La Ricerca Traslazionale nelle neoplasie polmonari:
stato dell'arte ed esperienze di ricerca

Parma, 27 novembre 2019

FARMACOGENOMICA nelle neoplasie polmonari

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Incipit

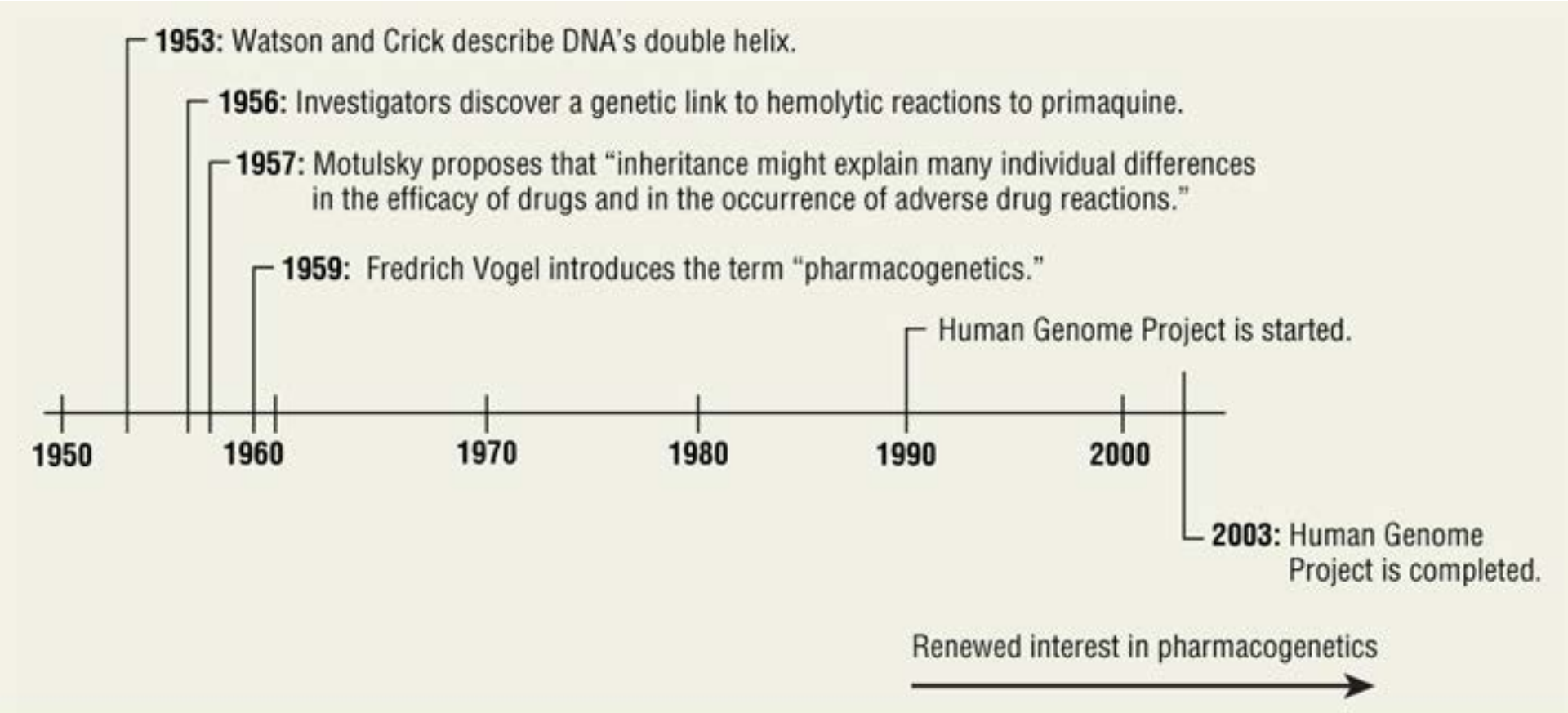
Stat Rosa pristina nomine,
nomina nuda tenemus

"The ancient Rose remains by its name, naked names (are all that) we have"

Picture at Marconi – Bologna Airport

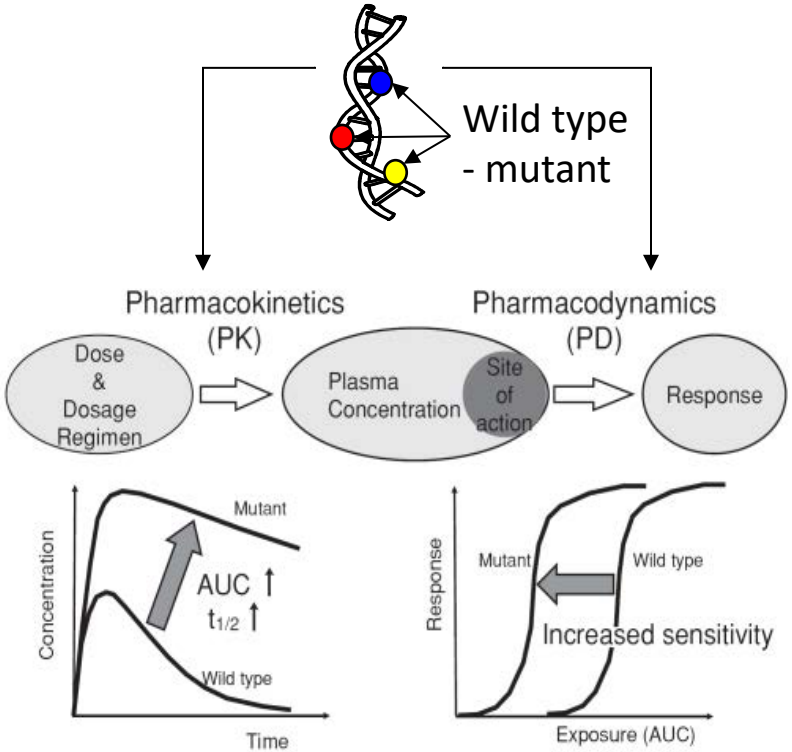
Pharmacogenetics & pharmacogenomics

- No universally accepted definitions of either
- Often used intechangeably
- The term pharmacogenomics coined in connection with the Human genome project

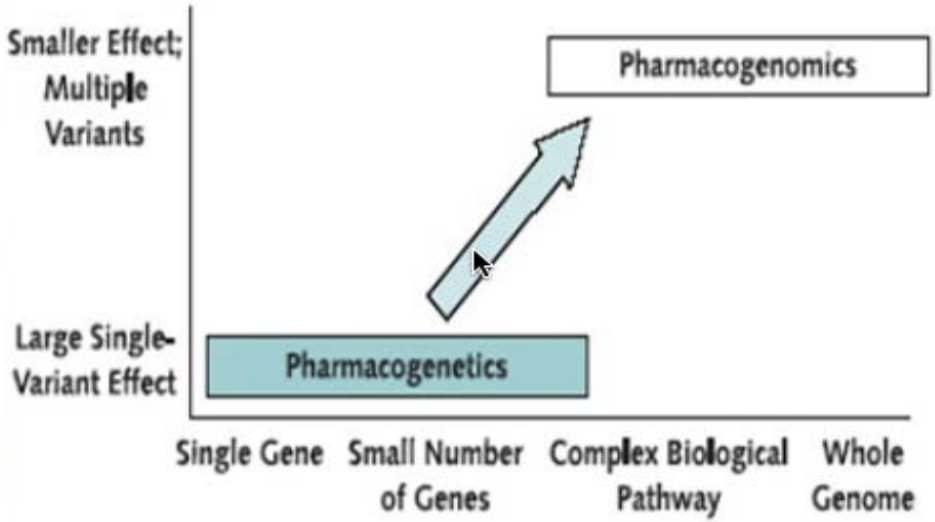


Pharmacogenetics & pharmacogenomics

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



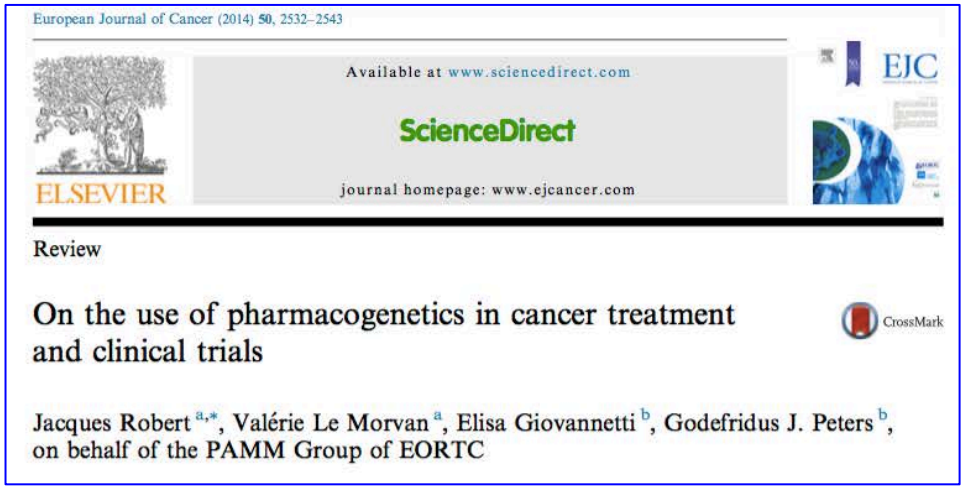
Adapted from J Clin Oncol 2005



Adapted from Ann Internal Med 2006

➢ **Pharmacogenomics** is the study of the role of **all the genome** in **drug response**

Pharmacogenetics & pharmacogenomics



European Journal of Cancer (2014) 50, 2532–2543

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC

Review

On the use of pharmacogenetics in cancer treatment and clinical trials

CrossMark

Jacques Robert [a,*], Valérie Le Morvan [a], Elisa Giovannetti [b], Godefridus J. Peters [b], on behalf of the PAMM Group of EORTC

Pharmacogenetics focuses on the association of one gene or several genes with drug activity, while
pharmacogenomics considers the whole genome,
through the broader application of new genomic technologies

However, in oncology
pharmacogenetics is often considered as concerning the individual patient's features and
pharmacogenomics as those of the tumour

