

Technologies
innovantes
pour la santé
et les nouvelles
thérapies

**Il est interdit
d'utiliser le contenu
de ces slides pour
des présentations
ou dans un but
commercial sans
l'accord de l'auteur**

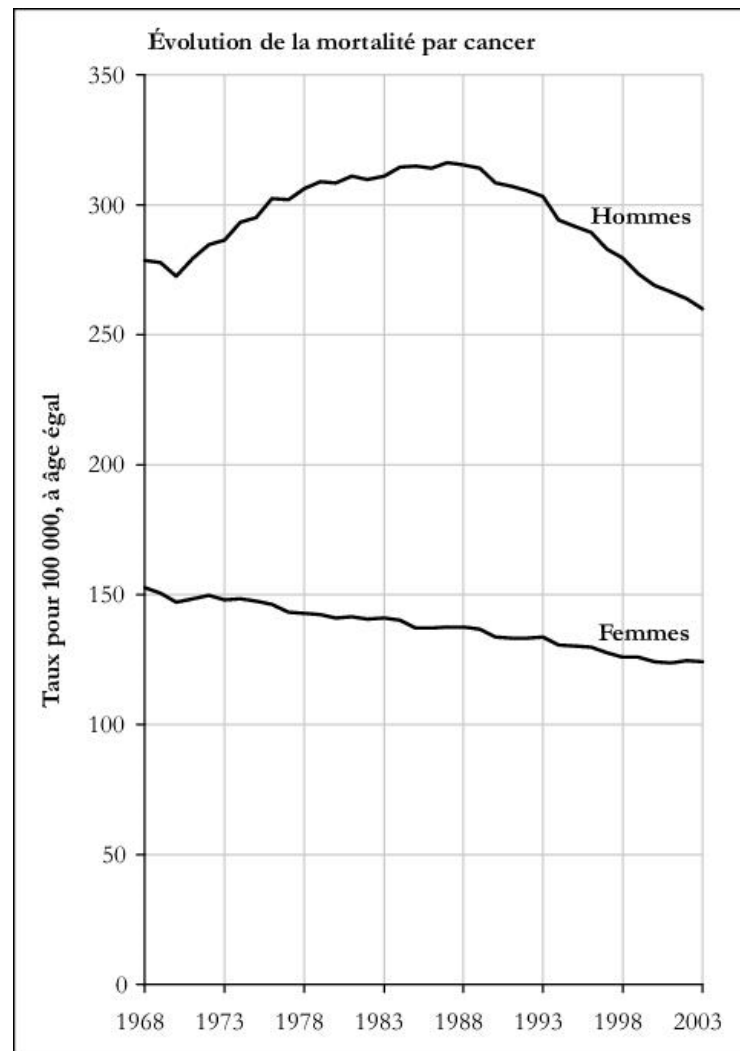
High performance computing and simulation in medicine: scope and challenges

**François Ballet MD, PhD
Président Comité R&D
Medicen Paris Region**

Cluster and project funding partners

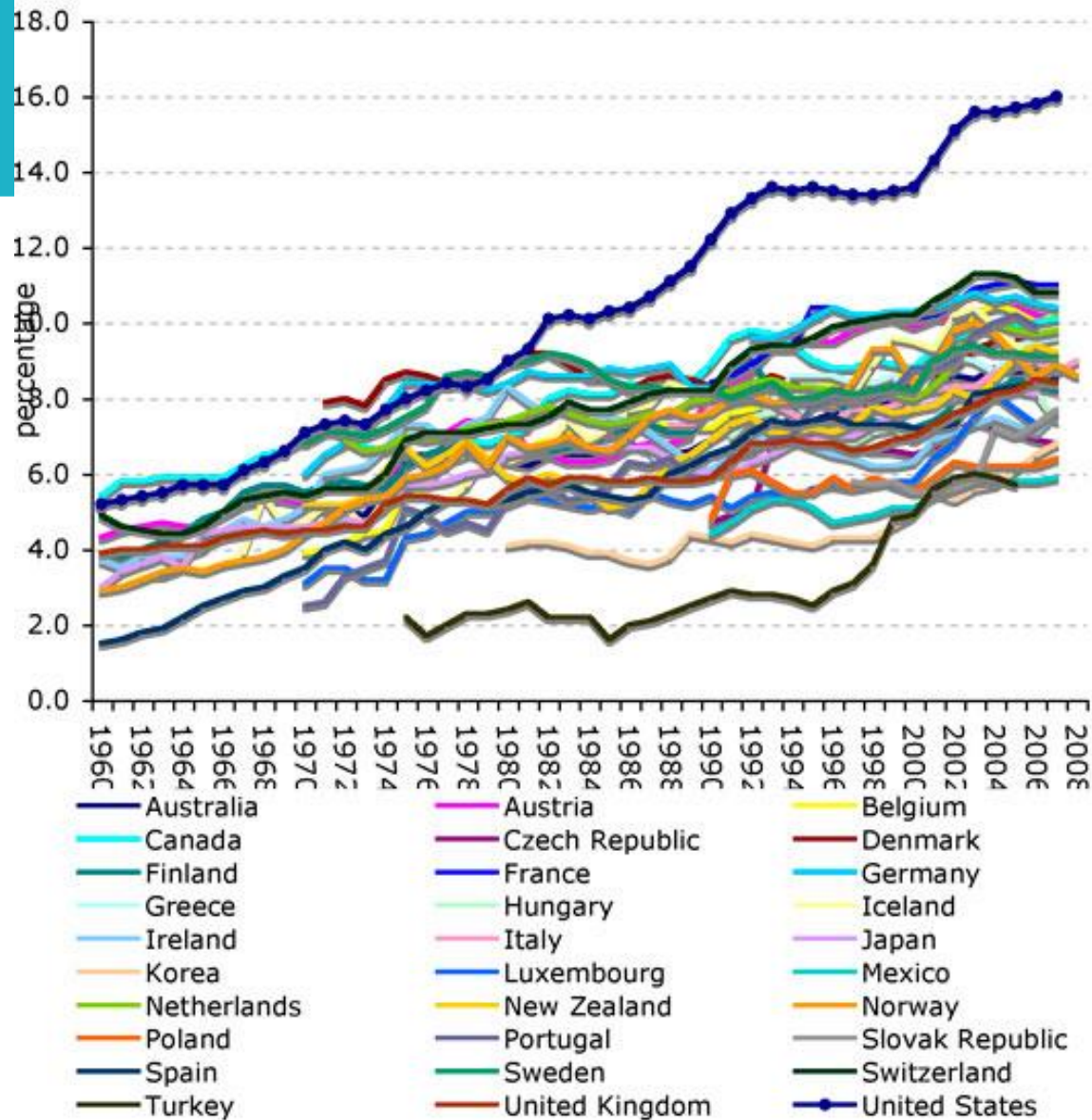


Evolution de la mortalité par cancer en France (1968-2003)

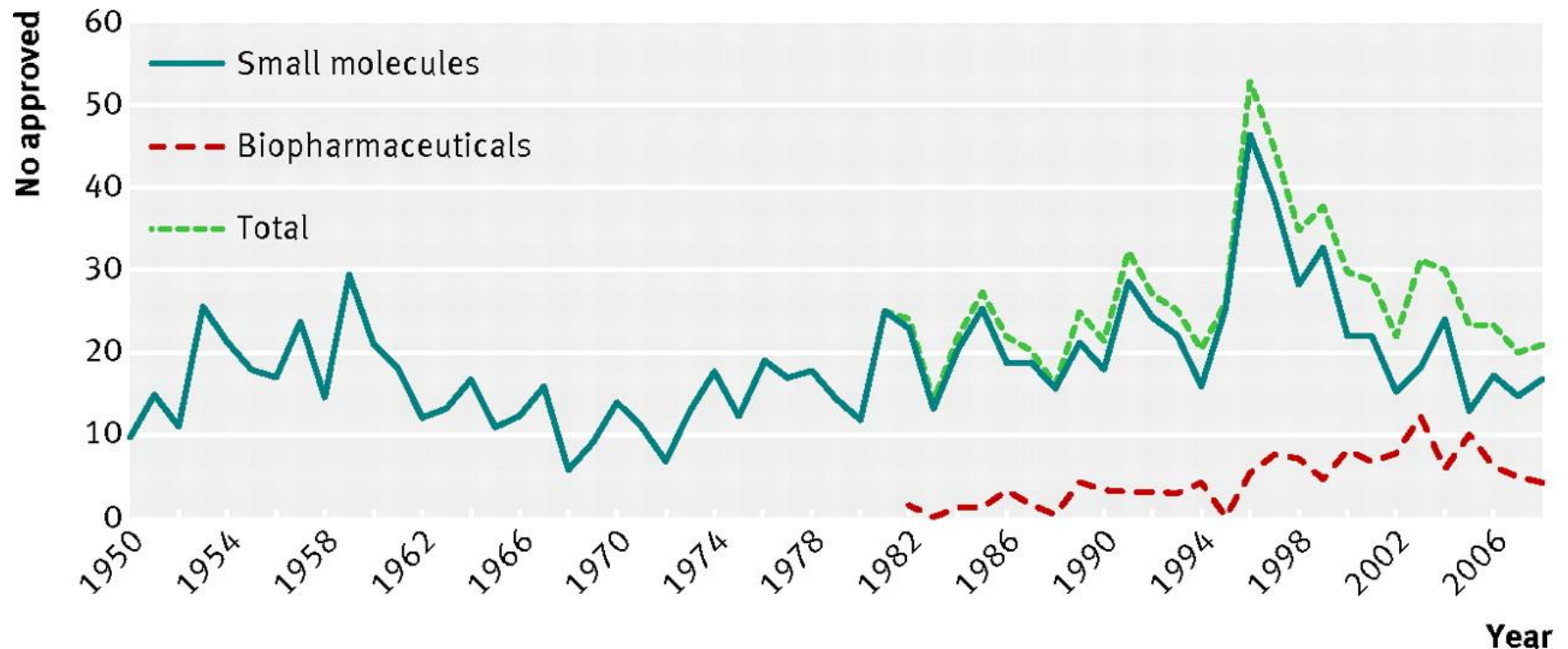


Hill C, Doyon F
Bull Cancer 94,7-13,2007

National Health Spending as a % of G.D.P.

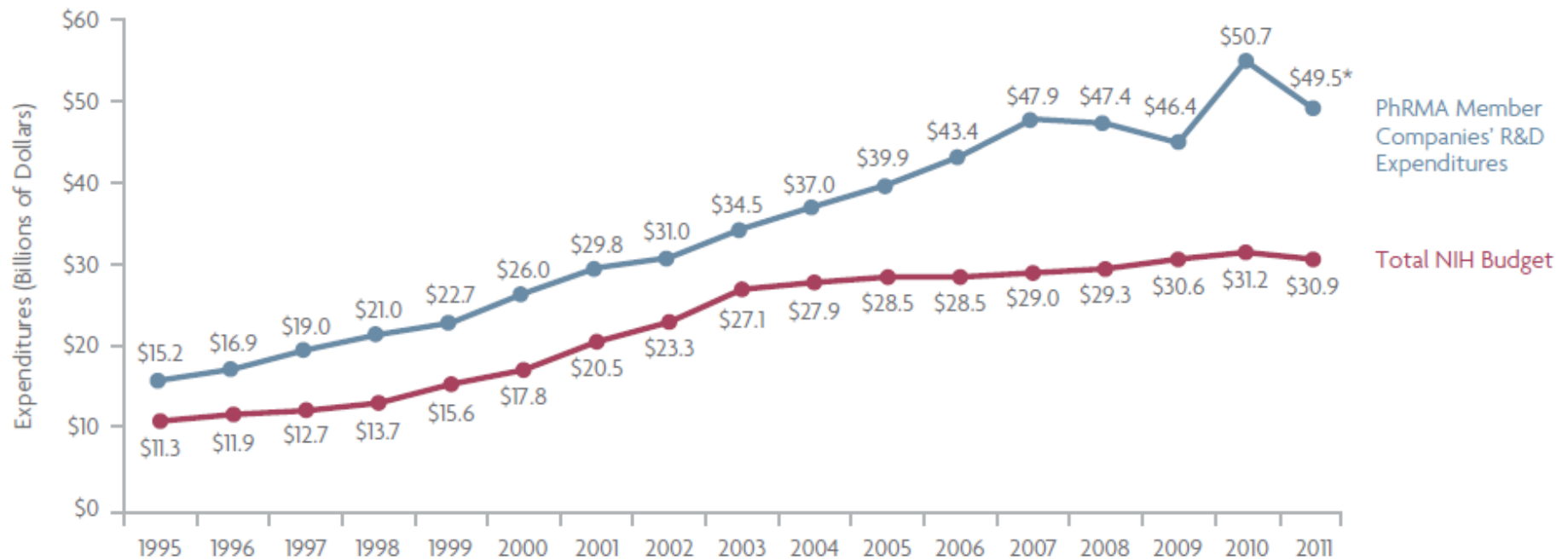


Number of annual drug approvals by FDA (1950 – 2008)

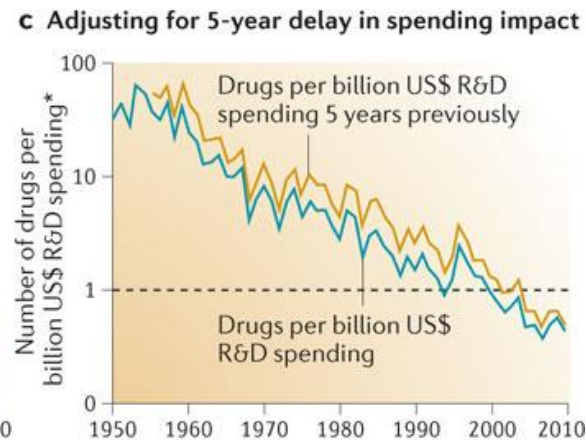
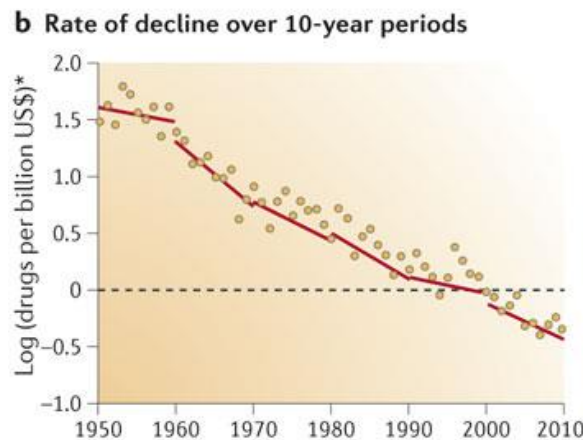
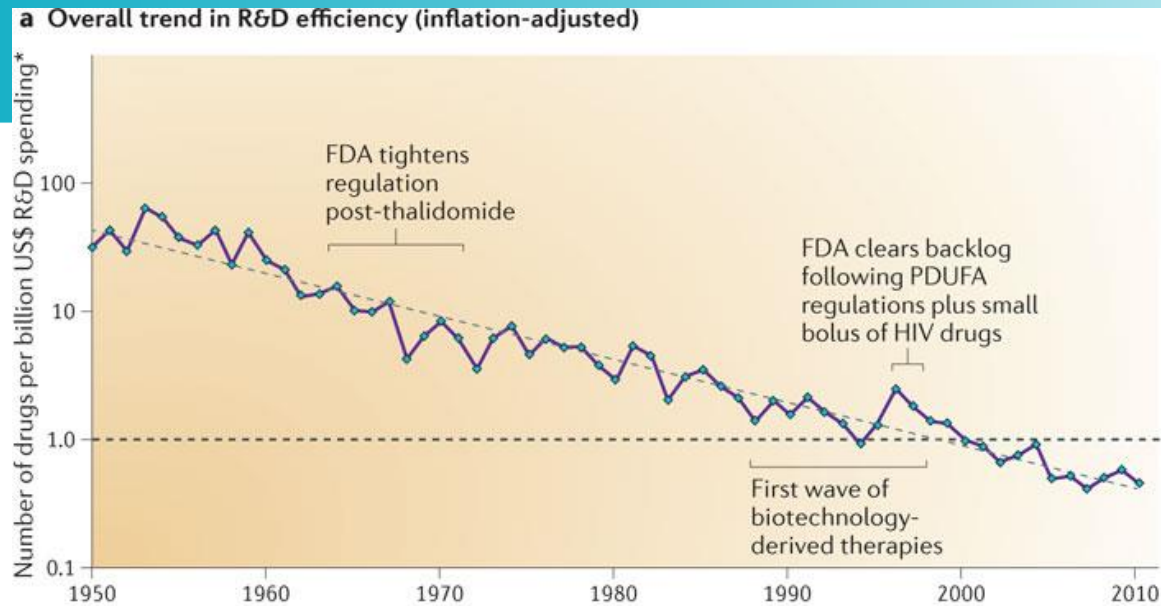


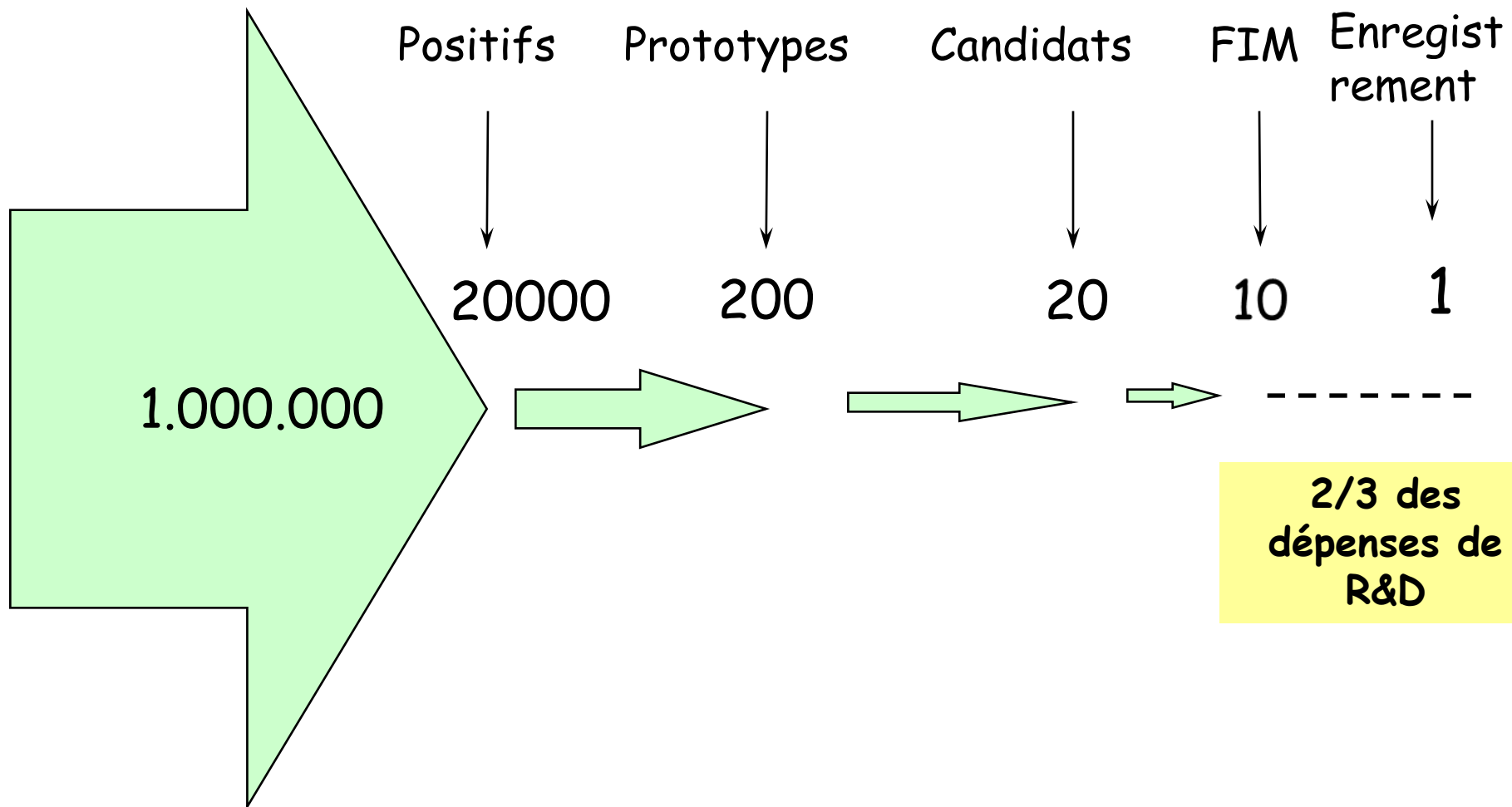
L'évolution des investissements de R&D aux USA dans l'industrie pharmaceutique et au NIH (OpEx 1995-2011)

