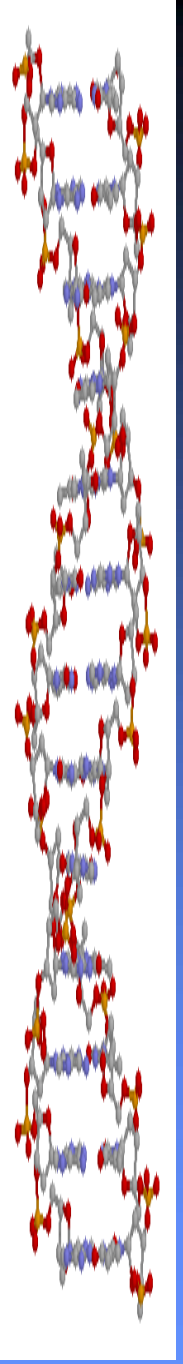
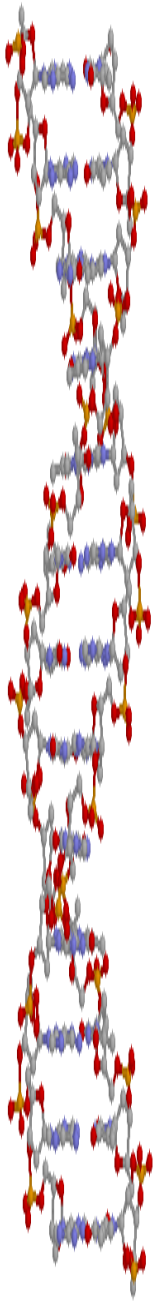


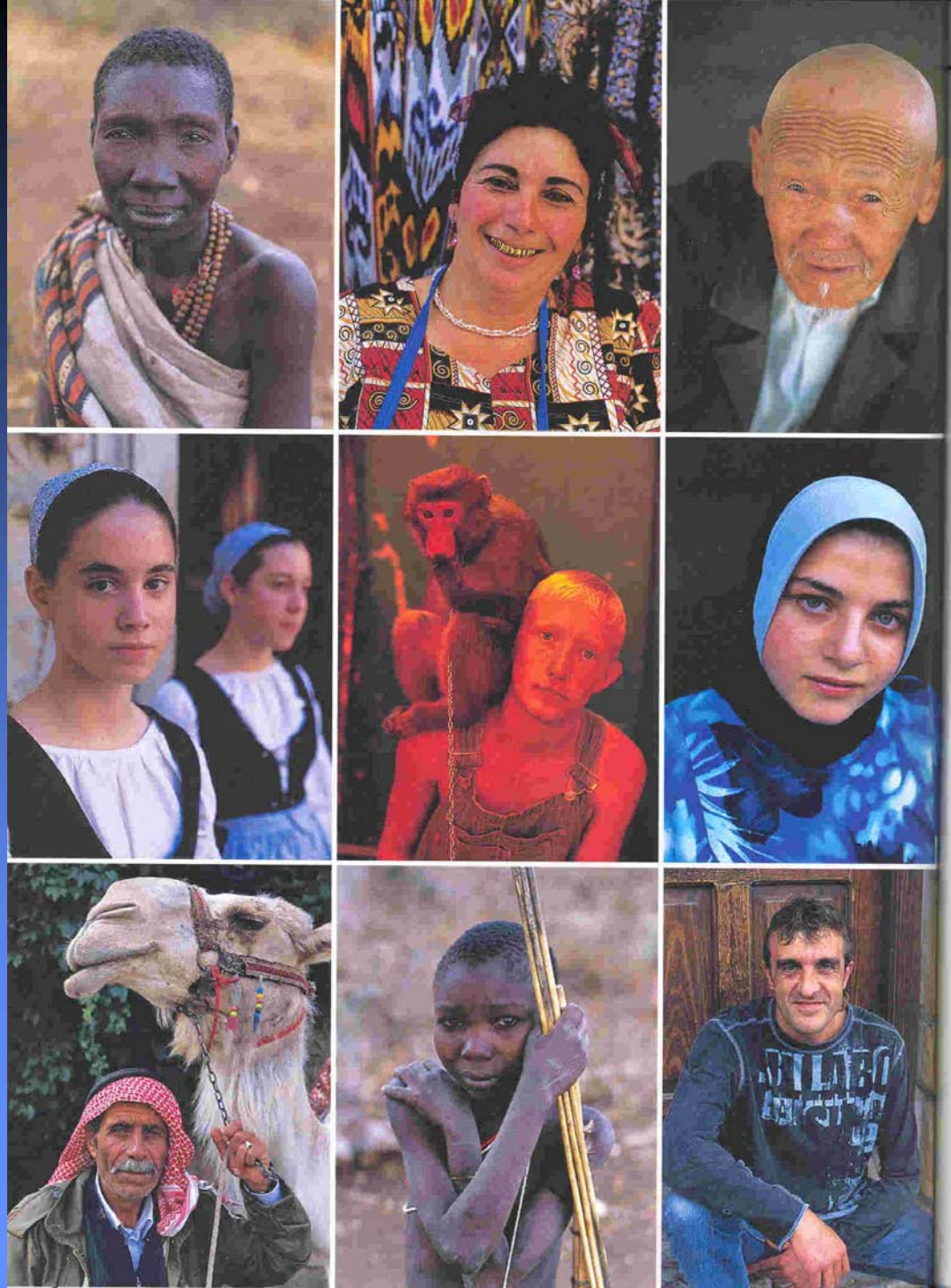
Pharmacogenomic Research Meets Clinical Practice: Examples of incorporating pharmacogenomic principles into clinical practice

Gilbert J. Burckart, Pharm.D.
Associate Director, Office of Clinical Pharmacology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

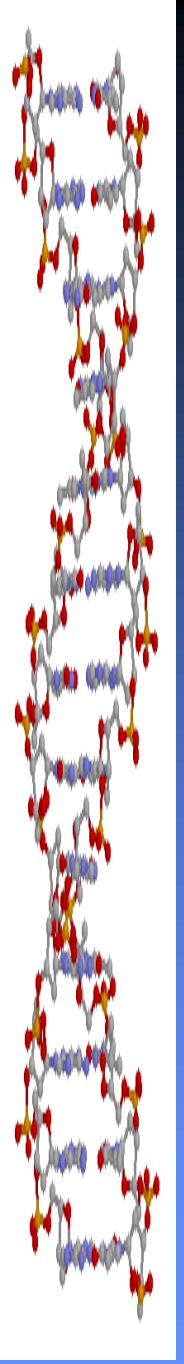


The faces associated with one person's DNA sample

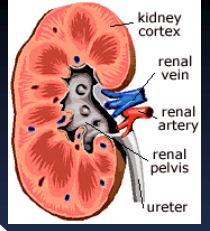
National Geographic Traveler
22:78, October 2005



G. Burckart
April, 2008



HLA match



SURGICAL

Cytokines

Chemokines

IMMUNE / INFLAM-MATORY RESPONSE

INFECTION

DRUGS

Adhesion molecules

CYPs

Pumps

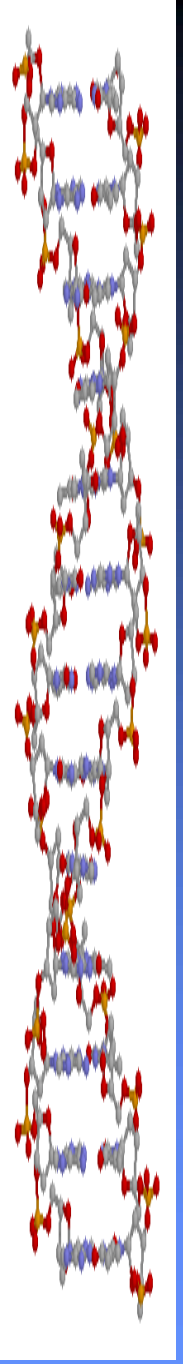
ADEs
Kidney
Liver
CNS
Pancreatic
Metabolic
Cardiovascular

Growth Factors

Antibody

Long term survival

G. Burckart
April, 2008



The Natural History of Any New Field

It's the Greatest!

It's the Worst!

It's useful when applied appropriately.

“It’s the best” scenario

The “Take Home” message for the consumer (and for the health professional!)

A Practical Guide To Better Health

As medicine is becoming more customized, care can be fine-tuned to work with a patient’s unique genetic makeup. The key: Know your family history.

Treatment Tailor-Made For You

By Dianne Hales

A PAP TEST EVERY THREE years is standard medical advice for women over 21. But this recommendation could jeopardize the lives of women like Cathy McCarty, 41, of Marshfield, Wis. “I’m one of three girls, and both of my sisters have had cervical cancer,”

How To Get Personalized Care

- **COMPLETE A FAMILY HISTORY** and leave a copy with your physician to file in your medical record.
- **DEVELOP A PERSONALIZED HEALTH PLAN** with your doctor that sets specific

sisters. That’s 15,000 genes—more than we can study with any lab test.” A thorough family history—which reveals family susceptibilities to par-

The Right Drug For The Right Patient

For most patients with most health problems, doctors traditionally have prescribed the same treatments. If one medication fails—which happens about 50% of

his personalized approach, “we have been able to take people who were miserable or near death and bring them back to a normal life.”

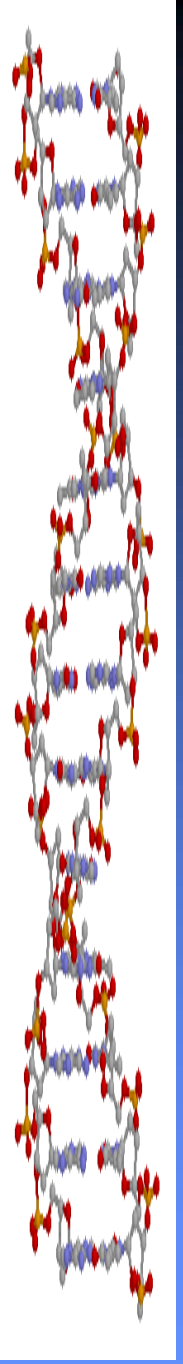
For 20 years, Gary Burcham, a retired Navy pilot from Burbank, Calif., thought he was taking the right medication to protect his heart: a daily aspirin. But after he was diagnosed with a clogged artery, a new blood test, approved last year, revealed that he was “resistant” to aspirin’s protective effects. “I had a false sense of security,” says Burcham, 74, who now relies on another anti-clotting agent to prevent a heart attack.

Of the 25 million Americans who take aspirin to protect their hearts, as many as 30% may be getting little or no benefit for a variety of reasons, including subtle genetic differences. Scientists have identified similar variations that may make certain drugs for high blood pressure, multiple sclerosis, Alzheimer’s and heart disease more or less effective in different people.

“This research provides a glimpse into the future,” says Dr. Paul Ridker, director of Harvard’s Center for Cardiovascular Disease Prevention, who recently identified two genetic abnormalities that lower the efficacy of a widely used cholesterol-lowering statin in certain in-

New tests can identify which individuals will respond well to a particular medication.

Parade Magazine, Sept. 19, 2004



"It's the worst" scenario [or at least its not going to be here for a long, long time!]

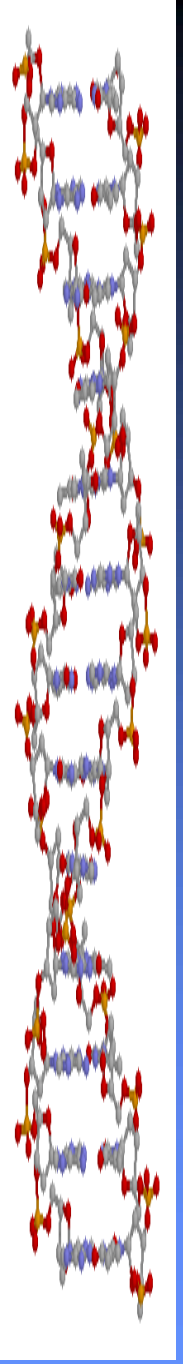
THE ROYAL SOCIETY

Personalised Medicines: Hopes and Realities
September, 2005

"Currently, pharmacogenetics has very little impact on clinical practice."

"Pharmacogenetics is unlikely to revolutionise or personalise medical practice in the immediate future."

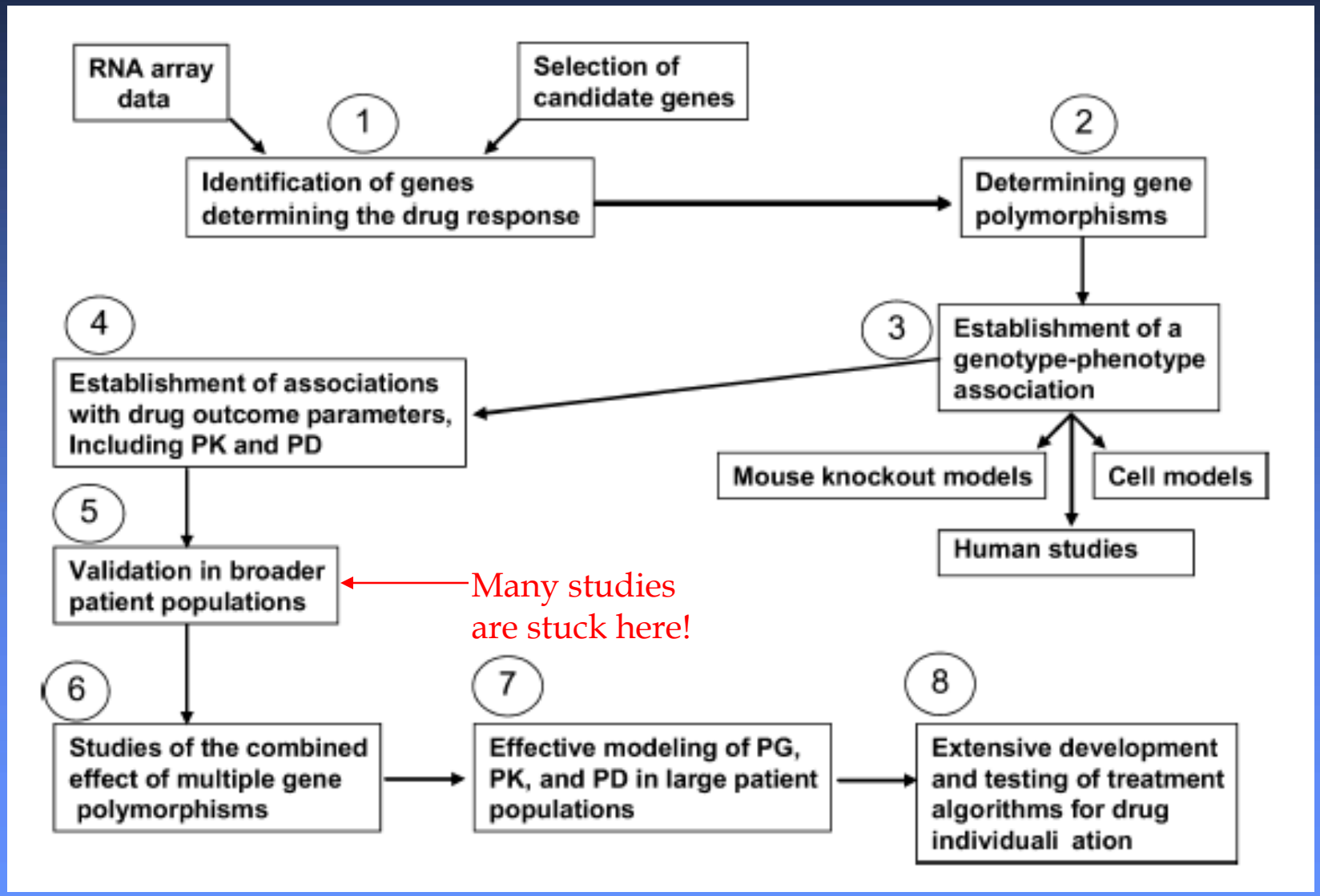
"As emphasised throughout this report, there is still virtually no information about the cost effectiveness of pharmacogenetic testing in clinical practice. Hence, it is difficult to offer advice on the future organisational and educational changes that would be required if, as seems likely, the field slowly develops over the next 20 years."



