Utilization of pharmacogenomics biomarkers in personalized pharmacotherapy and in clinical trials

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Inje Univ. College of Medicine and Busan Paik Hospital, located in Busan, the 2nd biggest city in S. Korea

Inje Univ., 1979

- City of Medical and Health Service in Southeast region of
- Busan Paik Hospital CTC - the mission of leading the clini
  Dongnam region as the only regional CTC funded by KM
- Closest to Japan, easy access to partner trial site in Jap

Dynamic BUSAN
Asian Gateway

Inje University Affiliated Paik Hospitals

8,000
No. of staffs including MDs, RNs etc

4,000,000
No. of patients visiting to OPD of Paik Hospitals every year

3,500 (4,000)
No. of beds that 5 Paik Hospitals have

Established at 1932

Seoul Paik

Sanggye

Seoul

Ilsan Paik

College of Medicine

Busan Paik

Busan

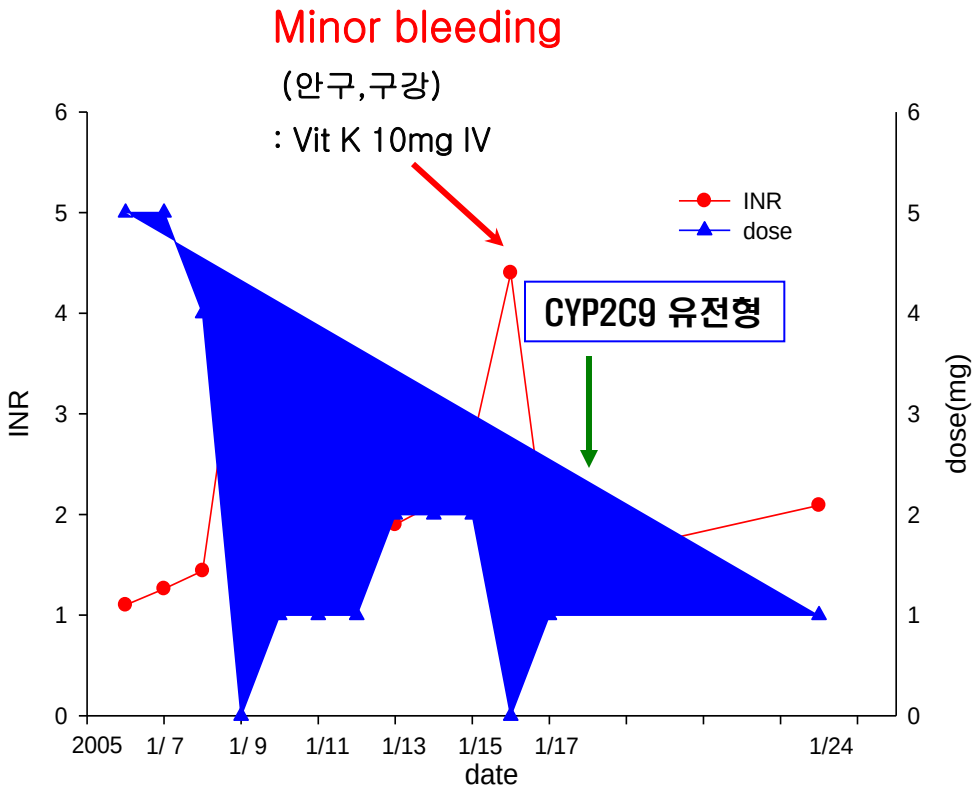
Hae-un-dae

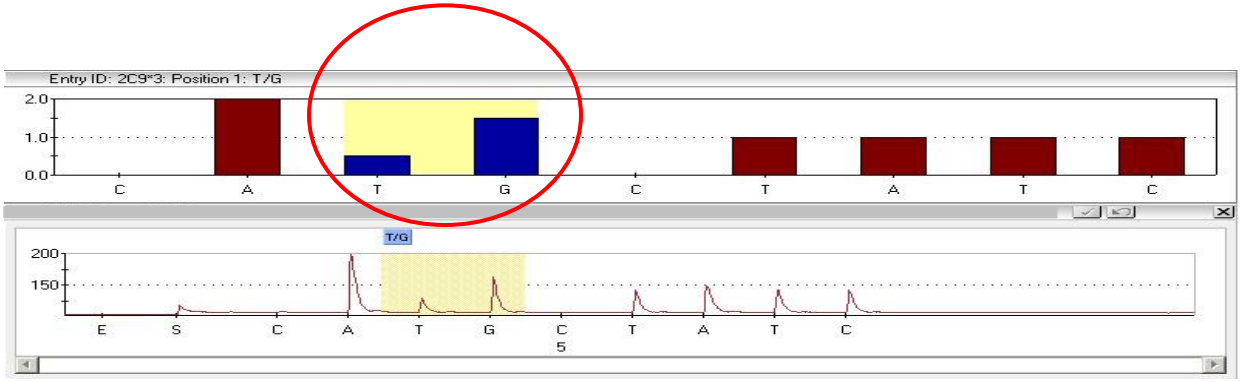
Contents…

- Introduction of PGx – a biomarker for personalized therapy
- PGx in drug development and clinical trials: example of experiences
- Validation of PGx biomarkers and *in vitro* diagnostics
- Ethnic issues of PGx and its application into personalized therapy and drug regulation
- PGx biomarker into clinical practice of personalized pharmacotherapy

Case 1: CYP2C9*3 genotype on Warfarin anticoagulant therapy

날짜	INR/PT	용량
2005.1.6	1.1/13	5
7	1.26/14.9	5
8	1.44/17.5	4
9	4.13/36.6	hold
10	3.45/34.8	1
11	2.96/30.9	1
12	2.30/25.3	1
13	1.90/21.8	2
14	2.10/23.6	2
15	2.70/28.7	2
16	4.4/38.4	minor bleeding – Vit K 10mg IV
17	1.49/18.0	1
24	2.09/23.5	1





유전형 검사:

☞ CYP2C9*1/*3

Case 2. Newborn death caused by codein administered to mother who has CYP2D6 ultraextensive metabolizer

NATIONAL REVIEW of MEDICINE
ESSENTIAL NEWS FOR CANADA'S PHYSICIANS
JUNE 15, 2007 | VOLUME 4 NO. 11

PATIENTS & PRACTICE

Codeine linked to breastfeeding danger

Warnings and class action suit follow Toronto neonate's poisoning death

BY OWEN DYER

A class action suit over the death of an apparently healthy Toronto newborn, who died last year from opiate toxicity from breast milk, has renewed the debate over prescribing Tylenol 3 to breastfeeding mothers. After the baby's death, doctors at Toronto's Hospital for Sick Children issued a warning that codeine given for postnatal pain can produce deadly concentrations of morphine in breast milk.

Asian and African babies are at greater risk of rapidly metabolizing codeine

Tariq Jamieson was delivered vaginally at full term and healthy weight — everything appeared normal. His mother Rani suffered some lingering pain from an episiotomy so she was prescribed two tablets of Tylenol 3 twice daily — a common pain treatment for mothers who have just given birth. Doctors halved that dose after two days due to constipation and somnolence.

Tariq developed increasing lethargy from the seven-day mark, and at 11 days was brought to a pediatrician due to concerns about his skin colour and poor feeding. He had, however, regained his birth weight. But two days later the family called an ambulance. Responders found the infant cyanotic and lacking vital signs. Attempts at resuscitation failed.

On post mortem, the child was found to have a blood concentration of acetaminophen at 5.9 µg/mL and morphine at 70 ng/mL. That morphine concentration is about six times higher than would normally be considered safe in a neonate.

Tylenol 3 contains 500mg of acetaminophen and 30mg of codeine. Codeine is metabolized to morphine in the body, but not all patients metabolize it at the

Tariq Jamieson; full term normal delivered newborn

His mother, took Tyrenol 3 for pain killing
(2 tablets, twice daily, 2 days>half)
Became difficulty to breast feed/lethargic
On 12 day, his skin became grey
On 13 day, he died at home

Mother's breast milk >>High morphine conc
Autopsy, blood conc of morphine 70 ng/ml
(6X higher than safe conc.)

She was a CYP2D6 ultra metabolizer

Codein —(CYP2D6)→ **Morphine**

If genetic profile was known before prescribing drugs, ……

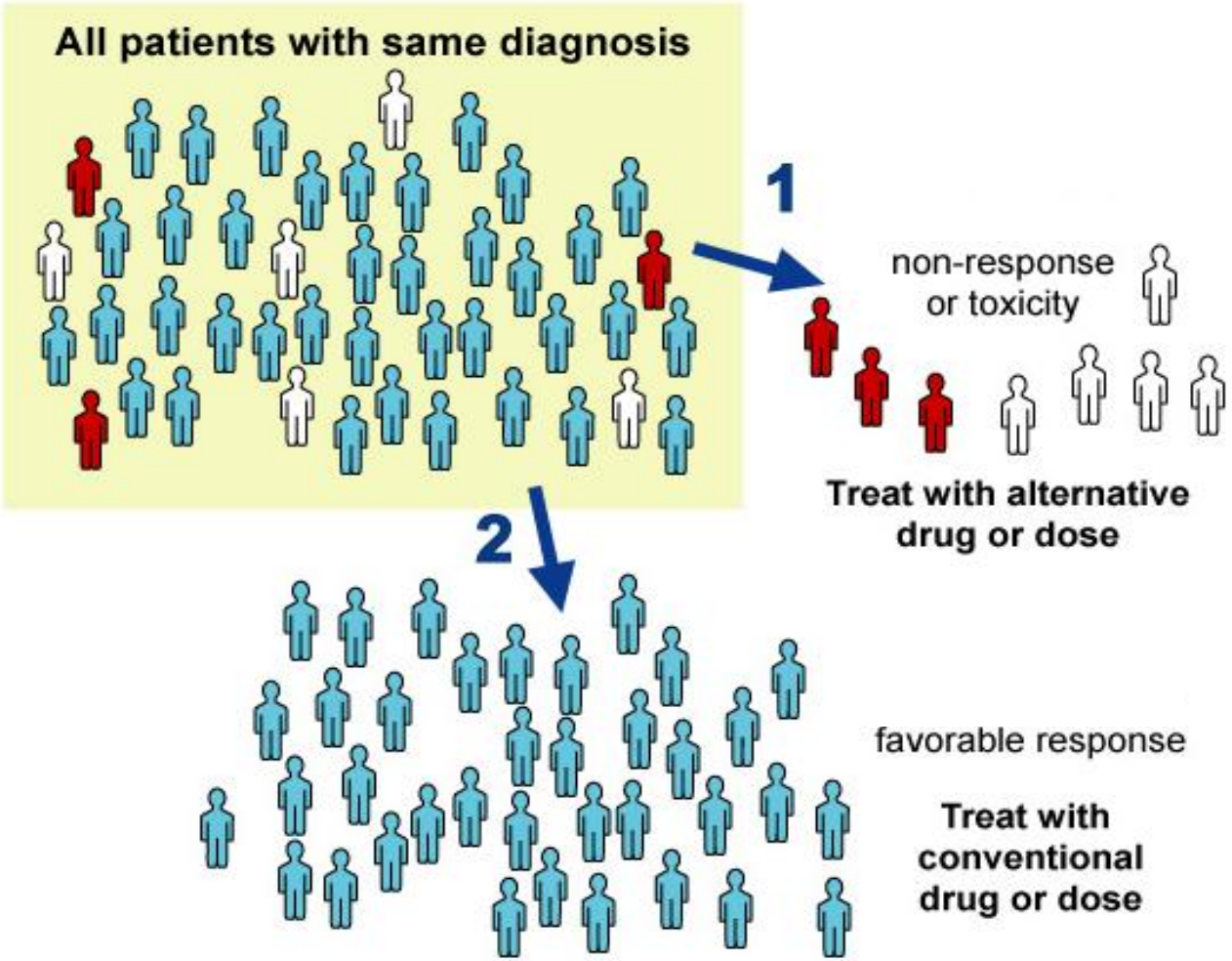
Koren et al. The Lancet. 2006 August

Many of patients are not respond to the conventional average therapeutic approach

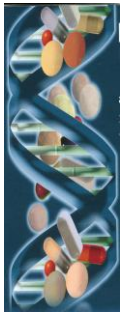
Therapeutic field	Responders
Alzheimer's	30%
Analgesics (Cox-2)	80%
Asthma	60%
Cardiac arrythmias	60%
Depression (SSRI)	62%
Diabetes	57%
HIV	47%
Hypertension	40%
Incontinence	40%
Migraine (acute)	52%
Migraine (prophylaxis)	50%
Oncology	25%
Osteoporosis	48%
Rheumatoid arthritis	50%
Schizophrenia	60%

PDR data analysis. Trends in Molecular Medicine 2001; 7:201-204.

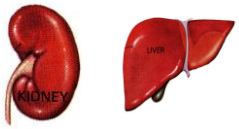
Dream of Personalized Pharmacotherapy



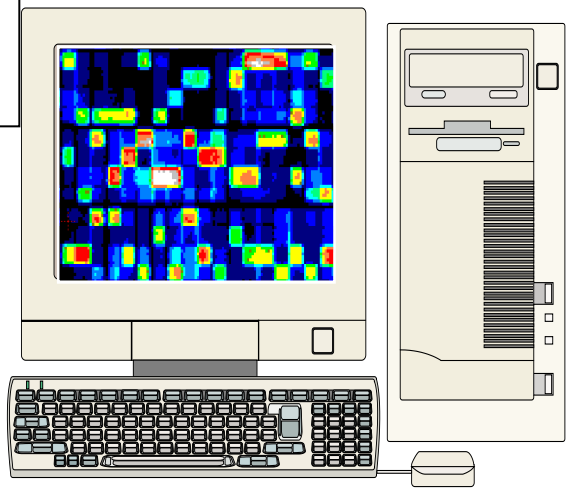
Need development of DB for Predictive Biomarkers (including PGt/PGx Biomarkers) : for Personalized Therapy



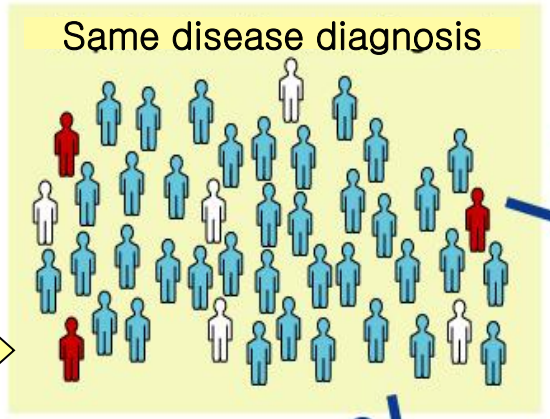
Genetic : SNP, CNV, Expression Profile etc.



Nongenetic Proteomic, Metabolomic, Immune etc. weight, age, sex, renal and hepatic function,drug interactions etc.



Biomarker



Level of Evidence to reach to the goal line of personalized pharmacotherapy
– from discovery to development of valid PGt Biomarker

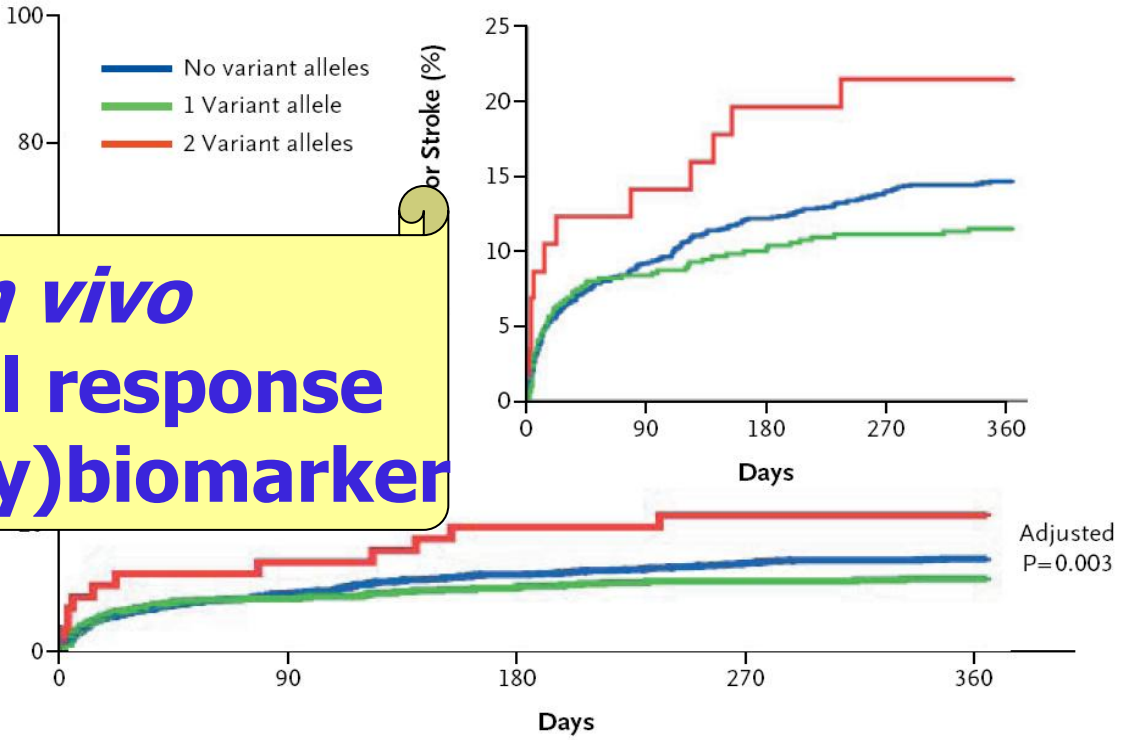
- **Identification of PGt marker**
  - Candidate gene approach
  - Genome wide association approach
- **Preclinical validation: *In vitro* /animal**
  - *In vitro* functional evaluation: molecular, cellular
  - Animal model approach
  - Development of genotype method and analytical validation
- **Clinical Validation**
  - Human clinical trial for PK/PD: healthy subjects or patients
  - Genotype-phenotype association study in patients
  - Large scale outcome study: genotype guided

- **Development of algorithm and clinical utility validation**
  - Algorithm for the PGx biomarker guided personalized therapy
  - Cost-benefit analysis type trial
  - Randomized Controlled trial for the personalized pharmacotherapy algorithm

CYP2C19 genotype as a predictive biomarker for clopidogrel therapeutic outcome

(N= 2208 patients)

In vivo
Clinical response (efficacy)biomarker



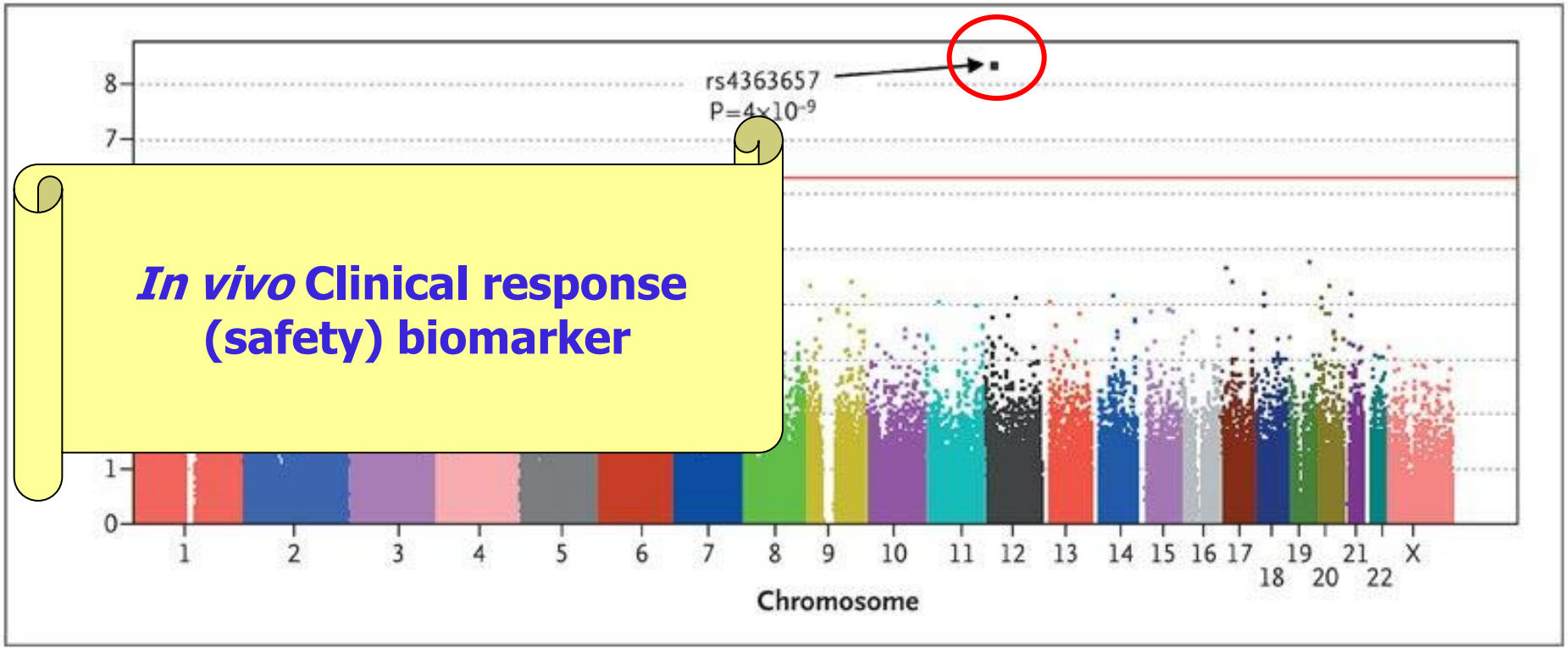
No. at Risk					
No variant alleles	1572	1334	1288	1211	1208
1 Variant allele	576	502	491	468	446
2 Variant alleles	58	47	44	42	40

Estimated rate of death from any cause, nonfatal myocardial infarction, or stroke, according to characteristics of CYP2C19 variant-allele polymorphisms

Simon T et al. , NEJM 2009

Genome-wide association study for the rare ADR of Statins induced myopathy

N= 12,000 patients including 90 cases for discovery, and 20,000 patients for replication study



***In vivo* Clinical response (safety) biomarker**

***SLCO1B1* SNP rs4363657, p = 4 x 10^{-9} (MAF 13%)**

Odd Ratio for myopathy 4.3 (95%CI 2.5-7.2) for one C allele, 17.4 (95%CI 4.8-62.9) for CC allele

The SEARCH Collaborative Group, NEJM Aug., 2008; 359

Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA. A significant increase of labels containing such information has been observed over the last decade. In order to provide a reference for genomic biomarkers in labels of FDA-approved drug products, we created the table shown below. Genomic biomarkers can play an important role in identifying responders and non-responders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. In the context of drug labels, these genomic biomarkers can be classified on the basis of their specific use, for example:

- Clinical response and differentiation,
- Risk identification,
- Dose selection guidance,
- Susceptibility, resistance and differential disease diagnosis,
- Polymorphic drug targets.

The table portrays a view on valid genomic biomarkers in the context of FDA-approved drug labels. It provides a comprehensive list of these markers and links to pharmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provide pharmacogenomic information with no immediate

does not address drug-drug interactions. More information on drug-drug interactions, please see Drug Development and Drug Interactions.

Biomarker	Label Context		Examples of other Drugs Associated with this Biomarker	References (PubMed ID)
	Representative Label	**Drug**		
C-KIT expression	**Gastrointestinal stromal tumor *c-Kit* expression** "*In vitro*, imatinib inhibits proliferation and induces apoptosis in gastro-intestinal stromal tumor (GIST) cells, which express an activating c-kit mutation." "Gleevec is also indicated for the [illegible] efficacy of maraviroc is being evaluated."	Imatinib mesylate		12851888 16226710 16294026
CYP2C19 Variants	**Diminished effectiveness in poor metabolizers.** Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 CYP system, principally CYP2C19. [illegible] reduced metabolic clearance."	Clopidogrel		19636246 19576320 19537521 19463375 19429918 19414633 19106083
CYP2C9 Variants with alternate context	**CYP2C9 Variant genotypes and drug dose** "The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles. Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele. For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients	Warfarin		18034618; 17989110; 17955230

Table 1 List of clinically valid pharmacogenetic biomarkers and level of recommendation for related drugs in the context of FDA-approved drug labels

Pharmacogenetic marker [106]	Representative drug	Disease	Test name[a]
CCR5 expression +++	Maraviroc	HIV infection	Trofile
c-KIT expression +	Imatinib	Gastrointestinal stromal tumor	DakoCytomation c-Kit pharmDx
CYP2C9 variants; *VKORC1* variants ++	Warfarin	Thromboembolism	Verigene Warfarin Metabolism Nucleic Acid Test
CYP2C19 variants +	Voriconazole	Fungal infection	Roche Amplichip CYP450 test
CYP2D6 variants +	Atomoxetine, fluoxetine	Attention-deficit hyperactivity disease, depression, OCD	Roche Amplichip CYP450 test
DPD deficiency +	Capecitabine, 5-FU	Colorectal cancer	TheraGuide 5-FU
EGFR expression +	Erlotinib	Non-small-cell lung cancer	DakoCytomation EGFr pharmDx
EGFR expression *and* *K-RAS* mutation +++	Cetuximab, panitumumab	Colorectal cancer	DakoCytomation EGFr pharmDx and Nucleotide sequencing-high-resolution melting (HRM) analysis
G6PDH deficiency +	Primaquine	Malaria	Glucose-6-phosphate dehydrogenase screening
G6PDH deficiency ++	Rasburicase	Hyperuricemia	Glucose-6-phosphate dehydrogenase screening
HER2/NEU overexpression +++	Trastuzumab	Breast cancer	Herceptest
HLA-B*1502[b] ++	Carbamazepine, phenytoin	Epilepsy	HLA typing
HLA-B*5701 ++	Abacavir	HIV infection	HLA typing
NAT variants +	Isoniazid, rifampin	Tuberculosis	Genelex
Ph1 chromosome +	Busulfan	Chronic myelogenous leukemia	BCR/ABL test
Ph1 chromosome +++	Dasatinib, imatinib	Acute lymphoblastic leukemia	BCR/ABL test
PML/RAR gene expression +	Tretinoin	Acute promyelocystic leukemia	PML/RARα quantitative real-time PCR
TPMT variants ++	Azathioprine, 6-MP, thioguanine	Acute lymphocytic leukemia	Prometheus TPMT Genetics
UGT1A1 variants +	Nilotinib	Chronic myelogenous leukemia	Invader UGT1A1 Molecular Assay
UGT1A1 variants ++	Irinotecan	Colorectal cancer	Invader UGT1A1 Molecular Assay

+++, required; ++, recommended; +, information

Gervacini et al. 2010. EJCP

PGx in many genes, drugs…

Imatinib mesylate – c-Kit expression
Voriconazole – CYP2C19
Atomoxetine, Tamoxifen – CYP2D6

Currently,

How close are we to use PGt / PGx

for the personalized pharmacotherapy ?

Many of PGx for cancer chemotherapeutic agents

Trastzumab - Her2/neu
Cetuximap, Panitumumab - EGFR / K-Ras
Maraviroc – CCR5

Pharmacogenetics (PGt)

"Classical Pharmacogenomics"

The study of how genetic differences influence on the variability in patient's response on PKs (absorption, distribution, metabolism, excretion) and PDs (actions of medicines; receptor, target enzyme, etc.) to drugs.

- genotype from DNA, phenotype from patient's characteristics

Variability and Personalized pharmacotherapy

Pharmacogenomics (PGx)

The study of human genome and its structure as relates to genes involved in PK and PD of medicine

– mechanism of genetics, expression, regulation, functional genomics, disease ….

Variability and Personalized therapy

Enhancing drug discovery

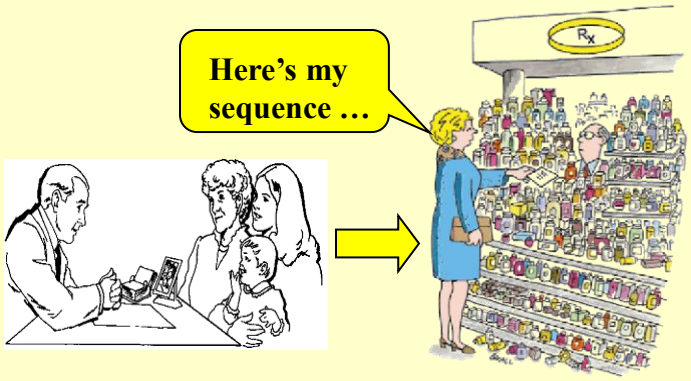
PGt vs. PGx ?

PHARMACOGENETICS

PHARMACOGENOMICS

Medicines for You

Why Pharmacogenomics?



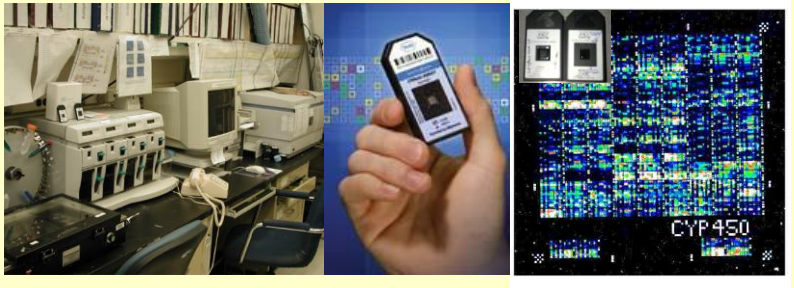
Personalized Pharmacotherapy

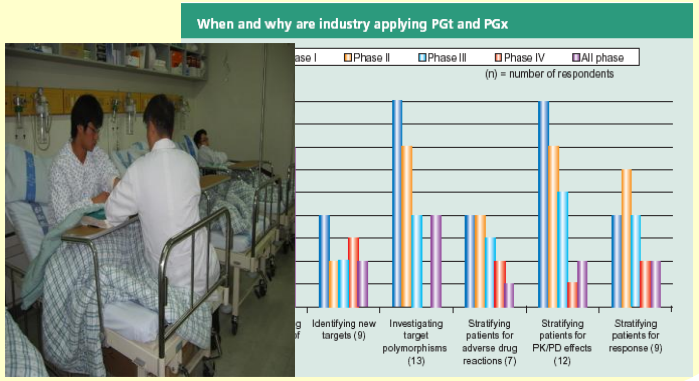
Drug Development

pharmaco-genomics

PGt/PGx Diagnostics

Clinical Trial





PGx potential in the pharmaceutical industry

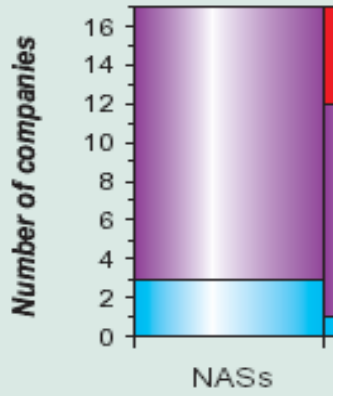
- Resurrect failed drugs
  - compound that mothballed in development due to potential toxicities, "drug repositioning", Iressa
- Reduce development costs and risks
  - Reduce size and length of cost, time by almost 7 years
- Increase profitability
  - Capture of a large portion of a small market, rather than a small percentage of a large market, competitive price from strong chance of benefit to patient, lower clinical trial and marketing cost
- Challenge the accepted paradigm for "blockbuster" drug sales
  - achieving blockbuster status due to PGx (e.g., Herceptin, $ 4.4 B, 2008)

The Potential Benefit of Pharmacogenomics in Drug Discovery and Clinical Trials

- Emergence of new gene targets for drug discovery
- Increase efficiency and reduce costs of target and lead discovery
- Reduce timelines and costs of clinical trials
- Reduce the unexpected ADR of study subject in clinical trial
- Product differentiation in the market place

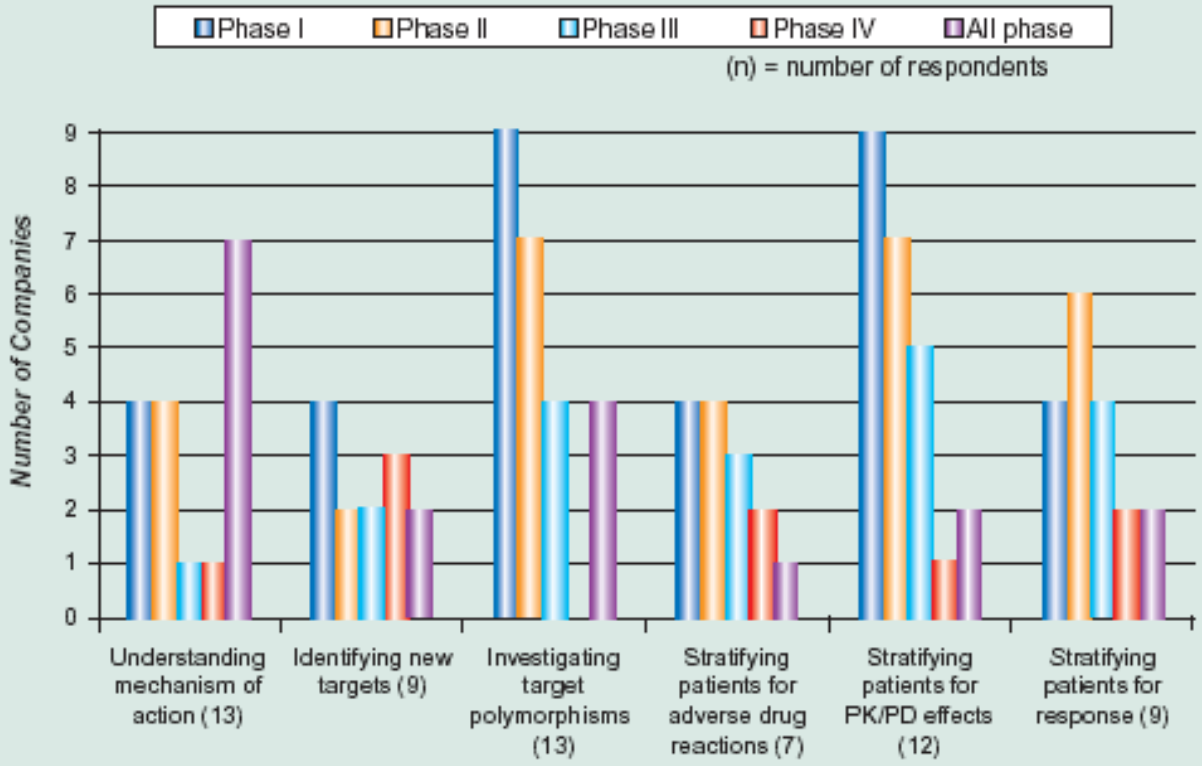
The PGt/PGx Biomarker in the Drug Development – Pharmaeutical Industry

Industry application of PGt and PGx technologies to drug development



Almost all Ph

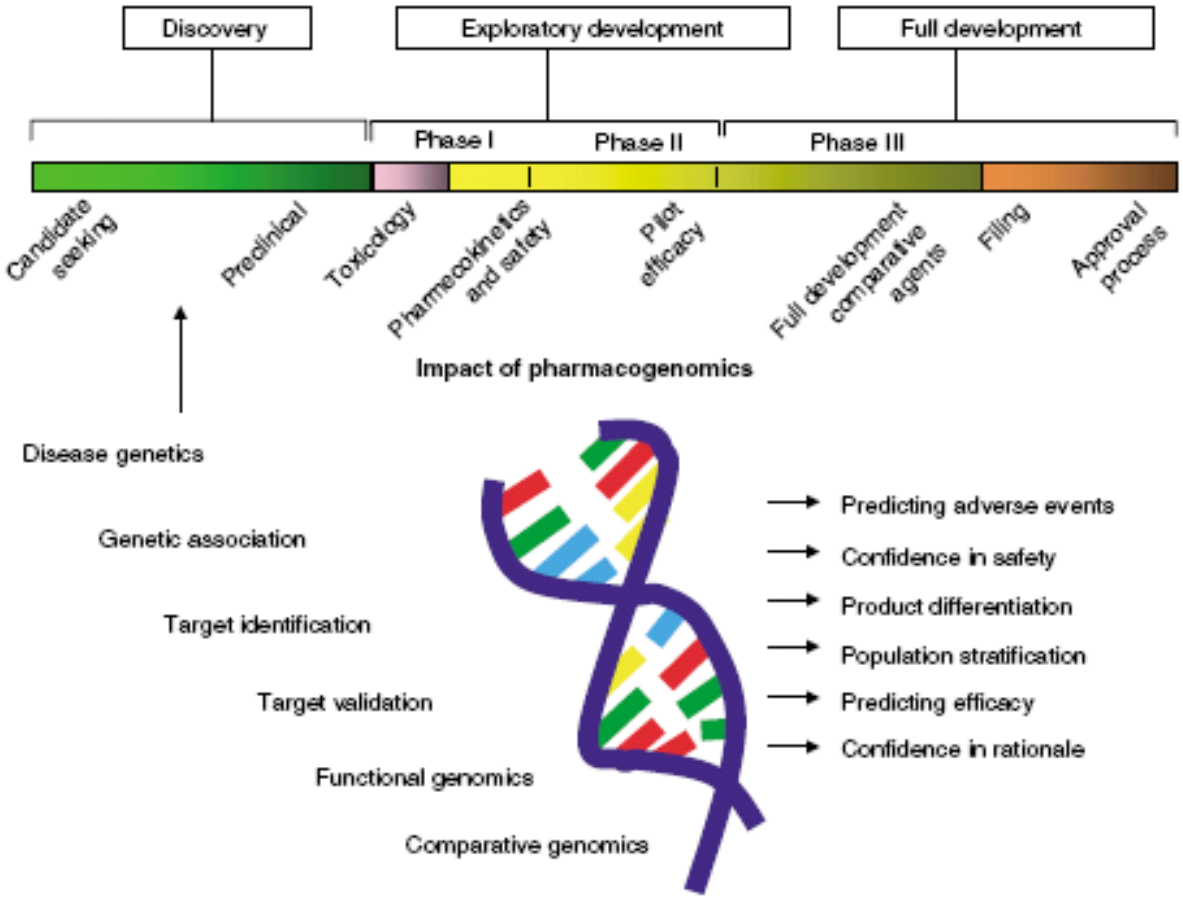
When and why are industry applying PGt and PGx



Application: from mechanism of action to stratifying the subjects of PK/PD, efficacy, ADR.

