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Pharmacogenetics in drug development

E. Jacqz-Aigrain

APHP

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Definition

Pharmacogenetics

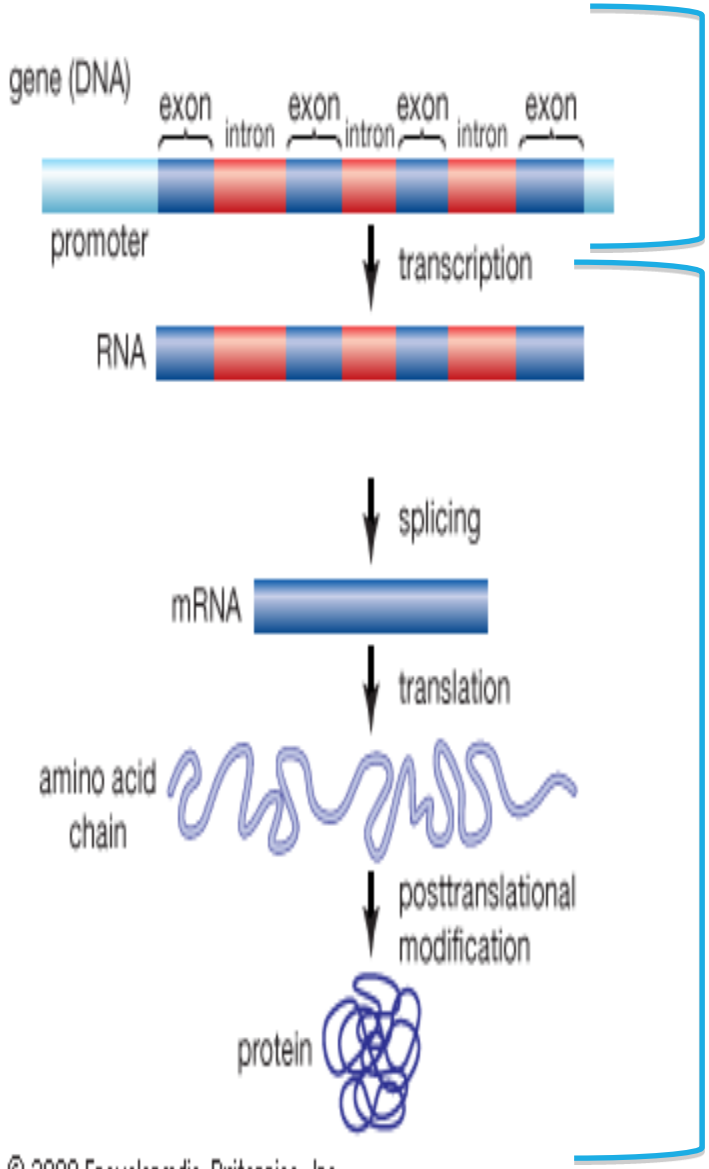
Study of interindividual variations in the DNA sequence that are related to drug response, efficacy and toxicity

Position paper in pharmacogenetics, Committee for Proprietary Medicinal Products – 2002.

Pharmacogenomics : broader sense

Genetic variations, alterations in gene expression and post-translational modifications

Genotype



Genomics

SNPs, deletion, duplication..