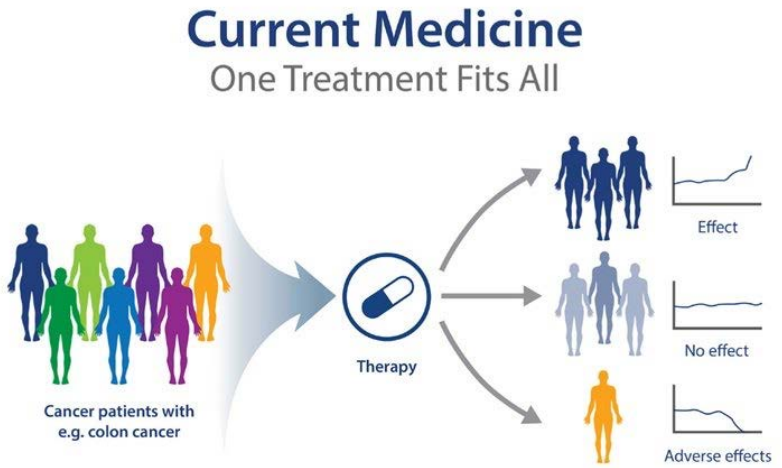
Pharmacogenetics & pharmacogenomics

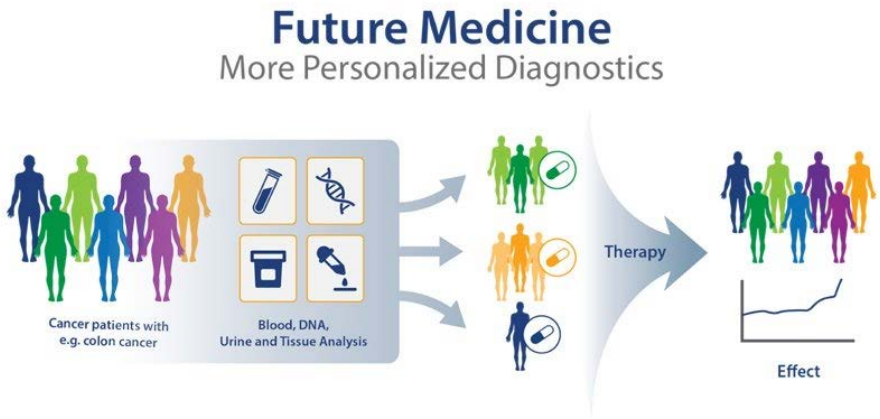
Goals

- Maximize drug efficacy
- Minimize drug toxicity

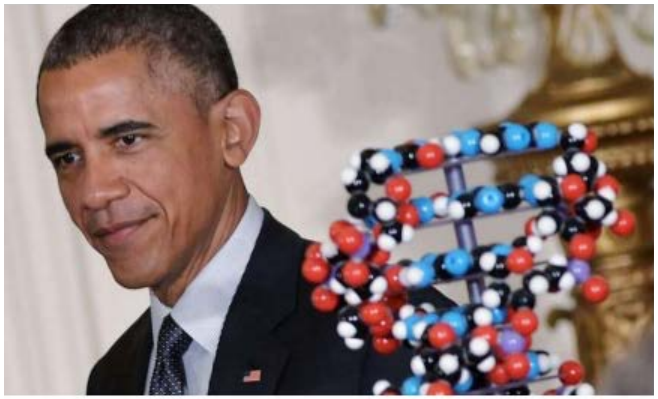
- Predict patients who will respond

- Aid in new drug discovery/development
- Decrease in costs of health care





The Precision Medicine Initiative



"an unprecedented effort to accelerate a new era of medicine, focused on delivering more tailored treatment and preventive strategies"

President's 2015 State of the Union address

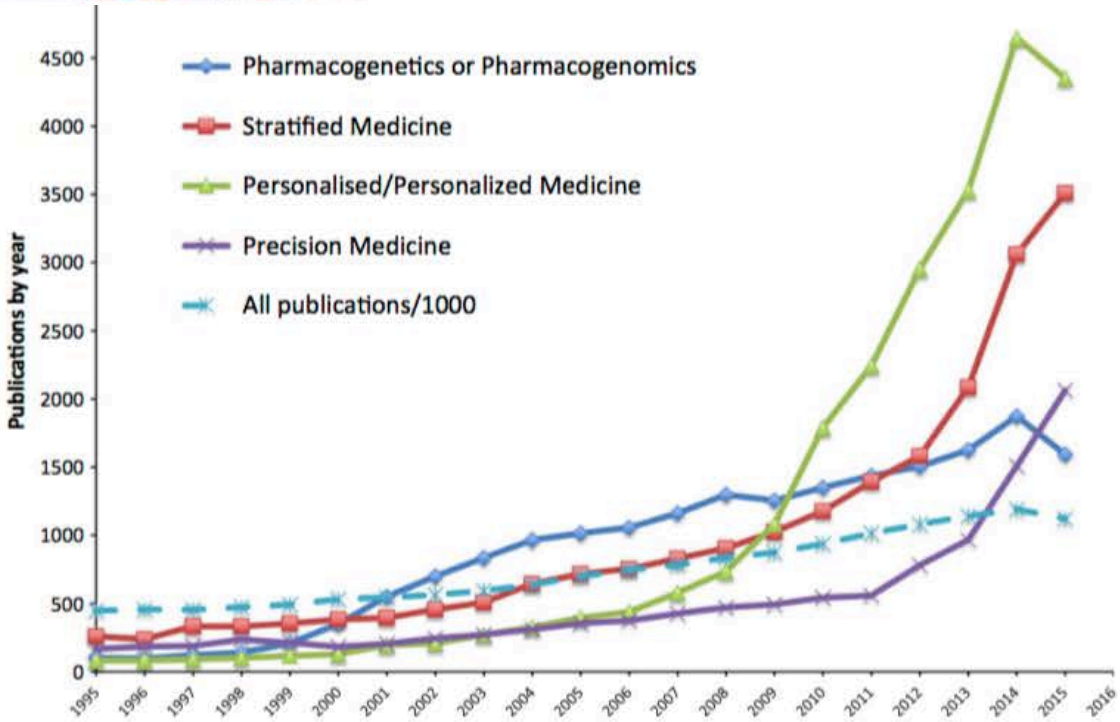
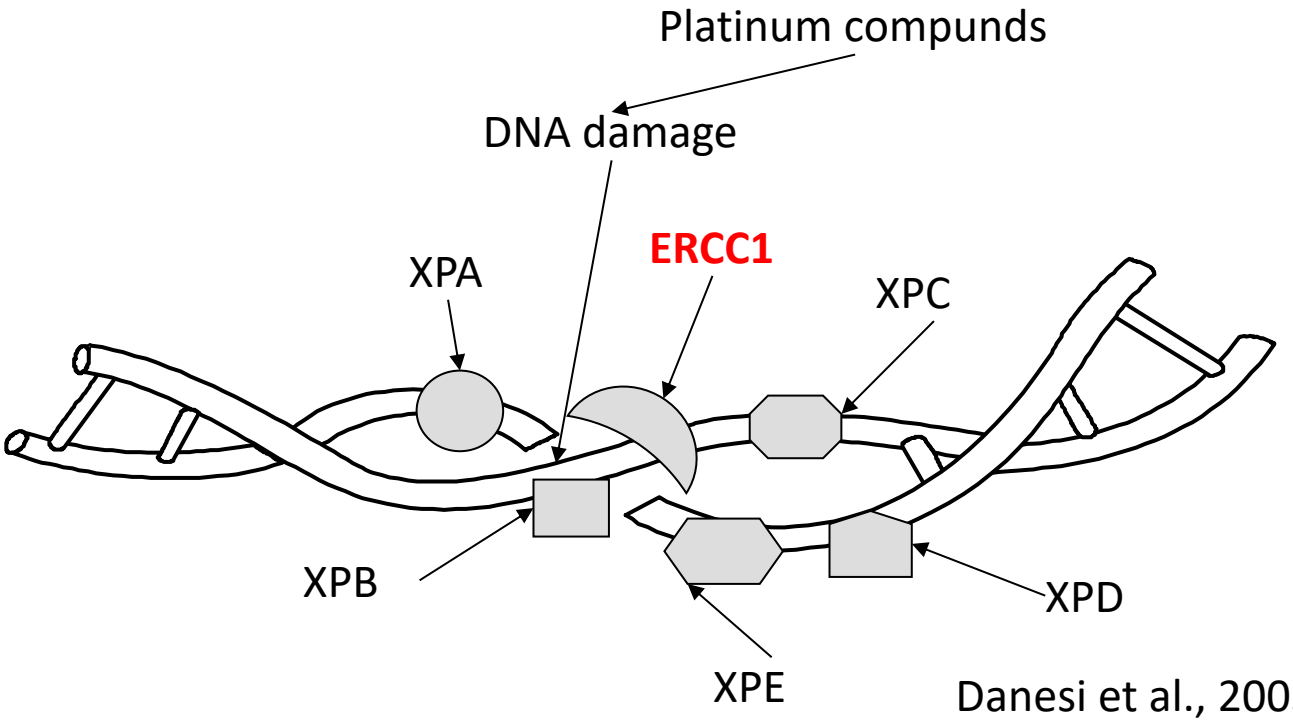


FIGURE 1 The number of publications per year where the search term was in the title. The search terms were (Pharmacogenetics OR Pharmacogenomics), 'Stratified Medicine', ('Personalised Medicine' OR 'Personalized Medicine'), 'Precision Medicine'. All publications (dashed line) were restricted by year with no search term and the total number was divided by 1000 to enable use of the same scale.

Pharmacogenetics of NSCLC

"A number of pharmacogenetic studies have been carried out in non-small-cell lung cancer (NSCLC) to identify and characterize genes involved in chemotherapy activity. However, the results obtained so far are controversial and no reliable biomarker is currently used to predict clinical benefit from platinum-based chemotherapy" - Toffalorio et al., 2018



Danesi et al., 2005

The most advanced biomarker to predict cisplatin efficacy seems **ERCC1** expression

ERCC1: highs and lows, …and a potential explanation

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 7, 2006 VOL. 355 NO. 10

DNA Repair by ERCC1 in Non–Small-Cell Lung Cancer and Cisplatin-Based Adjuvant Chemotherapy

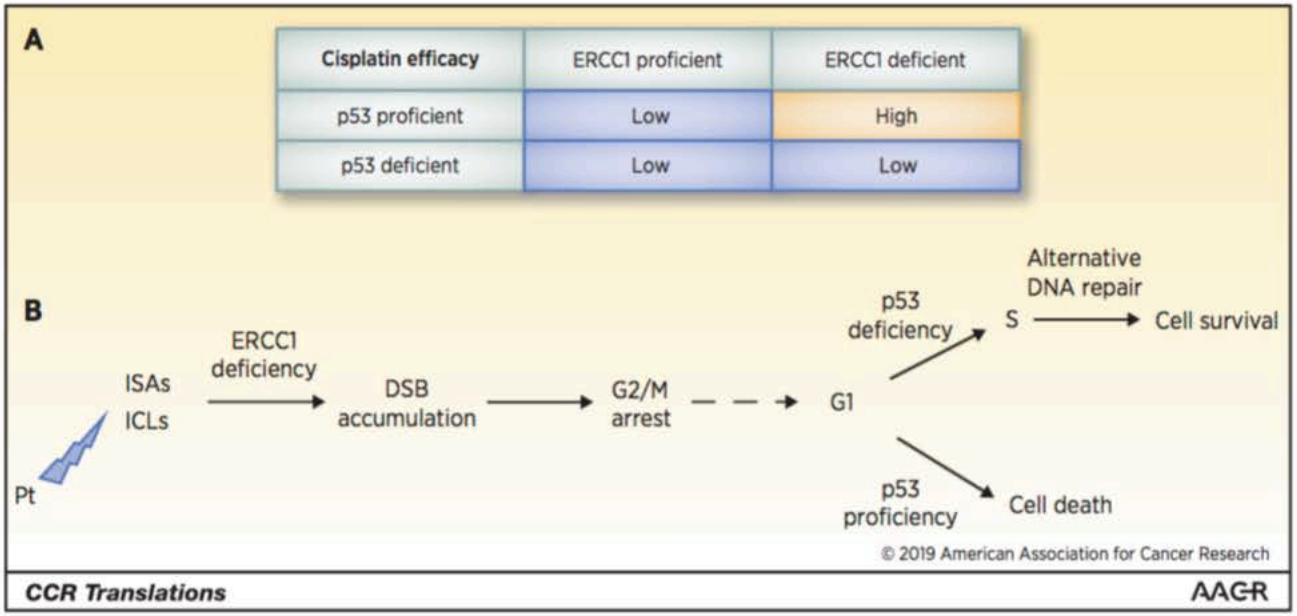
Ken A. Olaussen, Ph.D., Ariane Dunant, M.S., Pierre Fouret, M.D., Ph.D., Elisabeth Brambilla, M.D., Ph.D., Fabrice André, M.D., Ph.D., Vincent Haddad, M.S., Estelle Taranchon, M.S., Martin Filipits, Ph.D., Robert Pirker, M.D., Helmut H. Popper, M.D., Rolf Stahel, M.D., Ph.D., Laure Sabatier, Ph.D., Jean-Pierre Pignon, M.D., Ph.D., Thomas Tursz, M.D., Ph.D., Thierry Le Chevalier, M.D., and Jean-Charles Soria, M.D., Ph.D., for the IALT Bio Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

