PHARMACOGENOMICS & DRUG SAFETY

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Club Phase I (F)

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Philosophy

- Importance of inter-individual variation in drug response
  - Life threatening adverse drug reactions
  - Lack of desired therapeutic effect

- Inheritance is an important factor responsible for individual variation in drug response
  - Besides: age, sex, comediations, underlying disease ...

- Questions and applications of the knowledge of a patient’s DNA sequence
  - Maximize efficacy
  - Target patients that are likely to respond
  - Avoid Adverse Drug Reactions (ADR)

... goal of individualized drug therapy
Bridging the tolerability gap between healthy volunteers and patients?

Among the solutions what about pharmacogenetics and pharmacogenomics?
Definitions

- **Drug Safety**
  - Detection and prevention of adverse-drug-reactions
  - Pharmacovigilance: spontaneous reports; individual cases; other (PMS)
  - Toxicology in early phases of drug development (MTD)

- **Pharmacogenomics (PGx)**
  - Genetic basis for individual variations in response to therapeutics
  - Single nucleotide polymorphisms (SNPs) - single - base variations at a unique physical locations among different individuals - are the most frequent polymorphisms in the Human Genome

  **goals:**
  1) aid in target discovery
  2) prioritize and optimize lead compounds
  3) evaluate efficacy and safety
  4) stratify patients enrolled in clinical trials
  5) create predictive and diagnostic tests
The life of a drug

Clinical steps (Phase I – II – III Studies)
(IND)* → (NDA)** → Drug on the market

- Investment in research spending × 2.5 fold
- 80% IND fail it to market
- Cost of NCE = US $ 800 million; 50% for RCT
- Failure rate in phase III = 50%
  (SAFETY; EFFICACY; INDUSTRIALIZATION)

VALID BIOMARKERS

- Gefitinib (K) EGFR gene (success 10%)
- Atomoxetine (ADHD) – CYP2D6 (dosage)

DROP-OUTS

- Cox 2-inhibitors: vascular events
- SSRIs: suicide in children

ADRs IN HOSPITALS

- 2 million/year; 5% of admissions
- 100,000 deaths/year

IND* = Investigational New Drug applications; ADR = Adverse Drug Reaction
NDA** = New Drug Application
GTx: from exposure to disease & treatment outcome
## Types of ADR

Characteristics of type A and type B adverse drug reactions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose dependency</td>
<td>Usually shows a good relationship</td>
<td>No simple relationship</td>
</tr>
<tr>
<td>Predictable from known pharmacology</td>
<td>Yes</td>
<td>Not usually</td>
</tr>
<tr>
<td>Host factors</td>
<td>Genetic factors might be important</td>
<td>Dependent on (usually uncharacterized) host factors</td>
</tr>
<tr>
<td>Frequency</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Severity</td>
<td>Variable, but usually mild</td>
<td>Variable, proportionately more severe</td>
</tr>
<tr>
<td>Clinical burden</td>
<td>Hight morbidity and low mortality</td>
<td>Hight morbidity and mortality</td>
</tr>
<tr>
<td>Overall proportion of adverse drug reactions</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>First detection</td>
<td>Phases I-III</td>
<td>Usually Phase IV, occasionally Phase III</td>
</tr>
<tr>
<td>Animal models</td>
<td>Usually reproducible in animals</td>
<td>No known animal models</td>
</tr>
</tbody>
</table>
## ADR & HLA

### HLA & adverse drug reactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse reaction</th>
<th>HLA association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Severe hypersensitivity reactions</td>
<td>DR3, DQ2</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Agranulocytosis</td>
<td>B38, DR4, DQ3</td>
</tr>
<tr>
<td>Dipyrrone</td>
<td>Agranulocytosis</td>
<td>A24, B7, DQ1</td>
</tr>
<tr>
<td>Gold</td>
<td>Proteinuria, dermatological reactions, thrombocytopenia</td>
<td>DR3</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>SLE</td>
<td>DR4</td>
</tr>
<tr>
<td>Levamisole</td>
<td>Agranulocytosis</td>
<td>B27</td>
</tr>
<tr>
<td>Oxicam</td>
<td>Toxic epidermal necrolysis</td>
<td>A2, B12</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Penicillamine toxicity</td>
<td>DR3</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Toxic epidermal necrolysis</td>
<td>A29, B12, DR7</td>
</tr>
</tbody>
</table>

A The list of HLA associations is not exhaustive. Importantly, most of these findings are based on single studies, and therefore do need replication.

