

3RD ANNUAL COURSE OF PHARMACOGENETICS
AND PERSONALIZED MEDICINE

Emerging pathways in Personalized Medicine:
breaking barriers and moving forward



Pharmacogenomics and Personalized Medicine

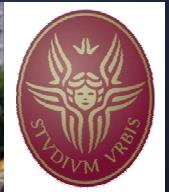
The Sant'Andrea Hospital Personalized Medicine Strategy

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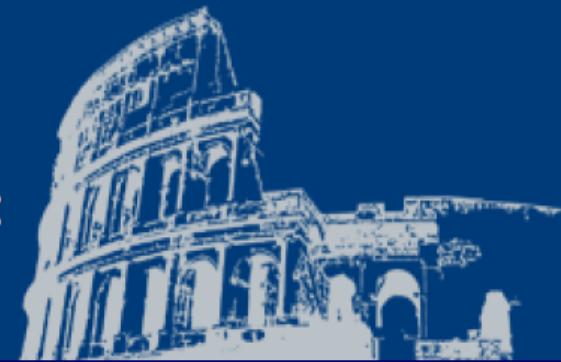
AZIENDA OSPEDALIERA
SANT'ANDREA
FACOLTÀ DI MEDICINA E
PSICOLOGIA



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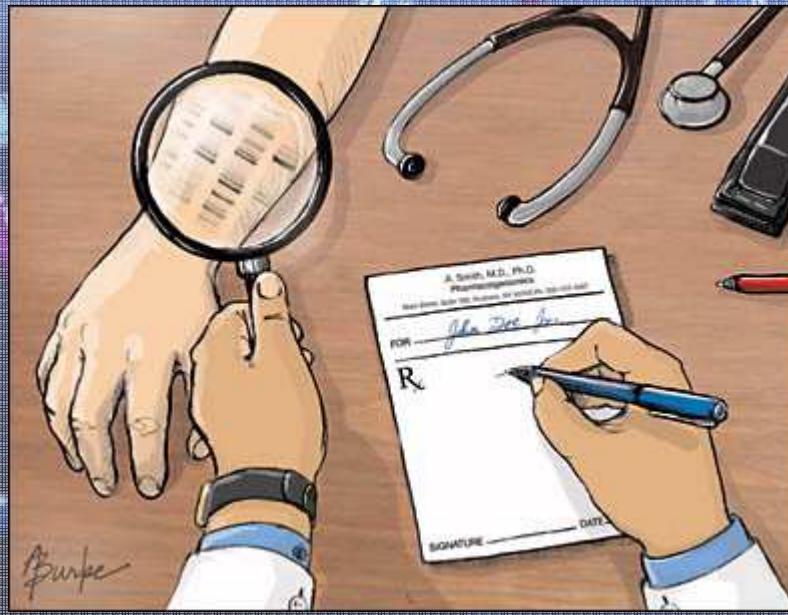
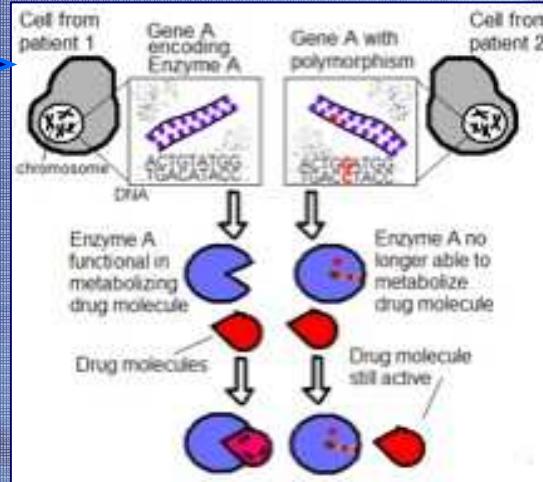
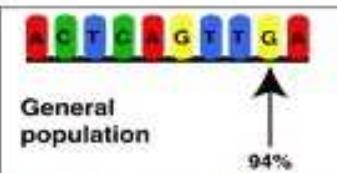
Emerging pathways in Personalized Medicine: breaking barriers and moving forward

- *Education*
- *R&D*
- *Information Health Technology*
- *Ethics, Economics, Policies*