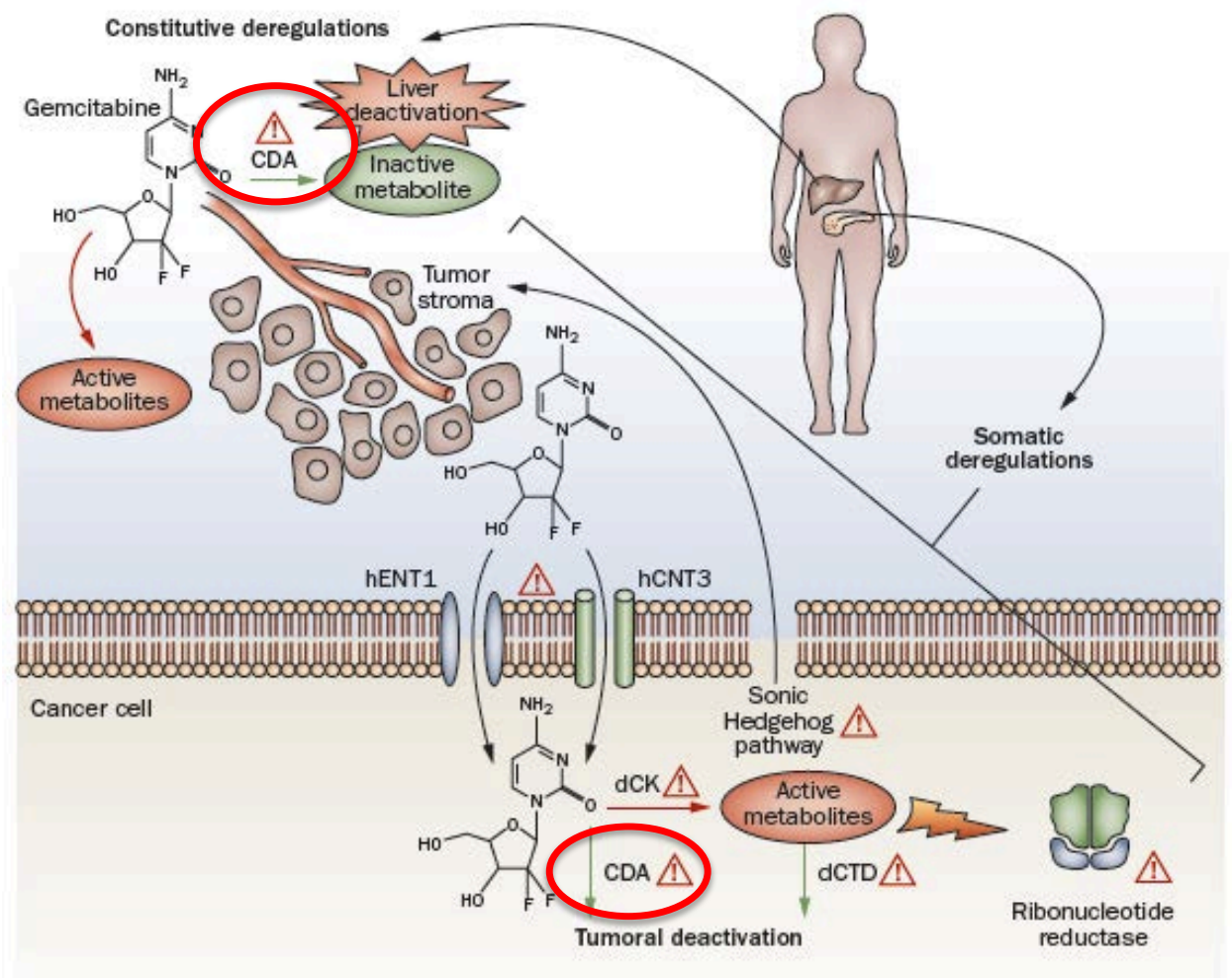
ERCC1 Isoform Expression and DNA Repair in Non–Small-Cell Lung Cancer

"We were unable to validate the predictive effect of immunostaining for ERCC1 protein. The discordance in the results of staining for ERCC1 suggested a change in the performance of the 8F1 antibody"



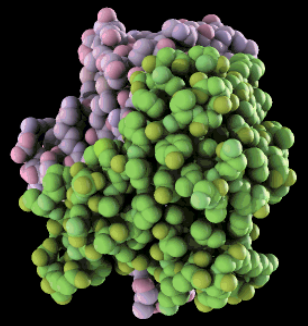
The "Guardian of the genome" – an old key to unlock the ERCC1 issue
Friboulet et al, commentary to Heyza et al., CCR Feb 2019

Pharmacogenetics of gemcitabine



Several studies evaluated polymorphisms of CDA

CDA structure



http://qutemol.sourceforge.net/
by Dr. M Tarini, CNR Pisa

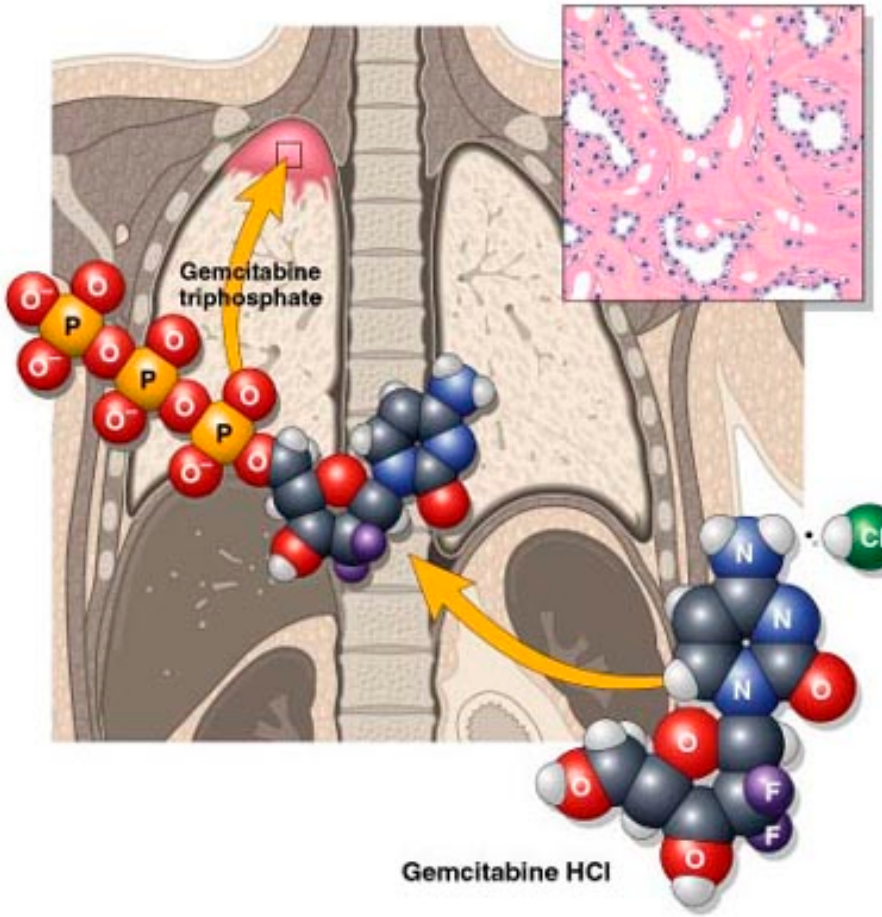
Ciccolini et al.,
Nat Rev Cancer 2011

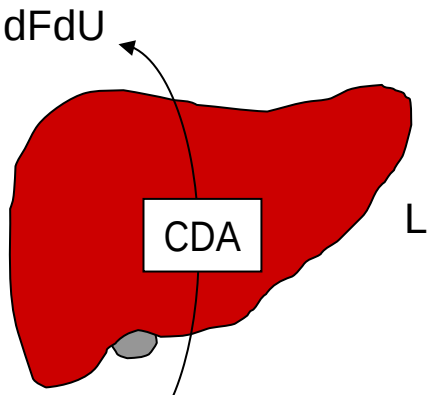
Evaluating CDA to predict gemcitabine activity

Pharmacogenetics

Pharmacodynamics

Pharmacokinetics

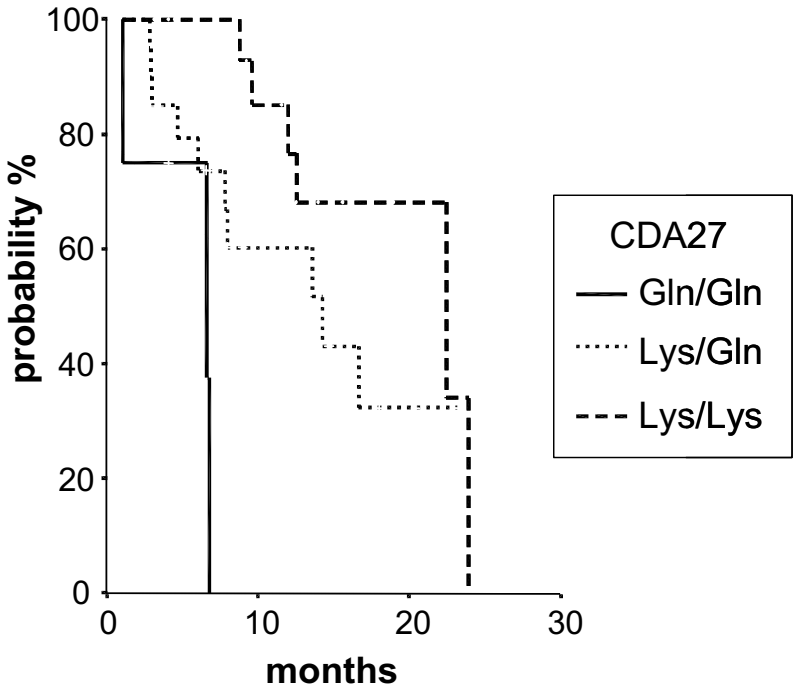




Difluorodeoxycytidine (dFdC)