Post-genomics

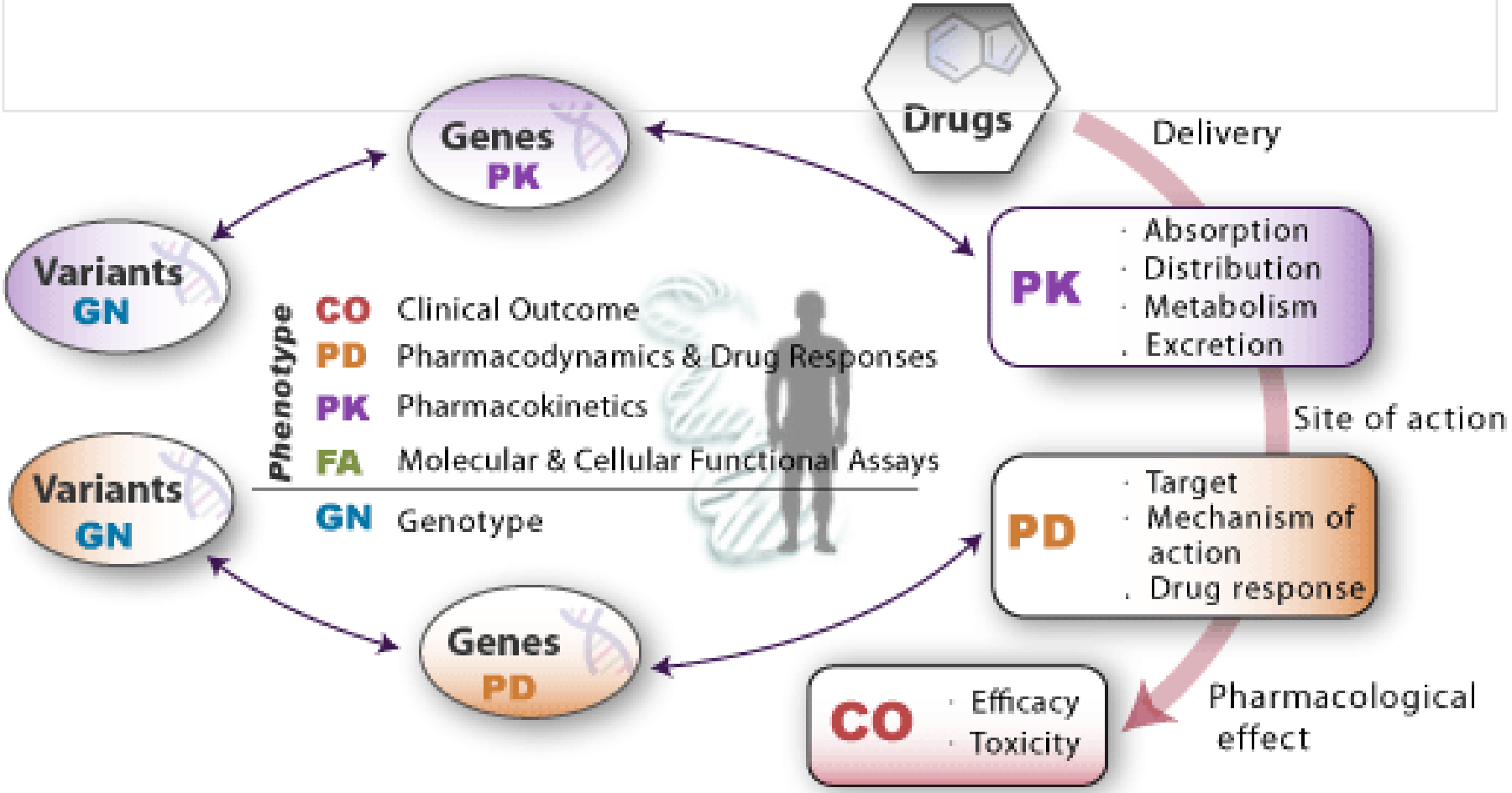
transcriptomics : how genes are transcribed into messenger RNA

proteomics : how genes are expressed as proteins

metabolomics how genes influence the chemicals that control cellular biochemistry and metabolism

