Education in Pharmacogenomics: Closing the Gap between Possibility and Reality

Drug Metabolizing Enzymes and Pharmacogenomic Testing Workshop

September 13-14, 2004
Johns Hopkins University
Rockville, Maryland

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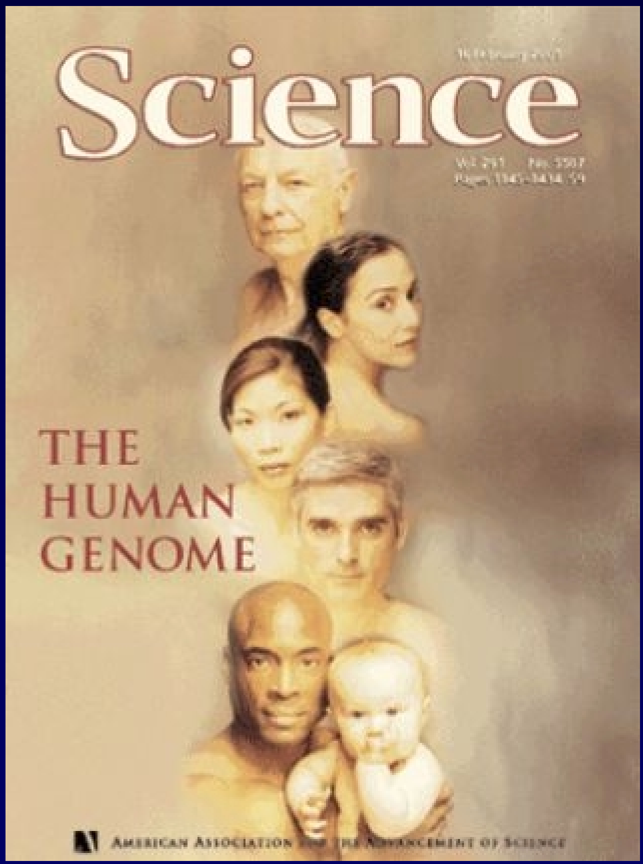
Office of Clinical Pharmacology and Biopharmaceutics
FDA/CDER

Genomics in Medical Education

“The explosion of information about the new genetics will create a huge problem in health education. Most physicians in practice have had not a single hour of education in genetics and are going to be severely challenged to pick up this new technology and run with it."

Francis Collins

2001


Science
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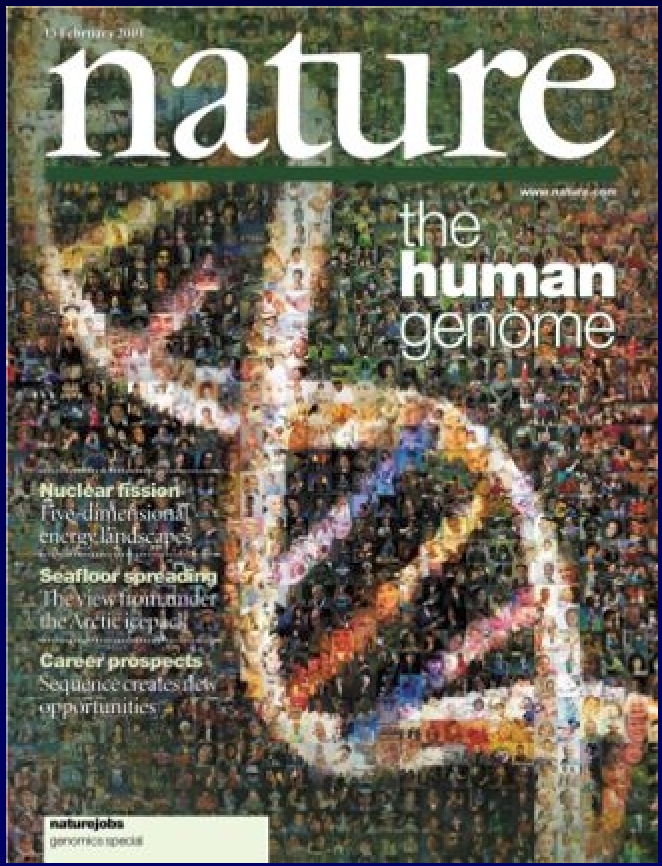
nature
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Nuclear fission
Five-dimensional energy landscapes
Seafloor spreading
The view from under the Arctic icepack
Career prospects
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2004

ELSEVIER

Education: Teaching pharmac… physician… personali…

David Gurwitz[1], Abr…

[1]Department of Human Genetic…
[2]Felsenstein Medical Research…
[3]Department of Physiology and…

Critical Issues in Dental Education: Genetics Education for Dental Health Professionals

A Call fo… Dental H…

Francis Collins, M…

Dr. Collins is Director, N…
Craniofacial Research, b…
Collins, Director, Nation…
Rockville Pike, Bethesd…

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OPINION

From pharmacogenetics to personalized medicine: a vital need for educating health professionals and the community