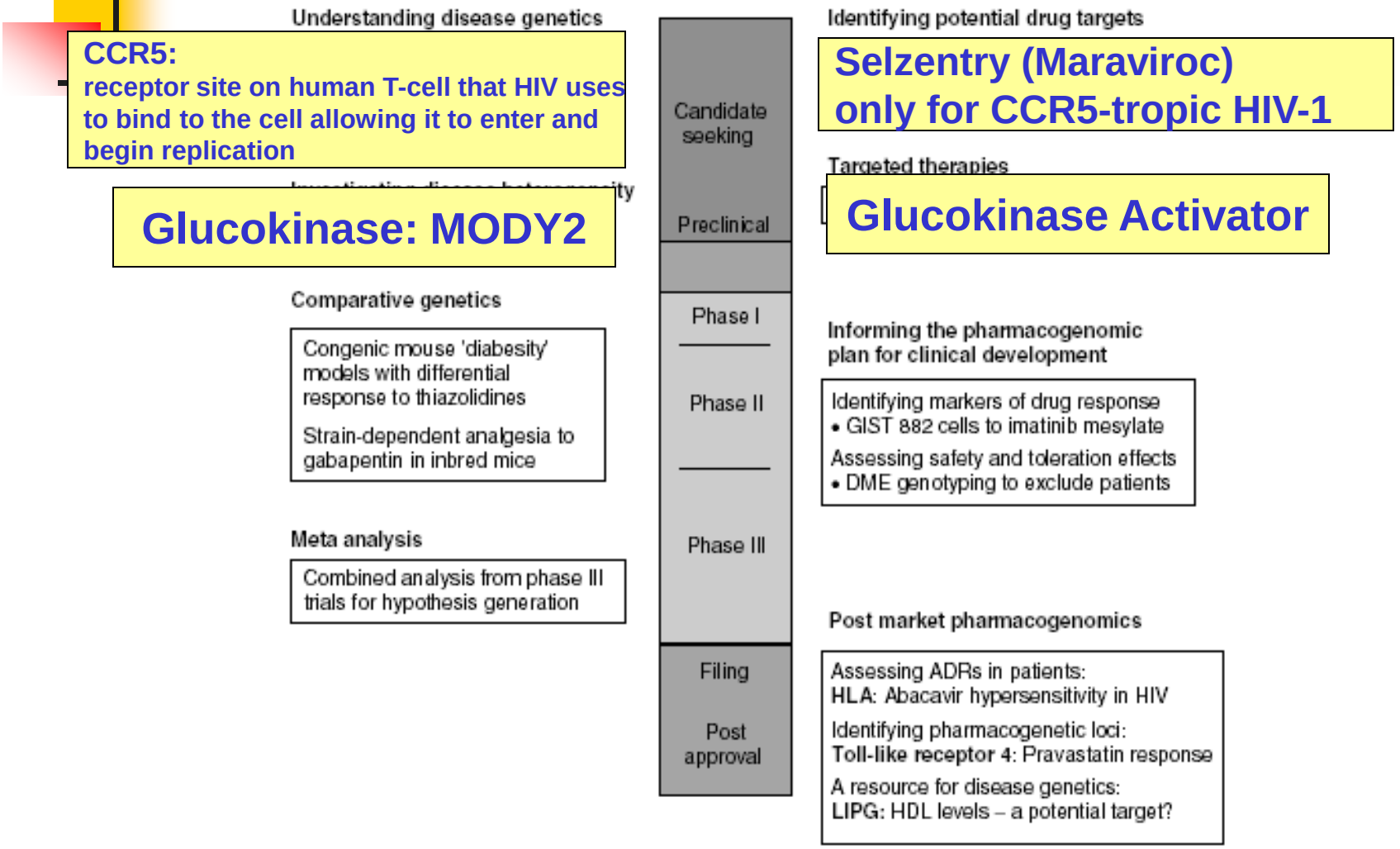
CMR International 2003

Potential Impact of Pharmacogenomics on the Drug Discovery/Development Pipeline



from Penny and McHale, 2005

Examples of Pharmacogenomic impact on the Drug Discovery



Modified from Penny and McHale, 2005

Glucokinase Mutants – MODY2 DM patients – Development of Glucokinase Activator

Human glucokinase gene: Isolation, characterization, and identification of two missense mutations linked to early-onset non-insulin-dependent (type 2) diabetes mellitus

PNAS, 1992

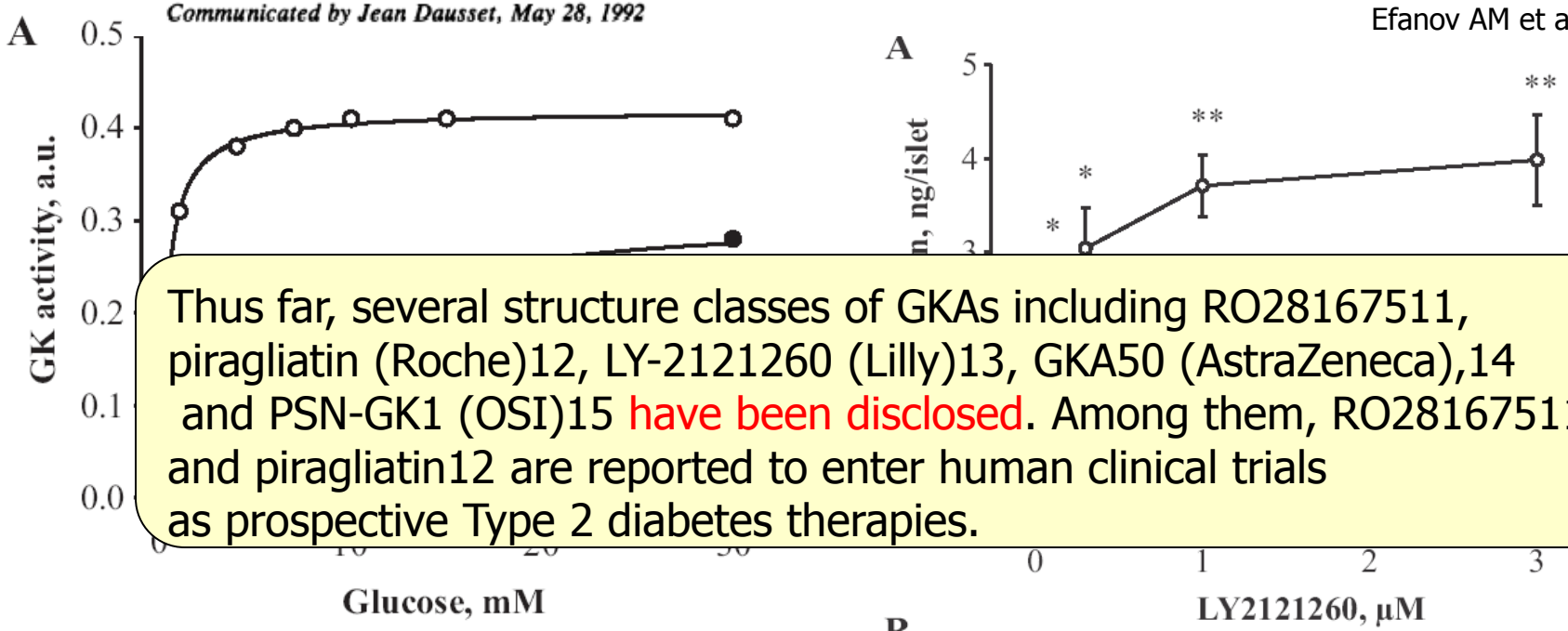
(glucose/metabolism/phosphorylation/structure–function/chromosome 7)

M. STOFFEL*, PH. FROGUEL†, J. TAKEDA*, H. ZOUALI†‡, N. VIONNET*, S. NISHI*§, I. T. WEBER¶, R. W. HARRISON¶, S. J. PILKIS‖, S. LESAGE†‡, M. VAXILLAIRE†‡, G. VELHO†‡, F. SUN†‡, F. IRIS†, PH. PASSA†, D. COHEN†, AND G. I. BELL*,**

*Howard Hughes Medical Institute, and Departments of Biochemistry and Molecular Biology, and of Medicine, The University of Chicago, 5841 South Maryland Avenue, MC1028, Chicago, IL 60637; §Second Division of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka 431–32, Japan; ¶Department of Pharmacology, Jefferson Cancer Institute, Thomas Jefferson University, Philadelphia, PA 19107; ‖Department of Physiology and Biophysics, State University of New York, Stony Brook, NY 11794; †Centre d'Etude du Polymorphisme Humain, 27 rue Juliette Dodu, and Service d'Endocrinologie, Hôpital Saint-Louis, 75010 Paris, France; and ‡Généthon, 1 rue de l'Internationale, 91000 Evry, France

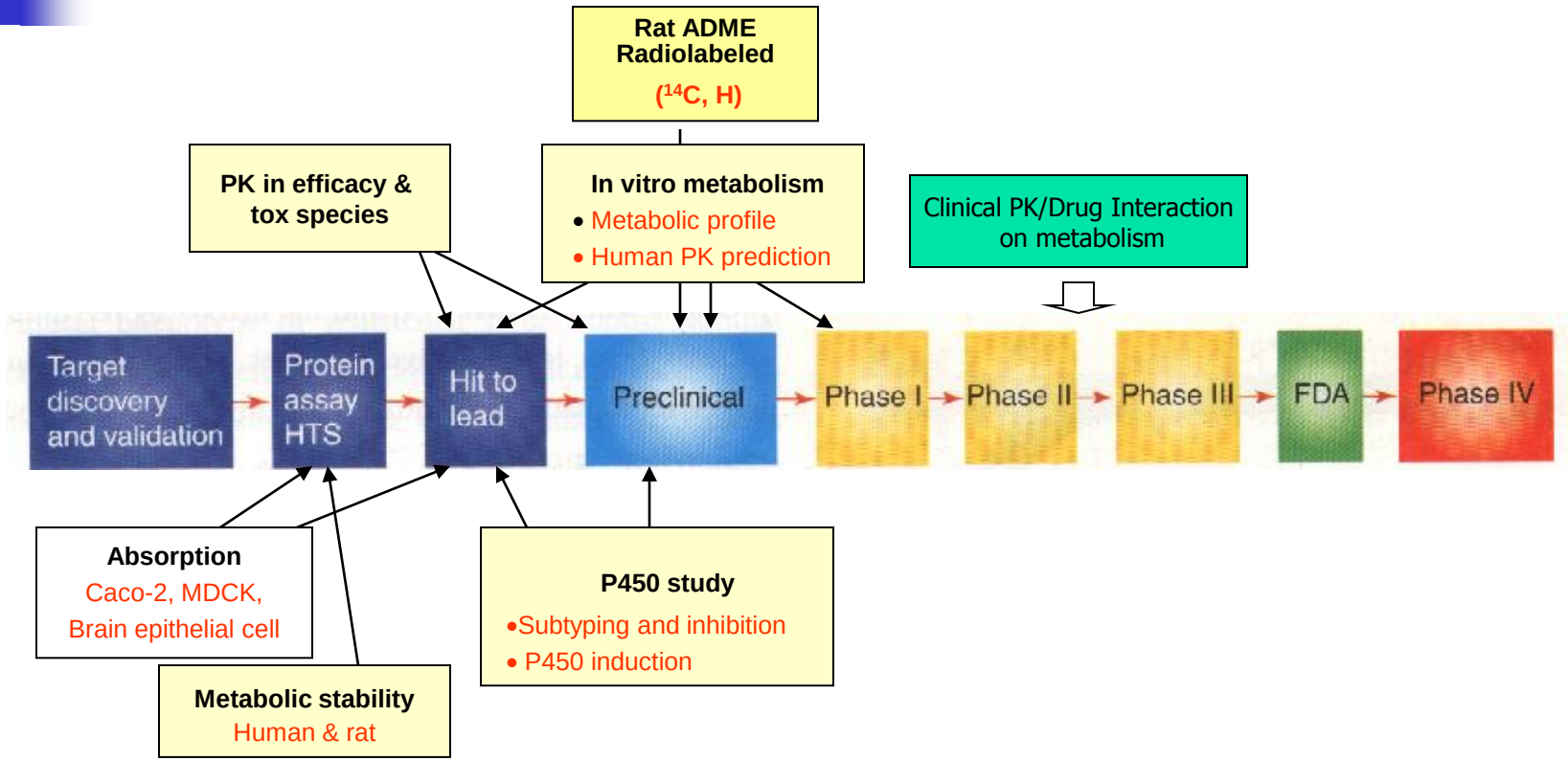
Communicated by Jean Dausset, May 28, 1992

Efanov AM et al., 2005



Thus far, several structure classes of GKAs including RO28167511, piragliatin (Roche)12, LY-2121260 (Lilly)13, GKA50 (AstraZeneca),14 and PSN-GK1 (OSI)15 have been disclosed. Among them, RO28167511 and piragliatin12 are reported to enter human clinical trials as prospective Type 2 diabetes therapies.

Pharmacokinetic Pharmacogenomics in Drug Discovery and Development



Hit, Lead or candidate: Substrate of CYP2D6, CYP2C19, CYP2C9 ??

Early Prediction of DMPK/Drug Interaction in Drug Discovery

In Vitro Screens

- Microsomal metabolism (rodents)
- P-gp efflux (CNS compounds)
- Caco-2 permeability
- Protein binding
- Microsomal metabolism (human)
- Microsomal inhibition
- Polymorphic P450 screen
- Phase Ⅱ metabolism

In Vivo PK Screens

- Clearance/t1/2/bioavailability (rodents)
- Target organ penetration (rodents)
- Clearance/t1/2/bioavailability (dog)
- Pilot ADME studies

Toxicology Support

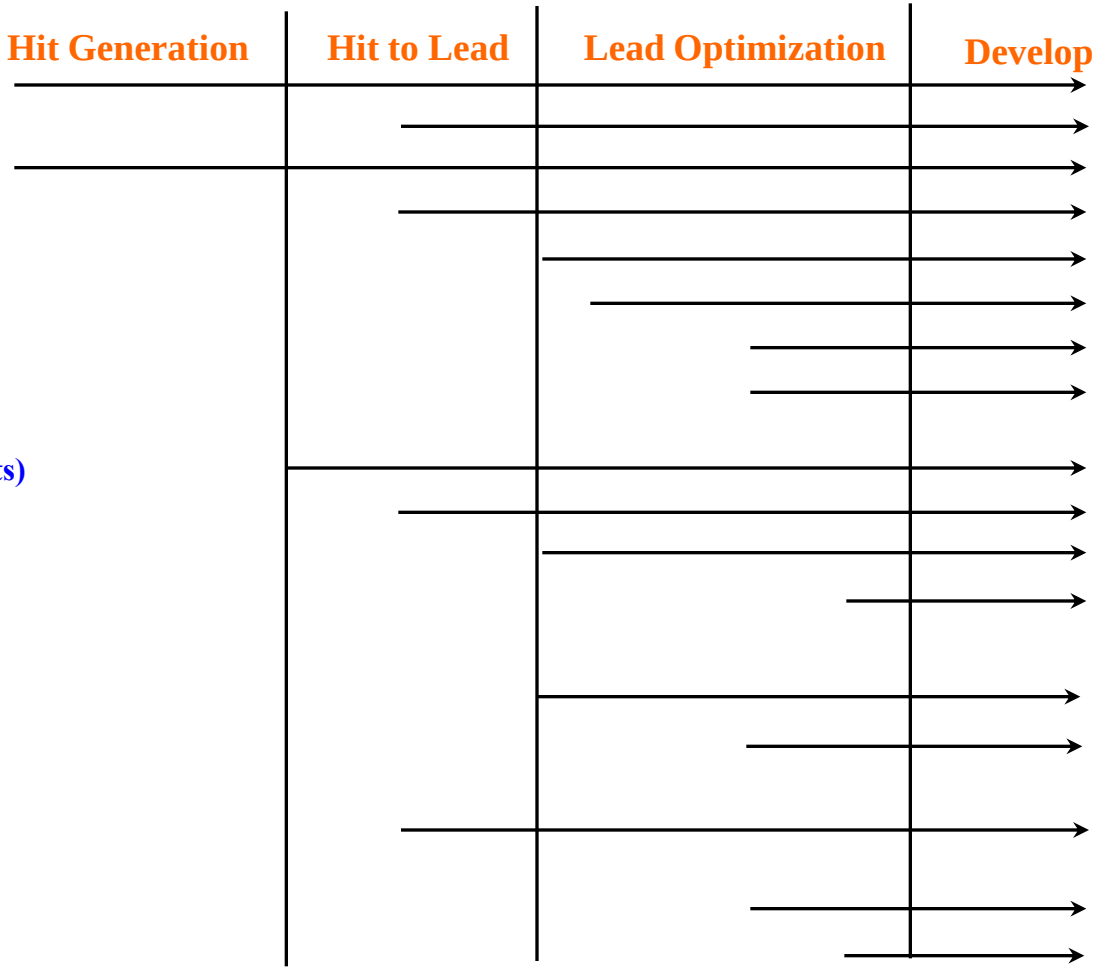
- Exposure in toxicology
- Selection of toxicity species

Pharmacology Support

- Exposure in efficacy models

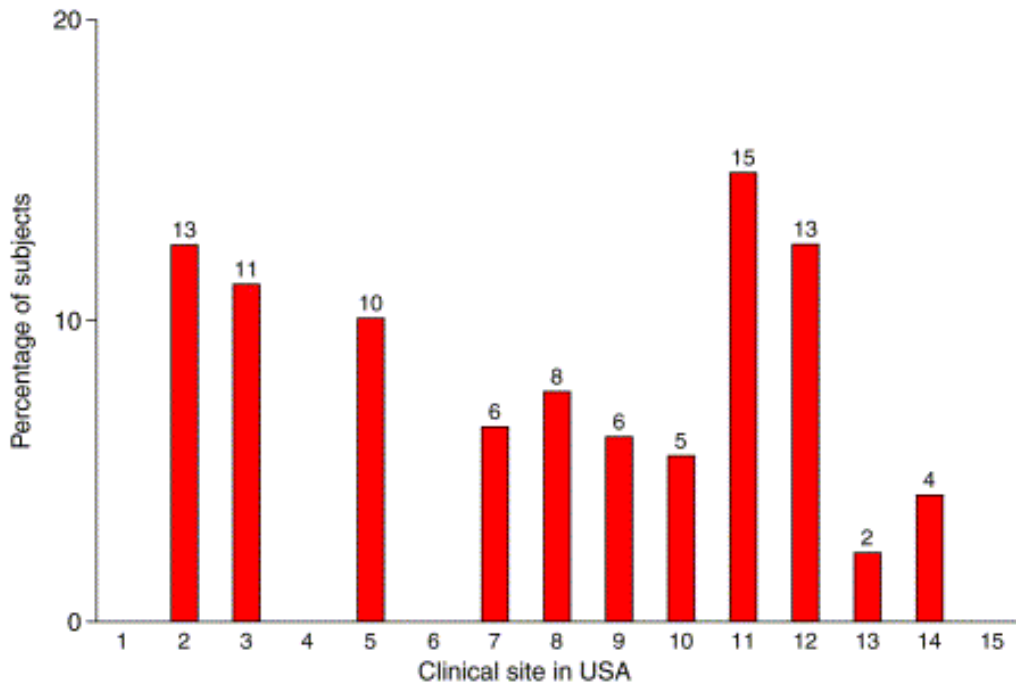
Formulation Support

- Salt and crystalline selection
- Formulation screen



DM/PK Pharmacogenetics in Clinical Trial

– why should genotype be considered ?



The incidence of CYP2D6 PMs in 15 clinical trial sites in USA

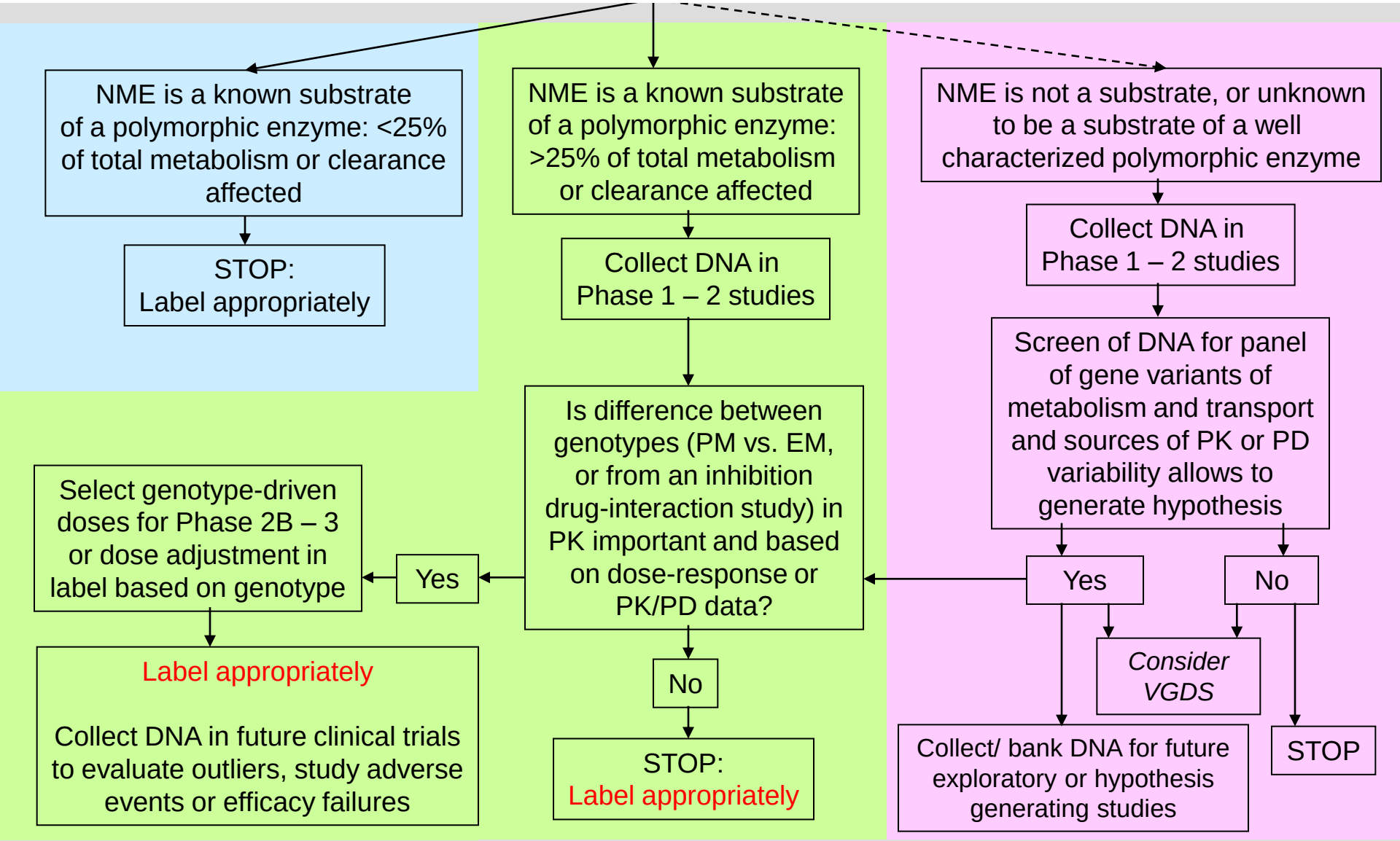
leading compound of CYP2D6 substrate,

Site to site variation of phase I, II, III safety and efficacy data ??

If this candidate has very narrow therapeutic window for concentration dependent serious ADR ?

Decision Tree of PGx Studies into New Drug Development

Goal: To assist in the integration of PGx studies early into the drug development process



from Clinical Pharmacology Advisory Committee, Felix W. Frueh, March 2008

Anticoagulant

Rx only

COUMADIN® TABLETS
(Warfarin Sodium Tablets, USP) Crystalline

COUMADIN® FOR INJECTION
(Warfarin Sodium for Injection, USP)

Label of Warfarin

WARNING:

Warfarin sodium can cause major or fatal bleeding. Bl
with a higher dose (resulting in a higher INR). Risk fa
(INR >4.0), age ≥65, highly variable INRs, history o
disease, serious heart disease, anemia, malignanc
PRECAUTIONS), and long duration of warfarin thera
treated patients. Those at high risk of bleeding may
adjustment to desired INR, and a shorter duration o
measures to minimize risk of bleeding and to report i
(see **PRECAUTIONS: Information for Patients**).

DESCRIPTION

COUMADIN (crystalline warfarin sodium) is an anti
coagulation factors. Chemically, it is 3-(α-acetonylbe
R- and *S*-enantiomers. Crystalline warfarin sodium i
sodium virtually eliminates trace impurities present in
and its structural formula may be represented by the

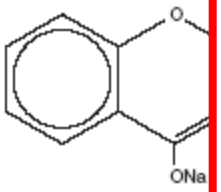


Table 1: Relationship Between S-Warfarin Clearance and CYP2C9 Genotype in Caucasian Patients

CYP2C9 Genotype	N	S-Warfarin Clearance/Lean Body Weight (mL/min/kg) Mean (SD)[a]
*1/*1	118	0.065 (0.025)[b]
*1/*2 or *1/*3	59	0.041 (0.021)[b]
*2/*2, *2/*3, or *3/*3	11	0.020 (0.011)[b]
Total	188	

[a] SD=Standard deviation.
[b] $p<0.001$. Pairwise comparisons indicated significant differences among all 3 genotypes.

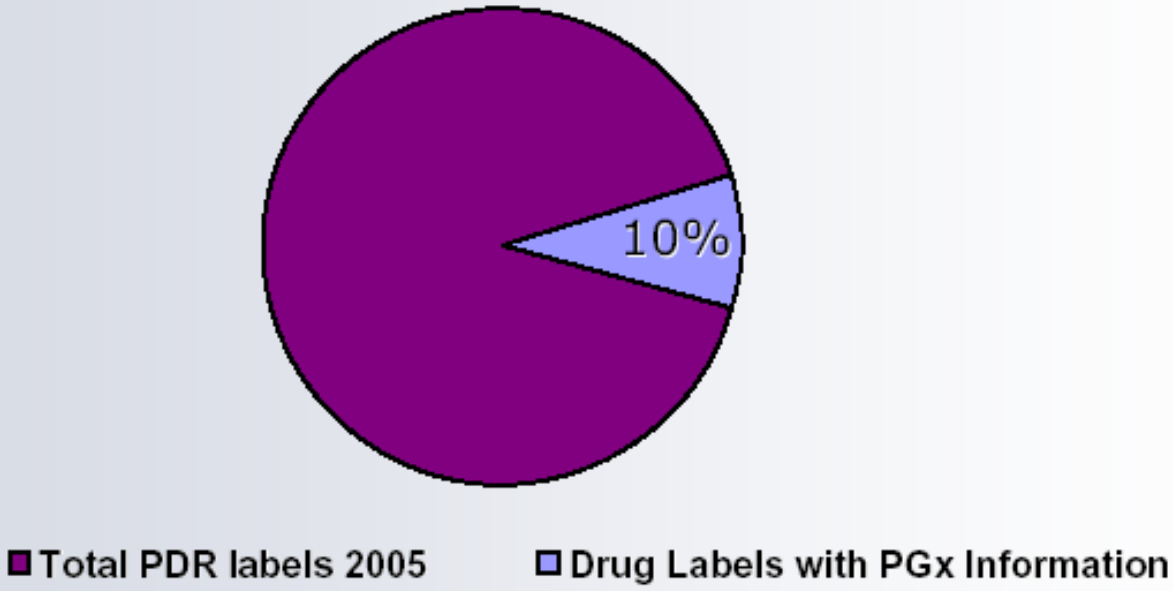
Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry and *5, *9, and *11 alleles in Caucasians.

Pharmacogenomics: A meta-analysis of 9 qualified studies including 2775 patients (99% Caucasian) was performed to examine the clinical outcomes associated with CYP2C9 gene variants in warfarin-treated patients.[3] In this meta-analysis, 3 studies assessed bleeding risks and 8 studies assessed daily dose requirements. The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles. Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele. For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele.

In an observational study, the risk of achieving INR >3 during the first 3 weeks of warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype. The relative risk of overanticoagulation as measured by INR >3 during the first 2 weeks of therapy was approximately doubled for those patients classified as *2 or *3 compared to patients who were homozygous for the *1 allele.[4]

Warfarin reduces the regeneration of vitamin K from vitamin K epoxide in the vitamin K cycle, through inhibition of vitamin K epoxide reductase (VKOR), a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (especially the –1639G>A allele) have been associated with lower dose requirements for warfarin. In 201 Caucasian patients treated with stable warfarin doses, genetic variations in the VKORC1 gene were associated with lower warfarin doses. In this study, about 30% of the variance in warfarin dose could be attributed to variations in the VKORC1 gene alone; about 40% of the variance in warfarin dose could be attributed to variations in VKORC1 and CYP2C9 genes combined.[5] About 55% of the variability in warfarin dose could be explained by the combination of VKORC1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients.[5] Similar observations have been reported in Asian patients.[6,7]

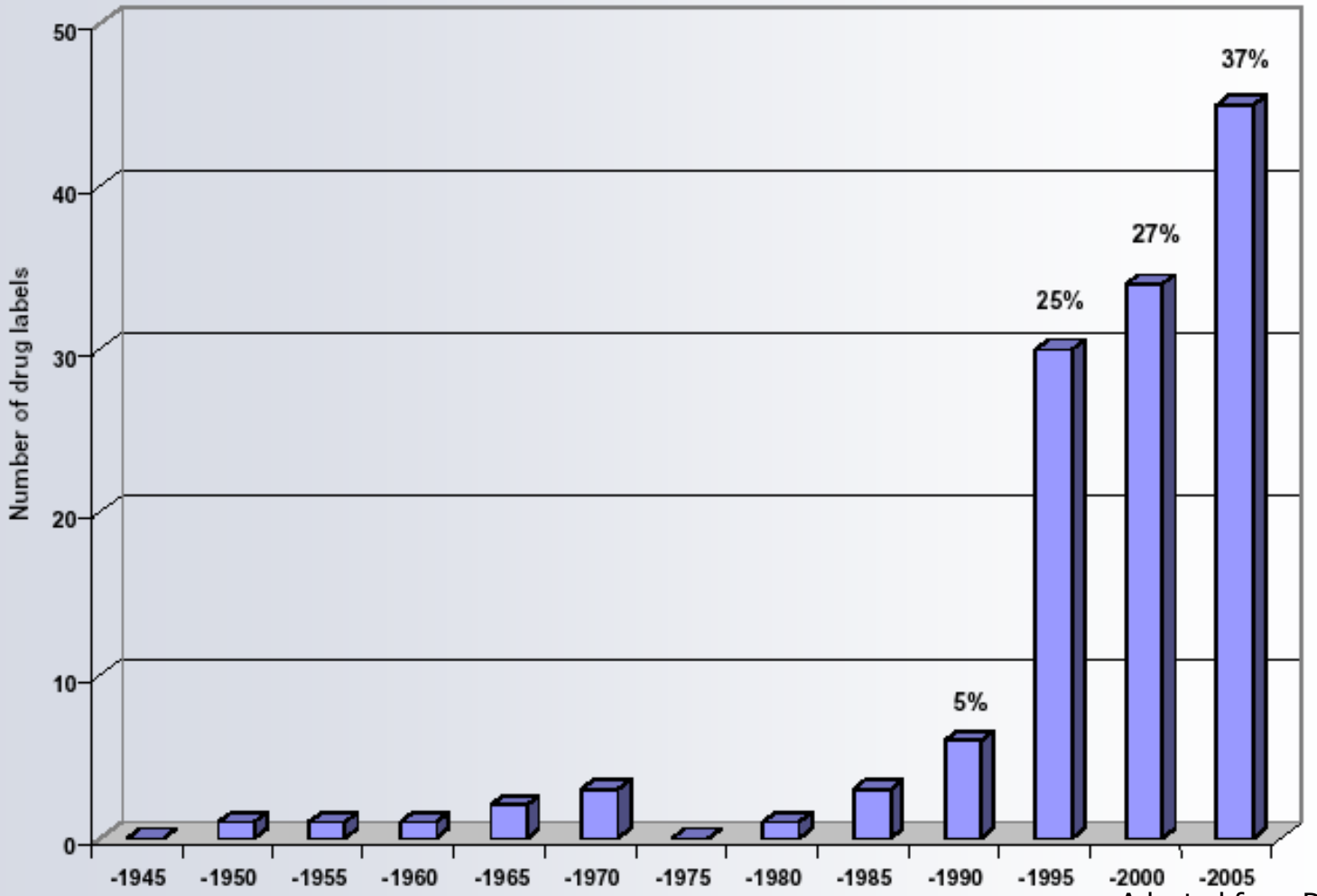
How Many Drug Labels Contain Pharmacogenomic Information ?