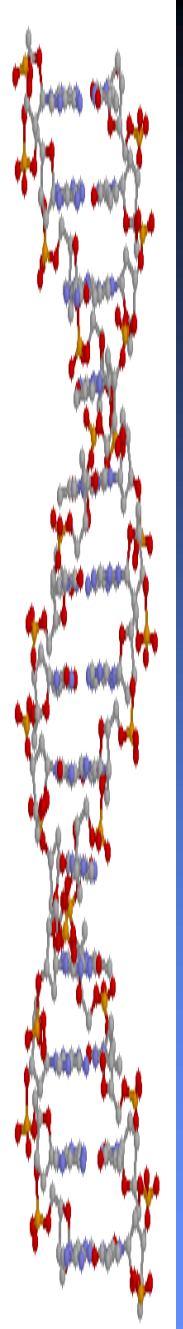
Objectives

- To review those genetic factors in patients which have established recognized effects on drug PK/PD, ADEs, and patient outcome;
- To assess the status of validation of genomic and other biomarkers in transplantation; and
- To provide examples of how pharmacogenetics and pharmacogenomics is being used in patient management.

Progression of Pharmacogenetic Information into Clinical Practice

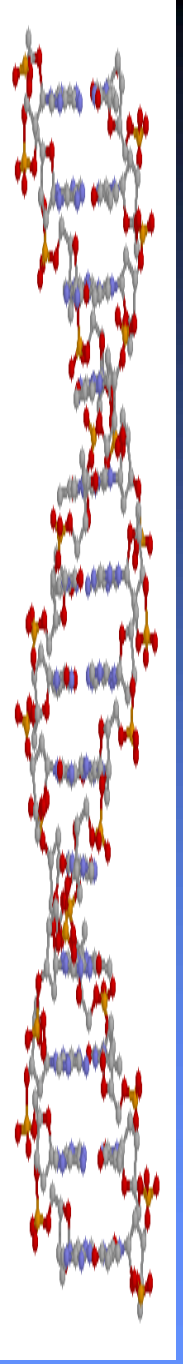


Burckart GJ, Liu XI. Ther. Drug Monit. 2006; 28:23-30.



Applications of Pharmacogenomics to Patient Care

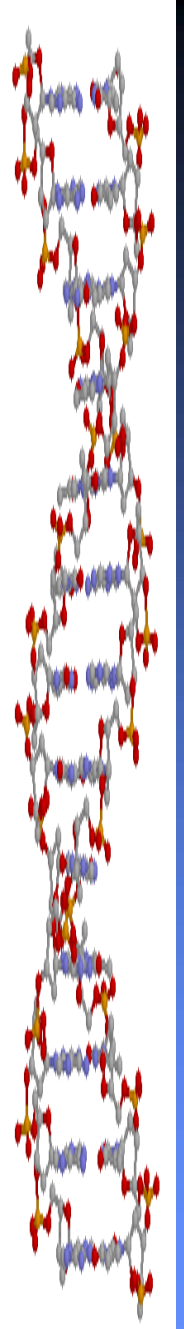
- 1. To predict dosage requirement
- 2. To help select a drug regimen
- 3. To optimize a patient's response to their medication
- 4. To prevent ADE's



Which polymorphisms should a clinician be concerned with right now?

	YES	NO	MAYBE
Information included in labeling	X		
Affects drug levels that I can measure		X	
Affects drug levels that I don't measure			X
Affects drug action/ADE's/outcome	X		

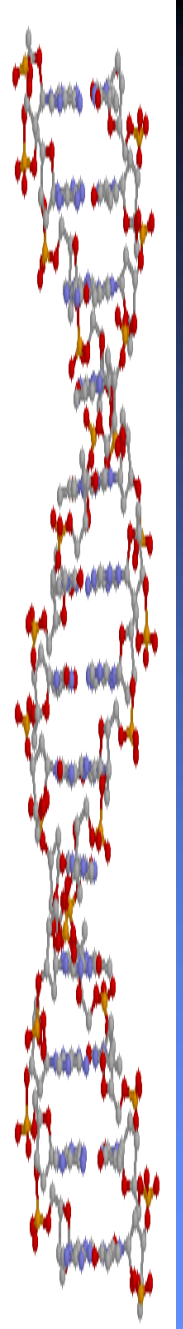
G. Burckart
April, 2008



Pharmacogenomic information included in drug labeling in the US

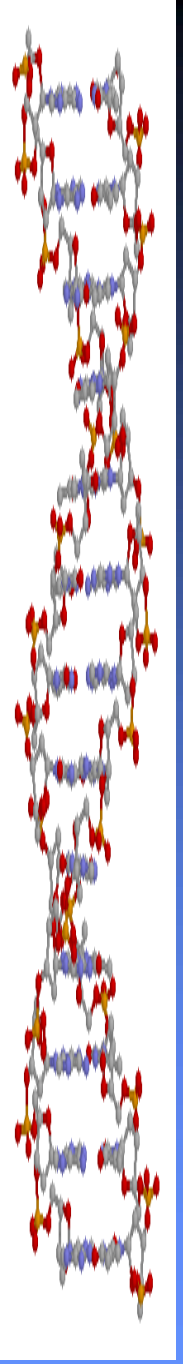
Biomarker	Drug	Label status
EGFR expression	Erlotinib	Required
Her2/neu Over-expression	Trastuzumab	Required
TPMT Low and intermediate Activity	Azathioprine	Recommended
UGT1A1*28 Allele	Irinotecan	Recommended
VKORC1 Variants	*Warfarin*	*Recommended*
C-KIT expression	Imatinib mesylate	Information only
CYP2C19 Variants	Voriconazole	Information only
CYP2C9 Variants	Celecoxib	Information only
CYP2D6 Variants	Fluoxetine HCL	Information only
DPD Deficiency	Capecitabine	Information only
G6PD Deficiency	Rasburicase	Information only
NAT Variants	Rifampin, isoniazid, and pyrazinamide	Information only

From (Mummaneni et al., 2006);
see http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm



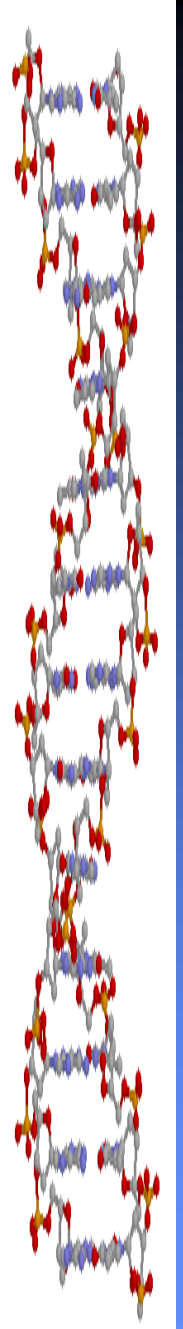
Prevalence of use for drugs with pharmacogenomic biomarker information in product labeling (2006)

Biomarker	Example(s)	User prevalence (%)
C-Kit expression	Imatinib	.01
CYP2C19 variants	Esomeprazole, omeprazole	10.91
CYP2C9 variants	Warfarin, celecoxib	3.91
CYP2D6 variants	Metoprolol, fluoxetine	13.56
DPD deficiency	Capecitabine, fluorouracil	0.31
EGFR expression	Erlotinib, gefitinib	0.02
G6PD deficiency	Chloroquine, dapsone	0.09
HER2/neu overexpression	Trastuzumab	<0.01
NAT variants	Rifampin, isoniazid	0.15
Philadelphia chromosome deficiency	Busulfan	<0.01
PML/RAR alpha gene expression	Tretinoin	0.68
TMPT variants	Azathioprine, mercaptopurine	0.17
Urea cycle enzyme deficiency	Divalproex sodium, valproic acid	0.48
UGT1A1 variants	Irinotecan	<0.01
Overall		24.32



Pharmacogenomics in Predicting Drug Dosage

- Examples
  - Warfarin
  - 6-mercaptopurine
  - Tacrolimus

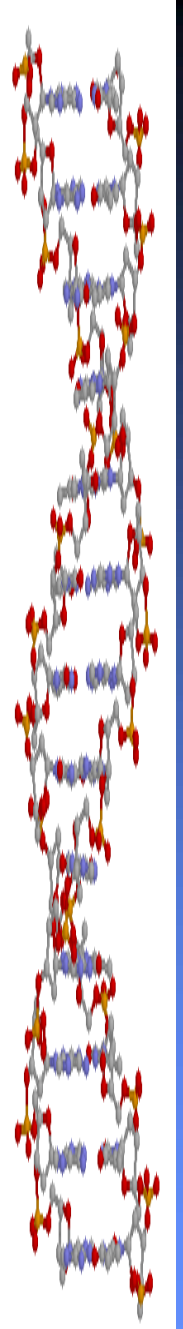


Magnitude of Risk: Vast Amount of Clinical Data on Bleeding Complications

- Warfarin ranks #1 in total mentions of deaths for drugs causing AEs from death certificates
- Warfarin ranks among the top drugs associated hospital emergency room visits for bleeding
- Overall frequency of major bleeding has been 10% to 16% (versus 0.1% for most drugs)
- Minor bleeding event rates in RCT of new anticoagulants has been as high as 25-27%

Wysowksi et al, Arch Int Med 2007 and SPORTIF III Trial 2003 (Exanta, Astra-Zeneca)

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf



Clinical Importance of Risk: Warfarin Eludes Patients Who Need It the Most

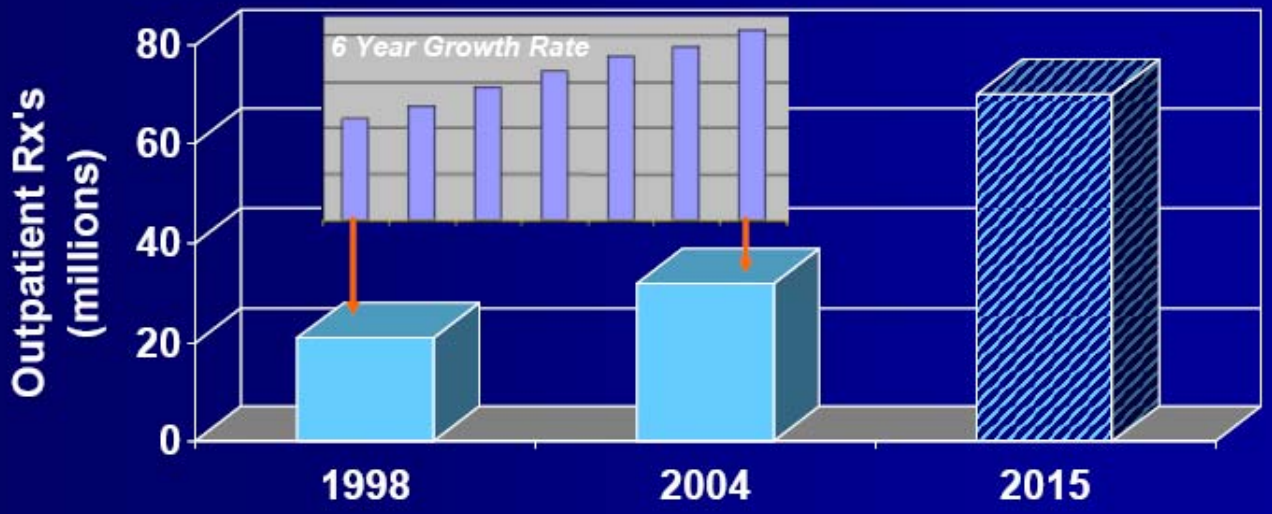
- Risk of stroke in A Fib increases by 40% in elderly while warfarin use decreases by 60%
- New patients with A Fib (1:130 over 65 yo) treated by physicians who had a patient with a bleeding event were 21% less likely to receive warfarin
- Other reasons for not starting warfarin treatment in A Fib patients (n = 300)
  - 28% prefer treatments without INR monitoring
  - 20% fear of bleeding
  - 18% would have difficulty to get INR monitored

Choudhry et al, Br Med J, 2006; Patient Record Review on File at Astra-Zeneca; White et al, Am J Med 1999; Wolf, Arch Int Med 1987

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf

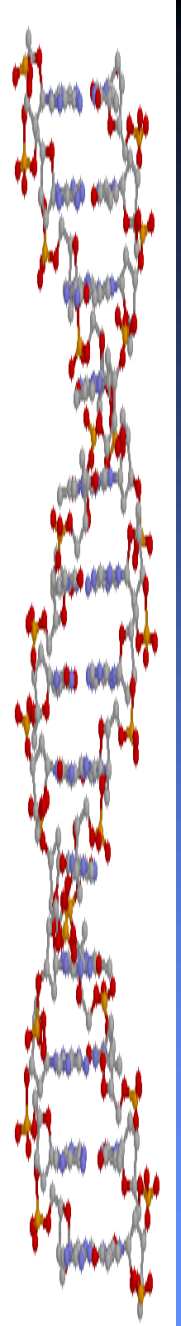
Public Health Implications of Risk: Most Widely Used Anticoagulant Worldwide

Real and Projected Growth in Anticoagulant Market: 600,000 New Patients Per Year



Note: Anticoagulant market projected to increase 3 to 4-fold between 2004 and 2015
Sources include National Rx Audit, IMS Health Forecast (MIDAS)

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf



Added New Black Box Warning About Bleeding to US Product Label

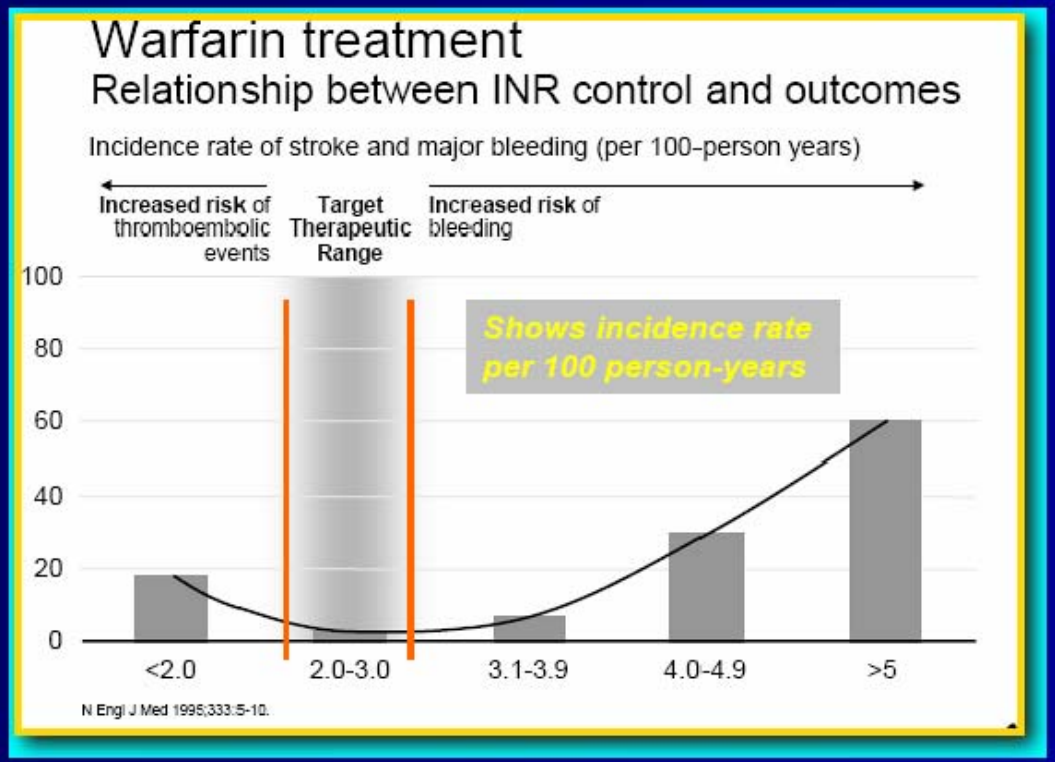
WARNING: BLEEDING RISK

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see **PRECAUTIONS**), and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding (see **PRECAUTIONS: Information for Patients**).