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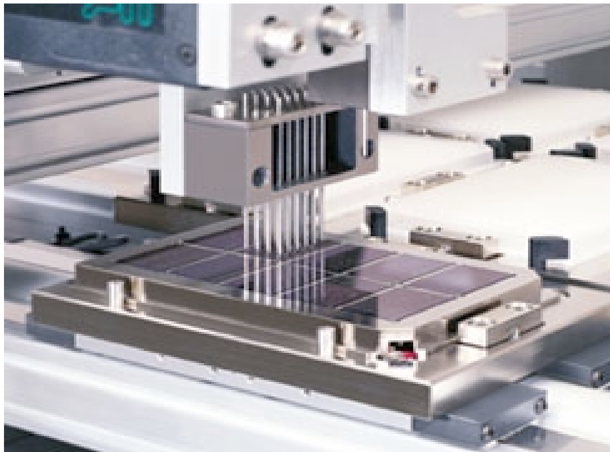
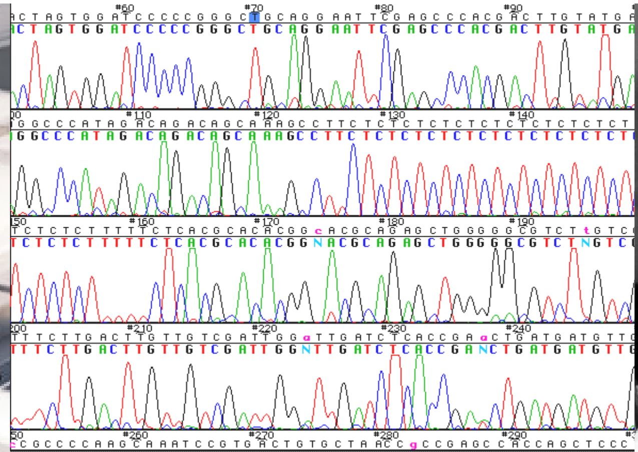
The field of pharmacogenetics will soon celebrate its 50th anniversary. Although science has delivered an impressive amount of information in these 50 years, pharmacogenetics has suffered from lack of integration into clinical practice. There are several reasons for this, including the unmet need for education at medical schools and the lack of awareness about the impact of genetic medicine on healthcare in the community. Recently, the FDA announced that it considers pharmacogenomics one of three major opportunities on the critical path to new medical products. This notion by the FDA is filling the regulatory void that existed between drug developers and drug users. However, in order to bring pharmacogenetic testing to the prescription pad successfully, healthcare professionals and policy makers, as well as patients, need to have the necessary background knowledge for making educated treatment decisions. To effectively move pharmacogenetics into everyday medicine, it is therefore imperative for scientists and teachers in the field to take on the challenge of disseminating pharmacogenetic insights to a broader audience.

Stakeholders

Patients	Education Privacy and Informed Consent Legal Protection
Physicians	Education When and How to Use a Test ? Pharmacodiagnostics
Health Care Providers	Coverage General Availability Recommendations
Regulators	Regulation of Pharmacogenetic Tests, Usage Use of Test Results on Drug Labels
Pharmaceutical Industries	Impact on Revenue Incentives to Develop Tests New drug development
Technology Developers	Numerous Platforms and Methods Biology, Genetics





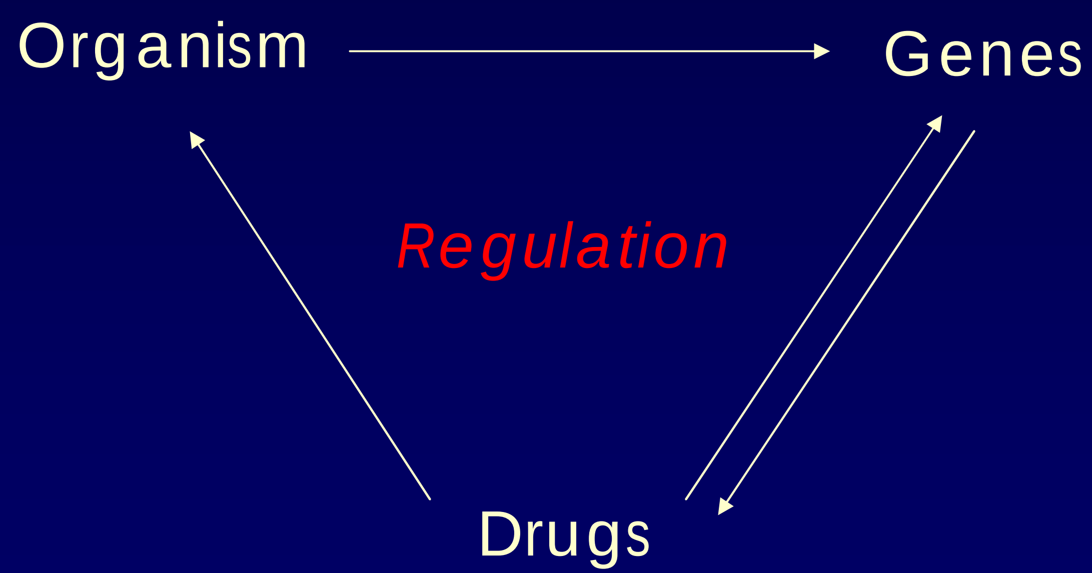
VISION:

Pharmacogenomics will improve health care.

PGx is part of biomedical research providing a toolkit to assess an individual's response to drug therapy.

PGx should be used in the clinic as every other analytical tool is used: to identify the best possible care for the patient.