~ 1200 labels screened (PDR, Drugs@FDA)
121 found to contain pharmacogenomic information

from Dr. Frueh, FDA

Labels of Approved Drugs with Pharmacogenomic Information



Adapted from Dr. Frueh, FDA

What Type of Pharmacogenomic Information is Provided in Label ?

- Mostly pharmacokinetic (e.g., drug metabolizing enzymes) – relevance for drug dosing, AEs
- Increasingly, pharmacodynamic information is found (e.g., receptors) – relevance for identification or responders, non-responders
- Broadly, the impact of pharmacogenomic information on the treatment decision can be put into 3 categories:
  - "Test required" e.g., Herceptin, Erbitux
  - "Test recommended" e.g., Irinotecan, 6-MP
  - "Information only" e.g., Tarceva, Strattera

Adapted from Dr. Frueh, FDA

An Informative Label Including PGt Information: Atomoxetine (Straterra®)

Human PK

A fraction of the population are PM's resulting in …

Drug-Drug Interactions

Inhibitors of CYP2D6 in EM's increase exposure…similar to PM's

Adverse Reactions

The following ADR's were either twice as frequent or statistically significantly more frequent in PM's compare to EM's...

Laboratory Tests

Laboratory tests are available to identify CYP 2D6 PM's

An Informative Label: Thioridazine (Mellaril[R])

- Contraindications
  - thioridazine is contraindicated in patients, comprising 7% of the normal population, who are known to have a genetic defect leading to reduced levels of P450 2D6
- Warnings
  - certain circumstances may increase the risk of torsade de pointes...its use in patients with reduced activity of P450 2D6

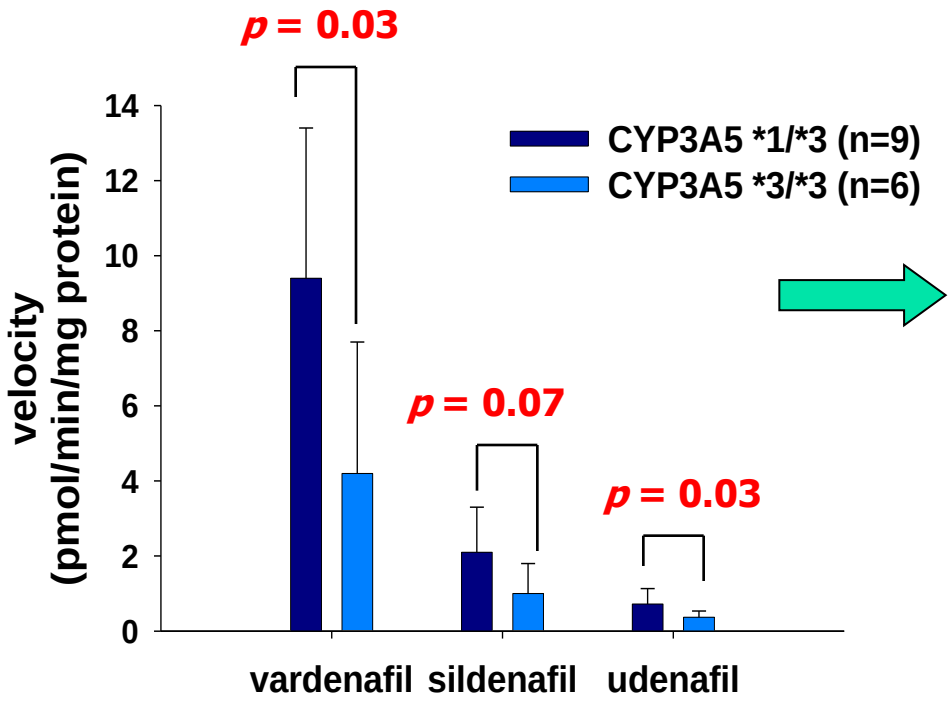
Relative Contribution of CYP3A4 and CYP3A5 on the metabolism of vardenafil, sildenafil, and udenafil (from *In vitro* metabolism)

Parameters	Vardenafil		Sildenafil		Udenafil	
	CYP3A4	CYP3A5	CYP3A4	CYP3A5	CYP3A4	CYP3A5
V_{max} (pmol/min/pmol rCYP)	1.5 ± 0.1	1.8 ± 0.2	1.0 ± 0.2	1.4 ± 0.1	3.9 ± 0.6	1.1 ± 0.1
K_m (μM)	7.8 ± 1.1	3.0 ± 0.9	15.0 ± 5.4	14.7 ± 1.6	531.9 ±246.3	216.4 ± 72.3
CL_{int} (μl/min/pmol rCYP)	0.19	0.60	0.07	0.09	0.007	0.005

3-fold higher in CYP3A5 than in the CYP3A4

Koo HW, Shin JG et al. DMD 2008

Significant, but different extent of genetic effect on the formation of a metabolites from PDE5 Inhibitors *in vitro* HLM incubation

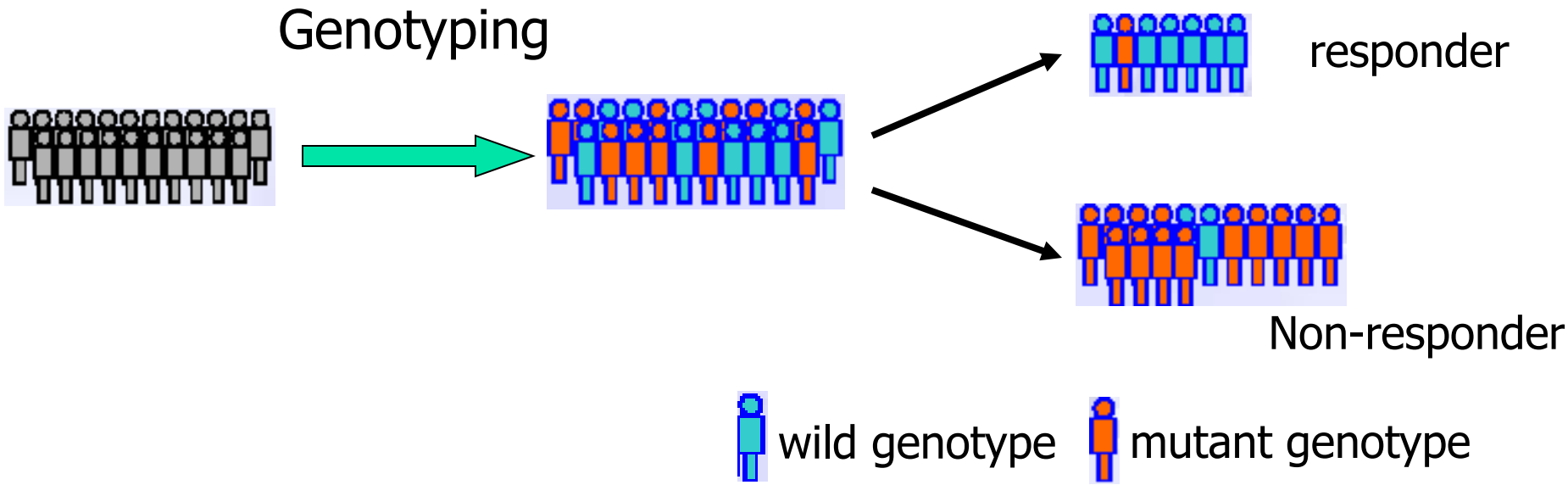


What about in human *in vivo*?

Mean metabolite formation activities in 15 human liver microsomes from liver bank of PGRC

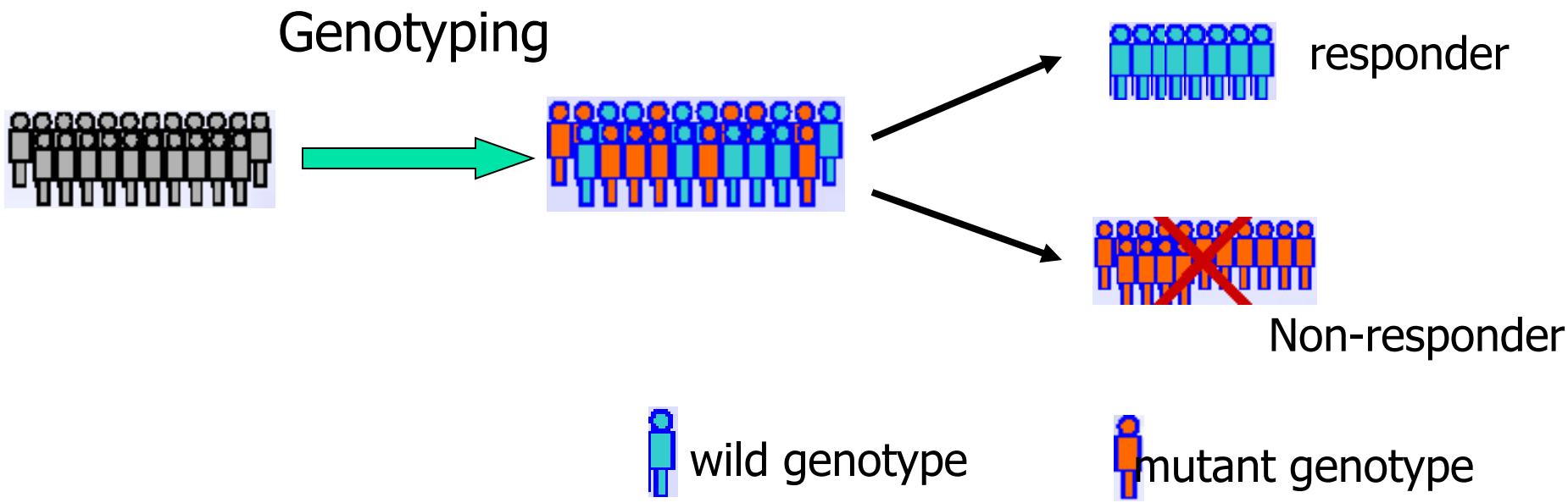
Exploratory Approach for Phase I & IIa trial using PGt/PGx information

- Prospective genotyping
- correlation between genotype and response (PK/PD), exploratory
- low response rate, no correlation – no go of phase III trial
- low response rate, but good correlation – proceed to phase III trial

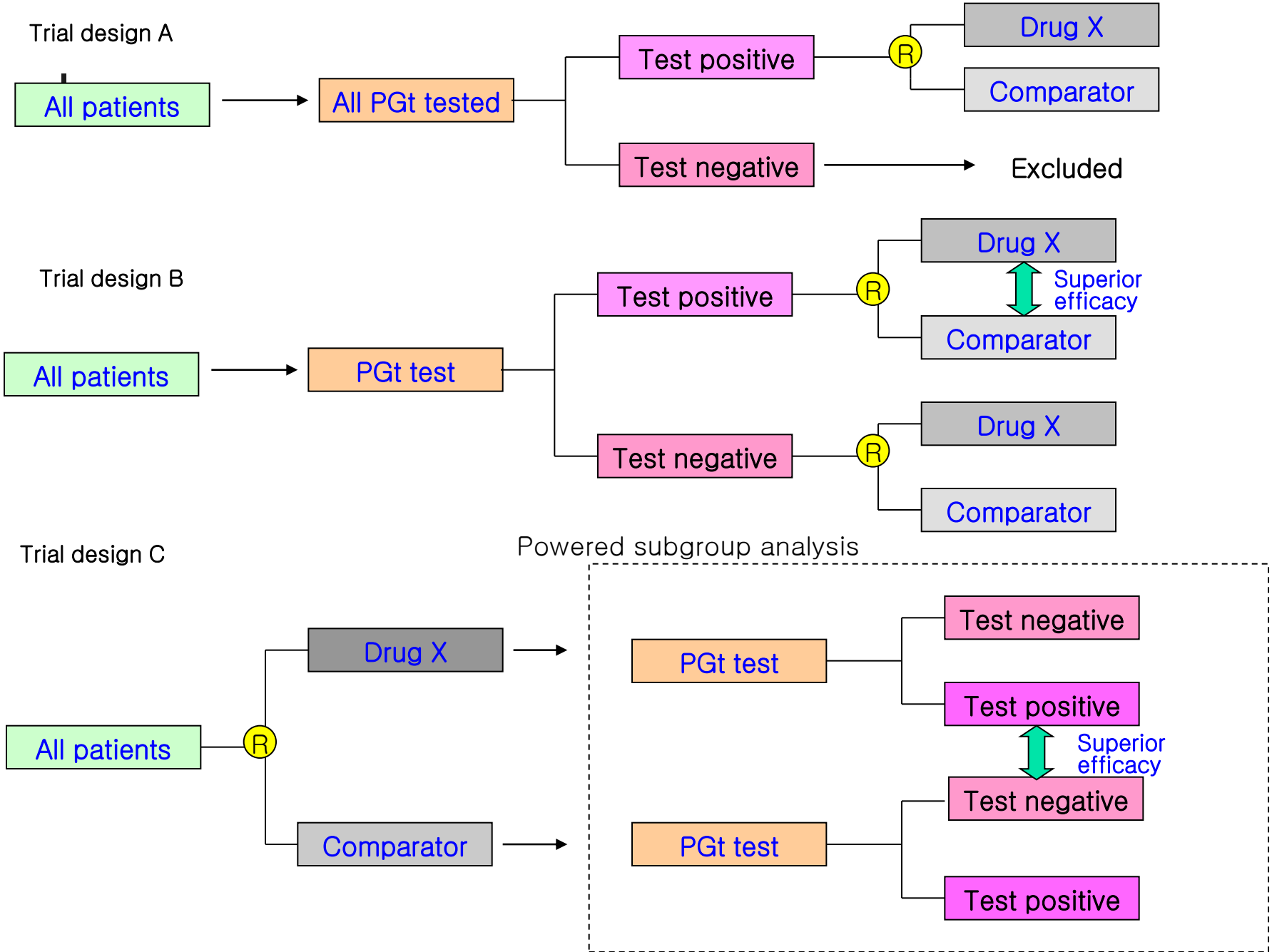


PGt/PGx in Phase IIb & III trial

- Genostratification
- Enrollment of subject with genotype related to superior efficacy or adverse effect (obtained from phase I & II trial)
- decrease sample size, reduce the risk to failure in phase III
- impact on labeling



Examples of PGt/PGx based pivotal clinical trial design



Benefits of PGx in Clinical Trials and Drug Development

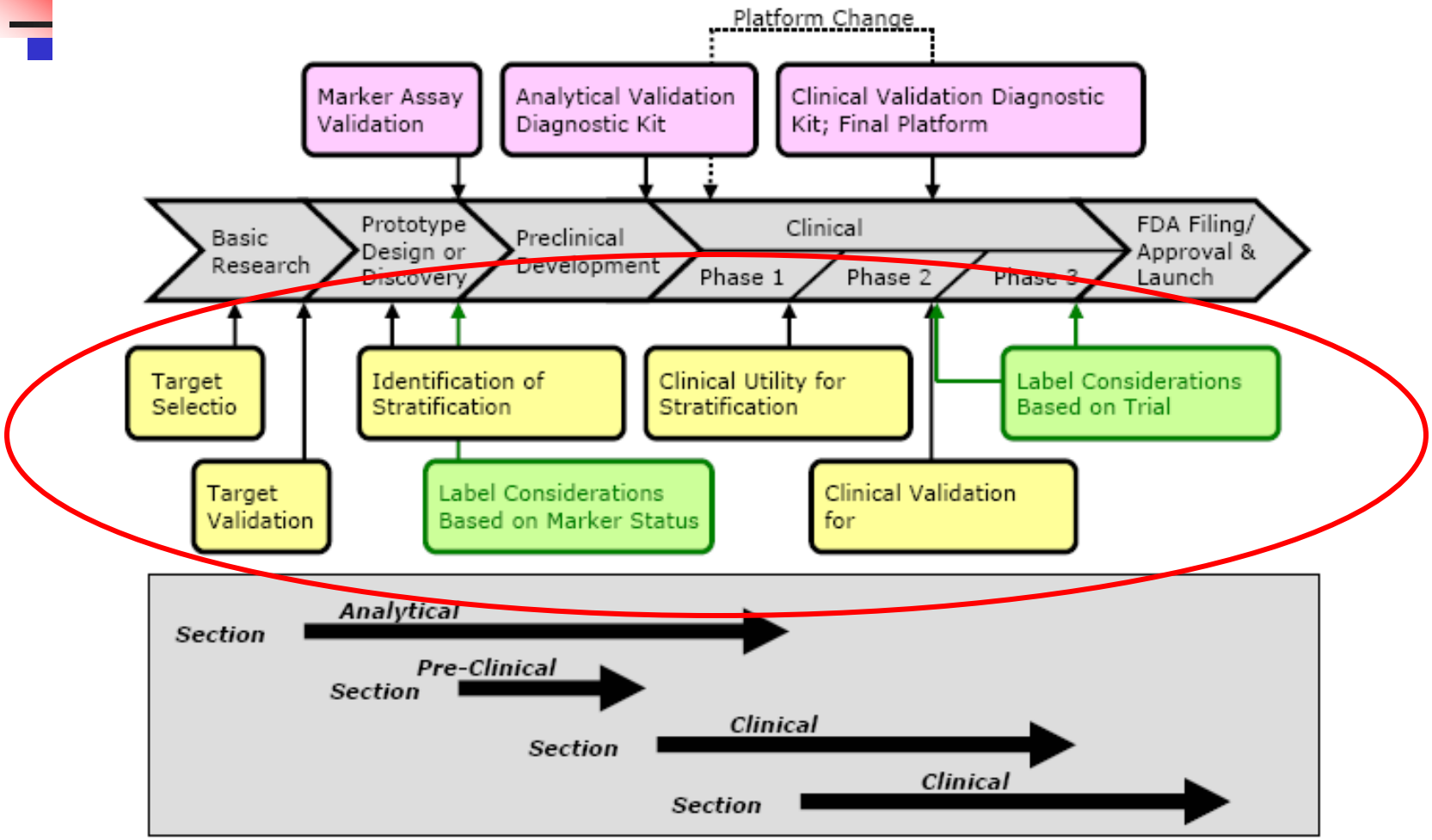
- Eliminate standardized trial and error, and "one size fits all" approaches to drug prescriptions
- Tailor accurate doses of medications to patients' genotypes
- Prescribe drug types appropriate to specific genotypes
- Revive failed drug candidates and expand indications for existing therapeutic medications
- Predict adverse reactions and identify genotypes that correlate to adverse drug response or side effects
- Facilitate the drug approval process and reduce time to market
- Minimize the failure of drugs in late developmental stages
- Create a new market of therapeutic products
- Reduce drug development expenses

Source: Biotechnology Associates

Validation Process for Personalized Medicine

- Validation of genetic biomarker for PK/PD, efficacy, adverse drug reaction
- Validation of companion diagnostics for the personalized medicine
- It takes long time and long way to reach to the personalized medicine
- Ethnic specific validation for its application

Validation of Genetic Biomarker for Personalized Medicine
: from discovery to labeling



Drug-Device Co-Development Concept Paper, April 2005

Level of Evidence to reach to the goal line of personalized pharmacotherapy
– from discovery to development of valid PGt Biomarker

- **Identification of PGt marker**
  - Candidate gene approach
  - Genome wide association approach
- **Preclinical validation: *In vitro* /animal**
  - *In vitro* functional evaluation: molecular, cellular
  - Animal model approach
  - Development of genotype method and analytical validation
- **Clinical Validation**
  - Human clinical trial for PK/PD: healthy subjects or patients
  - Confirmatory trial for the validation of marker for the efficacy, ADR in patients
  - Large scale outcome study: genotype guided
- **Development of algorithm and clinical utility validation**
  - Algorithm for the PGx biomarker guided personalized therapy
  - Cost-benefit analysis type trial
  - Randomized Controlled trial for the personalized pharmacotherapy algorithm

Candidate Gene Approach: OCT1/2/3 (*SLC22A1/2/3*)

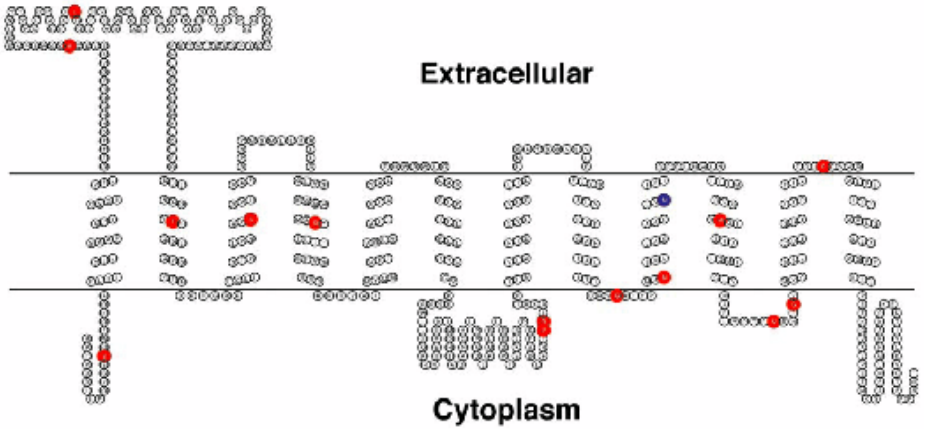
- **Clustered in chromosome 6q26-27 (all SLC22A1/2/3 genes contain 11 exon**

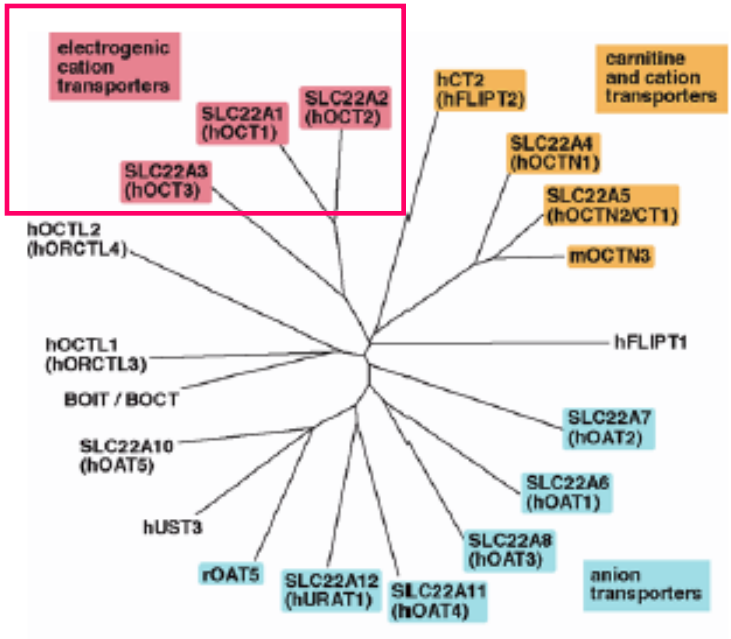
- **Proteins: OCT1/2/3**
- **Genes: *SLC22A1/2/3***

- **Substrates for OCT1/2/3:**
  Drugs, Endogenous amines, Prostaglandines
  Therapeutic drugs (Metformin, Cimetidine, Procainamide etc.)

Tissue distribution

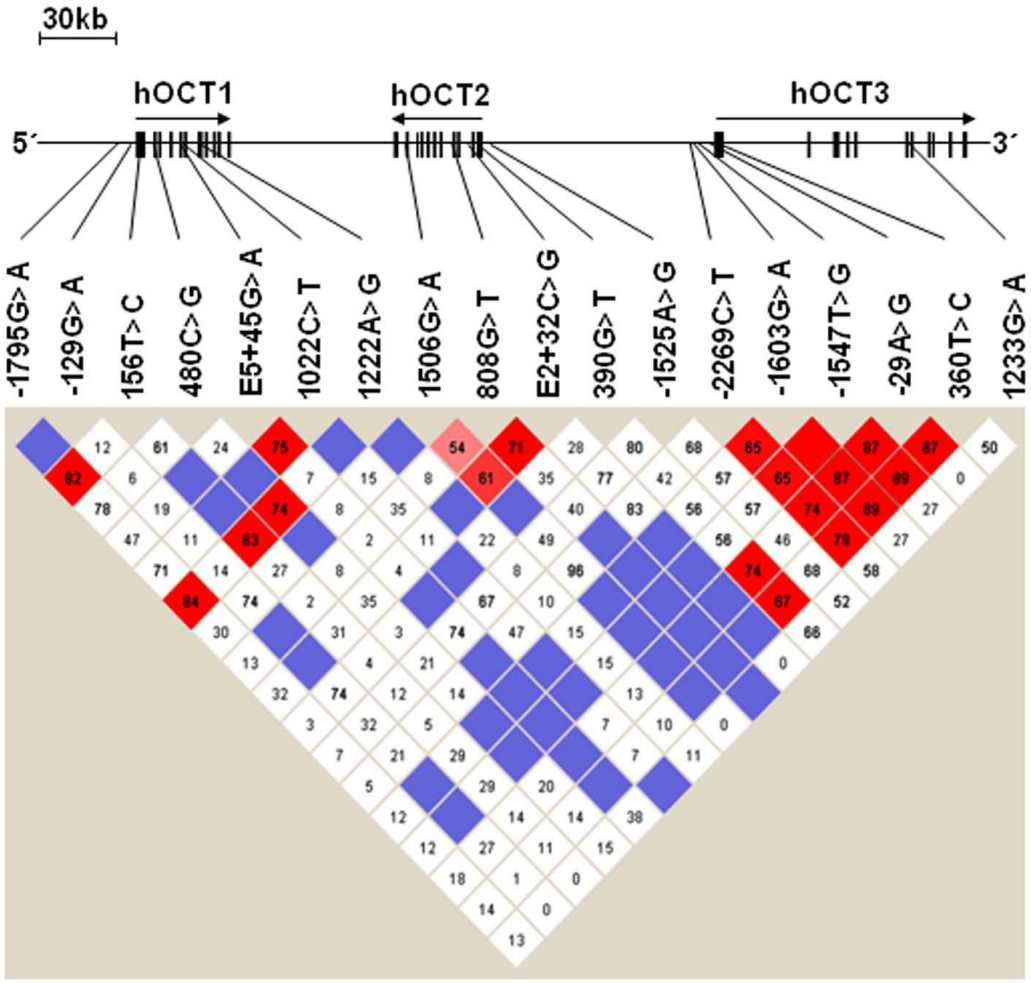
Transporter	Kidney	Liver	Intestine	Brain
OCT1	+	+++	+	+
OCT2	+++	–	–	+
OCT3	+	++	++	+





J Pharm Sci, 2001; JPET, 2004; NCBI GEO profiles

Identification of Genetic Variants and Linkage Disequilibrium of OCT genes in Korean subjects



- Sequencing of OCTs
- MAF 10%
- chr 6q26-27
- No significant linkage among OCT genes
- The mutations in these 3 transporters are independent
- Promoter 13
- Nonsynonymous
  - OCT1: F160L,P283L, P341L, M408V
  - OCT2: T199I, T201M, A270S
- Synonymous 6
- Intronic 3

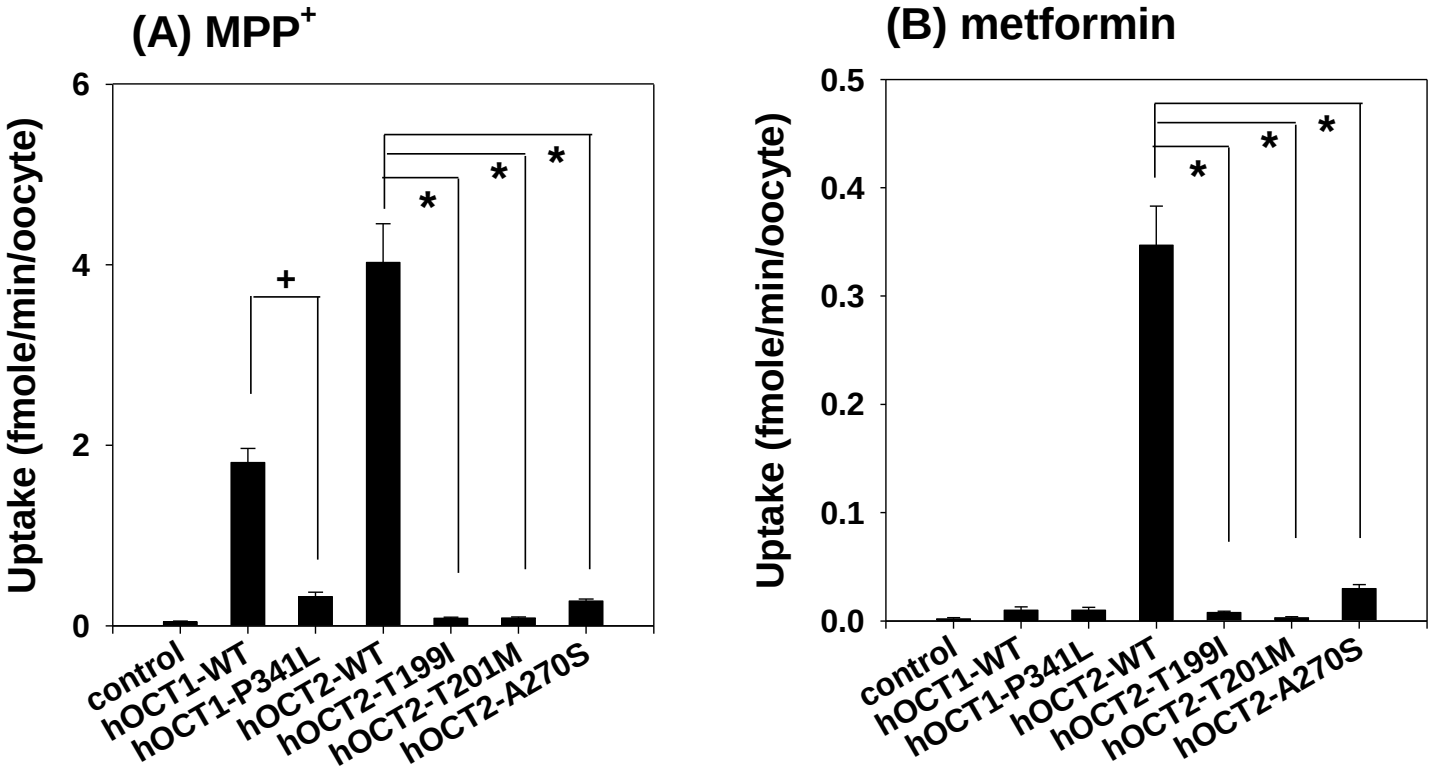
Kang, Shin et al. DMD 2007

Genetic variant of OCT2 (non-synonymous)

Exon	NT change	AA change	Functional change (in vitro)		Allele frequency (%)			
			MPP^+	Metformin	CA	AA	JP	Kor
1	160C>T	P54S	Similar	ND	0	0.5	0	0
2	481T>C	P161L	Similar	ND	0.5	0	0	0
2	493A>G	M165V	Similar	ND	0	0.5	0	0
2	495G>A	M165I	Decrease	ND	0	1	0	0
3	596C>T	T199I	Decrease	Decrease	0	0	0.9	1
3	602C>T	T201M	Decrease	Decrease	0	0	1.3	2
4	808G>T	A270S	Decrease	Decrease	15.7	11	16.8	14
5	890C>G	A297G	ND	ND	0.5	0	0	0
7	1198C>T	R400C	Decrease	ND	0	1.5	0	0
8	1294A>C	K432Q	Decrease	ND	0	1	0	0

Leabman et al., 2002; Fukushima et al., 2004; Kang, Shin et al., 2007; Song , Shin et al., 2008;

Effects of OCT2 Genetic Variants on Metformin uptake *in vitro*

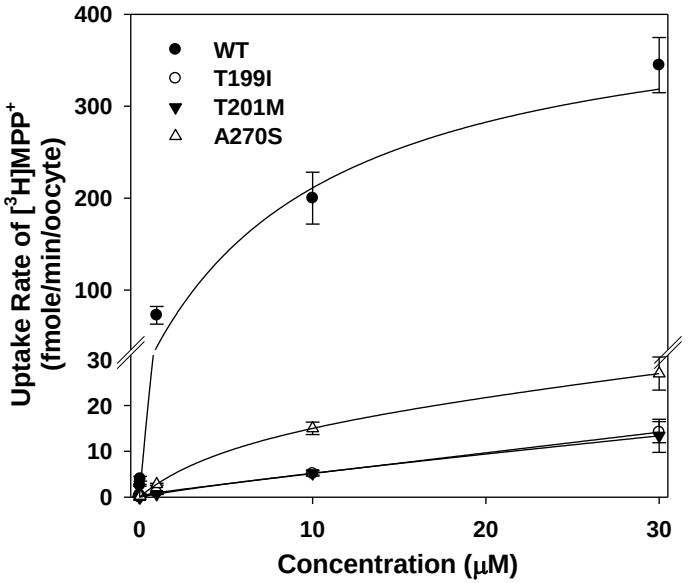


- Metformin uptake showed a much greater increase in oocytes expressing OCT2-WT than OCT1-WT, and the uptake was significantly decreased in oocytes expressing OCT2-T199I, -T201M, and -A270S, but not OCT1-P341L

Song , Shin et al., Xenobiotica, 2008

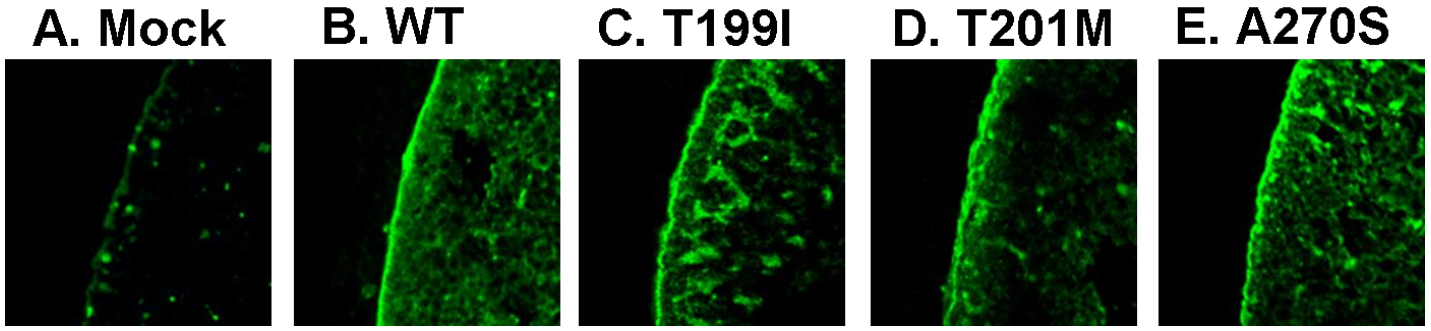
Kinetic Parameters of OCT2 Variants:
using Xenopus Ooctye expression system

- **Concentration Dependency of MPP+ uptake**

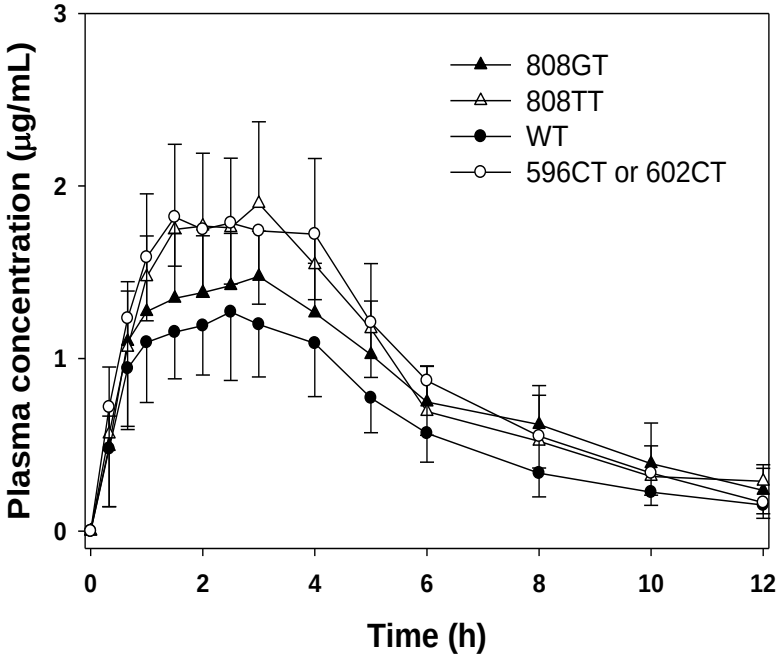


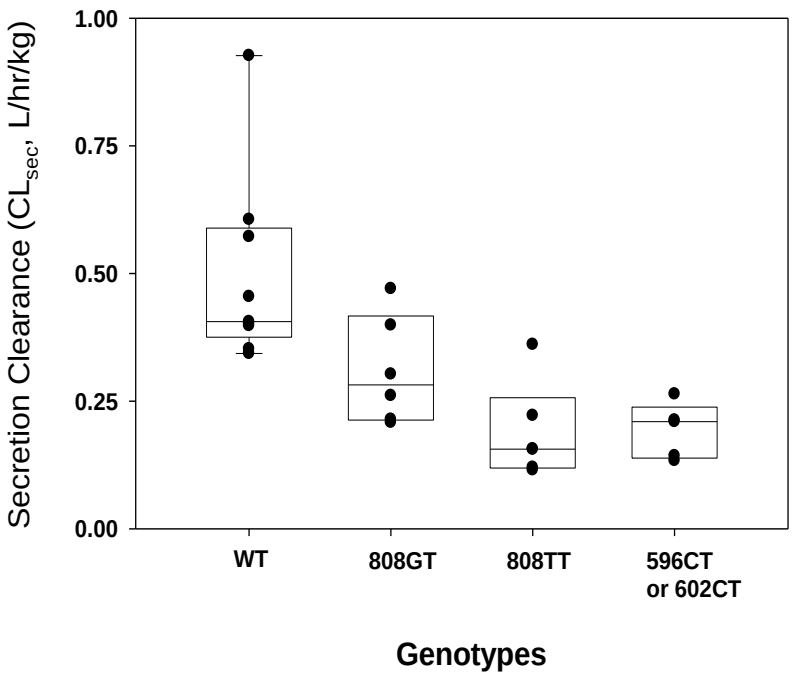
	V_{max} (fmole/min/oocyte)	K_m (μM)	CL_{int} (nL/min/oocyte)
WT	316.8	3.48	91.03
T199I	14.1	12.96	1.09
T201M	14.6	17.70	0.82
A270S	27.1	6.98	3.88

- Membrane localization of OCT2-WT and variants



Effects of OCT2 Variants on the Metformin Disposition in healthy subjects





- The *SLC22A2* variants as *in vivo* marker of metformin pharmacokinetics including C_{max}, AUC, Cl_R etc.
- Decreased renal tubular secretion of metformin

Song IS, Shin JG et al., CPT, 2008

More and more studies (evidence) required to reach to the personalized pharmacotherapy of metformin

- OCT2 genotypes on PK/PD of metformin in small scale trials
- Is this reliable biomarker for the prediction of efficacy?
  - Cohort study to see the association of OCT2 genotype and efficacy (glucose, HbA1c etc)?
- Clinical validity of OCT2 genotype for the prediction of therapeutic outcome on the treatment with metform in DM patients
- Should consider other genes/environmental factor related to the pathway of metformin drug response for the development of predictive model?
- ……
- ……
- Development of algorithm including OCT2 genotype for the personalized therapy
- Validation of the algorithm: cost-effectiveness analysis
- ……..