PhRMA Member Company R&D and NIH Operating Budget: 1995–2011



Evolution de la productivité de la R&D pharmaceutique





Un taux d'attrition très élevé

Des progrès limités en médecine

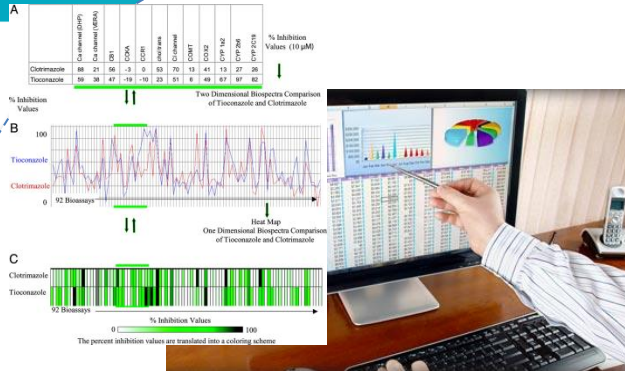
Pourquoi ?

- Connaissance très limitée des systèmes biologiques et des mécanismes des maladies
- Efficacité limitée des outils thérapeutiques dans les maladies les plus fréquentes
- Gestion des données biologiques/médicales et des outils d'aide à la décision très imparfaits ne permettant pas une prise en charge efficace des patients

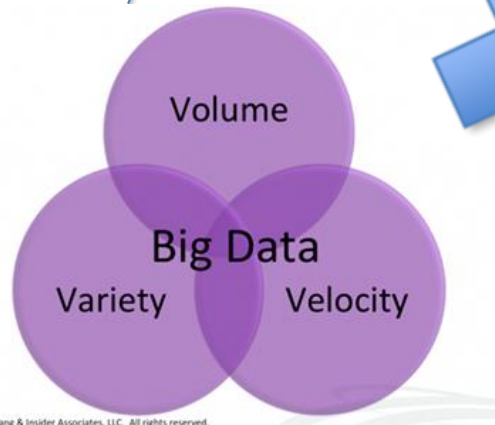
s biologiques
sances utiles



Big data challenge in medicine



R&D



Medical
practice



HPC

**Knowledge
Decisions
Products**

Molecule

Drug discovery and development is a « trial and error » process

Cellular models



Animal models



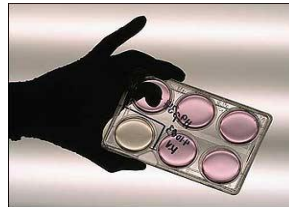
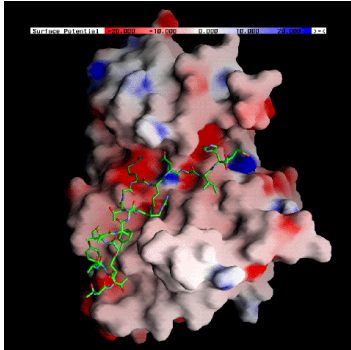
Man



?

?

?



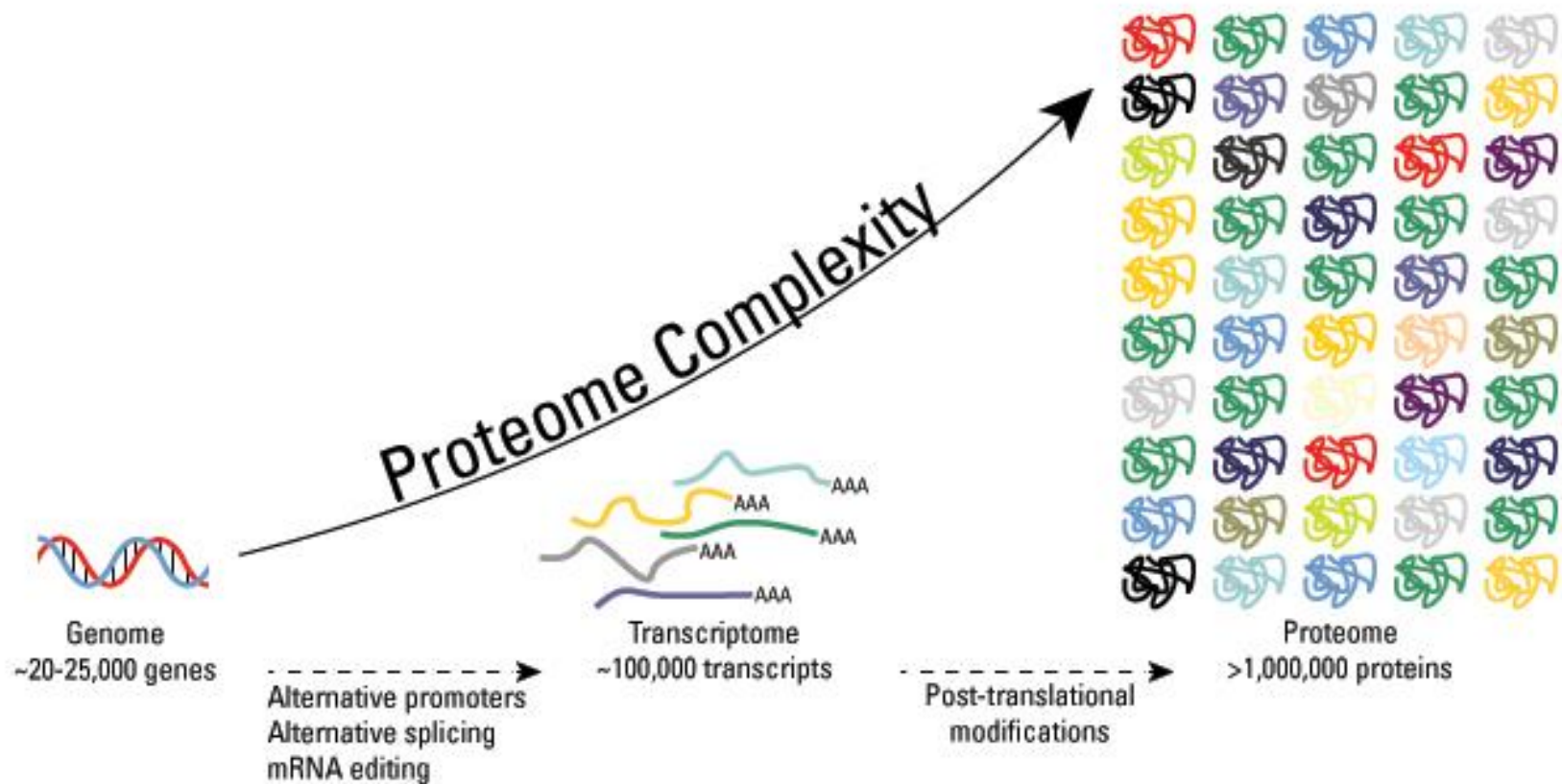
Les principaux défis de la R&D



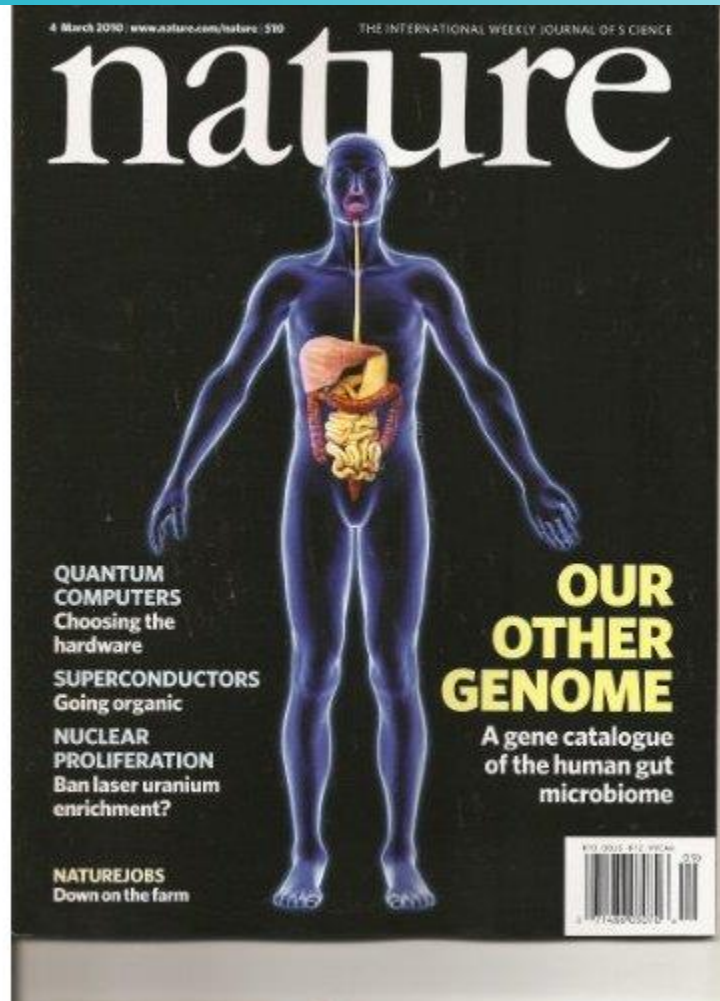
- Comprendre les systèmes biologiques et le mécanisme des maladies et les modéliser