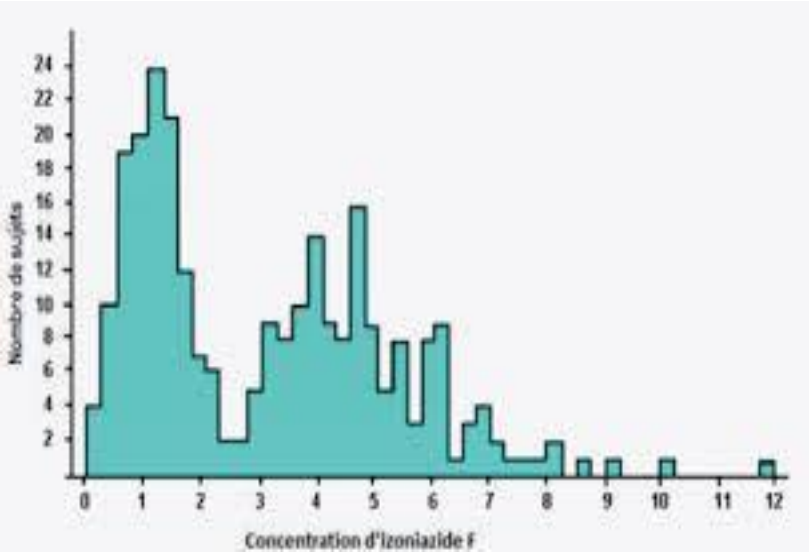
Phenotype

Pharmacogenetics participates to variability in drug pharmacokinetics and pharmacodynamics



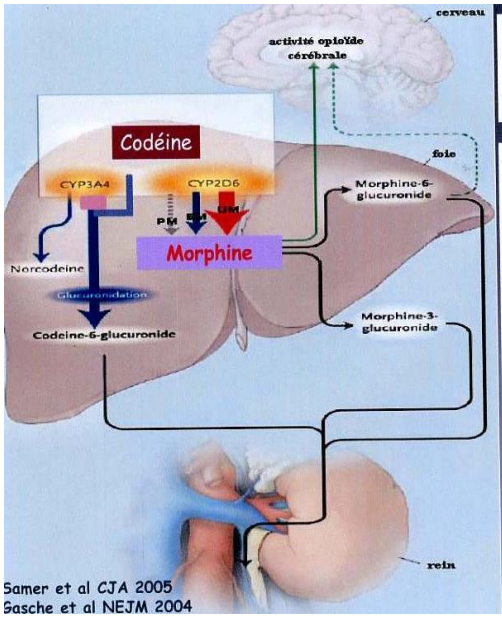
Pharm GKB Website, accessed 11/07/07

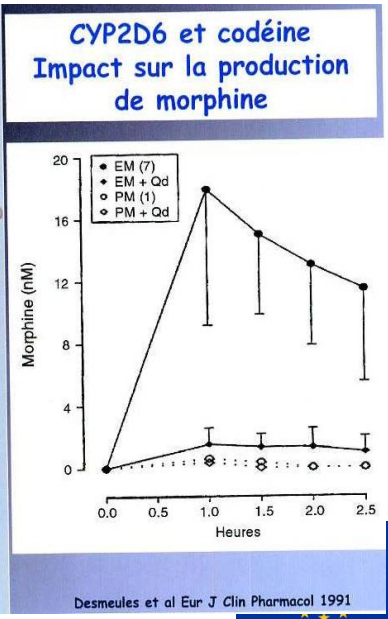
More than 50 years ago …



N-acetylation Polymorphism Bimodal distribution of isoniazide concentrations 6h after a standard dose in healthy adults (1964)

CYP2D6 polymorphism and impact on the metabolism of many drugs including codeine
(1978)





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Pharmacogenetic applications in drug development

Applications in preclinical drug development

Target identification based on the genomic data (Human Genome Project) :

- single gene disease versus much more complex diseases

Candidate selection to be transferred to the clinic :

- disease heterogeneity
- knowledge on the molecular mechanisms underlying disease,
- variability in drug response,
- impact of growth and maturation

Applications in clinical drug development (1)