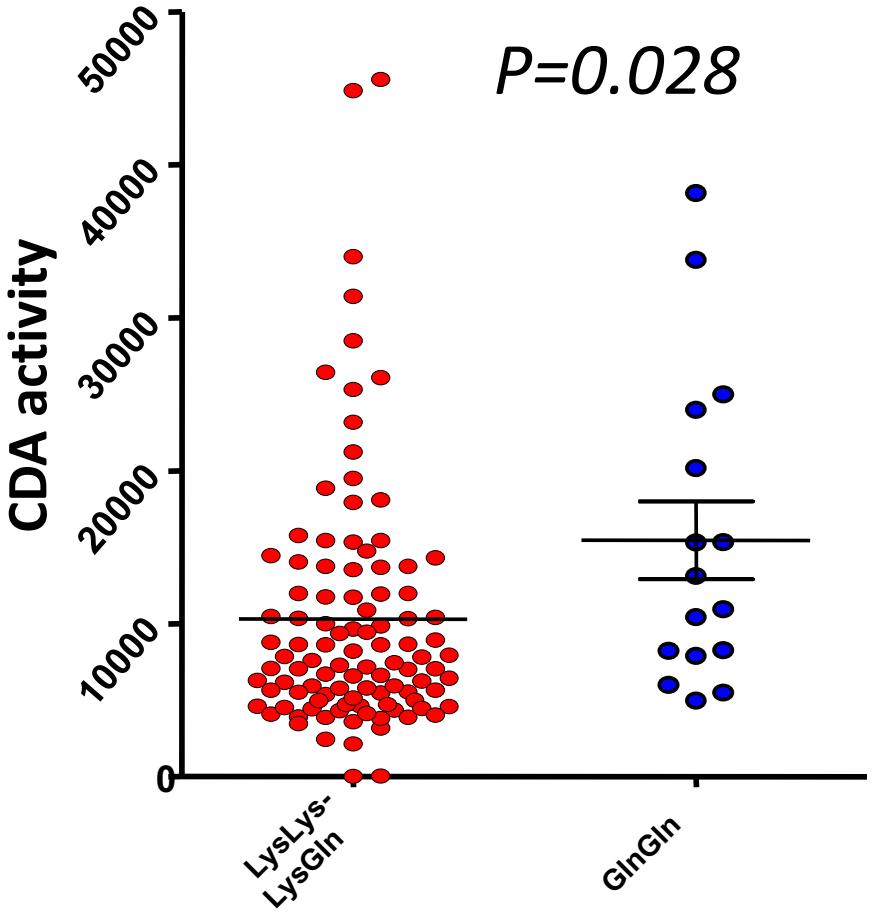
…from a genotype to a phenotype biomarker

Genotype	PR+SD	PD	P
	No. patients (%)		
CDA Lys[27]Gln			
Lys/Lys	25 (92.6)	2 (7.4)	0.04
Lys/Gln	22 (75.9)	7 (24.1)	
Gln/Gln	5 (55.6)	4 (44.4)	



Tibaldi et al., CCR 2008

Discussion on:
Ciccolini et al., J Clin Oncol 2010
Giovannetti et al., J Clin Oncol 2010



Giovannetti et al., NNNA 2008

…retrospective (and method) validation

Advanced NSCLC patients (N=132*) treated with gemcitabine-cisplatin, from Livorno (N=76) and Parma Civic Hospital (N=56)
*Genotype/Phenotype data in 126 patients

No significant association with:

- Response/ Clinical benefit

Trend toward significance with

- TTP (P=0.053)

Significant association with OS

Multivariate analysis

		Multivariate analysis		
	Covariates for OS	Hazard ratio (95% CI)	df	*P*
Sex	Female	0.628 (0.353–1.118)		0.114
	Male	1 (ref.)	1	
Histology	Adenocarcinoma	0.619 (0.358–1.068)		0.085
	Epidermoid carcinoma	1 (ref.)	1	
CDA A79C	AA-AC	0.357 (0.163–0.786)		0.011
	CC	1 (ref.)	1	
CDA C435T	CC-CT	0.794 (0.335–1.881)		0.600
	TT	1 (ref.)	1	
CDA activity	Low	0.512 (0.310–0.846)		0.009
	High	1 (ref.)	1	

Tibaldi et al, Ann Oncol 2012

SELECTION OF THE BEST BLOOD COMPARTMENT TO MEASURE CYTIDINE DEAMINASE ACTIVITY TO STRATIFY FOR OPTIMAL GEMCITABINE OR CYTARABINE TREATMENT

Nucleosides, Nucleotides and Nucleic Acids 2012

Godefridus J. Peters,[1] Richard J. Honeywell,[1] Marie Maulandi,[1,2] Elisa Giovannetti,[1] Nienke Losekoot,[1] Marie-Christine Etienne-Grimaldi,[3] Gerard Milano,[3] Cindy Serdjebi,[2] and Joseph Ciccolini,[2] for the EORTC-Pharmacology and Molecular Mechanism Group

[1]Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands
[2]Transfer Oncology Laboratory, Aix-Marseille University, Marseille, France
[3]Laboratoire d'Oncopharmacologie, Centre Antoine Lacassagne, Nice, France

EORTC
Pharmacology & Molecular Mechanisms Group
The future of cancer therapy

A prospective GOIRC study

The Cox proportional hazards regression model used for multivariate analysis confirmed CDA enzymatic activity as independent prognostic factor for progression and survival

Table 2. Multivariate analysis of CDA on progression-free survival (panel A) and overall survival (panel B) (cut-off 7.2 U/mg)

Parameter	DF	Parameter estimate	Standard error	Chi-square	Pr > Chisq	Hazard ratio	95% Confidence limits
Panel A							
Age	1	−0.01623	0.01491	1.1847	0.2764	0.984	0.956–1.013
Sex: female	1	0.55047	0.28231	3.8020	0.0512	1.734	0.997–3.016
ECOG PS 1	1	0.50064	0.23169	4.6691	0.0307	1.650	1.048–2.598
ECOG PS 2	1	1.20025	0.46382	6.6964	0.0097	3.321	1.338–8.243
Stage IIIB	1	−0.49090	0.27448	3.1987	0.0737	0.612	0.357–1.048
CDA high > 7.2	1	0.47659	0.22985	4.2993	0.0381	1.611	1.026–2.527
Panel B							
Age	1	−0.01091	0.01466	0.5536	0.4569	0.989	0.961–1.018
Sex: female	1	0.18483	0.25073	0.5434	0.4610	1.203	0.736–1.967
ECOG PS 1	1	0.64678	0.22697	8.1206	0.0044	1.909	1.224–2.979
ECOG PS 2	1	0.98242	0.41952	5.4839	0.0192	2.671	1.174–6.078
Stage IIIB	1	−0.81212	0.28671	8.0236	0.0046	0.444	0.253–0.779
CDA high > 7.2	1	0.58208	0.22099	6.9376	0.0084	1.790	1.161–2.760

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *CDA* cytidine deaminase

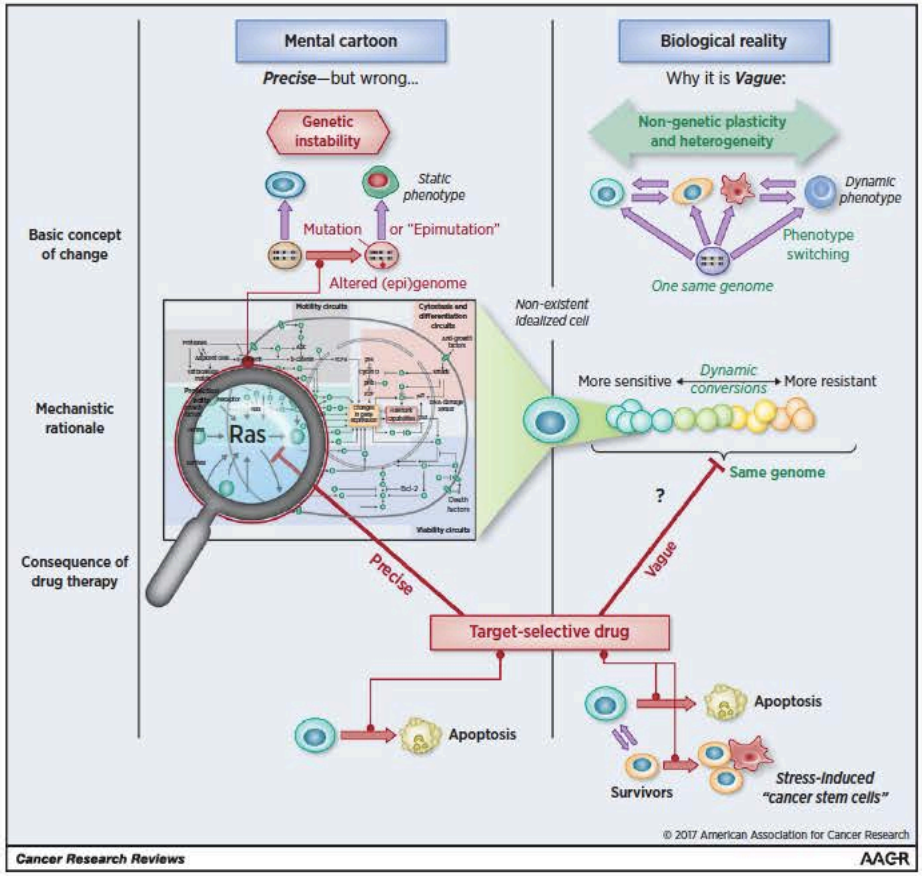
Large-scale validation in a phase-ii biomarker-trial, including a matched cohort of patients treated with another regimen, is needed to further verify the predictive potential of CDA

Future studies should also evaluate the modulation of CDA activity in inflammatory conditions