Personalized Medicine: the workflow

Polymorphism
"Poly" many "morphe" form



Basic and Molecular Sciences

Clinical Trials Informatics

“From the bench to the bedside”: an in-hospital built experience

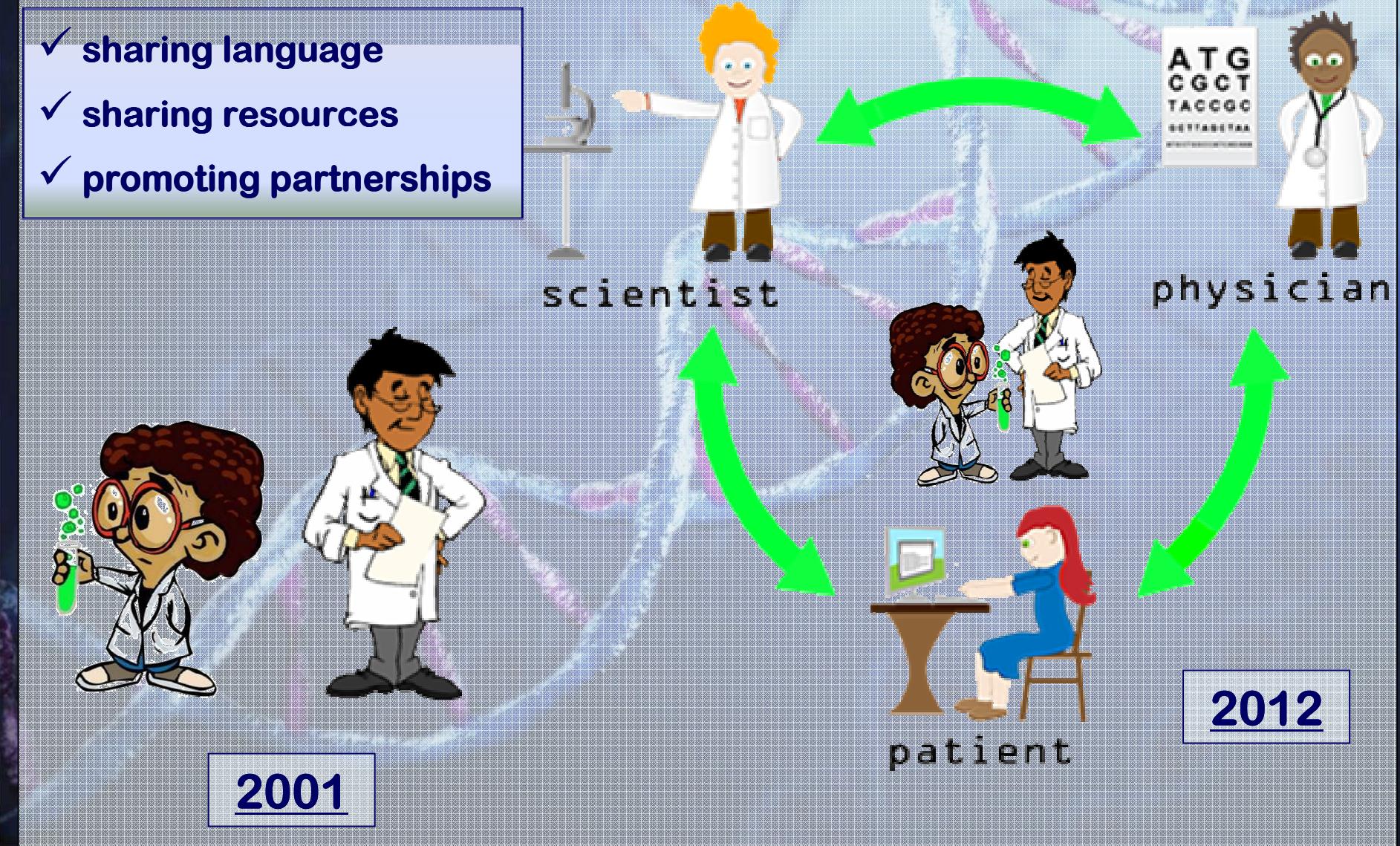


Department of Biochemical Science
“A. Rossi Fanelli”



Basic science – clinical science integration: how to reach the goal?