Context: Genes and Drugs

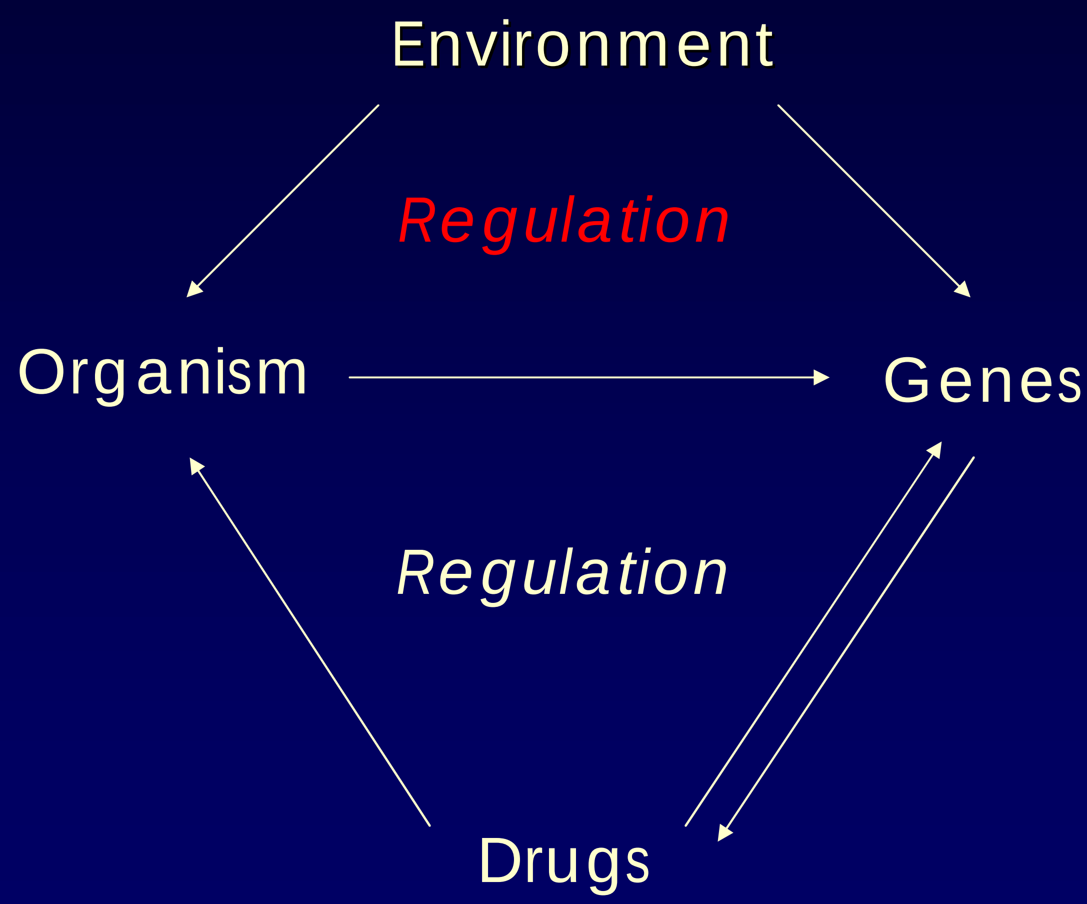


How are genes regulated by drugs ?

Which genes are regulated ?

What genetic variations are important for drug response ?