aaggaagggg
cgcgagacgcg
acgcgagcgc

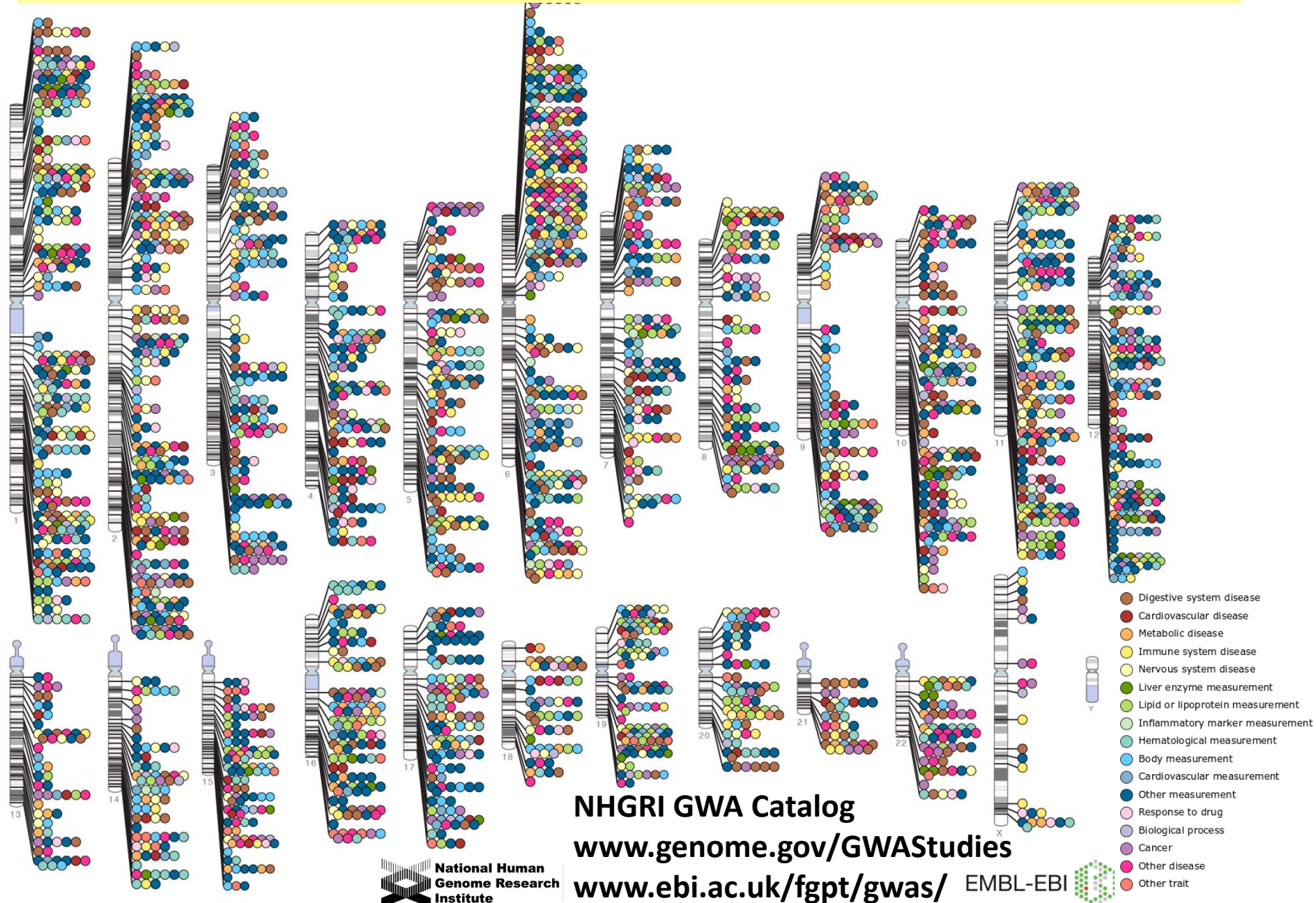




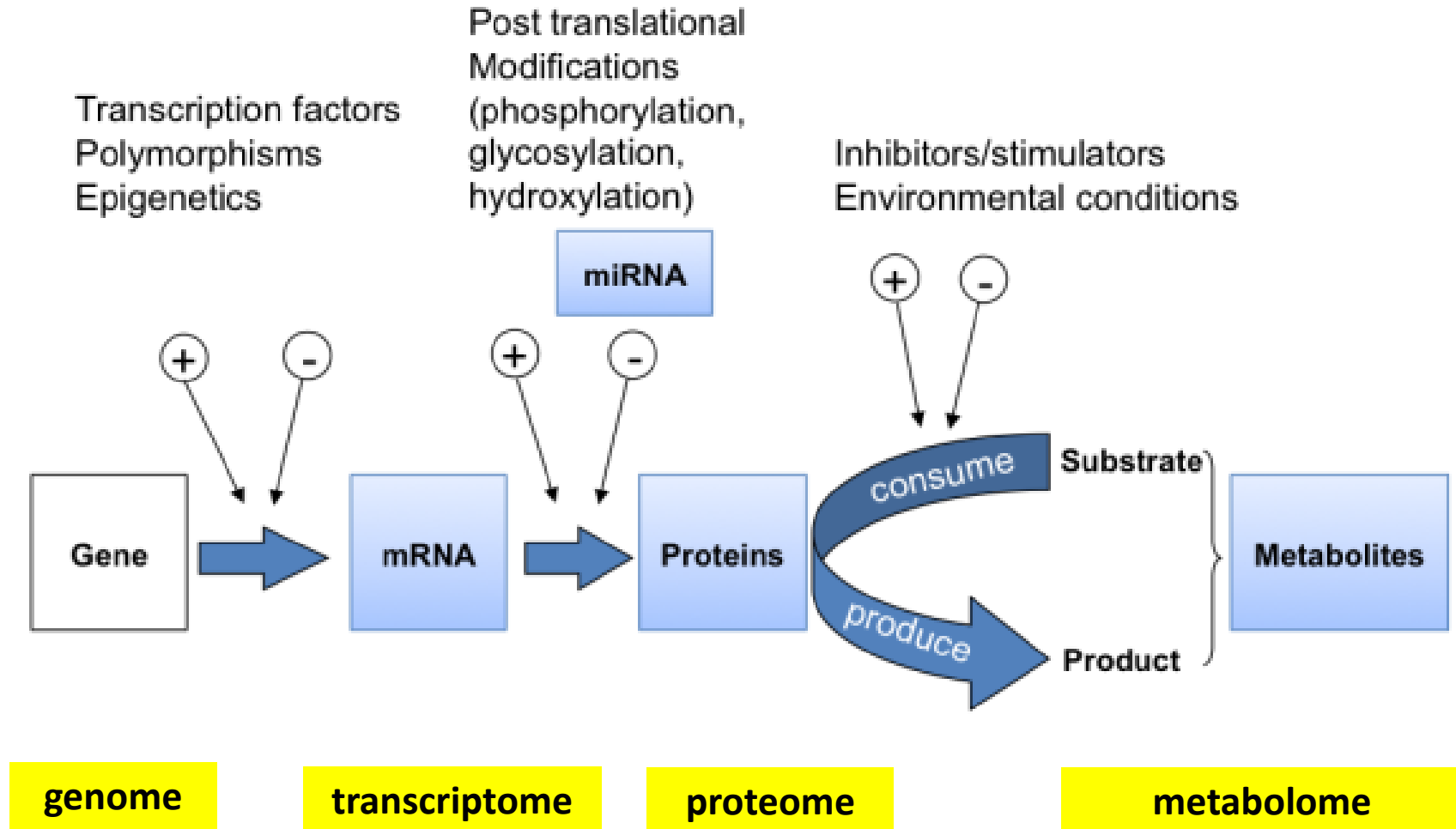
Nature, 4 march
2010



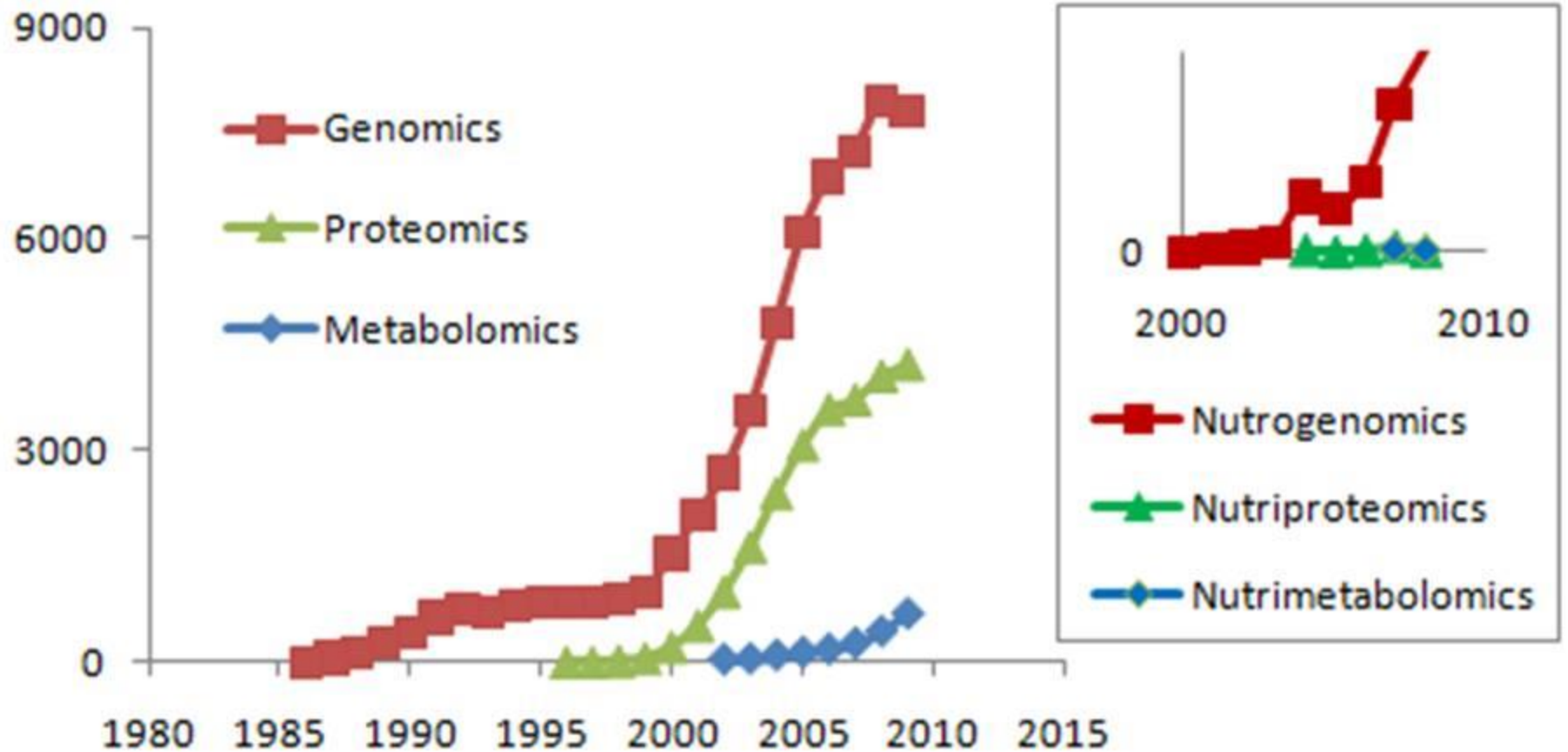
**Published Genome-Wide Associations (GWA) through 12/2012
(at $p \leq 5 \times 10^{-8}$ for 17 trait categories (24 human chromosomes))**



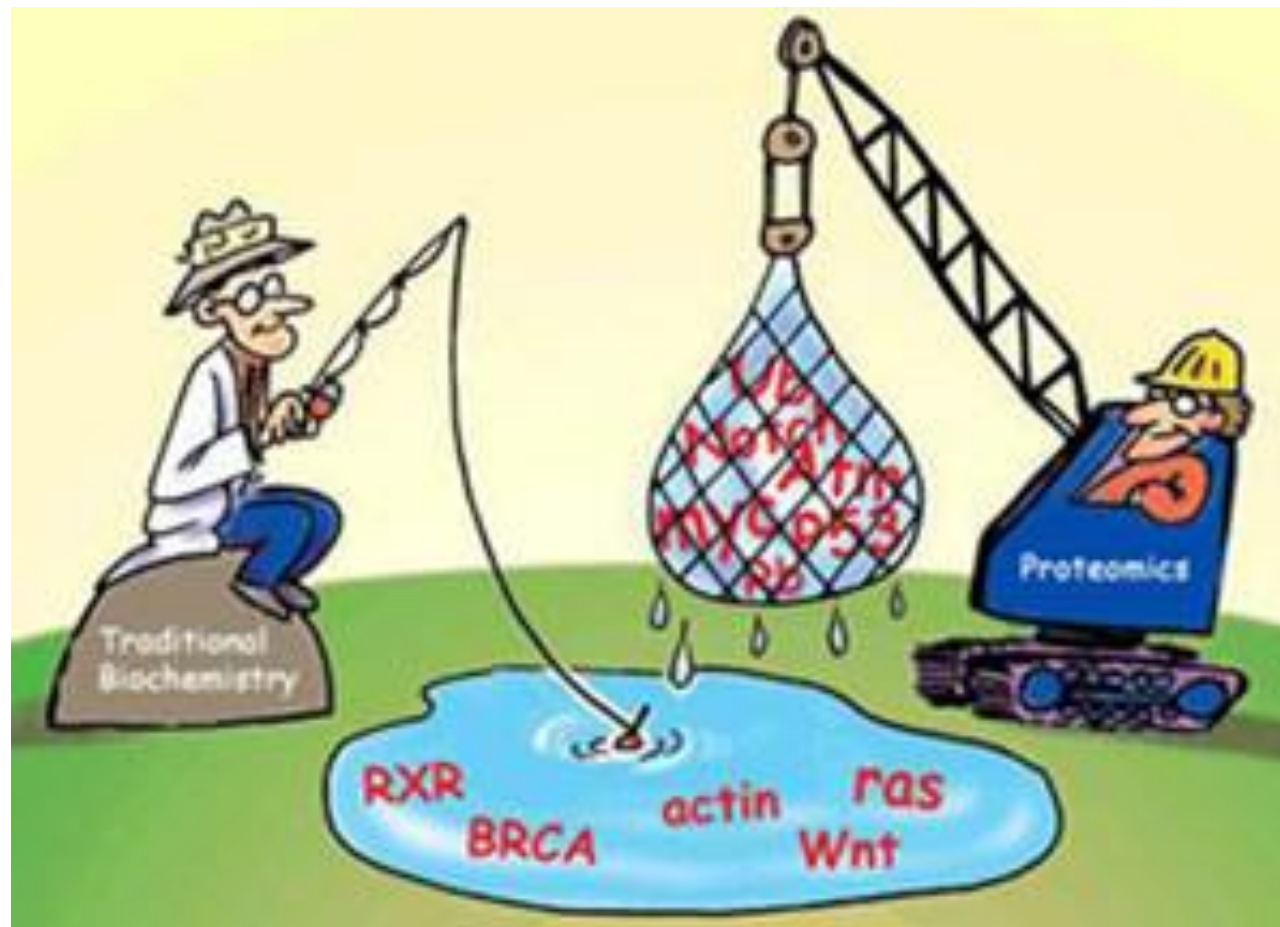
Large scale analytical techniques for all biological component categories (the OMICS revolution)



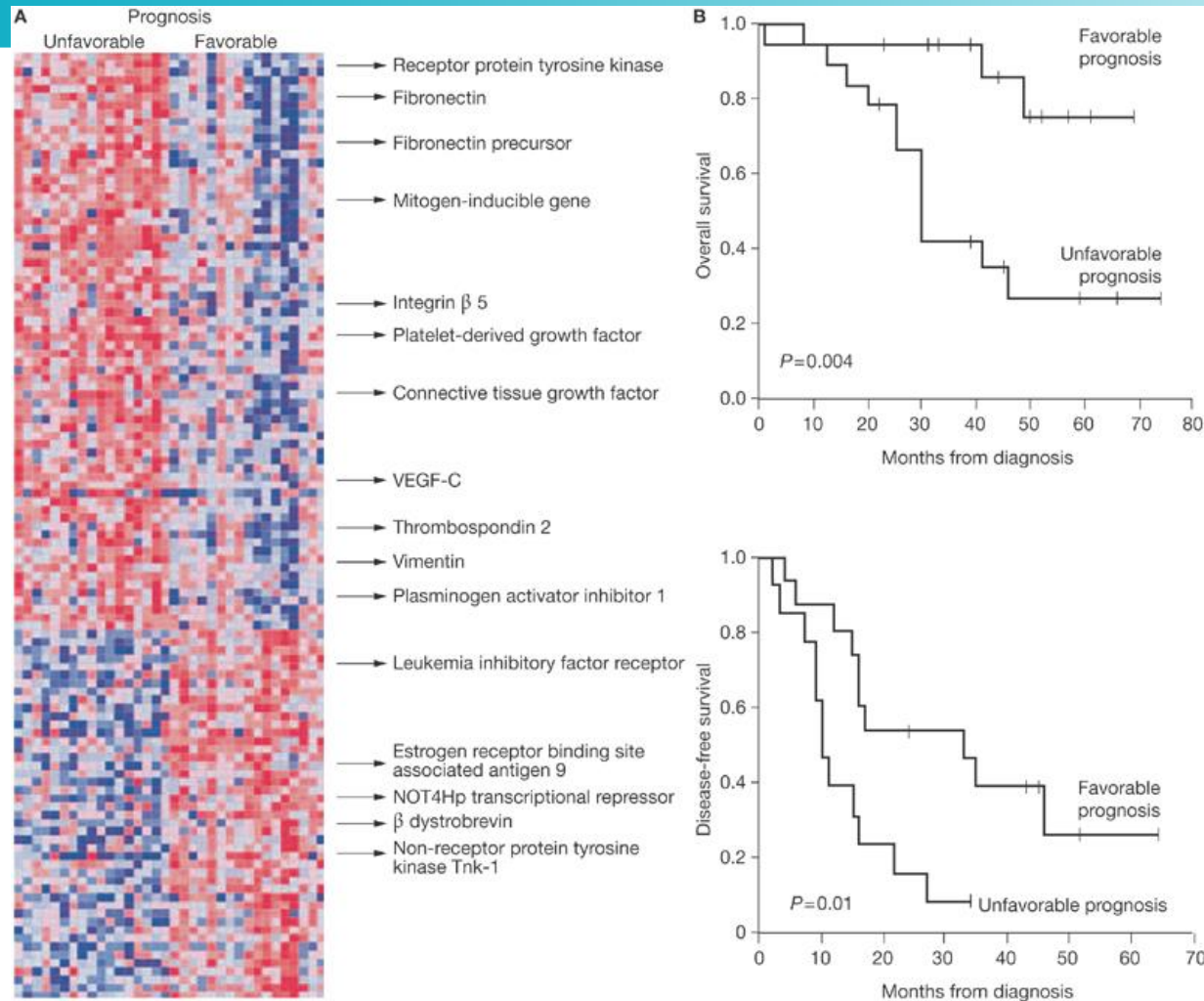
Medline Trends



Non-biased approaches associated with the development of large scale analytical methods ("-omics")



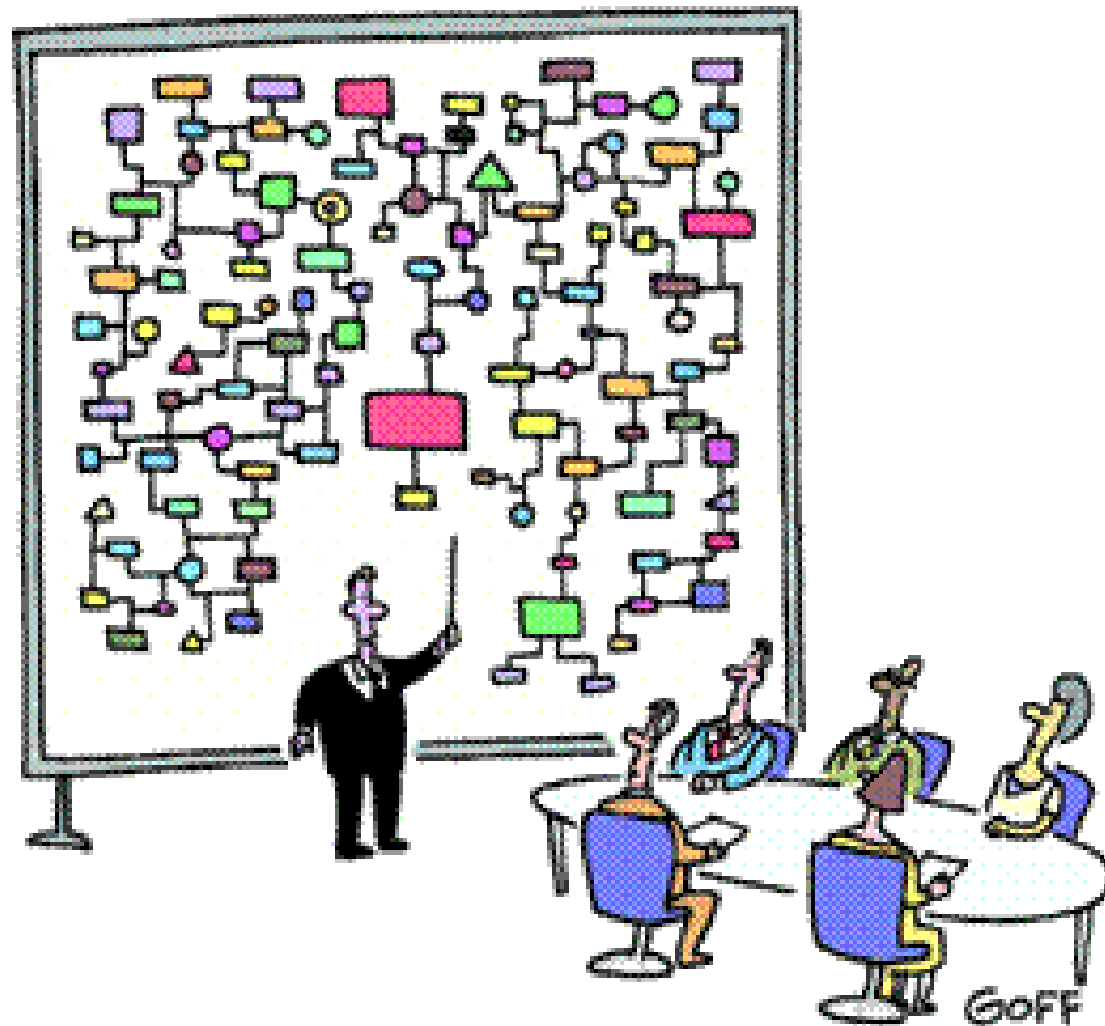
Molecular signatures for cancer patient stratification



(Gene-expression profiling in epithelial ovarian cancer Panagiotis A et al Nature Clinical Practice Oncology (2008) 5, 577-587)

[illegible]

22

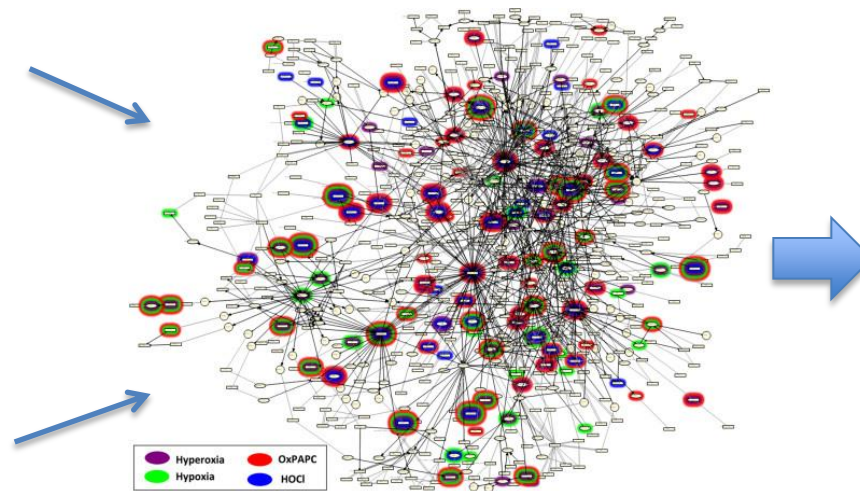


"And that's why we need a computer."