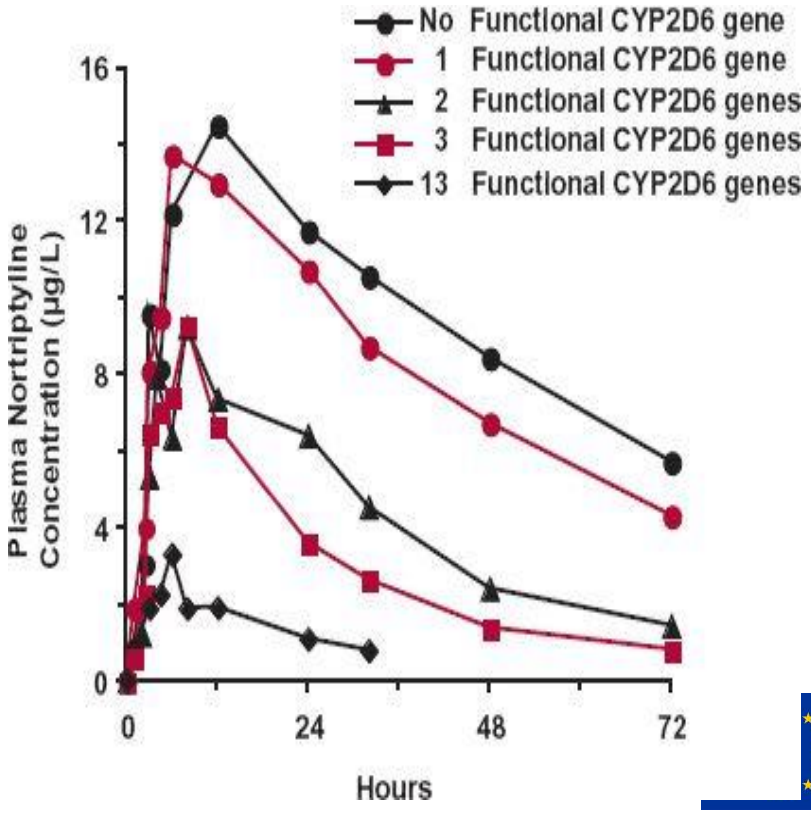
Pharmacogenetics / Pharmacokinetics

Retrospective analysis of clinical trials results, based on genotype data, to explore and explain

Variability in pharmacokinetics

Issues on pharmacodynamics

Analysis of adverse drug reactions



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Applications in clinical development (2)

