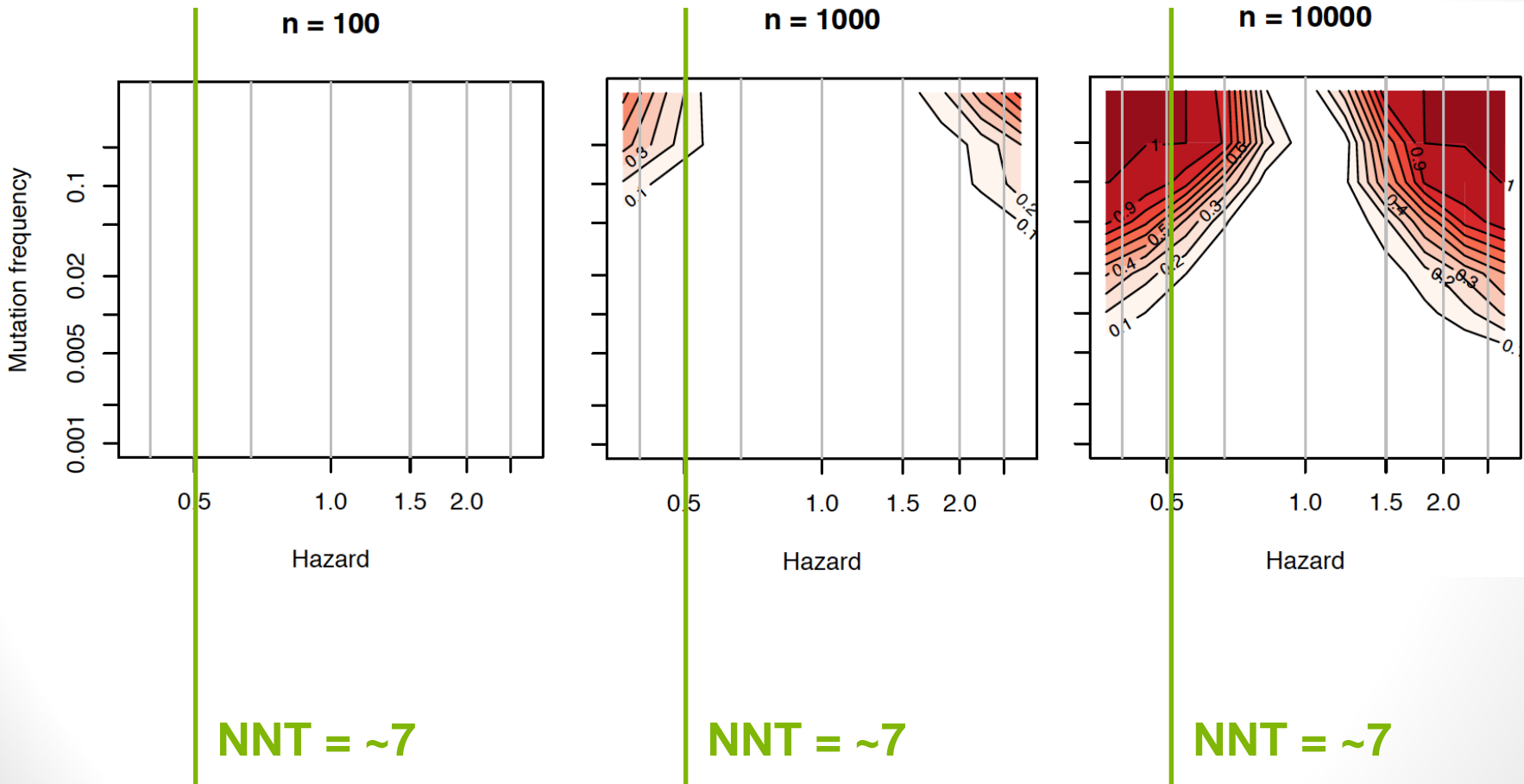
J. Guillermo Paez,<sup>1,2\*</sup> Pasi A. Jänne,<sup>1,2\*</sup> Jeffrey C. Lee,<sup>1,3\*</sup> Sean Tracy,<sup>1</sup> Heidi Greulich,<sup>1,2</sup> Stacey Gabriel,<sup>4</sup> Paula Herman,<sup>1</sup> Frederic J. Kaye,<sup>2</sup> Neal Lindeman,<sup>6</sup> Titus J. Boggon,<sup>1,3</sup> Katsuhiko Naoki,<sup>1</sup> Hidefumi Sasaki,<sup>7</sup> Yoshitaka Fujii,<sup>7</sup> Michael J. Eck,<sup>1,3</sup> William R. Sellers,<sup>1,2,4†</sup> Bruce E. Johnson,<sup>1,2†</sup> Matthew Meyerson<sup>1,3,4†</sup>



# 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



# Number of driver mutations