Tibaldi et al,
Br J Cancer 2018

Expanding “precision oncology” studies to embrace complexity

*“**Precision Oncology: Between Vaguely Right and Precisely Wrong**”*

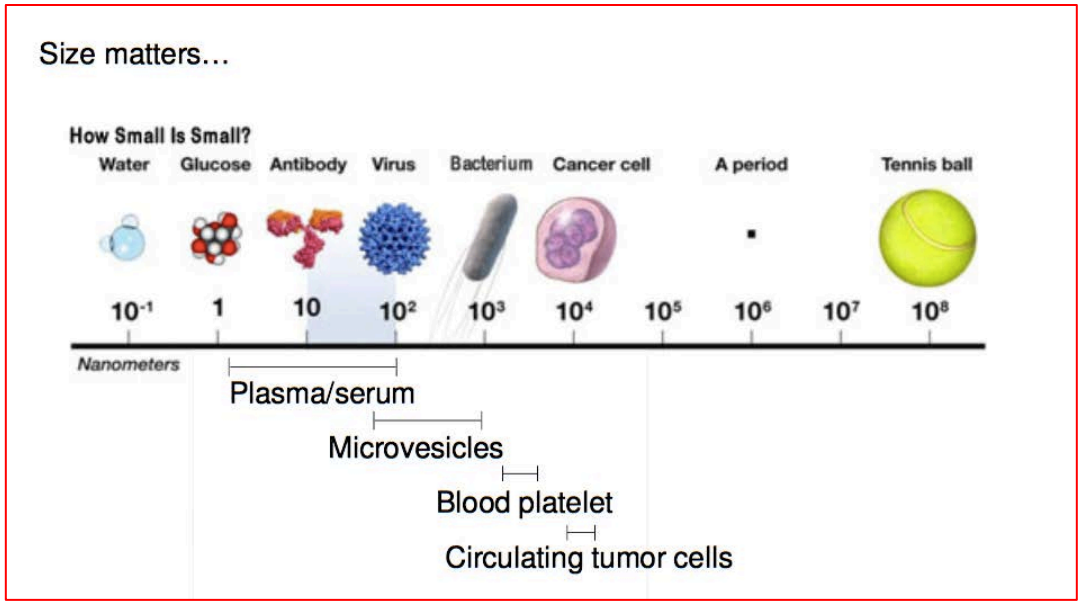


- Precision Oncology relies on indiscriminate sequencing of genomes in biopsies that barely represent the heterogeneous mix of tumor cells
- so-called "driver mutations" are not actual omnipotent "drivers” but represent, in the simplest scheme, molecular lesions that are causatively necessary but not sufficient for pathogenesis
- Nongenetic heterogeneity is a critical consideration as cells respond to broad, environmental perturbations and drug treatments by converting to many other cell states, including stem-like, resistant cell phenotypes

new technologies for studying genetic and nongenetic cell population heterogeneity, tumor cell plasticity, and intercell communication are warranted

New –omics approach: in (some) liquid biopsies RNA may outperform DNA

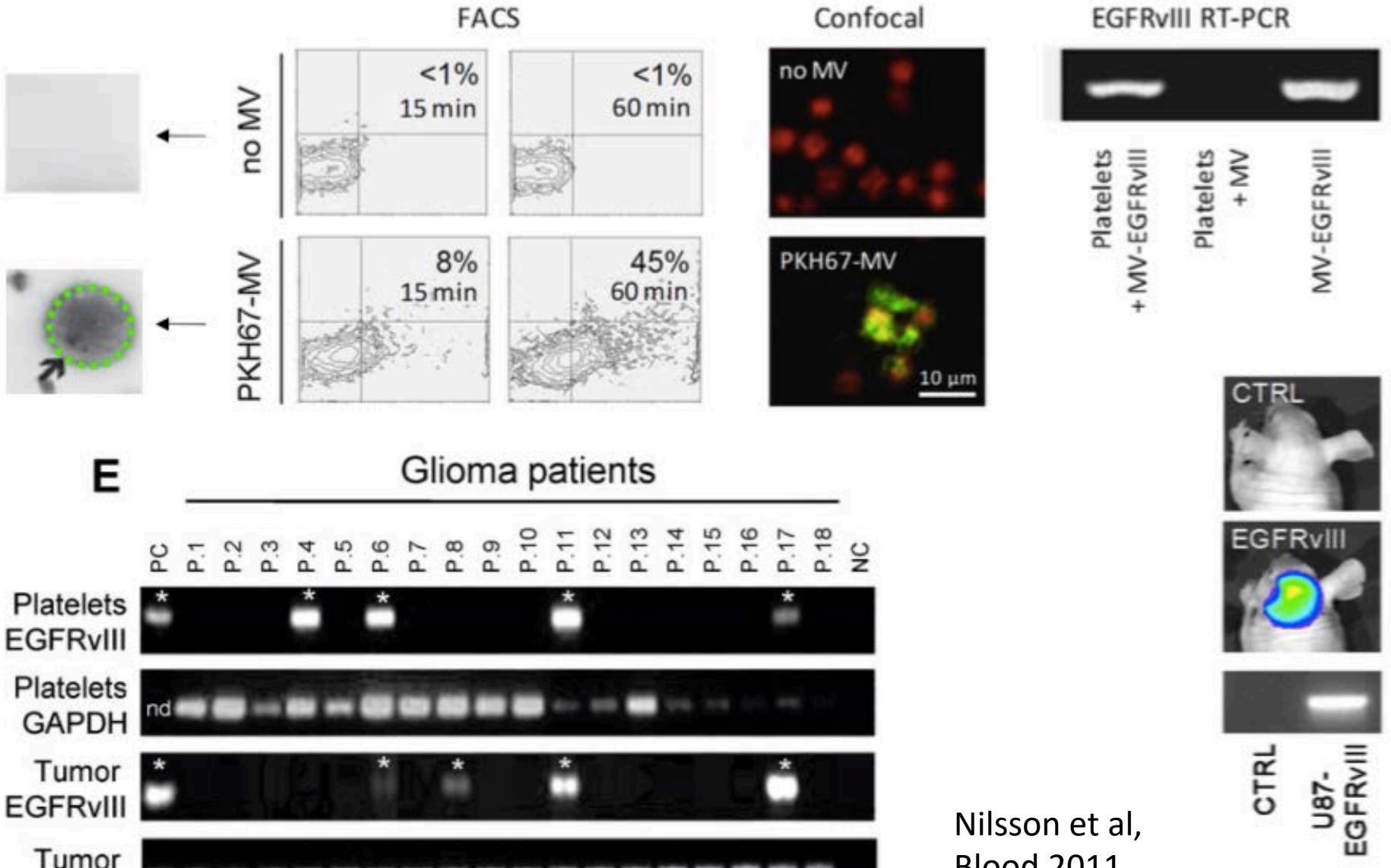
- The “information density“ of DNA might be insufficient
- Static (DNA) vs. dynamic (RNA) snap shot of individual or tumor
- RNA useful for re-arrangements, splice variants, expression patterns, etc.
- Therapy resistance via pathway activation, not by mutation per se



Nucleic acid platforms

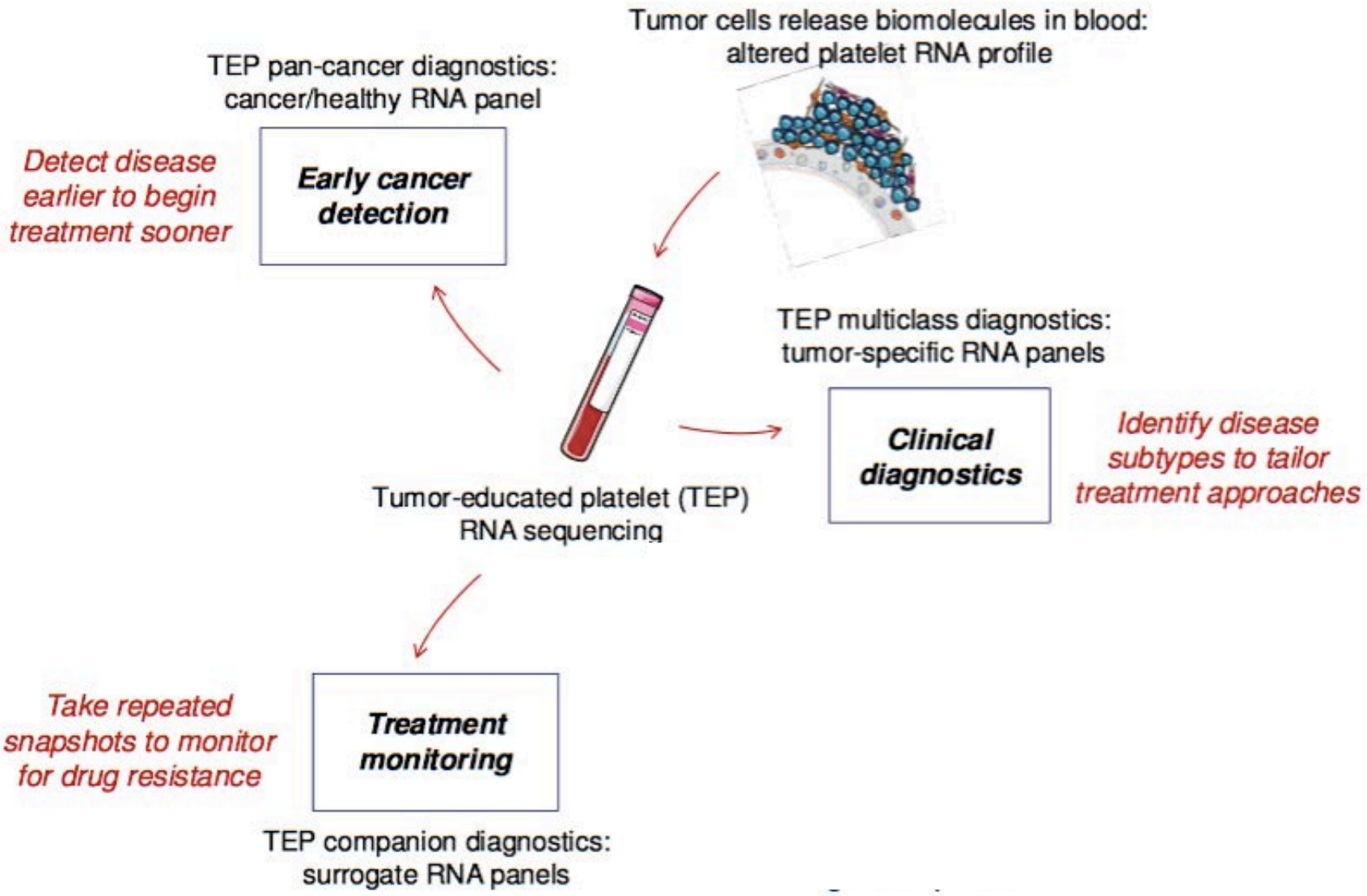
1) **Plasma**: low quality mRNA, high quality ctDNA
2) **Extracellular vesicles**: low quality mRNA, low quality ctDNA
3) **CTCs**: complex isolation, low CTC mRNA yield
4) **Platelets**: easy isolation, high quality mRNA