Context: Genes and Drugs



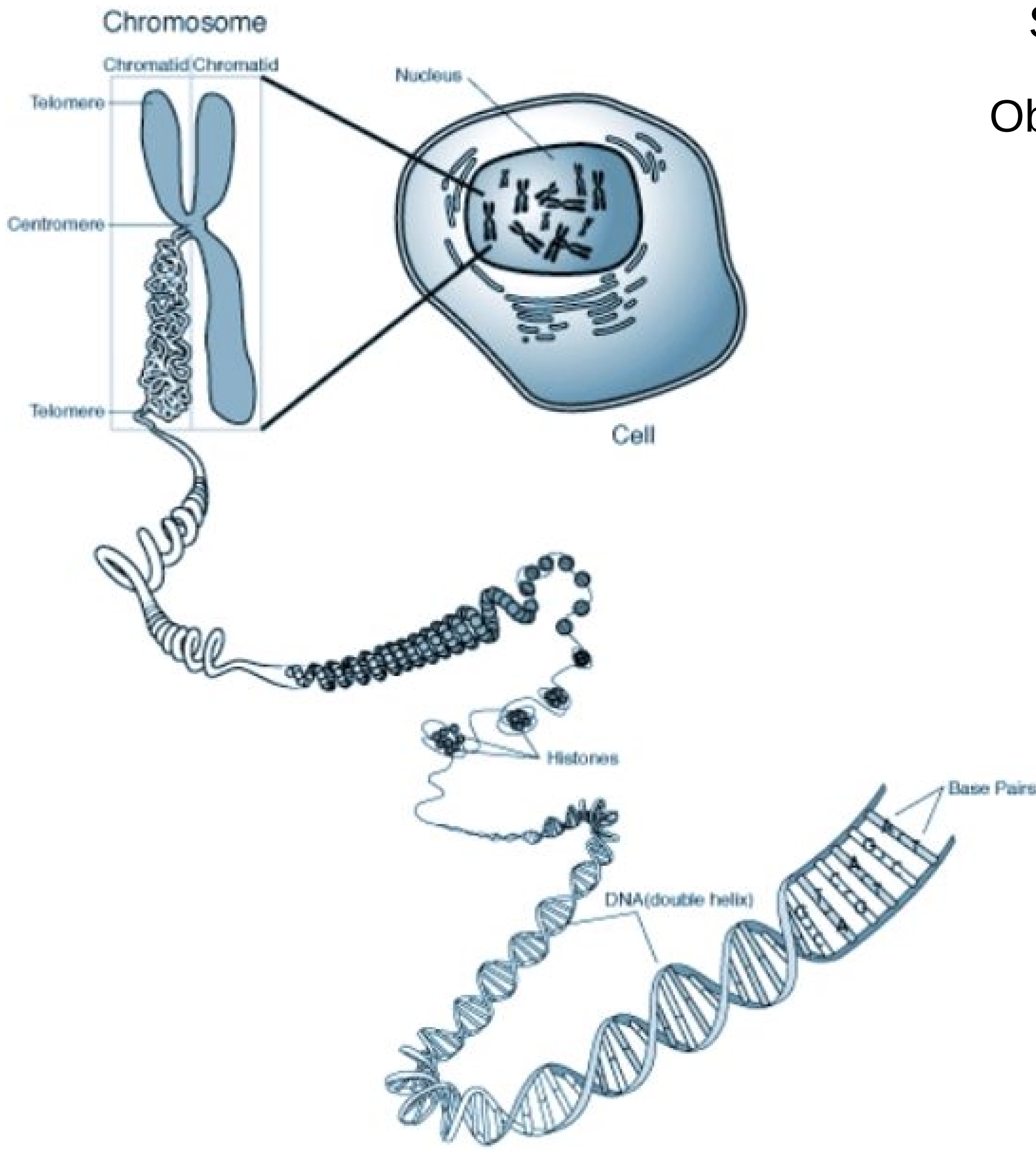
How are genes regulated by drugs ?

Which genes are regulated ?

What genetic variations are important for drug response ?

Environment

- Age
- Gender
- Race
- Body mass index
- Alcohol
- Tobacco
- Diet
- Co-morbid conditions
- Drug interactions
- Concomitant conditions
- Altered organ function
- …



Safety and/or efficacy:

Observation Prevention

Cause Prediction

Table 1. Milestones in PGx.

Year	Event	Ref.
1955	Bonicke and Orlowski describe the relation of excretory levels to therapeutic results for the antituberculosis drug isoniazid	[28,29]
1957	Arno Motulsky describes that 'idiosyncratic drug reactions might be caused by otherwise innocuous genetic traits and enzyme deficiencies,' and delineates the field	[30]
1959	Friederich Vogel coins the term 'pharmacogenetics' and defines it as 'clinically important hereditary variations'	[31]
1962	Werner Kalow publishes the book entitled 'Pharmacogenetics – Heredity and the Responses to Drugs'	[32]
1963	Remmer and Merker describe phenobarbital-induced changes in liver endoplasmic reticulum and associate the observation with changes in drug-metabolizing enzymes	[33]
1964	Arno Motulsky describes glucose-6-phosphate dehydrogenase (G6PD) deficiency, thalassemia and abnormal hemoglobins in the Philippines	[34]
1977	Mahgoub *et al.* describe the polymorphic hydroxylation of debrisoquine in man	[35]
1988	Gonzalez *et al.* characterize a common genetic defect in the *CYP2D6* gene in humans deficient in debrisoquine metabolism	[36]
2000	The NIH announces the formation of the Pharmacogenetics Research Network	[104]
2003	Completion of the Human Genome Project	[105]
2003	FDA issues draft 'Guidance for Industry: Pharmacogenomic Data Submissions'	[106]

NIH: National Institutes of Health; PGx: Pharmacogenetics/pharmacogenomics.

Frueh and Gurwitz (2004), *Pharmacogenomics* 5(5)

Today:

- CYP2D6, 2C9, 2C19
- UGT1A1
- TPMT

Known/probable valid biomarkers

But:

Table 2. Increase in publications with 'pharmacogenetics' or 'pharmacogenomics' as keywords.	
Period	**Number of published articles**
1960–1969	147
1970–1979	228
1980–1989	156
1990–1999	603
2000–present	1160

Medline search performed April 21, 2004.