Identification of Novel Genetic Biomarker

Clinical validation for the prediction of therapeutic outcome in a given indication
, efficacy)

Chance to drop on the way

The steps forward to the clinical practice of personalized therapy based on PGx biomarker: Validation processes

Long Way to Go !!!

In vivo evidence on PK/PD of drugs in human:

- Smal scale clinical studies
- Effect of Gene-Gene interaction
- Gene-Environmental interaction…etc.

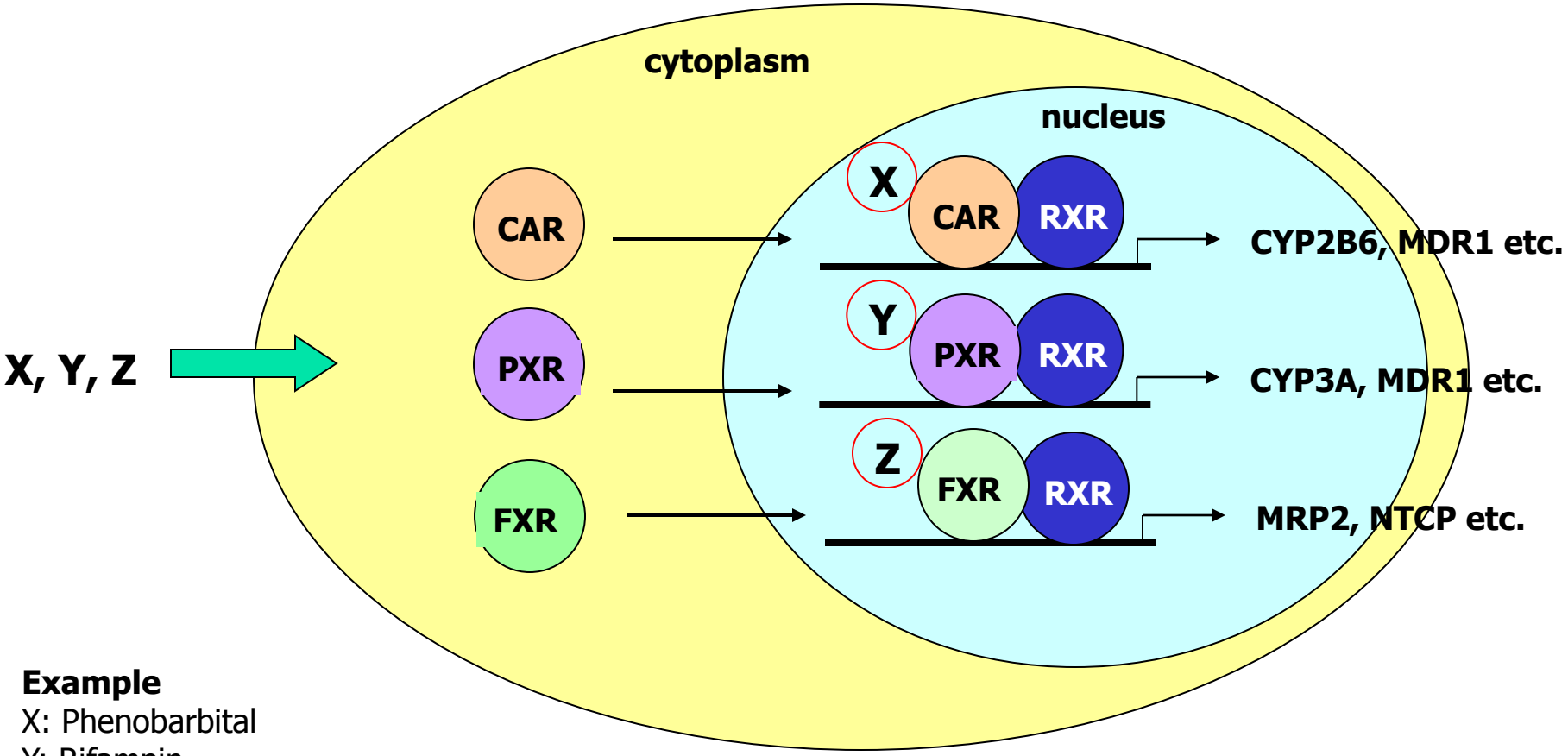
Development of dosing algorithm: from many of gene/environmental factors

Validation for the clinical utility of PGx based personalized therapy algorithm: Cost-effectiveness evaluation

Additional Genomics Biomarkers of Personalized Medicine

- ✓ **Expression regulation for better PGx prediction**
- Genomics of gene regulation
  - SNPs in nuclear receptor, e.g. PXR, CAR, HNF4α
  - Alternative Splicing Variants
  - Allelic imbalance
  - Copy Number Variation
- Epigenomics
  - microRNA
  - DNA methylation
  - Histone modification

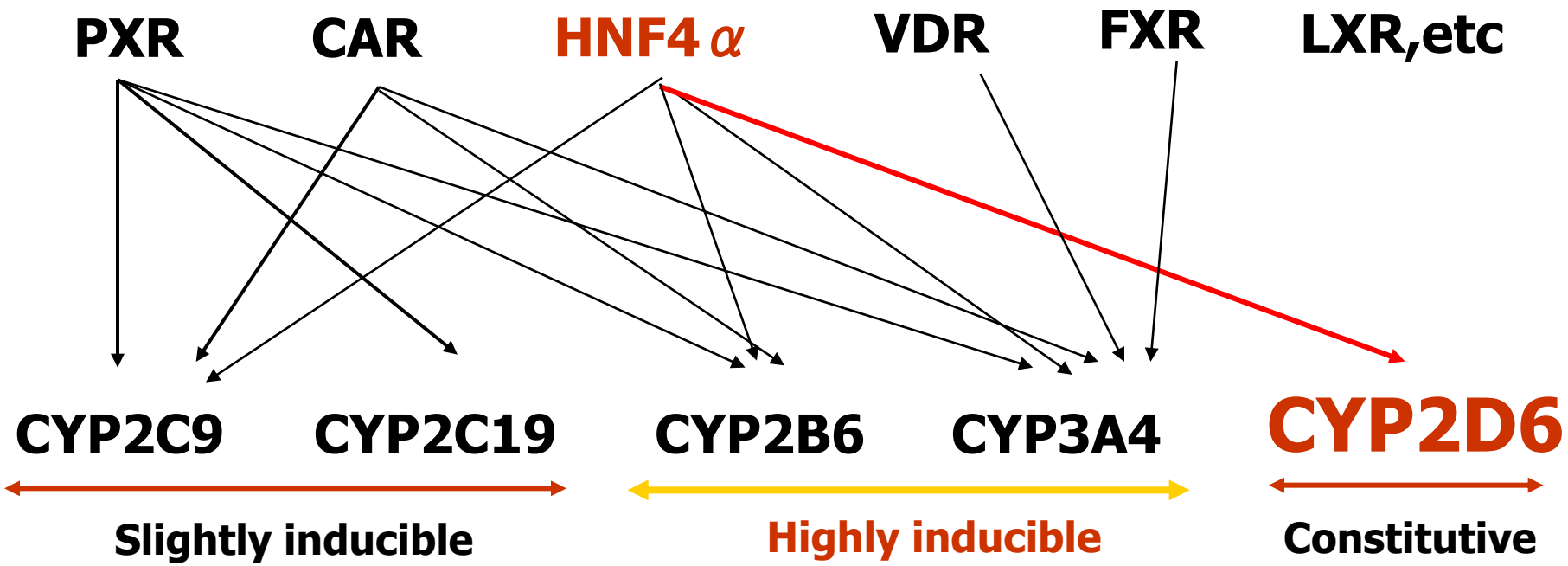
Nuclear receptors and xenobiotic mediated transcription regulation



Example
X: Phenobarbital
Y: Rifampin
Z: Bile acid

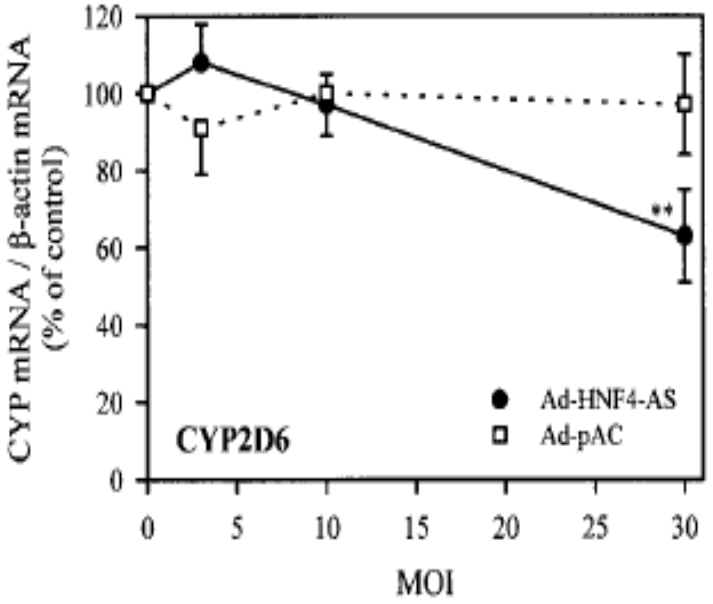
Gene–Gene Interaction between CYP2D6 and HNF4A

Regulation of CYP Expression by Nuclear Receptors



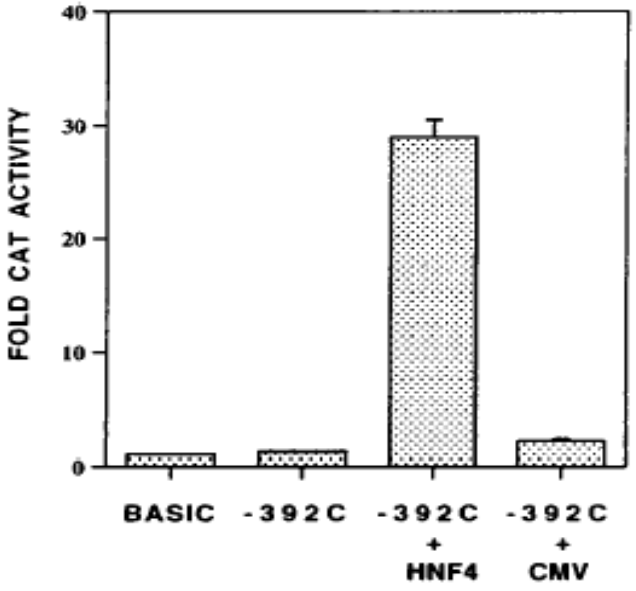
Constitutional expression of CYP2D6 is regulated by HNF4 α

Anti-mRNA of HNF4α



Jover et al. (2001) Hepatology

CYP2D6 promoter



Cairns et al. (1996) J Biol Chem

*HNF4*α SNPs identified in a Korean population

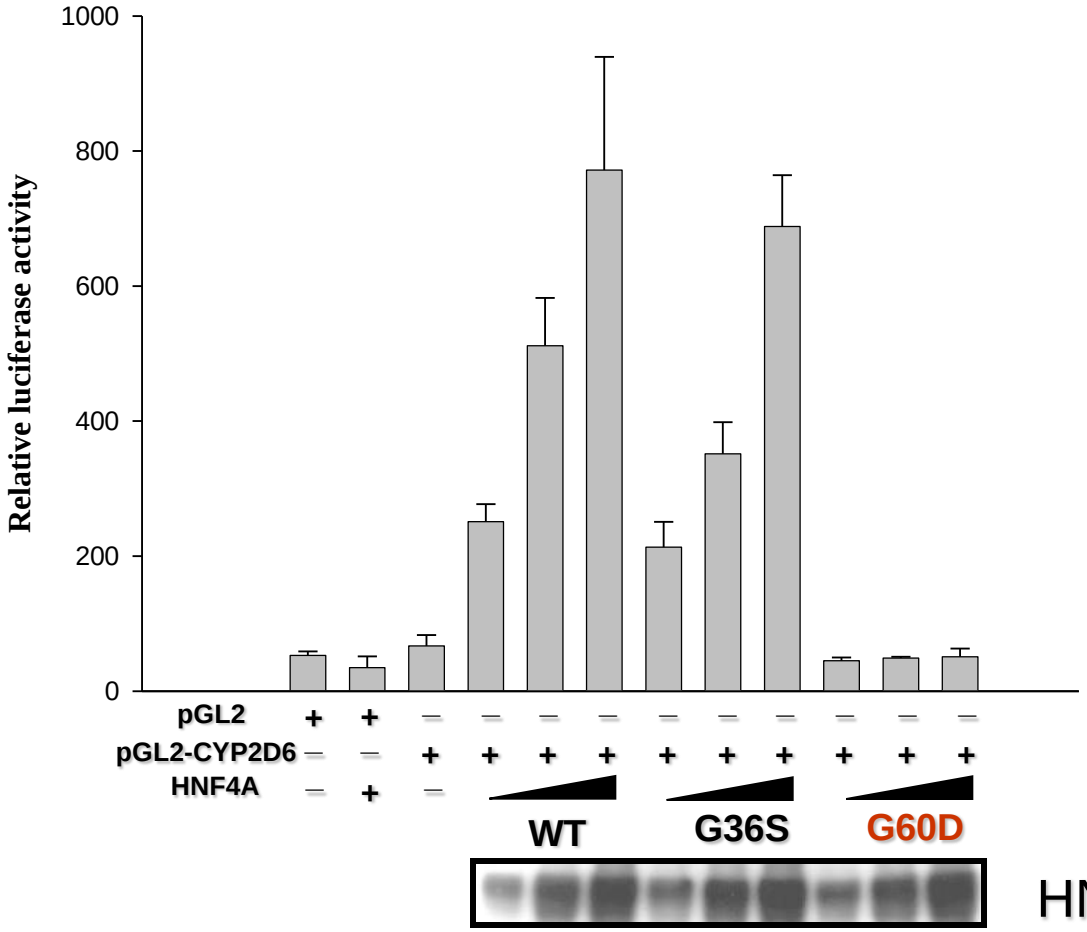
Position	Location	Effect	Frequency(%)
-2130A>C	Promoter		1
-2003G>A	Promoter		19
-2002T>C	Promoter		2
-1650A>G	Promoter		25
-1461C>T	Promoter		2
-1072C>G	Promoter		1
-1048GGG>delGGG	Promoter		37
-755A>C	Promoter		19
4654C>T	IVS2-5		2
4676G>A	Exon2+18	G36S	3.8
4749G>A	Exon2+91	G60D	1.3
4768G>C	Exon2+110	S66S	3
28152G>T	Exon10+1189	P428P	1
28278G>A	IVS10+1315		1
28421G>A	IVS10+1343		4
29172A>C	IVS10+2209		51

- 22 SNPs in HNF4α genes
  (exon: 4, intron: 8, promoter: 8)
- HNF4α G36S and G60D are nove
  HNF4α variants
  G36S (3.8% in 612 subjects)
  G60D (1.3% in 612 subjects)

Genetic variants of HNF4α: minor, but may contribute to fine tuning of CYP2D6 genotype-phenotype prediction

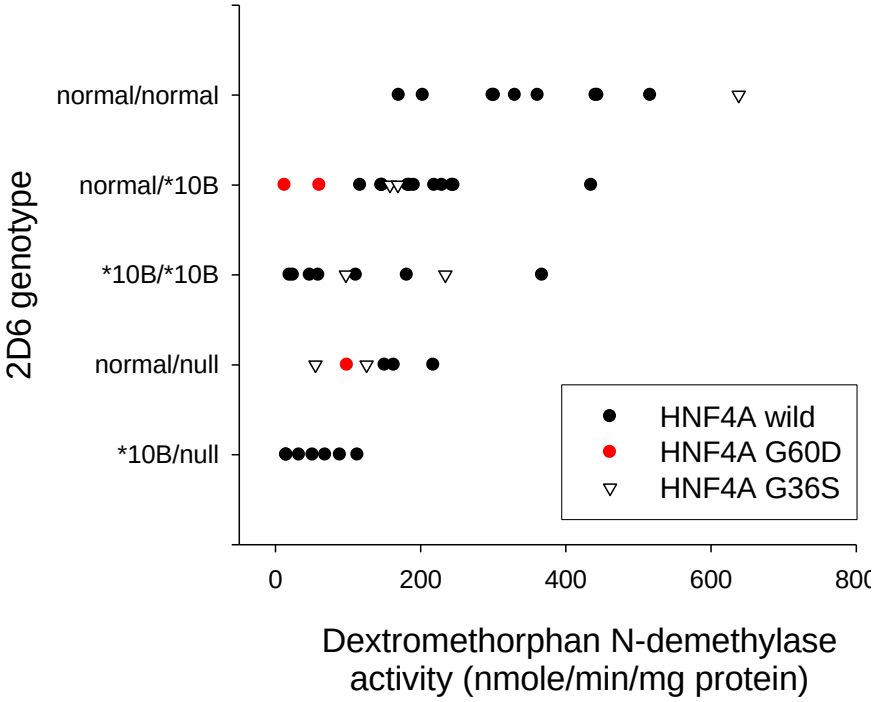
Lee SS, Shin JG et al. Hepatology, 2008

No Transactivation activity of HNF4α variants from the CYP2D6 promoter assay

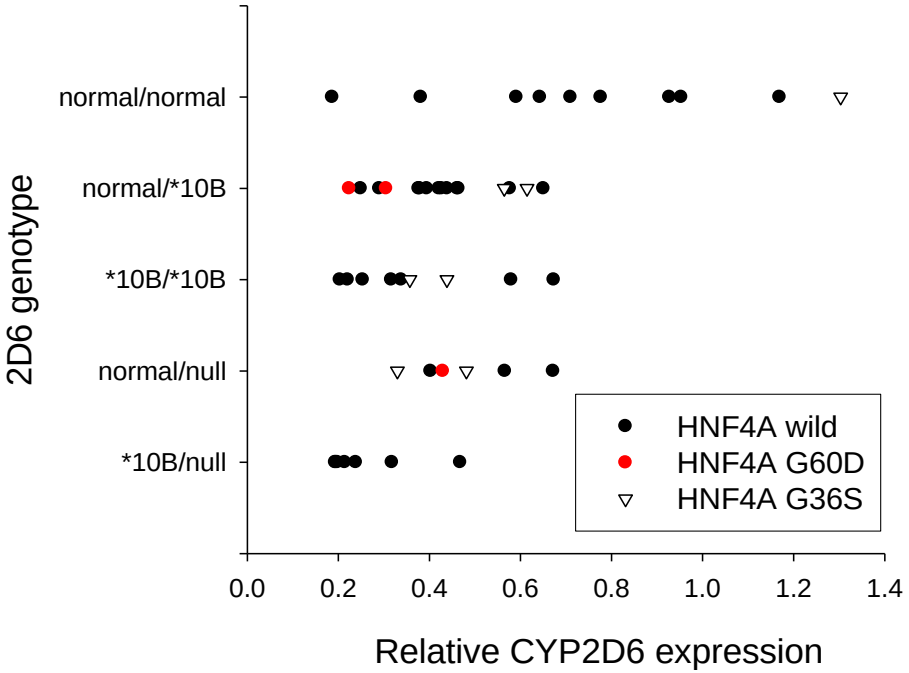


Effect of HNF4a G60D variant on CYP2D6 function in human liver tissues

CYP2D6 Activity *in vitro*

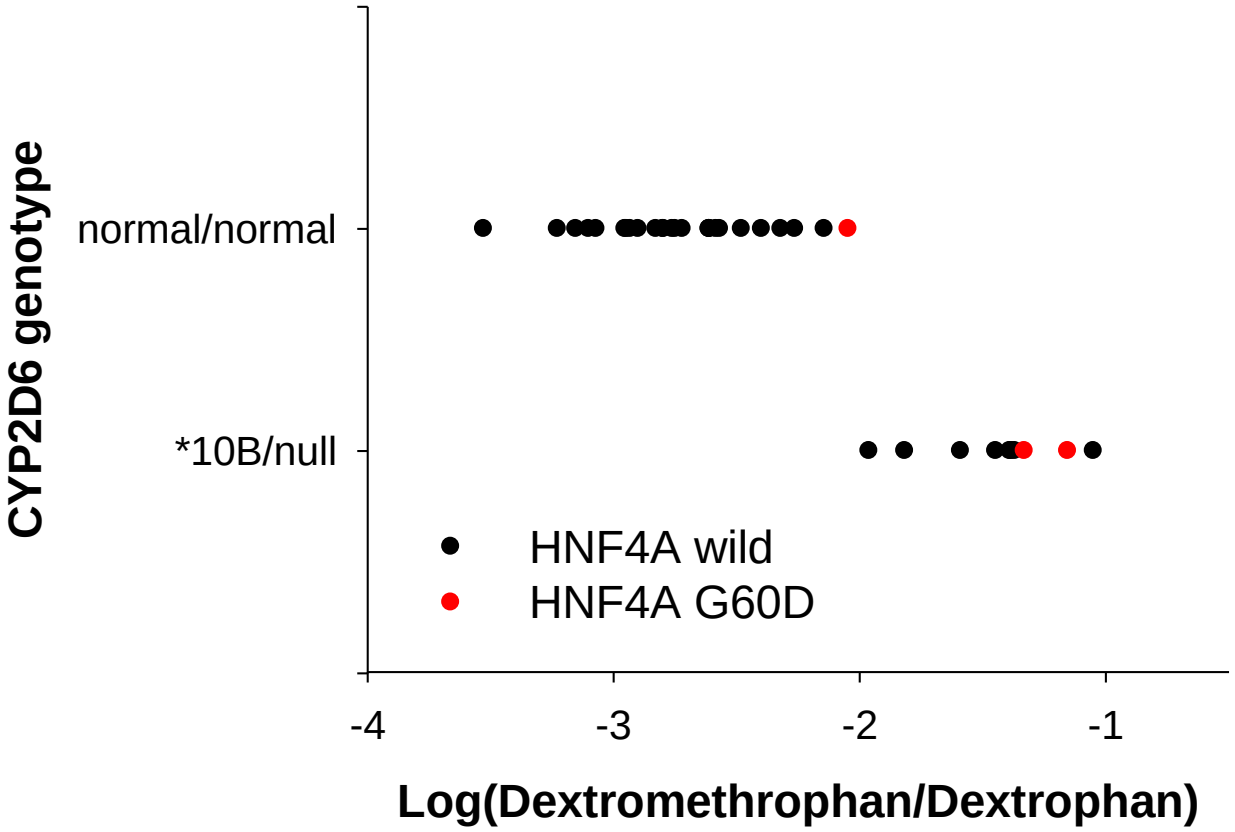


CYP2D6 Expression



tendency of decreased activity and reduced expression of CYP2D6 of liver tissue with HNF4α G60D variant

Effect of HNF4a G60D variant on CYP2D6 activity *in vivo*



tendency of decreased CYP2D6 activity *in vivo* in subjects with HNF4α G60D

Ethnic difference of HNF4α G36S and G60D Variants

Population	n	Allelic Frequency (%)	
		G36S	G60D
Korean	612	3.8	1.3
Chinese	94	1.1	0.5
Vietnamese	139	3.6	0.7

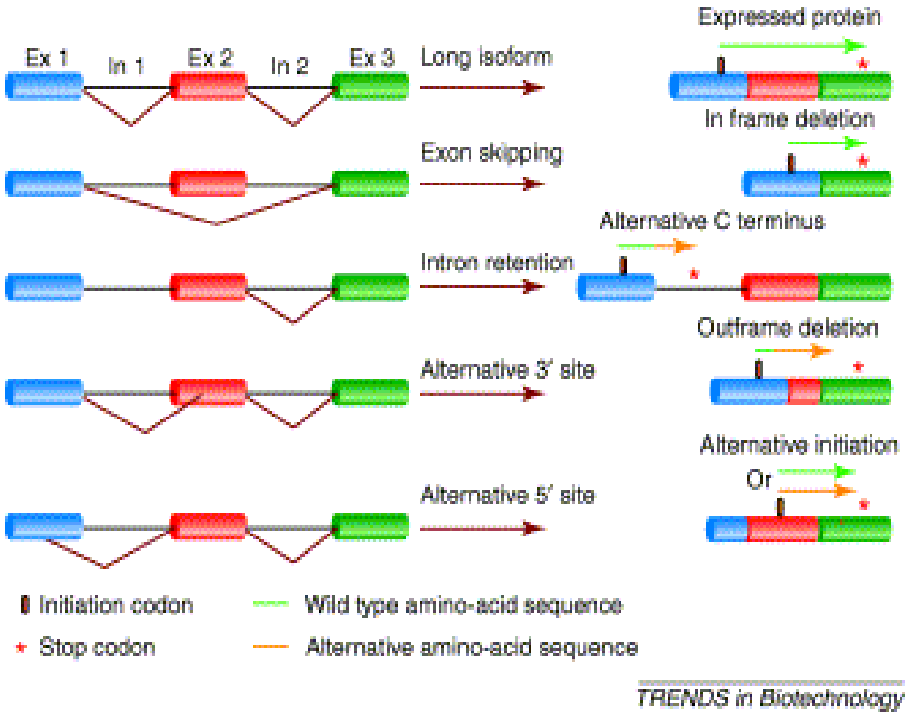
Minor allelic variant, but a nuclear receptor HNF4α genetic variant may cause the altered transcription of downstream gene CYP2D6.

- ☞ **may contribute in part to the ethnic difference in genotype to phenotype prediction**

Alternative splicing variant:

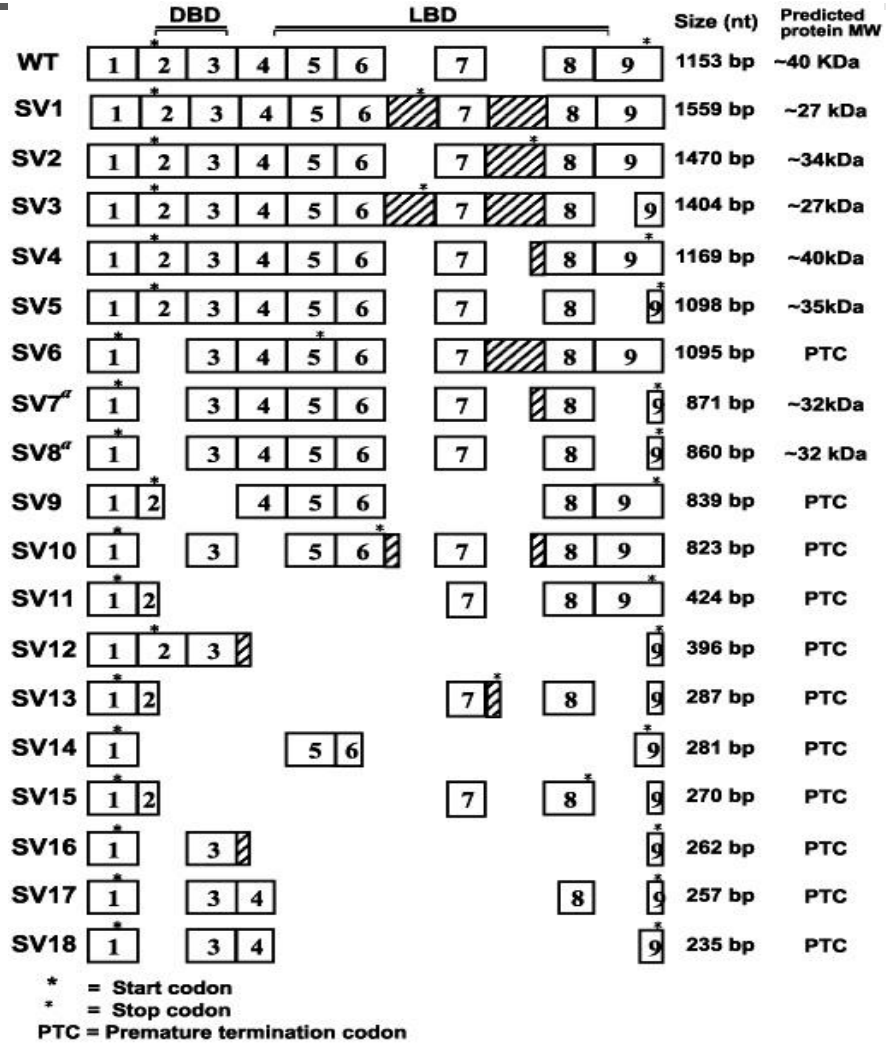
another potential of being confounder for genotype-phenotype prediction

- A major factor of post transcriptional regulation
- increase complexity (mutiple protein isoforms from a single gene)
- 30–65% of human genes are alternatively spliced
- can lead to qualitative changes in protein sequence
- can lead to quantitative changes of functional protein
- the types of alternative splicing that have been observed include ①exon skipping, ②intron retention and ③use of alternative splice donor or acceptor site



ASV of Constitutive Androstane Receptor (CAR) : identification from Korean liver tissues

Novel ASVs



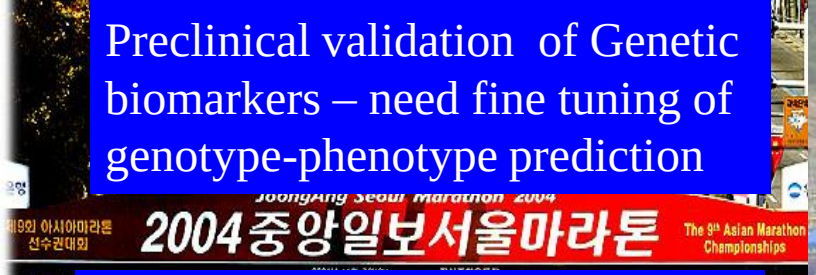
- ✓ 18 hCAR splicing variants (SVs)
- ✓ including 4 novel
- ✓ identified from 30 Korean human liver tissues

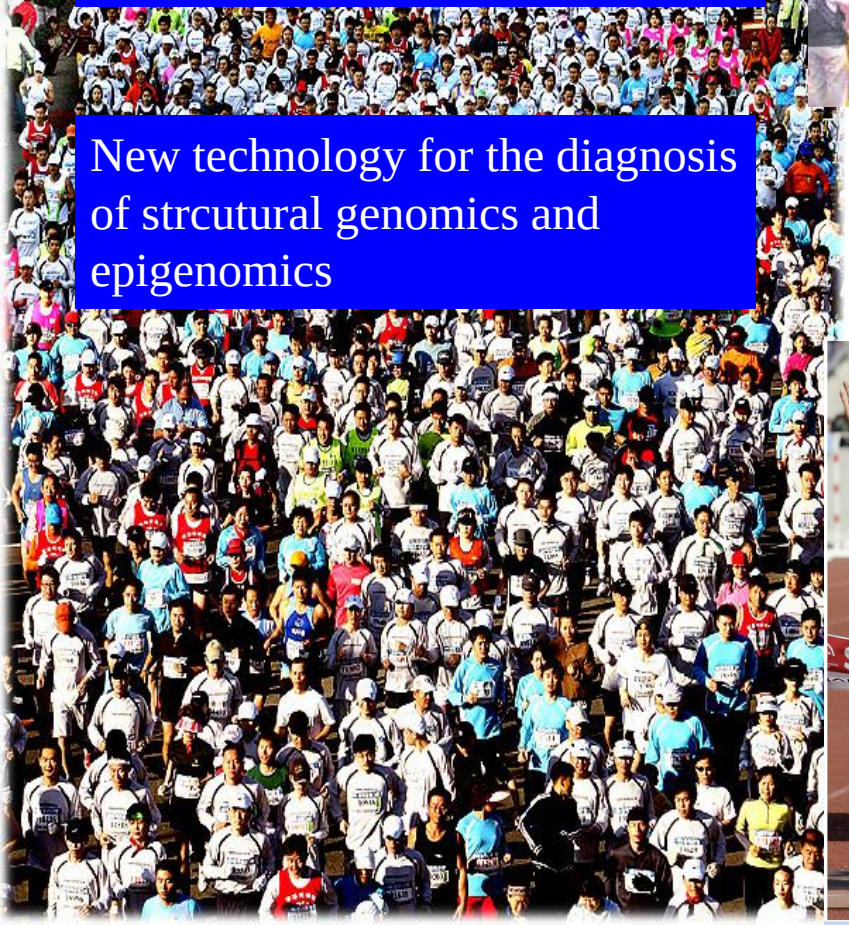
Preclinical validation of Genetic biomarkers – need fine tuning of genotype-phenotype prediction

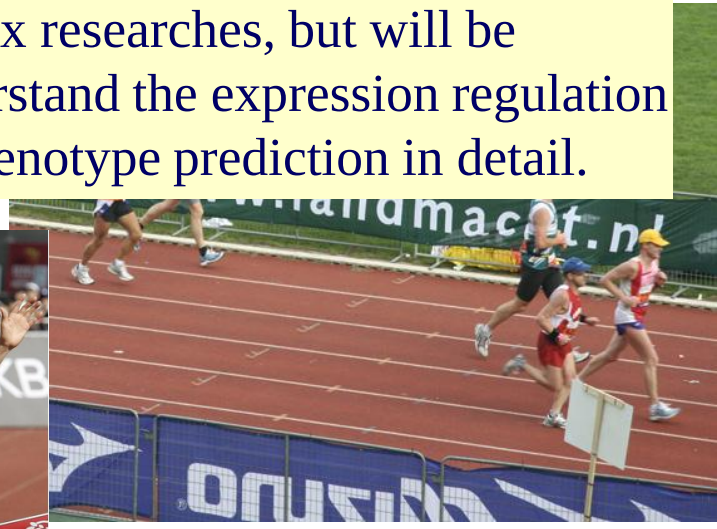
Identification of additional genetic biomarkers which may confound the genotype-phenotype prediction: expressional regulation

New technology for the diagnosis of strcutural genomics and epigenomics

Long tail of PGx researches, but will be helpful to understand the expression regulation of genotype-phenotype prediction in detail.