- ✓ sharing language
- ✓ sharing resources
- ✓ promoting partnerships



ADVANCED MOLECULAR DIAGNOSTICS LAB:

HI-TECH PLATFORM and Diagnostic tests

MOLECULAR BIOLOGY



Thrombophilic profile:

- APOE C112R R158C
- Factor II G20210A
- PAI 1 4G/5G
- Factor V G1691A
- MTHFR C677T
- MTHFR A1298C
- Beta-Fibrinogen G-455A
- Cistathionine beta synthase CBS I278T

Oncohematology:

- BCR-ABL e1a2 quantitative analysis
- BCR-ABL b3a2 quantitative analysis
- JAK-2 quantitative analysis
- Leukemia diagnosis: panel of - 26 translocations

Gene fusions:

- PML/RARAlfa t(15;17)
AML1/ETO t(8;21)

Hemochromatosis:

- Hemochromatosis H63D
- Hemochromatosis C282Y
- Hemochromatosis S65C

Metotrexate:

- ABCC2 C24T
- TSER 28bp VNTR

Oxidative-stress resistance :

- MPO G-463A
- GSTM1, gene deletion
- GSTT1, gene deletion
- GSTP1 A313G
- SOD2, Ex2+24T>C
- CAT C-262T
- PON1 A575G
- PON1 108C/T
- OGG1 C315>T
- eNOS3 Asp298Glu

Methylation profile in hypomethylating therapies:

BDNF
E-cad
DAPK
p15
RAR beta2
SOCS1

Coumadin Response:

CYP2C9*2 C430T
CYP2C9*3 A1075C
VKORC1 G-1639A

Triptans response:

GNB3 C825T
CYP1A2 C-163A
CYP1A2 G-3860A

CYP 3A4 A-392G

MAO-A (promotore)

Thiopurines response:

TPMT G460A

TPMT A719G

Ribavirin Response:

IL28Beta rs12979860

hCNT3 C602R

Opioid metabolism and pain therapy:

-OPRM1 A118G

-CYP3A4*1B

-CYP3A5*3

-ABCB1 C3435T

-ABCB1 C1236T

Insulin-resistance:

•ENPP1 K121Q

•IRS1 G972R

•TRIB3 Q84R

•NOS3 rs1799983

Citocromo P450 genotypization:

CYP2C19

- *2 19154G/A
- *3 17948G/A
- *4 1AG
- *5 90033C/T
- *6 12748G/A
- *7 19294T/A
- *8 12711T/C
- *9 12884G/A
- *10 19153C/T

CYP2D6

- *2 2850C/T
- *3 2549 delA
- *4 1846G/A
- *5 Deletion
- *6 1707delT
- *7 2935A/C
- *8 1785G/T
- *9 2613_2615 del AGA
- *10 100C/T
- *12 124G/A

CYP2C9

- *12 1785G/A
- *17 1023C/T
- *29 1659G/A
- *41 2988G/A

*XN (gene duplications)

CYP2C9

- *2 C430T

- *3 A1075C

CYP1A2

- *1C C-163A

- *1F G-3860A

CYP 3A4

- *1B A-392G

CYP3A5

- *3 A6986G

5- Fluoruracil response:

DPYD IVS14

DPYD A166G

DPYD A949T

TSER VNTR

MTHFR C677T

MTHFR A1298C

Platinum derivatives response:

GSTP1 A313G

XRCC1 G28152A

ERCC1 C8092A

ERCC1 T19007C

Irinotecan and taxane response:

UGT 1A1*28

ABCB1 C3435T

ABCB1 C1236T

CYP3A4*1B

CYP3A5*3

Anthracycline-Induced Cardiotoxicity:

CYBA C242T

NCF4 A-212G

RAC2 T7508A

MRP1 G671V

MRP2 V1188E

MRP2 C1515T

CBR3 V244M

GSTP1 A313G

Radiotherapy response:

XRCC3 A4541G

XRCC3 C18067T

RAD51 G135C

GSTP1 A313G

Immunoreaction analysis

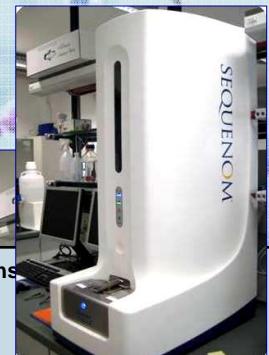
Neurotropic viruses (Liquor)

HSV-1; HSV2; CMV; VZV; EBV; JCV; T.Gondii;
HHV-6

Enterovirus (Liquor)

NGAL dosage (Plasma and Urine)

Anti-cerebellar antibodies (serum)



MassArray

ADVANCED MOLECULAR DIAGNOSTICS LAB:

HPLC–UV/fluorimetry/tandem mass spectrometry analysis:

- 5-Fluorouracil degradation rate (by PBMC *ex vivo*)
- Intestinal permeability test
- 2-3-N-Metilipuric acid (Urine)
- Homogentisic acid (Urine and Serum)
- Amino acid profile (Urine and Plasma)
- Cholestanol (Serum)
- Catecholamines (Urine and Serum) and metabolites (5-HIAA, VMA, HVA)
- Oxalates (Urine)
- Metanephrides (Urine)
- Vitamins : E – B1 – B6 – C – Lycopene
- Homocystinuria
- Serotonin (Urine and Plasma)

- Drug monitoring:
 - Antidepressants
 - Antipsicotics
 - Antiepilectics
 - Antiarrhythmics
 - Antivirals
 - Diuretics



Antidepressants

Fluoxetine
Paroxetine
Clomipramine
Amitriptyline
Imipramine.....

Antipsicotics

Aripiprazole
Clozapine
Risperidone.....

Antiepilectics

Levetiracetam
Lamotrigine
Oxcarbazepine
Gabapentin
Topiramate
Felbamate
Zonisamide
Etosuccimide
Primidone

Antiarrhythmics

Flecainide
Verapamil.....

Antivirals

Ribavirin

Diuretics

Acetazolamide.....

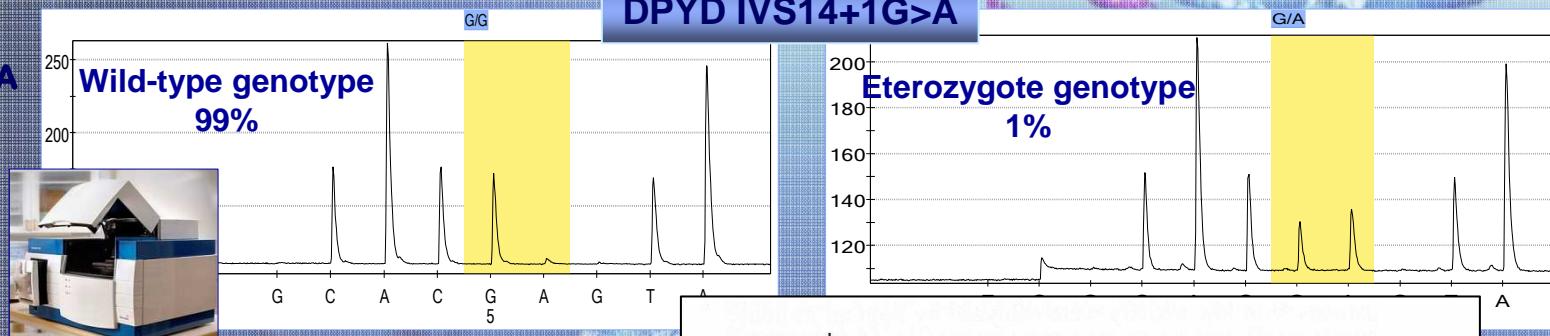
Purine metabolites

Xantine
Ipxoxantine.....

Pharmacogenomics and Drug monitoring synergism: Evaluation of 5-fluorouracil response

Pharmacogenomics

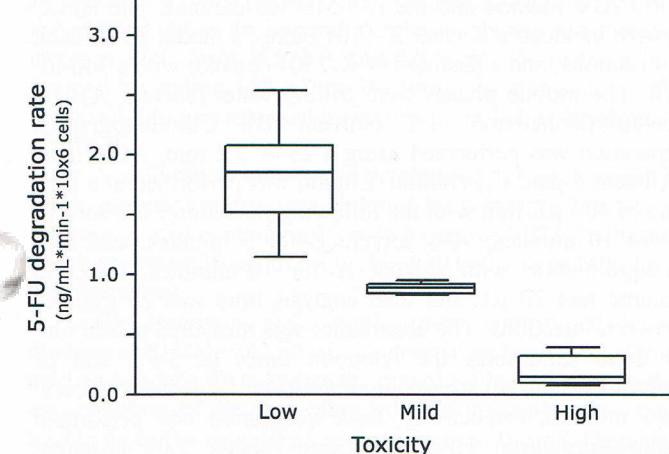
DPYD IVS14+1G>A
DPYD A166G
DPYD A949T
TSER 28bpVNTR
MTHFR C677T
MTHFR A1298C



5-FU degradation rate in intact PBMC

$$(5\text{-FU } t_0 - 5\text{-FUT}_{2h}) \text{ ng} \times \text{min}^{-1} \times 10^6 \text{ cell}^{-1}$$

Lostia AM et al. Ther Drug Monit. 2009 Aug;31(4):482-8.