B Abbreviations: HLA, Human Leukocyte Antigen; SLE, Systemic Lupus Erythematosus
Pharmacogenetics (GPt): a historical step
Pharmacogenetics (PGt)

**BACKGROUNDs**
- Twin studies
- Drug levels or metabolism (PK) are inherited as Mendelian traits
- Use of « probe drugs »
- Phenotypic variations

**Icons of PGX**
- N-acetyl-transferase (*NAT2*)
  - Isoniazid
  - Caffeine
- Thiopurine S-methyltransferase (*TPMT*)
  - *TPMT<sup>L</sup> and *TPMT<sup>H</sup>*
  - Individuals homozygous for TPMT*3A : great risk for myelosuppression (↓ dose 1/10) with 6 mercaptopurine
- Cytochrome P4502D6
  - Debrisoquine
  - Poor, extensive, ultra rapid metabolisers
Pharmacogenetic defects in enzymes that lead to undesirable pharmacodynamic adverse effects

<table>
<thead>
<tr>
<th>Enzyme defect</th>
<th>Drug</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-6-phosphate dehydrogenase deficiency</td>
<td>Primaquine, sulfonamides, dapsone, nitrofurantoin</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Methaemoglobin reductase deficiency</td>
<td>Nitrites, dapsone</td>
<td>Methaemoglobinaemia, haemolysis</td>
</tr>
<tr>
<td>Porphobilinogen deaminase deficiency</td>
<td>Barbiturates, estrogens, alcohol, anticonvulsants and sulfonamides</td>
<td>Acute porphyric crises</td>
</tr>
<tr>
<td>Acetylcholinesterase</td>
<td>Anticholinesterase agents</td>
<td>Neurotoxicity</td>
</tr>
</tbody>
</table>
## Phase II drug metabolizing enzyme gene polymorphisms & putative adverse drug reactions

<table>
<thead>
<tr>
<th>Phase II enzyme</th>
<th>Drug</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma butyrylcholinesterase</td>
<td>Succinylcholine</td>
<td>Prolonged apnoea</td>
</tr>
<tr>
<td>(N)-acetyltransferase</td>
<td>Sulfonamides, Amonafide, Procainamide, hydralazine, isoniazid</td>
<td>Hypersensitivity, Myelotoxicity, SLE</td>
</tr>
<tr>
<td>Thiopurine methyltransferase</td>
<td>6-Mercaptopurine, azathioprine</td>
<td>Myelotoxicity, treatment-related second tumours</td>
</tr>
<tr>
<td>Dihydropyrimidine dehydrogenase</td>
<td>5-Fluorouracil</td>
<td>Myelotoxicity</td>
</tr>
<tr>
<td>UDP glucuronosyl transferase 1A1</td>
<td>Irinotecan</td>
<td>Diarrhoea, Myelosuppression</td>
</tr>
</tbody>
</table>

Abbreviation: SLE, Systemic Lupus Erthematosus
Pharmacogenomics: more informative than GPt

Genotype > Phenotype?
Pharmacogenomics (PGx): genomic science

- Definitions
  - Effects of inheritance on PK and PD pathways involving multiple gene products
  - Development of expression profiling and high-throughput DNA sequencing and genotyping

- Question
  - Translation of this information to the bedside

- Results
  - Application are limited to a few tests and to rare academic referral centers
    - The monogenic model does not apply to the majority of drugs
    - Necessity to simultaneously study genes encoding a variety of proteins involved in PK + PD (large number of polymorphisms, haplotypes, genome-wide scans)
    - Trials designed to test pharmacogenomic hypotheses
PGx: a new tool in medicine

Pharmacogenomics

Pharmacokinetic examples: drug metabolism
- CYP2D6 (germline DNA)
  - Lack of codeine response

Pharmacodynamic examples: drug targets
- NAT2 (germline DNA)
  - Autoimmune response to hydralazine & procainamide
- AOX5 (germline DNA)
  - Lack of 5-lipoxygenase inhibitor response
- EGFR (tumour DNA)
  - Tumour regression response
Pharmacogenomics/personalised medicine

Single Nucleotid Polymorphism (SNPs)

- SNPs:
  - Single base differences in the DNA sequence observed between individuals
  - Simplest form of DNA polymorphism

- SNPs impact:
  - Vast majority of SNPs are biologically silent
  - If present in the promoter: affect gene expression
  - If within the gene itself: impact on protein function

- Consequence
  - Correlate information from patients' DNA with their response to a medicine (beneficial/adverse)
  - Linkage disequilibrium
  - Degree of association between the genotype and the phenotype
  - Pharmacogenomic stratification of patients in RCT

« know yourself »
PGt versus PGx in monitoring?