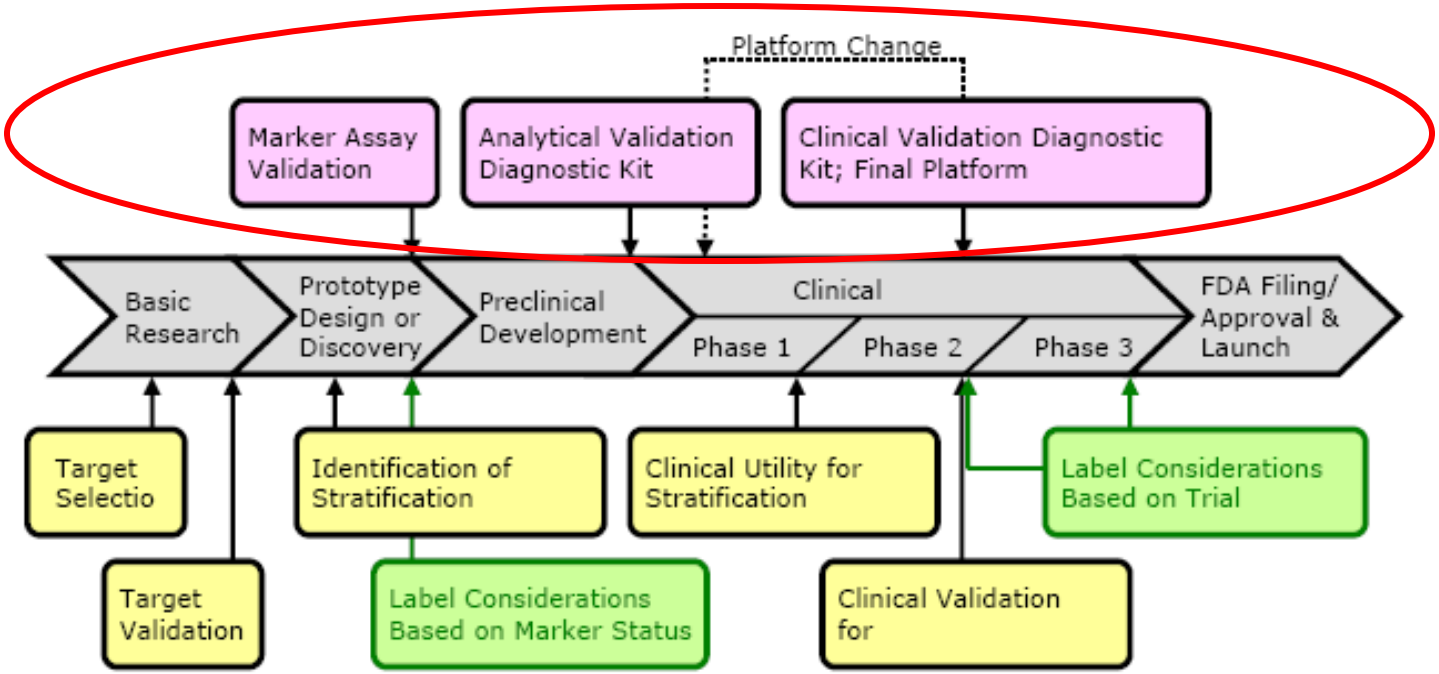






Validation issues of Companion Diagnostics

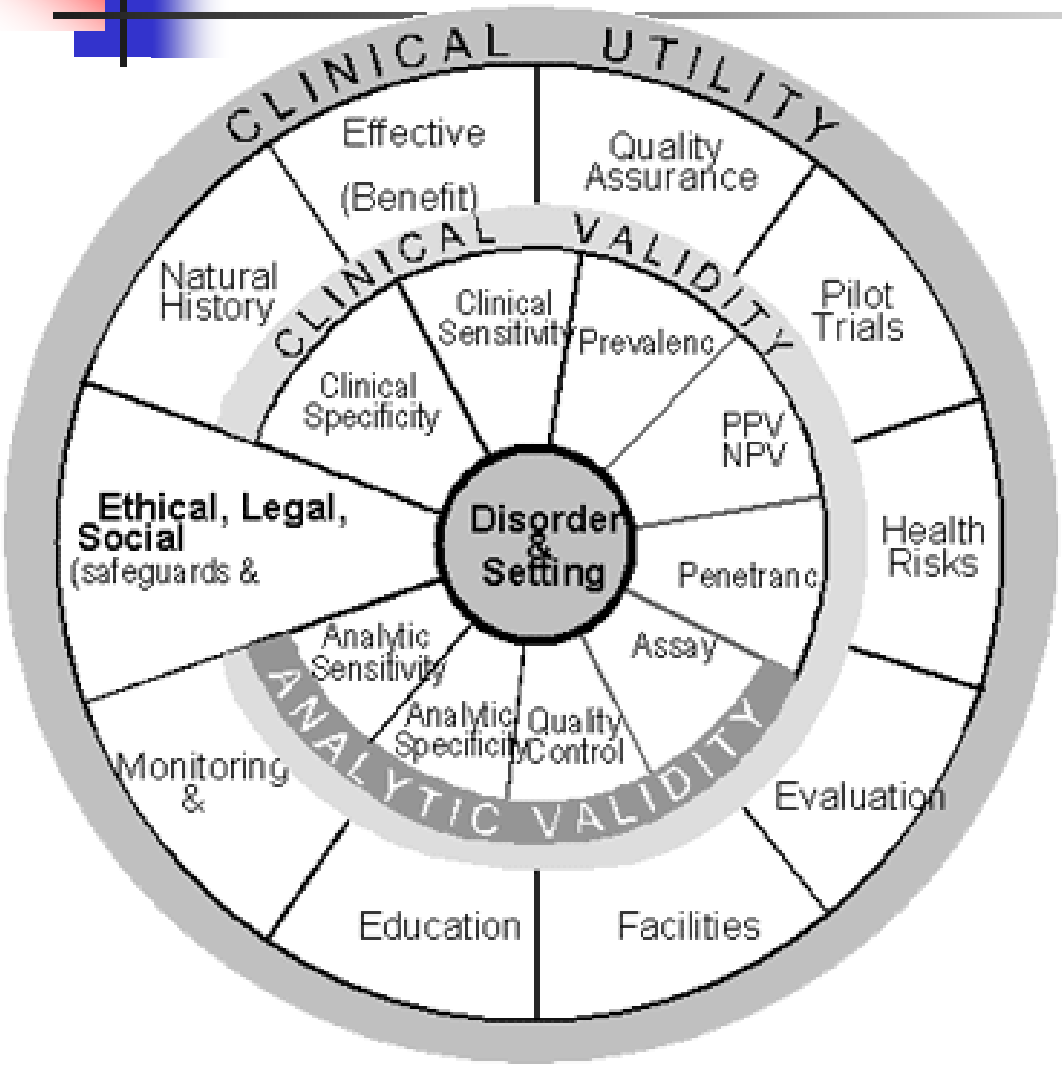
Drug-Device Co-Development Process in relation to PGt/PGx



Drug-Device Co-Development Concept Paper, April 2005

ACCE model for Evaluation of Genetic Testing

- to be applied to clinical practice of personalized pharmacotherapy



ACCE: from 4 component of evaluation
- Analytic validity, Clinical validity, Clinical utility, and associated Ethical, Legal, and Social implication

The process includes collecting, evaluating, interpreting, and reporting about DNA testing for disorders with genetic component.

Policy maker access to up-to-date and reliable information for decision making.

CDC-sponsored project carried out by Foundation of Blood Research

Ethnic specific *in vitro* diagnostic tool for better genotype-phenotype prediction

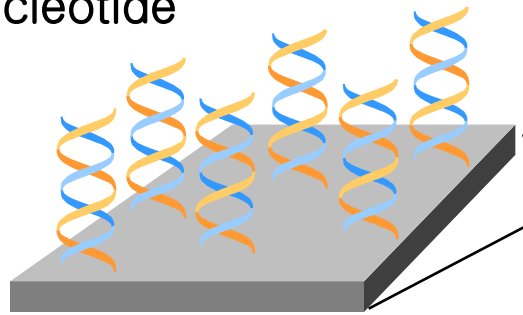
Roche AmpliChip™ CYP450 Microarray

The first in vitro diagnostic-approved microarray for clinical pharmacogenetics

- *CYP2D6* and/or *CYP2C19* genotyping

- Powered by Affymetrix GeneChip® technology

Each probe cell or feature
Contains millions of copies
Of a specific oligonucleotide



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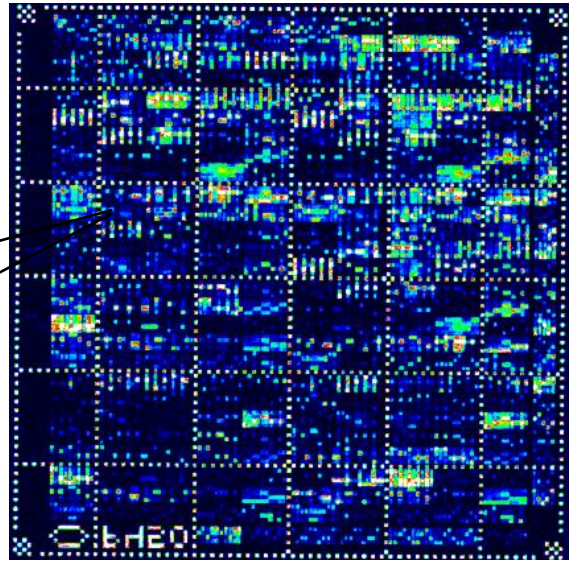


Ethnic Difference in CYP2D6 Allelic Frequencies

Allele	Predicted Enzymatic Activity	Japan	China	Caucasian EU	Caucasian US	Black American	Black African	Amerindian	Saudi Arabia	Turkey
*1	Normal	42-43%	23%	33-37%	37-40%	29-34%	28-56%	66%	*	37%
*2	Normal	9-13%	20%	22-33%	26-34%	20-27%	11-45%	19%	*	35%
*3	None	*	1%	1-4%	<2%	<1%	<1%	0%	*	0%
*4	None	<1%	0-1%	12-23%	18-23%	7-9%	1-7%	4%	4%	11%
*5	None	5-6%	6%	2-7%	2-4%	6-7%	1-6%	4%	<1%	15%
*6	None	*	*	<2%	1%	<1%	0%	1%	*	7%
*9	Reduced	*	*	0-3%	2-3%	<1%	0%	0%	*	<1%
*10	Reduced	39-41%	50-70%	1-2%	4-8%	3-8%	3-9%	1-17%	<1%	6%
*17	Reduced	*	*	<1%	*	15-26%	9-34%	*	<1%	<1%
*41	Reduced	*	*	20%	*	*	*	*	*	*
*1XN	Increased	<1%	*	<1%	<1%	1%	3%	*	*	<1%
*2XN	Increased	<1%	1%	<2%	<1%	1%	3%	*	10%	<1%
*4XN	None	*	*	<1%	<1%	2%	1%	*	*	<1%

Note: Percentages represent ranges of allelic frequencies reported in published studies.
*No published data available

(AmpliChip package insert)

Only 27 CYP2D6 Alleles on AmpliChip CYP450 Test

Allele	1	2	3	4	5	6	7	8	9	10	11	15	17	19	20	29	35	36	40	41	1Xn	2Xn	4Xn	10Xn	17Xn	35Xn	41Xn
1	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	U	U	E	E	E	U	E
2		E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	U	U	E	E	E	U	E
3			P	P	P	P	P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I
4				P	P	P	P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I
5					P	P	P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I
6						P	P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I
7							P	P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I
8								P	I	I	P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I
9									I	I	I	I	I	I	I	I	E	I	I	I	E	E	I	I	I	E	I
10										I	I	I	I	I	I	I	E	I	I	I	E	E	I	I	I	E	I
11											P	P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I
15												P	I	P	P	I	E	I	P	I	E	E	P	I	I	E	I
17													I	I	I	I	E	I	I	I	E	E	I	I	I	E	I
19														P	P	I	E	I	P	I	E	E	P	I	I	E	I
20															P	I	E	I	P	I	E	E	P	I	I	E	I
29																I	E	I	I	I	E	E	I	I	I	E	I
35																	E	E	E	E	U	U	E	E	E	U	E
36																		I	I	I	E	E	I	I	I	E	I
40																			P	I	E	E	I	I	I	E	I
41																				I	E	E	I	I	I	E	I

E Extensive
I Intermediate
P Poor
U Ultrarapid
N Unknown

CYP450 Gene	Alleles Not Reported by AmpliChip CYP450 Test
CYP2C19	4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16
CYP2D6	12, 13, 14, 16, 18, 21, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 34, 37, 38, 39, 42, 43, 44, 45, 46

In Asians, rare alleles such as 14, 18, 21, 49, 52, and 60 are found.

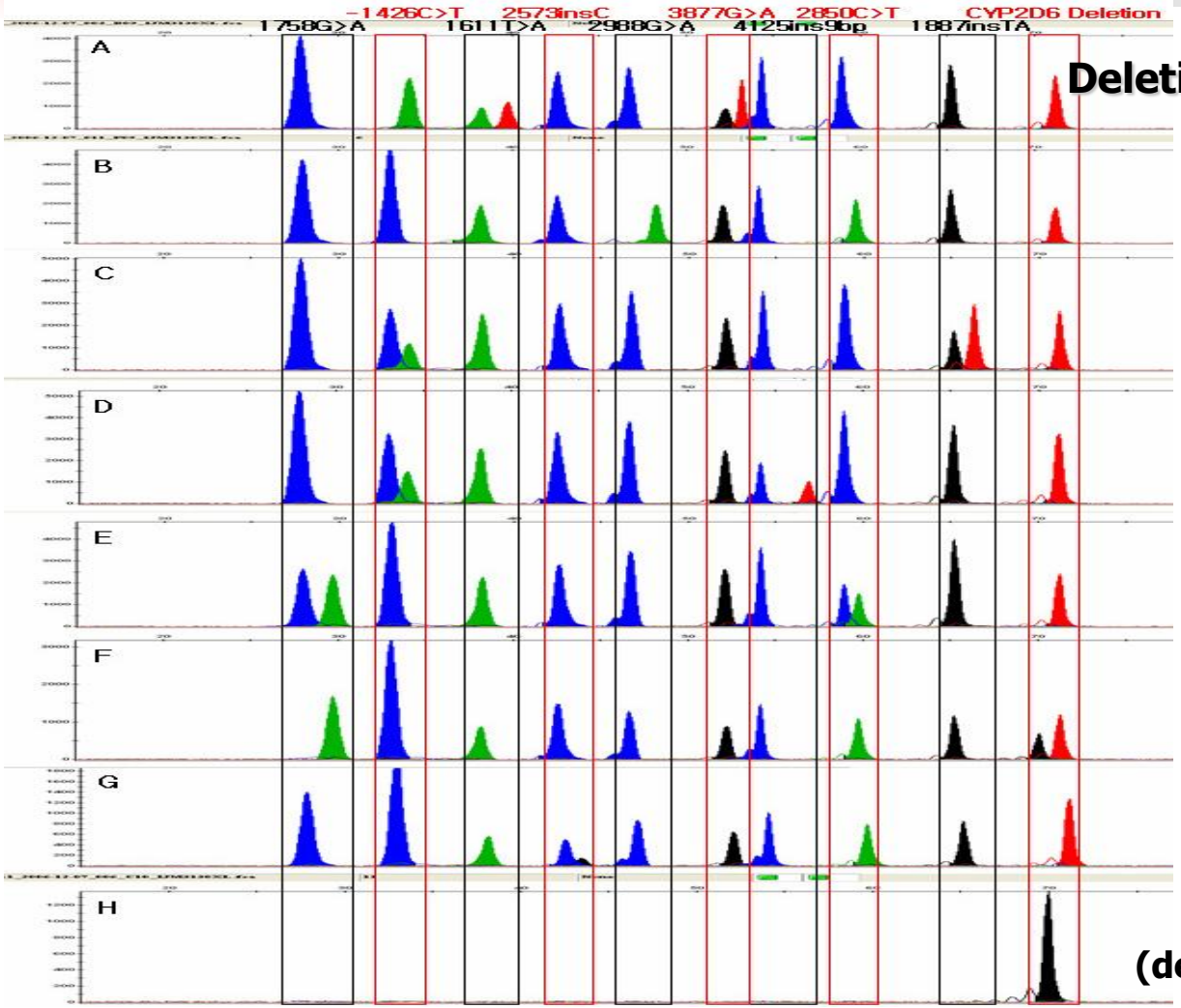
(AmpliChip package insert)

May need Ethnic Specific Diagnostics

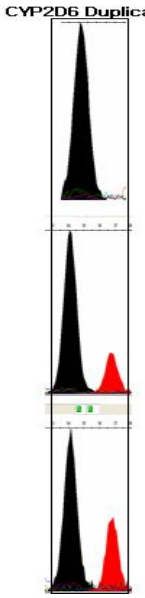
Roche chip dose not cover all of identified Korean CYP2D6 Alleles (data of PGRC, Inje Univ., n=758)

Allele	N	Allelic frequency (95% C.I.) (%)	Function
*1	489	32.32 (28.67-35.32)	Normal
*2	151	9.89 (7.76-12.01)	Normal
*5	85	5.61 (3.97-7.24)	None
*10	691	45.58 (42.03-49.12)	Decrease
*14	5	0.33 (0.00-0.73)	None
*18	4	0.26 (0.00-0.62)	None
*21	5	0.33 (0.00-0.73)	None
*41	34	2.24 (1.34-3.53)	Decrease
*49	21	1.39 (0.55-2.22)	Decrease
*52	5	0.33 (0.00-0.73)	Dec/Inc
*60	1	0.07 (0.00-0.26)	None
*1N	2	0.07 (0.00-0.26)	Increase
*2N	15	0.99 (0.28-0.16)	Increase

Multiplex SNaPshot Analysis of CYP2D6 for Far Eastern Asians (Koreans)



Deletion



Duplication

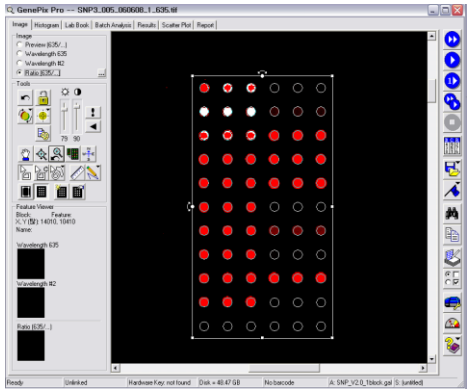
11 SNP Multiplex

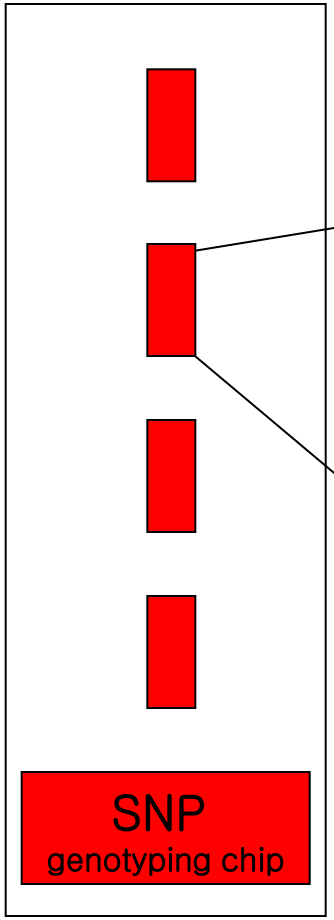
in 2 tubes

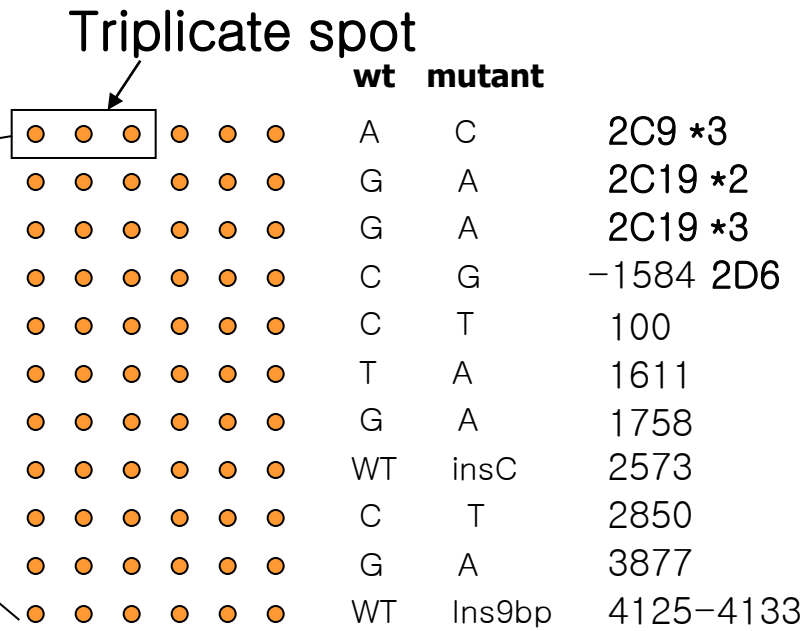
Copy number assay

(developed and patented by PGRC)

Development of *In vitro* diagnostic chip for CYP450 specific for Far Eastern Asian populations



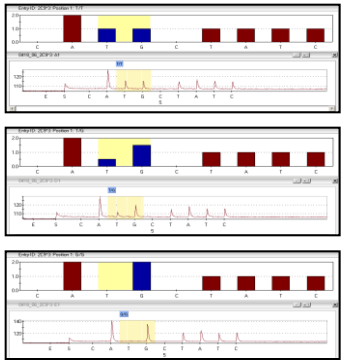




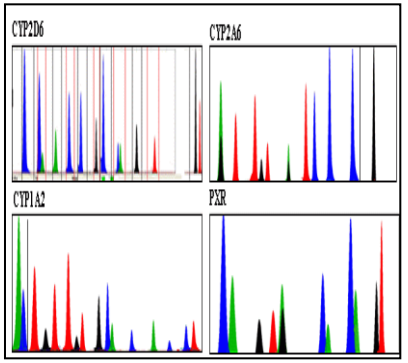
SNP chip format

Inje PGRC Technology Platform for Genotyping

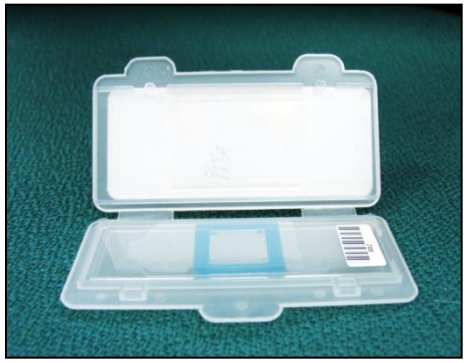
Pyrosequencing

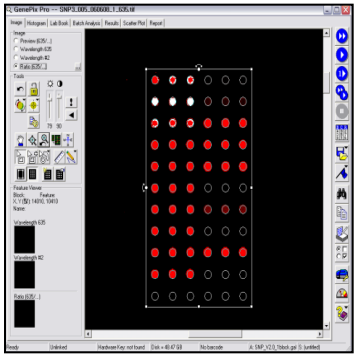


Snapshot

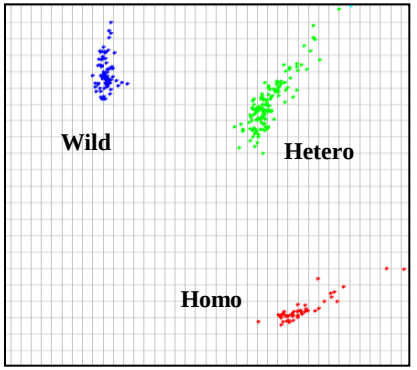


DNA chip





Real time PCR



List of genotype method established in PGRC (in part)

CYP450s

Gene	Assay Variants	No	All SNPs	Genotyping method
CYP1A2	*1C*1D,*1E,*1F,-3860G>A, -3598G>T, -3594T>G, -3113G>A, -2847T>C, -2808A>C, -2603A7>A8, -2467T>delT, -1708T>C, -739T>G, -163C>A	11	17	SNaPshot, RFLP
CYP2A6	*1B,*4,*5,*7,*8,*9,*10,*11,*13,*15,*29,*30,567C>T	11	21	SNaPshot, RFLP
CYP2B6	*4,*5,*6,*7,*9	5	17	Pyrosequencing, RFLP
CYP2S1	*4, *5A, *5B	2	10	Pyrosequencing
CYP2C8	*11	1	17	Pyrosequencing
CYP2C9	*2,*3,*13,*14, A161P	5	18	Pyrosequencing, TaqMan, RFLP
CYP2C19	*2,*3,*17	3	15	Pyrosequencing, TaqMan, RFLP
CYP2D6	*2,*5,*10B,*14B,*18,*21B,*41A,*49, *52,*60,*1N,*2N,*10BN	11	38	SNaPshot, Pyrosequencing, RFLP
CYP2D7	138delT	1	1	Pyrosequencing
CYP2J2	*7,*8,*9	3	12	Pyrosequencing, RFLP
CYP3A4	*4,*5,*6,*11,*16,*18	6	4	Pyrosequencing
CYP3A5	*3	1	1	Pyrosequencing
CYP3A7	*2,*3	2	13	Pyrosequencing
CYP7A1	-267C>A	1	9	Pyrosequencing

5 ~ >10 SNPs: SNaPshot, RFLP, Sequencing
1 ~ 5 SNPs: Pyrosequencing, TaqMan, RFLP

List of Genotyping method established in PGRC (in part)

Phase II, Transporters, and Regulators

Gene	Assay Variants	No	All SNPs	Genotyping method
UGT1A type	1A1*6, *17, *18, *60,1A1-233C/T, 1A4-142T/G,292C/T,1A7-701T/C	>10	67	Pyrosequencin, SNaPshot, Sequencing
SULT1A2	G110A, G148A, G649T, C804A	4	21	Pyrosequencing
SULT1A1	*2	1	30	Pyrosequencing
TPMT	*3B,*3C,*2,*6	4	4	Pyrosequencing
FMO3	K158E,E308G	2	2	RFLP
POR	-1822A>G, 26367A>G, A503V, L577P	4	24	Pyrosequencing, RFLP
VKORC1	-1639G>A, 1173T>C, 3730G>C	3	4	Pyrosequencing
MDR1	2677G/A/T, 3435C/T	2	3	Pyrosequencing, RFLP
BCRP	V12M, Q126Stop,Q141K,P269S	4	20	Pyrosequencing
OCT1	P283L, P341L	2	13	Pyrosequencing
OCT2	T199I, T201M, A270S	3	11	Pyrosequencing
NTCP	A64T	1	6	Pyrosequencing
OAT1	R50H, R293W, R454Q	3	9	Pyrosequencing
OATP-C	388A>G, 521C>T	2	2	Pyrosequencing
PXR	-25385C>T'-24113G>A, 7635A>G, 8055C>T, 11156A>C, 11193T>C	6	12	SNaPshot
HNF4	4676G>A, 4749G>A	2	20	Pyrosequencing

>200 variants from UGT2B7, UGT2B15, SULT1E1, FXR, LXR, HNF1, HNF6A, SHP, CAR, HIF1A, OCT3, ASBT, OAT2, OAT7, ENT1, ENT2, CNT1, CNT2, CNT3, etc

Ethnic Difference of PGx

– what about within Asian Populations?

Drug product labeling includes ethnicity factor

Table 1 Examples of recent FDA drug product labeling that included ethnicity or genetic information

Therapeutic area	Drug products: generic (brand) names	Ethnicity information	Genetics information
Cardiorenal	Isosorbide dinitrate–hydralazine (BiDil)	Indicated for self-identified blacks	
	Angiotensin II antagonists and ACE inhibitors	Smaller effects in blacks[a]	
Metabolic	Rosuvastatin (Crestor)	Lower dose for Asians	
Transplant	Azathioprine (Imuran)		Dose adjustments for TPMT variants
	Tacrolimus (Protopic)	Higher dose for blacks	
Oncology	Trastuzumab (Herceptin)		Indicated for HER2 overexpression
	Irinotecan (Camptosar)		Dose reduction for *UGT1A1*28*
	6-Mercaptopurine (Purinethol)		Dose adjustments for TPMT variants
	Erlotinib (Tarceva)		Different survival and tumor response in EGFR-positive and -negative patients reported
Antiviral	Maraviroc (Selzentry)		Indicated for CCR5-positive patients
	Oseltamivir (Tamiflu)	Neuropsychiatric events mostly reported in Japan	
	Abacavir (Ziagen)		Boxed warning for HLA-B*5701 allele
Pain	Codeine		Warnings for nursing mothers that CYP2D6 UM metabolized codeine to morphine more rapidly and completely[b]
Hematology	Warfarin (Coumadin)	Lower dose for Asians	Lower initial dose for CYP2C9- and VKORC1-sensitive variants
Psychopharmacological	Thioridazine (Mellaril)		Contraindication for CYP2D6 PM
	Atomoxetine (Strattera)		Dosage adjustments for CYP2D6 PM; no drug interactions with strong CYP2D6 inhibitors expected for PM
Neuropharmacological	Carbamazepine (Tegretol)	Box warning for Asians with variant alleles of *HLA-B*1502*	Box warning for Asians with variant alleles of *HLA-B*1502*

ACE, angiotensin-converting enzyme; CCR5, chemokine (C-C motif) receptor 5; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; PM, poor metabolizer; TPMT, thiopurine methyl transferase; UGT, uridine diphosphate glucuronosyl transferase; UM, ultra-rapid metabolizer; VKORC, vitamin K reductase complex. Data from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.

[a]A general statement in the candesartan (Atacand) labeling. [b]http://www.fda.gov/cder/drug/infopage/codeine/default.htm.