ULTRA-metabolizers: poor prognosis (*manuscript in preparation*)

Metabolic classes:

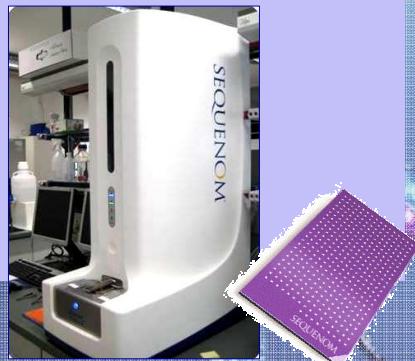
- $DR > 1,36$
- $1,36 < DR > 1,16$
- $1,16 < DR > 0,68$
- $DR < 0,68$

Pharmacogenomics and Drug monitoring synergism: Managing Compliance in psychiatric patients

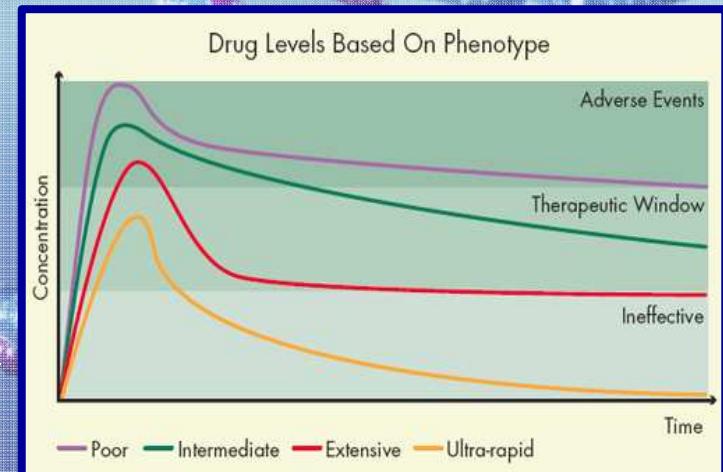
Pharmacogenomics of antipsychotics antidepressants and antiepileptic drugs

Cyp P450 genotypization:

Cyp2D6
Cyp2C19
Cyp3A4
Cyp1A2
Cyp3A5



LC-MS/MS



Antiepileptics	Antipsychotics	Aripiprazole	Antivirals
Gabapentin	Imipramine	Antiarrhythmics	Ribavirin
Lamotrigine	Paroxetine	Verapamil	Zidovudine
Levetiracetam	Clomipramine	Flecainide	Lamivudine
Ethosuximide	Amitriptiline	Metabolites	Idoxuridine
Primidone	Clozapine	Xantine	Dideoxyinosine
Oxcarbazepine	Risperidone	Ipxoxantine	Diuretics
Topiramate	Fluoxetine	Aripiprazole	Acetazolamide

“The right drug for the right patient”

DRUGBANK
Open Data Drug & Drug Target Database

Home Browse Search Downloads News & Updates About Help Contact Us

Search: Search DrugBank Help / Advanced

Identification Taxonomy Pharmacology Pharmacoeconomics Properties References Interactions 0 Comments

targets (25) enzymes

Identification

Name	> Home
Accession Number	Drug
Type	> Drug search
Groups	> Drug-drug interaction
	> Chemotherapy
	> ATC tree

CYP

> CYP-drug interaction	1A1	1A2	2B6	2C19	2D6	3A4	3A5	3A7	nocyp	
> Polymorphism	Aripiprazole				S Ind Inh	S	S	S		
> Alignments	alternative drugs for Aripiprazole	1A1	1A2	2B6	2C19	2D6	3A4	3A5	3A7	nocyp
> 3D structures	Reserpine							Ind		
> Browse	Risperidone					S Inh	S Inh	S	S	
> Phase 2 enzymes	Clotiapine							S		
> Transporter	Zotepine	S	S	S	S	S	S	S		
> Upload	Prothipendyl								X	

Description

Substrate-Substrate Interaction If more than one drug is metabolized by the same CYP, it is possible that its metabolism is inhibited because of the competition between the drugs. That means, it can be useful to lower the dosage of the drugs in the drug-cocktail because they remain longer in the organism than in monotherapy.