Genetic polymorphisms

Pharmacokinetic
- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamic
- Receptors
- Ion channels
- Enzymes
- Immune system

TRENDS in Pharmacological Sciences, 2001, 22 : 298-305
Examples

- Codein intoxication
- Torsades de Pointes (TdP)
- HIV & antiretroviral drugs
- 5-FU
- Clinical trials
PGt & PGx: an explanation of a severe adverse effect

- **An example**: codeine intoxication associated with ultra rapid CYP2D6 metabolism (Gasche Y et al, *NEJM* 2004; 351: 2827)
  
  - Oral codeine (25 mg tid) in a 62 yo man in a context of pneumonia and comedication
  - 4 days later deterioration of consciousness; unresponsiveness; miotic pupils
  - Recovery 2 days later

- **Biological management**
  
  - Blood levels of codeine, morphine, metabolites
  - Duplication or multiduplication of the CYP2D6 gene
  - CYP2D6 and CYP3A4 phenotype
  - CYP phenotypic activity (probe drug: dextromethorphan 25 mg)
Results: opioid intoxication

- **CYP2D6 ultrarapid-metabolism genotype and phenotype**
- **Drug-induced inhibition of CYP3A4 activity**

... diagnosis based on PGt, PGx and drug monitoring
Drug - induced torsades de pointes (TdP) tools of predictivity ?

1. Significant iatrogenic cause of morbidity and mortality (10-17%)
2. Major reason for the withdrawal of a number of drugs from the market
3. Wide variety of drugs are incriminated : pimozide, terfenadine, thioridazine, cisapride, astemizole...
4. QT interval as a surrogate of TdP
5. Congenital LQTS (1/5000 in USA)
   - Brugada syndrome – nocturnal sudden death
     sodium channel anomaly (SCN5A)
   - « formes frustes » (↓repolarisation reserve)
6. Ion - channels and voltage - gated potassium channels are the arrhythmia - related pharmacological targets
### Long-QT syndrome: genes, locations, currents

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal location</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ1</td>
<td>11p 15.5</td>
<td>Iks</td>
</tr>
<tr>
<td>KCNE1</td>
<td>21q22.1</td>
<td>Iks</td>
</tr>
<tr>
<td>KCNE2</td>
<td>21q22.1</td>
<td>Ikr</td>
</tr>
<tr>
<td>KCNH2</td>
<td>7q35-36</td>
<td>Ikr</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>11p15</td>
<td>Iks</td>
</tr>
<tr>
<td>SCN5A</td>
<td>3p21-24</td>
<td>Ina</td>
</tr>
<tr>
<td>KCNJ2</td>
<td>17q23</td>
<td>Ikir2,1</td>
</tr>
<tr>
<td>ANK2</td>
<td>(sodium pump, Na/Ca exchanger, IP3)</td>
<td></td>
</tr>
</tbody>
</table>

Problem of modifier gene(s): same HERG (KCNH2) and variable clinical expression.
Role of diseases: cardiomyopathy, diabetes, cirrhosis, automic failure...
Major role of CYP polymorphisms: 2B6 (methadone), 2C19 (nelfinavir, citalopram), 2D6 (antipsychotics, antidepressants), 3A4 (antirhythmics, tacrolimus, halofantrine...)
**PGt and PGx in TdP**

- **PGt and PGx** are recommended in individual cases and clinical research
- Intensive study of specially targeted subjects/patients enrolled in phase I, II, III studies (ie: QT outliers)
- Post-hoc analysis (DNA banks)
- Question of ethnicity
  - Japan: LQTS 1/1164 school children; Brugada syndrome, SCN5A mutation 12%

**TECHNIQUES**
- PCR based high-throughput assay detecting SNPs in CYP, NAT2, TMPT, UGT1A1, MDE1
- Potassium channels: genes and protein encoding

**Ref:**
HIV : antiretroviral drugs

- **Drugs**:
  - nucleoside reverse transcriptase inhibitors (Abacavir, Zidovudine)
  - non nucleoside reverse transcriptase inhibitors (Efavirenz)
  - protease inhibitors (Ritonavir, Nelfinavir)

- **Toxicity**:
  - mitochondrial toxicity : myopathy
  - hypersensitivity : skin rashes, hepatitis ...
  - lipodystrophy : fat atrophy, TGR ...
  - miscellaneous : CNS symptoms, hemorrhage, interactions ...

