Thoracic Oncology: Where are we going?
Parma, 20 Settembre 2013

FARMACOGENOMICA nelle neoplasie polmonari

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The NEW ENGLAND JOURNAL of MEDICINE

The Beginning of the End of the Beginning in Cancer Genomics

David P. Steensma, M.D.

N ENGL J MED 368;22 NEJM.ORG MAY 30, 2013

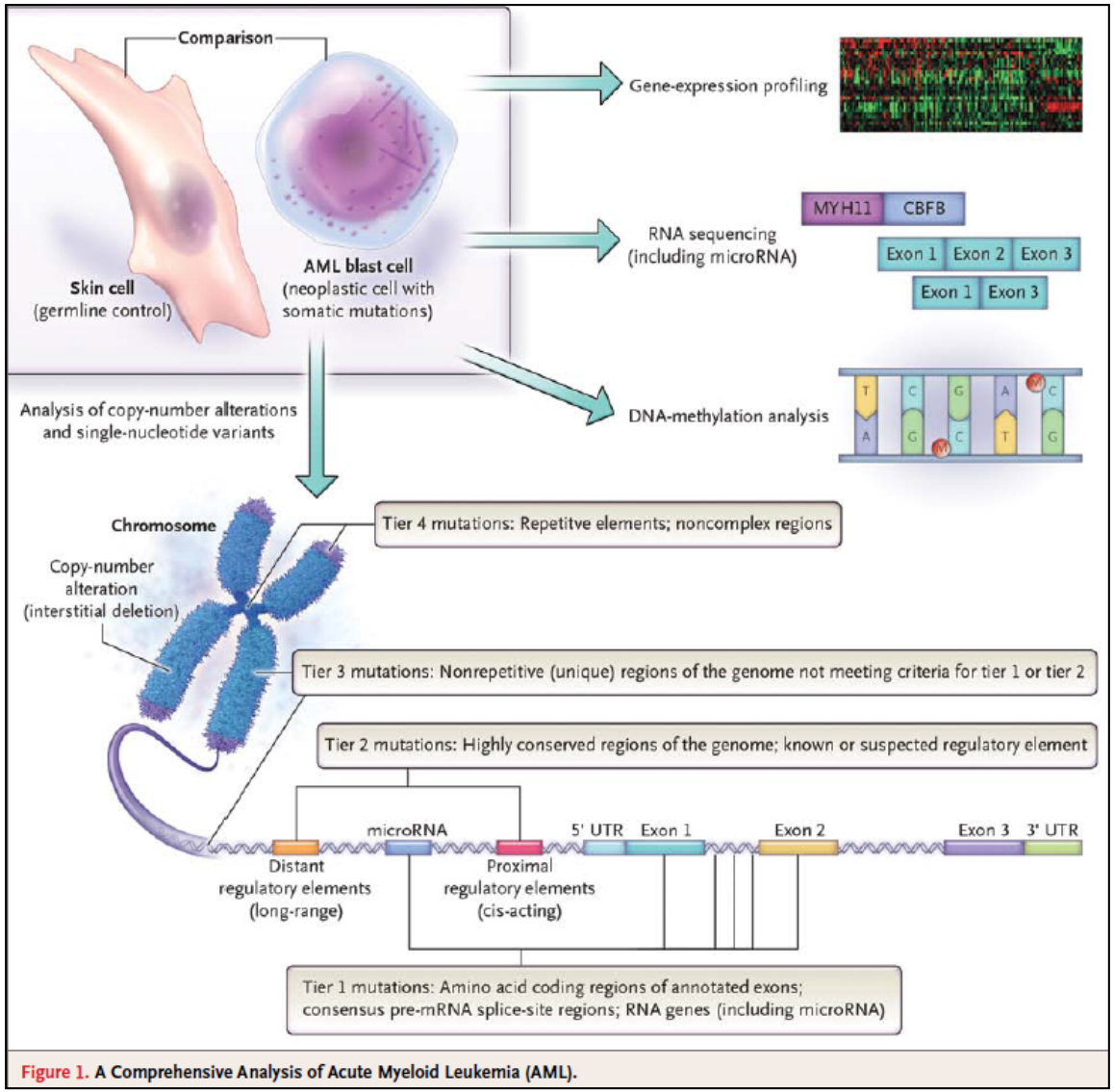


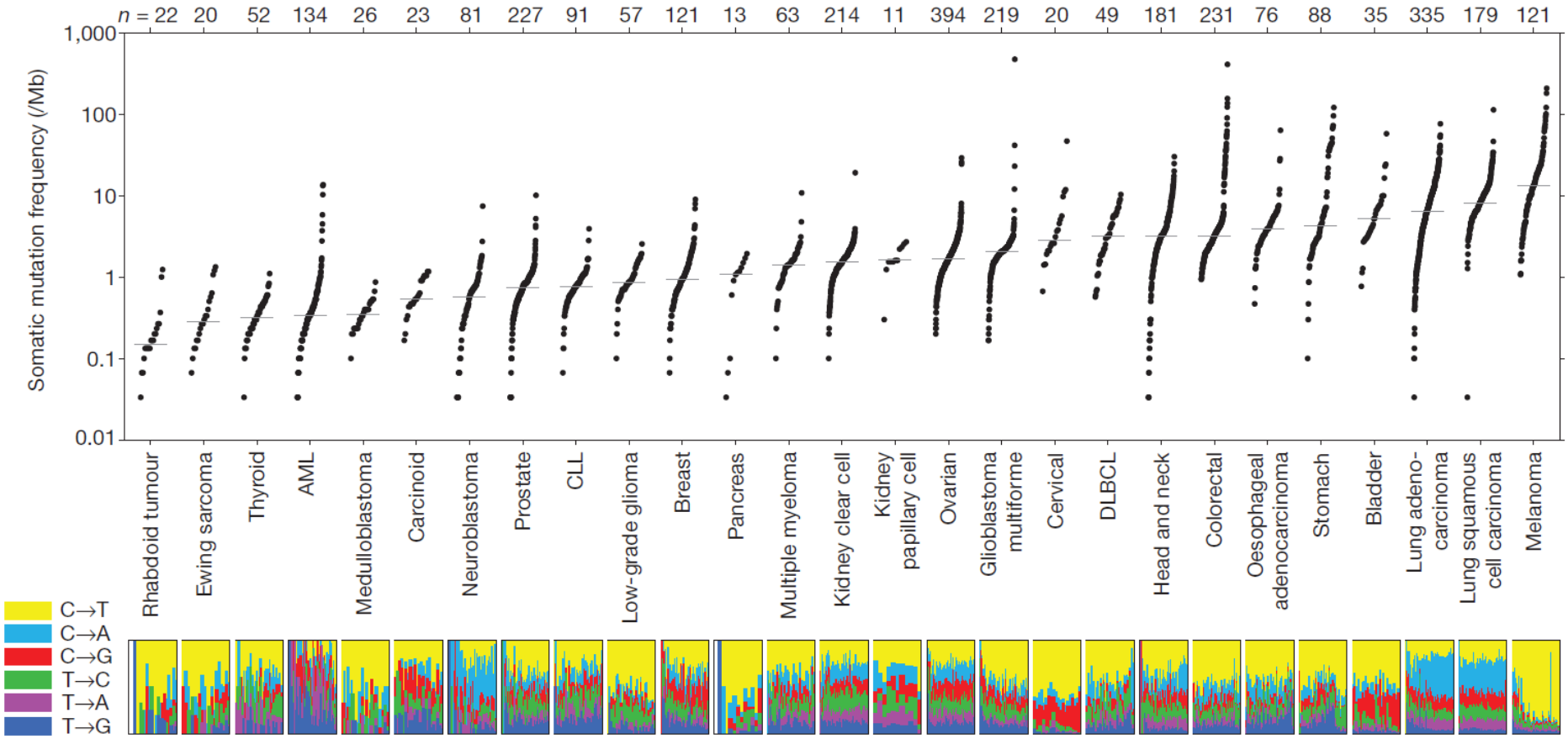
Figure 1. A Comprehensive Analysis of Acute Myeloid Leukemia (AML).

The Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med 2013;368:2059-74.

.. In 1803, a few years before the inaugural issue of the *Journal*, Thomas Jefferson commissioned Meriwether Lewis and William Clark to survey the vast unknown American frontier. Lewis and Clark departed from St. Louis, where Ley et al. initiated the AML genome survey. Less than a century later, the western frontier was declared "closed," but land surveyors did not disappear; today, they focus on construction projects and property boundaries. Likewise, although the initial epic AML genomic survey that began in St. Louis is now largely complete and surveys of other neoplasms will soon conclude, the use of genomics in quotidian practice is just beginning.

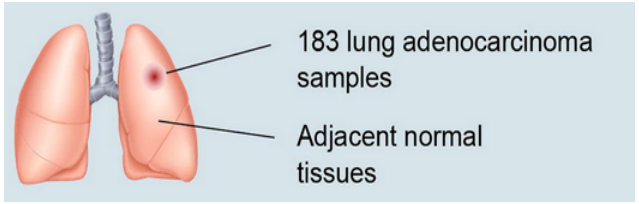
The complexity of lung cancer genomics

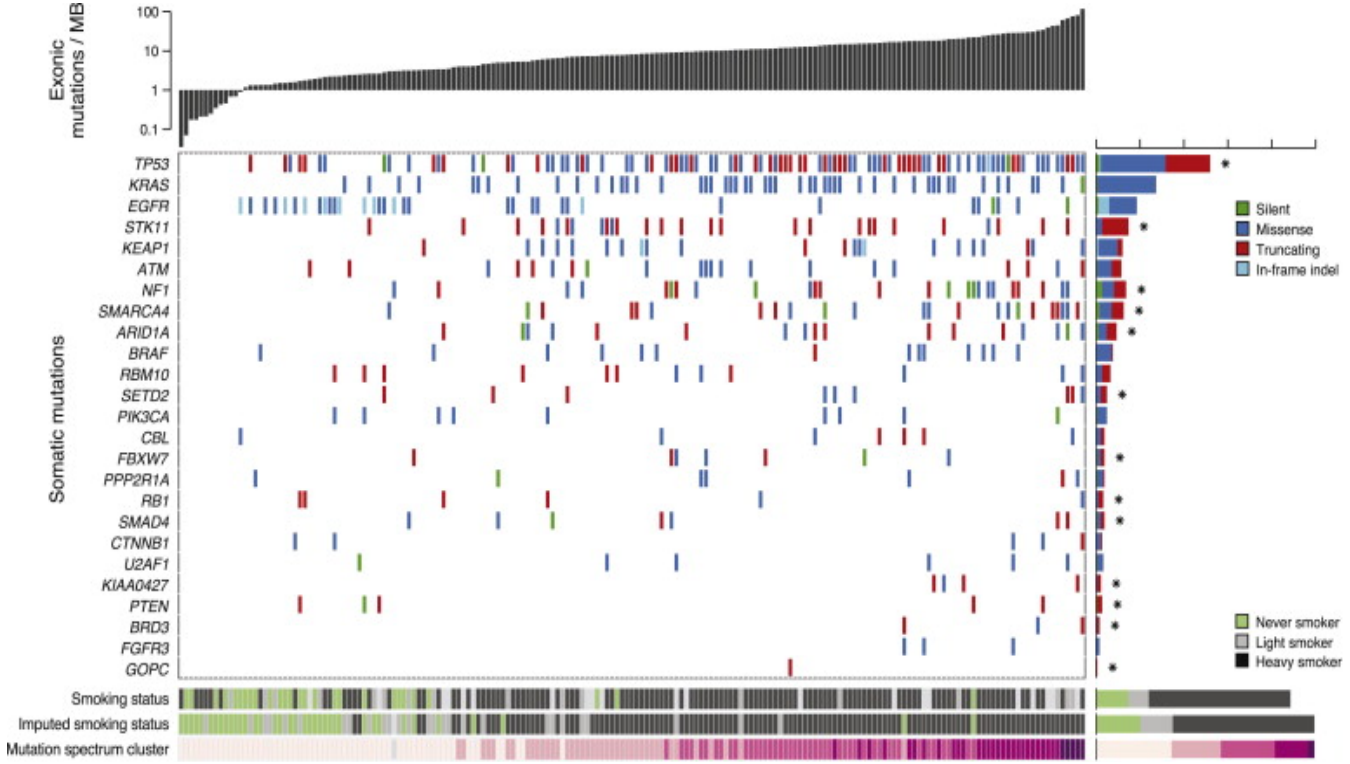
- Frequency of non-synonymous mutations varied by more than 1,000-fold across cancer types
- Paediatric cancers showed frequencies as low as 0.1/Mb (~ one change across the entire exome), whereas at the opposite extreme, melanoma and **lung cancer** exceeded 100/Mb