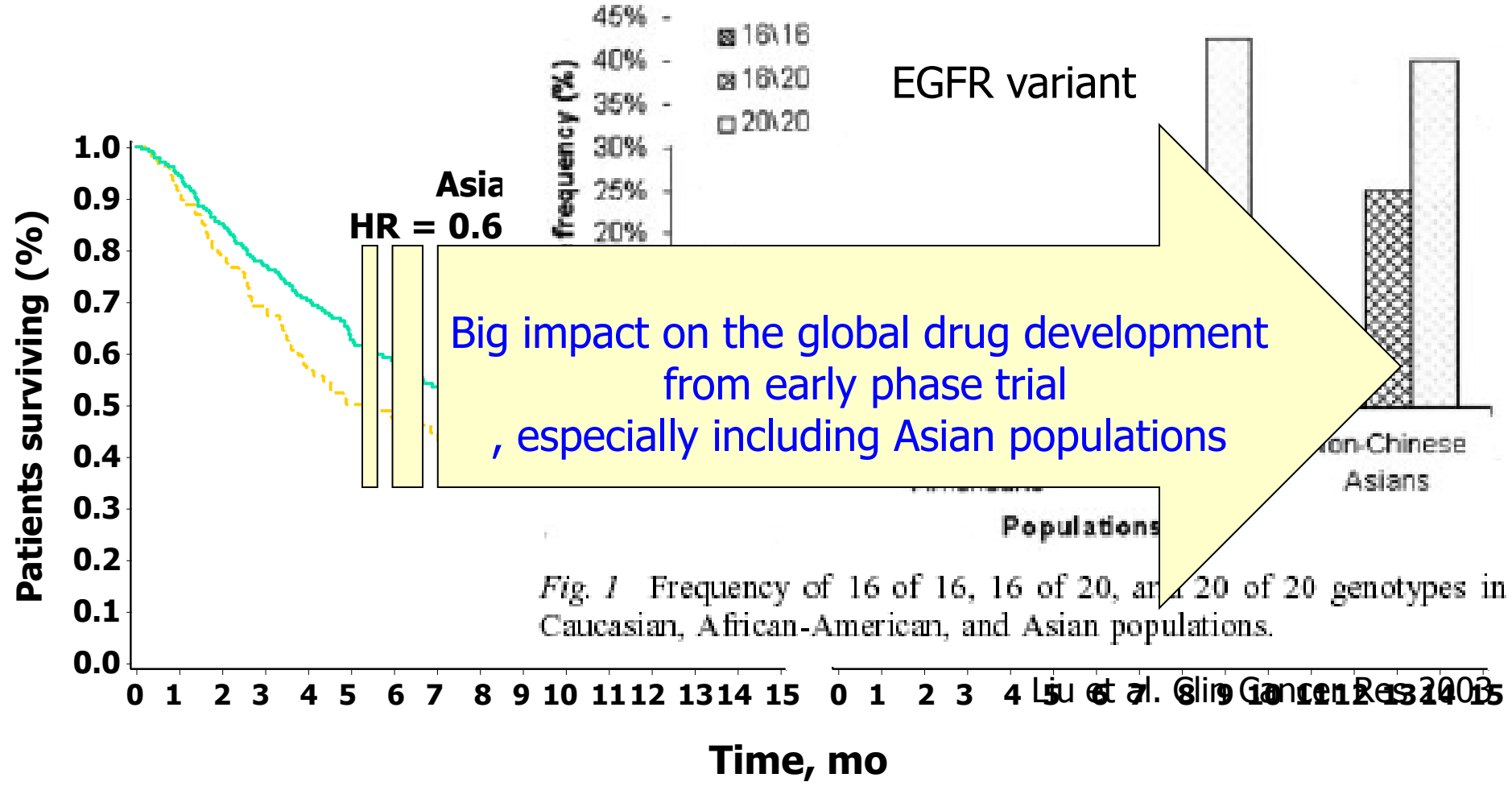
Huang S-M and Temple R, Clin Pharmacol & Ther 2008. 84; 287~294

Ethnic Drug: BiDil®

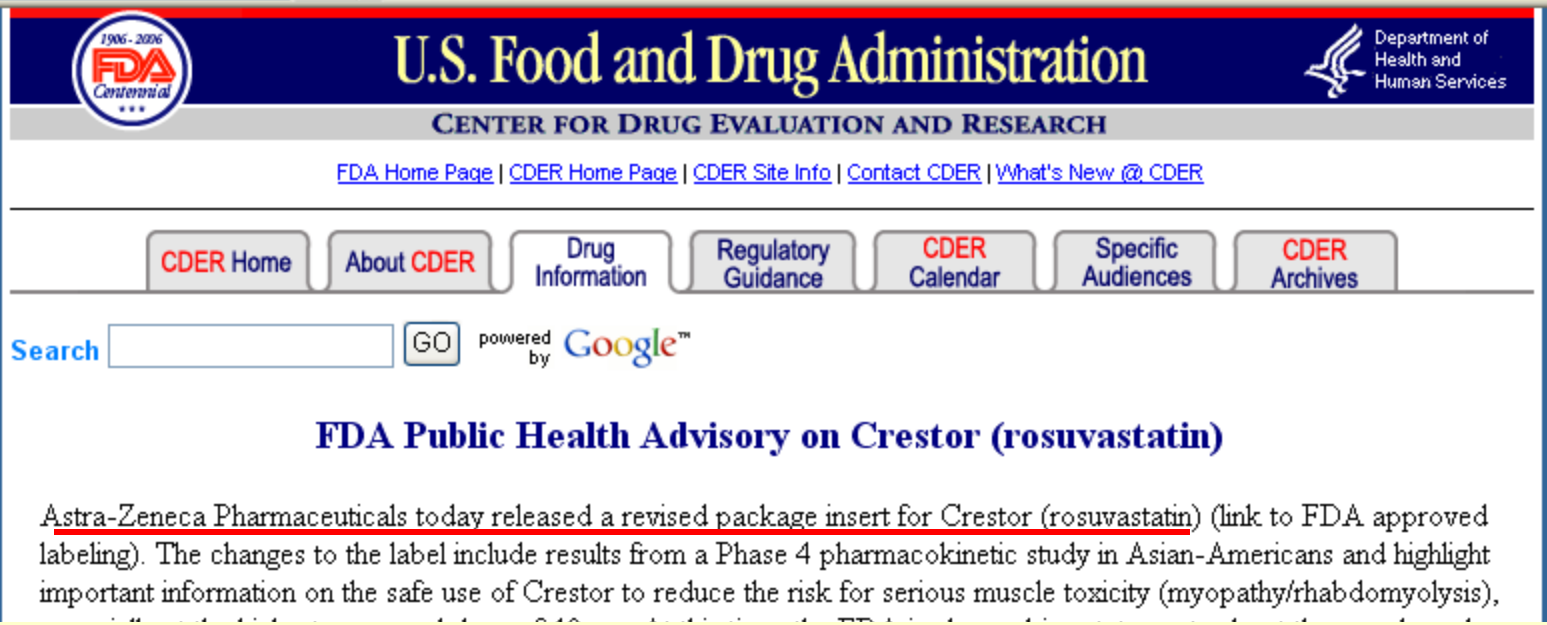
Aldosterone synthase –344 C>T,
ß-ad receptor Gly386Arg
NOS3

BiDil: isosorbide dinitrate/hydralazi

Survival by Ethnic Origin
– Gefitinib (Iressa®)



Ethnic issues in different dose regimen



(F) 편집(E) 보기(V) 즐겨찾기(A) 도구(T) 도움말(H)

뒤로

http://www.fda.gov/cder/drug/advisory/crestor_3_2005.htm

검색 G마켓 야후! 월드컵 많이 본 뉴스 스포츠 금융 무료검사 게임

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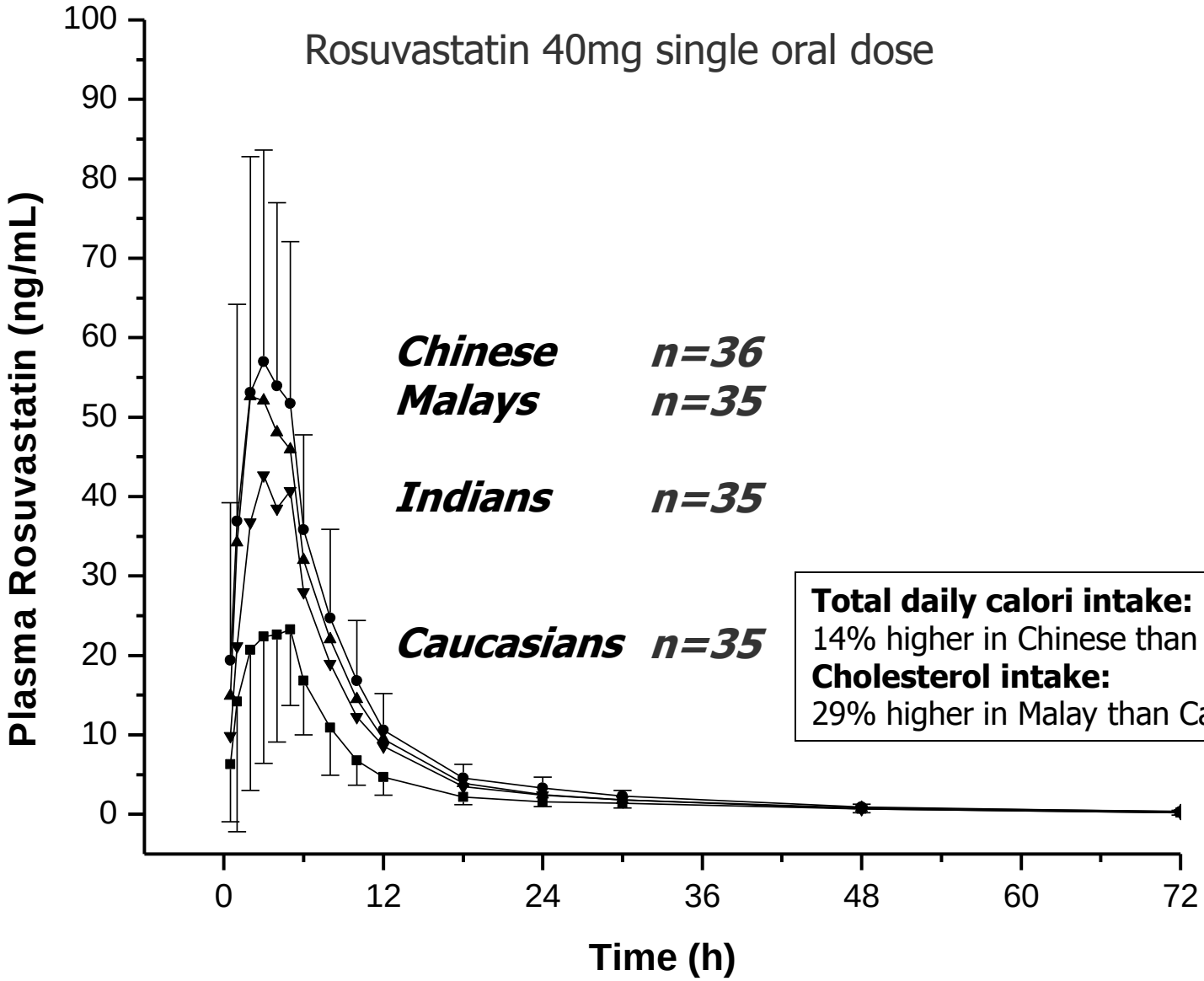
FDA Public Health Advisory on Crestor (rosuvastatin)

Astra-Zeneca Pharmaceuticals today released a revised package insert for Crestor (rosuvastatin) (link to FDA approved labeling). The changes to the label include results from a Phase 4 pharmacokinetic study in Asian-Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis),

Description of current changes to the Crestor label

In a pharmacokinetic study involving a diverse population of Asians residing in the United States, rosuvastatin drug levels were found to be elevated approximately 2-fold compared with a Caucasian control group. As a result of these findings, the “Dosage and Administration” section of the label now states that the 5 mg dose of Crestor should be considered as the start dose for Asian patients and any increase in dose should take into consideration the increased drug

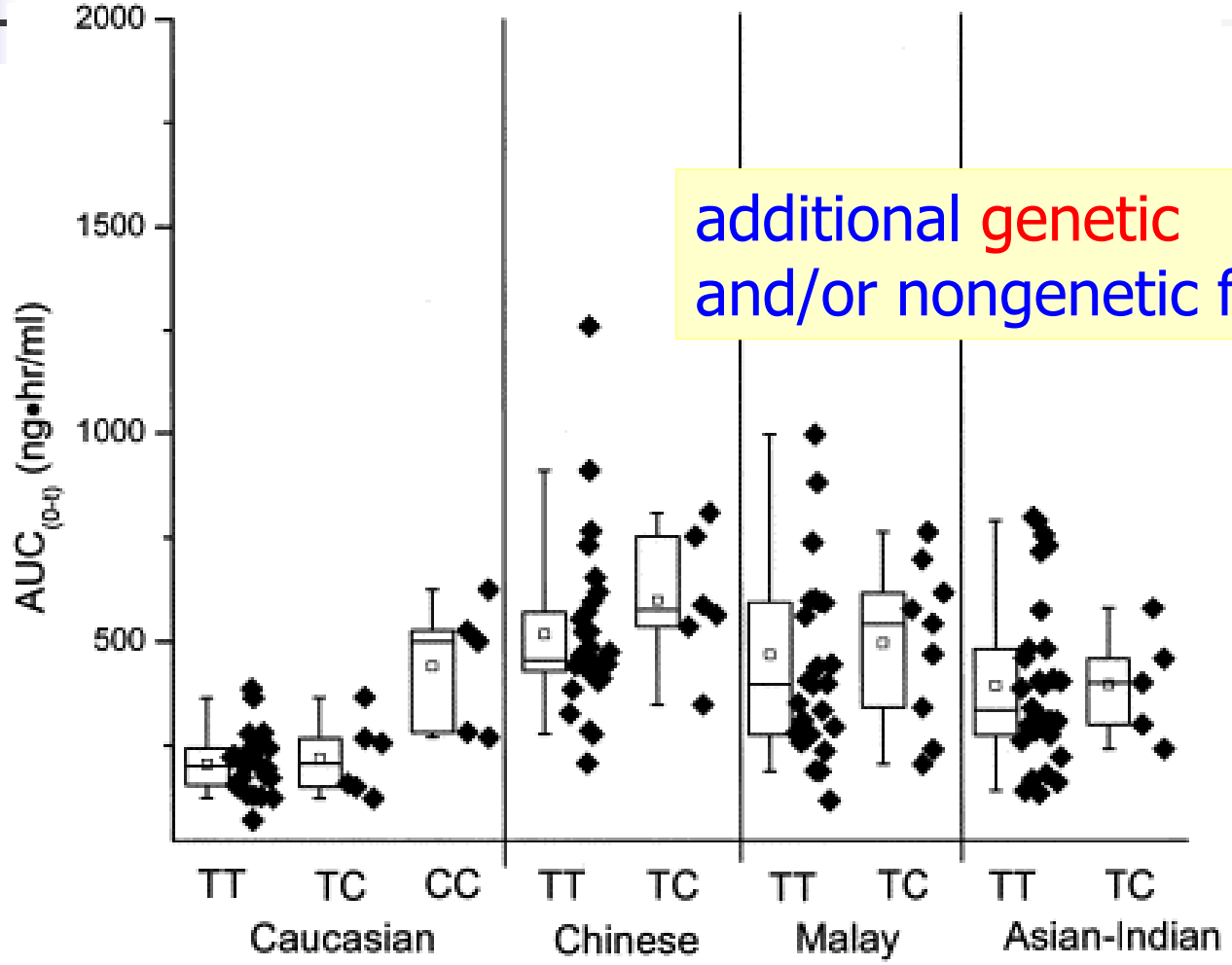
Ethnic Difference of Rosuvastatin PKs between White and Asian Subjects Residing in the Same Environment



Total daily calori intake:
14% higher in Chinese than Caucasian subjects
Cholesterol intake:
29% higher in Malay than Caucasian subjects

Lee et al. CP&T 2005;78(4):330-41

Comparison of Rosuvastatin pharmacokinetics among Caucasian and Asian subjects in relation to SLCO1B1 genetic polymorphism

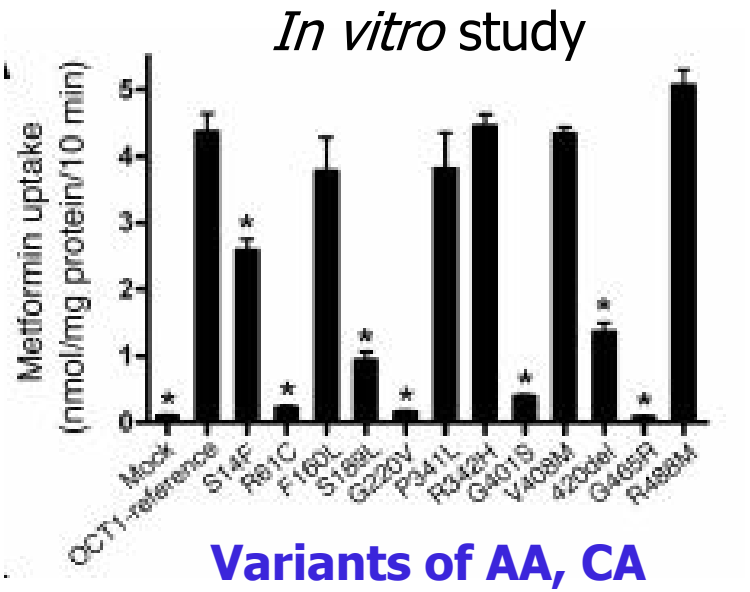


additional genetic
and/or nongenetic factors ??

Lee et al. CP&T 2005;78(4):330-41

Ethnic Differences of Functional SNPs of OCT1/2 (*SLC22A1/2*): composition and allelic frequency

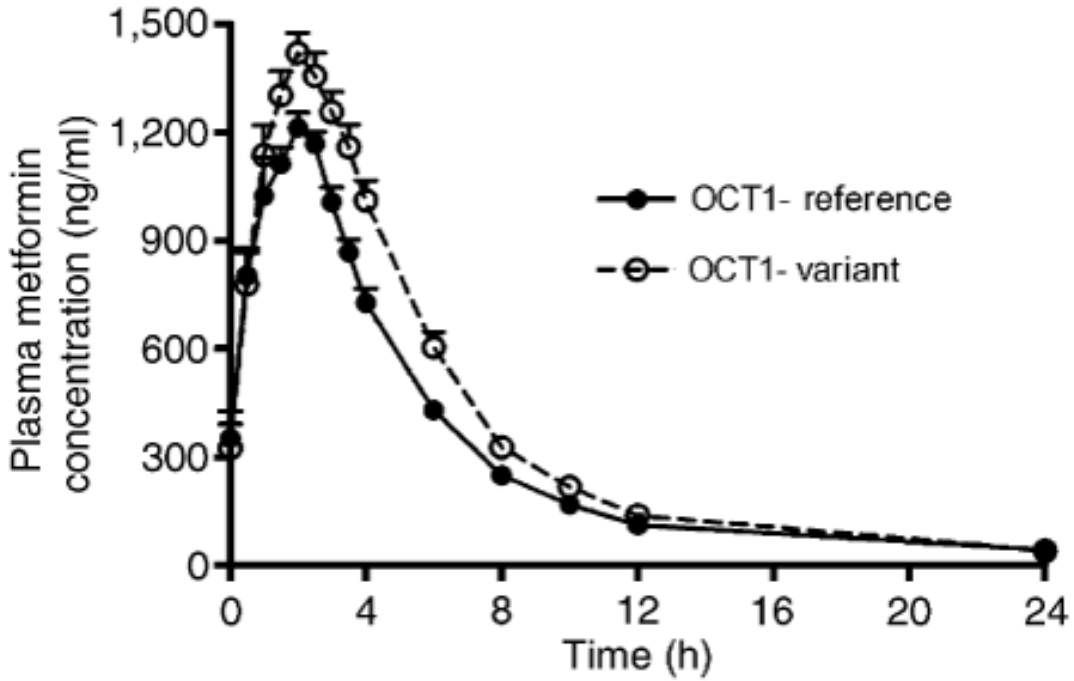
	AA change	Allele frequency (%)		
		[a] AA (n=200)	[a] CA (n=200)	[b] Korean (n=150)
OCT1 *(SLC22A1)*	S14F	3.1	0	0
	R61C	0	7.2	0
	S189L	0	0.5	0
	G220V	0.5	0	0
	G401S	0.7	1.1	0
	M420del	2.9	18.5	0
	G465R	0	4.0	0
OCT2 *(SLC22A2)*	T199I	0	0	0.7
	T201M	0	0	0.7
	A270S	11.0	15.7	11.0



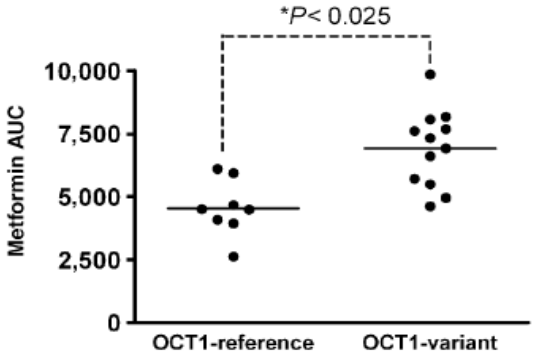
[a] PharmGKB, Shu et al., JCI, 2003
and Leabman et al., PGx, 2002

[b] PGRC,
Kang HJ, Shin JG et al., DMD, 2007

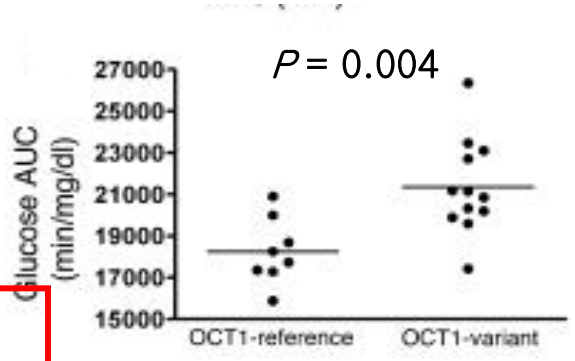
Effect of hOCT1 genetic variants (AA, CA) on metformin disposition



metformin AUC



Glucose AUC

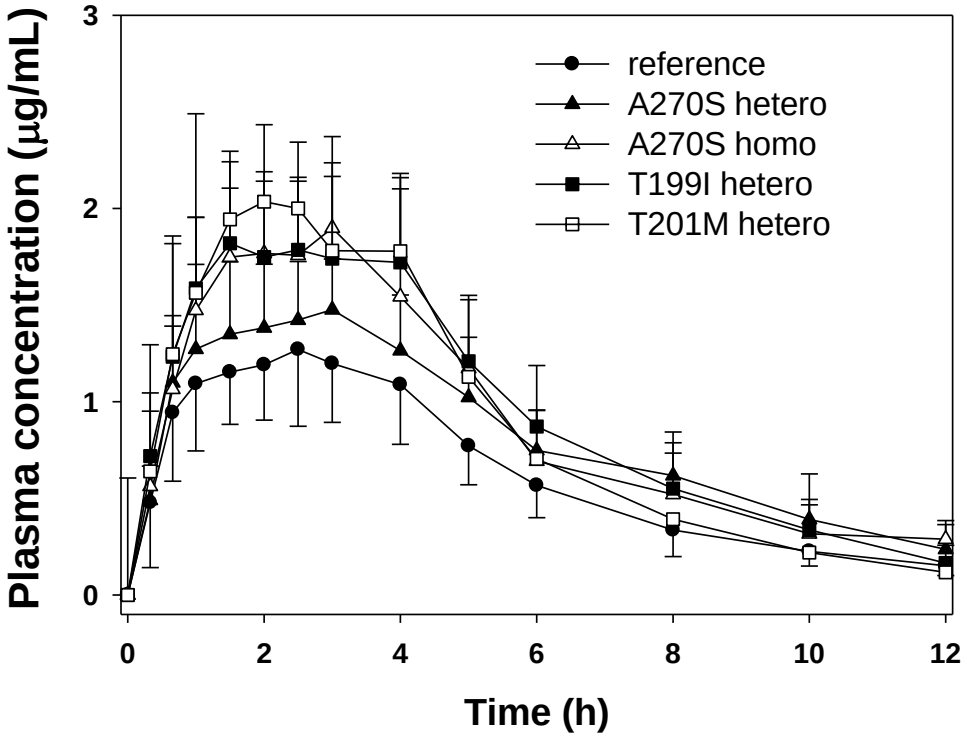


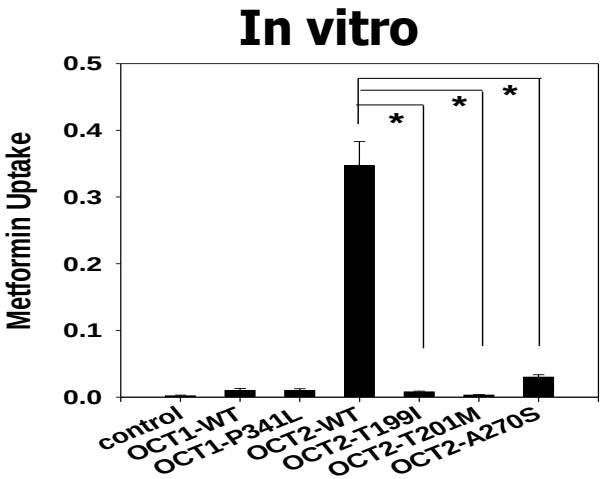
All these hOCT1 variants are not identified from Korean and other East Asian ethnic subjects.

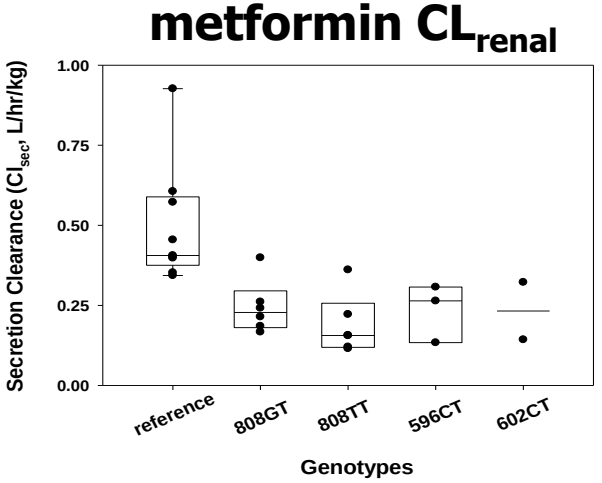
Shu et al., JCI, 2007 and CPT, 2008

In Korean, metformin disposition seems to be influenced by hOCT2 genetic polymorphism, not by hOCT1 genetic variants.

☞ because of their different genotype profile.



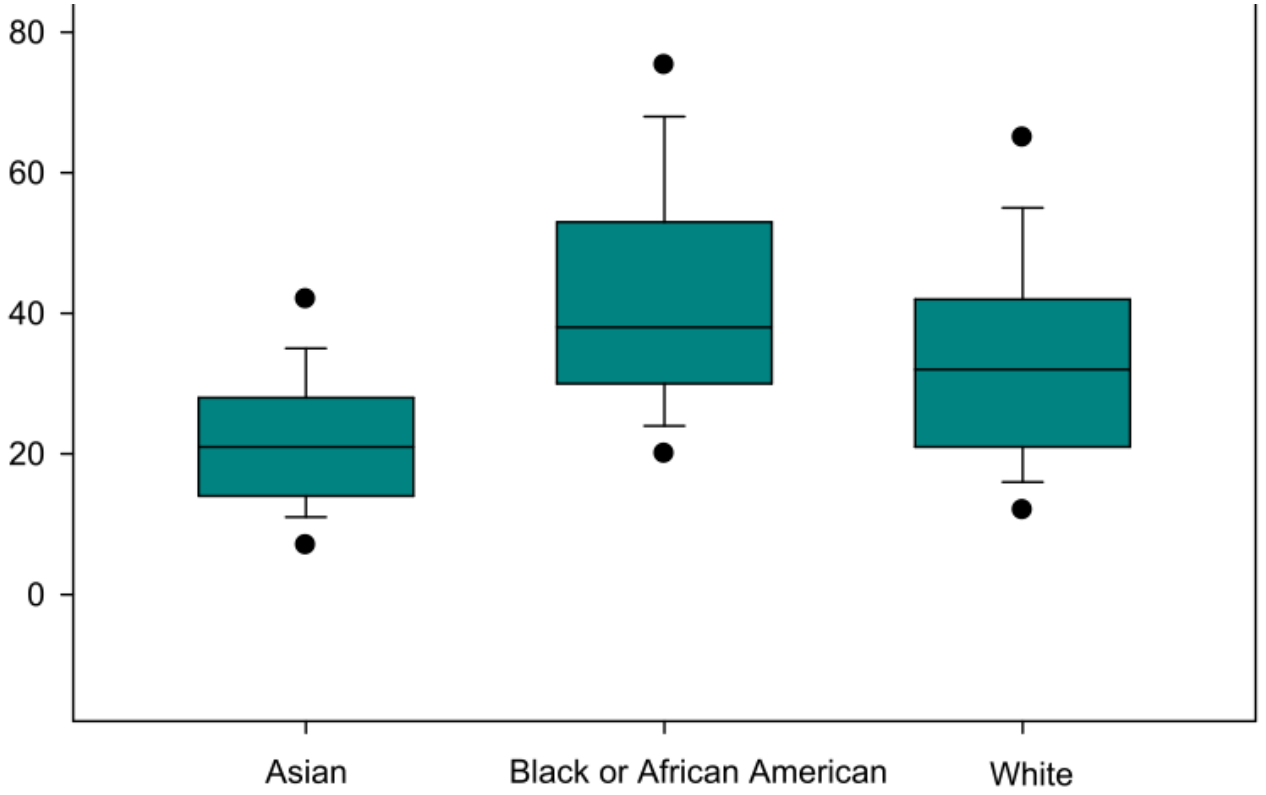




Two OCT2 variants, T199I and T201M, were identified only in Korean and Japanese.

Song IS, Shin JG et al., CPT, 2008

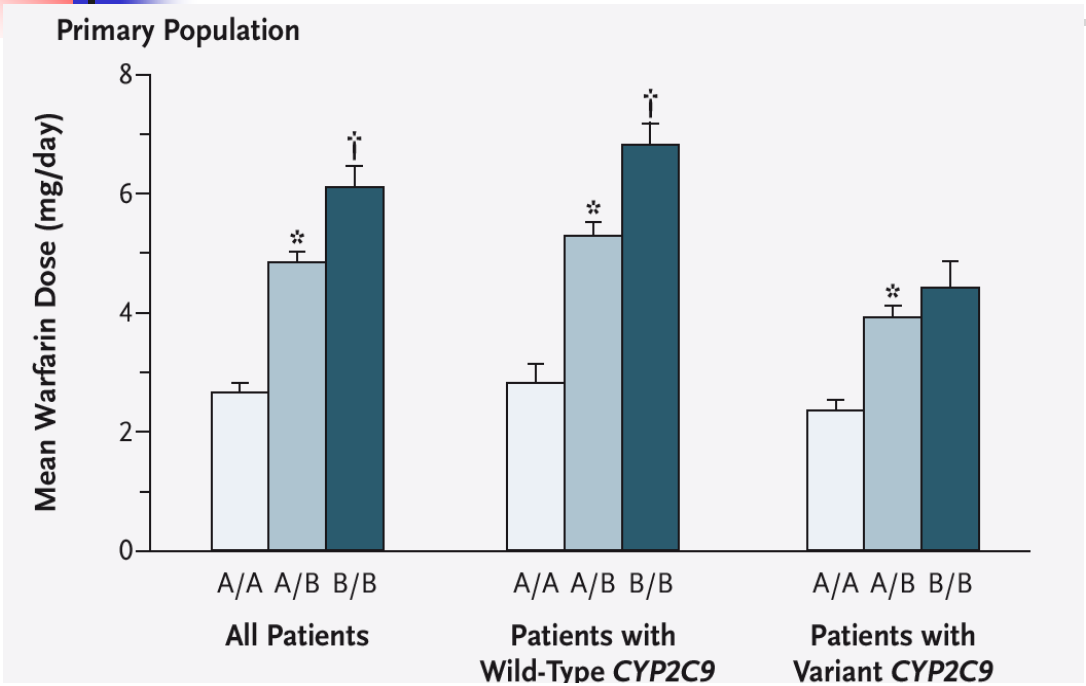
Ethnic difference of Average warfarin doses required for stable INR (median – 2.5)

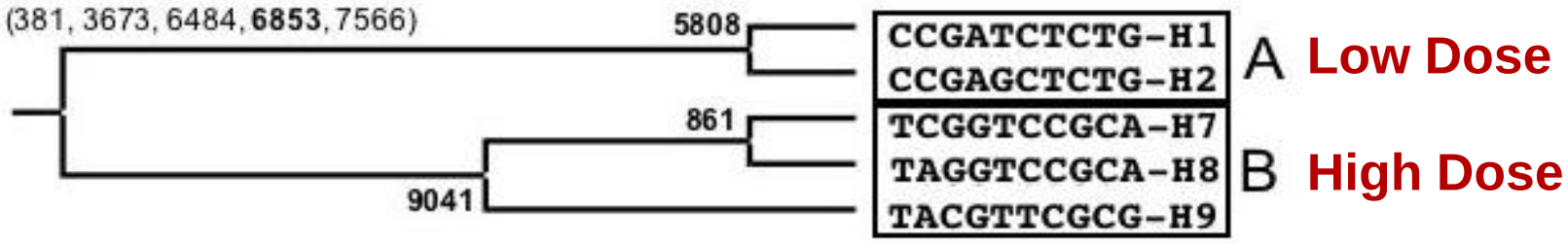


Distribution of Therapeutic Warfarin Dose by Race
Boxes show median, 25th and 75th percentile; whiskers show 10th and 90th percentile, and points show 5th and 95th percentile.

Data from IWPC

Effect of VKORC1 Genotype on warfarin dose to be within therapeutic INR





Rieder et al. N Engl J Med 2005

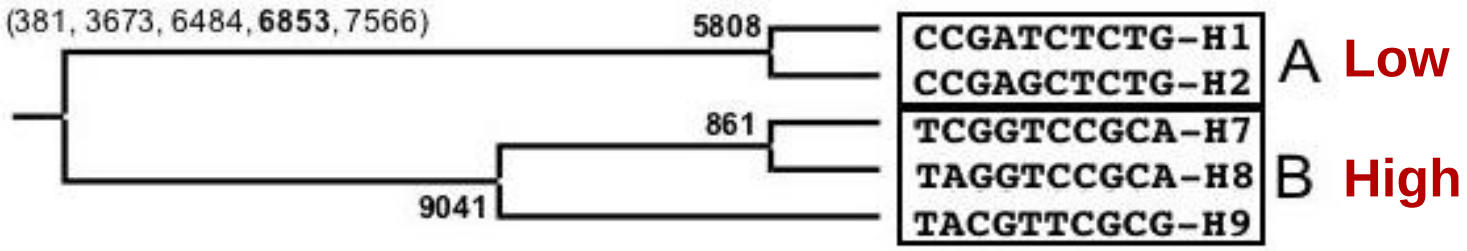
Ethnic Difference of Haplotype Profiles of VKORC1
: Asian populations – only H1 and H7

Haplotype Identification Code or Group	Haplotype Sequence	Frequency of Haplotype in American Populations*		
		European (N=119)	African (N=96)†	Asian (N=120)†
		proportion (number of haplotypes)		
Haplotype distribution				
H1	CCGATCTCTG	0.12 (28)	0.07 (14)	0.89 (213)
H2	CCGAGCTCTG	0.26 (61)	0.06 (12)	0
H7	TCGGTCCGCA	0.21 (49)	0.42 (80)	0.10 (25)
H8	TAGGTCCGCA	0.14 (34)	0.01 (2)	0
H9	TACGTTCGCG	0.24 (56)	0.06 (11)	0
Other haplotypes	—	0.04 (10)	0.38 (73)‡	0.01 (2)
Group distribution				
Group A (H1, H2)	—	0.37 (89)	0.14 (26)	0.89 (213)
Group B (H7, H8, H9)	—	0.58 (139)	0.49 (93)	0.10 (25)
Total of groups A and B	—	0.96 (228)	0.62 (119)	0.99 (238)

Rieder et al. NEJM 2005

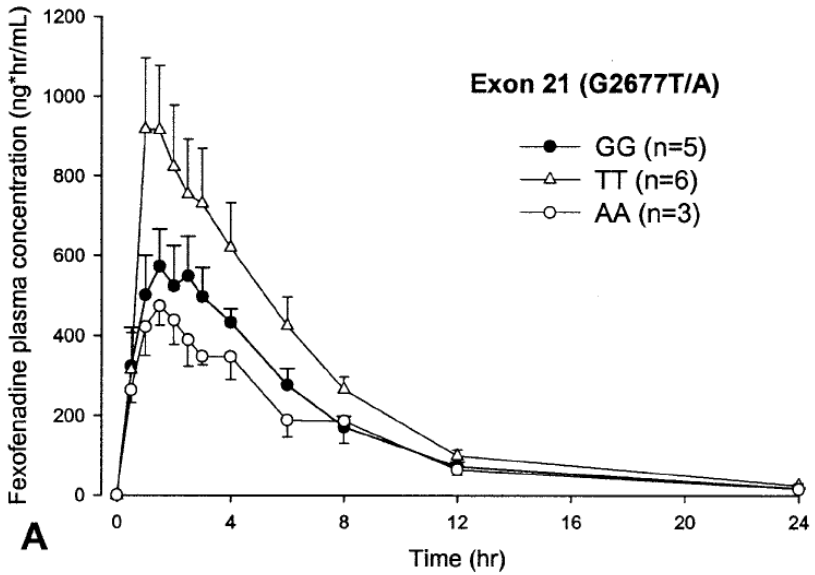
Ethnic Comparison of VKORC1 diplotype

Population	Frequency (%) of Low dose warfarin allele			
	Our Data	Previous studies		
Korean	93			
Vietnamese	86			
Chinese	87.5	91	92	
Japanese		89.1	91	92
Caucasian	39.4	38	42.2	
African-American	14.3	8.6		



Example of Ethnic Difference of the Frequency of Allelic Variants among Asian populations: ABCB1 (MDR1)

Haplotype	Frequency of Linkages (%)				
	Korean	Vietnamese	Chinese	Japanese	Malay
2677G-3435C	**39.8**	**52.3**	**48.4**	**39.0**	**53.7**
2677T-3435C	5.4	4.8	5.4	4.0	2.3
2677A-3435C	**15.4**	6.3	5.8	**16.4**	6.6
2677G-3435T	4.0	5.8	2.1	4.0	5.1
2677T-3435T	**33.6**	**30.8**	**38.3**	**36.4**	**32.3**
2677A-3435T	1.7	0	0	0.2	0



Frequency of functional MDR1 2677A allele is significantly higher only in Korean and Japanese than other Asian ethnics as well as non-Asians

Example of Ethnic Difference of the Frequency of Allelic Variants among Asian populations: ABCG2 & SLCO1B1

ABCG2 (BCRP)