Label as of October 2006

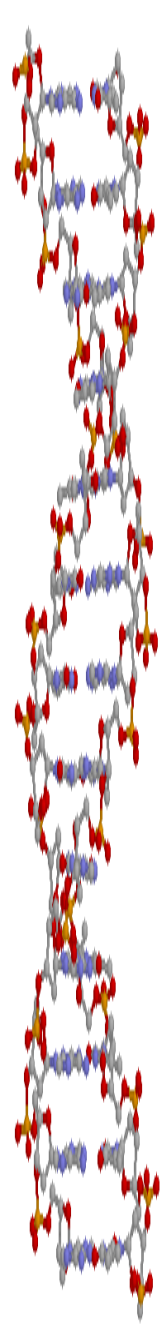
http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf

Control of INR (Surrogate) Is Critical to Maintaining Therapeutic Anticoagulation

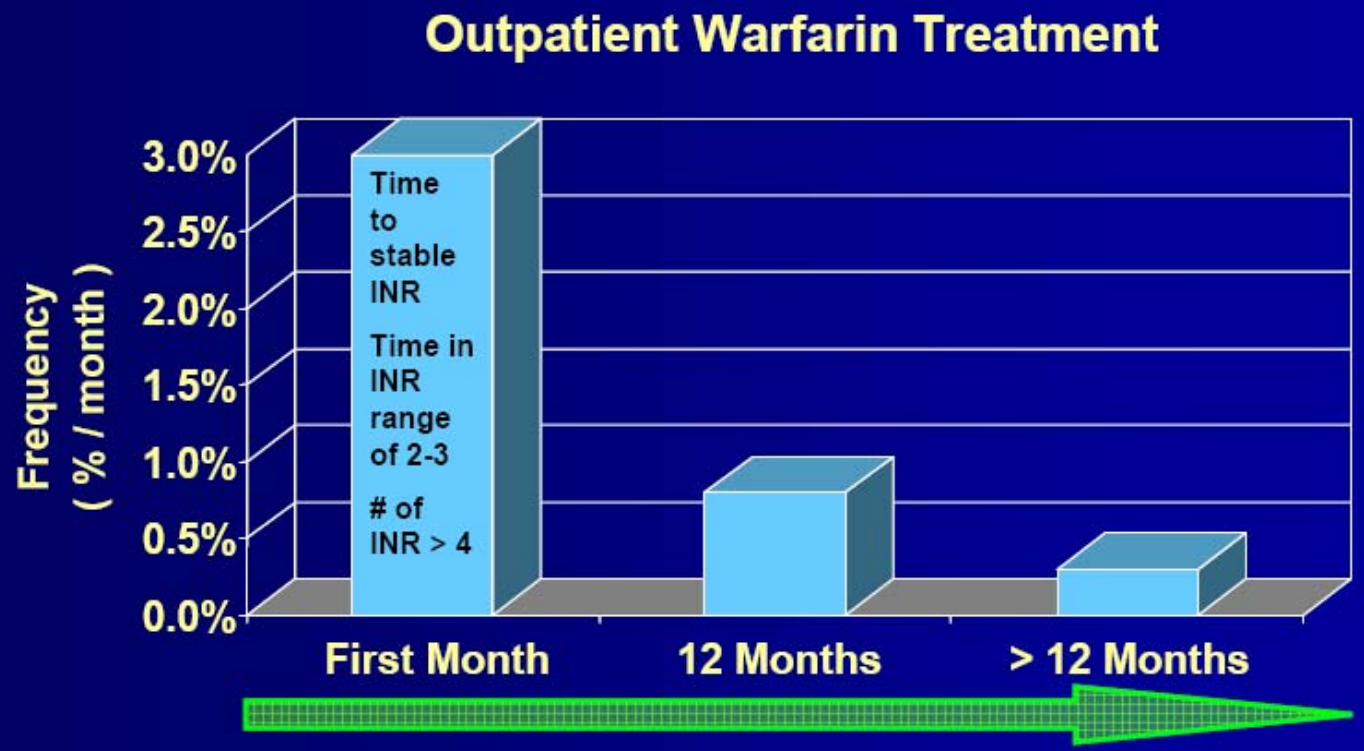


Adapted from http://www.astrazeneca.se/download/2003/2003Cameron.pdf

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf

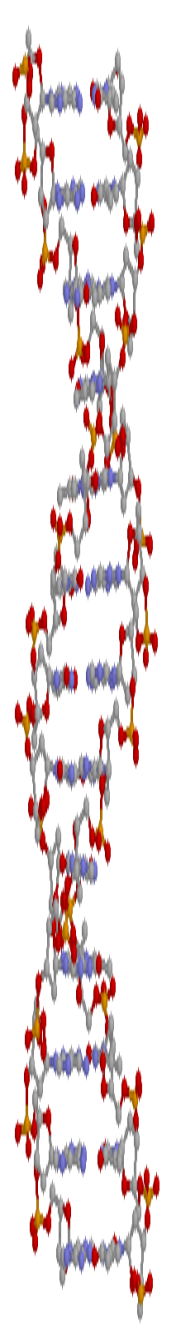


Result: High % of Major Bleeding Events During Dosing Initiation Phase

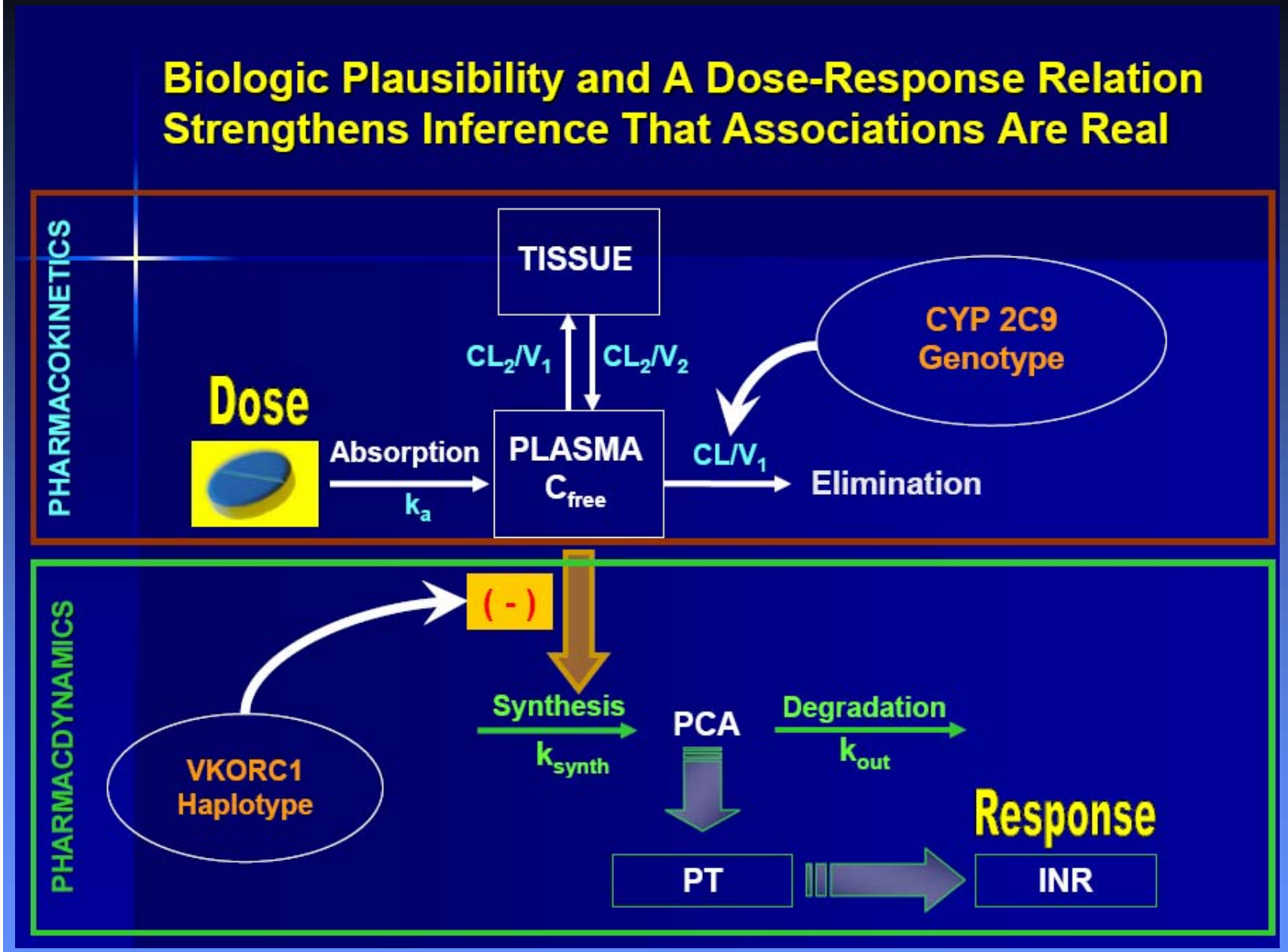


Landefeld et al Am J Med 1989, White et al, Am J Med 1999, Ezekowitz et al, J Cardiovasc Pharmacol Ther, 1999, Higashi, et al, JAMA 2002, Hirsh et al, Circulation 2003

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf

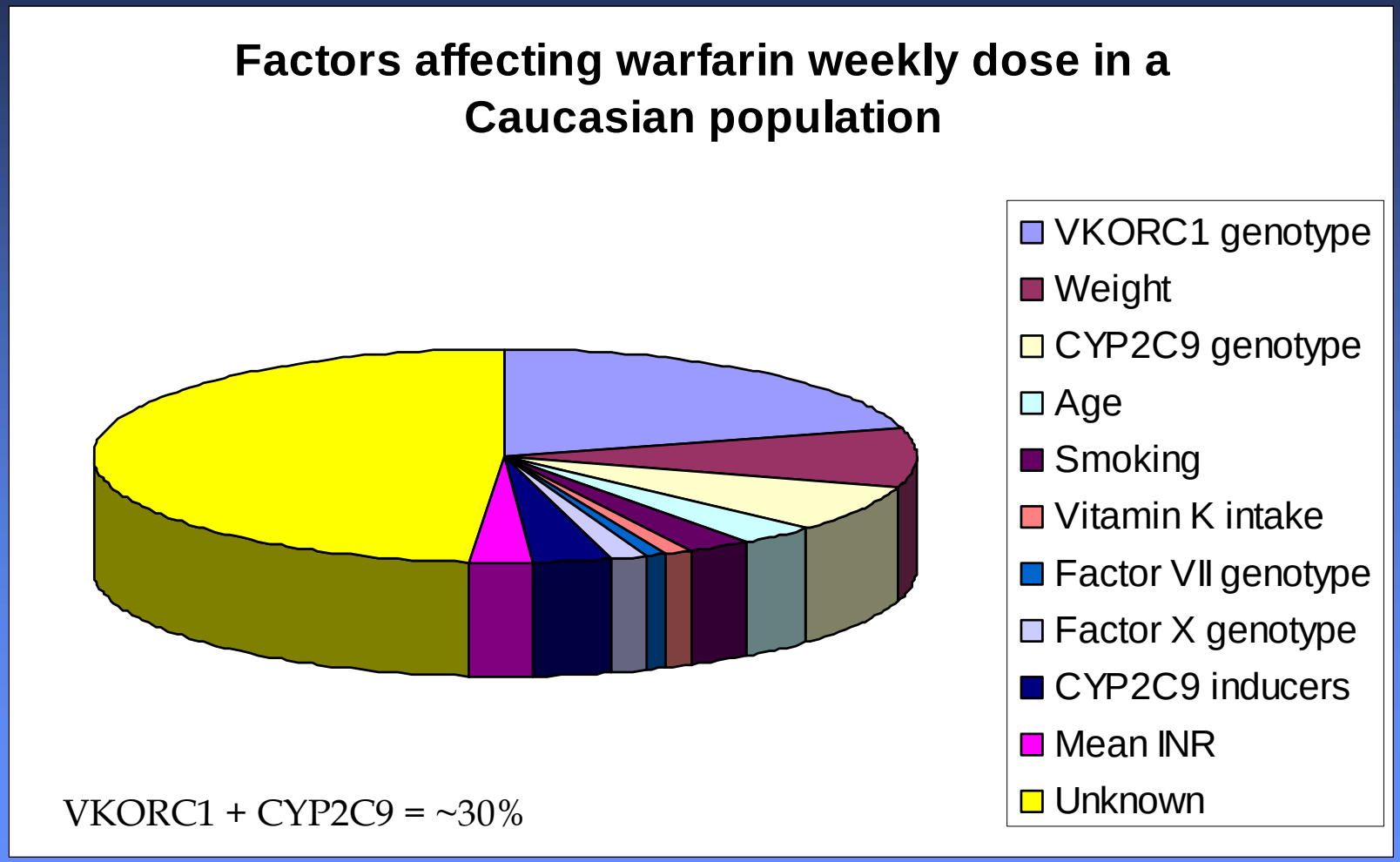


Biologic Plausibility and A Dose-Response Relation Strengthens Inference That Associations Are Real



http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf

How much variability can we account for In a pharmacogenetic model?



Derived from data in Aquilante CL et al: Clin. Pharmacol. Ther. 2006; 79: 291-302.