Platelets contain tumor-derived RNA biomarkers



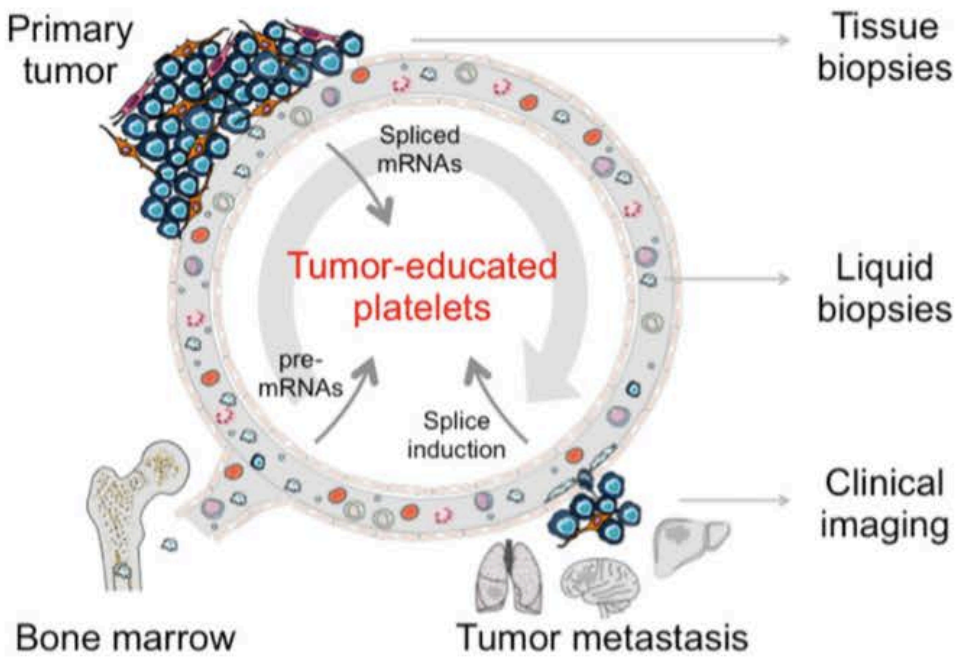
Nilsson et al,
Blood 2011

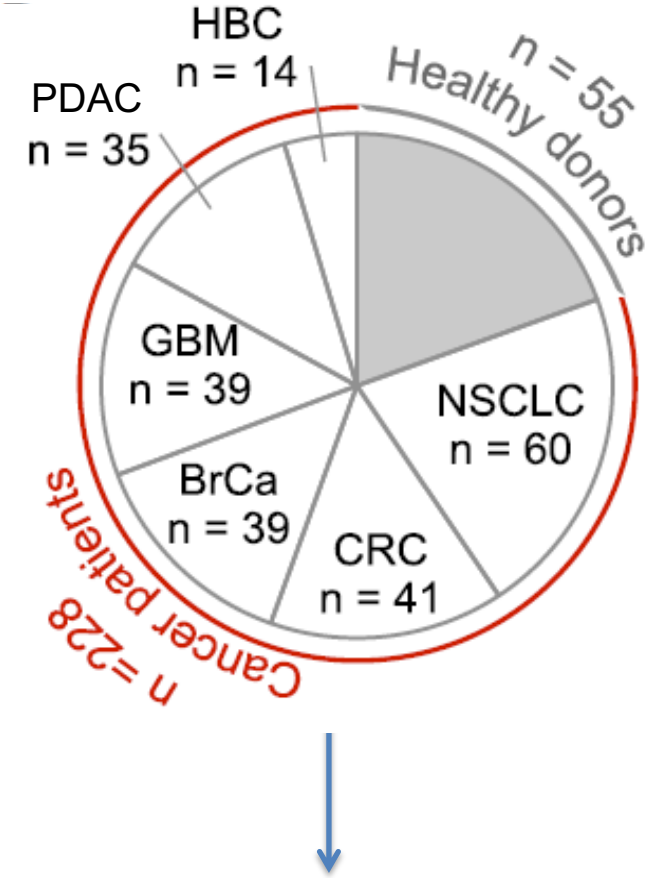
TEP for detection, diagnostics and prevention



[Thanks to ThromboDX, Prof. Wurdinger]

Patients and Healthy donors

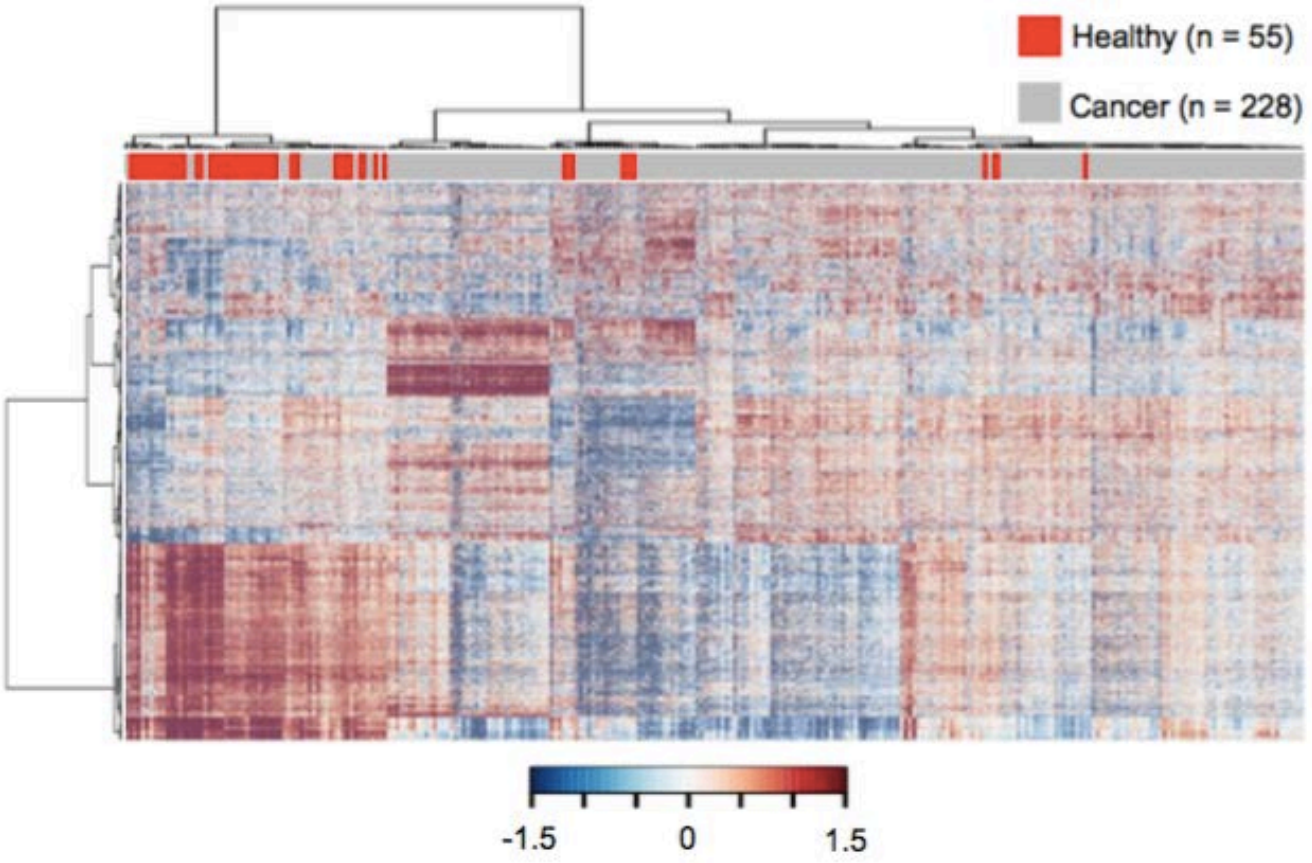




Training cohort: Cancer n=136
Validation cohort: Cancer n=92

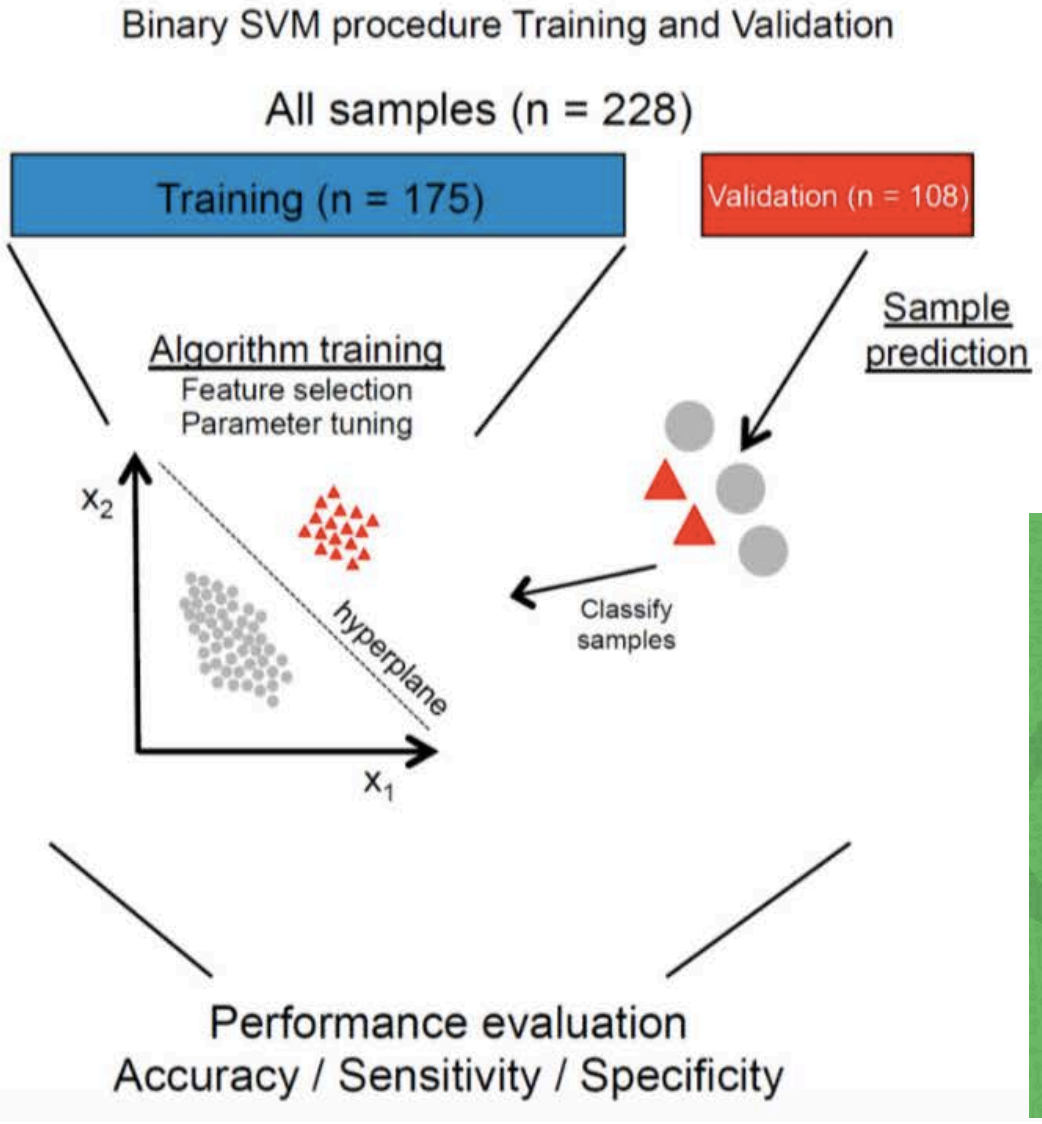
Heatmap of unsupervised clustering

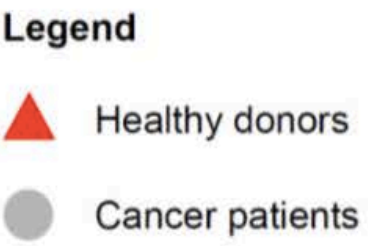
P<0.0001
Fisher's Exact text

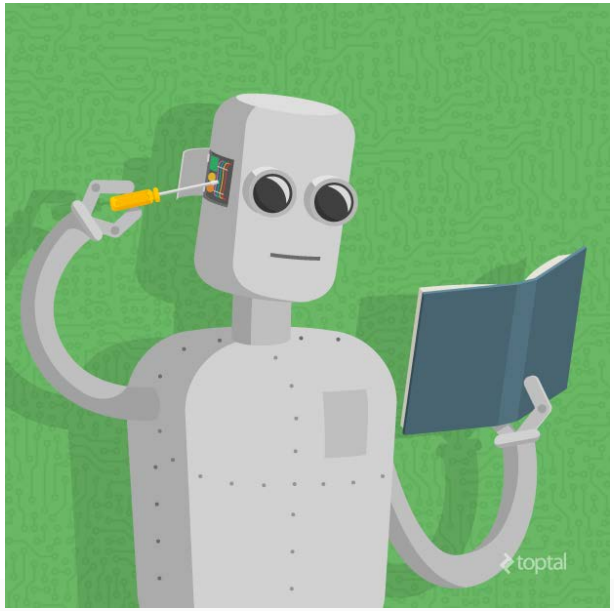


A total of **5003 significantly differential RNAs in TEPs** were identified between cancer and healthy controls