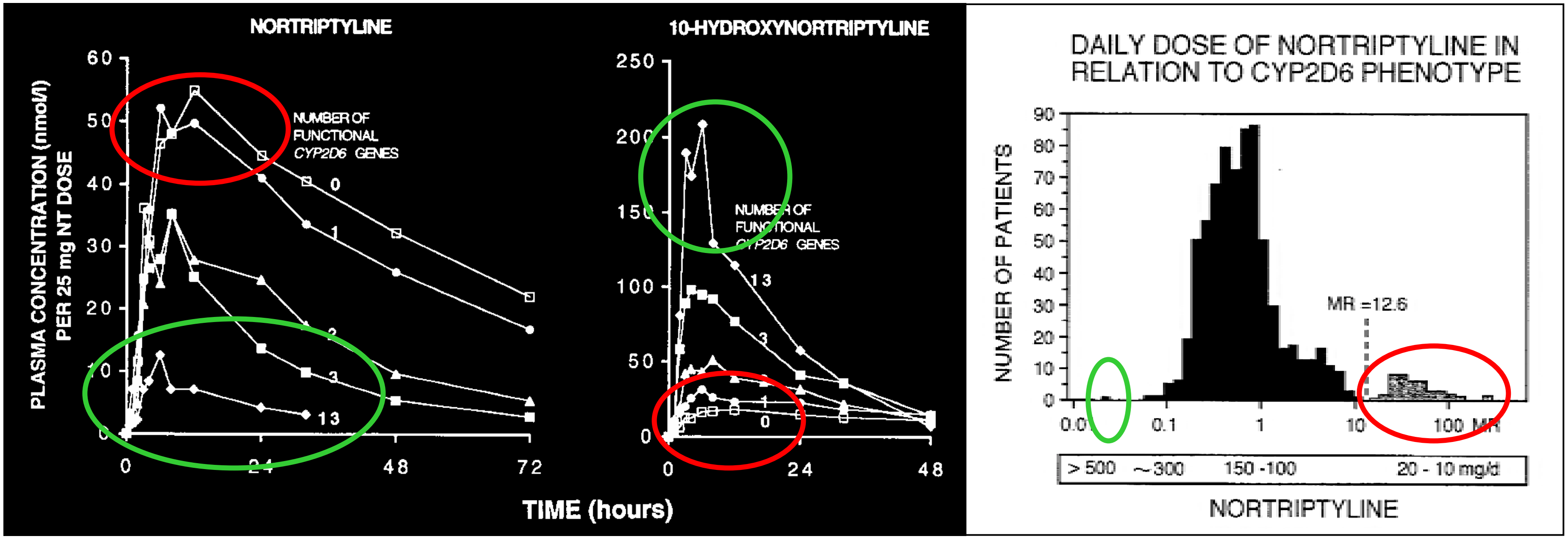
Frueh and Gurwitz (2004), *Pharmacogenomics* 5(5)

The number of PGx articles is increasing exponentially.
We need to capitalize on this knowledge: Education is the fist step.

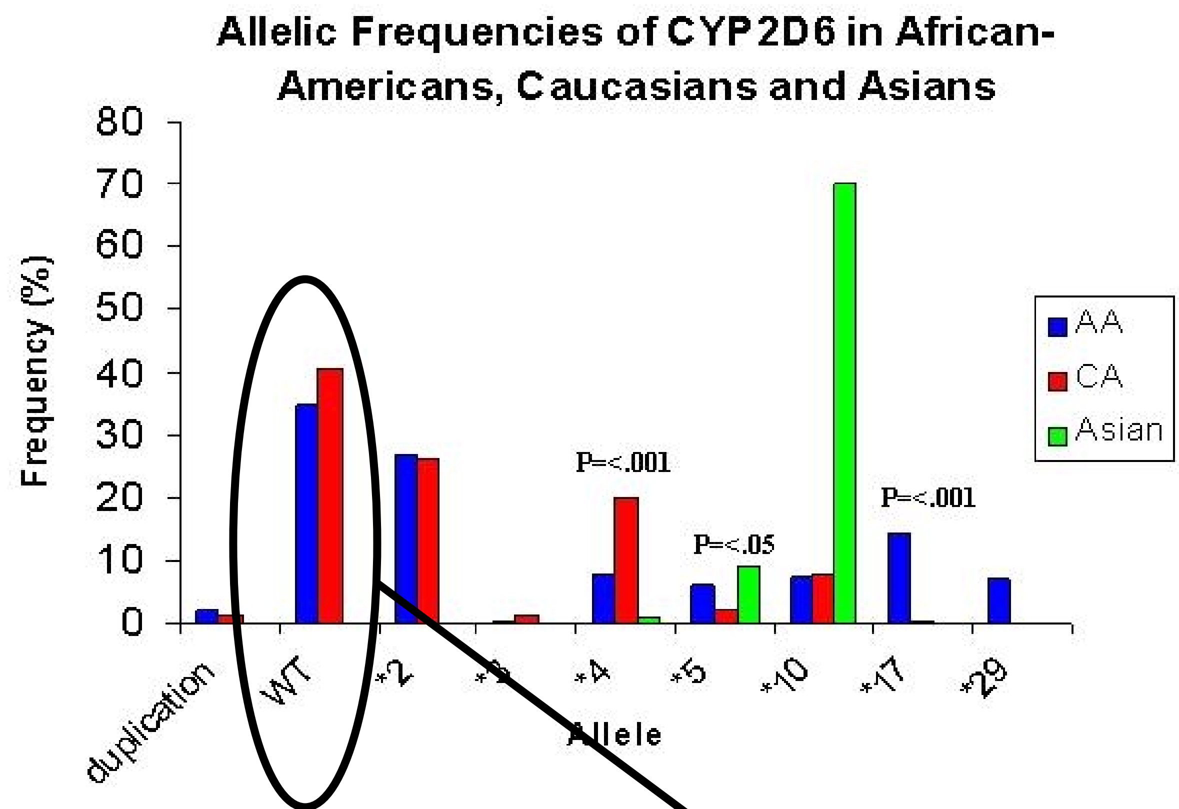
Tomorrow: {
CYP2D6, 2C9, 2C19
CYP3A4
UGT1A1
TPMT
…
} Known/probable valid biomarkers

We Know It, Are We Using It ?