Announcement of First FDA-Approved Genetic Test for Warfarin

U.S.News & WORLD REPORT

Saturday, September 29, 2007

Nation & World | Health | Money & Business | Education | Opinion

Health

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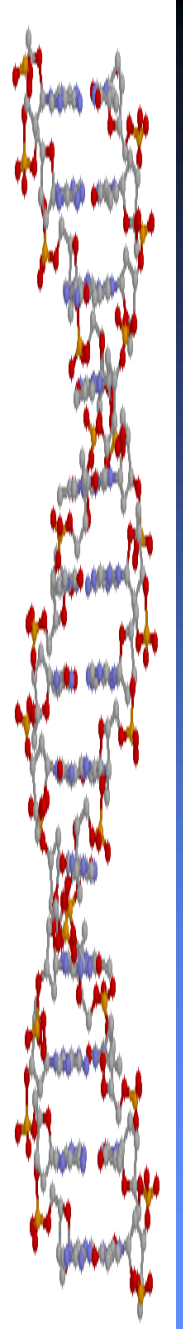
Genetic Test Approved for Sensitivity to Blood Thinner

Some people who take Coumadin at higher risk of bleeding

Physician adoption of test will be challenging since a genetic screening test represents deviation from established practices

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf

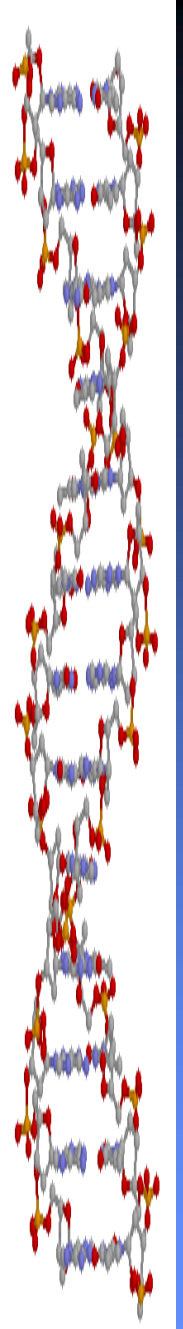


Prospective Clinical Trial with Bleeding Outcomes

Limdi et al, Clin Pharmacol Ther, July 2007

- Prospective clinical cohort study in 446 (88 with 1 or more gene variants) outpatients eligible for warfarin treatment
- Mean age of 60.5 yrs, 50% men, 50% African-American followed for average of approximately 15 months
- Clinical endpoints of major and minor hemorrhage stratified by INR range and time to stabilization of target INR
- *A variant 2C9 genotype yielded a HR of 3.0 for increased risk of major hemorrhage*
- *Risk of major hemorrhage was 5.3-fold higher before stabilization of INR, and 2.2-fold higher after stabilization*

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf

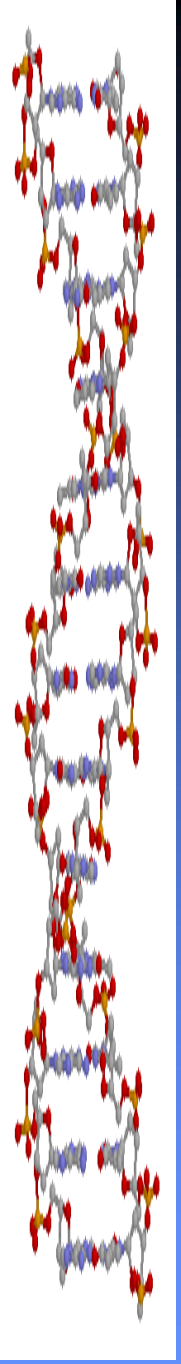


Prospective Clinical Trial with INR and Bleeding Endpoints

Caraco et al, Clin Pharmacol Ther, September 2007

- Prospective clinical cohort study in 191 (95 2C9 genotyped cases vs. 96 controls) outpatients eligible for warfarin
- Matched for mean age of 58 yrs, 46% men, followed to time of stable anticoagulation up to 3 months (no VKORC1 measures)
- Clinical endpoints of time to stable anticoagulation, time spent in therapeutic range (INR 2-3) and % minor bleeding
- *Cases achieved stable anticoagulation (initiation) 18 days earlier and stayed between INR 2-3 twice as long (45% vs. 24%)*
- *Minor bleeding in the cases was ¼ that observed in the control group (3.4 vs. 12.5%)*

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf



Genetic-Based Dosing Algorithm in Orthopedic Patients Starting Warfarin Therapy

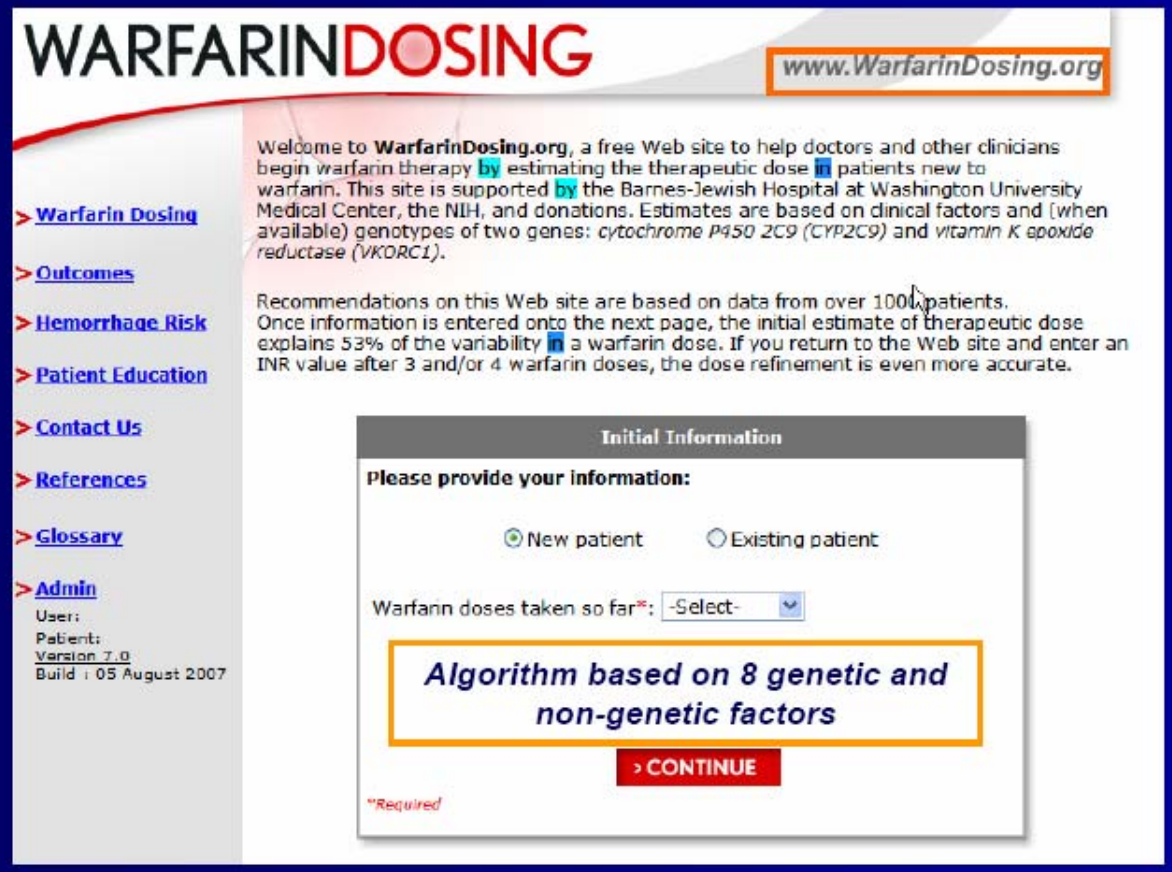
Millican et al, Blood, September 2007

- Retrospective (historically prospective) clinical cohort study in knee or hip replacement patients (CYP 2C9 and VKORC1)
- Matched for mean age of 58 yrs, 56% men, 13% African-American
- Clinical endpoint was the stable maintenance warfarin dose (INR in therapeutic range of 2-3)
- Genetic-based dosing model explained 79% of the variability in warfarin dose (note: r^2 = 64% in 59 non-surgical patients**)
- Significant predictors of dose were 2C9 genotype, VKORC1 haplotype, INR after 3rd dose, first warfarin dose, smoking, EBL

*** Personal communication, Dr. Brian Gage, Oct 1, 2007*

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf

Clinical Decision Support Tool: Algorithm to Estimate Dose With and Without Genetic Information and/or INR Values



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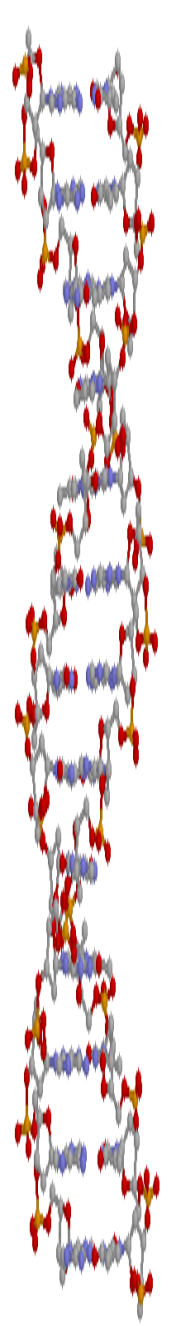
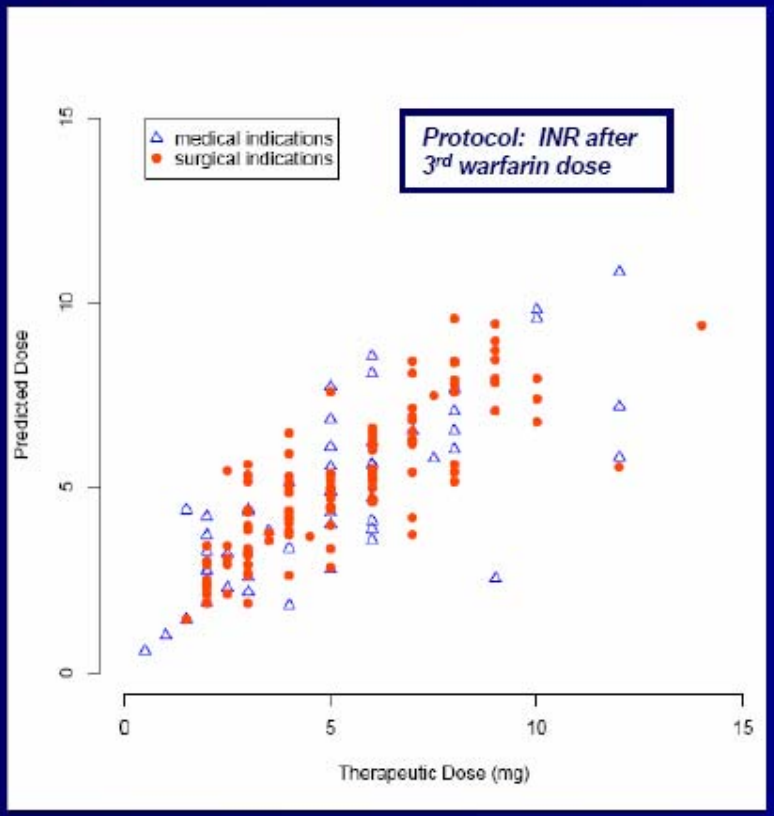


Performance of Dosing Algorithm: Matched Actual Dose by Nearly 80%



With Genetic Factors

Surgical R^2 (n = 119) = 79%
Median Absolute Error = 0.6 mg

Medical R^2 (n = 49) = 64%
Median Absolute Error = 1.1 mg

Clinical Factors Alone

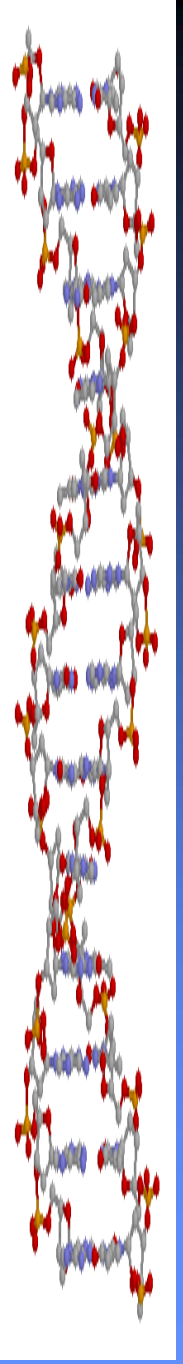
Surgical R^2 (n = 353) = 53%
Median Absolute Error = 0.9mg

"…..We rarely get an INR over 4 using this dosing algorithm."

Data courtesy of Dr. Brian Gage and Petra Jacobsen, Washington University School of Medicine (9 Oct 2007)

Petra et al, Ann of Pharmacotherapy, published online 2 October 2007

http://www.fda.gov/cder/genomics/presentations/lesko_warfarin.pdf



Thiopurine S-Methyltransferase (TPMT) Deficiency

6-mercaptopurine
azathioprine

6-thioguanine nucleotides
(myelosuppressive action)

TPMT

*3/*3 variant

1:300 patients
11% heterozygous

Degradation products

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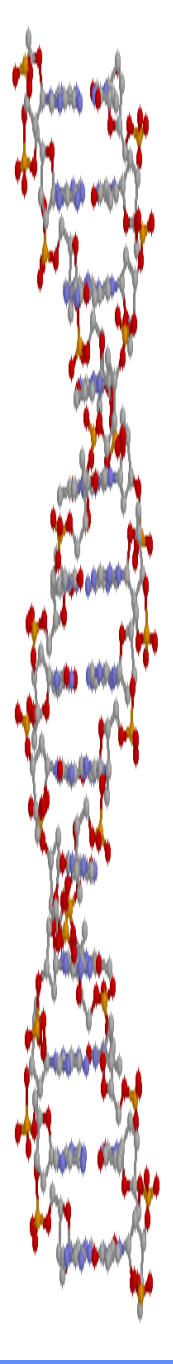
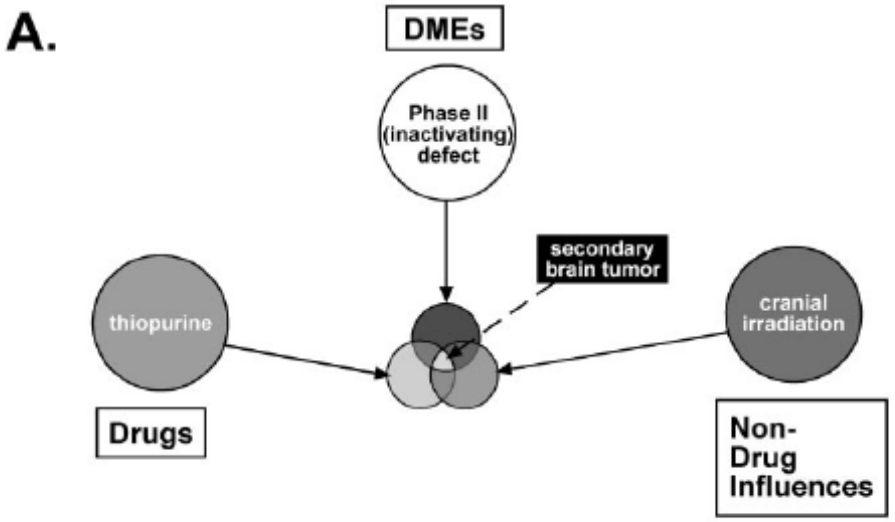
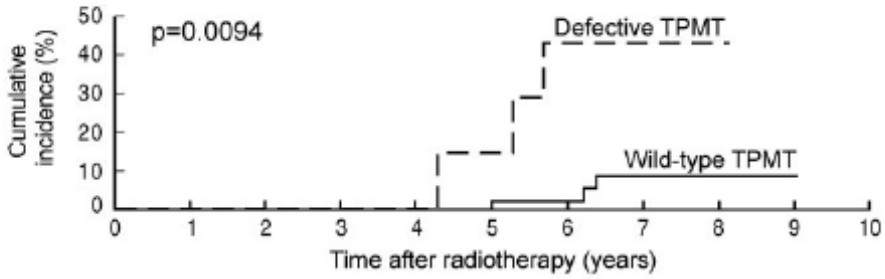


Risk of secondary Malignant brain tumor In ALL patients with Defective TPMT

Interactions of Genetic Polymorphisms and Treatment May Result in Adverse Effects