ABCG2 Variant	Frequency of Linkages (%)		
	Korean	Vietnamese	Chinese
V12M	23 (19.6 - 26.6)	36* (30.8 - 42.0)	33* (28.5 - 37.9)
Q126Stop	1.9 (0.9 - 2.9)	0.4 (0 - 1.1)	0.5 (0 - 1.2)
Q141K	28 (23.8 - 31.2)	31 (25.7 - 36.5)	29 (24.3 - 33.3)
P269S	0.2 (0 - 0.4)	0.7 (0 - 1.7)	0 (0 - 0.1)

BCRP V12M shows different allelic frequency among Koreans and other Asians

Lee SS, Shin JG et al. DMD 2007

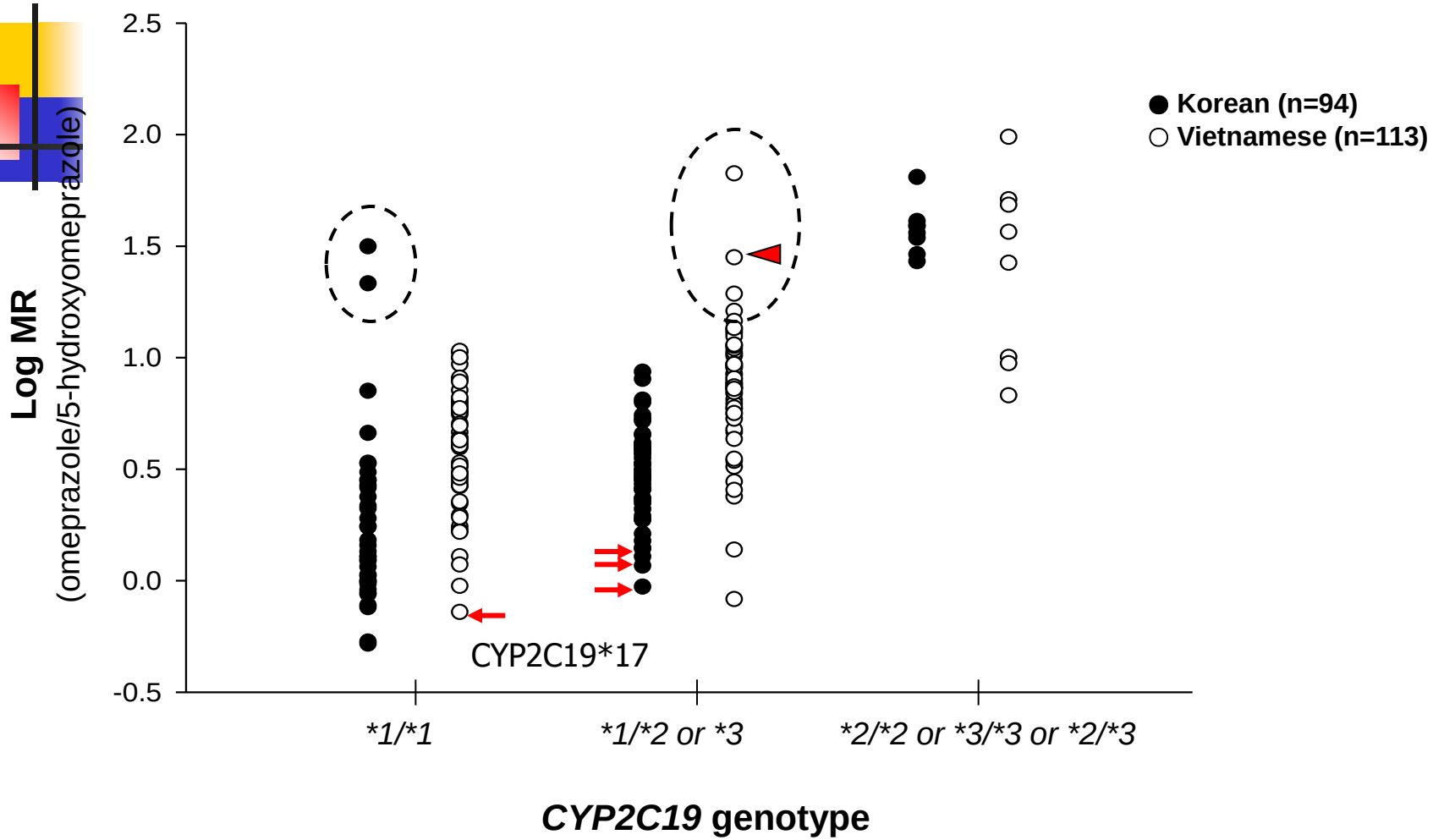
SLCO1B1 (OATP-C)

SLCO1B1 Allele	Frequency of Linkages (%)		
	Korean	Vietnamese	Chinese
SLCO1B1*1a (388A, 521T)	26.3	21.9	21.2
SLCO1B1*1b (388G, 521T)	59.7	68.7	62.5
SLCO1B1*5 (388A, 521C)	0	1.2	0
SLCO1B1*15(388G, 521C)	14.0	8.2	16.3

SLCO1B1 variants show different allelic frequency among Asian ethnics

Kim EY, Shin JG et al. 2008

Identification novel CYP2C19 SNP from Vietnamese subjects who were outlier of genotype-phenotype : Still we may find rare variant of CYP2C19*26



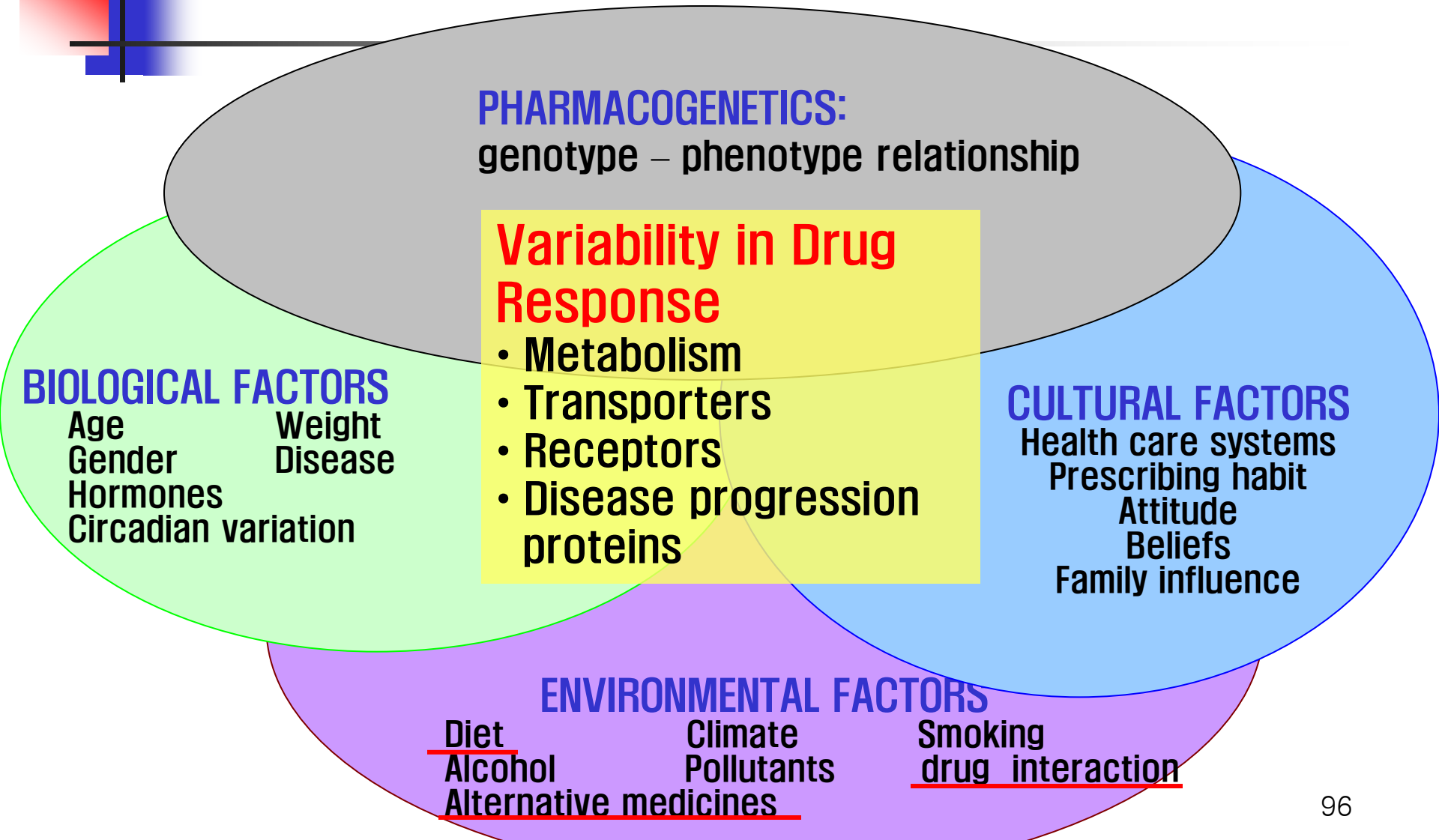
Although circled genotype were heterozyfous for *2 and *3 or wild-type, their MR values were similar to that of PM subjects. So, their DNA of CYP2C19 were sequenced and found one variant (D256N) which was assigned as CYP2C19*26 now after functional study. Four arrows bottom and an arrow head in the dashed circle depict the location on the plot of the *CYP2C19*17* allele and new *CYP2C19*26* variant, respectively.
Indicating that *17 increased CYP2C19 activity as shown other reports.

Lee SJ, Shin JG, DMD 2010

		Turkey	Korean	Japan	China
VKORC1	-1639G>A	40-50	92.3	99.7	99.0
CYP2C9	*2	9~13	0	0	0
	*3	8.8~15	4.5	0.2	5
CYP2C19	*2	11.5~16.2	27.9	27.4	45.5
	*3	0~1	9.5	10.8	4.5
	*17		1.1		2.2
CYP2D	*2	50	11	12.3	7.98
	*3	2.5	0		
	*4	11~21	0	0.2	0
					4.62
					2
MDR1	3435C>T	43~60	37.4	64.9	68
UGT1A1	*28	27	5.7	13.3	
TPMT	*2	0	0	0	0
	*3A	0.9	0	0	0
	*3C	0.9	0.3	0.3~0.8	2.3
	*6		0.9		
Reference		Turk J Gastroenterol. 2009;20(3):161-4. Rheumatol Int. 2009;29(12):1431-4. Cell Biochem Funct. 2005;23(2):133-5. Eur J Clin Pharmacol. 2008;64(9):889-94 Heart Vessels. 2010;25(2):155-62. Eur J Clin Pharmacol. 2004;60(5):337-42 Br J Clin Pharmacol. 1999,48(3):409-15. Basic Clin Pharmacol Toxicol. 2006;98(4):377-80. American Journal of Hematology.2005;26-34 Am J Hematol. 2007;82(10):906-10. Transplant Proc. 2006;38(5):1290-2.	our data	Pharmacogenetics. 2000;10(6):567-70. Am J Hematol. 2007;82(10):906-10. Pharmacogenetics 1997; 7: 405-409. Pharmacogenetics 1996; 6: 265-267.	Mutation Research,1999. 441-449 Eur J Clin Pharmacol. 2007;63(4):419-21. J Psychopharmacol. 2007;21(8):837-42. Br J clin Pharmac 1994; 37: 605-607 Can J Physiol Pharmacol 2001;79: 841-847.J Gastroenterol 2001; 36: 669-672.

Big difference of genotype profiles
between Turkish and Far East Asian populations

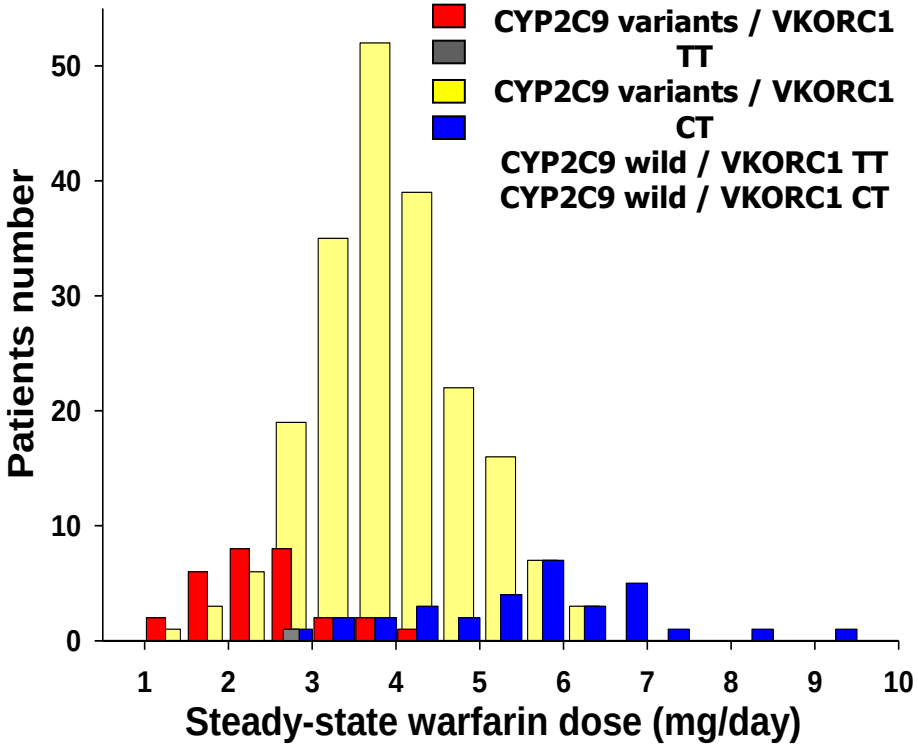
Factors can confound the genotype–phenotype relationship of drug response: Ethnic difference

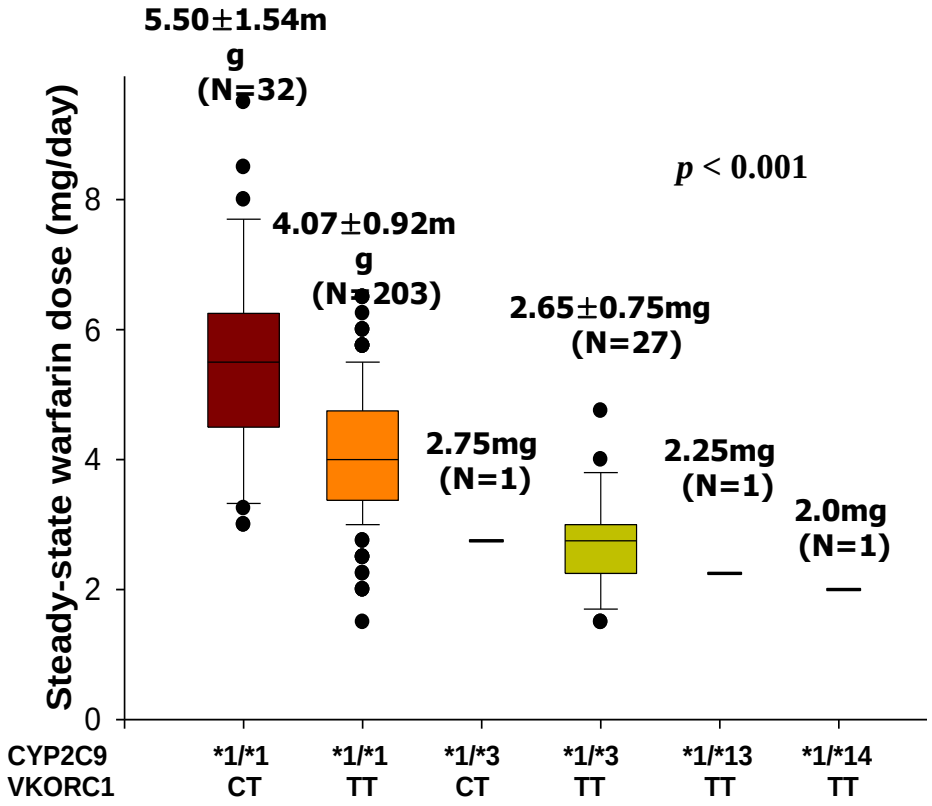


Warfarin – Representative model drug for the quantitative prediction of personalized pharmacotherapy

The effect of CYP2C9 & VKORC1 on the stable warfarin dose to keep therapeutic INR in Korean patients with MHVR

n = 256





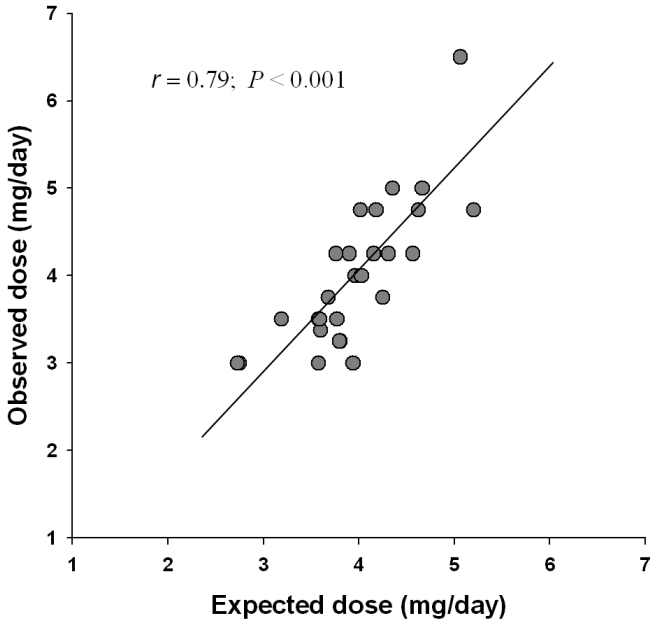
※ **CYP2C9 variants include heterozygous CYP2C9*3, *13 or *14 variants**

Kim HS, Shin JG et al. Pharmacogenetics and Genomics, 2009

Development of dosing algorithm for stable warfarin dose in Korean Patients with MHVR (subset population)

- Model development in 90% training set
  - Dose = (1.87434 – 0.39677 × CYP2C9
    + 0.41738 × VKORC1
    – 0.00487 × Age + 0.00683 × Weight
    – 0.14930 × CHF/Cardiomyopathy
    – 0.24163 × INR-increasing Drug
    – 0.17099 × Aspirin
    + 0.07370 × INR-decreasing Dietary supple.)^2
    - CYP2C9 : input 0 for *1/*1 and 1 for non*1/*1
    - VKORC1 : input 0 for 1173TT and 1 for 1173TC
    - input is 1 for each of: presence of CHF/cardiomyopathy, co-administration of an INR-increasing drug, aspirin, or an INR-decreasing dietary supplements; input is 0 if not
    - INR-increasing drugs include amiodarone, fluconazole, doxifluridine
    - INR-decreasing dietary supplements include broccoli, soy beans, nutrition pills containing vitamin K and Korean ginseng
  - R^2 = 0.56

- Validation in 10% test set



Kim HS, Shin JG et al. Pharmacogenetics and Genomics 2009

Global effort for the development of Warfarin dose prediction algorithm for global clinical application in diverse ethnic populations

IWPC – 21 teams involved from the world

4 continents and 9 countries

- Asia
  - Israel, Japan, Korea, Taiwan, Singapore
- Europe
  - Sweden, United Kingdom
- North America
  - USA (11 states: Alabama, California, Florida, Illinois, Missouri, North Carolina, Pennsylvania, Tennessee, Utah, Washington, Wisconsin)
- South America
  - Brazil

Development of Warfarin dose prediction algorithm for global clinical application in diverse ethnic populations

		5.6044	
-		0.2614 x	Age in decades
+		0.0087 x	Height in cm
-		0.2188 x	*CYP2C9* genotype unknown
-		0.1092 x	Asian race
-		0.2760 x	Black or African American
-		0.1032 x	Missing or Mixed race
+		1.1816 x	Enzyme inducer status
-		0.5503 x	Amiodarone status
Square root of weekly warfarin dose**			

IWP

- 3 patients for model development
- 1009 patients for validation cohort

Still more steps are remained !

Validation of the algorithm for clinical utility

- Prospective randomized clinical trial comparing genotype-guided versus usual dosing
- Optimal Anticoagulation through Genetics (COAG) trial supported by NHLBI (PI, Stephen Kimmel, MD)

Is this last model of wafarin dose estimation based on PGx information?
In each of Asian countries?

IWPC, NEJM 2009

Different Warfarin dosing among different Asian ethnic populations

Should we consider the ethnic difference among Asian populations for the dose prediction?
What factor may influence on the such ethnic difference among Asian population?
Fine tuning of global predictive model for warfarin dose in Asian population?

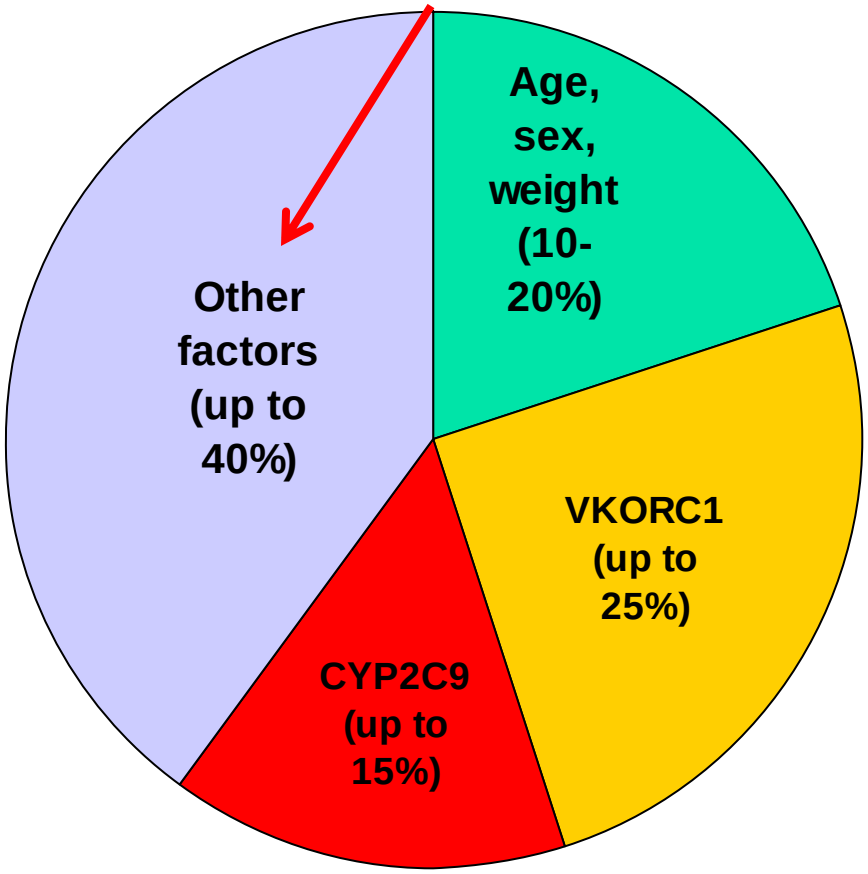
Ethnic	Warfarin dose (mg/day)	Indication	INR	N	Allele frequency (%)			Ref
					CYP2C9*2	CYP2C9*3	VKORC1	
Korean	4.07±1.22	MHVR	1.7-2.8	265	-	5.3	1173C>T: 93.8	(1)
	4.1±1.6	A Fib	1.8-2.7	108	-	5.5	1173C>T: 90.3	(2)
Japanese	2.89±0.75	MHVR	1-2.6	31	-	-	1173C>T: 90.3	(3)
	2.5 (median)	-	1.6-2.5	828	-	2.4	1173C>T: 91.3	(4)
	3.2±1.26	MHVR, A Fib, DVT, PE	1.1-3.5	125	-	2.8	1173C>T: 89.2	(5)
Chinese	3.53±1.6	A Fib, DVT	1.8-3.2	69	0	2.9	H1: 86.2	(6)
	3.68±1.68	MHVR, A Fib, DVT	2-3	139	0	7	H1: 87	(7)
Malays	3.28±1.39	MHVR, A Fib, DVT	2-3	82	1	9	H1: 67	(7)
Indians	6.21±2.94	MHVR, A Fib, DVT	2-3	35	4	18	H1: 14	(7)

(1) Pharmacogenet Genomics 2009, 103–12 ; (2) Pharmacogenomics 2007, 329-37 ; (3) Pharmacogenomics 2007, 713-19 ; (4) J Hum Genet 2006, 249–53 ; (5) Clin Pharmacol Ther 2006, 169-78 ; (6) Pharmacogenetics and Genomics 2005, 687–691 ; (7) Clin Pharmacol Ther 2006, 197–205

Many factors influencing on Warfarin Dose : genetic and nongenetic factors

- Age
- BSA or weight
- Amiodarone & drug-drug interaction
- Target INR
- Race
- Sex
- Plasma vitamin K level / diet containing high ingredient of Vit K
- Decompensated CHF or post-operative state
- The patient's genetic status

Why Koreans higher dose?



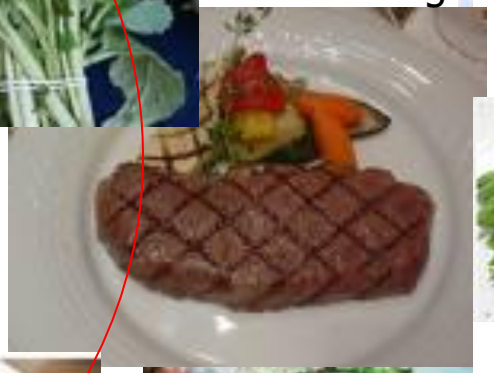
Major Korean diet composed of vit K1 rich food . Japanese diet?

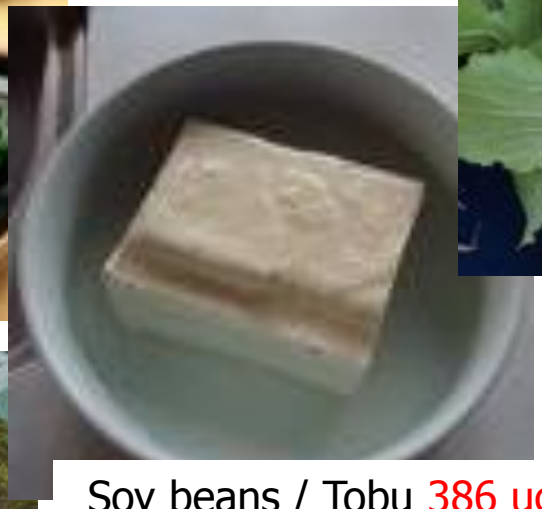
Spinach 324 ug

Turnip greens 324 ug

Shrimp <0.01 ug

Beef 85 ug





Soy beans / Tobu 386 ug

asparagus 72 ug

Lettuce 68 ug

Scallions 103 ug

Broccoli 88 ug

Fish 5.8 ug

Fried egg 3.2 ug

As phylloquinone (vit K1) contents per one serving

Plasma concentration of vit K in Chinese and UK

Table 1. Subject characteristics and plasma biochemical markers of vitamin K status in older individuals in Shenyang and Cambridge

(Mean values and standard deviations)

	Chinese				British			
	Men (*n* 86)		Women (*n* 92)		Men (*n* 67)		Women (*n* 67)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	66·9	4·7	64·4*	4·4	68·8	6·0	67·9††	6·5
Weight (kg)	68·8	9·5	59·9**	10·5	78·8††	9·6	69·5** ††	12·2
Height (m)	1·669	0·062	1·551**	0·053	1·734††	0·063	1·597** ††	0·071
Phylloquinone (nmol/l)								
Geometric mean	1·88		2·48*		0·66††		0·73††	
95 % CI	1·61	2·19	2·14	2·88	0·57	0·75	0·64	0·84
Triacylglycerol (mmol/l)	1·25	0·70	1·63**	0·80	1·12	0·51	1·31* †	0·59
tOC (μg/l)	13·9	5·9	19·0**	6·1	18·2††	7·3	24·5** ††	10·8
ucOC (% of tOC)	13·3	9·1	22·8**	9·9	31·6††	12·9	32·7††	9·5

tOC, total osteocalcin; ucOC, undercarboxylated osteocalcin.
Mean value was significantly different from that for men in the same population: *$P<0·05$, **$P<0·01$.
Mean value was significantly different from that for the Chinese counterparts: †$P<0·05$, ††$P<0·01$.

British Journal of Nutrition 2004.939-945

Comparison of serum vit K concentrations between in Japanese and Korean

Japanese

Table 1. Subject characteristics

n	379
Age (years)	63.0 (10.8)
Body weight (kg)	52.1 (7.3)
Body height (cm)	151.6 (6.0)
BMI (kg/m^2)	22.6 (2.8)
K_1 (nmol/l)	3.51 (2.70)
MK-4 (nmol/l)	0.20 (0.31)
MK-7 (nmol/l)	10.0 (15.1)
ucOC (ng/ml)	4.68 (3.15)
iOC (ng/ml)	8.69 (7.13)
25-OH-D (nmol/l)	51.8 (16.3)
iPTH (pmol/l)	4.9 (1.8)
Ca (mmol/l)	2.30 (0.10)
P (mmol/l)	1.12 (0.15)
BAP (U/l)	31.4 (11.2)
NTX (pmol BCE/μmol Cr)	57.3 (25.5)
L_{2-4} BMD (g/cm^2)	0.970 (0.186)
L_{2-4} Z-score	0.178 (1.405)
FN BMD (g/cm^2)[a]	0.750 (0.128)
FN BMD Z-score[a]	0.398 (0.857)

J Bone Miner Metab 2008. 79-85

Korean

Table 2. Dietary vitamin K intake and serum vitamin K concentration of the subjects N=24

Variables	Mean±SD(range)
Dietary vitamin K(μg/day)	690.9±422.0(172.2–1331.3)
Serum vitamin K (ng/ml)	3.3± 2.0(0.6– 6.7)

Values are mean±SD

7.32±4.44 nmol/L

Korean Journal of Nutrition 1999. 287-295

May need more Warfarin dose estimation algorithm for the fine tuning in Asian populations….

If we want know how much similar, how much different among Asian ethnic populations. e.g., Far Eastern Asian, South East Asian, Middle East Asian?

What is a way to have the answer?

Effort for Collaboration of the PGx based PP in Asian Populations

Initiation of Asian Network for Pharmacogenomics Research (ANPR)

1st ANPR Conference

Date: April, 2008 (after 2008 International Conference on PGx, Busan, Korea)

Place: Inje University College of Medicine

Participants: 30 scientists from 9 different countries

Elected a Coordinator: Jae-Gook Shin

1st ANPR Conference

1st ANPR Conference

1st ANPR Conference

Asian Network for Pharmacogenomics Research – What is this?

- Place of research community for the international and/or multi-site collaboration of PGt/PGx research for Asian ethnic population
- Collection of Information on the scientists who are studying PGt/PGx of Asian populations
- Sharing this information for support any scientist to develop specific consortium for the PGt/PGx for the personalize pharmacotherapy and efficient drug R&D including the concept of bridging.
- As a gate of this scientific collaboration, open place for the scientific communications for all scientists

http://www.asianpr.org/popup.ph...

http://www.asianpr.org/popup.php

Asian Network for Pharmacogenomics Research

Welcome to Asian Network for Pharmacogenomics

Updated News

- **Looking for collaboration:**
  Association study using
  candidate SNPs with platinum toxicity in a large
  Asian cohort

- **Looking for collaboration:**
  Genetics of drug-induced
  QT prolongation and torsades

For detailed information, please click here click

인터넷 100%

Bing

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페이지(P) 안전(S) 도구(O)

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Pharmacogenomics Research

DATABASE | FORM | COMMUNITY

arch

· Registration Information
· History

or Pharmacogenomics Research (ANPR).
nunity of the international and/or multi-center
ics(PGt) and pharmacogenomics (PGx) research for Asian ethnic populations. In order to reach personalized pharmacotherapy with using PGt/PGx, the collection of a large database from thousands of subjects/patients is an essential requirement for the development of predictive models including genetic and non-genetic co-variates for individual drug response. In addition, international and multi-center collaboration is highly necessitated to accelerate the development of PGt/PGx database for Asian ethnic populations, which will be possible from sharing the PGt/PGx data, genotyping technologies, ideas and even friendship among investigators. In the era of globalization, therefore, we would like to develop the ANPR as the hub of network resources for PGt/PGx research in Asia. This ANPR is an open place for scientific communication for all scientists interested in PGt/PGx research in Asian populations. Thank you for your interest in ANPR.