Lawrence et al., Nature 2013

Massively Parallel Sequencing of lung adenocarcinoma

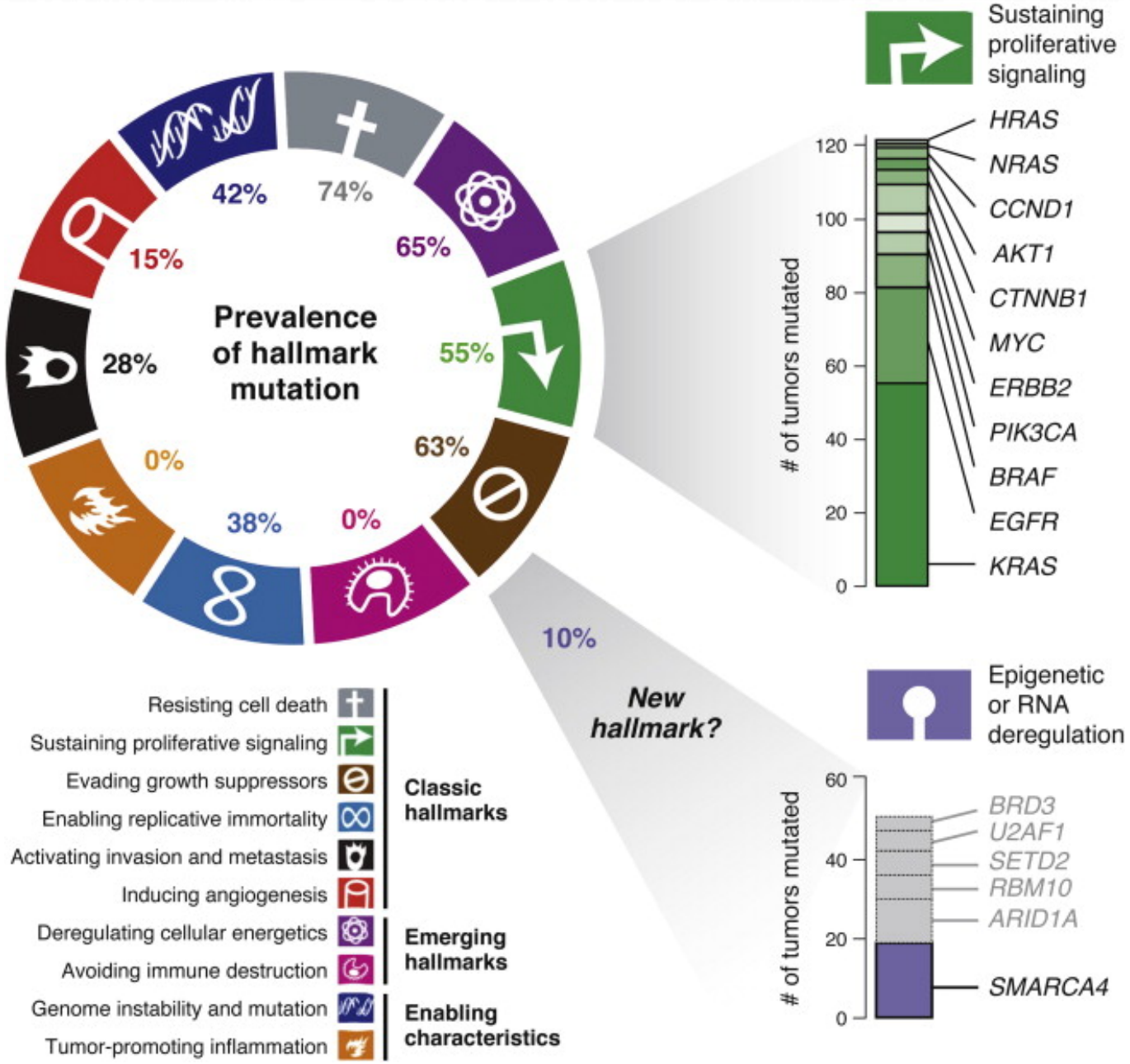




- Known genes include *TP53*, *KRAS*, *EGFR*, *STK11*
- Novel genes include *ARID1A*, *RBM10, U2AF1*
- Structural alterations:
  - rearrangement of tumor suppressors
  - in-frame *EGFR* deletion

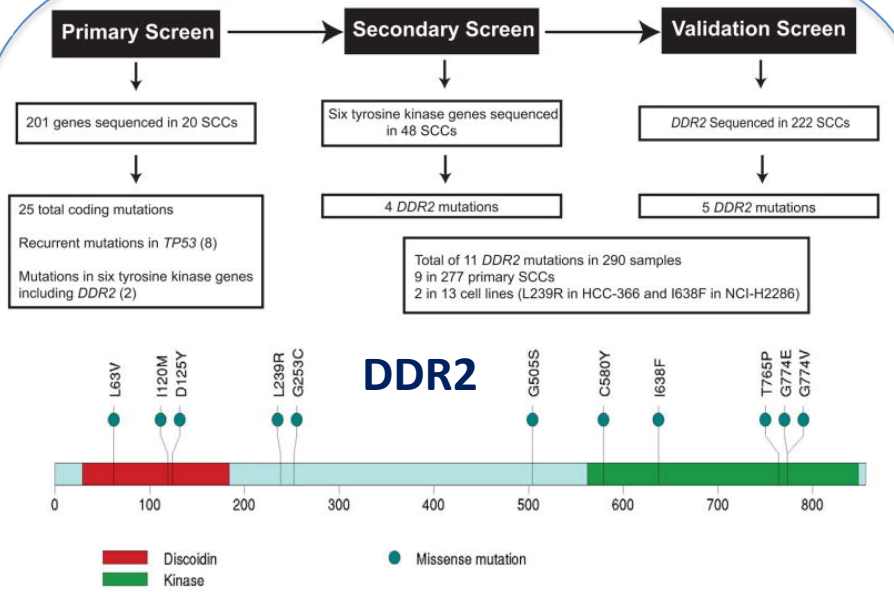
Imielinski et al., Cell 2012

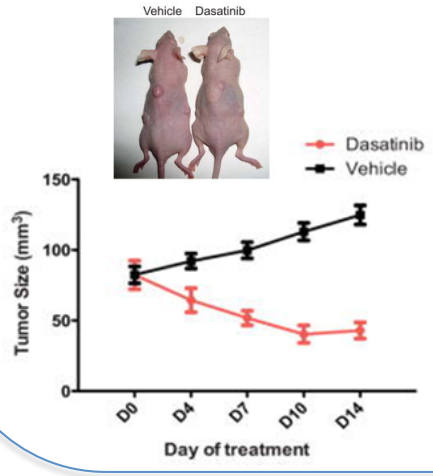
Mapping the “next generation” hallmarks

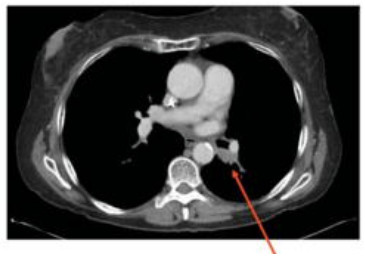


Novel targets

The Cancer Genome Atlas (TCGA) showed that FGFR tyrosine kinases are frequently altered in SCC (Hammerman et al, Nature 2012)

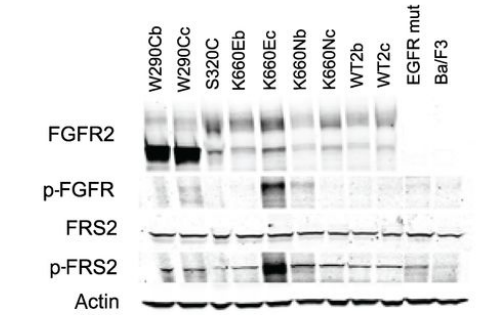




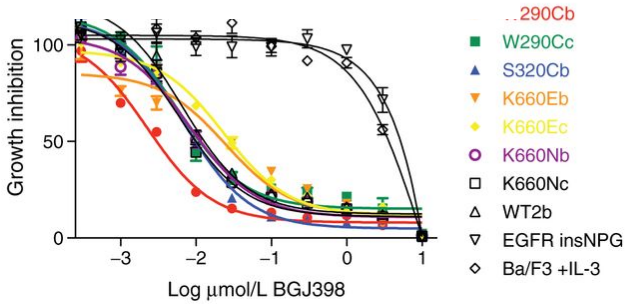


PR to dasatinib

Hammerman at al, Cancer Disc 2012



FGFR2

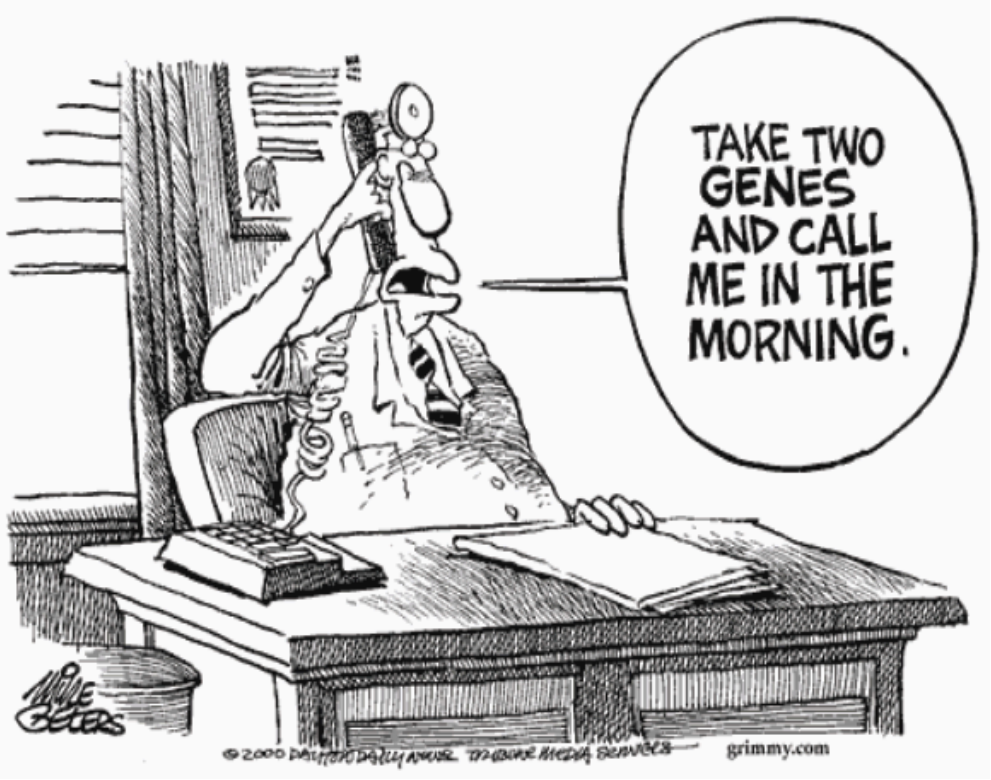


1 H&N patient with *FGFR2 P253R mut* had an impressive response to pazopanib (Liao et al, Cancer Res 2013)

Ongoing trials with FGFR inhibitors in patients harboring FGFR events NCT01004224, NCT01457846 & NCT00979134