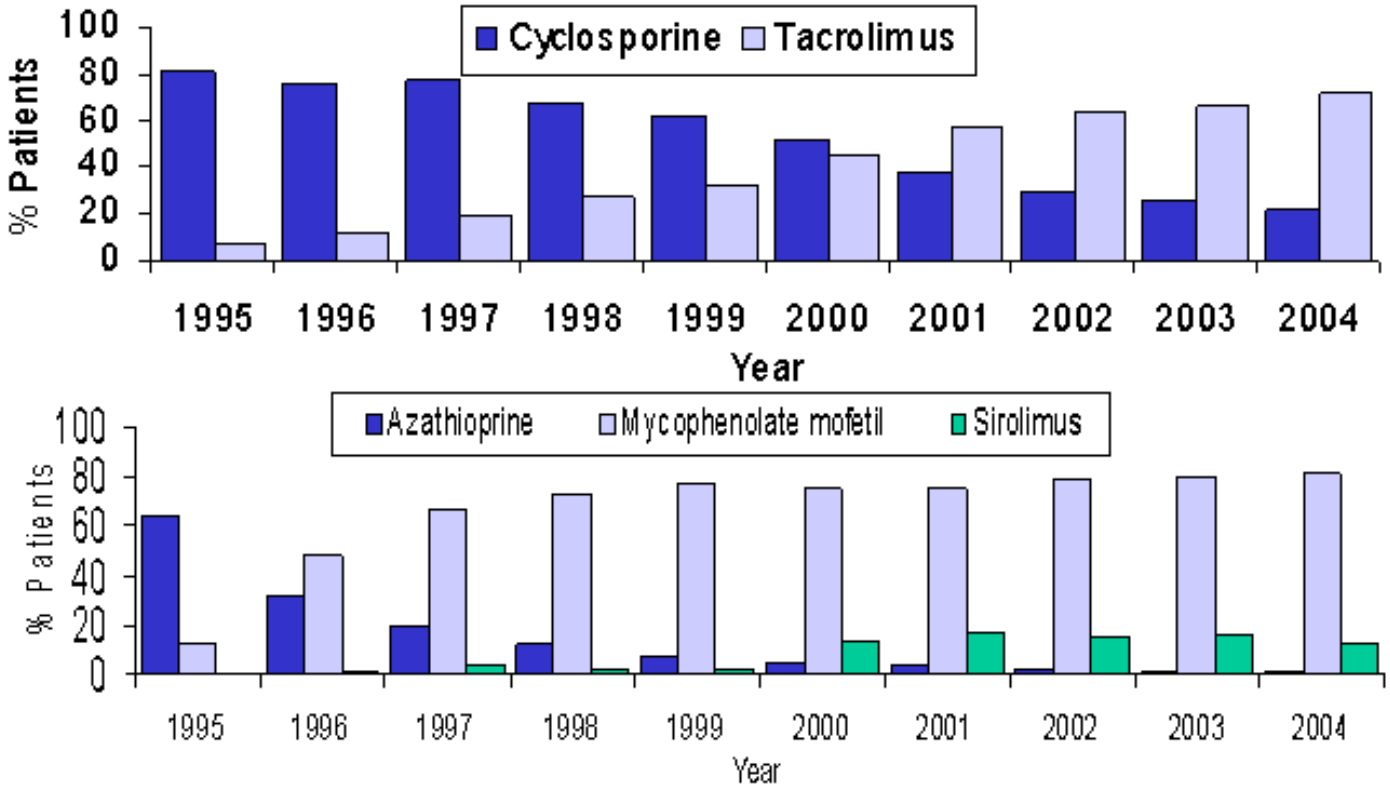


Estimated cumulative incidence of radiation-associated secondary malignant brain tumor in patients treated with concomitant mercaptopurine and irradiation.

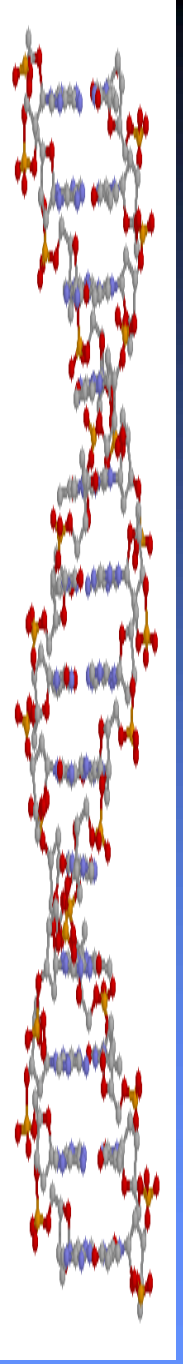
Evans WE, Johnson JA: Annu. Rev. Genomics Hum. Genet. 2001. 2:9–39

Falling use of azathioprine in transplantation

Figure III-2. Trends in Maintenance Immunosuppression Prior to Discharge for Kidney Transplantation, 1995-2004

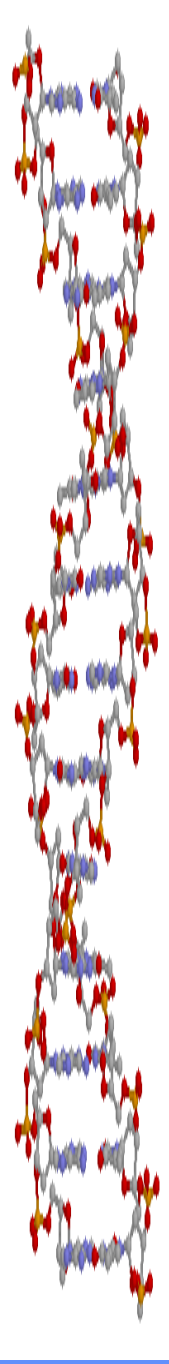


Source: *2005 OPTN/SRTR Annual Report*, Table 5.6e.

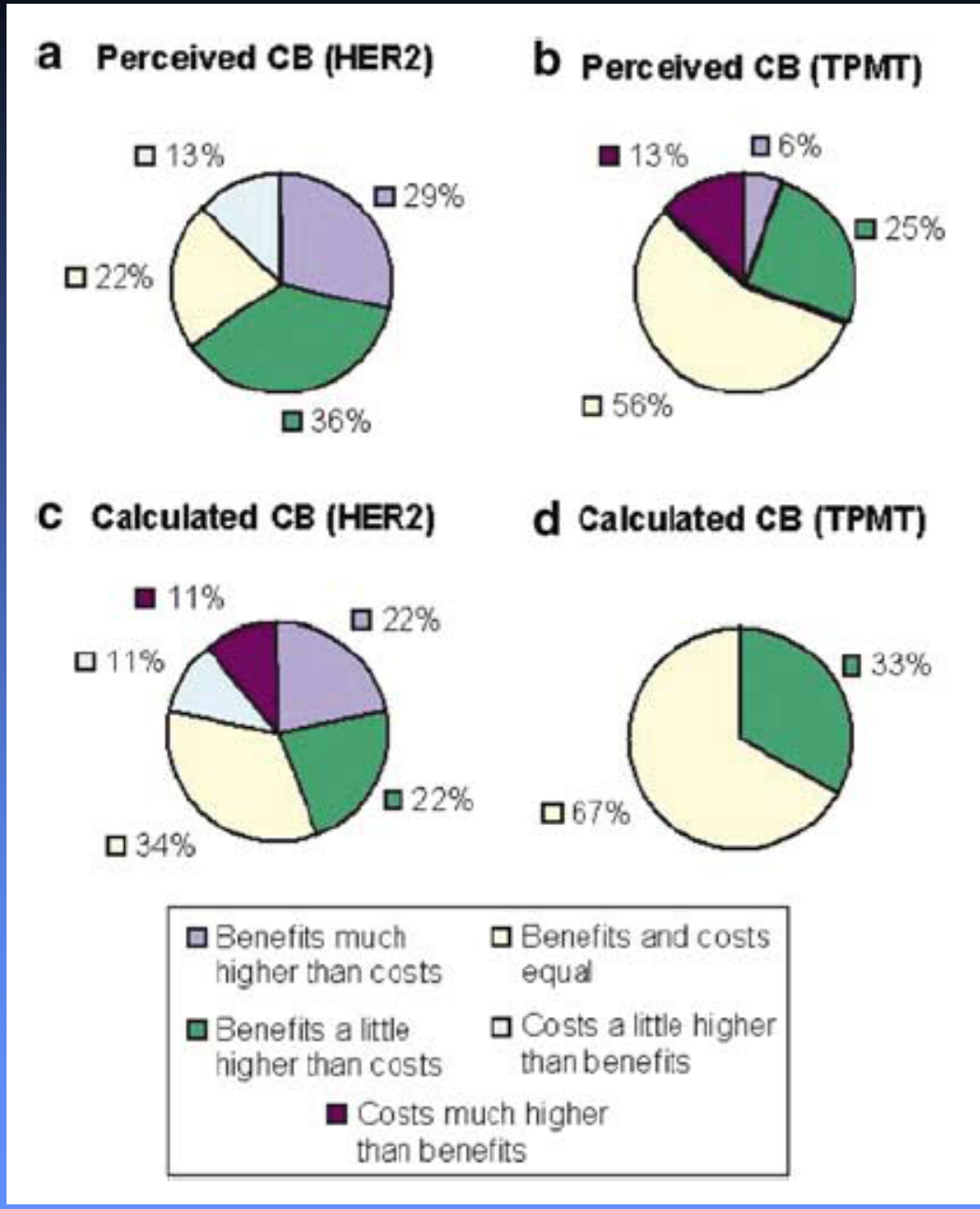


Why is azathioprine still important?

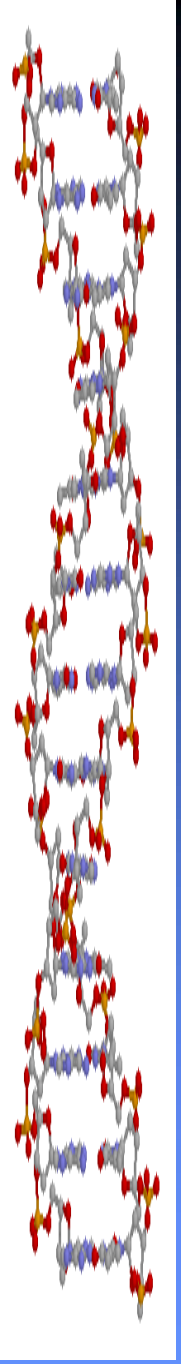
- Most widely used antiproliferative agent in transplantation outside North America
- *3/*3 homozygote transplant recipients are at grave risk of leukopenia, infection and death
- Will probably go undetected, since TGN are not measured, and there are multiple other reasons for leukopenia, sepsis and death in the first 2 weeks post transplantation
- Could have resulted in hundreds of deaths in transplant patients over the past 20 years
  - 17,000 transplants/year should mean that 51 are *3/*3



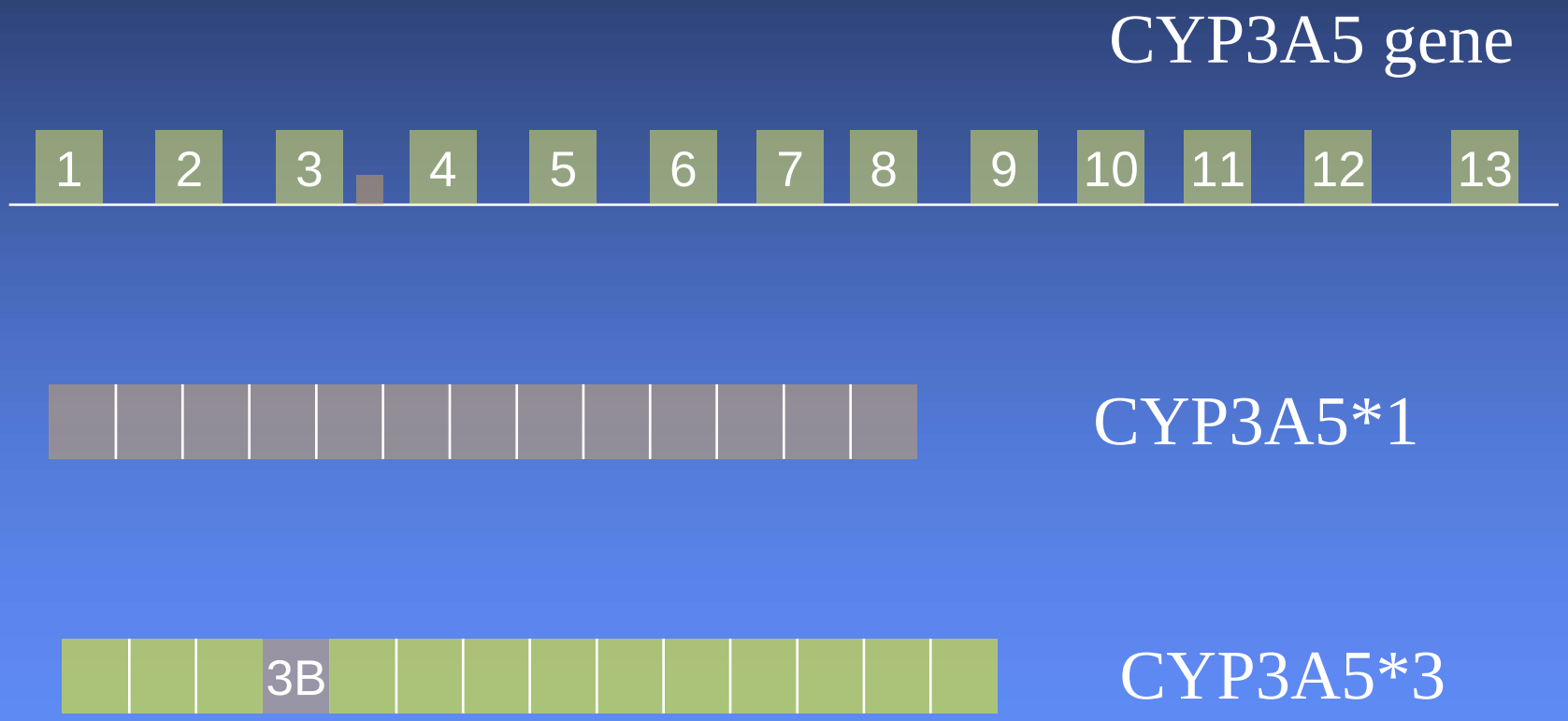
Perception of perceived and calculated utility of HER2 and TPMT testing in Europe by practicing physicians



Woelderink A et al: The Pharmacogenomics Journal 2006; 6: 3-7.



