Precision medicine: Panacea or false dawn?

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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

- FLT3 inhibitors
- IDH1/2 inhibitors
- ATRA
- JAK2 inhibitors
- BRAF inhibitors?
Number of mutations per patient

![Graph showing the frequency of number of driver mutations per patient. The x-axis represents the number of mutations ranging from 0 to 10, and the y-axis represents frequency ranging from 0 to 400. The graph shows a peak for 0-2 mutations, with a decline as the number of mutations increases.]
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

Patients 1-1579
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

- Adverse 163
- Favorable 438
- Inter-1 350
- Inter-2 220

Recurrence-free fraction vs Time after CR
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?

Estimated maximum

[Diagram showing a scatter plot with the x-axis labeledMutations/patient and the y-axis labeled Explained var. There are multiple data points plotted along the line, with a red marker at the estimated maximum point.]
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**
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Distribution of mutations

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

**Test of uniform dist\textsuperscript{n} truncating muts**

*WT1*

\[ p < 0.0001 \]

*TET2*

\[ p = 0.1 \]
The gene-drug interaction

Wild-type KRAS

Mutant KRAS

Karapetis et al, NEJM 2008
Known gene-drug interactions

- Predictable
- Easy to find

- BRAF mut<sup>n</sup> → BRAF inhibitor
- EGFR mut<sup>n</sup> → EGFR inhibitor
- BRCA1/2 loss → PARP inhibitor
- KRAS wt → EGFR inhibitor

- 5q deletion in MDS → Lenalidomide

Not predictable
Difficult to find
Discovery of gene-drug interactions

- Retrospective analysis of pivotal randomised trials
- Enrichment trials
- Exceptional responder studies

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**Discovery of gene-drug interactions**

- **Retrospective analysis of pivotal randomised trials**

  - [Image of New England Journal of Medicine](https://example.com)
  - **K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer**
    - Christos S. Karapeti, M.D., Shrinivas Khambata-Ford, Ph.D., Derek J. Jenike, M.D., Chris J. O'Callaghan, Ph.D., Dongsheng Tu, Ph.D., Neil C. Tsuchiya, M.D., E. John Stopeck, M.D., Haiqin Chen, M.D., Finlay D. Slama, M.D., Sara Reisfeld, M.S., Timothy J. Price, M.D., Lois Shepherd, M.D., M.C., Heather Jane Au, M.D., Christine Langer, M.D., Malcolm J. Moore, M.D., and John R. Zickler, M.D., Ph.D.

- **Enrichment trials**

  - [Image of New England Journal of Medicine](https://example.com)
  - **Adjuvant Trastuzumab in HER2-Positive Breast Cancer**
    - Dennis Slamon, M.D., Ph.D., Wolfgang Eiermann, M.D., Nicholas Robert, M.D., Tatjana Piernikowski, M.D., Miguel Martin, M.D., Michael Press, M.D., Ph.D., John Mackey, M.D., John Glaspy, M.D., Arlette Cote, M.D., Marek Pawlicki, M.D., Tamas Piter, M.D., Vicente Valero, M.D., Mei-Ching Liu, M.D., Guido Sauter, M.D., Gunther von Minckwitz, M.D., Frances Vescio, J.D., Valerie Bex, M.Sc., Marc Buyse, Sc.D., Belgium Breast Group, M.D., Isabelle Talah-Fisch, M.D., Mary Ann Lindsay, Ph.D., Alessandro Riva, M.D., and John Crown, M.D., for the Breast Cancer International Research Group

- **Exceptional responder studies**

  - [Image of New England Journal of Medicine](https://example.com)
  - **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. Hasserat, 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.

  - [Image of New England Journal of Medicine](https://example.com)
  - **EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy**
    - J. Guillermo Pez, 1,2,5 Pasi A. Jänne, 1,2,5 Jeffrey C. Lee, 1,3,5 Sean Tracy, 1,5 Heidi Grousl, 1,5 Stacey Gabriel, 1,5 Paula Herman, 1,5 Frederic J. Kaye, 1,5 Neal Lindeman, 1,5 Titus J. Boggon, 1,5 Katsuhiko Naoki, 1,5 Hidefumi Sasaki, 1,5 Yoshitaka Fujii, 1,5 Michael J. Eck, 1,3 William R. Sellers, 1,2,5 Bruce E. Johnson, 1,2,5 Matthew Meyerson 1,2,5,6
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

NNT = ~7

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Number of driver mutations