- Poor Metabolizers require 10x lower dosage (~20 mg/day) of nortriptyline than Extensive Metabolizers (~200 mg/day)



Dalen et al., *Clin Pharmacol Ther* (1998), 63(4)



Wan Y et al. Pharmacogenetics 2001, 11:489-499.
Gaedigk A et al. Clin Pharmacol Ther. 2002 Jul;72(1):76-89.

Less than half of the population carries the "wildtype" allele !

Drug Labeling Regulations

- 21 CFR 201.57:

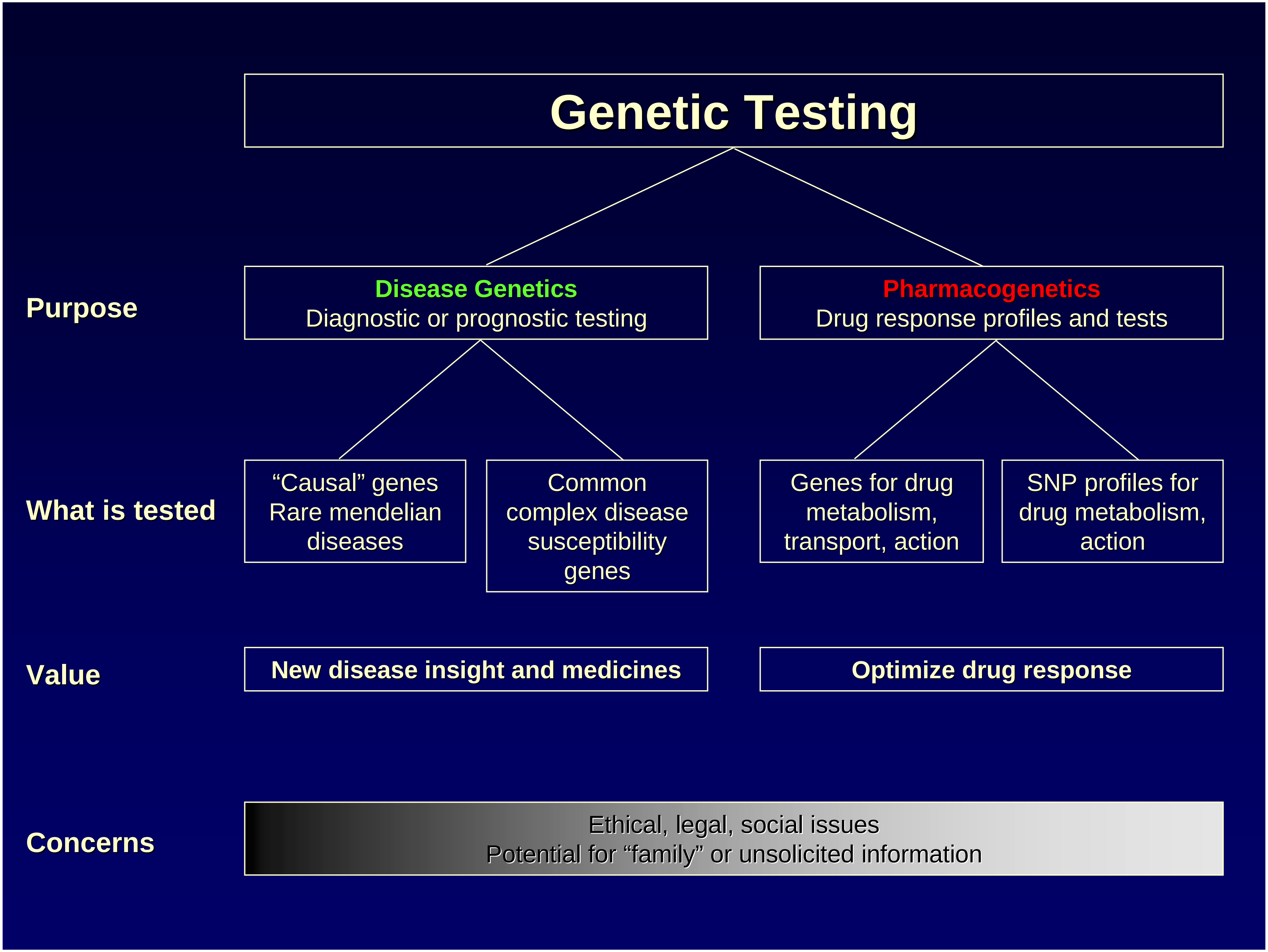
  "…if evidence is available to support the safety and effectiveness of the drug only in selected *subgroups of the larger population* with a disease, the *labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug*."