CYP3A5 Polymorphism



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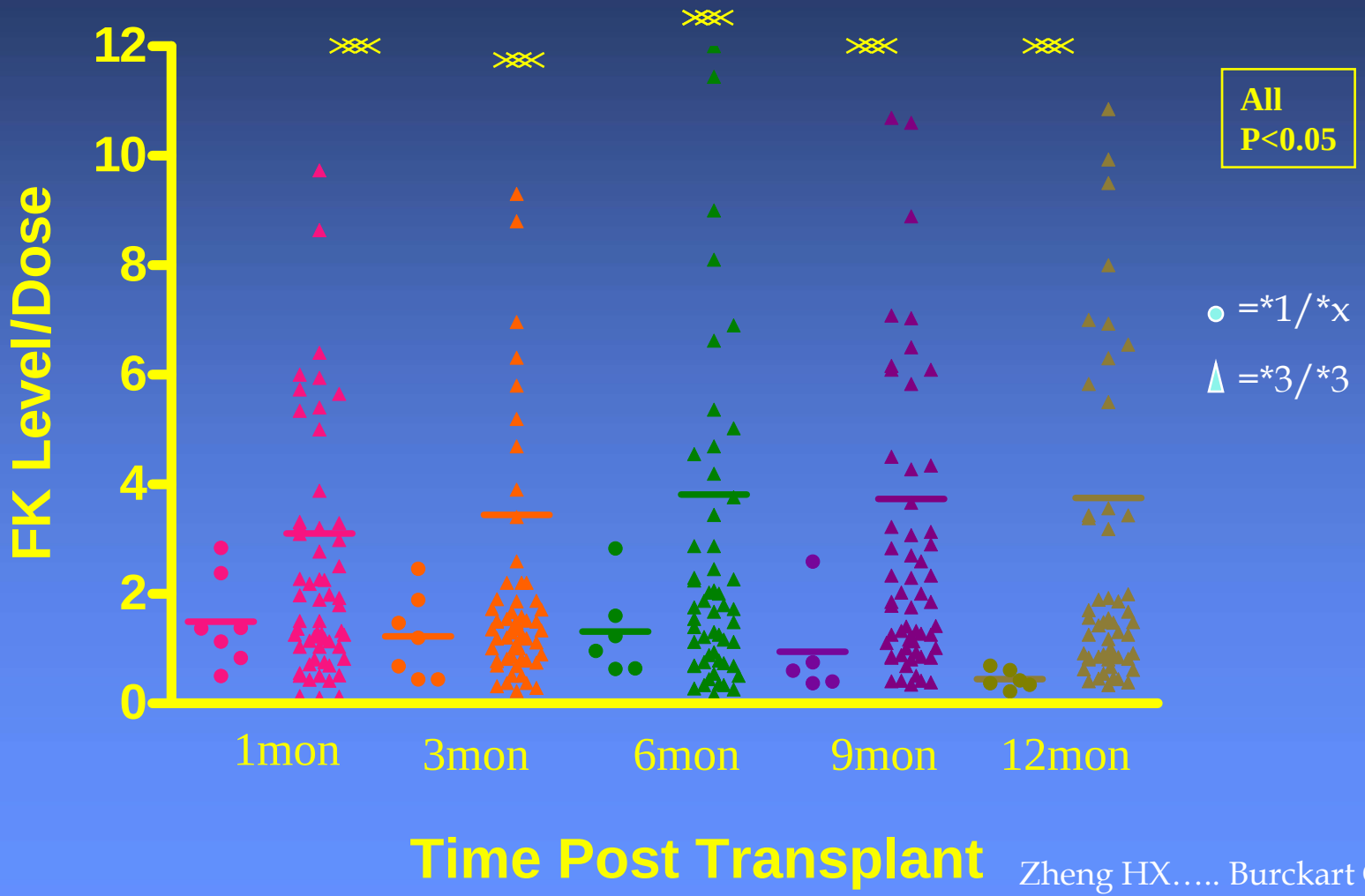
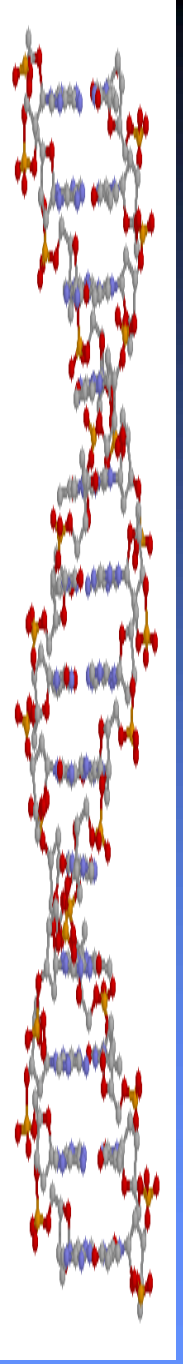
Relling and Dervieux, Nature Reviews 2001; 1:99-108

Tacrolimus Levels Per Dose in the CYP3A5 Genotypes in Lung Transplant Patients



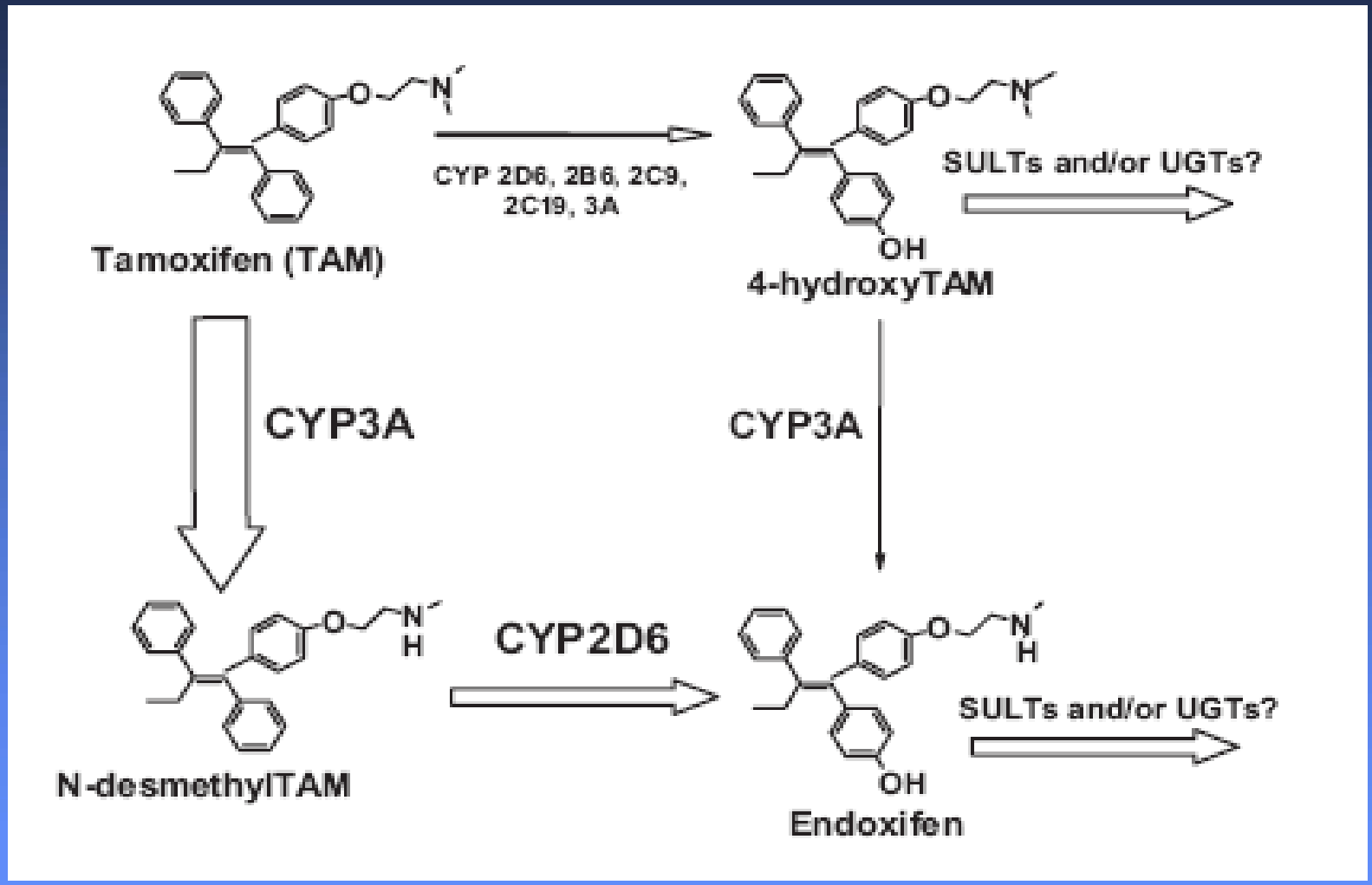
Zheng HX….. Burckart GJ:
J Clin Pharmacol 2004; 44:135



Pharmacogenomics to Help Select a Drug Regimen

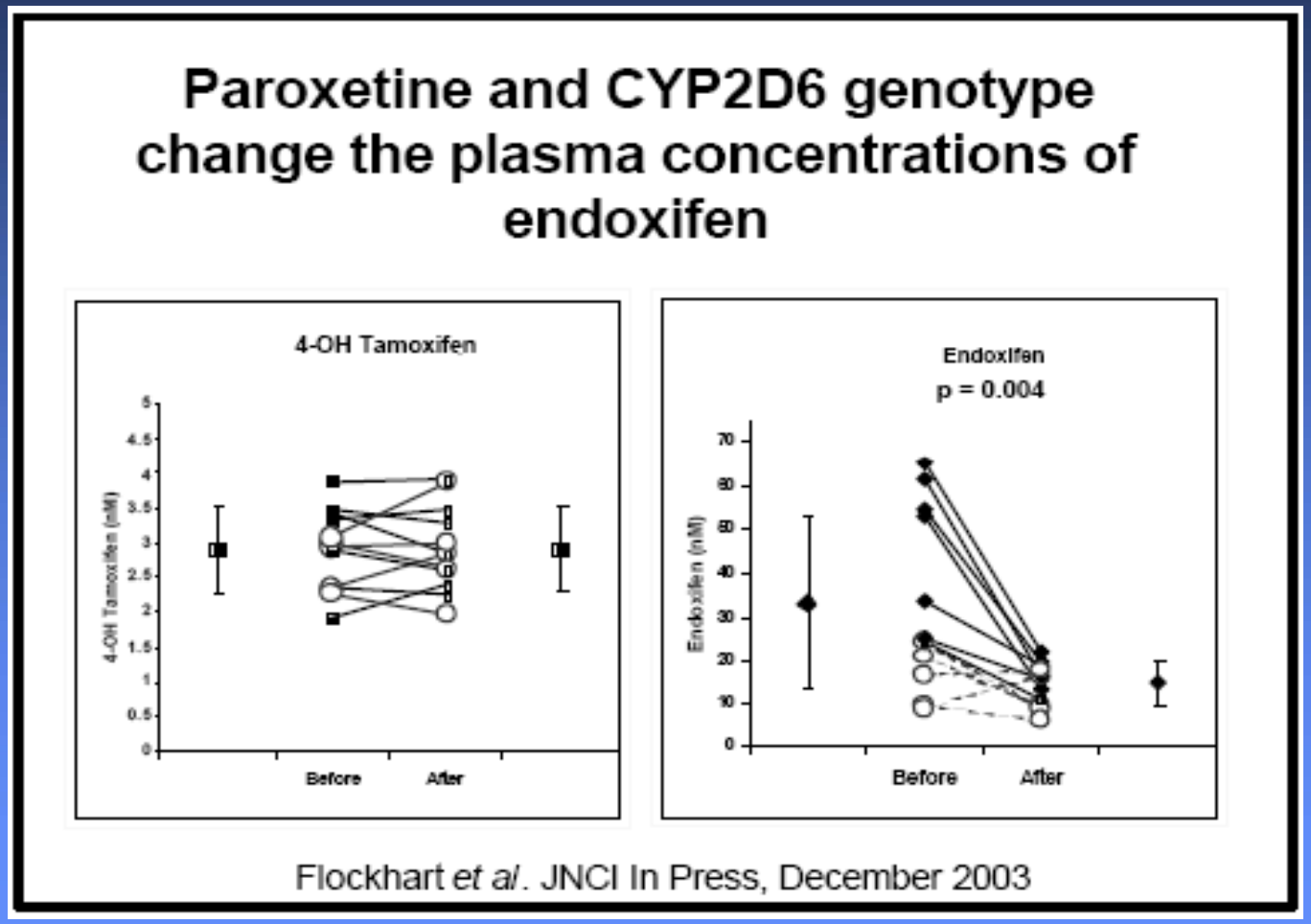
- Example
  - HER2 and the use of trastuzamab
  - Tamoxifen and CYP2D6

Tamoxifen metabolism

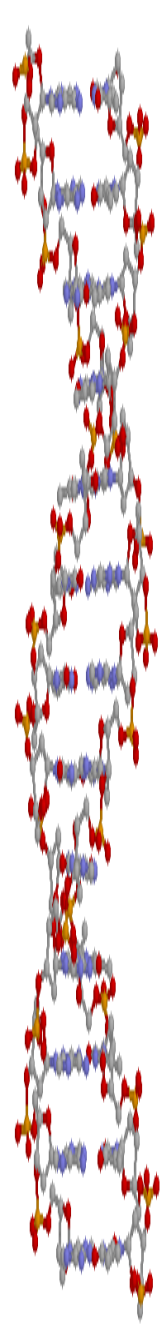


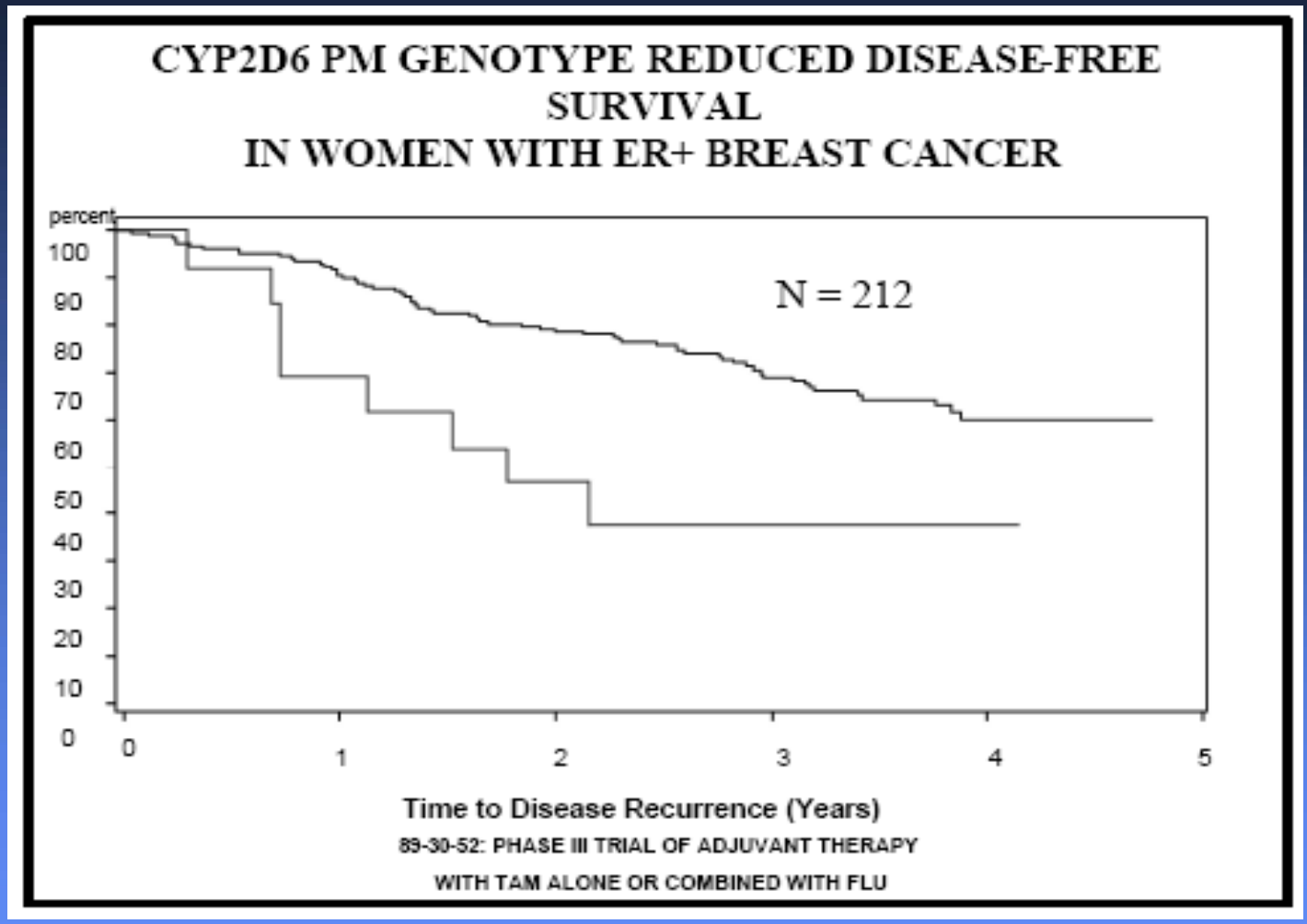
Slides courtesy of David Flockhart, Indiana Un. School of Medicine