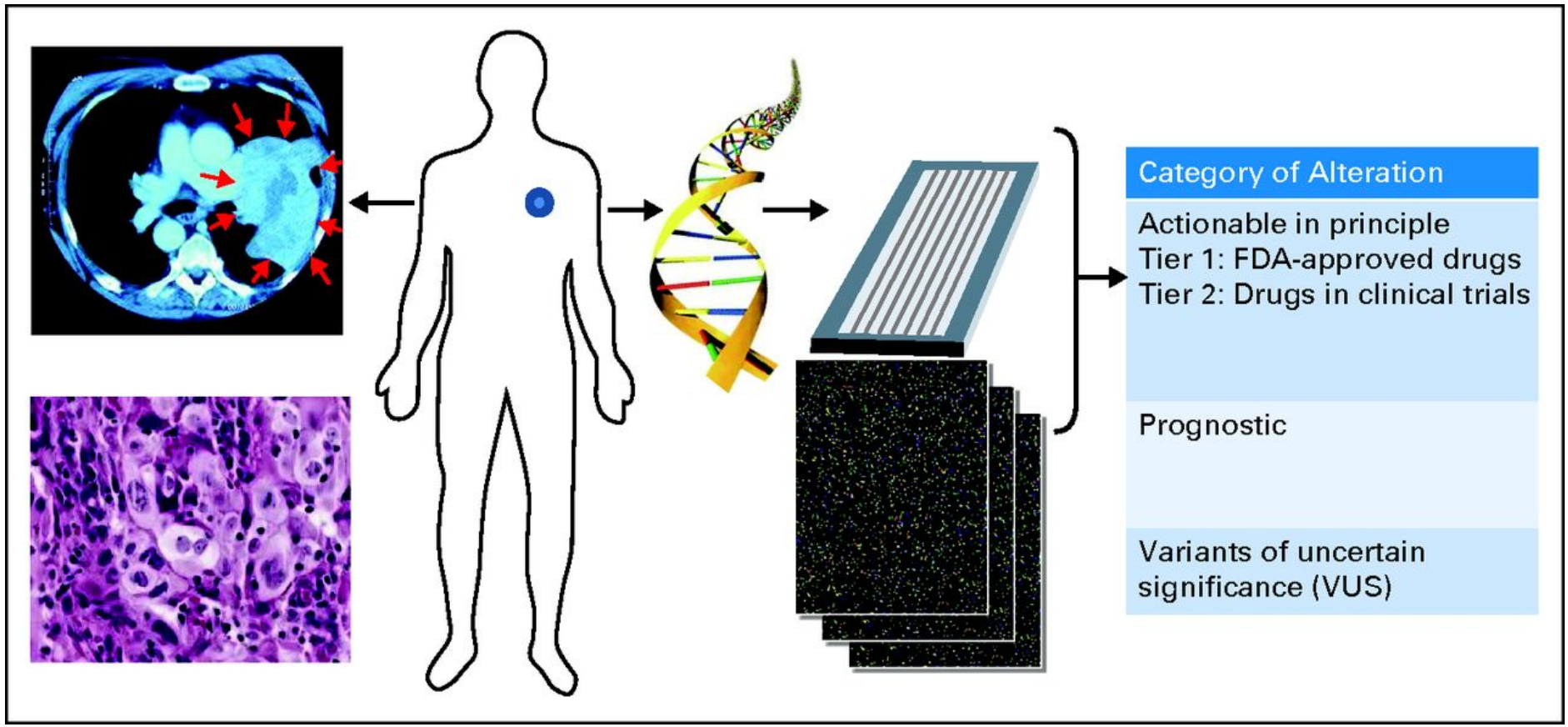
The ultimate goal

Using genomic information from each individual patient to guide the treatment



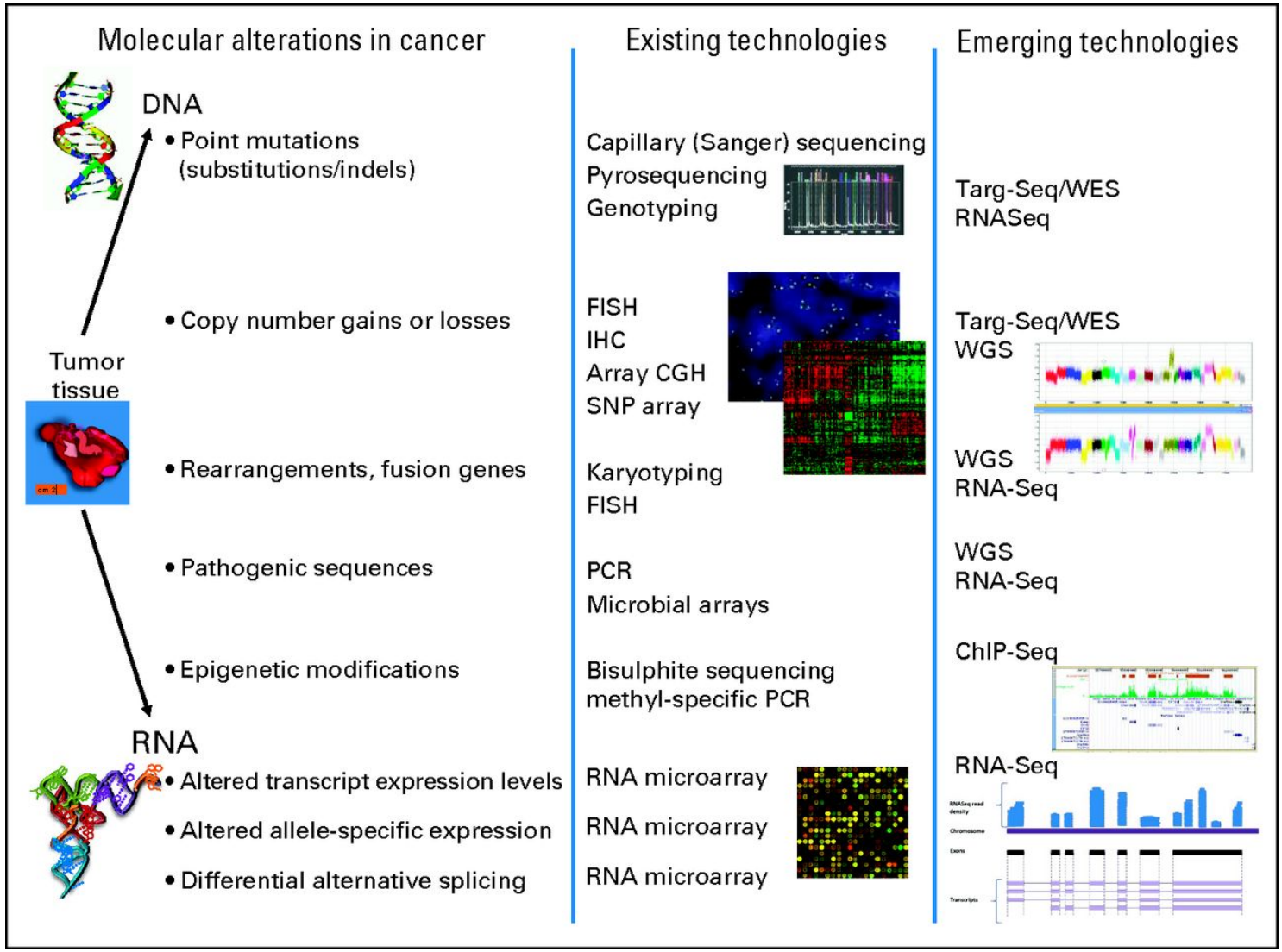
Towards “precision oncology”