Knowledge of molecular network systems is key for disease treatment

Genetic perturbations

Environmental perturbations



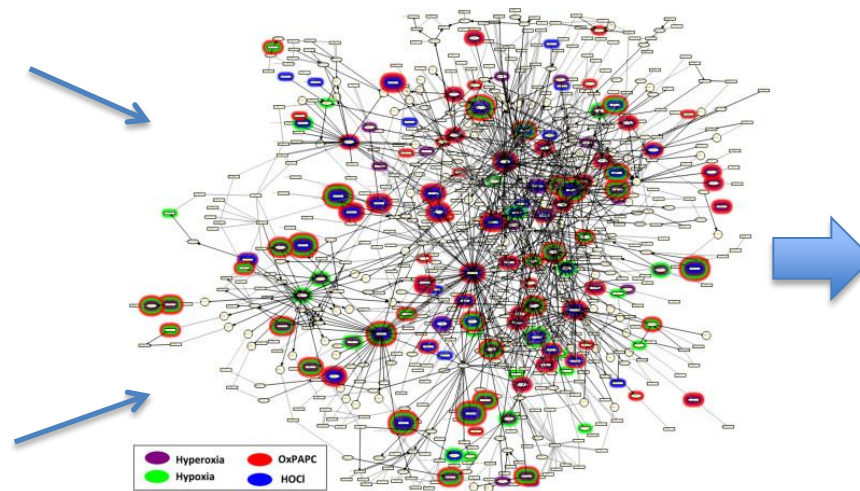
Disease

**Molecular network
systems**

Knowledge of molecular network systems is key for disease treatment

Genetic perturbations

Environmental perturbations



Disease

**Molecular network
systems**

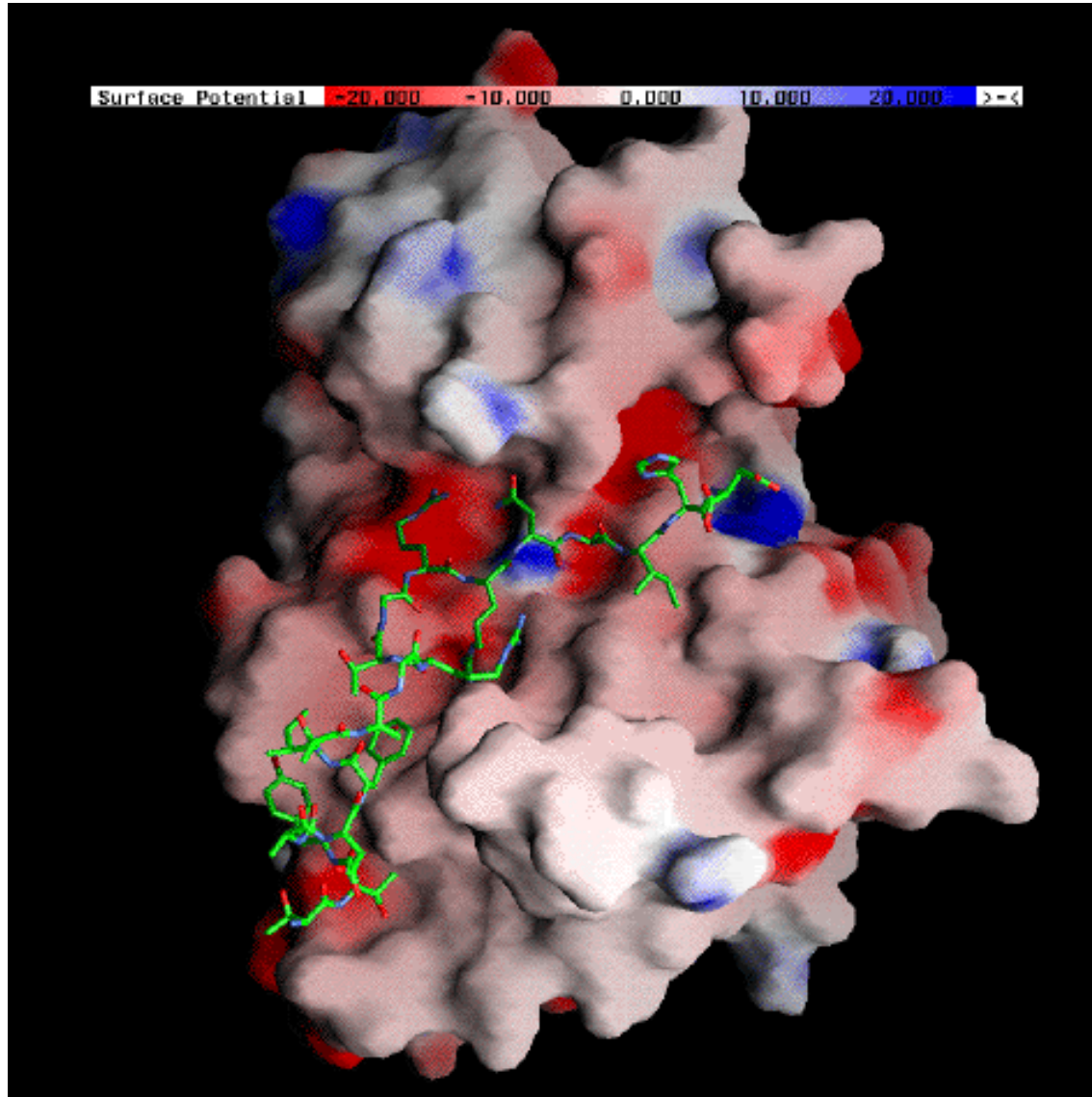
**Mechanism-based
treatment**

Les principaux défis de la R&D

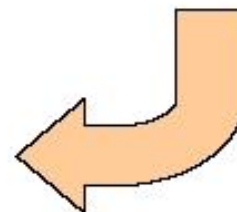
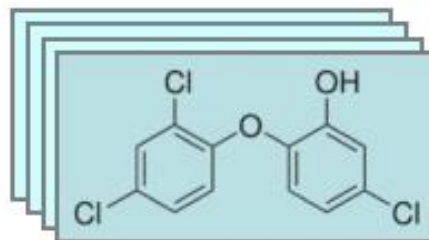
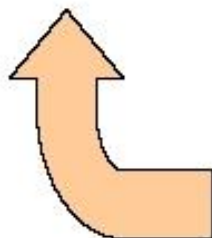
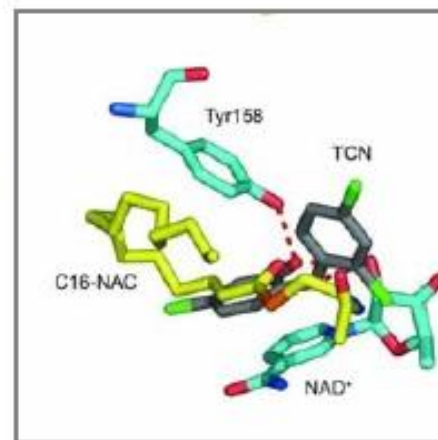
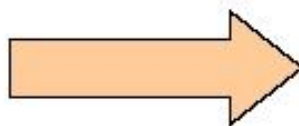


- Comprendre les systèmes biologiques et le mécanisme des maladies et les modéliser
- Mettre au point des médicaments qui prennent en compte la complexité des systèmes biologiques et des maladies

The drug-protein interaction dogma

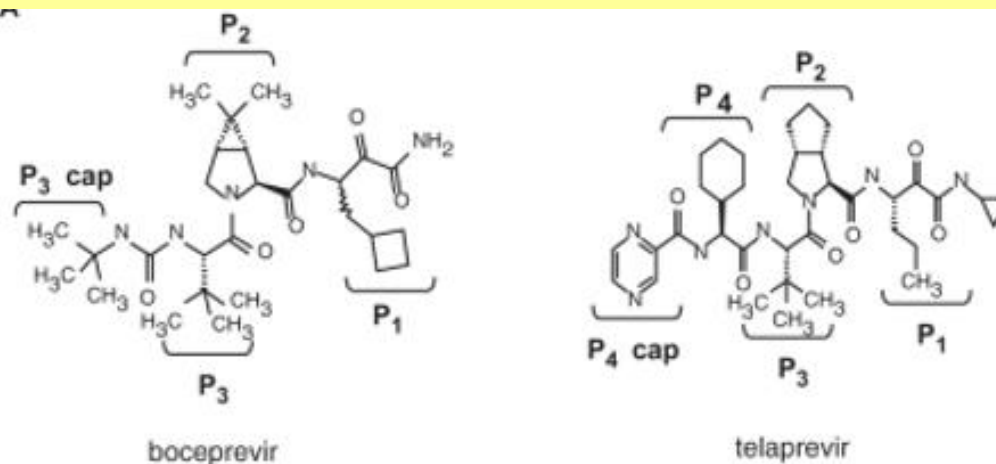


Structure-based drug design

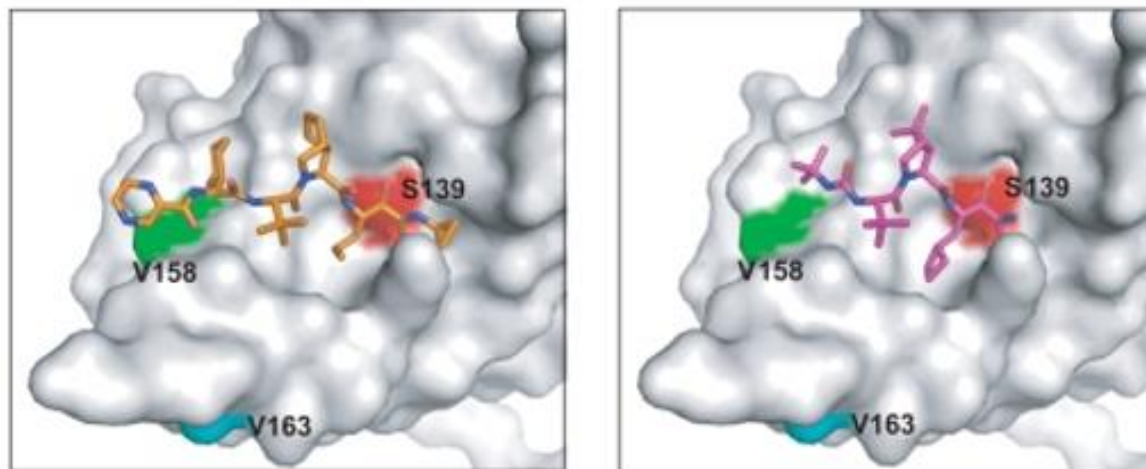


Structure Based Drug Design: The iterative process whereby compounds generated by molecular modeling are synthesized and crystallized with their target protein. The interactions between the lead compound and the protein can then be analyzed and the knowledge gained by this analysis will be used to synthesize new lead compounds with higher affinity to their target protein.

Structures of boceprevir and telaprevir and 3-D structure of NS3 protease-inhibitor complex of HCV

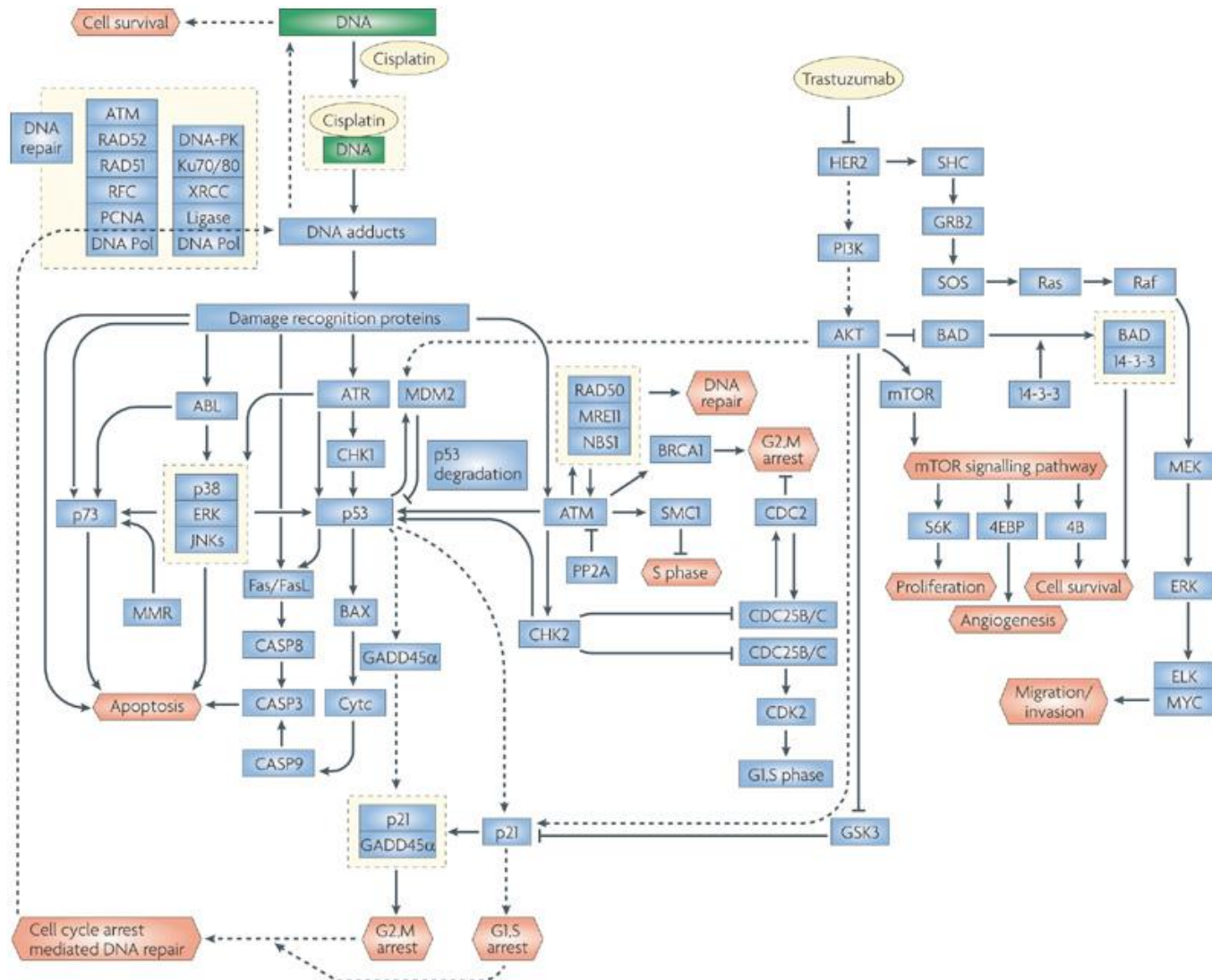


B



Side chains of the active site Ser (Ser139) and two mutation sites (V158 and V163) are depicted on the Connolly surface of the NS3 protease.

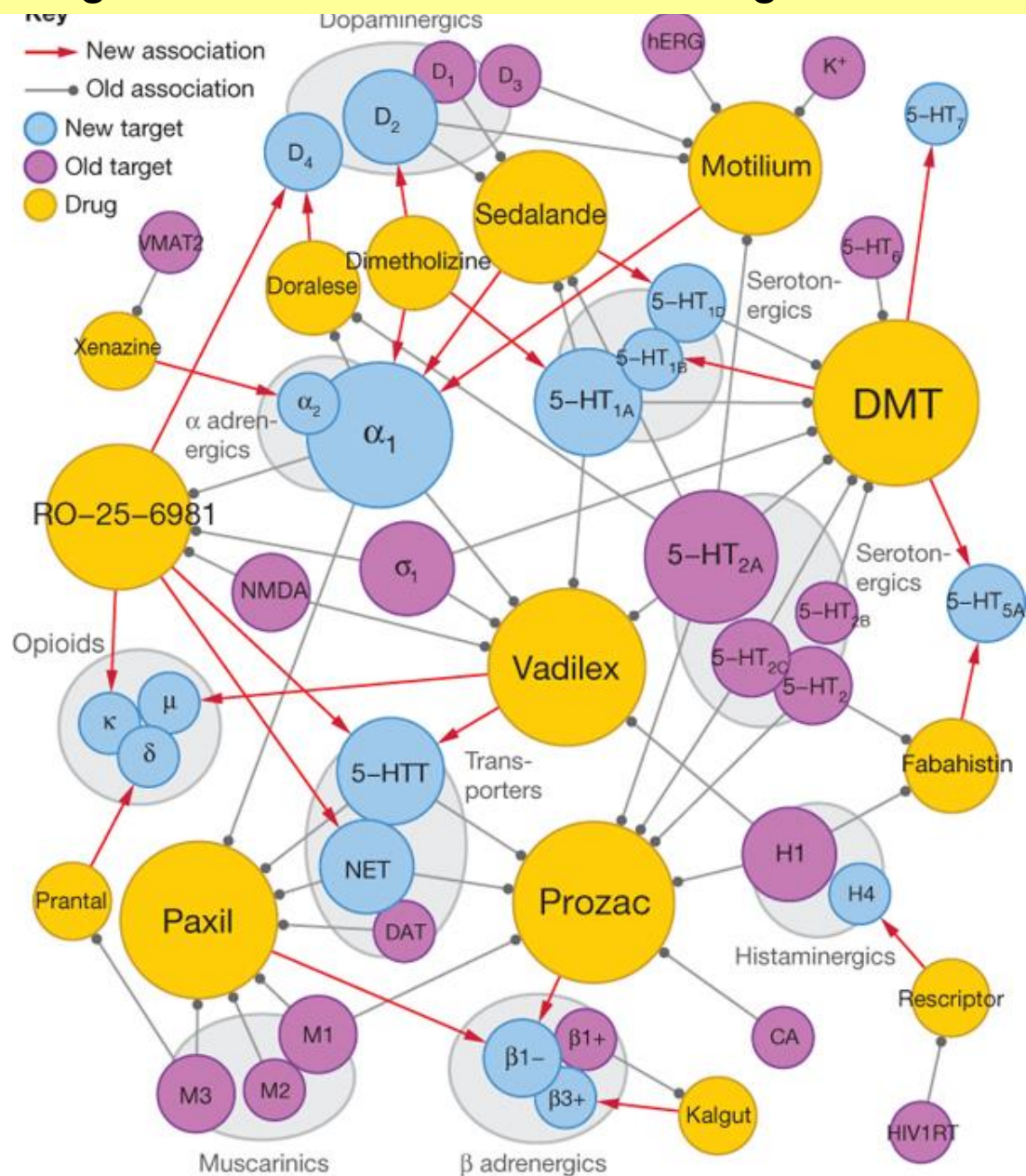
Drug combinations to overcome network complexity



Most marketed drugs bind to several molecular targets

Bipartite network where drugs (gold) are linked by grey edges to their known targets (violet) and by red arrows to their discovered off-targets (cyan). Grey edges denote binding at 1 M or better, where these affinities are known. Node sizes increase with number of incident edges. Target abbreviations: 5-HT_x, serotonin receptor type *x*; 5-HTT, serotonin transporter; 1+, 1 adrenergic agonist; 1-, 1 adrenergic antagonist; 3+, 3 adrenergic agonist; 1, 1-receptor; CA, carbonic anhydrase; DAT, dopamine transporter; HIV1RT, HIV-1 reverse transcriptase; hERG, human Ether-a-go-go related gene channel; K⁺, potassium channel; NET, noradrenaline transporter; NMDA, *N*-methyl-D-aspartate receptor; VMAT2, vesicular monoamine transporter 2.