Paroxetine effect on Tamoxifen metabolism

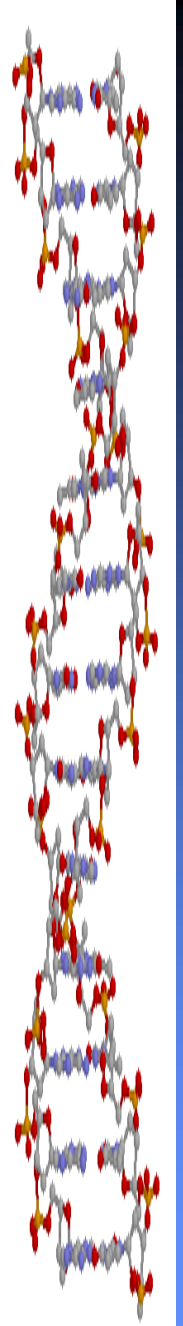


Slides courtesy of David Flockhart, Indiana Un. School of Medicine



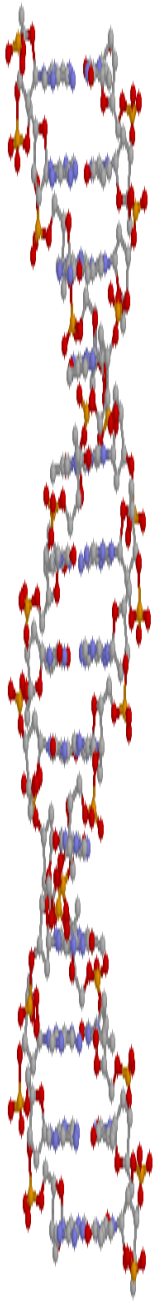


Slides courtesy of David Flockhart, Indiana Un. School of Medicine



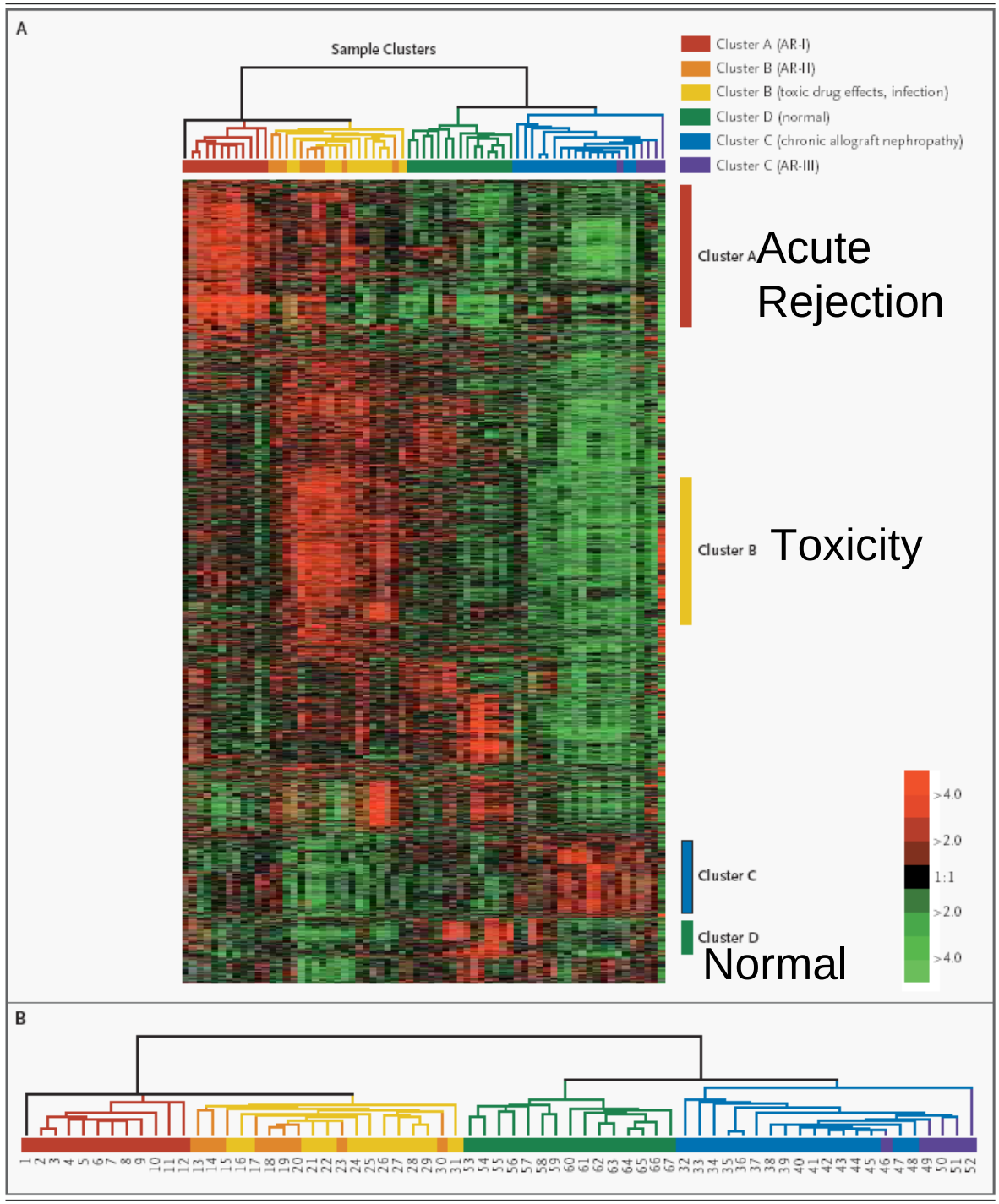
Pharmacogenomics to optimize a patient's response to their drug regimen

- Example:
  - Allomap array data for a heart transplant patient

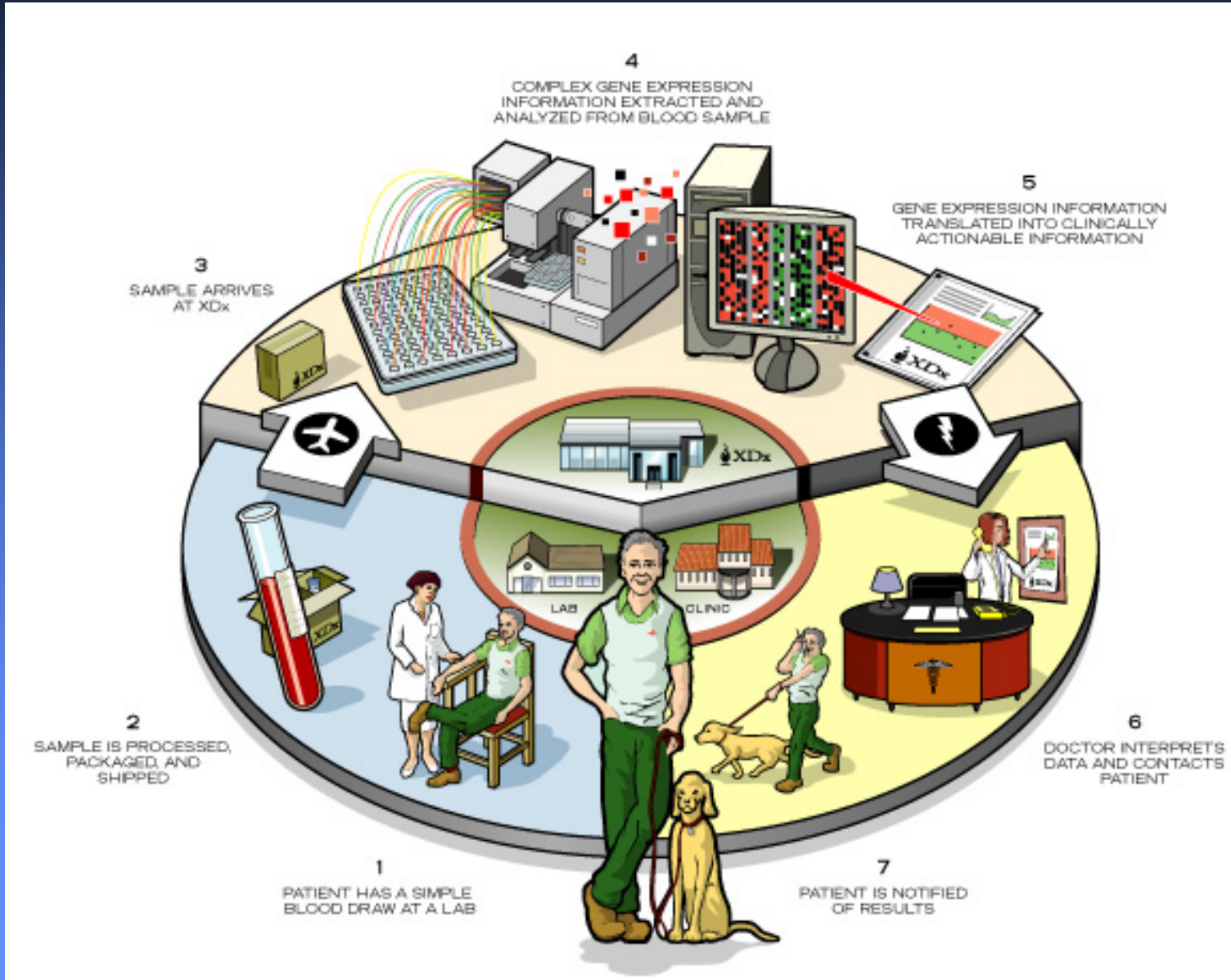


Use of a gene array for monitoring therapy by mRNAs

Sarwal et al:
NEJM 2003;
349: 125-138

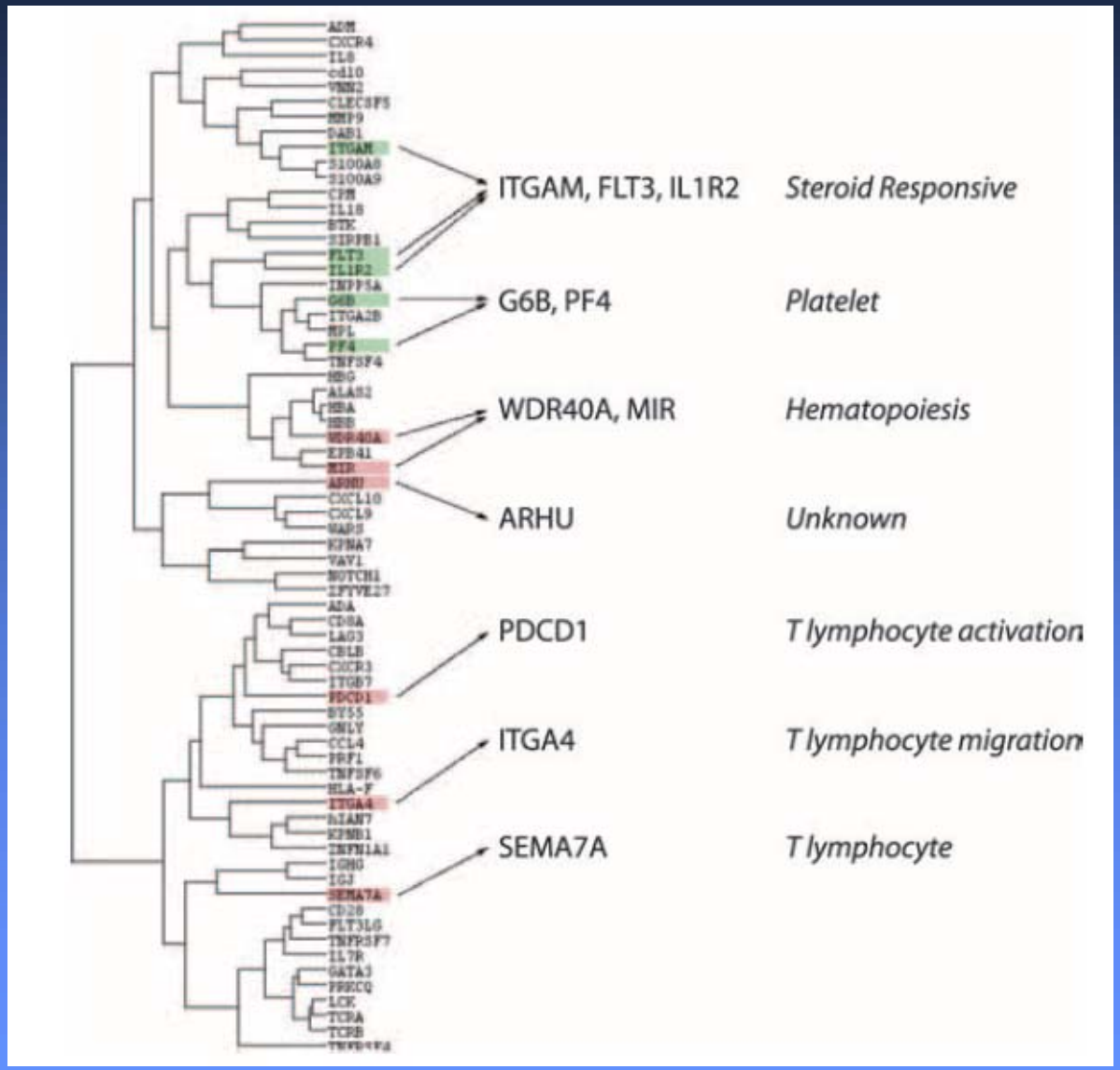


Clinical Application of mRNA Data to Tx Patient Care: Allomap

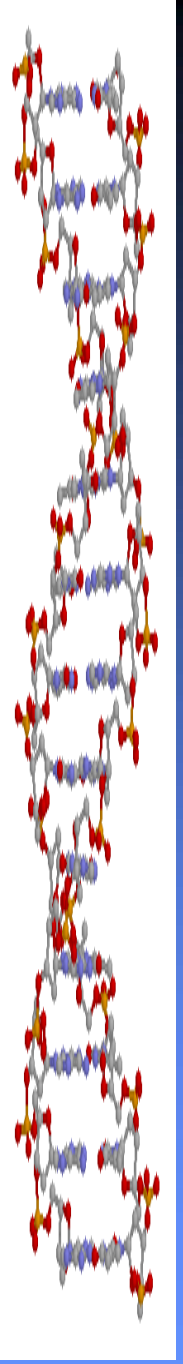


XDx Inc. Web site

Allomap Gene Distribution for Prediction of Heart Transplant Rejection

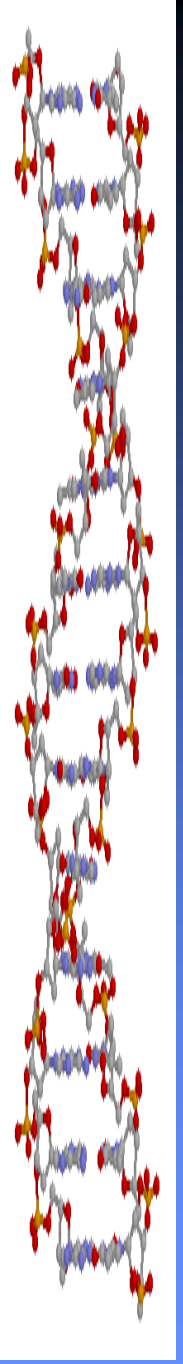


Deng MC et al: American Journal of Transplantation 2006; 6:150



Pharmacogenomics to prevent adverse drug effects

- Example
  - Hypersensitivity reaction with abacavir
  - Hypersensitivity reactions with carbamazepine in Asian patients
  - Irinotecan
  - Nephrotoxicity of calcineurin antagonists
  - Preventative regimens for post transplant diabetes mellitus



Hypersensitivity as predicted by HLA typing

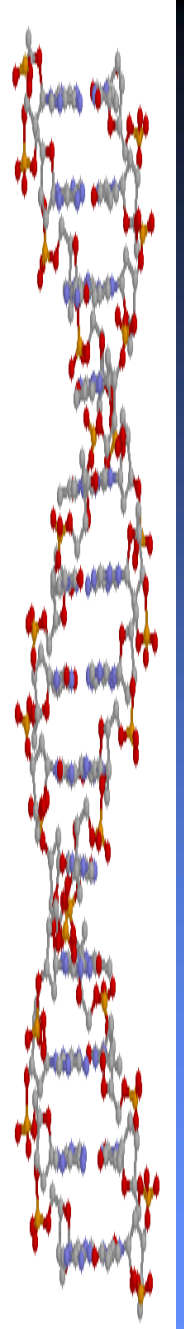
- Abacavir causes up to 8% hypersensitivity reactions which can be fatal (>30,000 pts treated)
  - In Caucasians, almost uniformly associated with HLA-B*5701
  - Incidence can be reduced to 2% by HLA testing (Rausch et al. Clin. Inf. Dis. 2006; 43:99-102)
  - Manufacturer has not changed the label, and the label belongs to the manufacturer

HLA Haplotype Predicts Abacavir Hypersensitivity Reaction

	Abacavir hypersensitive (n=18)	Abacavir tolerant (n=167)	Odds ratio (95% CI)	p_c
*HLA-B*5701*	14 (78%)	4 (2%)	117 (29–481)	<0·0001
HLA-DR7, HLA-DQ3	13 (72%)	6 (3%)	73 (20–268)	<0·0001
*HLA-B*5701, HLA-DR7, HLA-DQ3*	13 (72%) ..	0 (0%) ..	822 (43–15 675)	<0·0001 ..

