Are health care systems ready to deliver pharmacogenetics as standard of care?

Predicting the needs and setting the strategies

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OECD, Rome, October 19, 2005

Are we ready for personalized medicine?

- If not ready yet, when?
- Priorities?
- Barriers?
- Solutions?

Hooked on Drugs:
Mean lifetime drug consumption (UK)

Prescription ~ 14,000

OTC ~ 30,000

Annual USA expenditures on prescription drugs: ~US$ 70 Billions

"*Cradle to Grave*"at The British Museum

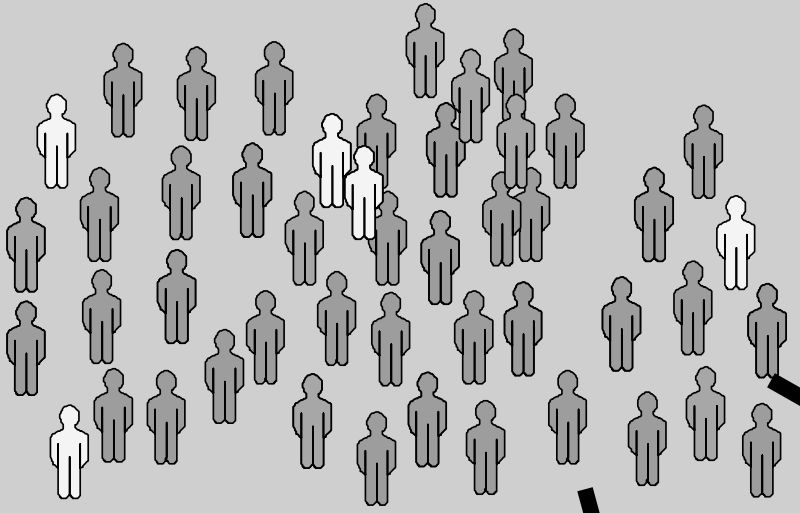
UK ADRs Study

Directly related to ADRs:

- 6.5% of new hospital admissions
  (1,225 admissions out of 18,820 during six months)
- 4% of hospital bed occupancy
- UK direct annual costs: EUR 706 million
- Women: 59% of ADRs (while only 52% of admissions)

Pirmohamed *et al* (July 2004) *BMJ*. 329:15-19.

All patients with same diagnosis

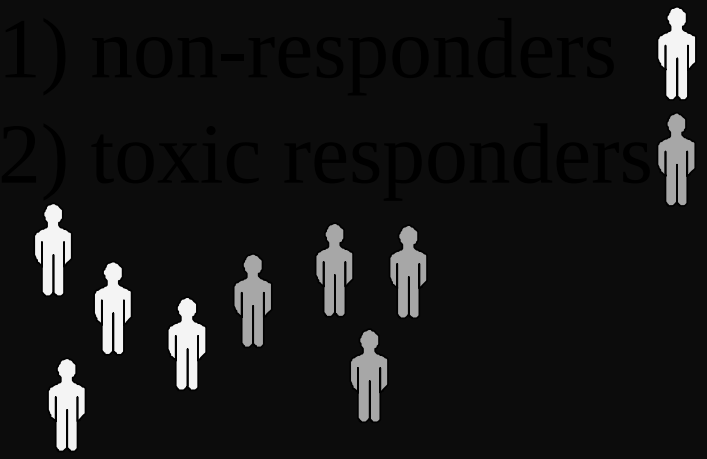


Personalized Medicine:

Remove:

(1) non-responders

(2) toxic responders

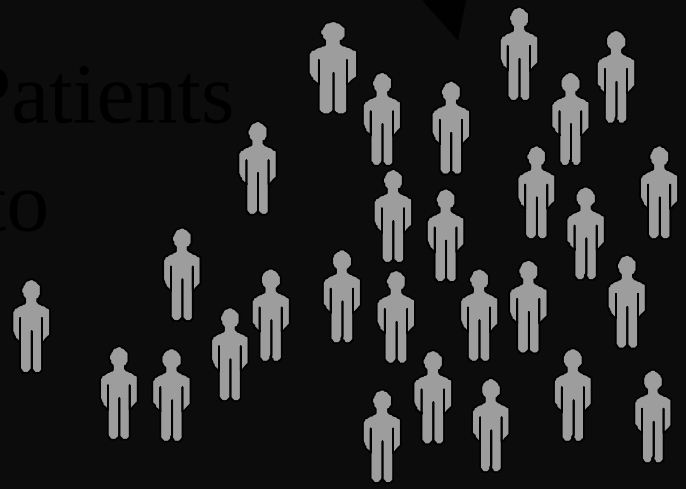


Which is more urgent?

What should our priorities be?

Treat:

Responders and Patients Not Predisposed to Toxicity



"Primum non nocere" (Galen, 131-201 AD)

- Priorities for personalized medicine should be like fitting a belt for your trousers or skirt:

- The first priority is that it does not hurt!

- Ensuring that it holds your trousers is only a second priority..

Consideration #1: Society is almost ready..

Growing public awareness on:

- Costs of drug toxicity
- Genetic factors affecting complex diseases
- Soaring health care costs

Consideration #2:
Regulatory bodies are almost ready

FDA has issued the "Guidance for Industry: Pharmacogenomic Data Submissions" (March 2005)

WHO/CIOMS* Working Group on Pharmacogenetics has issued the report, "Pharmacogenetics: Towards improving treatment with medicines" (February 2005)

*Council for International Organizations of Medical Sciences

Consideration #3:
Diagnostic Tools are coming!