(Keiser MJ et al. Nature 462: 175-181, 2009)



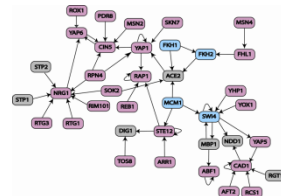
Les principaux défis de la R&D



- Comprendre les systèmes biologiques et le mécanisme des maladies et les modéliser
- Mettre au point des médicaments qui prennent en compte la complexité des systèmes biologiques et des maladies
- Cibler les populations en fonction des altérations moléculaires spécifiques de leur maladie et de leur risque d'effet indésirable (médecine personnalisée/biomarqueurs)

Knowledge of molecular network systems is key for disease treatment and prevention

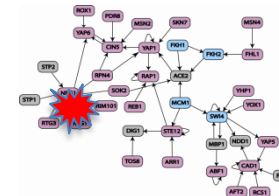
Genetic perturbations



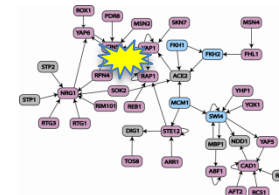
Environmental perturbations



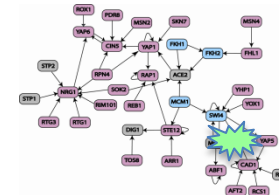
Disease



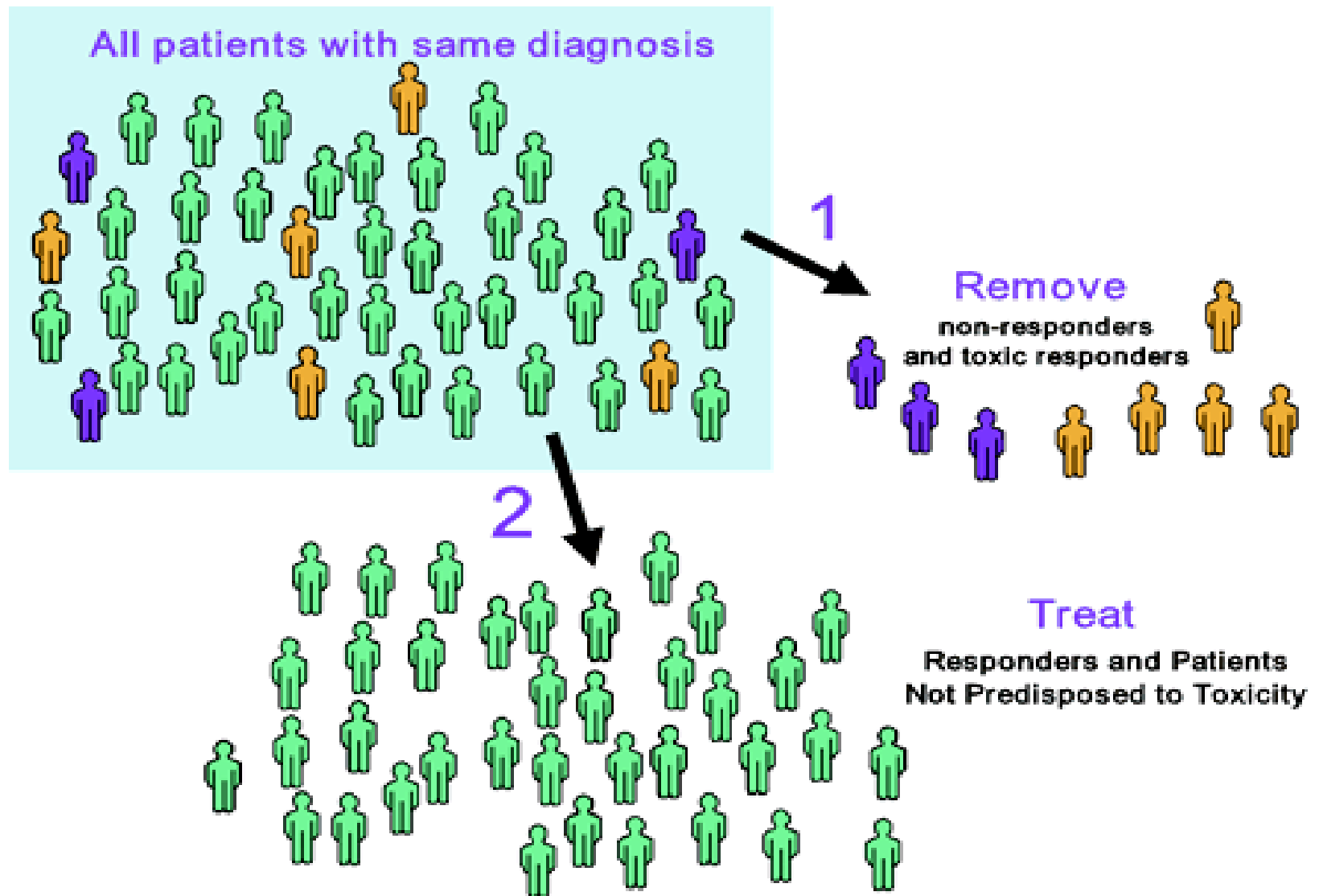
Patient A



Patient B

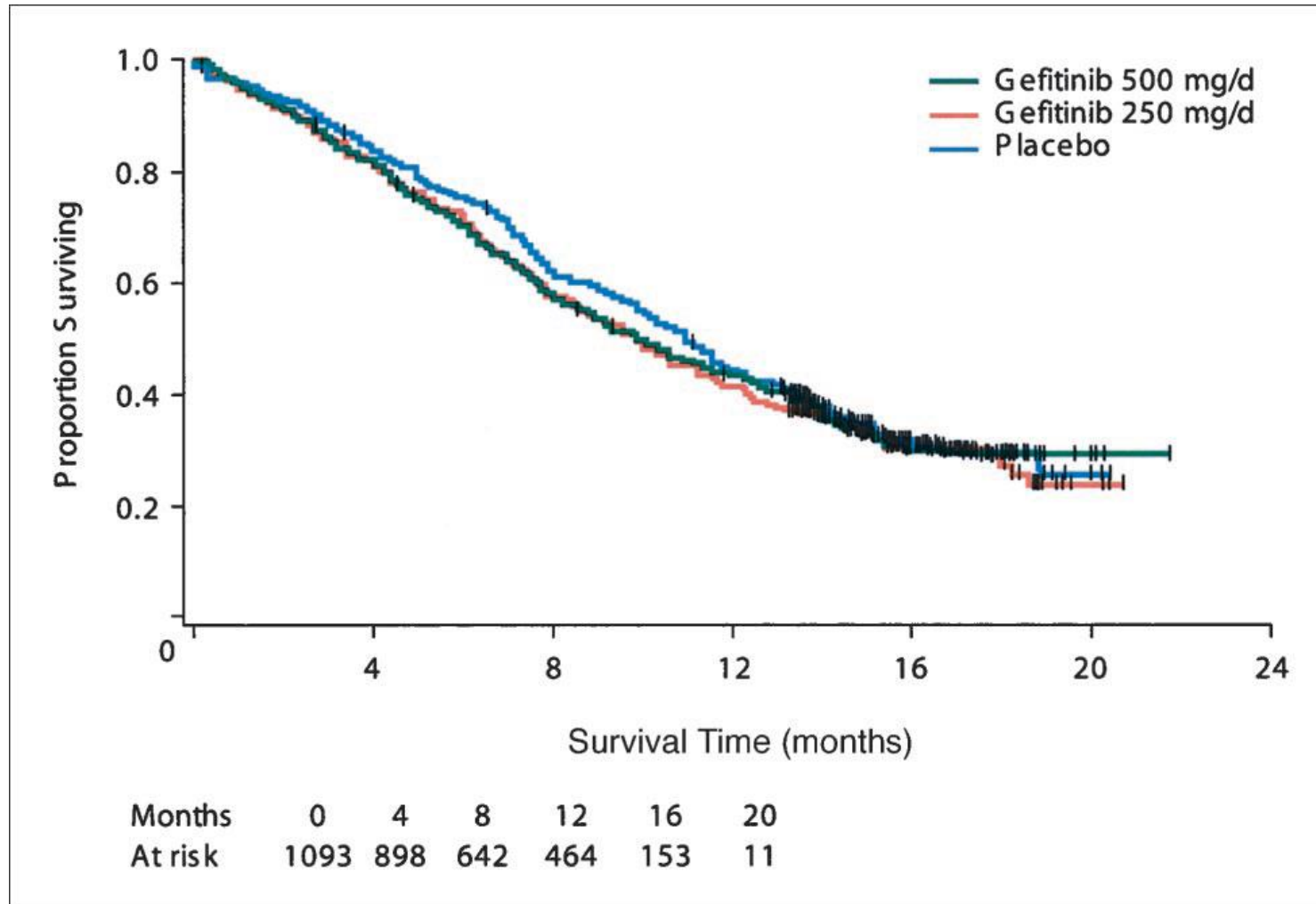


Patient C



(McLeod H, Evans WE. *Ann Rev Pharm Tox* 41: 101-121, 2001)

Gefitinib (Iressa, Astra Zeneca) in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: phase III trial – INTACT 2



(Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial – INTACT 2 J Clin Oncol 2004;22:785-94)

EGFR
mutation
positive

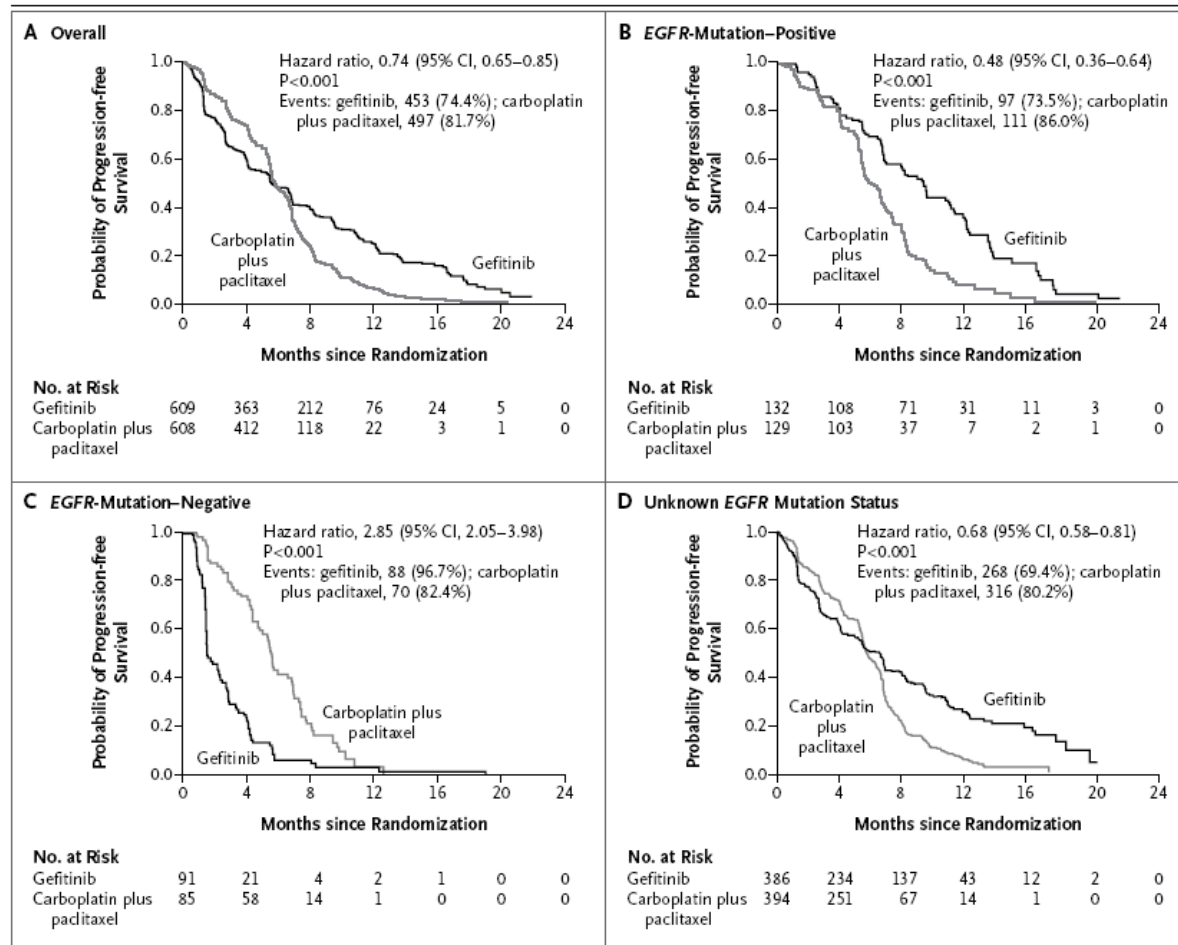
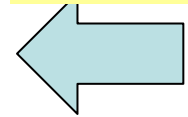


Figure 2. Kaplan–Meier Curves for Progression-free Survival.

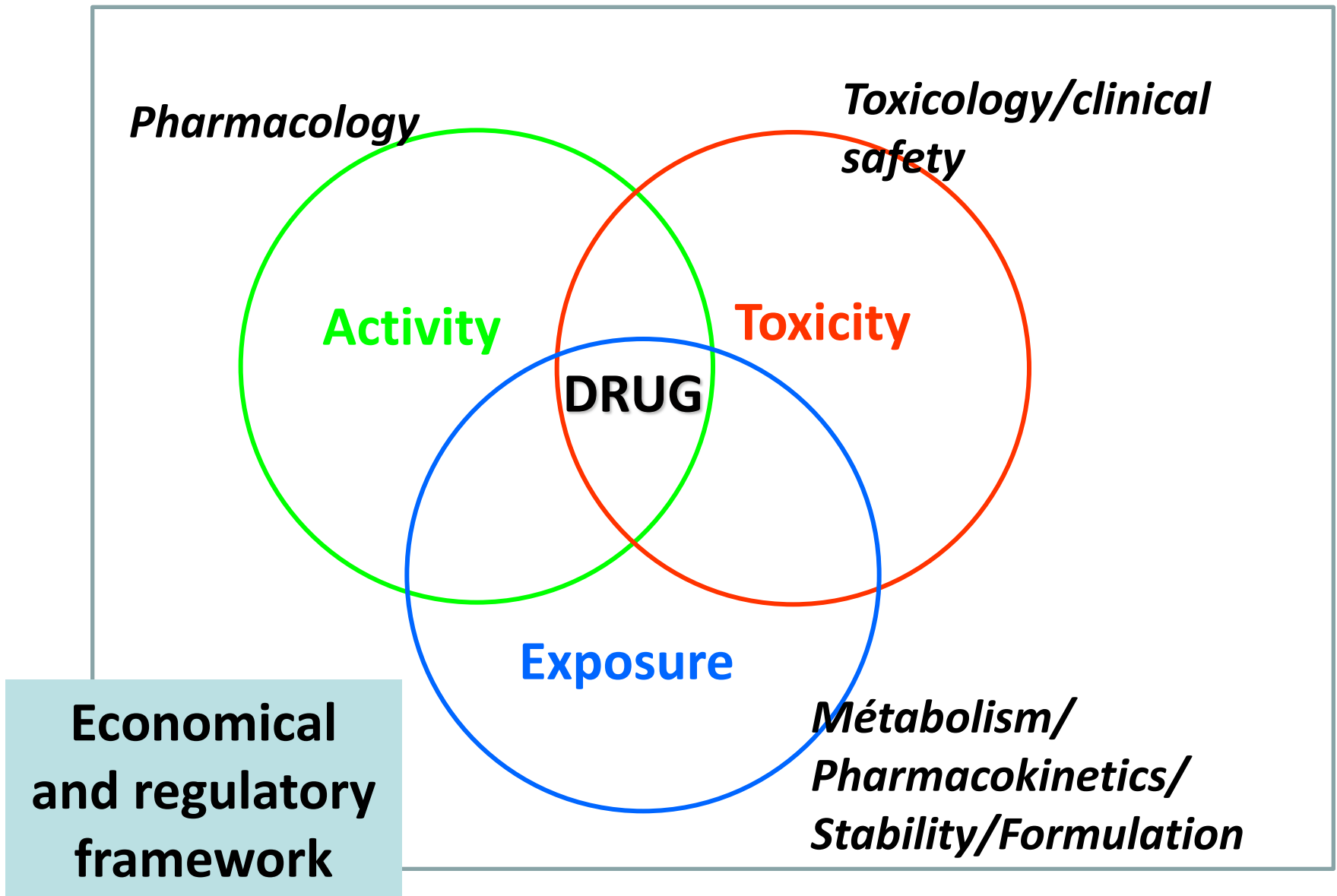
Kaplan–Meier curves for progression-free survival are shown for the overall population (Panel A), patients who were positive for the *EGFR* mutation (Panel B), patients who were negative for the *EGFR* mutation (Panel C), and patients with unknown *EGFR* mutation status (Panel D). Analyses were performed on the basis of the intention-to-treat population. With respect to the overall population, results of the supportive secondary analyses (including a log-rank test, which is valid under the null hypothesis even when hazards are not proportional, and analysis in the per-protocol population) were consistent with the result of the primary analysis. Hazard ratios were calculated with the use of a Cox proportional-hazards model, with the WHO performance status (0 or 1, or 2), smoking history (nonsmoker or former light smoker), and sex as covariates. *EGFR* denotes epidermal growth factor receptor.

Les principaux défis de la R&D

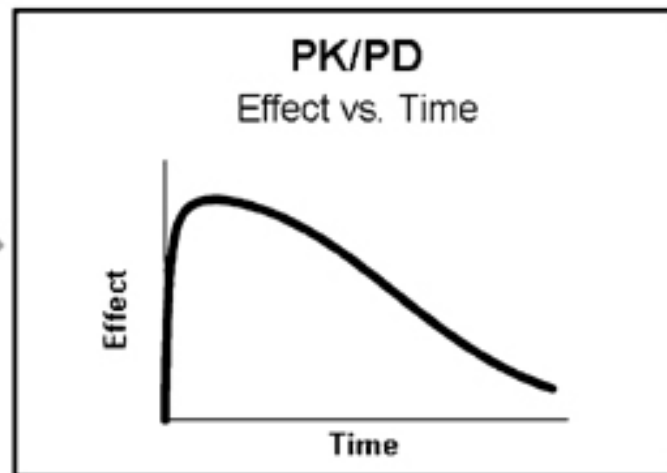
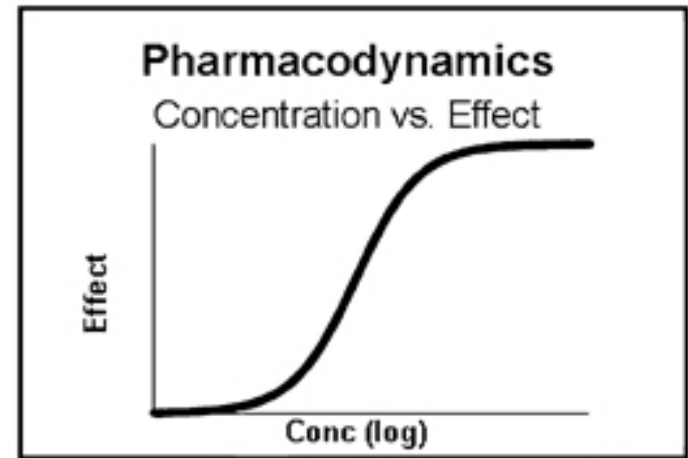
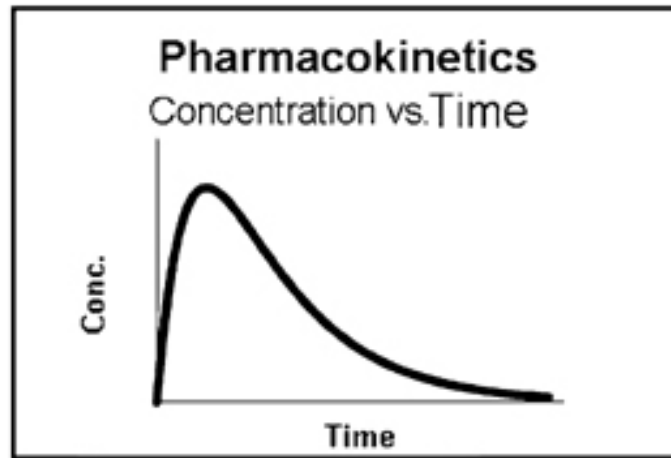


- Comprendre les systèmes biologiques et le mécanisme des maladies et les modéliser
- Mettre au point des médicaments qui prennent en compte la complexité des systèmes biologiques et des maladies
- Cibler les populations en fonction des altérations moléculaires spécifiques de leur maladie et de leur risque d'effet indésirable (médecine personnalisée/biomarqueurs)
- Mieux prédire le devenir du médicament dans l'organisme et ses effets indésirables potentiels