Substrates							
1A2	2B6	2C19	2C9	2D6	2E1	3A4,5,7	
amitriptyline caffeine clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine N-DeMe mexiletine naproxen ondansetron phenacetin=> acetaminophen=>NAPQI propranolol riluzole ropivacaine tacrine theophylline verapamil (R)warfarin zileuton zolmitriptan	bupropion cyclophosphamide efavirenz ifosfamide methadone	Proton Pump Inhibitors: lansoprazole omeprazole pantoprazole E-3810 Anti-epileptics: diazepam=>Nor phenytoin(O) S-mephenytoin phenobarbitone amitriptyline carisoprodol citalopram clomipramine cyclophosphamide hexobarbital imipramine N-DeME indomethacin R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin=>8-OH	NSAIDs: diclofenac ibuprofen meloxicam S-naproxen=>Nor piroxicam suprofen Oral Hypoglycemic Agents: tolbutamide glipizide Angiotensin II Blockers: losartan irbesartan amitriptyline celecoxib fluoxetine fluvastatin glyburide phenytoin=>4-OH rosiglitazone tamoxifen torsemide S-warfarin	Beta Blockers: carvedilol S-metoprolol propafenone timolol Antidepressants: amitriptyline clomipramine desipramine imipramine paroxetine Antipsychotics: haloperidol perphenazine risperidone=>9OH thioridazine alprenolol amphetamine bufuralol chlorpheniramine chlorpromazine codeine (=>O-desMe) debrisoquine dexfenfluramine dextromethorphan encainide flecainide fluoxetine fluvoxamine lidocaine metoclopramide methoxyamphetamine mexiletine nortriptyline minaprine ondansetron perhexiline phenacetin phenformin propranolol quanoxan sparteine tamoxifen tramadol venlafaxine	Anesthetics: enflurane halothane isoflurane methoxyflurane sevoflurane acetaminophen =>NAPQI aniline benzene chlorzoxazone ethanol N,N-dimethyl formamide theophylline =>8-OH	Macrolide antibiotics: clarithromycin erythromycin (not 3A5) NOT azithromycin Anti-arrhythmics: quinidine=>3-OH (not 3A5) Benzodiazepines: alprazolam diazepam=>3OH midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Antivirals: indinavir nelfinavir ritonavir saquinavir Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine terfenidine Calcium Channel Blockers: amlodipine diltiazem felodipine lercanidipine nifedipine nisoldipine nitrendipine verapamil	HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin NOT pravastatin simvastatin Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone Miscellaneous: alfentanyl buspirone cafergot caffeine=>TMU cocaine dapsone codeine- N-demethylation dextromethorphan eplerenone fentanyl finasteride gleevec haloperidol irinotecan LAAM lidocaine methadone odanestron pimozide propranolol quinine salmeterol sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon zolpidem

Drugs, Genes, Tools

AmpliChip CYP450: Novel
DNA chip-based test

It Concerns All of Us


Genetic Testing
Purpose
Disease Genetics
Diagnostic or prognostic testing
Pharmacogenetics
Drug response profiles and tests
What is tested
"Causal" genes
Rare mendelian diseases
Common complex disease susceptibility genes
Genes for drug metabolism, transport, action
SNP profiles for drug metabolism, action
Value
New disease insight and medicines
Optimize drug response
Concerns
Ethical, legal, social issues
Potential for "family" or unsolicited information

Ethical, ***L***egal, ***S***ocial ***I***ssues

- What to do if no alternatives are available
- Consequence of not performing a test if available
- Privacy and confidentiality of genetic information
- Fairness in the use of genetic information by insurers, employers, courts, schools, adoption agencies, and the military, among others
- Psychological impact, stigmatization, and discrimination due to an individual’s genetic differences
- Uncertainties associated with gene tests for susceptibilities and complex conditions (e.g., heart disease, diabetes, Alzheimer’s)
- Fairness in access to advanced genomic technologies.
- Conceptual and philosophical implications regarding human responsibility, free will vs genetic determinism

Socio-Economical Aspects: An Incentive

1973: 28% of hospitalized patients had adverse drug reactions
(Miller, Am. *J. Hosp. Pharm.* 30: 584-592)

1979: 17% of hospitalized children had adverse drug-attributed events
(Mitchell et al., *Am. J. Epid.* 110: 196-204)

1994: 2,216,000 serious adverse drug reactions in hospitalized patients
(Lazarou et al., *JAMA* 279: 1200-1205)

1995: Adverse drug reactions identified as 4th to 6th leading cause of death, causing >100,000 deaths per year
(Johnson & Bootman, *Arch. Intern. Med.* 155: 1949-1956)

1995: Drug-related morbidity and mortality estimated at **US$ 76.6 billion**
(Johnson & Bootman, *Arch. Intern. Med.* 155: 1949-1956)

2000: Drug-related morbidity and mortality estimated at **US$ 177.4 billion**
(Ernst & Grizzle, *J. Am. Pharm. Assoc.* 41: 192-199)

Now, what about EDUCATION ?

Pharmaceutical Sciences and Pharmacogenomics Graduate Program - Microsoft Internet Explorer

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Graduate Program in

Pharmaceutical Sciences and Pharmacogenomics

Department of Biopharmaceutical Sciences

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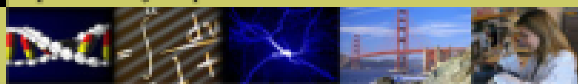

Training the next generation of scientists to explore new drugs in novel ways.

The graduate program in Pharmaceutical Sciences & Pharmacogenomics (PSPG) leads to a PhD degree in one of the most quickly expanding and dynamic fields of contemporary science.

The program is multidisciplinary and has a dual focus.

•*Pharmaceutical Sciences*: includes the scope of disciplines from chemistry to biology and from pharmacology to bioinformatics, involved in the discovery and development of medications.