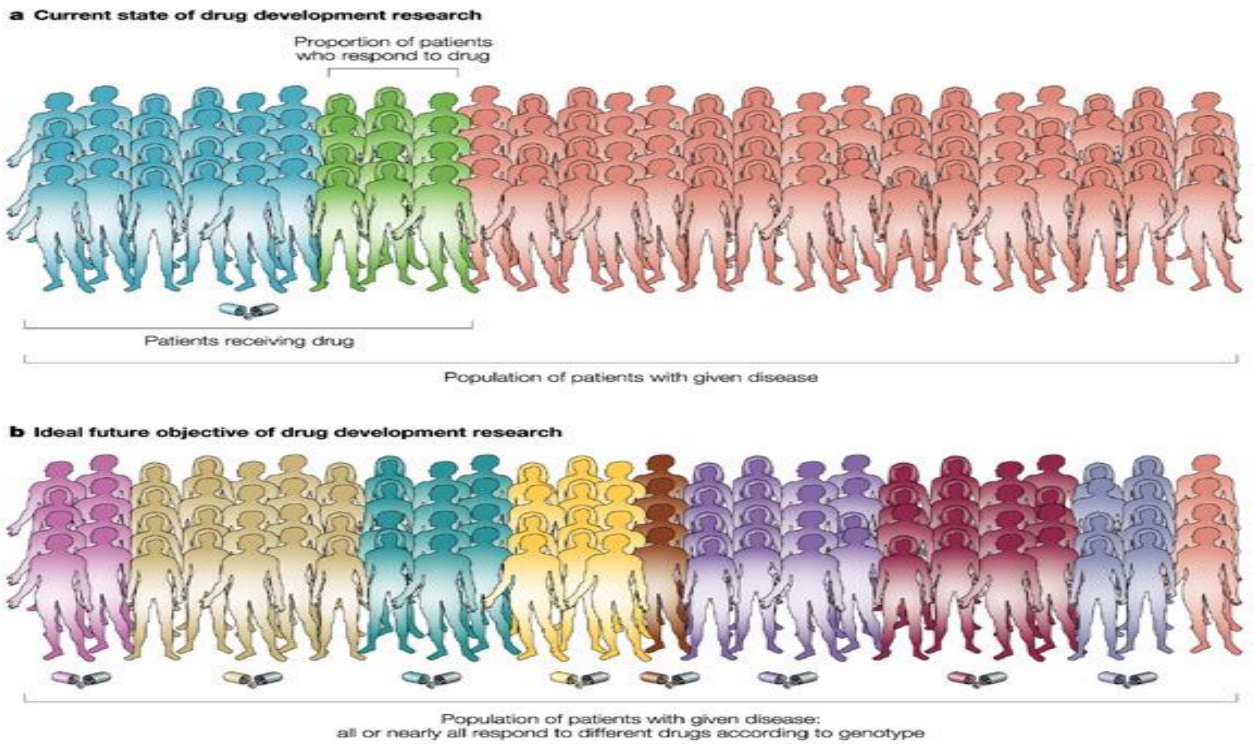
Pharmacogenetics / Drug response

Prospective studies for selection of patients in subgroups based on :

- Disease subtypes
- Pharmacokinetic subgroups (rapide and slow metabolizers)

But remembering the potential impact of additional variables on drug response

- Age
- Environnement
- Ethnicity
- Compliance
- Diet ….



Nature Reviews | Drug Discovery

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Applications in clinical development (3)

Pharmacogenetics / Safety

Medical genetics

A marker for Stevens–Johnson syndrome

Stevens–Johnson syndrome and the related disease toxic epidermal necrolysis are life-threatening reactions of the skin to particular types of medication[1–3]. Here we show that there is a strong association in Han Chinese between a genetic marker, the human leukocyte antigen *HLA–B*1502*, and Stevens–Johnson syndrome induced by carbamazepine, a drug commonly prescribed for the treatment of seizures. It should be possible to exploit this association in a highly reliable test to predict severe adverse reaction, as well as for investigation of the pathogenesis of Stevens–Johnson syndrome.

Chung *et al*
Nature. 2004

Frequency of HLA B*1502 allele in patients with SJS	
CBZ-SJS	44 (100%)
CBZ-tolerant	3 (3%)
Normal	8 (8.6%)

From Bruce Carleton with permission

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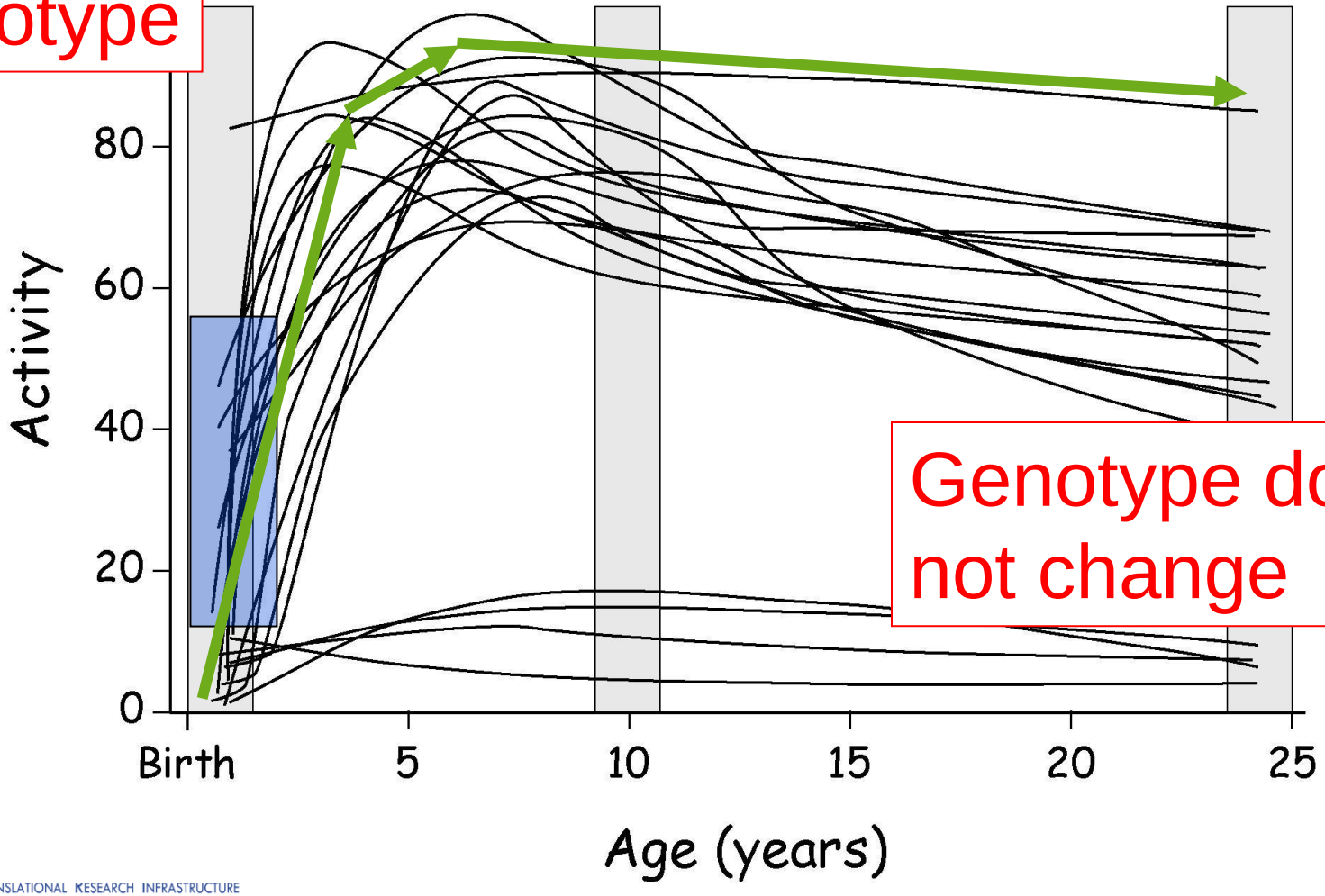
Pharmacogenetics in developmental pharmacology