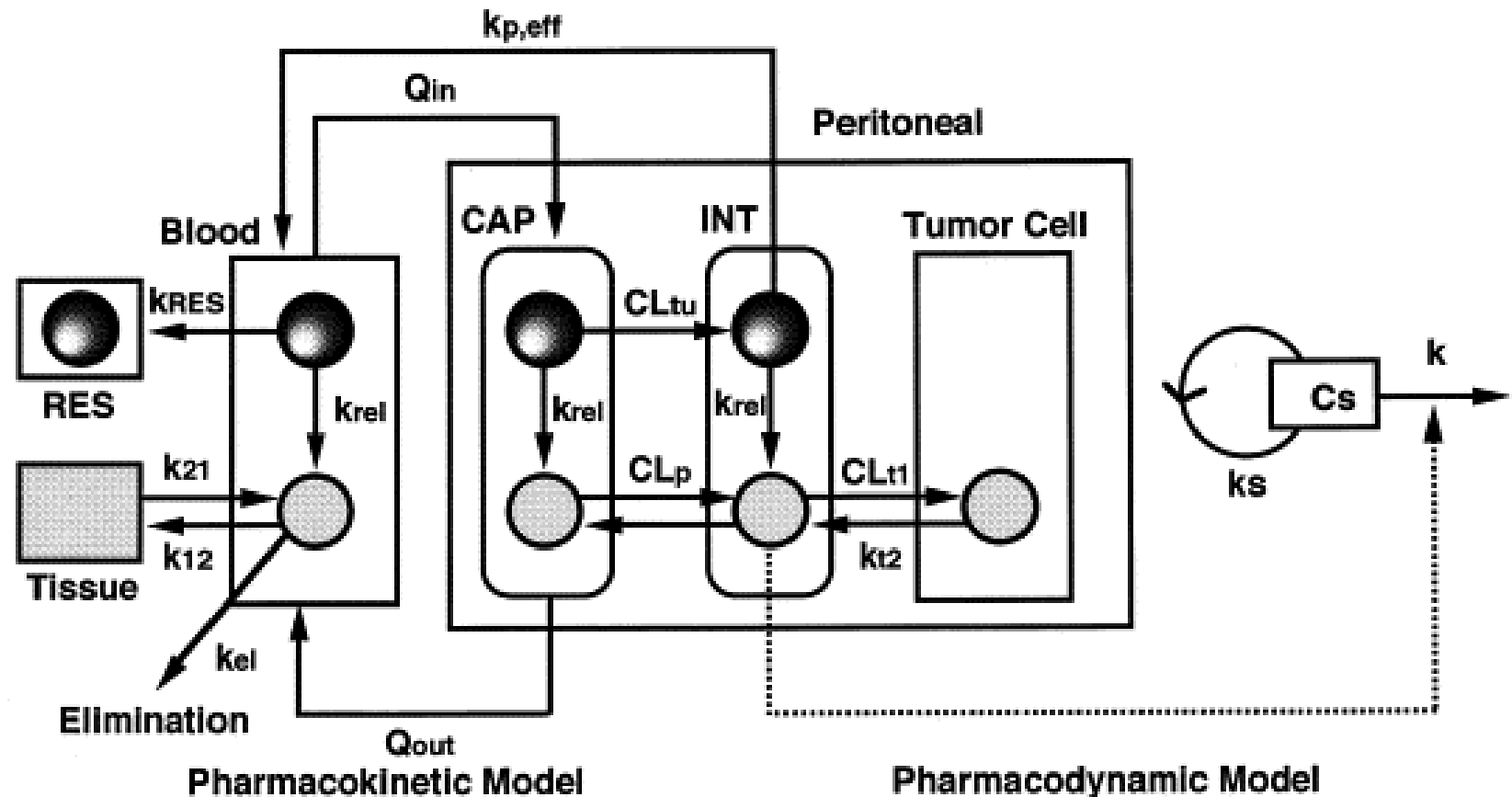
What makes a drug ?



General concept of pharmacokinetic/pharmacodynamic (PK/PD) modeling.

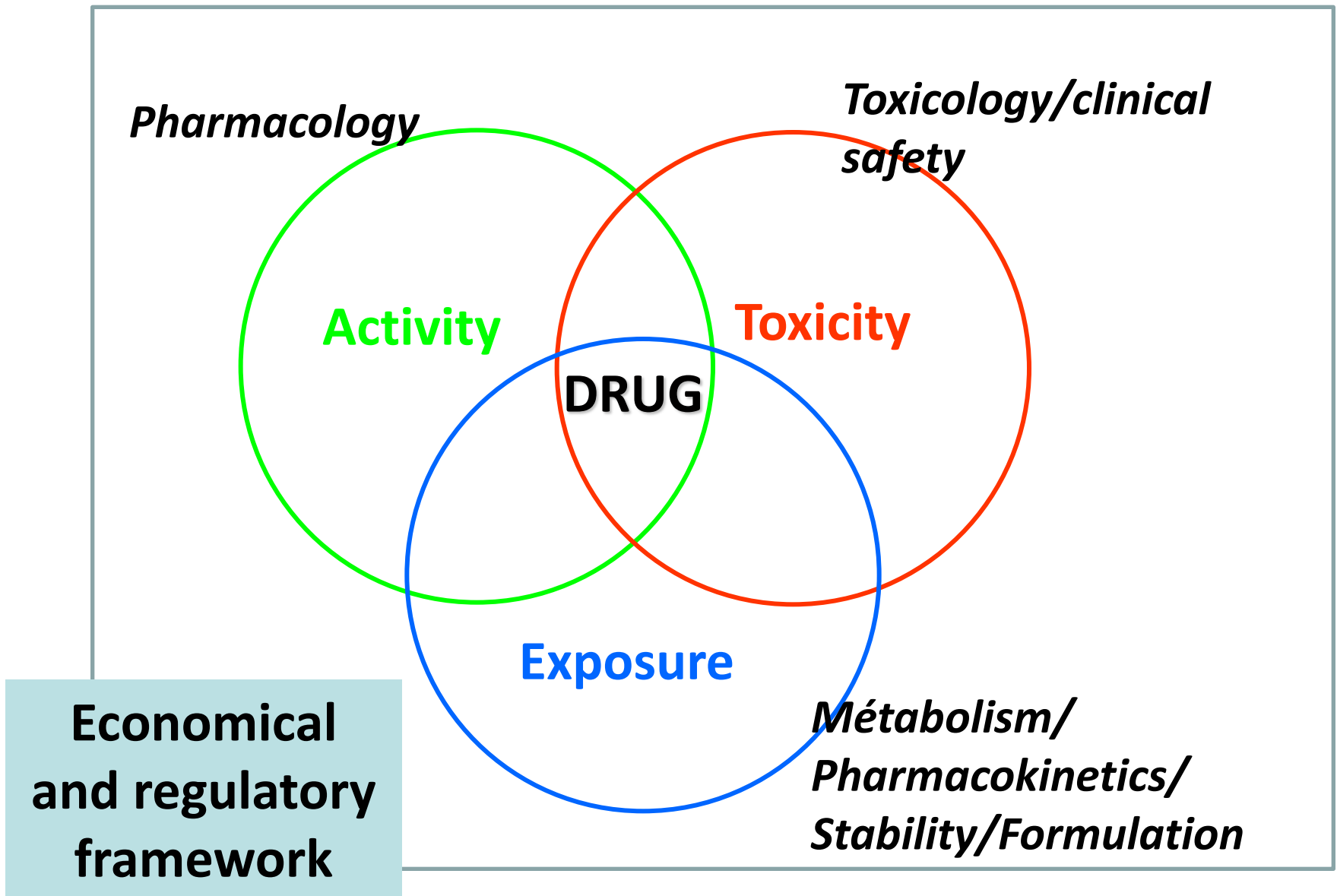


PK/PD modeling



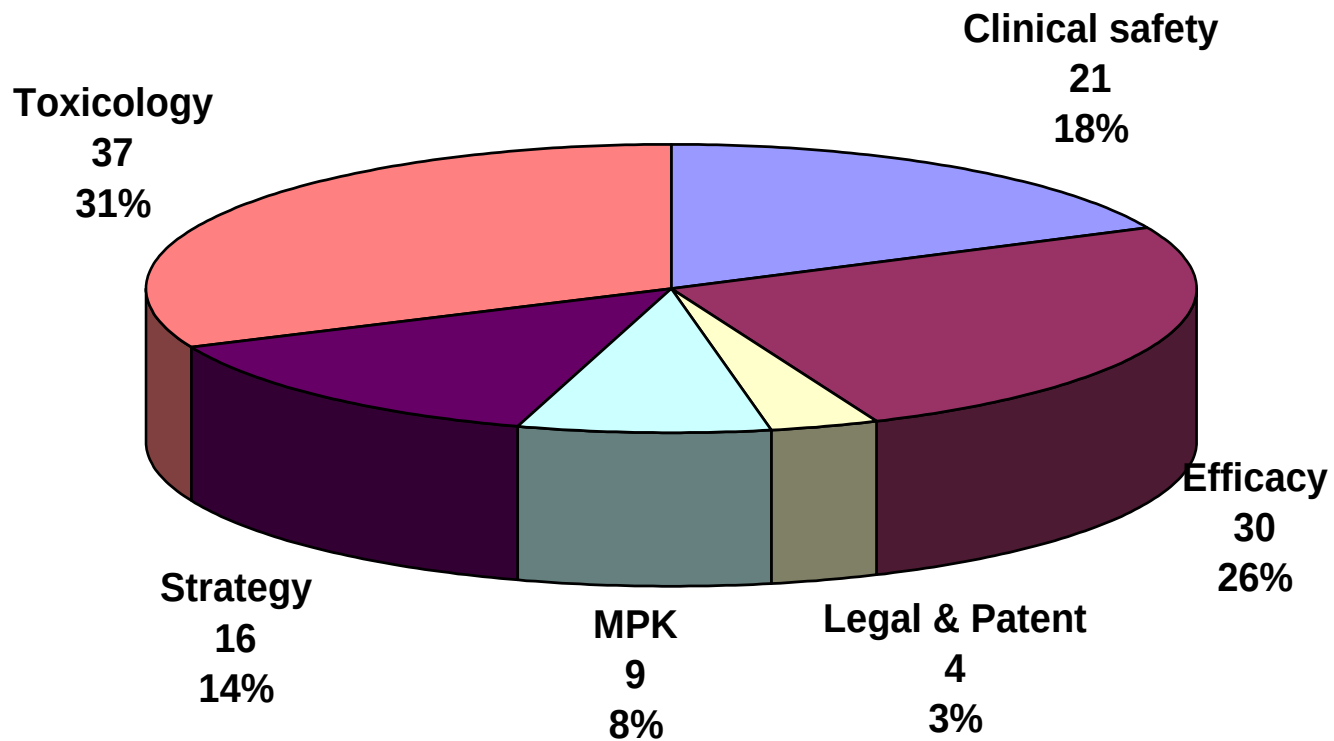
Tsuchihashi M et al , Journal of Controlled Release 61, 1999, 9–19

What makes a drug ?



Main reasons for project termination

2002-2007 (117 projects)