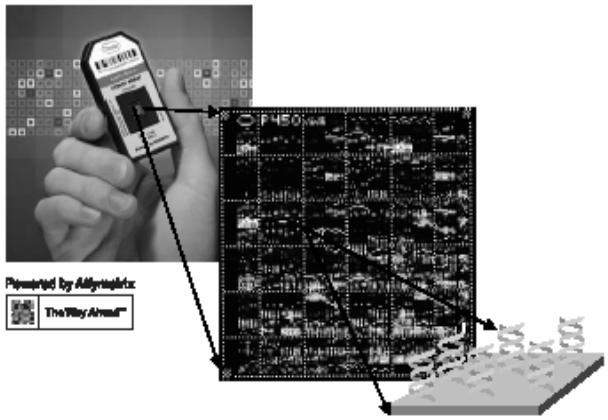
Recent FDA approvals:

- Roche Diagnostics "AmpliChip P450" (December 2004)

- Third Wave UGT1A1 test for Irinotecan

  (August 2005)

As part of its landmark January 2003 collaboration agreement, Affymetrix agreed to manufacture AmpliChip microarrays for Roche Diagnostics under strict quality controlled conditions. The Affymetrix array technology and systems integrate semi-conductor fabrication techniques, solid phase chemistry, molecular biology, software, and robotics. Photolithography, or the predetermined layering done molecule by molecule using light-directed chemical synthesis and masks, enables the building up of thousands of predetermined DNA sequences in 25-molecule-long elements at specific locations on the chip. Together, these DNA fragments (called oligonucleotides), packed by the thousands into even tiny 20μm² cells on the array, represent the biological system to be analyzed.



The Next Diagnostic Chips?

Additional approved diagnostics are needed:

General: CYP2C9; CYP3A5; CYP3A4; CYP2B6; MDR-1; UDP Glucuronosyltransferases (UGTs); N-acetyltransferases (NATs)

Oncology: thiopurine methyltransferase (TMPT); Thymidilate synthase (TS); dihydropyrimidine dehydrogenase (DHD) (for 5-FU dosing)

PGx is almost 50 years old..

☐ **1:** J Am Med Assoc. 1957 Oct 19;165(7):835-7. Related Articles, Links

Drug reactions enzymes, and biochemical genetics.

MOTULSKY AG.

PMID: 13462859 [PubMed - OLDMEDLINE for Pre1966]

Pharmacogenetics: Evans & Clarke (1961) *Bri. Med. Bull.* 17: 234-240

Pharmacogenomics: Marshal (1997) Nature Biotechnology 15: 829-830

Personalized Medicine: Langreth & Waldholz (1999) *Oncologist* 4: 426-427

50 Years Later: Where are the barriers?

- Insufficient knowledge – need for better studies
- Insufficient data-sharing
- Complex regulations
- Insufficient awareness of health professionals

Tentative solutions?

- More public funding for PGx research
- NHS funding for established PGx tests
- Incentives for data-sharing by private sector
- Simplifying regulatory measures
  (EU: EMEA is less pro-active *vs.* FDA)
- Better PGx education for health professionals

PGx education for health professionals

122 Opinion *TRENDS in Pharmacological Sciences* Vol.24 No.3 March 2003

ELSEVIER

Education: Teaching pharmacogenomics to prepare future physicians and researchers for personalized medicine