Impact of growth and maturation on gene expression

Phenotype



Genotype does not change

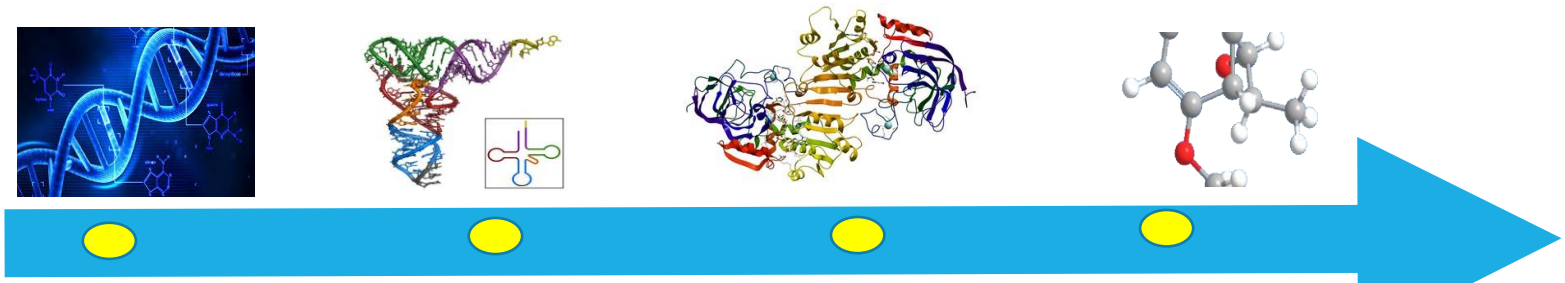
Several Potential Goals for Pharmacogenetics in drug development

To ensure the **sub-division of common diseases** into different molecular sub-types which may be more or less susceptible to specific treatments.

To evolve more **logical approaches to dosage**, **efficacy** and the **prevention of adverse reactions** by analyzing the genetic basis for differences in the pharmacokinetic or pharmacodynamic properties of drugs.

To identify **genetic susceptibility** to various common diseases that offer targets for pharmacological intervention.