The term “precision” refers to prospects for enhanced molecular resolution, mechanistic clarity, and therapeutic cogency that may accompany clinical implementation of genomics technologies



Garraway et al, J Clin Oncol 2013

A technology & economical revolution



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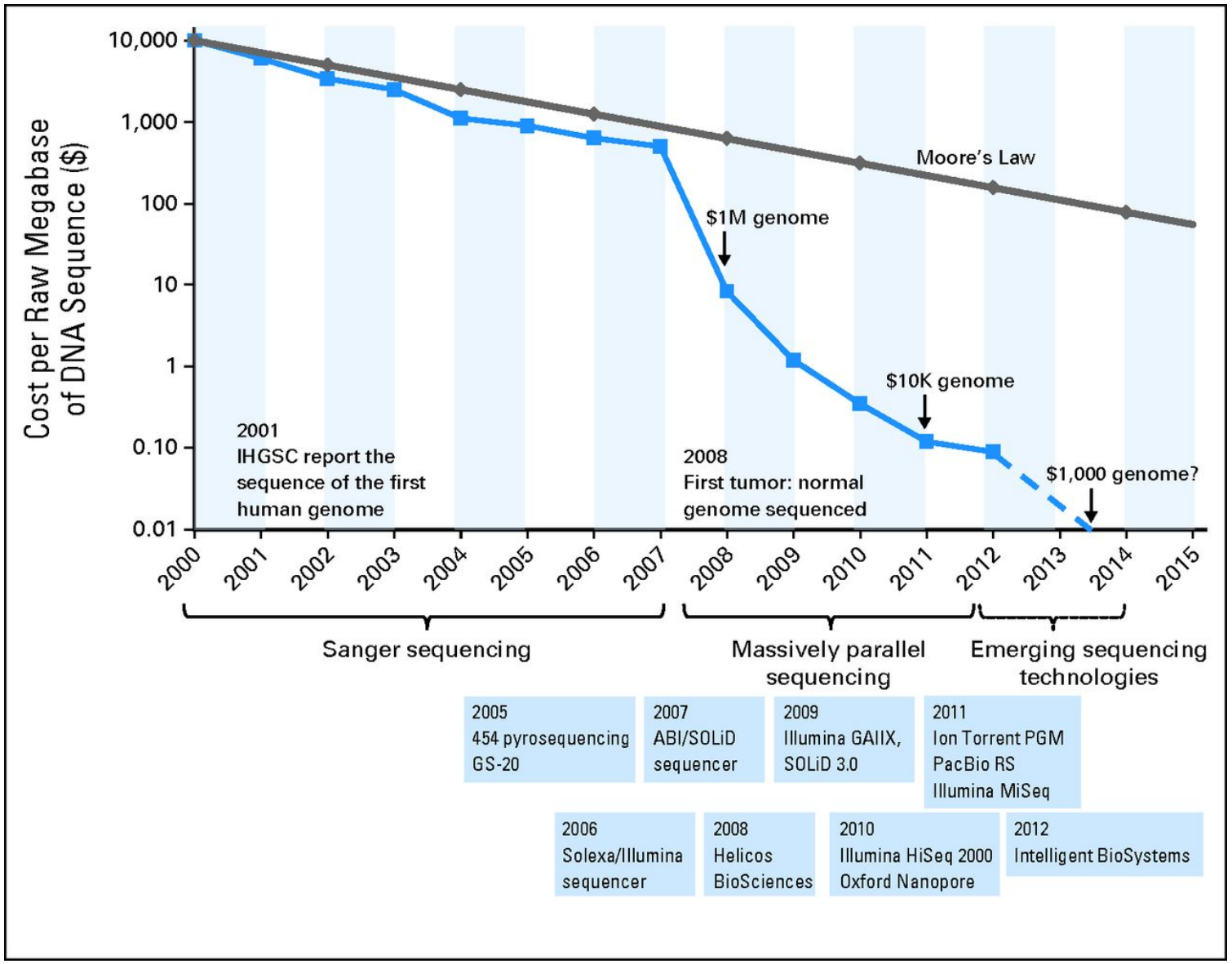
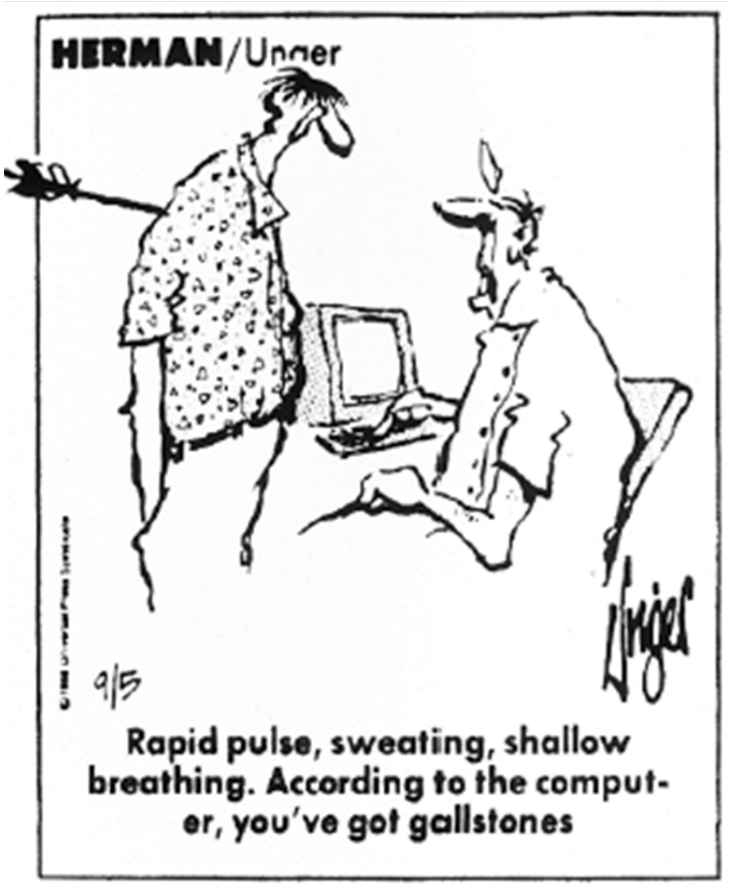