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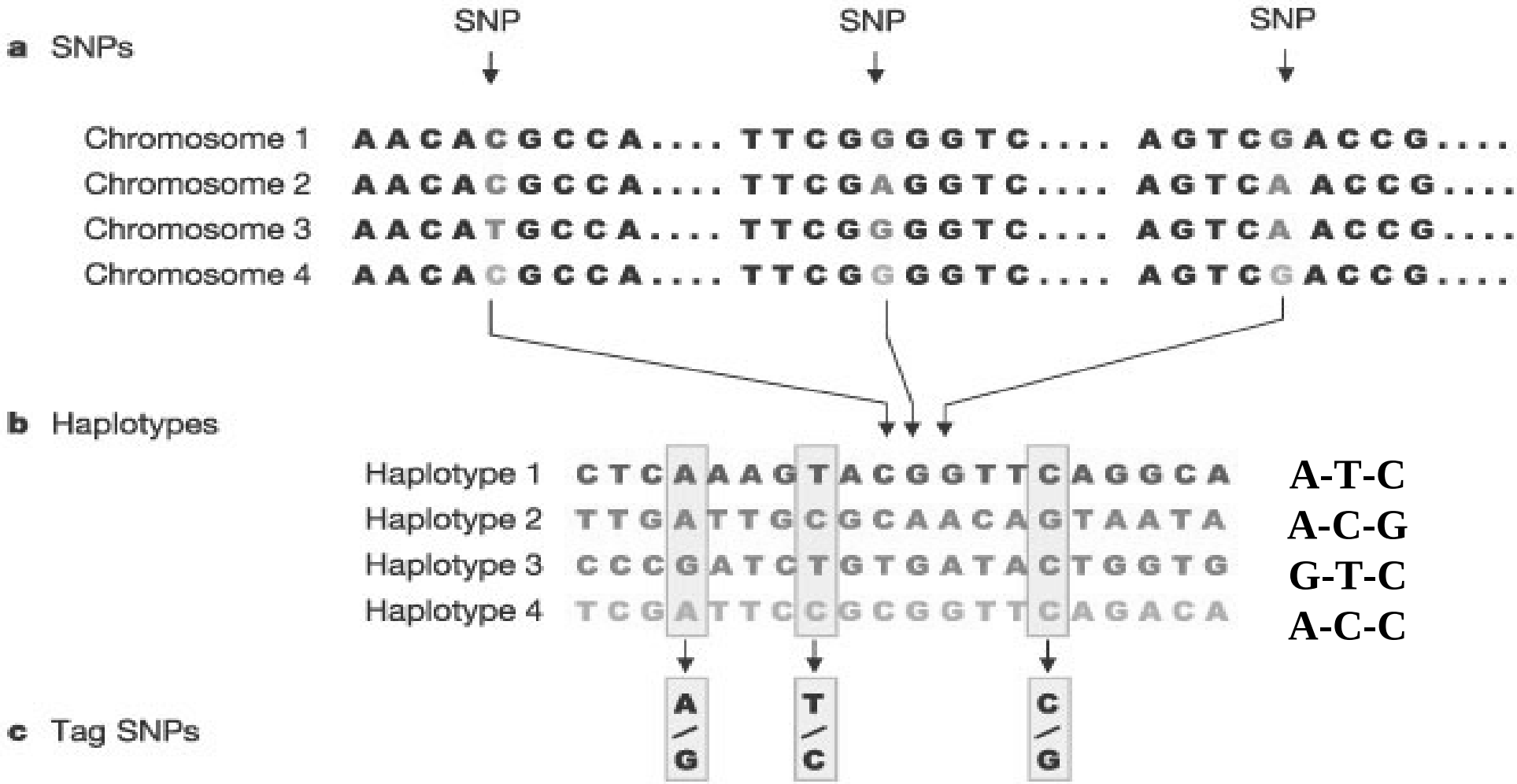
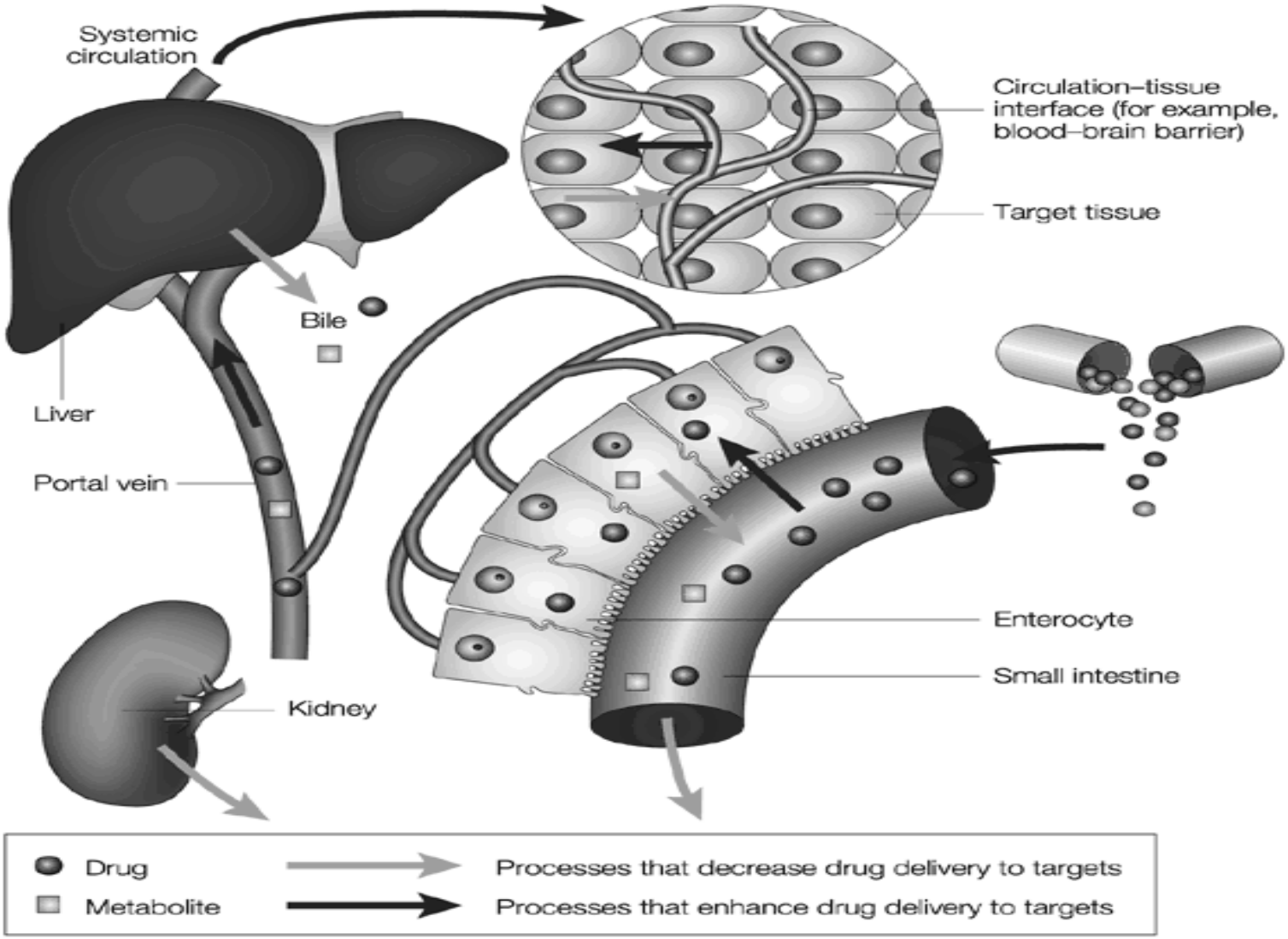
SNPs and Haplotypes