Inhibitor-Substrate Interaction Combining drugs that have inhibitory effect and are substrates of one particular CYP, should be compensated by lowering the dosage. They rest longer in the organism than in monotherapy. Not adapting the dosage bears the risk of even more side effects.

Inducer-Substrate Interaction Combining drugs that are inducers and substrates of one CYP should be compensated by increasing the dosage because metabolism is stimulated and faster than in monotherapy. Therefore, the drugs are even earlier eliminated.

Inducer-Inducer Interaction Combining two or more inducers of one CYP, should be compensated by increasing the dosage to reach the normal therapeutic effect because their metabolism is stimulated. Therefore, the drugs are even earlier eliminated.

Inhibitor-Inhibitor Interaction Combining two or more inhibitors of one CYP, should be compensated by lowering the dosage of these drugs because the metabolism is reduced and the drugs remain longer in the organism than in monotherapy. Not adapting the dosage bears the risk of even more side effects.

Structure

SuperCYP

Results

In this table you can see all cyps that are involved in the metabolism of your drug-cocktail. If two or more drugs are metabolized by the same CYP, the column is coloured yellow (2 drugs), orange (3 drugs) or red (4 and more drugs). The table gives alternatives for all chosen drugs and their metabolism based on their ATC-groups.

Legend

s = substrate, inh = inhibitor, ind = inducer
By clicking on the drug you get information about it.
By clicking on the cyp you get information about it.
By clicking on a relation (s, inh or ind) you get the source.

Name	1A1	1A2	2B6	2C19	2D6	3A4	3A5	3A7	nocyp
Aripiprazole					S Ind Inh	S	S	S	
alternative drugs for Aripiprazole	1A1	1A2	2B6	2C19	2D6	3A4	3A5	3A7	nocyp
Reserpine								Ind	
Risperidone						S Inh	S Inh	S	S
Clotiapine								S	
Zotepine	S	S	S	S	S	S	S	S	
Prothipendyl									X

CHARITÉ Charité Berlin Structural Bioinformatics Group

Interactome

Oncology

- Radiotherapy and Chemotherapy response and toxicity (5FU, platinum-derivatives, taxanes, irinotecan, Anthracyclines, aromatase inhibitors)
- 5-FU degradation rate in intact PBMC
- Aromatase inhibitors dosage

Psychiatry

- Metabolic profile of Cyp450 (CYP2D6, e CYP2C19)

Neurology

- Insulin-resistance profile
- Neurotropic viruses
- Anti cerebellum antibodies

Sport Medicine

- Oxidative stress resistance profile

Hematology

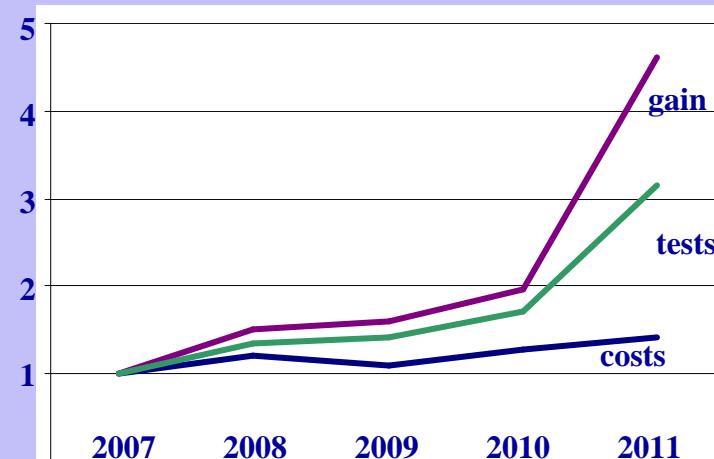
- Metabolic profile for Coumadin
- Thrombophytic profile (Hemochromatosis, APOE, Factor II, Factor V, F5, MTHFR, Beta-thalassemia, Cystathione beta-ase)

Cohematology

- Mutation BCRABL, JAK2
- Molecular screening for acute and chronic leukemia
- Cytarabine response and toxicity (TPMT)
- Quantitative methylation profile in methylation therapy (e-cad, K-ras, p15, SOCS1, RARbeta)