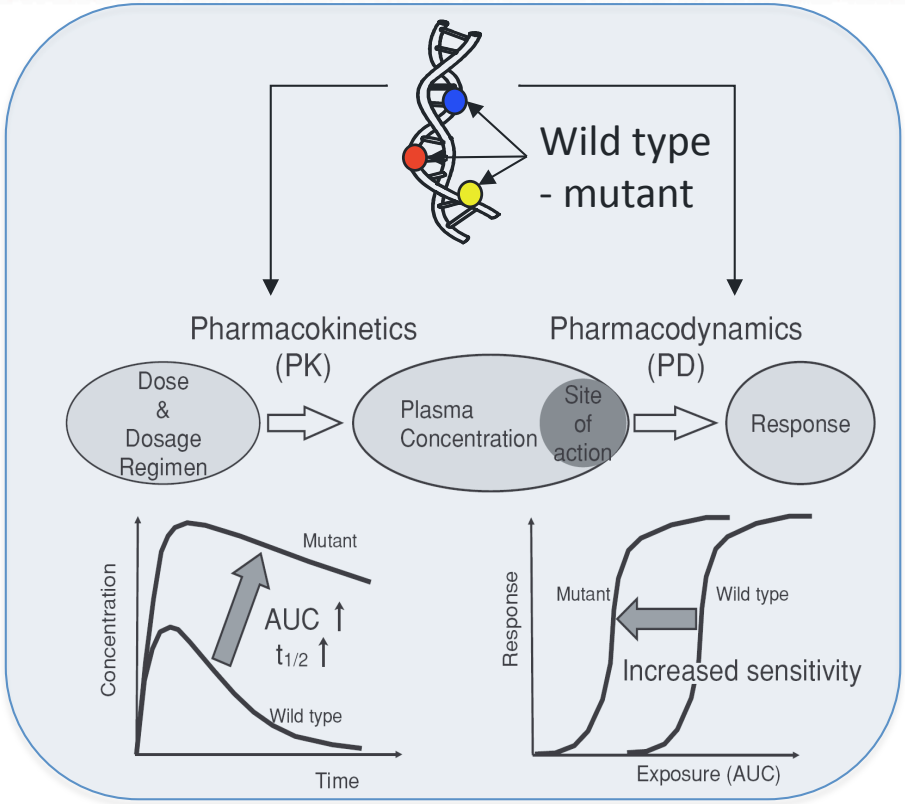
Major challenges

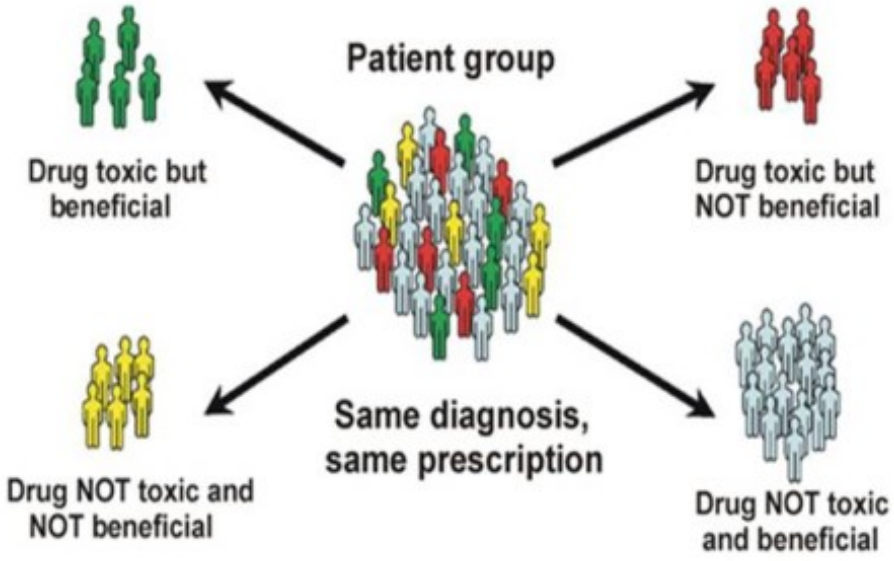
- Sparse amount of tissue
- Tumor heterogeneity
- Build adequate infrastructure
- Analytical challenges in the interpretation of computational algorithms
- Clinical trial design challenges
- Ethical issues for genetic studies and data sharing



Pharmacogenetics

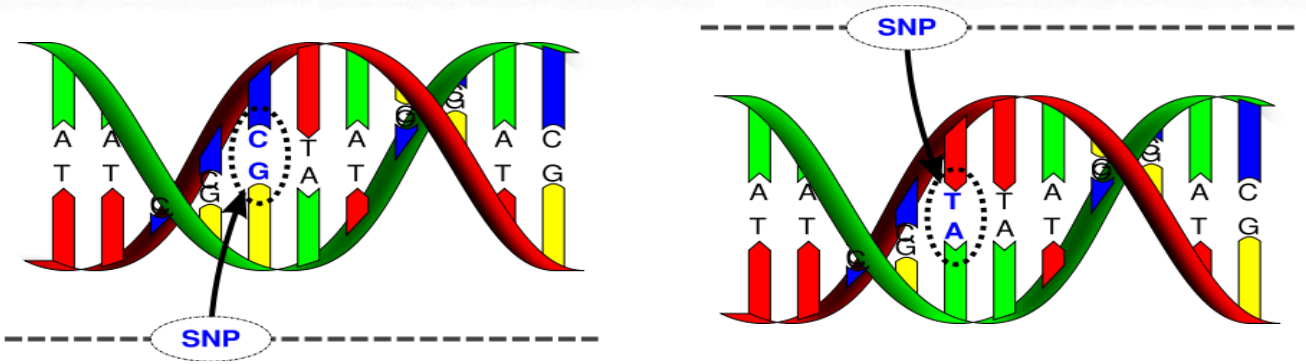
➢**Pharmacogenetics** is the study or clinical testing of **genetic variations** that give rise to **differing drug response**, including disposition, tolerability, and efficacy





➢**Towards personalized medicine**

Pharmacogenetic studies



Single-gene approach

- Analyses the favourite candidate gene
- Requires a large cohort to test the association
- – Carries the risk of not finding an association
- \+ Provides proof of principle if an association is found

Genome-wide approach

- Analyses the whole genome (expression and SNP)
- Requires smaller cohorts to test associations
- – Biological meaning is difficult to assess because this approach carries a risk of false positives
- \+ Might identify new associations

Drug-related phenotype

Candidate-pathway-gene approach

- Analyses several functionally related candidate genes
- Requires a smaller cohort to test the association
- – Carries the risk of missing important genes
- \+ Provides a more biologically meaningful association

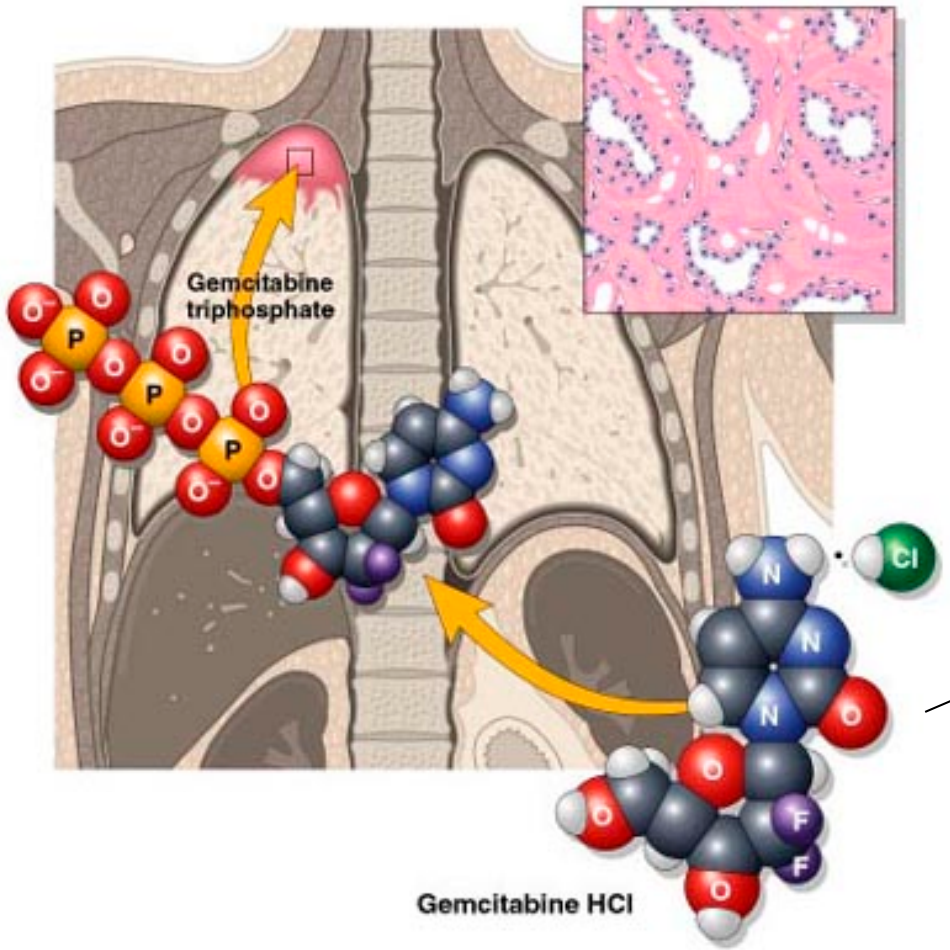
Cheok & Evans,
Nat Rev Cancer 2006

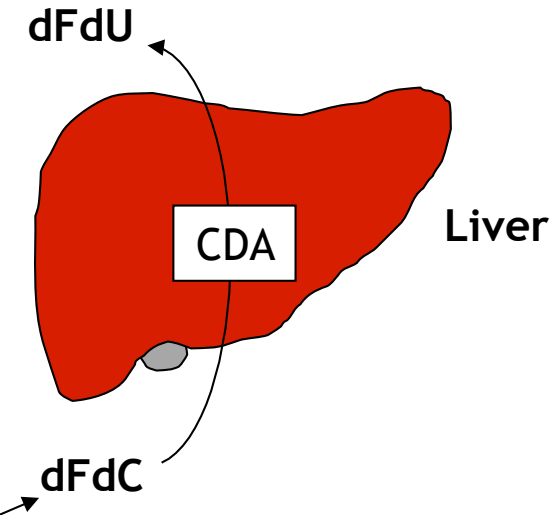
A SNP to predict gemcitabine activity: CDA