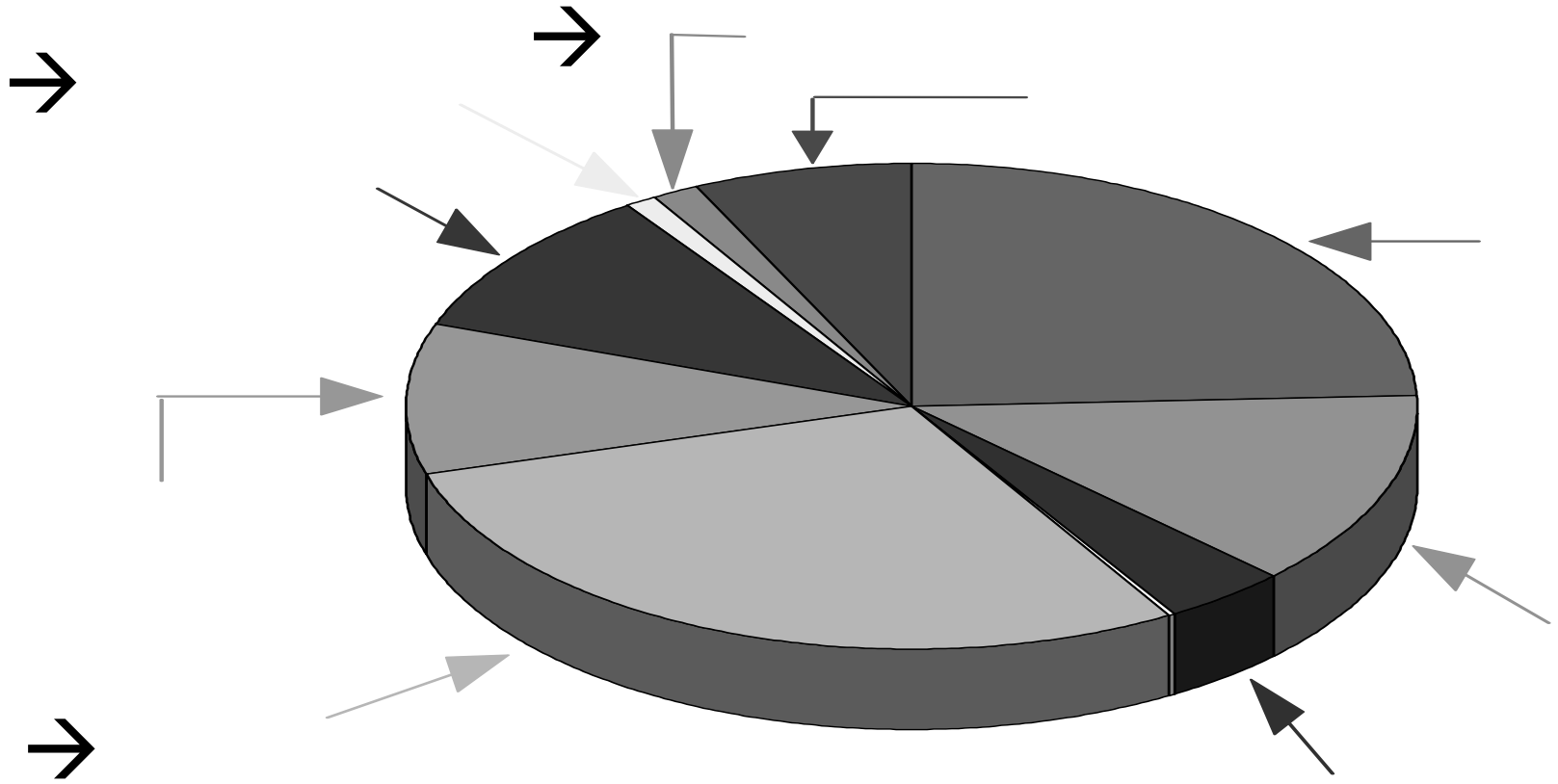


Drug Pharmacokinetics



CYP450 Content in Human Liver

Low levels of P4502D6 & P4502C19



CYP2D6 Substrates

Debrisoquine
Amphetamine
Dexfenfluramine
Ouanoxan
Ondansetron

Beta Blockers

Propafenone
S-metoprolol
Propranolol
Timolol
Alprenolol
Bufuralol
Carvedilol

Antiarrhythmics

Encainide
Flecainide
S-mexillitene
Lidocaine

Antidepressants

Fluoxetine
Fluvoxamine
Paroxetine
Venlafaxine
Amitriptylline
Clomipramine
Imipramine