Perspectives : ..omics sciences



Genomics | Transcriptomics | Proteomics | Metabolomics | Phenotype

Multidisciplinary understanding of biology / disease pathology

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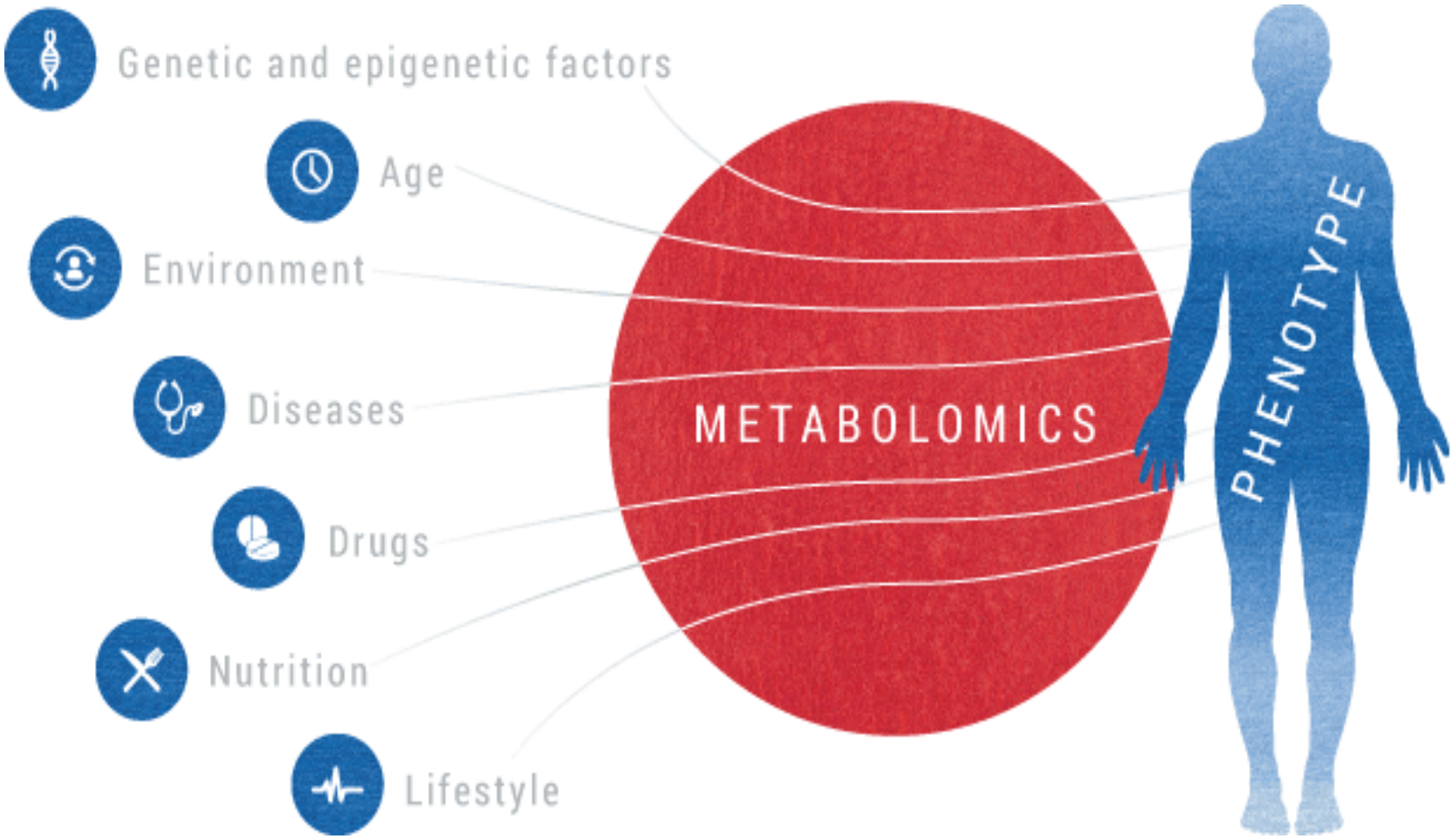
« Multiple environmental factors »