Pharmacogenetics

Pharmacodynamics

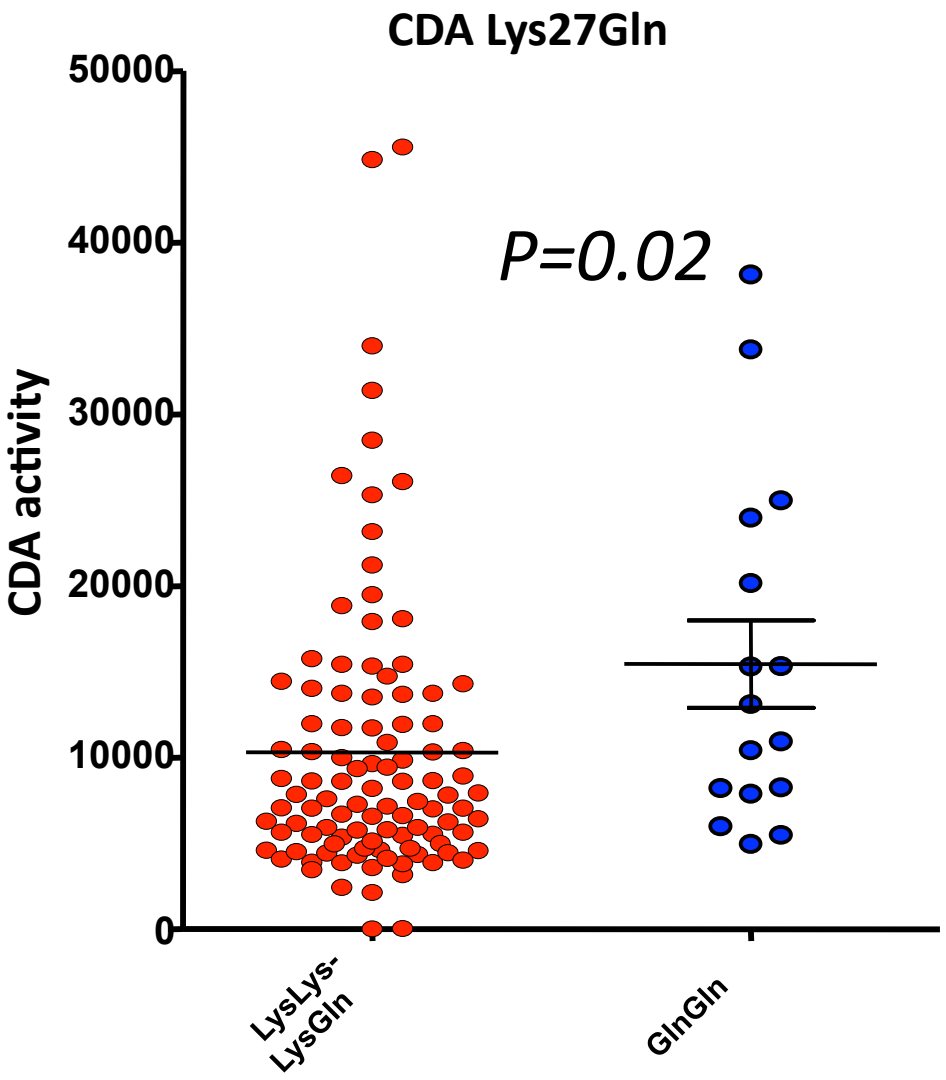
Pharmacokinetics

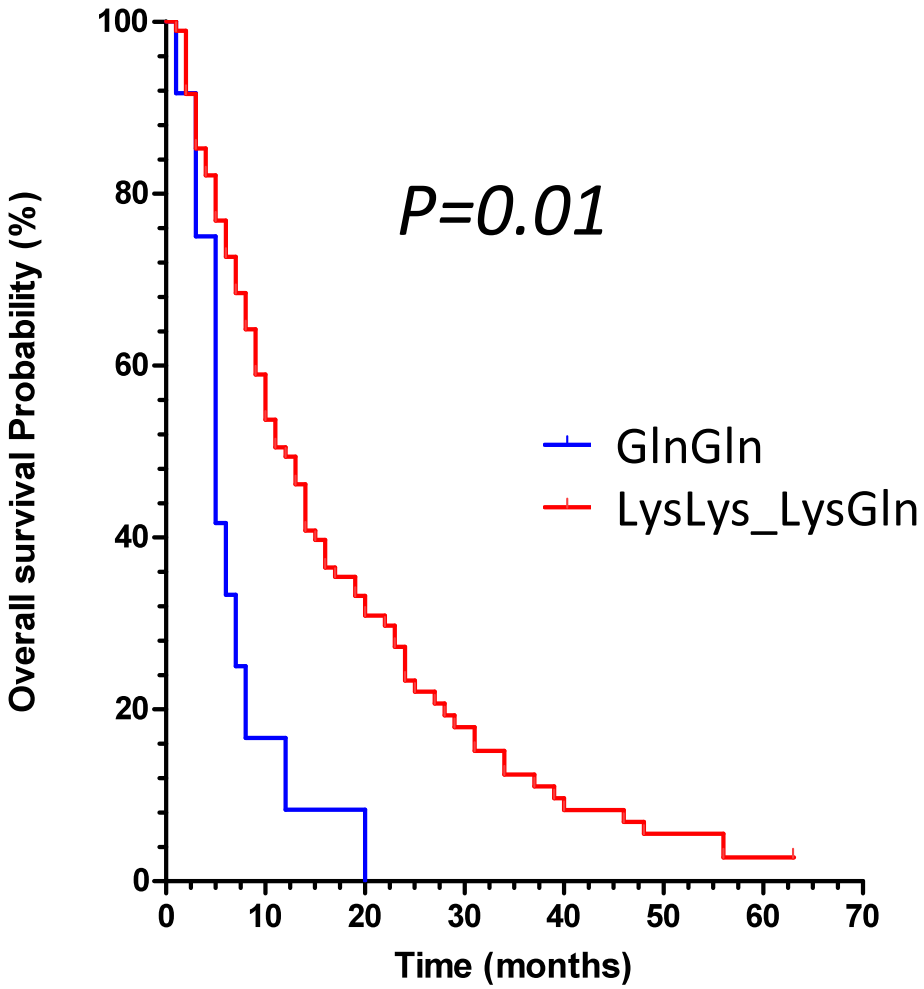




Difluorodeoxycytidine (dFdC)