Antipsychotics

Perphenazine
Thioridazine
Haloperidol
Risperidone
Minaprine

Analgesics

Dextromethorphan
Codeine
Tramadol

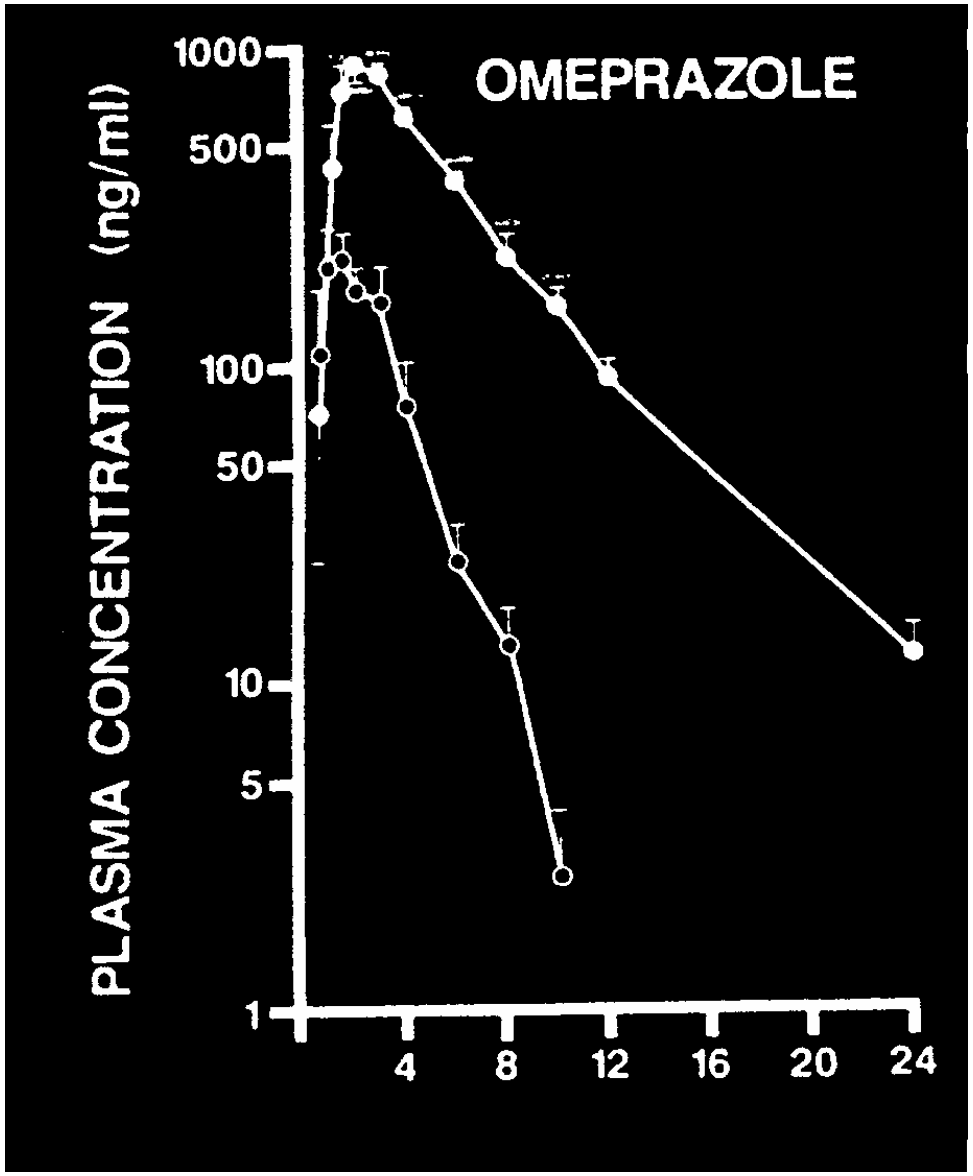
CYP2D6 Poor Metabolizers

Caucasians	5% -10%
African-Americans	6%
Africans	2% – 19%

Japanese	0.5%
Chinese	0.7%

Opposite situation for CYP2C19

CYP2C19 Polymorphism



Omeprazole and CYP2C19

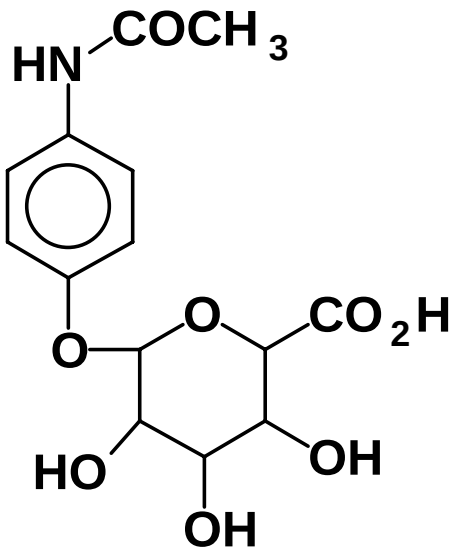
- ● Poor metabolizers
- ○ Extensive metabolizers

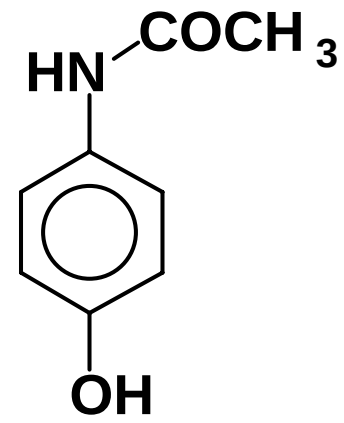
Sohn *et al* (1992) *JPET* 262, 1195-1202

Acetaminophen Metabolism:

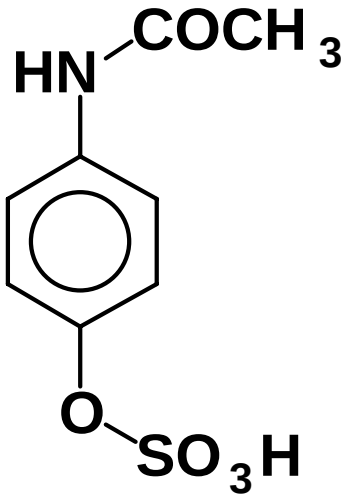
Identifying "UGTs poor metabolizers" could save lives

Glucuronidation (60%)

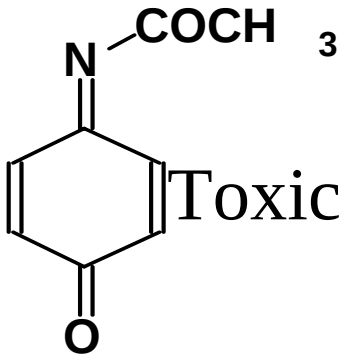




Sulfation (35%)

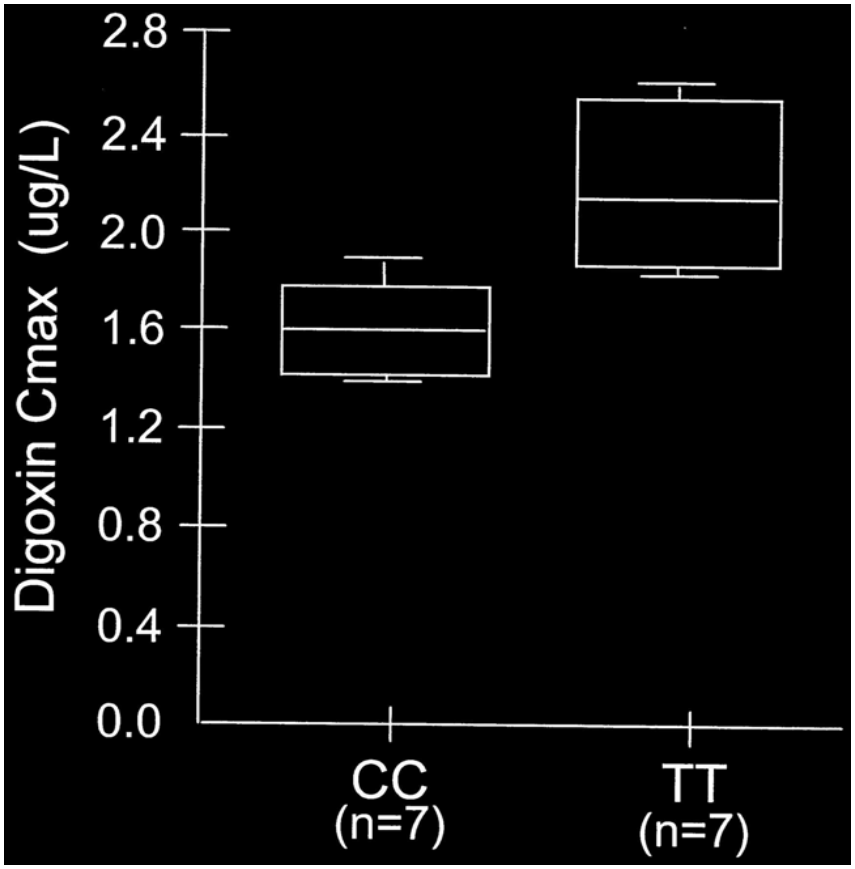


↓ CYP2E1(5%)



Toxic!

MDR-1 C3435T Genotype and Digoxin Cmax



C3435T (exon 26):

- Lower P-glycoprotein levels
- Higher blood digoxin levels

Hoffmeyer *et al* (2000), *PNAS* 97, 3473-3478

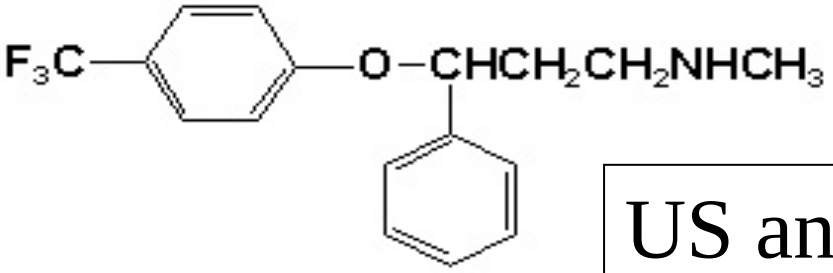
Personalized Psychiatry

Notable example:

- The SSRIs antidepressants:
Selective Serotonin Reuptake Inhibitors
(fluoxetine, fluvoxamine, paroxetine, etc.)

→ Only ~60% of patients respond favorably; this is unrelated to blood SSRI concentrations

SSRIs: Excellent Money Makers..