Login

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ID
PW
OK

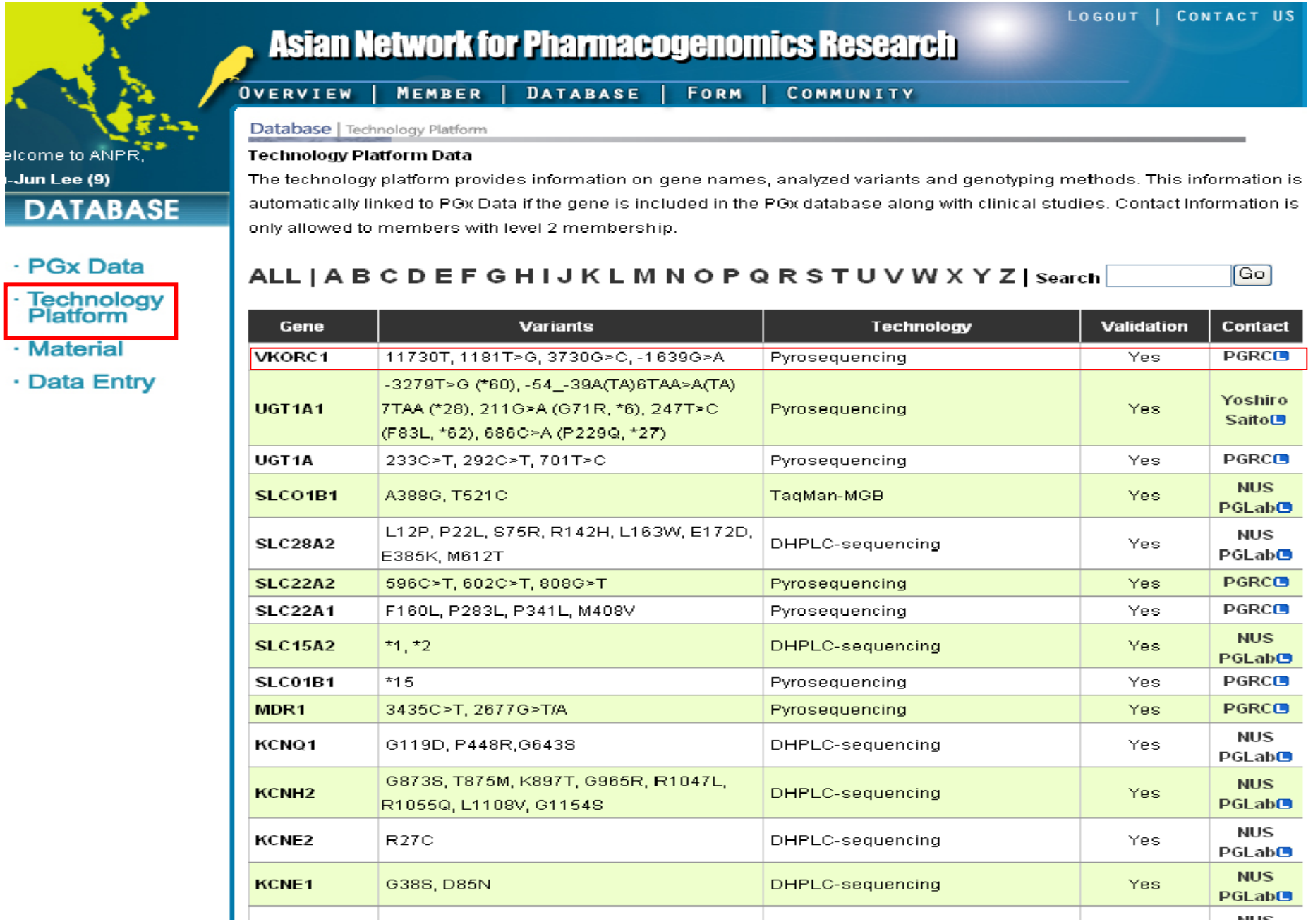
[Register for ANPR] [Find ID/PW]

ANPR Initiation Meeting
2008.04.13

Main Issues of ANPR Networking

Drug Name	Category	Gene	Ethnic	Subject	Target Disease	Contact	Publication
warfarin	anticoagulant				mechanical heart		No
	anticoagulant						No
verapamil	antihypertensive						Yes
tolbutamide	sulphonylurea class						Yes
	sulphonylurea class						Yes
rosuvastatin	HMG-CoA reductase inhibitor						yes
pravastatin / pitavastatin	statins	SLC01B1	Korean	healthy volunteer	-	PGRC	Yes
nitrofurantoin	antibiotics	ABCG2	Chinese	healthy		NUS PGLab	yes
midazolam	benzodiazepine derivative	CYP3A4	Korean	healthy volunteer	none	PGRC	Yes
metoprolol / paroxetine	beta1 receptor blocker / ssri	CYP2D6	Korean	healthy volunteer	none	PGRC	Yes

Main Issues of ANPR Networking



Asian Network for Pharmacogenomics Research

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OVERVIEW | MEMBER | DATABASE | FORM | COMMUNITY

elcome to ANPR,
-Jun Lee (9)

DATABASE

- PGx Data
- Technology Platform
- Material
- Data Entry

Database | Technology Platform

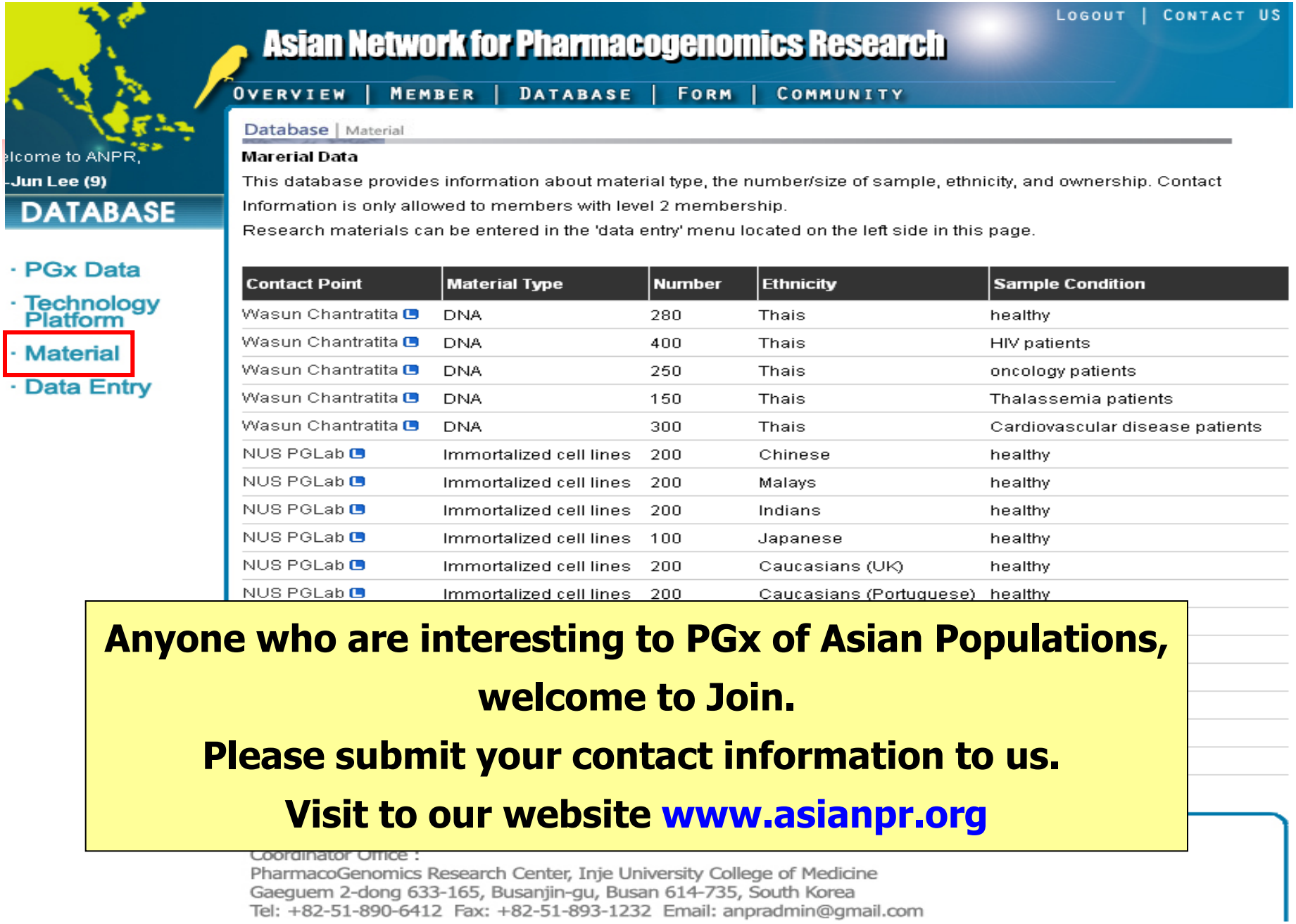
Technology Platform Data

The technology platform provides information on gene names, analyzed variants and genotyping methods. This information is automatically linked to PGx Data if the gene is included in the PGx database along with clinical studies. Contact Information is only allowed to members with level 2 membership.

ALL | A B C D E F G H I J K L M N O P Q R S T U V W X Y Z | Search Go

Gene	Variants	Technology	Validation	Contact
VKORC1	11730T, 1181T>G, 3730G>C, -1639G>A	Pyrosequencing	Yes	PGRC
UGT1A1	-3279T>G (*60), -54_-39A(TA)6TAA>A(TA)7TAA (*28), 211G>A (G71R, *6), 247T>C (F83L, *62), 686C>A (P229Q, *27)	Pyrosequencing	Yes	Yoshiro Saito
UGT1A	233C>T, 292C>T, 701T>C	Pyrosequencing	Yes	PGRC
SLCO1B1	A388G, T521C	TaqMan-MGB	Yes	NUS PGLab
SLC28A2	L12P, P22L, S75R, R142H, L163W, E172D, E385K, M612T	DHPLC-sequencing	Yes	NUS PGLab
SLC22A2	596C>T, 602C>T, 808G>T	Pyrosequencing	Yes	PGRC
SLC22A1	F160L, P283L, P341L, M408V	Pyrosequencing	Yes	PGRC
SLC15A2	*1, *2	DHPLC-sequencing	Yes	NUS PGLab
SLC01B1	*15	Pyrosequencing	Yes	PGRC
MDR1	3435C>T, 2677G>T/A	Pyrosequencing	Yes	PGRC
KCNQ1	G119D, P448R,G643S	DHPLC-sequencing	Yes	NUS PGLab
KCNH2	G873S, T875M, K897T, G965R, R1047L, R1055Q, L1108V, G1154S	DHPLC-sequencing	Yes	NUS PGLab
KCNE2	R27C	DHPLC-sequencing	Yes	NUS PGLab
KCNE1	G38S, D85N	DHPLC-sequencing	Yes	NUS PGLab

Main Issues of ANPR Networking

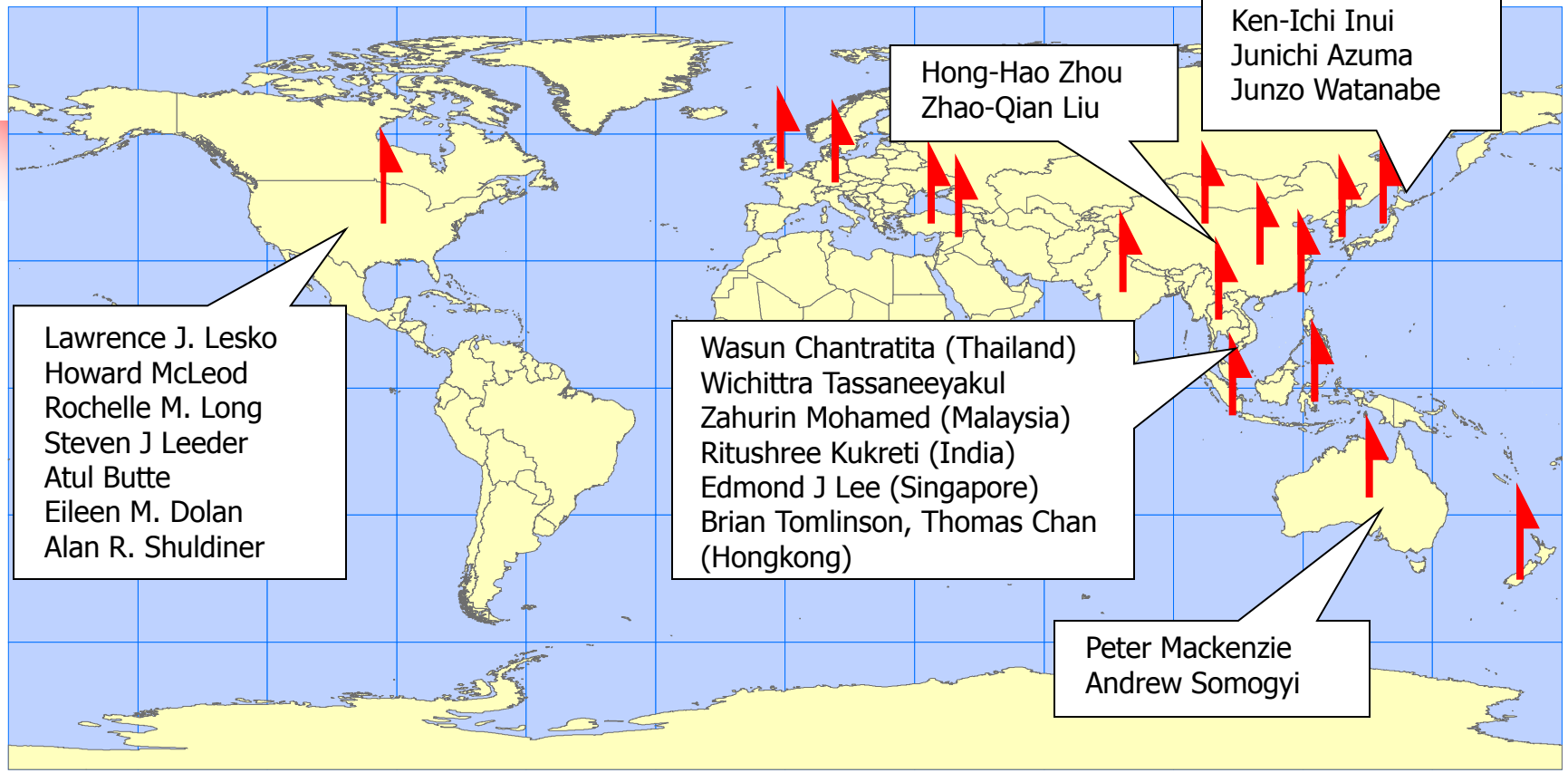


Anyone who are interesting to PGx of Asian Populations, welcome to Join.

Please submit your contact information to us.

Visit to our website www.asianpr.org

Current ANPR Member



Countries

Korea	Australia	China	Israel
India	UK	Turkey	New Zealand
Japan	Thailand	Malaysia	Hong Kong
USA	Singapore	Taiwan	Germany

16 countries with 157 members

Current DB & Materials

Number of Drug with PGx data: 23
Number of Genotyping Tech: >25
Number of DNA: 4,046
Others: immortalized cell lines, tissues, etc.

Not enough space, so this is just brief summary of ANPR members.

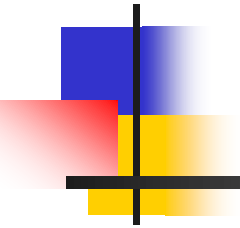
Sample list of PGt/PGx data base in our center (PGRC)

Function Group	Code	Gene symbol	Aliase	Entrez	Location	Template1	Template2: sequencing (scoring)						Additional Data (KPGRN, Clinical Research)
						No. Position	KR	JP	CN	VN	Caucasian	African	
Drug Metabolizing Enzymes													
Phase I		CYP											
	P1-01	CYP1A2		CYP1A2	15q24	20	96 (796)						
	P1-02	CYP2A6		CYP2A6	19q13.2	27	50 (150)						
	P1-03	CYP2B6		CYP2B6	19q13.2	17	96 (964)		(188)				clopidogrel, efavirenz
	P1-04	CYP2C8		CYP2C8	10q23.33	17	100 (894)		(200)	(200)	(200)		epilepsy, rosiglitazone
	P1-05	CYP2C9		CYP2C9	10q24	18							epilepsy, diphenylhydantoin
	P1-06	CYP2C19		CYP2C19	10q24.1-q24.3	21	100 (1084)						epilepsy
	P1-07	CYP2D6		CYP2D6	22q13.1	38	51 (570)			(161)			
	P1-08	CYP2D7		CYP2D7P1	22q13	1							
	P1-09	CYP2J2		CYP2J2	1p31.3-p31.2	12	93 (430)		(196)	(159)	(99)	(100)	
	P1-10	CYP2S1		CYP2S1	19q13.1	12	50 (200)						
	P1-11	CYP3A4		CYP3A4	7q21.1	8	50 (349)						
	P1-12	CYP3A5		CYP3A5	7q21.1	1	(124)						verapamil
	P1-13	CYP3A7		CYP3A7	7q21-q22.1	13	48 (232)			(160)	(100)	(100)	
	P1-15	CYP19A1		CYP19A1	15q21.1	19	100						
Phase II	P2-01	UGT1A				68	100 (1006)		(190)	(178)			
	P2-02	UGT2B7		UGT2B7	4q13	19	50						
	P2-03	UGT2B15		UGT2B15	4q13	13	48						
	P2-04	TPMT		TPMT	6p22.3	4	400			(159)			
	P2-05	SULT1A1		SULT1A1	16p12.1	30	50						
	P2-06	SULT1A2		SULT1A2	16p12.1	21	50						
	P2-07	SULT1E1		SULT1E1	4q13.1	13	50						
Transcription Factor													
	TF-01	NR0B2	SHP	NR0B2	1p36.1	2	50						
	TF-02	NR1I2	PXR	NR1I2	3q12-q13.3	26	54 (130)		(88)	(56)	(86)		
	TF-03	NR1I3	CAR	NR1I3	1q23.3	9	50						
	TF-04	NR1H3	LXR-a	NR1H3	11p11.2	11	50 (175)		(181)	(159)	(191)		
	TF-05	NR1H4	FXR	NR1H4	12q23.1	13							
	TF-06	NR2A1	HNF4A	HNF4A	20q12-q13.1	20	50 (679)		(94)	(139)	(153)	(83)	dextromethorphan, genotype data(70 liver)
	TF-07	TCF1	HNF1	TCF1	12q24.2	21	50 (126)						
	TF-08	ONECUT1	HNF6	ONECUT1	15q21.1-q21.2	7	50						
Transporter													
	TP-01	ABCB1	MDR1	ABCB1	7q21.1	3	47 (684)			(141)			fexofenadin, genotype data(VN)
	TP-02	ABCG2	BCRP	ABCG2	4q22	20	92 (183)		(191)	(140)			lamivudine
	TP-03	SLCO1B1	OATP-C	SLCO1B1	12p	2							
	TP-04	SLC22A1	OCT1	SLC22A1	6q26	11	50						
Other													

One lab., One institute, One country can not collect
all PGx data base enough for the development
of globally relevant algorithm for the personalized pharmacotherapy
even, not the algorithm for one ethnic populations....

(KR: Korean, CN: Chinese, VN: Vietnamese)

Clinical Application of PGx Information into Clinical Practice



Medco, Mayo Clinic Study Reveals Using a Simple Genetic Test Reduces Hospitalization Rates by Nearly a Third for Patients on Widely Prescribed Blood Thinner

First study to show gene tests improve clinical outcomes in 'real world' settings

Research presented at American College of Cardiology annual meeting finds incorporating pharmacogenomics substantially reduces risks associated with the blood thinner warfarin

ATLANTA, March 16, 2010 – Hospitalization rates for heart patients taking warfarin, the world's most-prescribed blood thinner, dropped by approximately 30 percent when genetic information was available to doctors prescribing the drug, researchers from Medco Health Solutions, Inc.-- in association with the **Medco Research Institute™** -- and Mayo Clinic announced today. Results of the first nationwide prospective study examining outcomes when incorporating genetic testing into the management of warfarin as part of the usual care of patients were presented today at the American College of Cardiology's 59th annual scientific session and will be published in the *Journal of the American College of Cardiology*.

Warfarin, marketed under the brand names Coumadin® and Jantoven®, is a blood thinner that is exceptionally difficult to properly dose because the two million patients starting the drug annually have widely varying responses to the medicine due to a variety of factors including genetics. It is estimated that up to 20 percent or more of patients can be hospitalized for bleeding within six months of starting on the drug. This comparative effectiveness study, conducted in national "real world" settings, validates that testing for an individual's unique genetic predisposition can significantly improve warfarin's safety and

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Genetic Pharmacology Service

Building a Future of Personalized Medicine for Children and Adults Through Pharmacogenetics

Explanation | What's Inside | Benefits | Goal

Scientific evidence indicates that **pharmacogenetics** -- the study of drug interactions with an individual's genetic makeup -- may improve patient safety. Pharmacogenetic testing for some medications adds genetic information to the usual considerations of patient age, weight, disease process, use of other medications, health behaviors and environment. The additional information gained from pharmacogenetics can help physicians and nurse practitioners choose and dose medication that best meets the needs of the individual patient.

Back to Top

What's Inside

The Genetic Pharmacology Service web site includes information about:

- Why Choose Us
- Drugs Tested / Panels
- Meet the Team
- Request a Consult
- Order a Test

Research Highlights

Developing Computer Models for Personalized Drug Dosing
Alexander (Sander) Vinks, PharmD, PhD is principal investigator for several studies examining variations in how pediatric patients absorb and metabolize drugs and what role

Newsroom
Events
Maps / Directions
Find a Researcher / Health Professional
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Adult and Pediatric Drugs Tested / Panels

The Genetic Pharmacology Service for children and adults at Cincinnati Children's Hospital Medical Center uses pharmacogenetics to customize patient care. We offer genetic pharmacogenetic tests for drugs metabolized by major **cytochrome (CYP)** P450 drug metabolizing enzymes (CYP2D6, CYP2C9, CYP2C19) and TPMT. We also offer psychiatry drug panels.

Drugs Tested | Panels Available

Drugs Tested

The tables below list many commonly prescribed drugs that are metabolized through the pathways listed above.

Physicians can download a fact sheet about selected medications in portable document format (.pdf). Family-friendly information about selected drugs can be found by visiting the Health Topics area of our web site.

Drugs by Generic Name

| View Drugs Sorted by Brand Name |

6-mercaptopurine	desipramine	imipramine	propafenone
6-thioguanine	doxepin	lansoprazole	tolbutamide
amitriptyline	flecainide	losartan	trimipramine
atomoxetine	fluoxetine	maprotiline	venlafaxine
azathioprine	fluvastatin	metoprolol	warfarin
carvedilol	fluvoxamine	nortriptyline	
celecoxib	glimepiride	omeprazole	
citalopram	glipizide	pantoprazole	
clomipramine	glyburide	paroxetine	
codeine	haloperidol	phenytoin	

If your drug is not listed above, you may wish to refer to our list of Other Resources or visit the Micromedex web

HEALTH & DNA

genelex

http://www.healthanddna.com/

Welcome to Genelex

Started in 1987, Genelex is a comprehensive, licensed and accredited provider of DNA testing services to medical professionals and the general public.

"Personalized Medicine available today."

Choose One:

For the Public

For the Public

Public Pages describing Genelex's DNA testing services and the benefits that can be gained from genetic testing.

Prescription Drug Reaction Testing helps reduce the incidence of adverse drug reactions, a serious medical

Benefits and Applications

Diagnostic

- Resolve adverse drug reaction caused medical conditions.
- Proof of need for higher dose or more expensive drug.
- Understand sudden changes in behavior triggered by adverse drug reactions induced by drugs of abuse.
- Optimize drug therapy at an earlier stage in treatment, by narrowing the therapeutic options for the patient.
- Help patient understand difficulties

Screening

- Patients who have had therapeutic failures and need to receive a problem drug again.
- Patients who have had adverse drug reactions or severe side effects in the past.
- Family members of patients who have had an adverse drug reaction.
- Patients who want to be prepared for emergent situations.

CYP metabolized drugs of abuse

- Dextromethorphan (Nyquil etc.)
- Oxycontin

Questions?
Ready to Order?
Call 800-523-3080 to speak with a DNA

Questions?
Ready to Order?
Call 800-523-3080 to speak with a DNA Testing Consultant.

Adverse Drug Reaction Standard Panel
2D6, 2C9, and 2C19
Price: $600.00
Add to Shopping Cart

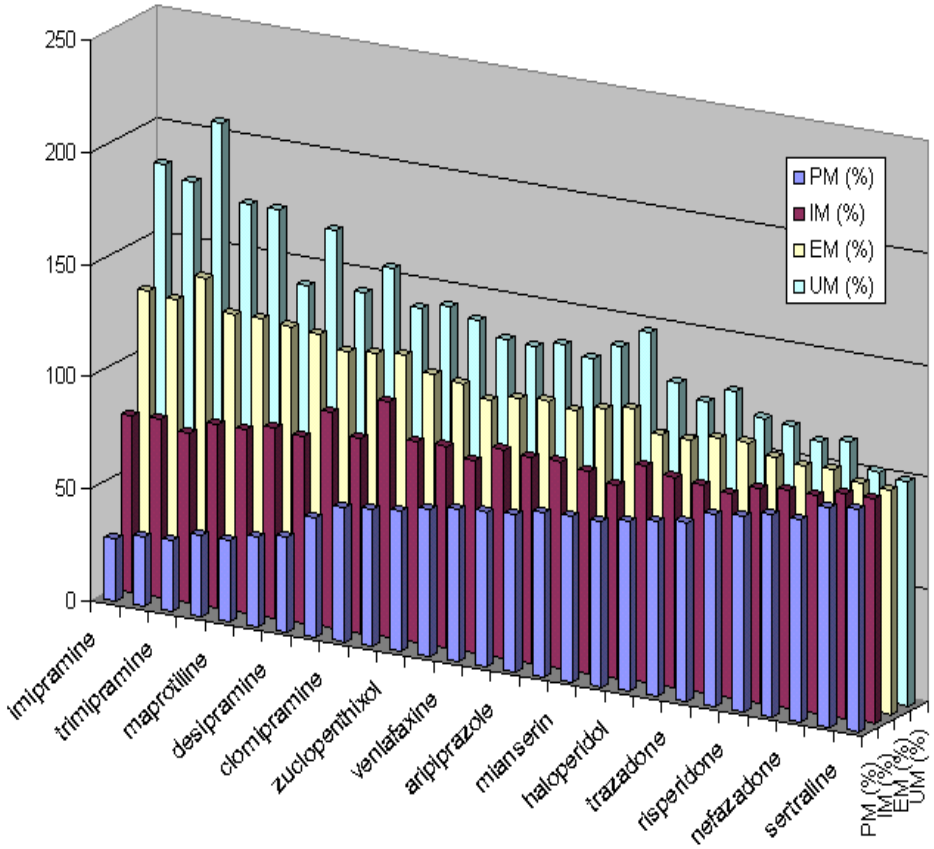
Adverse Drug Reaction Extended Panel
2D6, 2C9, 2C19, 1A2, and NAT2
Price: $1000.00
Add to Shopping Cart

Most Requested Pages:

Antidepressant Pharmacogenetics

Pharmacogenetics of Pain Medication

Pharmacogenetics of Antidepressants and Antipsychotics : CYP2D6 Case



Dose adjustment based on CYP2D6 Genotypes

Which TCA is better?

	Drug	PM (%)	IM (%)	EM (%)	UM (%)
Tricyclic antidepressants	amitryptiline	73	92	111	130
	clomipramine	60	87	121	155
	desipramine	42	83	125	167
	doxepin	36	82	127	172
	imipramine	28	79	131	183
	nortriptyline	53	96	119	142
	trimipramine	32	76	141	206
SSRIs	citalopram	98	100	101	102
	fluoxetine	78	94	107	120
	fluvoxamine	69	93	112	131
	paroxetine	66	90	114	138
	sertraline	99	100	100	100
Other antidepressants	buproprion	90	97	104	111
	maprotiline	36	82	127	172
	mianserin	74	90	114	138
	mirtazapine	102	101	99	97
	moclobemide	121	107	92	77
	nefazadone	90	97	105	113
	trazadone	80	93	110	127
	venlafaxine	68	86	109	132
Antipsychotics	aripiprazole	70	92	113	134
	flupentixol	74	86	116	146
	haloperidol	76	97	107	126
	olanzapine	61	105	122	139
	perazine	86	91	110	117
	perphenazine	31	80	129	178
	risperidone	87	96	106	116
	thioridazine	40	85	126	140
	zuclopenthixol	63	90	116	142

"당신의 유전자에는 이 약입니다"

"For your genotpe, this the best drug regimen for you!"

유전자 검사로 환자 개개인에게 맞춤 약을 처방하는 시대가 열렸

PGt service for personalized pharmacotherapy in Korea

- A few Korean institutes provide genotype service
- for well known valid genotype marker
- Genotype service: approved by Korean Ministry of Health and Welfare
  - ➢ payment by patients, not covered by government insurance: 7 DM/PK genes

이와 같은 맞춤약치료는 1990년대 말 인간유전체지도 완성이 밑바탕이 됐다. 이후 특정 유전자형을 가진 사람에게는 어떤 약이 위험한지, 부작용을 줄이거나 치료효과를 높이기 위해선 용량을 어떻게 조절해야 하는지를 연구하는 '약물유전학'이 비약적으로 발전했다.

약물유전학은 유럽과 미국 등 선진국에선 2~3년 전부터 환자 치료에 적용됐으며, 우리나라에선 1년 전부터 부산백병원 약물유전체연구센터, 삼성서울병원 진단검사의학과 등 일부 병원을 중심으로 적용되고 있다.

chosun.com 헬스조선 2006.09.12

Interest of Payers for PGt Service
(Insurance Company)

Covered:
TPMT for mercaptopurine
Her-2/neu for trastuzumab
Oncotype for breast cancer
HLA-B57 for Abacavir (UK)
(UGT1A1 for irinotecan)

Medicare: for Warfarin (CYP2C9, VKORC1)

Not Covered:
CYP
BRCA1/2

In Korea

- **Approved to charge fee for genotyping by MOHW**
- **Not Covered by Governmental Insurance**
- **CYP2C9, CYP2C19, CYP2D6, TPMT, UGT1A1, NAT2, VKORC1**

In Closing….

Current Status of PGt/PGx

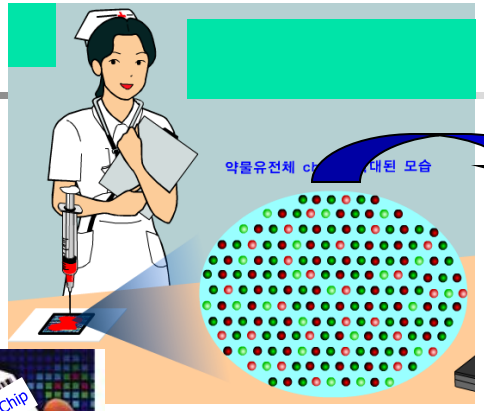
- A number of causal genetic variants already known (through candidate gene studies)
- Hundreds of genetic tests available
- PGx is even being used in clinical practice
  (TPMT, UGT1A1, CYP2D6, CYP2C19, HER2 test, etc)
- Industry using PGx data for drug development
- FDA pursuing PGx policy initiatives
- Diagnostics accelerating data collections
- In Korea, very active and leading country of PGx researches, and domestic pharmas are interested to PGx application into drug R&D, and KFDA is very active to follow the global stream.

Additional Challenges to reach to personalized medicine in addition to academic (scientific) issues

- PGx-based diagnostics with enough accuracy and predictive value
- Regulation of PGx product: ensure patient safety and improved outcome
- Coverage and reimbursement: validation of clinical utility and value of PGx product
- Health information technology infrastructure: robust, detailed, and interoperable to support PGx research and PGx-based diagnostics and treatment decision
- Education and Training for physicians and other clinicians and also for public, evidence based clinical practice guideline and dosing guideline
- Ethical, legal and social issues: protection of personal information, reduce health care disparity, improve health care quality, prevent genetic discrimination etc.

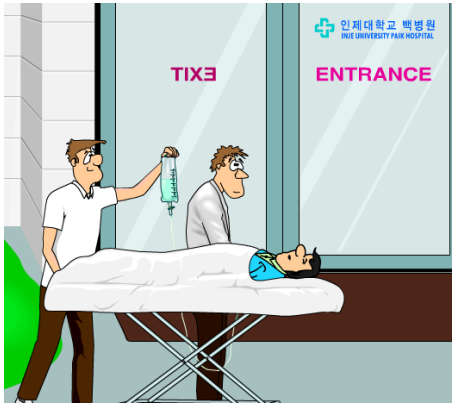
Future scheme of PGx Application into Personalized Pharmacotherapy : Genotype guided prescription

<blood sampling >



<genotyping>

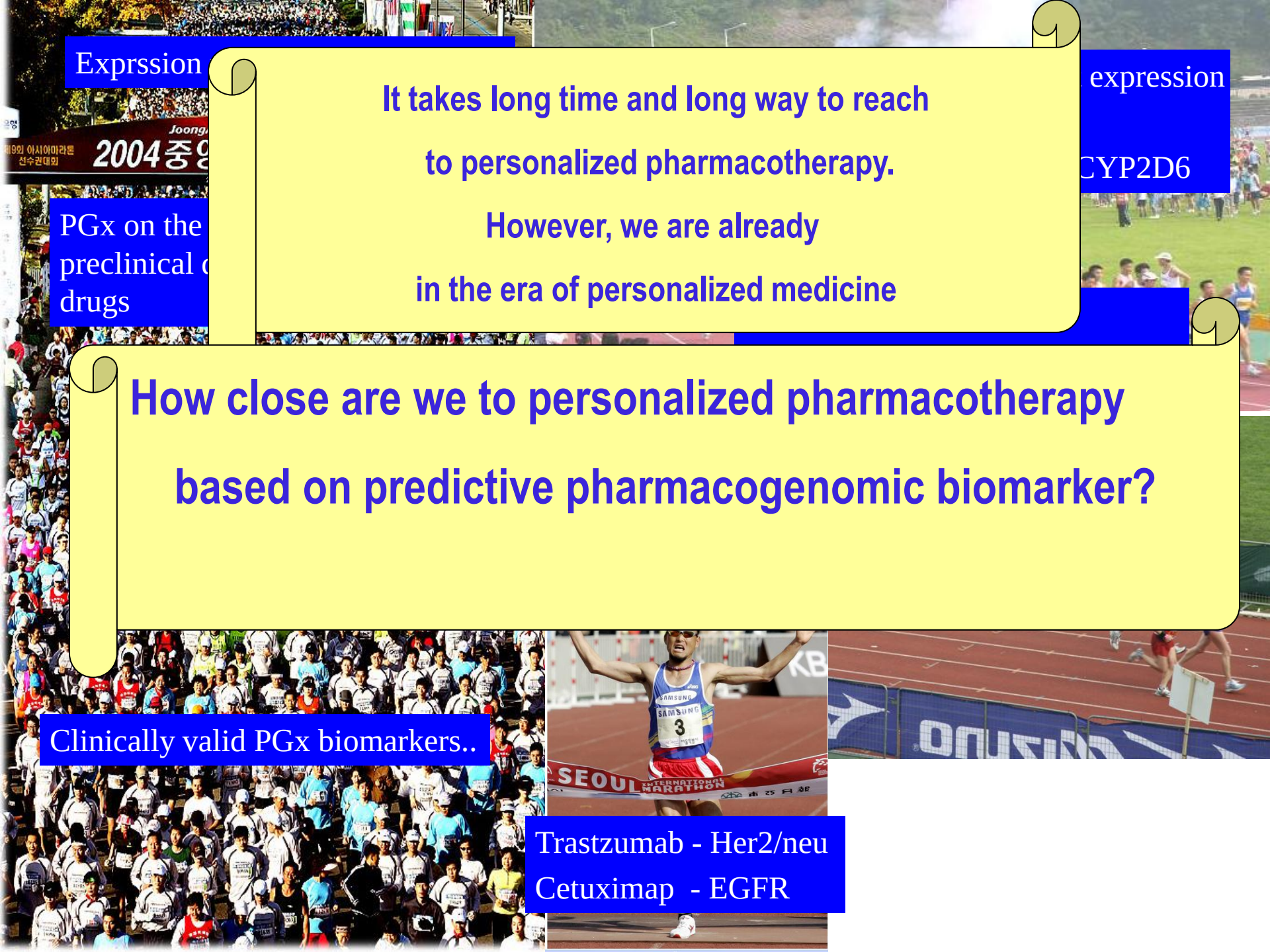
<genotype information on ID card>



<visiting to hospital>

<Genetic information to doctor>

<PGx information based prescription >


Exprssion
expression
CYP2D6
PGx on the
preclinical
drugs
It takes long time and long way to reach
to personalized pharmacotherapy.
However, we are already
in the era of personalized medicine
How close are we to personalized pharmacotherapy
based on predictive pharmacogenomic biomarker?
Clinically valid PGx biomarkers..
Trastzumab - Her2/neu
Cetuximap - EGFR

Acknowledgement

Inje University

PharmacoGnom
Research Cent

Financial Support..

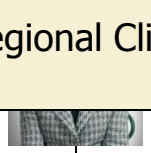
National Research Lab. for PGx (KOSEF, KMOST)

Biomarker Research Center for Personalized Therapy (KOSEF, KMEST)

Korean Pharmacogenomics Research Network (KMOHWF)

Regional Clinical Trial Center (KMOHWF)

Steering Committee



Clinical Pharmacogenomics

Clinical Pharmacology
Ji Hong Shon, MD., PhD
Doo Yeon Cho, MD
Chang Woo Yeo, MD

PharmacoMetabolomics
Kwang Hyun Liu, PhD
Soo Kyeong Bae, PhD

Molecular Epidemiology
Ji Yeop Choi, PhD

Molecular Pharmacogenomics

Molecular Pharmacogenomics
Sang Seop Lee , PhD/ Su Jun Lee, PhD
Im Sook Song, PhD

PharmacoProteomics / Chemical Genomics
Sangtaek Oh. PhD

Research Supports

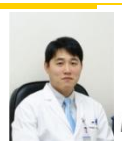
Eun Young Kim, MD, PhD

Genotyping Team
Hye Eun Jung

Analytical Team
Min Jung Kim

Informatics Team
Seok-ki Lee

Administration
Myung Sook Kang








Established at May 1st, 2003

2008 MT, Pharmacogenomics Research Center

Clinical Trial Center funded by MOHW

http://www.paikctc.ac.kr/

INJE PAIK CTC

Inje University
Busan Paik Hospital
Clinical Trial Center

Thank you very much for your attention

경청해 주셔서 감사합니다.

非常謝謝

聞いていただいてありがとうございます

Gwangan Bridge over the sea, a Beautiful Harbor city Busan