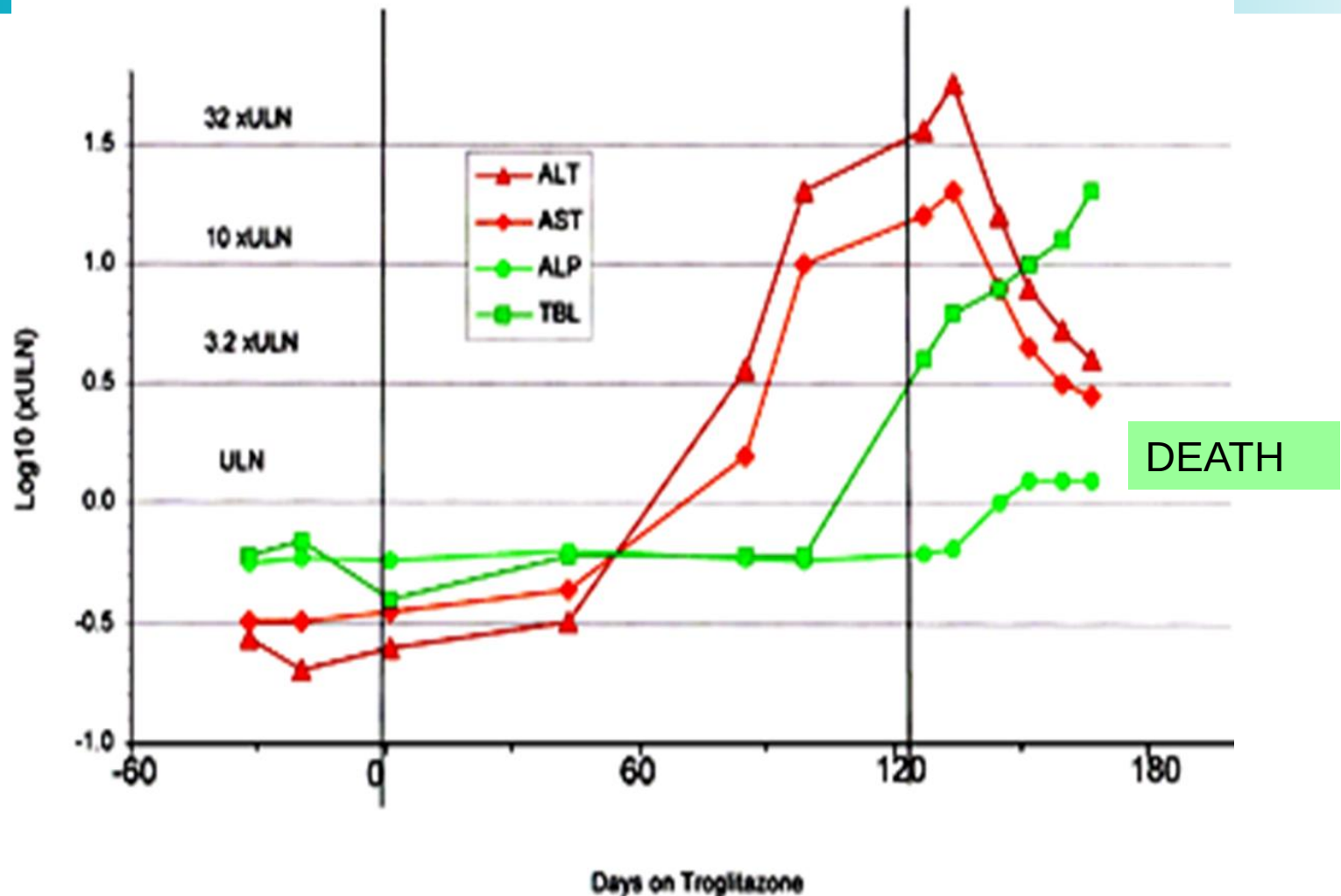


50% of pharmaceutical R&D projects are terminated for safety reasons

Drug-induced liver injury - troglitazone

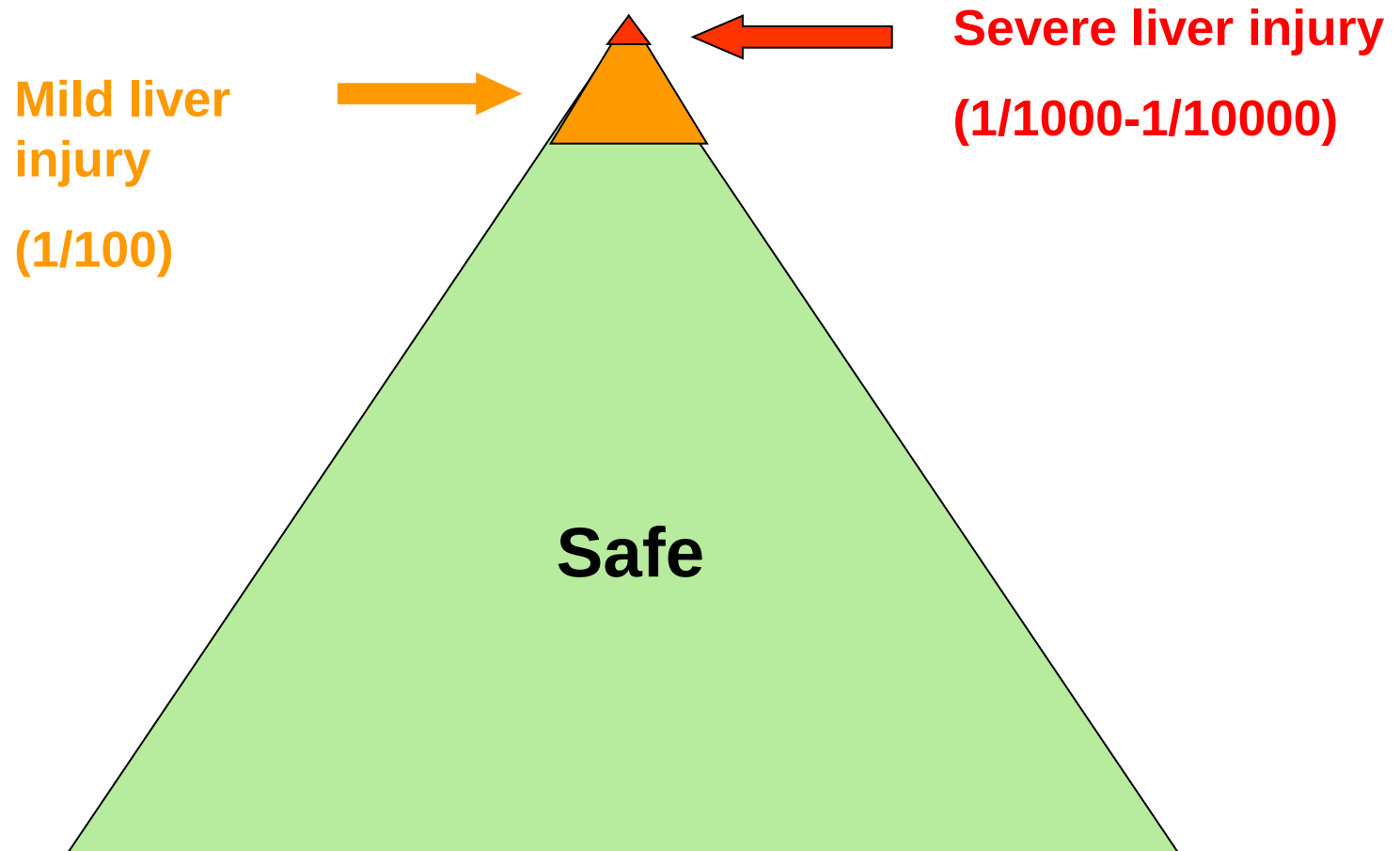
START

STOP

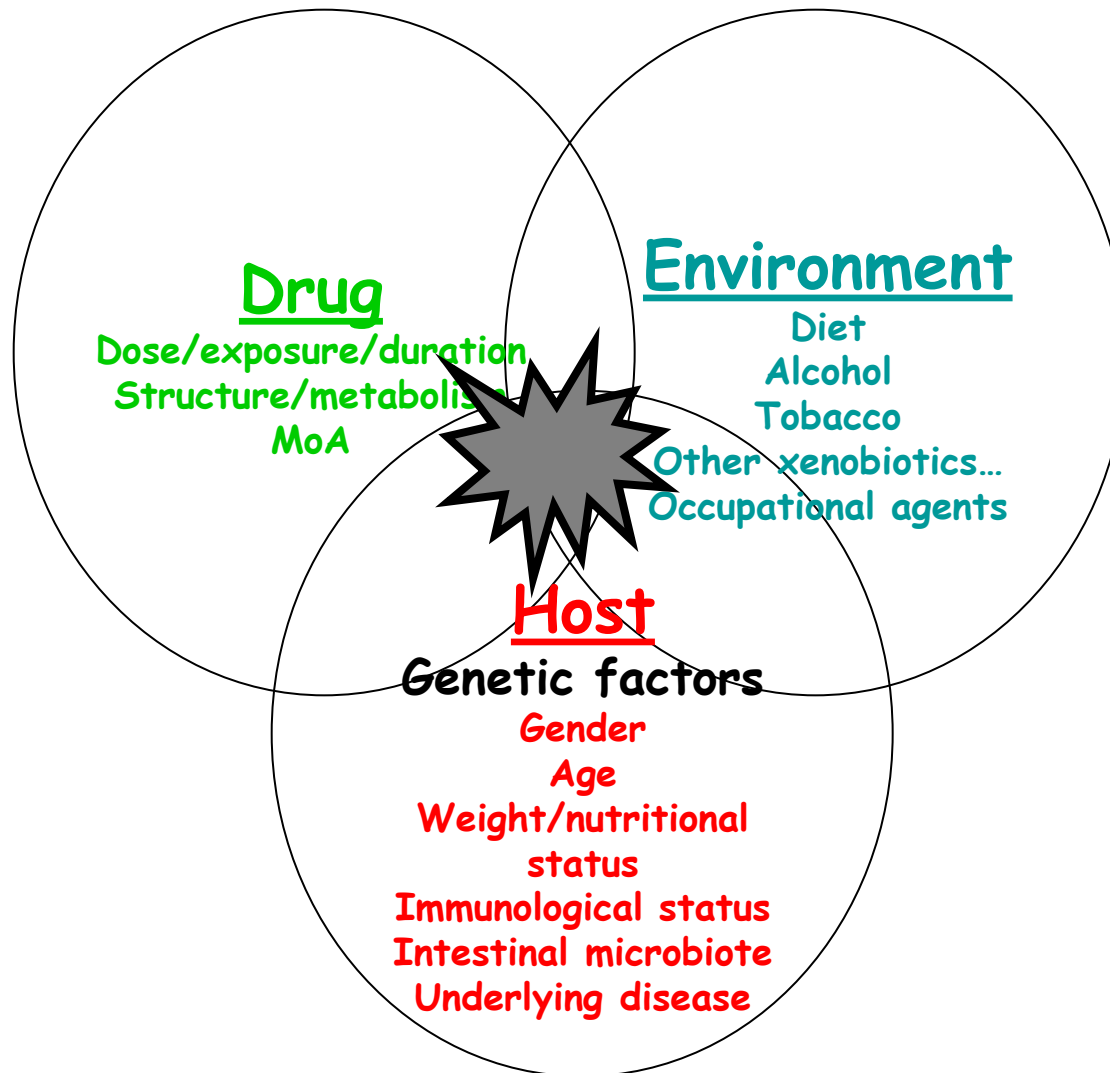


(Watkins P. Toxicol Pathol 33, 1-5, 2005)

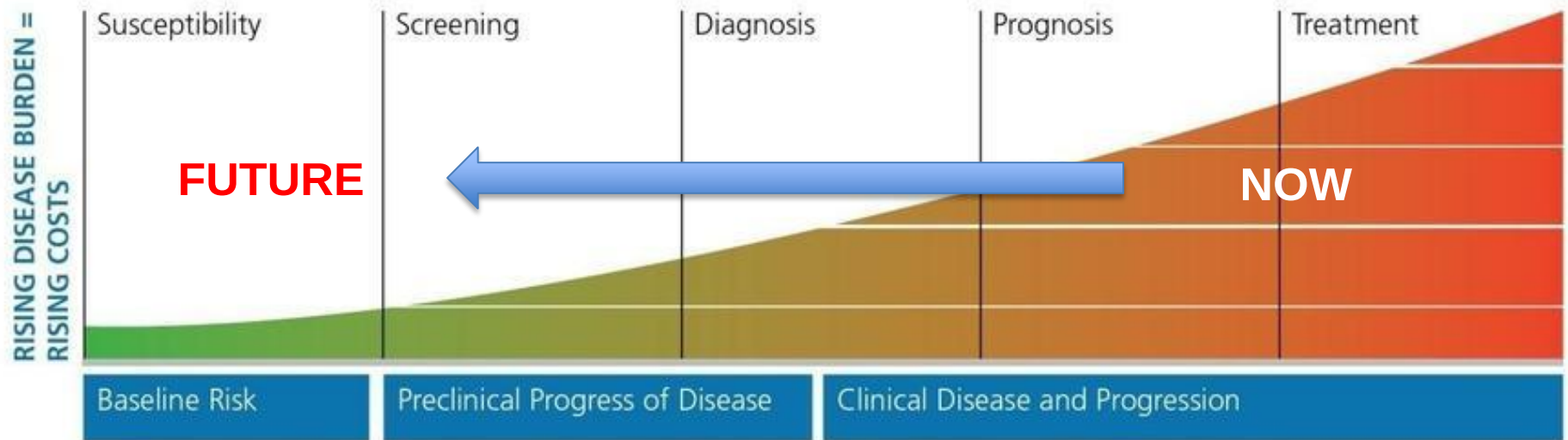
What is idiosyncratic toxicity ?



Idiosyncratic toxicity occurs when several (risk) factors converge



Shift to Prevention and Personalized care for every phase of health



Knowledge of molecular network systems is key for disease treatment and prevention

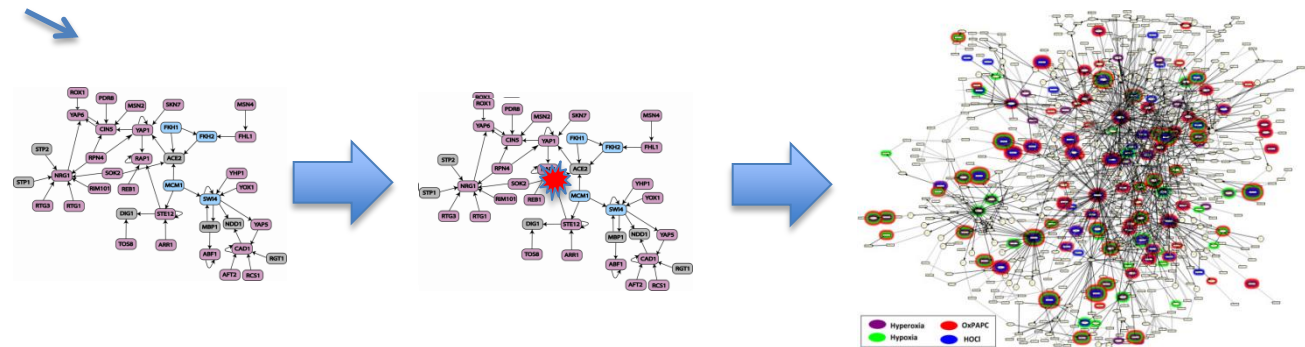
Genetic perturbations

Environmental perturbations

Disease

early

late



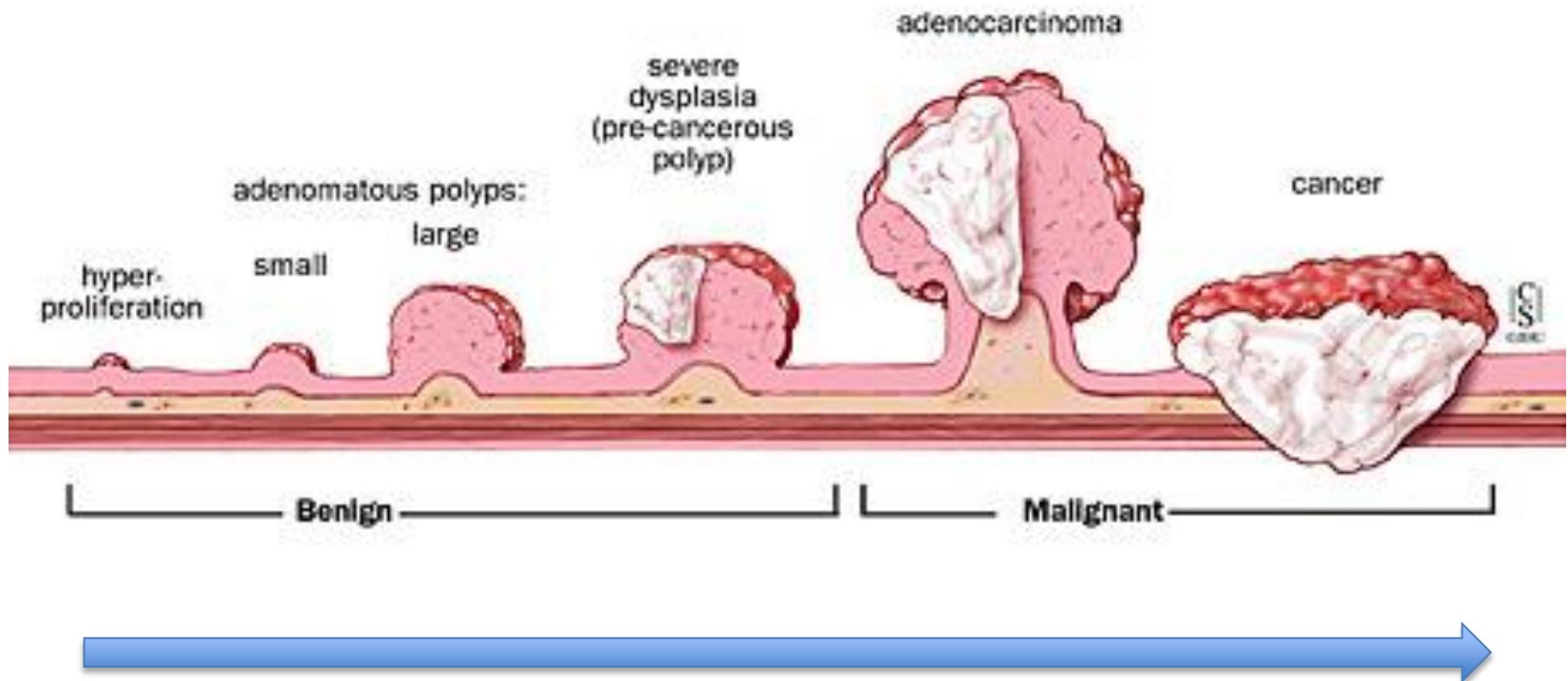
Risk prediction
and prevention

Ultra early
diagnostic

Late diagnostic

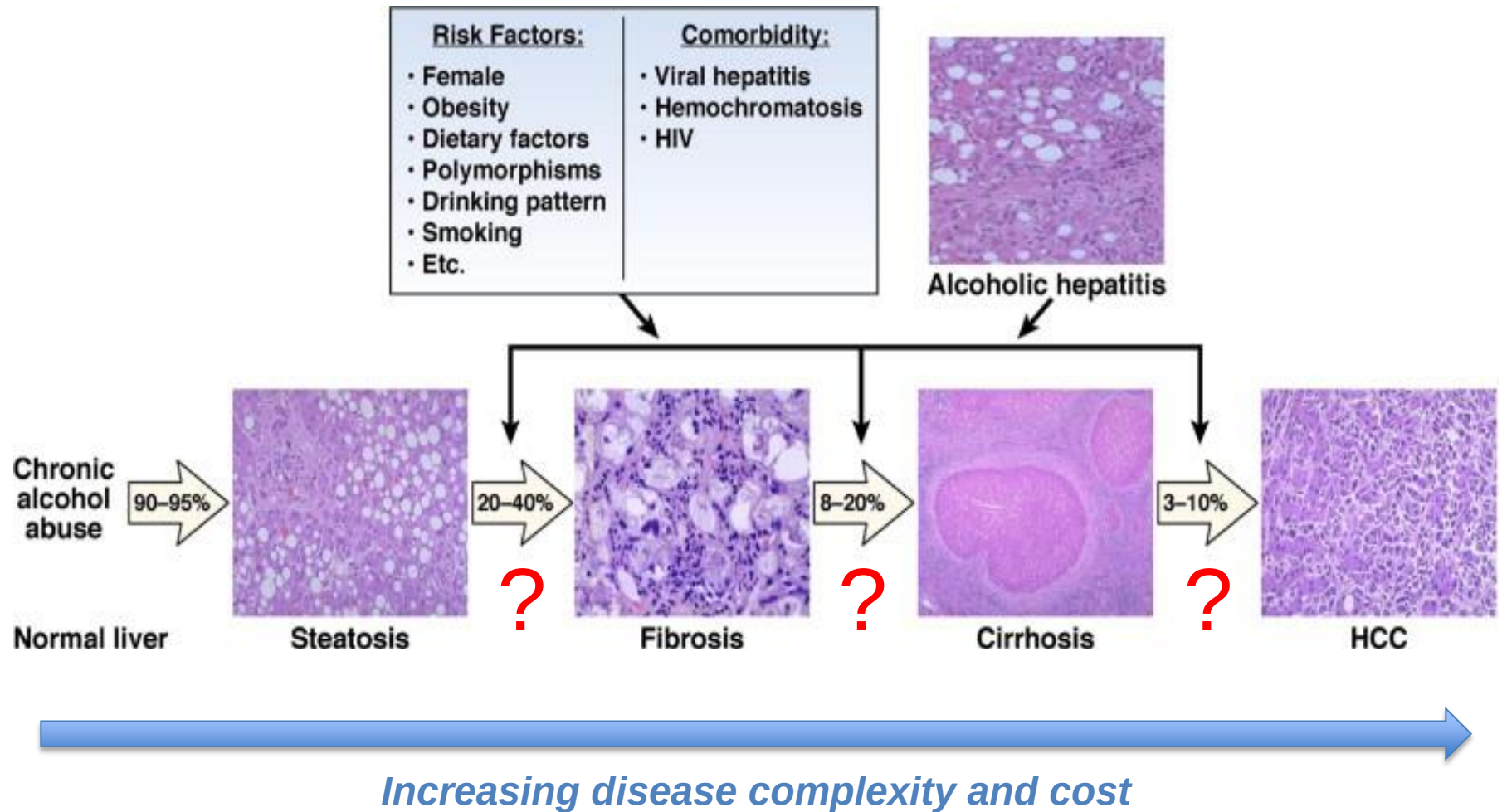
Increasing disease complexity and cost

From polyps to colorectal carcinoma

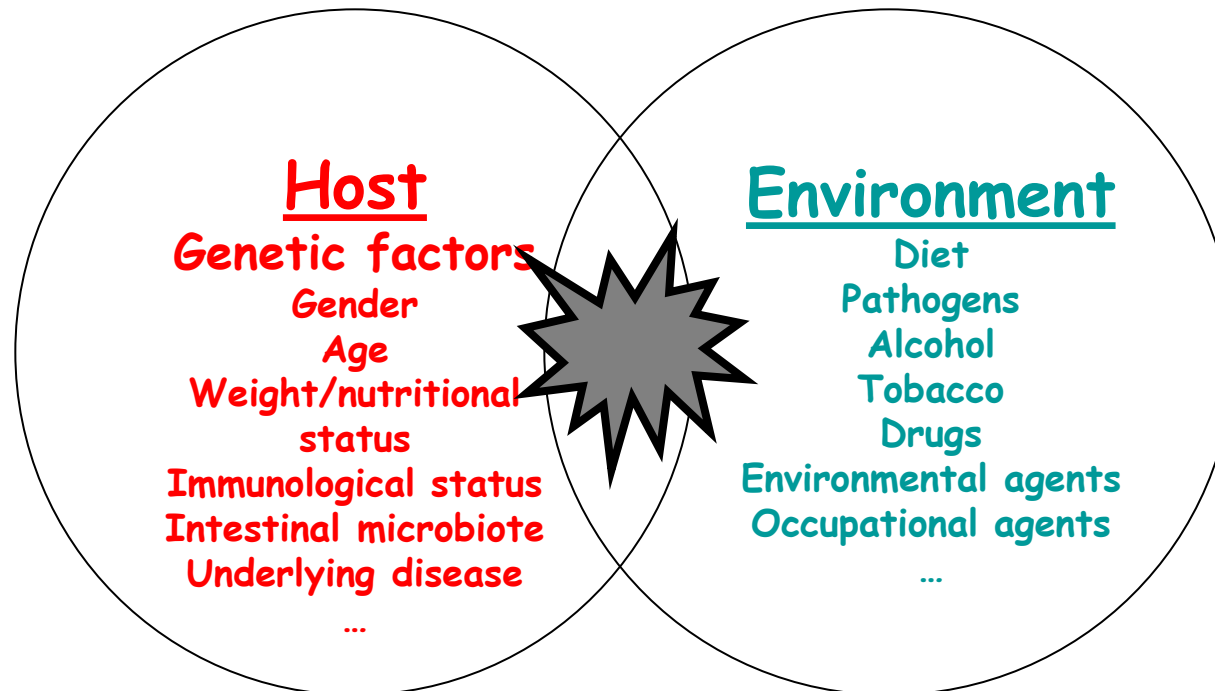


Increasing disease complexity and cost

More than 95% of heavy drinkers develop fatty liver, **but only up to 35% develop more severe forms of ALD**, including fibrosis, alcoholic hepatitis, cirrhosis, and HCC.