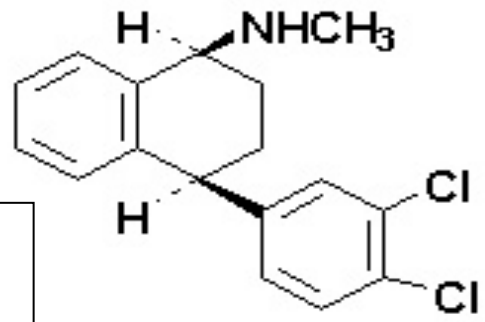


FLUOXETINE

Prozac: $1,577M

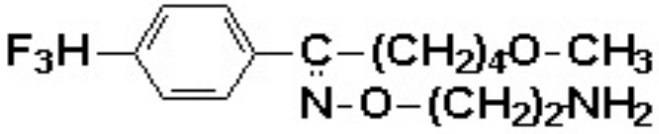
US annual sales

Phillips & Van Bebber 2005
NRDD 4:500-509



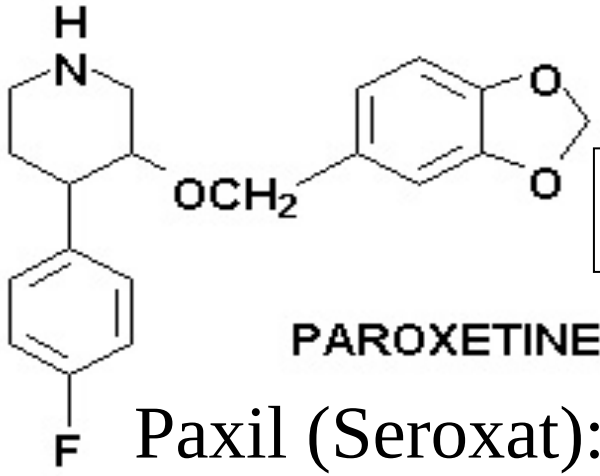
SERTRALINE

Zoloft



FLUVOXAMINE

Luvox: $126M

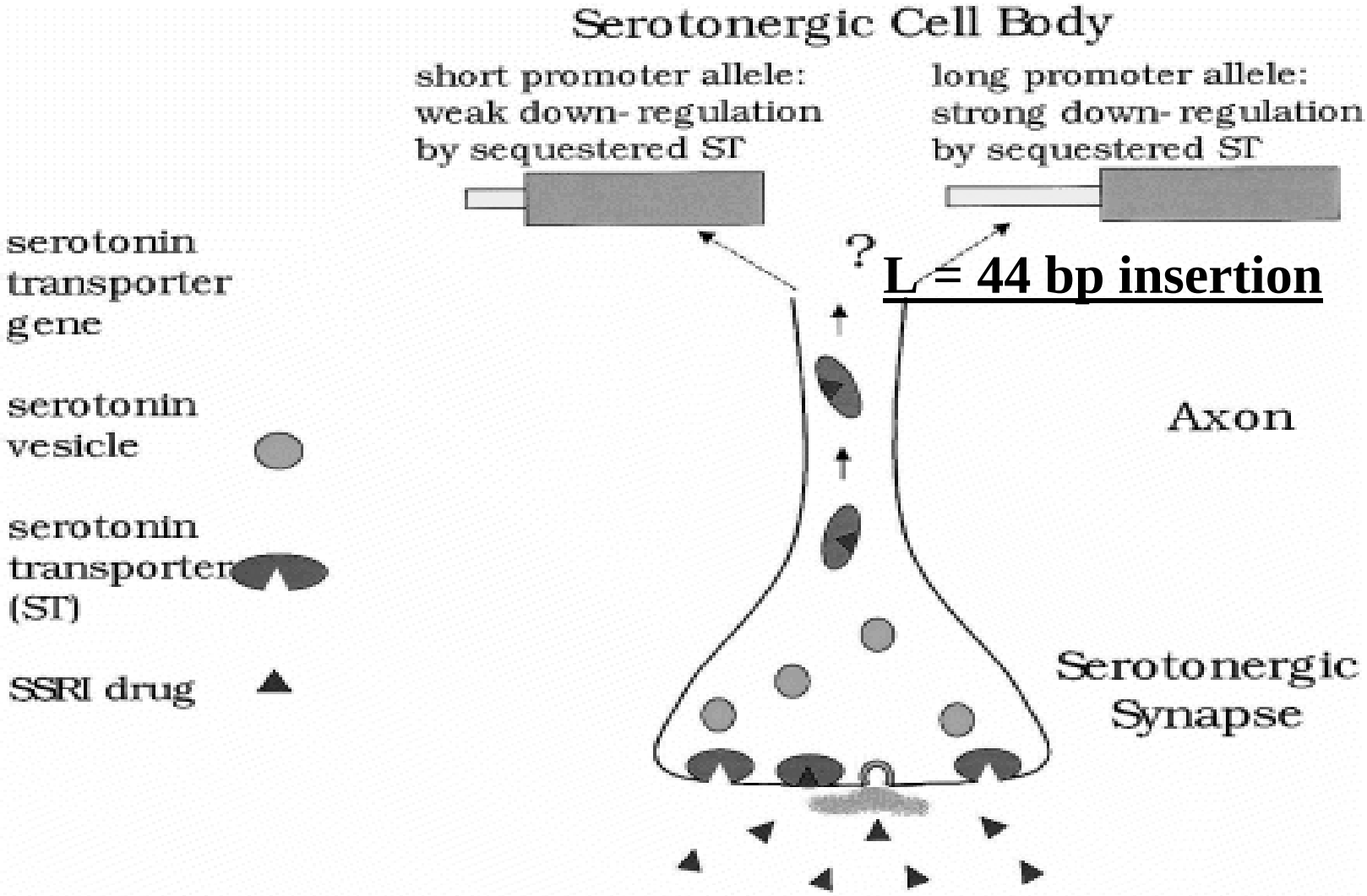


PAROXETINE

Paxil (Seroxat): $2,468M

All: metabolized by CYP2D6

Drug Efficacy and 5-HTT Polymorphism



Gurwitz D (2000). *Clinical Genetics* 57, 247-249

SSRI Efficacy

HAM-D rating	L/L	L/S	S/S	
N	16	26	16	
Week 0	25.1	28.4	27.7	
Week 1	21.5	24.4	24.8	
Week 2	16.6	20.0	23.4	
Week 3	11.0	15.3	22.2	
Week 4	7.4	10.3	20.6	(p = 0.030)