Gastroenterology

- Metabolic profile of P450 (CYP2C19)
- Thioguanine toxicity profile (TPMT)
- 5-OH-Indoleacetic Acid in plasma



Cardiology

- Anthracycline-Induced Cardiotoxicity
- Metabolic profile of Antihypertensive drugs

- Antiarrhythmics and diuretics serum dosage

Headache Center -

- Metabolic profile of triptans
- Plasmatic dosage of topiramate

Occupational Medicine

- 2-3-N-Methylpurinic acid dosage

Gynecology

- Thrombophytic profile

HPLC and/or mass spectrometry analysis

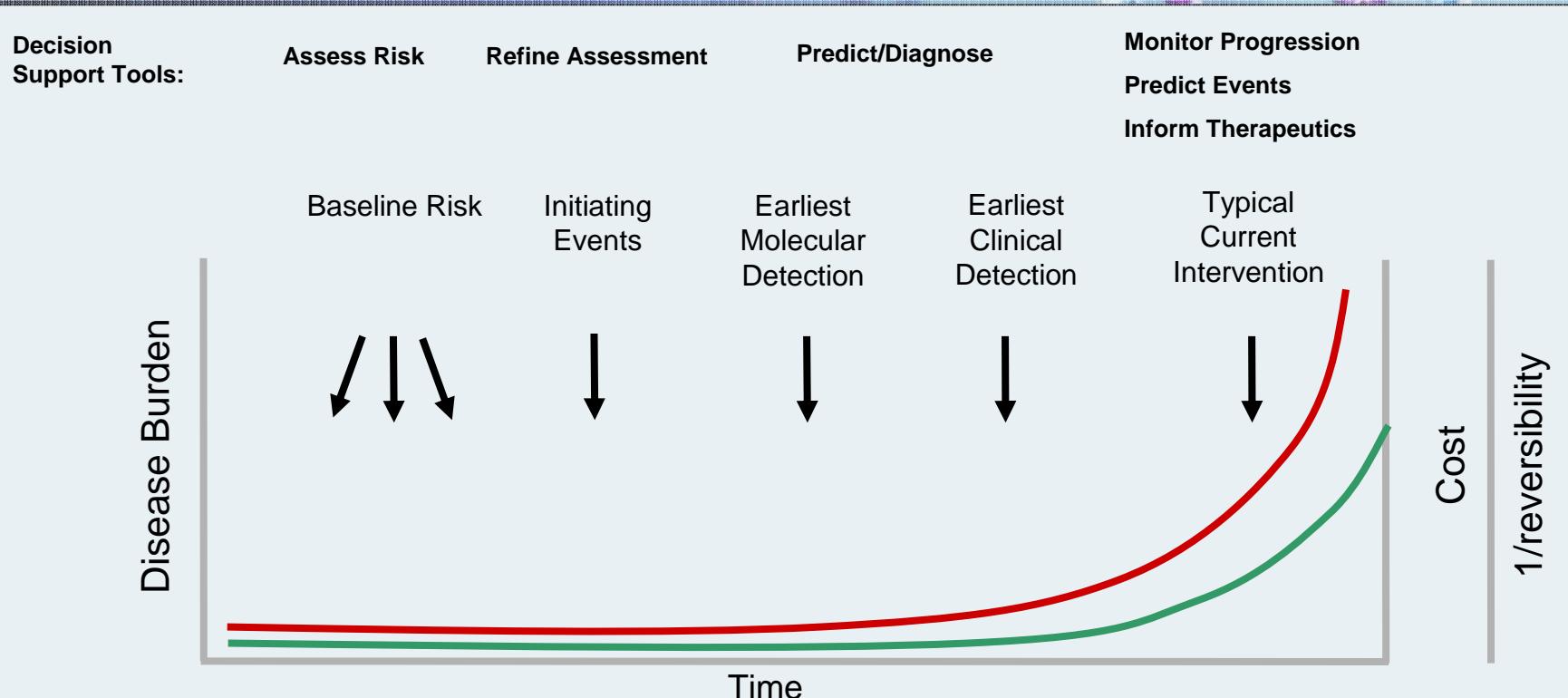
Molecular biology analysis

Pediatry

- Respiratory viruses (RSV-RNA, ADENOVIRUS-DNA, METAPNEUMOVIRUS-RNA)

- Intestinal permeability test
- Aminoacids dosage in Urine and plasma

Sustainability: does personalized medicine provide good value for money?



CREDITS

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