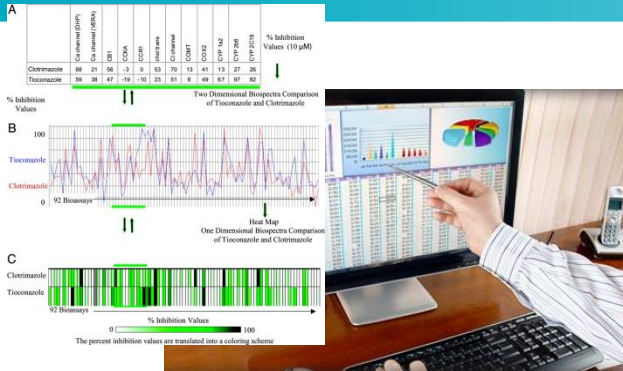


Diseases result from the combination of host and environmental factors

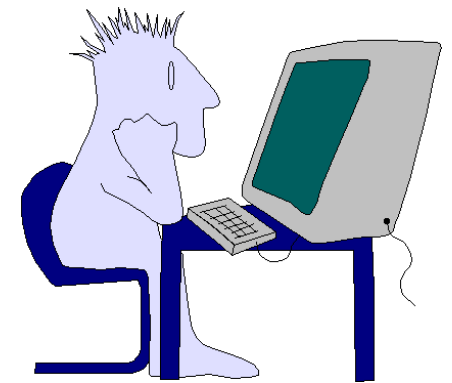


Complex algorithms for individual risk prediction

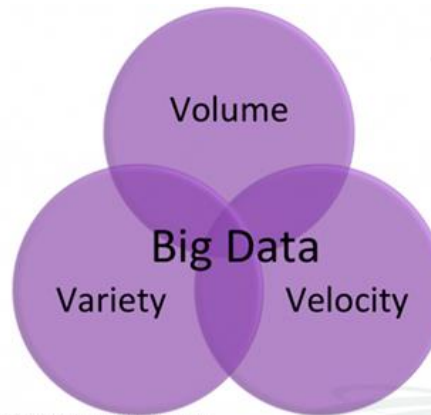
Big data challenge in medicine



R&D



HPC



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Medical practice



Knowledge
Decisions
Products



The New England
Journal of Medicine

ASCO

medical
information

telemedicine

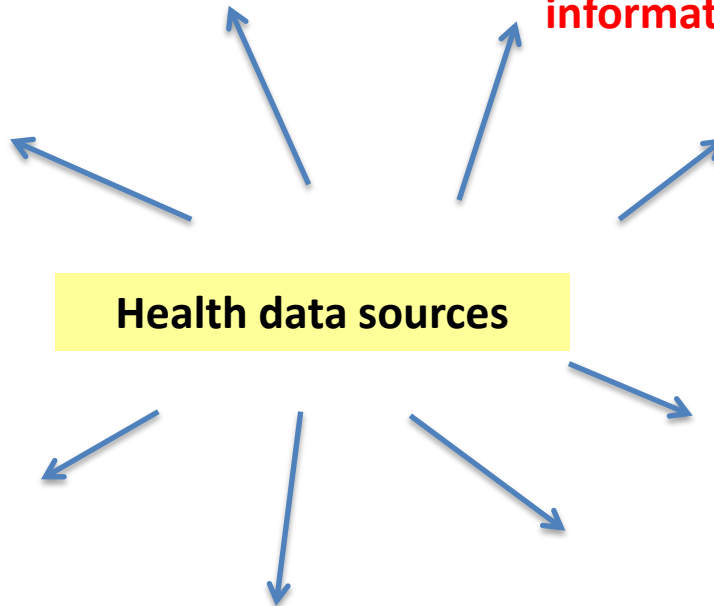
Health data sources

mobile apps

medical devices

drugs

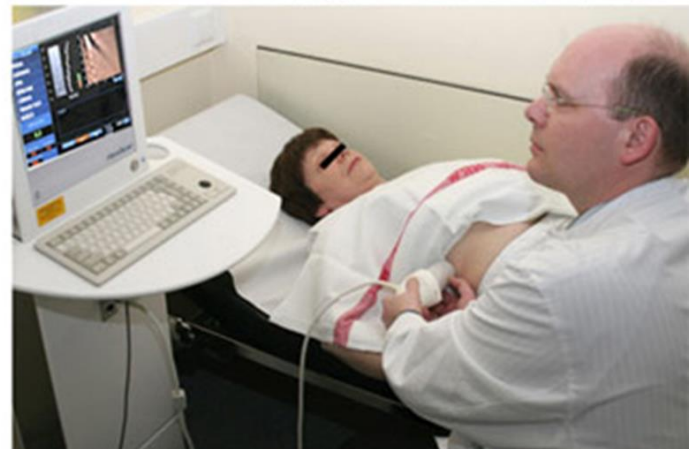
patient data



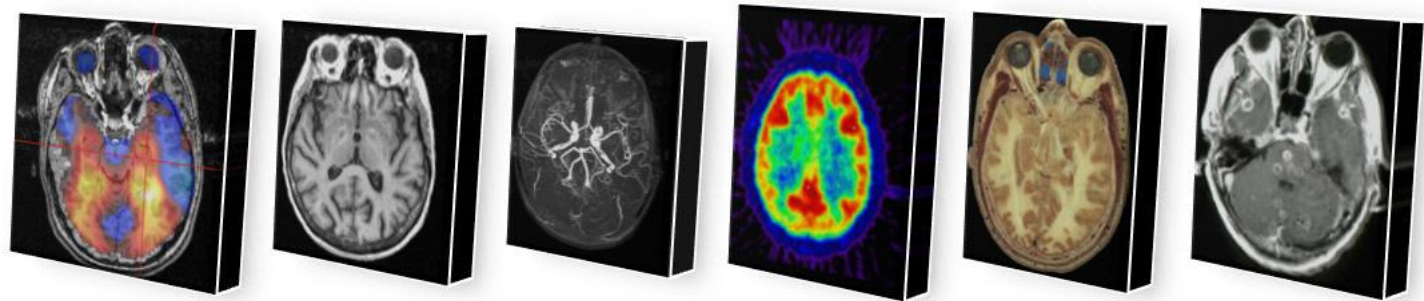
Medical imaging as part of routine clinical examination



Fibroscan

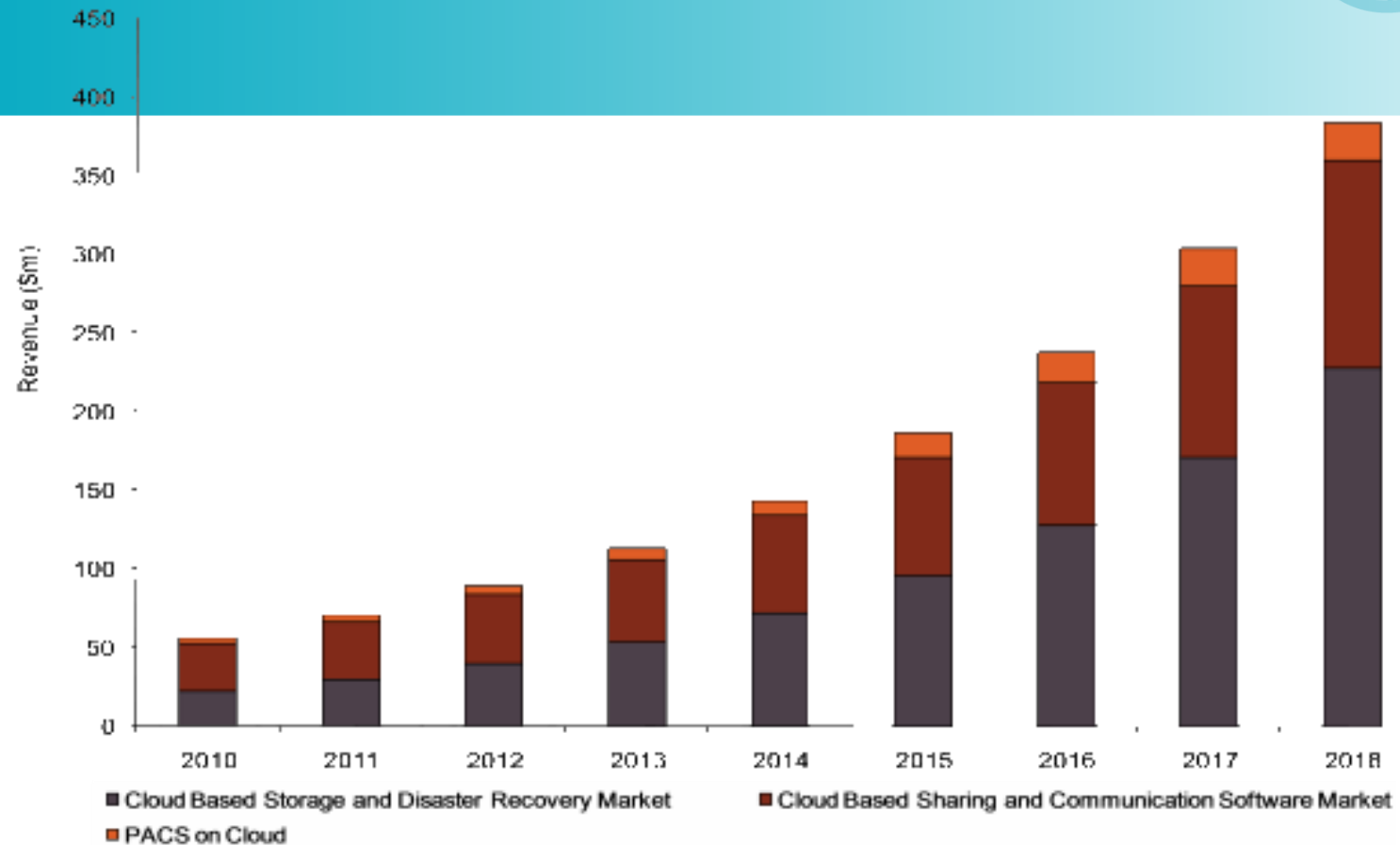


Integration of different imaging modalities by multimodal and multiparametric approaches



Clinical decision

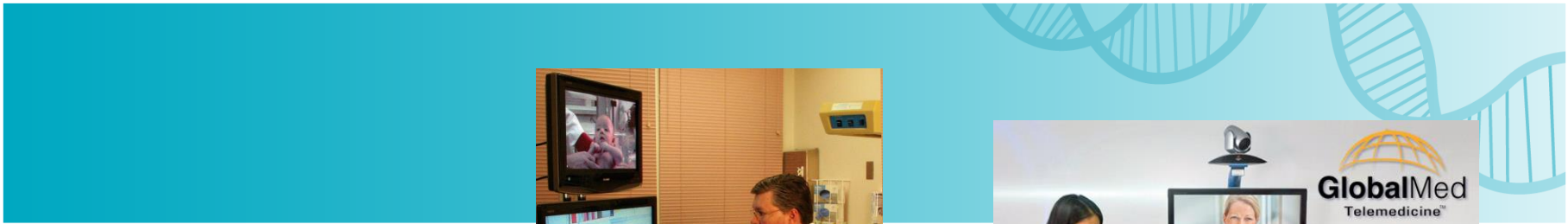
Figure 1: Cloud Computing Market for Medical Images, the US, Revenue (\$m), 2010-2018



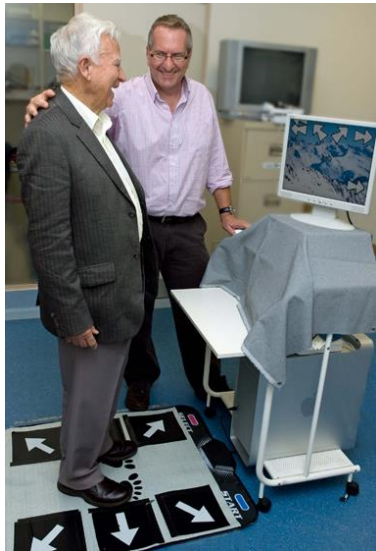
Source: GlobalData, Annual Reports, Company Websites, News and Press Releases, Research Papers, Primary Interviews with Key Opinion Leaders

ICU monitoring





**multiple
applications of
telemedicine**



s biologiques
sances utiles



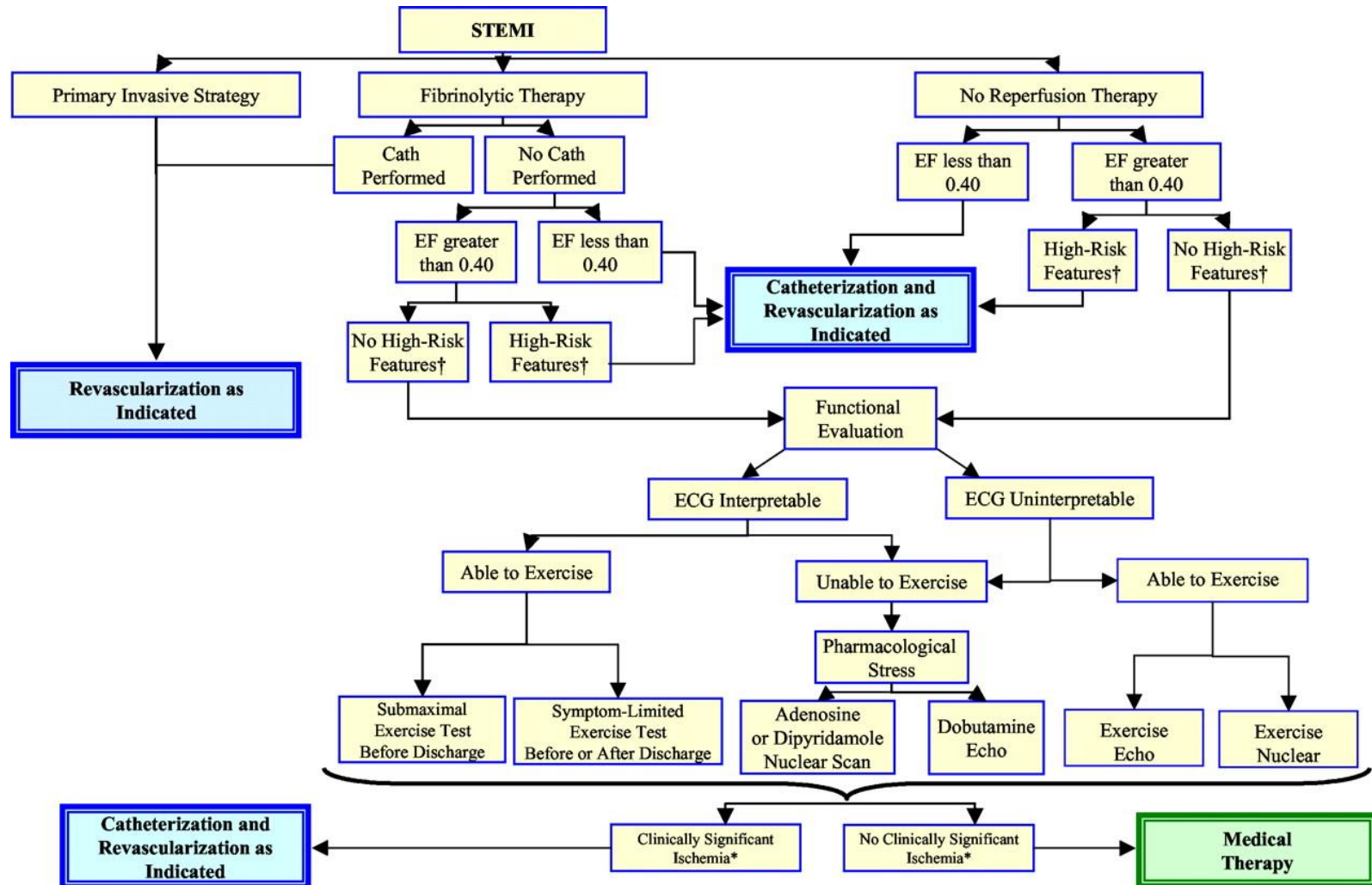
Electronic health/medical record (EHR/EMR)



NOW

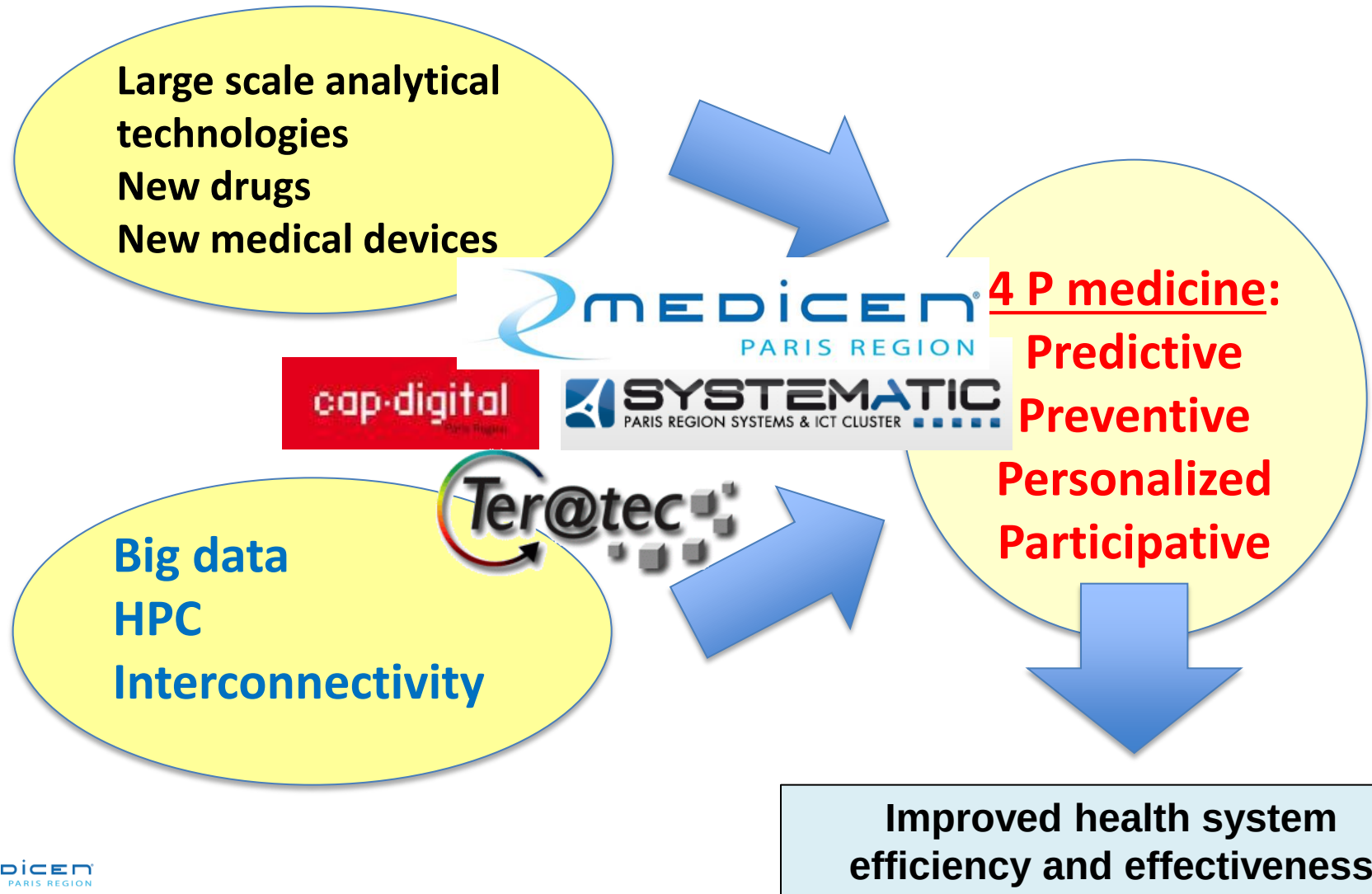
FUTURE

Evidence-based approach to need for catheterization (cath) and revascularization after STEMI



Writing Committee Members et al. Circulation
2004;110:588-636

Key role of complementary competency clusters





www.medicen.org