*Beyond serum drug monitoring ...*
Mitochondria:
- Mitochondrial DNA levels ↓ if hyperlactatemia
- CAG repeat mutations in the second exon DNA polymerase-α gene (POL G): peripheral neuropathy, lactic acidosis

Lipodystrophy:
- TNF-α: -238 allele = susceptibility factor

Hypersensitivity:
- Abacavir: HLA-B region HLA-B* 5701
  TNF-α (308 G → A polymorphism)
Fluorouracile (5-FU) : technical problem

- 5-FU : use in adenocarcinoma pro-drug

- Dihydropyrimidine deshydrogenase (DPD) : 5-FU catabolites

- Toxicity of 5-FU : Cardiac, CNS, hematology due to a total or partial deficit in DPD

- Problem : measurement of DPD activity
  - Lymphocyte DPD not correlated with liver DPD
  - Observed in 50 % of ADR

Conclusion : DPD genotype is a necessity
Benefits of PGx in clinical trials

1. Reduction of drug development time
   - Efficacy/Safety in specific populations

2. Optimization of clinical utility
   - Linkage between subtypes and E/S

3. Reduction of time to market
   - Specificity to the predicted population

4. Explanation of response & identification of groups at risk

5. Increased reimbursement
   - By differentiated responder (R) and non-R populations
Clinical trials & PMS

Development

- Phase II trials
- Phase III studies
- Approval of medicine for marketing

Initial post-launch surveillance

- Patients taking the new drug
- Patients with ADRs
- Patients without ADRs
- DNA comparison (e.g., comprehensive genome scan)

Genetic markers

Severino et al, Pharmacol Res 2004; 49: 363-373
Summarizing the data on ADR & Pharmacogenomics
Summarizing ADR & PGx

- Listing and tables!

- What can we do with those data?
  - Contemplation?
  - Dissemination?
  - Practical use?
    - Drug-surveillance strategies
    - Systematic blood spot + storage
    - Analysis of individual cases
    - Problems of specificity

« One drug fits all » — « Personalized therapy »
### Predominantly monogenic pharmacogenetic disorders


<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose - 6 - phosphate deshydrogenase deficiency</td>
<td>G6PD</td>
</tr>
<tr>
<td>Isoniazid slow N-acetylation</td>
<td>NAT2</td>
</tr>
<tr>
<td>Sensitivity to alcohol</td>
<td>ALDM2</td>
</tr>
<tr>
<td>P - glycoprotein transporter defect</td>
<td>ABCBI</td>
</tr>
<tr>
<td>Dihydropyrimidine deshydrogenase deficiency</td>
<td>DPYD</td>
</tr>
<tr>
<td>Dopamine transporter defect</td>
<td>SLC6A3</td>
</tr>
<tr>
<td>Calcium channel defect</td>
<td>CACN1A</td>
</tr>
<tr>
<td>Serotonin transporter defect</td>
<td>SLC6A4</td>
</tr>
<tr>
<td>Caffeine 3 - demethylase defect</td>
<td>CYP1A2</td>
</tr>
<tr>
<td>Cyclophosphamide metabolism deficiency</td>
<td>CYPZB6</td>
</tr>
<tr>
<td>Medication</td>
<td>Clinical Consequence</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Debrisoquine</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td>Sparteine</td>
<td>Oxytocic effects</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Ventricular tachyarrhythmias</td>
</tr>
<tr>
<td>Perhexiline</td>
<td>Neuropathy and hepatotoxicity</td>
</tr>
<tr>
<td>Phenformin</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Propafenone</td>
<td>CNS toxicity</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Hypotension</td>
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<tr>
<td>Terikalant</td>
<td>↑ QT interval</td>
</tr>
<tr>
<td>L-tryptophan</td>
<td>Eosinophilia – myalgia syndrome</td>
</tr>
<tr>
<td>Indoramin</td>
<td>Sedation</td>
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<tr>
<td>Drug/drug class</td>
<td>Adverse effect</td>
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<td>-------------------</td>
<td>----------------------------------------------------</td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>drugs</td>
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<td>Heparin</td>
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<td>ACE inhibitors</td>
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<td>Procainamide,</td>
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<tr>
<td>hydralazine</td>
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<td>Antiarrhythmics</td>
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<td>Heparin-induced thrombocytopenia</td>
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<td>Drug-induced cough</td>
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<td>Drug-induced lupus</td>
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<td>QT prolongation &amp; Torsades de Pointes</td>
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<tr>
<td>Psychoactive</td>
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<tr>
<td>drugs</td>
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<tr>
<td>Warfarin</td>
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<td>Antipsychotics</td>
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<td>Ethanol</td>
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<td>Levodopa</td>
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<td>Bleeding risk</td>
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<td>Tardive dyskinesia, acute akathisia</td>
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<td>Alcohol dependence</td>
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<td></td>
<td>Drug-induced dyskinesias, drug-induced hallucinations</td>
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<tr>
<td>Other</td>
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<tr>
<td>Thiopurines</td>
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<tr>
<td>Thiopurines</td>
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<tr>
<td>Abacavir</td>
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<td>Erythromycin,</td>
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<td>terfenadine, etc</td>
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<tr>
<td>Anesthetics</td>
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<td>Oral contraceptives</td>
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<td></td>
<td>Myelosuppression</td>
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<td>Secondary tumors</td>
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<td></td>
<td>Hypersensitivity</td>
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<td></td>
<td>QT prolongation &amp; Torsades de Pointes</td>
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<td></td>
<td>Malignant hyperthermia</td>
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<td>Drug-induced venous thrombosis</td>
</tr>
</tbody>
</table>