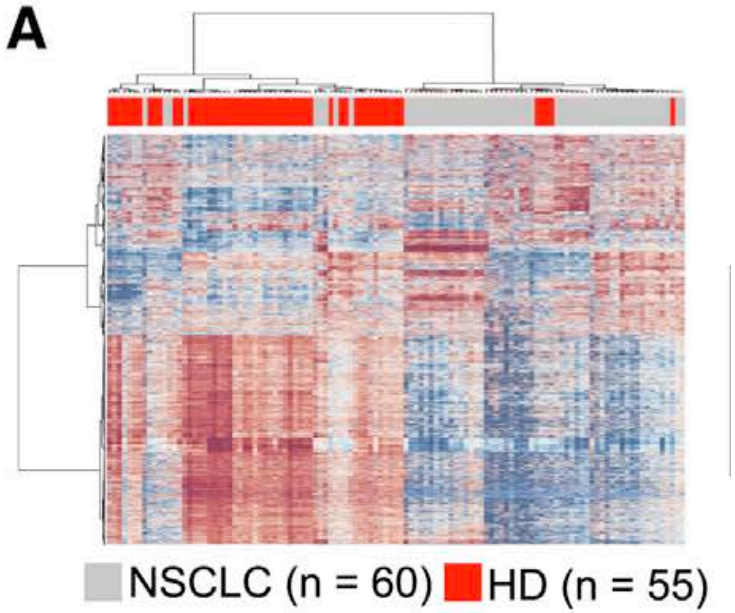
Self-learning algorithm

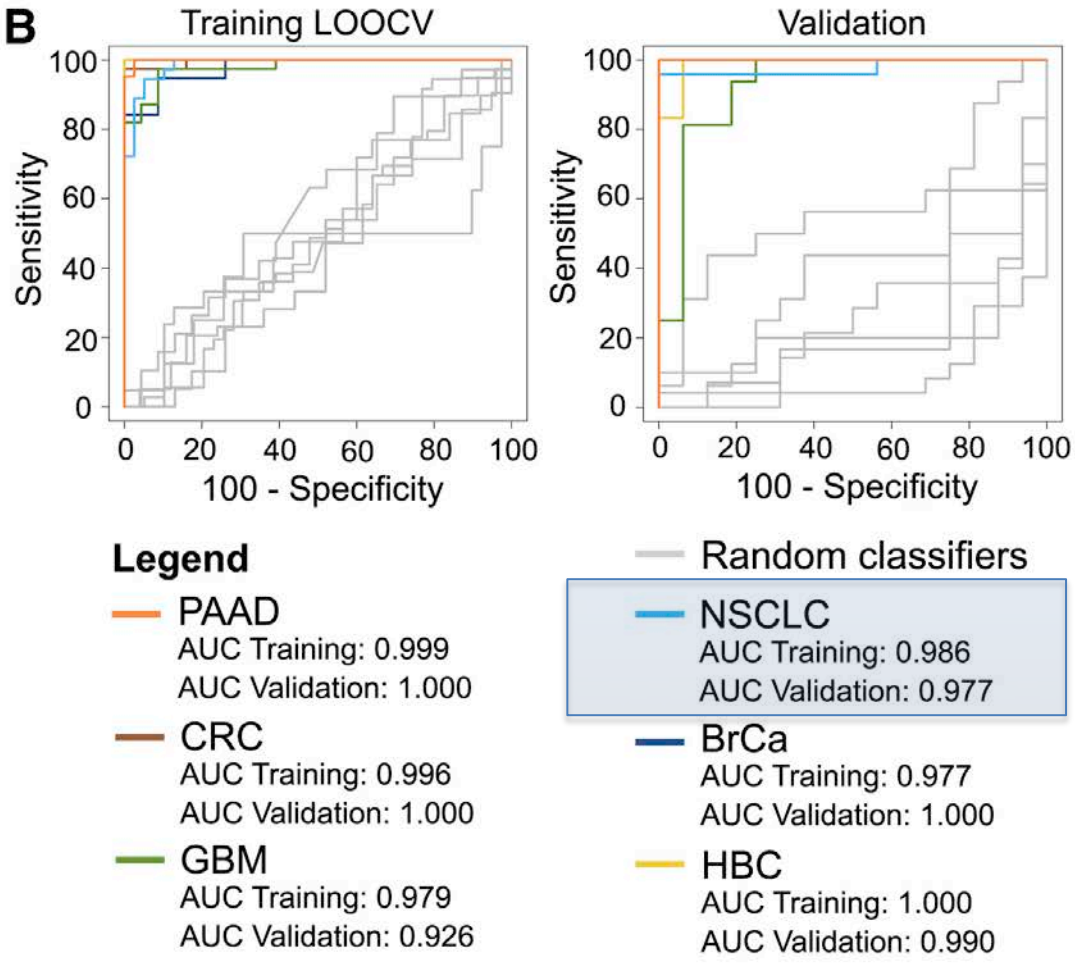






Results in NSCLC

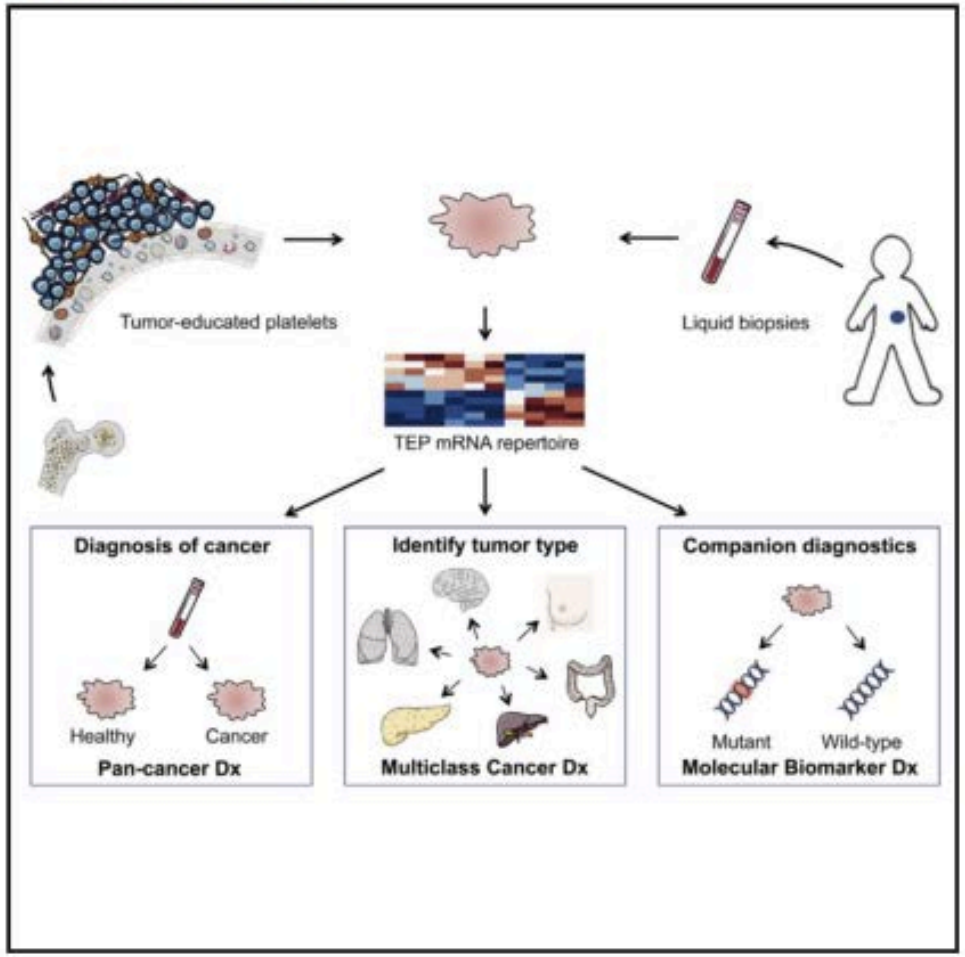




Cancer Cell

RNA-Seq of Tumor-Educated Platelets Enables Blood-Based Pan-Cancer, Multiclass, and Molecular Pathway Cancer Diagnostics

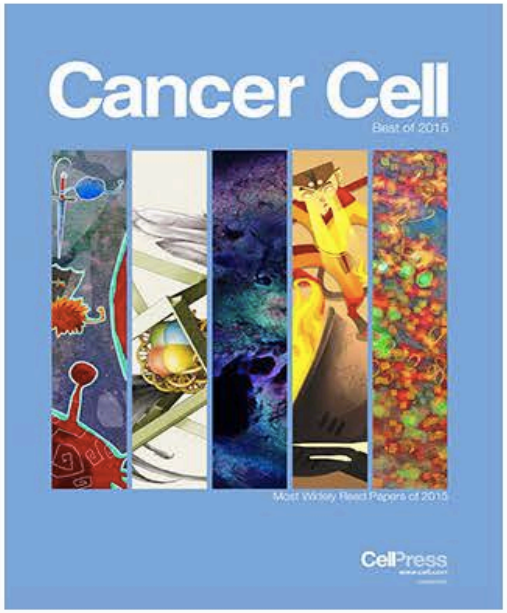
Graphical Abstract



Authors

Myron G. Best, Nik Sol, Irsan Kooi, ..., Bakhos A. Tannous, Pieter Wesseling, Thomas Wurdinger

Download Best of *Cancer Cell* 2015



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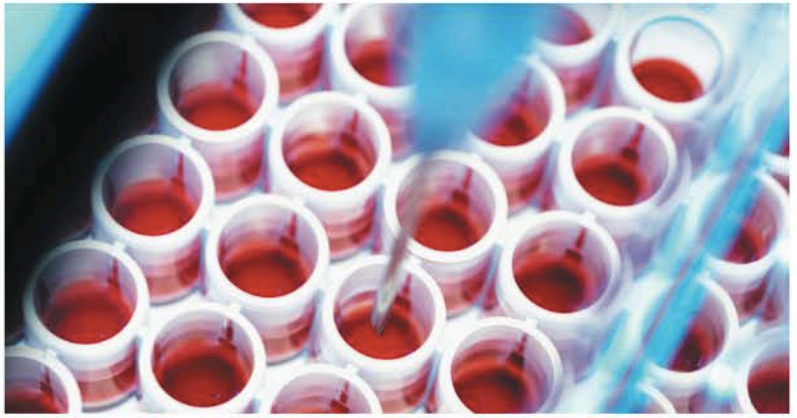
TECHNOLOGY FEATURE

THE TUMOUR TRAIL LEFT IN BLOOD

Liquid biopsies can detect cancer signs from a blood sample, without the need for invasive procedures. But further work is needed before they can become reliable diagnostic tools.