•*Pharmacogenomics*: the application of genetics and genomics to drug action and disposition.

PSPG in the News

Kathleen M. Giacomini and Leslie Z. Benet Honored by International Peers at the Pharmaceutical Sciences World Congress, May 29 to June 4, 2004.

Upcoming Events

Annual PSPG Faculty and Student Retreat
September 13-15, 2004
Marconi Conference Center
Tomales Bay, Marshall, California

IRA HERSKOWITZ, Ph.D.
1946-2003

On April 28, Dr. Ira Herskowitz passed away after a battle with pancreatic cancer. We, the faculty and students of the PSPG program, are deeply saddened, both personally and professionally.

Dr. Herskowitz played a pivotal role in establishing pharmacogenomics at UCSF and in the inception and success of the PSPG graduate program, of which he was a founding member. Before his death, he established an endowed fund for excellence in research for graduate students in the PSPG program.

Ira Herskowitz Award for Excellence in Research

Please see Dr. Herskowitz's website for information about his life and work.

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FOCUS AREAS

Students can undertake fundamental research in either of the program's focus areas:

Pharmaceutical sciences, including molecular pharmacology, drug transport and metabolism, mathematical modeling of complex systems, and gene delivery

Research focus areas in the pharmaceutical sciences include the following:
Molecular/cellular studies of mechanisms involved in drug absorption, distribution, metabolism, toxicology and elimination
Molecular pharmacologic studies focused on the mechanisms of drug action
Integrative systems research in pre-clinical and clinical pharmacokinetics/pharmacodynamics
Modeling of complex systems
Drug delivery systems; gene therapy

Pharmacogenomics or toxicogenomics, which is the application of genetics and genomics to the study of pharmacology or toxicology

Research focus areas in pharmacogenomics include the following:
Use of model organisms to study mechanisms of drug action, resistance, metabolism or transport
Analysis of drug response by functional genomics using DNA expression arrays
Development of computational tools to analyze expression data (this is the new bullet)
Understanding the genetic basis for variation in drug response clinically
Understanding the genetic basis for variation in response to environmental agents (toxicogenomics)
Students may choose from a variety of electives offered by this program and other programs on campus, including courses in mathematical modeling, toxicology, drug metabolism, transport, molecular biology, cell biology, genetics, and bioinformatics.

PGx Education in Medical Schools

- *Example: Tel-Aviv University, Israel*
  - Incorporated PGx in the 2nd year MD pharmacology course
  - Additional elective PGx courses are offered to graduate students
  - Graduate course includes human genetics, and description of PGx-oriented clinical trials
  - Graduate students present on PGx studies and discuss PGx aspects of therapeutic areas
- *Other Medical Schools have similar programs, but most schools do not*
- *World-wide Survey of Medical Schools re PGx education is being conducted*

World-wide Survey: Questionnaire

1. Does your MD program include some form of PGx education as part of the pharmacology or the human genetics studies?
2. How many hours of lectures are given?
3. During which year of preclinical studies?
4. Does your PGx education for MD students include case studies?
5. If your school does not yet offer PGx education, do you expect that it will be incorporated to the MD program
6. What are the most often used educational tools?
7. Do you offer a dedicated PGx course for PhD students?
8. Comments and suggestions

World-wide Survey: Questionnaire

Which of the following topics/concepts are included

- SNPs
- CYP450 genes
- CYP2D6 "poor metabolizers"
- CYP2D6 gene duplication and "super metabolizers"
- Ethnic differences in CYP450 alleles
- P-glycoprotein (MDR-1)
- Thiopurine methyltransferase (TPMT) alleles
- Dihydropyrimidine dehydrogenase (DPD) and 5-FU pharmacokinetics
- Beta-2 adrenergic receptor polymorphism and asthma drugs
- Apo-E polymorphism and Alzheimer drugs
- Serotonin transporter (5-HTT) promoter polymorphism and antidepressants

World-wide Survey: Results

- At most, 4 hours of PGx teaching for MD students
- Typically on their 2nd year Pharmacology classes

- Case studies often included
- CYP450s, oncology PGx, given high priority

- Lack of textbook materials is evident; journal articles are often used
- Many Med Schools do not include PGx teaching

- Graduate-level courses are very rare (TAU; UCSF)

David Gurwitz, pers. communication

Summary: Possibility

- It's true: PGx research has generated a large amount of information
- This information is more than basic research and is often clinically relevant
- We can capitalize on this information and actively contribute to improve health care

Summary: Reality

- There is an unmet need for PGx education at medical schools
- PGx suffers from a lack of integration into clinical practice
- There is also a lack of awareness about the impact of genetic medicine on healthcare in the community at large
- Half of the amount of PGx research of the last 50 years was published in the last 5 years only: “give us some time!”

Summary: Closing the Gap

- Public awareness rises with the use of PGx in the clinic: it is a synergistic process, but it will start in the clinic
- A number of well-understood, clinically proven applications for PGx exist: we need to start using them more broadly (e.g. DMEs) – new ones are emerging (e.g. EGFR)
- Novel scientific approaches will lead to a better understanding of complex genotype-phenotype relationships
- Standards to validate probable genomic biomarkers need to be established to thrive the future clinical use of PGx

But We Need to Do It Right !