Examples of adverse drug effects associated with genetic variability

Abbreviations: ACE, angiotensin converting enzyme; MHC, major histocompatibility complex
The limits of technology
Technologies for SNP analysis

1. **Mass spectrometry**
   - Allele specific products identification

2. **High-throughput micro array technologies**
   - DNA alterations such as SNPs, insertions and deletions can be identified

3. **Microsphere technology**
   - Direct hybridizations, oligonucleotide ligation and primer extension assay formats

4. **Invader assay**
   - Genotyping (SNPs) without PCR amplification FRET-based genotyping method

5. **Bioinformatics tools**
   - « discovery manager »

http://pubs.acs.org/subscribe/journalmdd/v04
CYP2D6 in routine?

- Procedures not available
- Typing is expansive
- Many of the drugs have a wide therapeutic index, ADR mild and amenable to dose reduction
- Routine typing not shown to be cost effective

... prospective RCT: clinically and cost effective
**CYP2C9 & warfarin in routine?**

- Anticoagulants (AC) response depends on R-warfarin (CYP1A2; CYP3A4)

- Sensitivity to AC: vitamin K & thyroïde disease

- Mutations in clotting factors (prothrombin) might alter AC

- Genotype required within 24 hours of admission to hospital

*... prospective RCT: include confounding factors*
PGx drug metabolism & pain medicine: recommendations *

1. Check whether the drug is metabolized by a polymorphic drug metabolizing enzyme
2. Consequence of this polymorphism (PM)?
3. Prevalence of the PM alleles in the patient population (ethnicity)?
4. Consider an alternate drug not subject to PM-enzyme
5. Advise the patient to carefully monitor ADR
6. Avoid drug inhibitors of the PM enzymes in question
7. PGx: cause of the ADR
8. If no response to treatment: Therapeutic Drug Monitoring

Other practical attitude

- **TPMT**: prospective genotyping

- **Transporters**: Pgp/\(ABCB1\) (multi-drugs resistance gene): digoxin, protease inhibitors, cyclosporin toxicity?

- **Receptors**: D3/tardive dyskinesia; malignant hyperthermia after anaesthetics. Ryanodine receptor??

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**Metabolism of Thiopurine in Red Blood Cell**

\(n > 300\)

\[ y = 0.0517x + 4.1059 \]

\(R^2 = 0.0002\)

Tribut O, Allain H, Bentué-Ferrer D, 2005

- RBC \((10^{12}/L)\)
**Example of hepatotoxicity**

- Most drugs induce hepatotoxicity. Rare events
- PGx can identify population at risk so contraindications (drug labeling)
- PGx and PGt are not required by FDA... mainly because nobody reaches « causation conclusions »
- Drug maker duty ?
- Testimony about PGt and PGx should be excluded in a trial about an alleged liver injury; studies must « fit the case » (poorly suited for courtroom opinions)
- Ethics : creation of extensive genetic database; role of ethnicity...
General attitude

- Pharmacogenomic detection of rare ADR: not practical
- Prospective storage of samples and evaluation in phase IV when a problem has been identified
- RCT to examine both the clinical and cost-effectiveness of prospective genotyping
Conclusion

Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing

Voltaire (1694-1778)

- Pharmacogenomics can improve the situation if translated at the bedside and widespread

- Trends towards transcriptomics (gene transcripts), metabonomics (metabolite profiling), proteomics (proteins encoded by genome) ...
Thanks to the team …

- Anne Beauplet
- Danièle Bentué-Ferrer
- Elisabeth Polard
- Olivier Tribut

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