Tumour DNA extracted from blood samples could be used to profile cancers, avoiding the need for surgical biopsies.

Cancer Cell Letters

A Word of Caution on New and Revolutionary Diagnostic Tests

AGE might influence mRNA

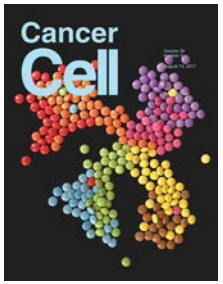
Pre- and post-analytical and bioinformatics artifacts

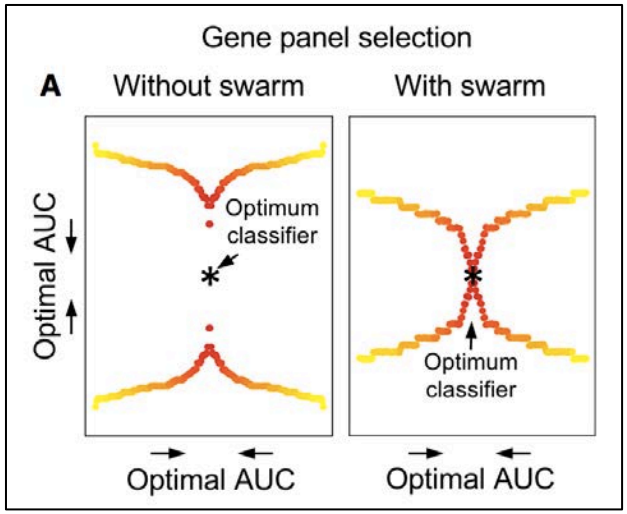
Effects of inflammatory diseases, benign tumors

…with a new algorithm

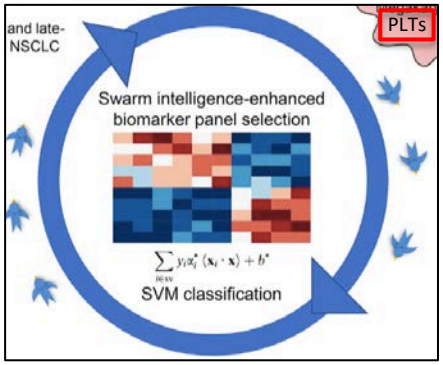
Swarm intelligence-enhanced algorithm: Nature-inspired programming recipes

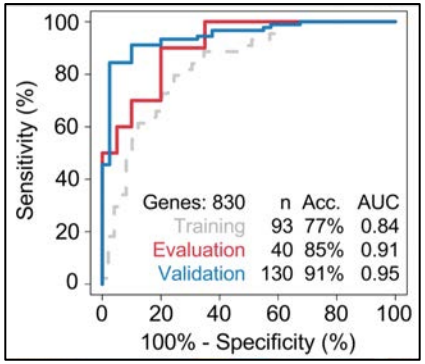
Best et al.
August 2017

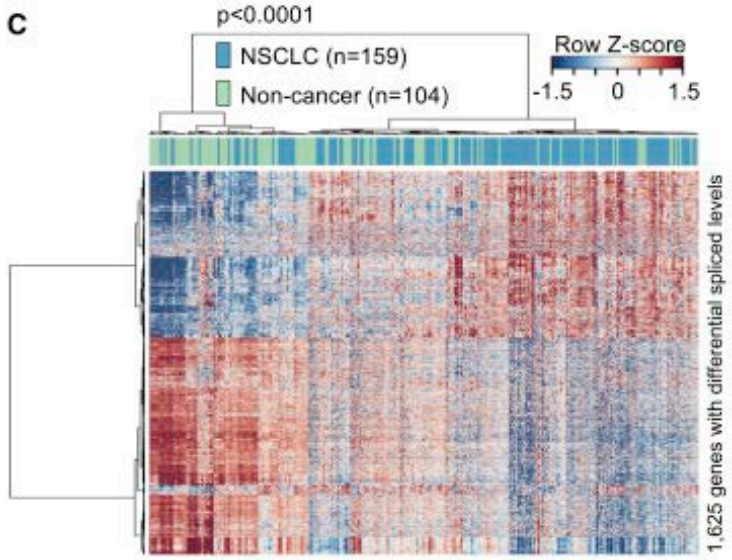




The validation study showed accurate TEP-based detection of early- (n=106) and late- (n-518) stage NSCLC independent of age, smoking, whole-blood storage time, and various inflammatory conditions







Conclusions

Despite pharmacogenetics/omics and precision oncology straightforward rationale, concerns about their effectiveness are mounting

In some cases (eg, CDA for gemcitabine/platinum treated NSCLC) the phenotype performs better than the genotype

Validation of methodologies and prospective trials are needed

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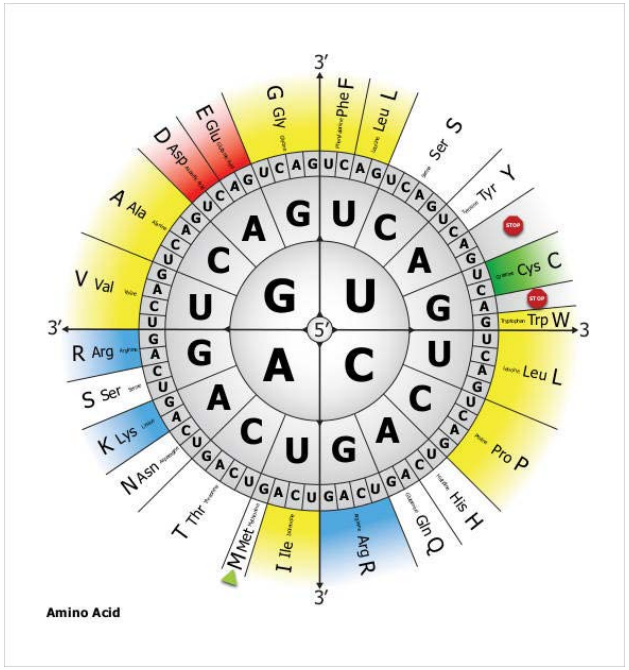
"Precision" Must Not Mean "Narrow"

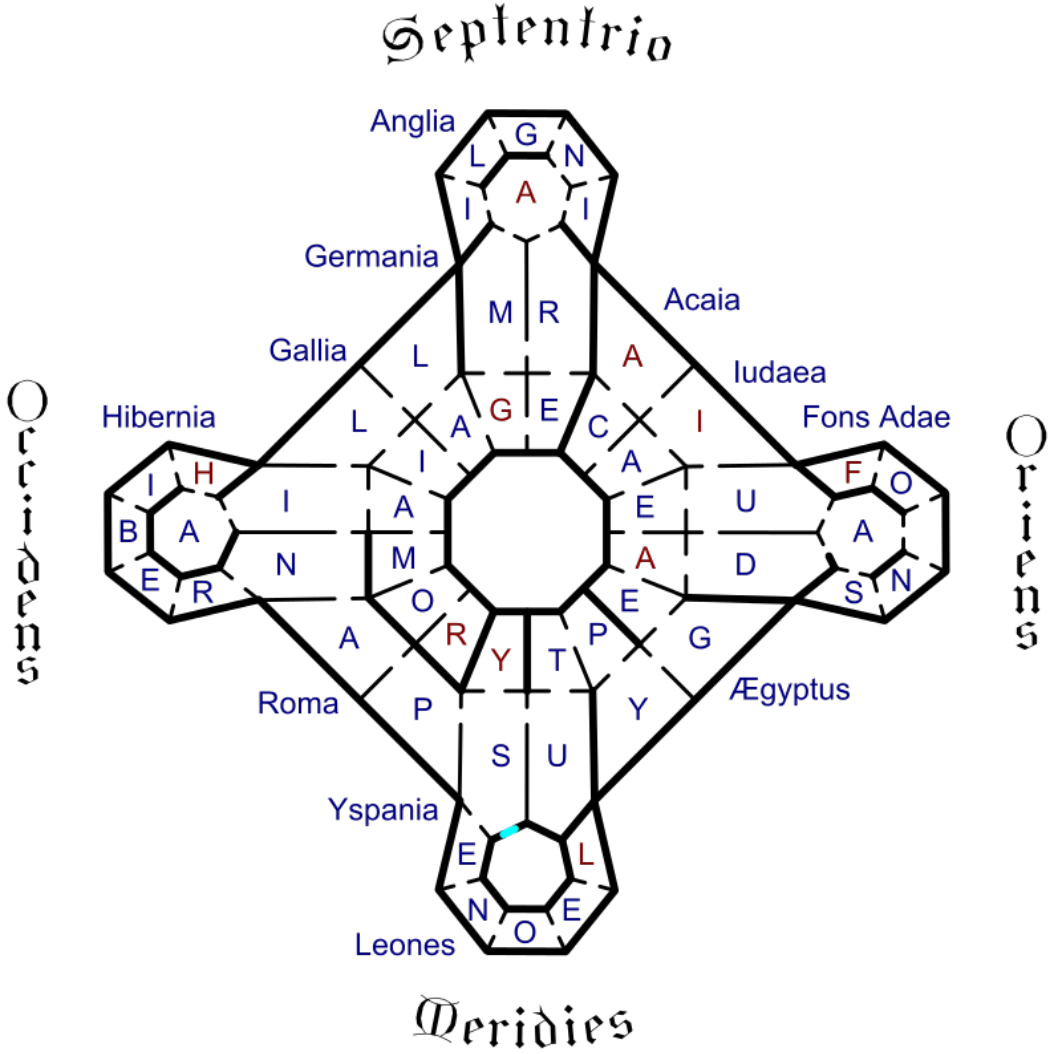
With new technologies for studying genetic and nongenetic cancer cell population heterogeneity, and tumor cell plasticity, we can achieve a new "precision" and hopefully guide better diagnostic/prognostic/predictive and preventive studies

Tumor-educated platelets (TEPs) can function as blood-based biosource for (early/differential) cancer diagnostics (including NSCLC), with 98% accuracy

Ongoing studies are evaluating the prognostic and predictive value of TEP

“Show not what has been done, but what can be. How beautiful the world would be if there were a procedure for moving through labyrinths”





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And the next meeting you should participate ;)