A SNP to predict gemcitabine activity: CDA





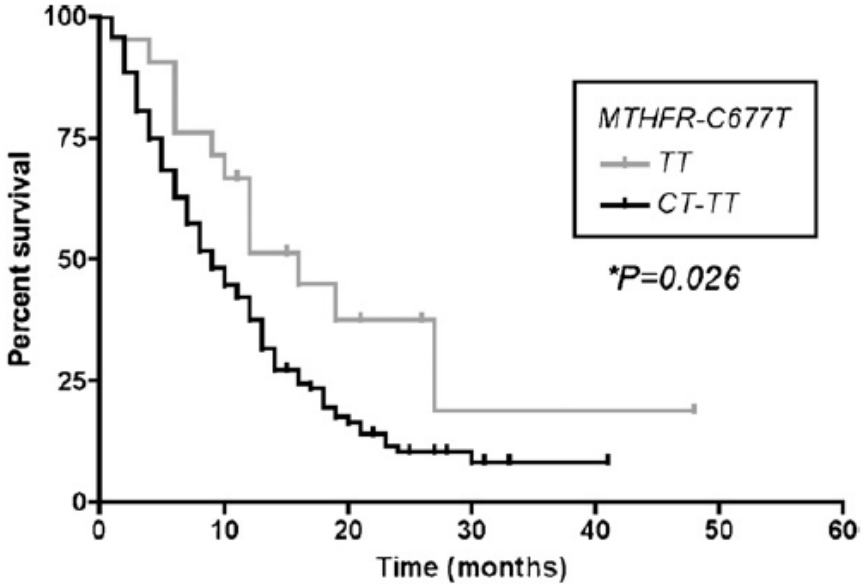
Tibaldi, Giovannetti, et al, Clin Cancer Res 2008
Tibaldi, Giovannetti, Tiseo et al, Ann Oncol 2012

A SNP to guide pemetrexed therapy

Pharmacogenetic study of 6 candidate SNPs in folate pathway in advanced NSCLC patients treated with second-line pemetrexed or pemetrexed–carboplatin

Clinical characteristics.

Characteristic	Patients, *n* (%)
No. patients	208
Age, median [range] yrs	60 [36–84]
≤65	136 (65.4)
>65	72 (34.6)
Sex	
Male	131 (63.0)
Female	77 (37.0)
Stage	
IIIB	39 (18.8)
IV	169 (81.2)
Histology	
Squamous cell carcinoma	49 (23.6)
Adenocarcinoma	106 (51.0)
Large cells	35 (16.8)
Not otherwise specified (NOS)	18 (8.6)
ECOG PS	
0	71 (34.1)
1–2	137 (65.9)
Therapy	
Pemetrexed	115 (55.3)
Pemetrexed + carboplatin	93 (44.7)



Factors associated with OS and PFS in the multivariate analysis.

	Multivariate analysis		
	Hazard ratio (95%CI)	df	*p*
Covariates for OS			
ECOG-PS			
0	0.67 (0.48–0.94)	1	0.021
1–2	1 (ref.)		
MTHFR-C677T			
CC–CT	2.00 (1.12–3.54)	1	**0.018**
TT	1 (ref.)		
Covariates for PFS			
ECOG-PS			
0	0.72 (0.52–0.99)	1	0.050
1–2	1 (ref.)		
Histology			
Squamous	1.41 (1.01–1.99)	1	0.046
Non-squamous	1 (ref.)		
MTHFR-C677T			
TT	1 (ref.)	1	**0.012**
CC–CT	1.94 (1.15–3.28)		

df, degrees of freedom; DFS, disease free survival; OS, overall survival, PS, performance status. Significant values in bold.

Tiseo, Giovannetti, et al, Lung Cancer 2012

Conclusions and Future Perspectives

New technologies identified aberrations, which:

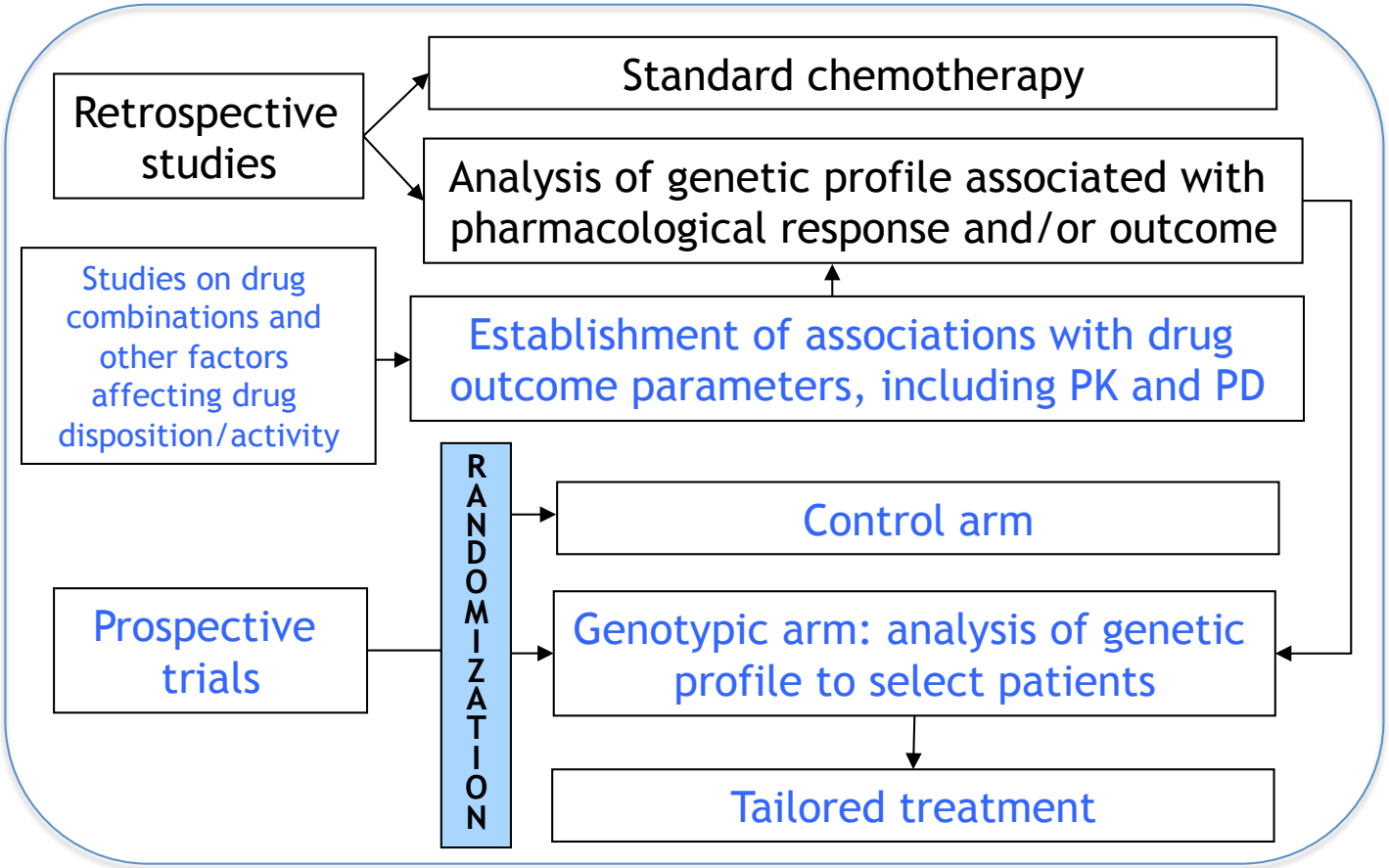
✓are correlated with lung cancer aggressive behaviour and chemosensitivity

✓represent promising targets for novel prognostic and therapeutic approaches

✓*might identify surrogate indicators, in more accessible tissues*

A major drawback has been the lack of a systematic approach to advancing the use of biomarkers in anticancer drug development

Hopefully, novel biomarkers will be validated in prospective studies in the near future



Acknowledgements

SIGILLVM • ALMAE • VNIVERSITATIS • STVDII • PARMENSIS

SST Azienda USL 6 Livorno
Servizio Sanitario della Toscana

EORTC
European Organization for Research and Treatment of Cancer

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MARIE CURIE ACTIONS

NWO
Nederlandse Organisatie voor Wetenschappelijk Onderzoek