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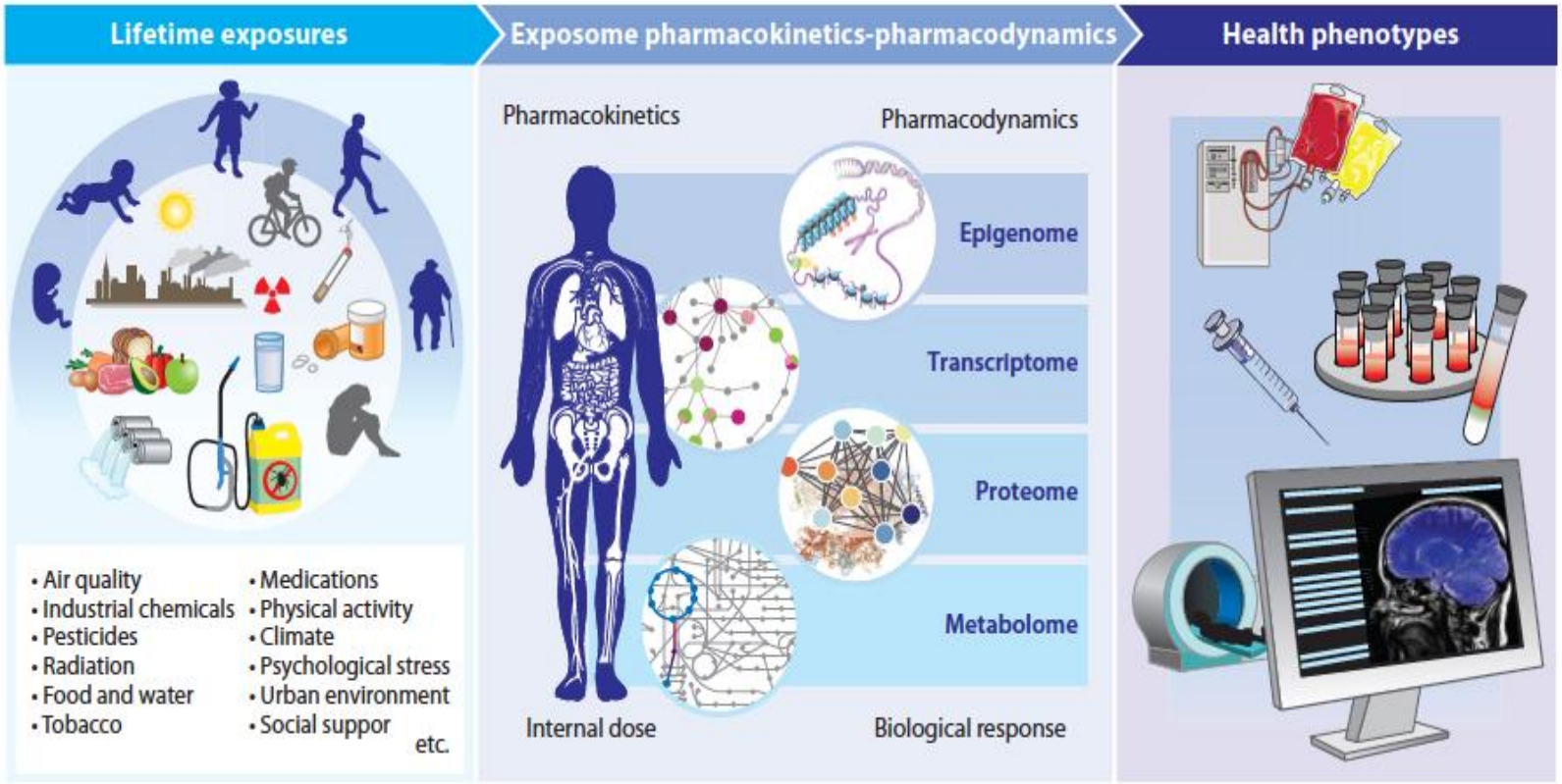
Perspectives：Bioinformatics and Integrative pharmacology / integrative medicine



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Thank you for your attention

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