(paroxetine = 40 mg/day)

Zanardi *et al* (2000) J *Clin Psychopharmacol*. 20, 105-107

NLGIP Study: CYP2D6 & CYP2C19

SHORT COMMUNICATION

Am J Pharmacogenomics 2004; 4 (6): 395-401
1175-2203/04/0006-0395/$31.00/0

Polymorphisms of *CYP2C19* and *CYP2D6* in Israeli Ethnic Groups

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Luo *et al (2004) American Journal of Pharmacogenomics* 4: 395-401

Table I. Allele frequencies for the cytochrome P450 genes *CYP2C19* and *CYP2D6* in Israeli ethnic groups

Allele	Yemenite Jews [% (95% CI)]	Sephardic Jews [% (95% CI)]	Ethiopian Jews [% (95% CI)]	Bedouins [% (95% CI)]
***CYP2C19* allele**				
*CYP2C19**1	87.5 (79.9, 95.1)	86.2 (79.2, 93.1)	80.4 (70.0, 90.8)	87.0 (80.4, 93.6)
*CYP2C19**2	12.5 (4.9, 20.1)	13.8 (6.9, 20.8)	19.6 (9.2, 30.0)	12.0 (5.6, 18.4)
*CYP2C19**3	0	0	0	1.0 (0, 3.0)
***CYP2D6* allele**				
*CYP2D6**1	38.9 (27.6, 50.1)	30.9 (21.6, 40.2)	23.2 (12.1, 34.3)	49.0 (39.2, 58.8)
*CYP2D6**2	4.2 (0, 8.8)	6.4 (1.5, 11.3)	5.4 (0, 11.3)	9.0 (3.4, 14.6)
*CYP2D6**3	0	1.0 (0, 3.0)	0	0
*CYP2D6**4[a]	7.0 (1.0, 12.8)	21.3 (13.0, 29.6)	5.4 (0, 11.3)	4.0 (0.2, 7.8)
*CYP2D6**5	2.8 (0, 6.6)	0	3.6 (0, 8.5)	3.0 (0, 6.3)
*CYP2D6**10[b]	16.6 (8.1, 25.3)	6.4 (1.5, 11.3)	5.4 (0, 11.3)	2.0 (0, 4.7)
*CYP2D6**17[c]	0	1.0 (0, 3.0)	14.3 (5.1, 23.5)	2.0 (0, 4.7)
*CYP2D6**41	27.7 (17.4, 38.0)	26.6 (17.7, 35.5)	33.8 (21.4, 46.2)	29.0 (20.1, 37.9)
*CYP2D6**2xN	2.8 (0, 6.6)	6.4 (1.5, 11.3)	8.9 (1.4, 16.4)	2.0 (0, 4.7)

a Yemenite Jews vs Sephardic Jews, $p < 0.01$; Sephardic Jews vs Ethiopian Jews, $p < 0.01$; Sephardic Jews vs Bedouins, $p < 0.001$.

b Yemenite Jews vs Sephardic Jews, $p < 0.05$; Yemenite Jews vs Ethiopian Jews, $p < 0.05$; Yemenite Jews vs Bedouins, $p < 0.001$.

c Yemenite Jews vs Ethiopian Jews, $p < 0.001$; Sephardic Jews vs Ethiopian Jews, $p < 0.01$; Ethiopian Jews vs Bedouins, $p < 0.001$.

CI = confidence interval.

PGx education for health professionals

The Pharmacogenomics Journal (2005), 1–5

www.nature.com/tpj

CONSENSUS ARTICLE

Pharmacogenomics Education: International Society of Pharmacogenomics Recommendations for Medical, Pharmaceutical, and Health Schools Deans of Education

D Gurwitz[1] JE Lunshof[2] G Dedoussis[3] CS Flordellis[4] U Fuhr[5] J Kirchheiner[5] J Licinio[6] A Llerena[7] VG Manolopoulos[8] LJ Sheffield[9] G Siest[10] F Torricelli[11] V Vasiliou[12] S Wong[13]

ABSTRACT

Pharmacogenomics would be instrumental for the realization of personalized medicine in coming decades. Efforts are evident to clarify the potential bioethical, societal, and legal implications of key pharmacogenomics-based technologies projected to be soon introduced into the core practice of

PGx education for Society

Barrier: the public fears new biotechnologies
(example: bioengineered foods)

Solutions:

- Public TV programming
- Science museum exhibits
- 'Medicine fairs' in community centers etc.

- Focus on: improving drug safety!

Frueh & Gurwitz (2004) *Pharmacogenomics* 5:571-579

Assuring non-discrimination

Example: Israeli Genetic Information Law 2000 (5761)

Article B: Communication of Results of Genetic Tests; Item 20.

> A treating practitioner… may provide genetic information to another treating practitioner… (only) for the purpose of imminent treatment of the subject, unless the subject has given his objection thereto.

Are We Ready?

"Here's my sequence..."
(New Yorker)

<u>Not yet! We need:</u>

- Comprehensive PGx data
- Better (affordable) diagnostics
- Professional PGx education
- Solving ethical issues!

Focus should primarily be:
<u>Improving drug safely!</u>