Table 2: **Contribution of combined or individual loci of 57·1 ancestral haplotype to susceptibility to abacavir hypersensitivity**

Mallal et al. *Lancet* 359:727, 2002



Carbamazepine hypersensitivity and HLA type in Asians

FDA ALERT [12/12/2007]: Dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Genetic tests for HLA-B*1502 are already available. Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B*1502. This new safety information will be reflected in updated product labeling.

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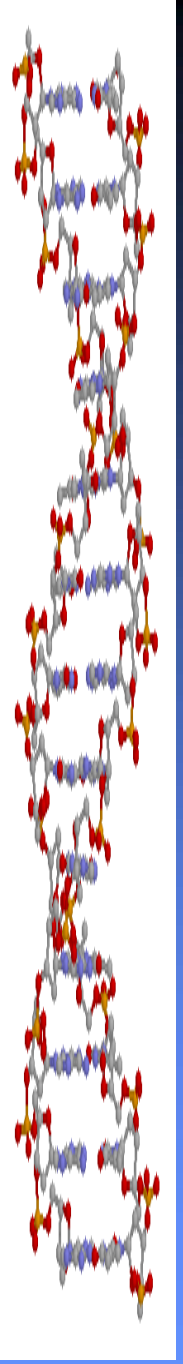
April, 2008



UGT1A1 PG testing with Irinotecan

Irinotecan

↓

SN-38 Active Metabolite

↓ UGT1A1

Inactive metabolite

UGT1A1 wild type has 6 TA repeats in the Promoter; 7 TA repeats causes decreased activity

Group (UGT1A1 genotype)	*Grade 4 Neutropenia*
All Patients	**10%**
Patients That Are *UGT1A128 (7/7)**	**50%**
Patients That Are *UGT1A128 (6/7)**	**12.5%**
Patients That Are *UGT1A128 (6/6)**	**0%**

Based on data from Innocenti et al (2004)

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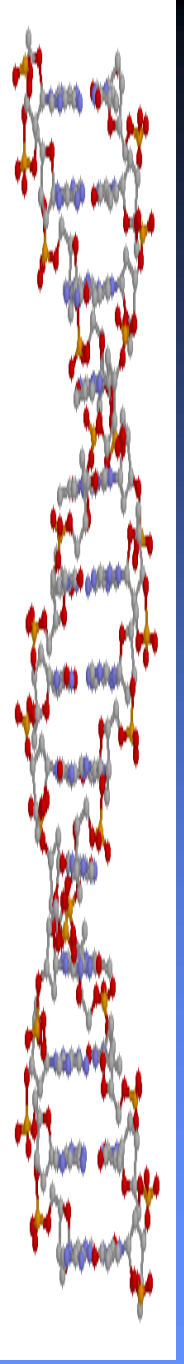


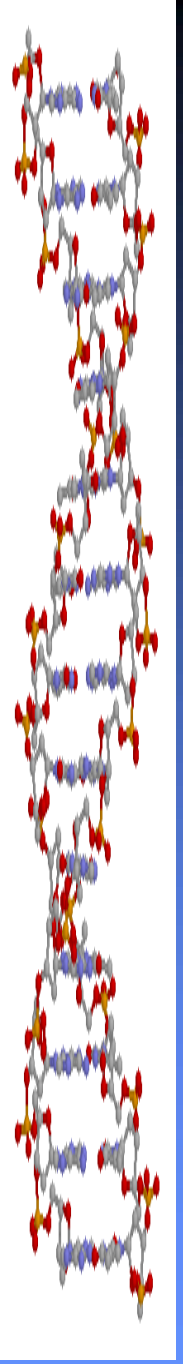
UGT1A1*6 predicts irinotecan toxicity in Asians, not UGT1A1*28

Table 3. Association of *UGT1A* Genotypes With Tumor Response, Toxicity, and Delivered Dose of Irinotecan

	Tumor Response				G4 Neutropenia*				G3 Diarrhea*				Delivered Dose of Irinotecan (mg/m²/wk)			
	Responder†				Yes				Yes							
	No.	%	P‡	P§	No.	%	P‡	P§	No.	%	P‡	P§	Mean	SD	Range	P¶
UGT1A9*22‖																
10/10	7/21	33	.109	.677	3/23	13	.108	.203	2/23	9	.058	.037	43.4	6.5	28.9-54.7	.529
10/9	25/44	57			14/45	31			2/45	4			44.8	6.4	30.5-53.3	
9/9	3/10	30			5/11	45			3/11	27			41.9	10.4	24.0-49.2	
UGT1A7			.086	.034			.084	.052			.087	.028				.972
*1/*1, *1/*2, *1/*3	34/67	51			16/70	23			5/70	7			43.7	6.2	28.9-54.7	
*2/*3	2/5	40			3/5	60			1/5	20			44.6	5.9	34.8-49.2	
*3/*3	0/5	0			3/6	50			2/6	33			41.7	10.6	24.0-52.5	
UGT1A1*60			.066	.098			.269	.242			.823	.624				.578
–/–	16/44	36			11/46	24			5/46	11			43.4	6.7	24.0-54.7	
–/+	19/30	63			9/32	28			3/32	9			45.0	6.1	32.0-53.3	
+/+	1/3	33			2/3	67			0/3	0			40.9	12.2	28.9-53.3	
UGT1A1*28			.531	.385			.726	.605			.999	.847				.312
–/–	29/65	45			18/69	26			7/69	10			44.3	6.3	24.0-54.7	
+/–	7/12	58			4/12	33			1/12	8			41.6	8.3	28.9-53.3	
UGT1A1*6			.038	.031			.044	.025			.475	.565				.823
–/– and –/+	36/72	50			18/75	24			7/75	9			44.1	6.0	28.9-54.7	
+/+	0/5	0			4/6	67			1/6	17			40.8	9.6	24.0-47.8	

NOTE. All *P* values are unadjusted for multiple comparisons.
*Toxicity grade by National Cancer Institute Common Toxicity Criteria version 2.0. A total of 81 patients were assessable for toxicity evaluation.
†Responder: complete or partial response, 77 patients were assessable for tumor response-evaluation.
‡Fisher's exact test for all genotypes.
§Exact test of Cochran-Armitage trend test across genotypes.
¶Kruskal-Wallis or Mann-Whitney test.
‖The UGT1A9*22 genotyping failed in two patients.

Han et al. J Clin Oncology 2006; 24:2237



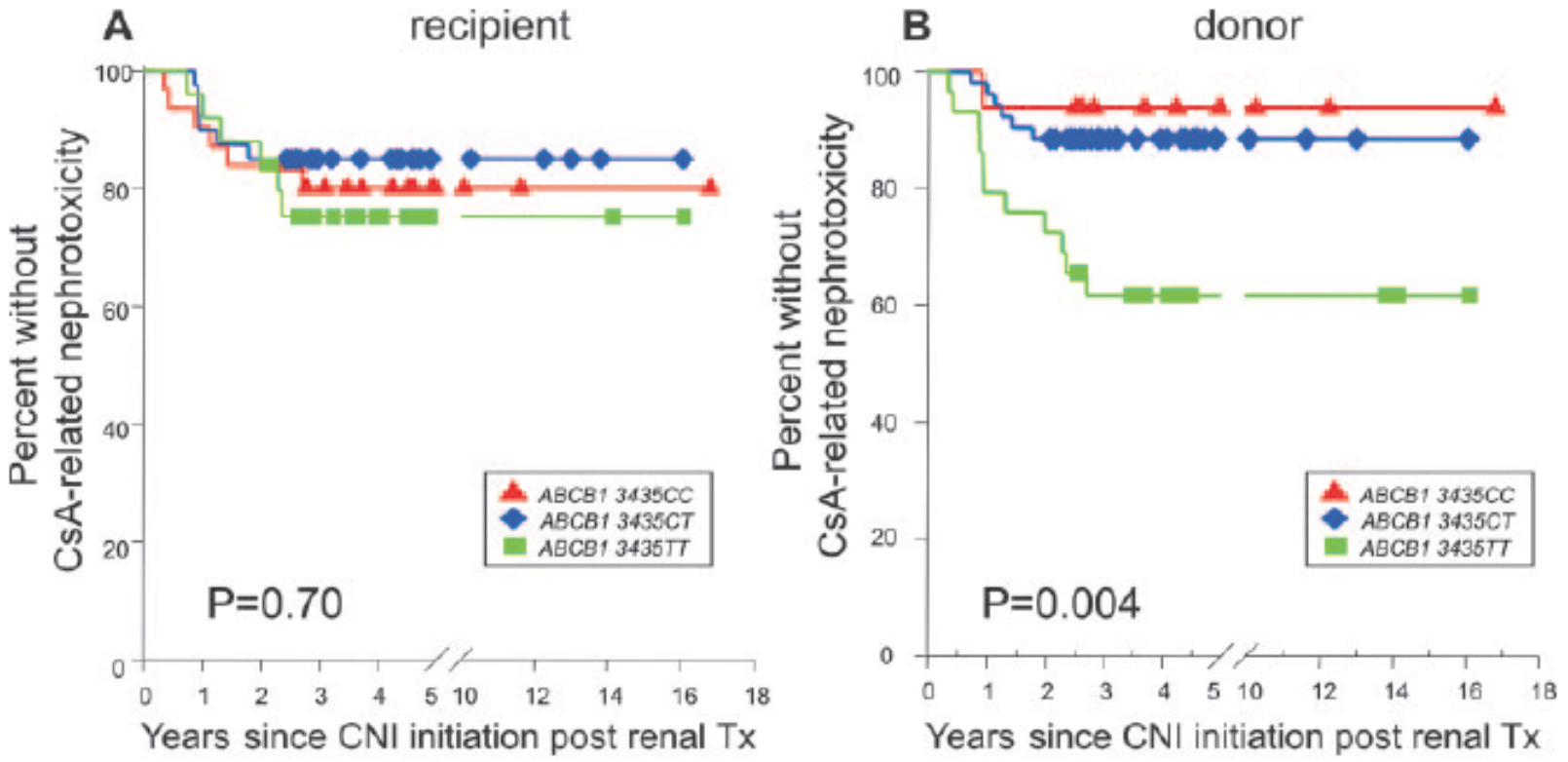
ABCB1 and patient outcomes

- Rejection
  - Acute Persistent Rejection in Lung Transplant Patients
  - Biopsy-proven acute rejection in kidney tx patients
- Adverse drug effects
  - Calcineurin Nephrotoxicity
  - Neurotoxicity
  - Osteoporosis after transplantation
  - Gingival hyperplasia
  - Mycophenolate-induced GI dysfunction
- Lung Transplant Patient Survival

CNI Nephrotoxicity and Donor *ABCB1* Genotype

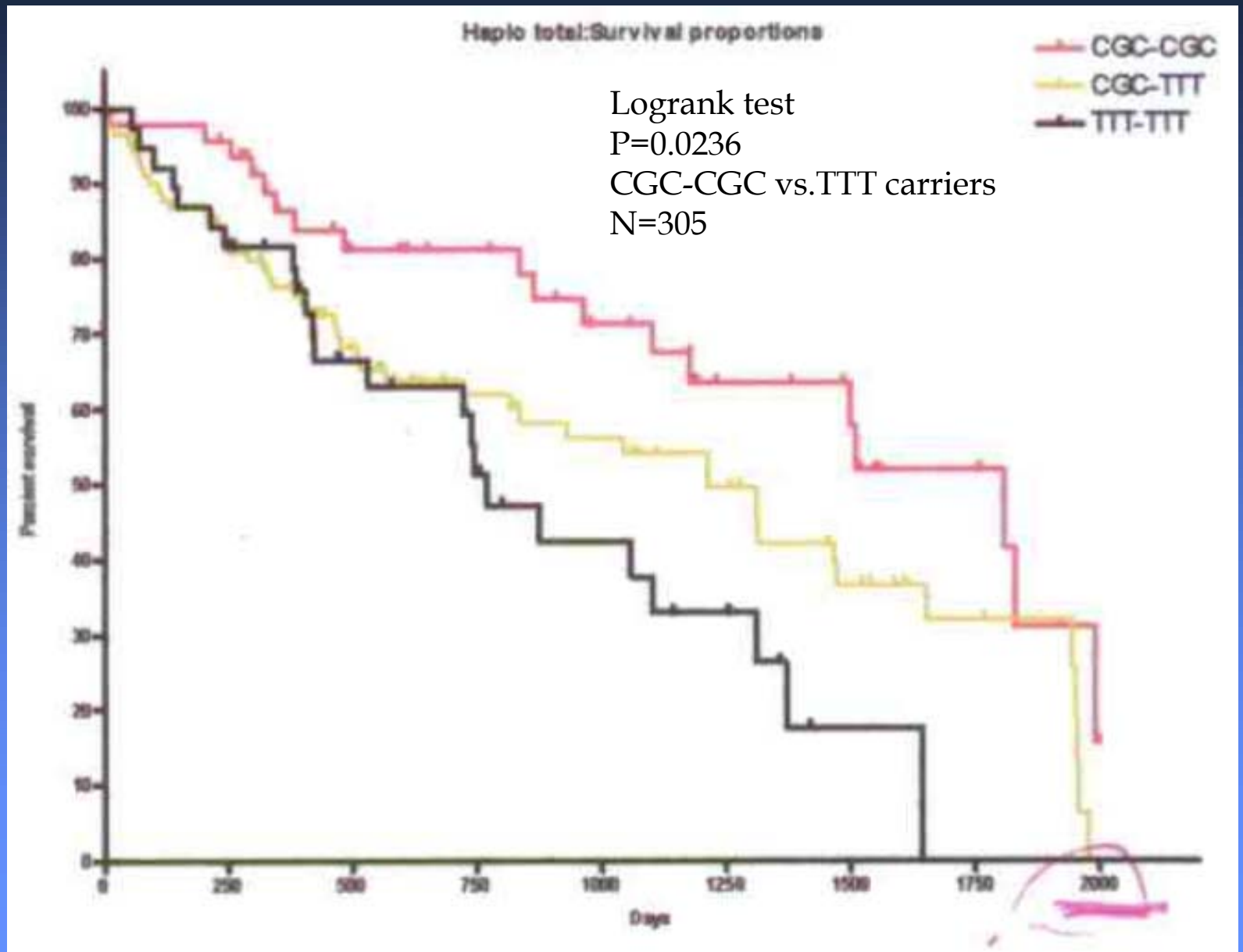
10% of patients whose donated kidney had high transporter expression developed nephrotoxicity

40% of patients whose donated kidney had low transporter expression developed nephrotoxicity



Hauser IA et al; Journal of the American Society of Nephrology 2005; 16: 1501.

Long term survival after lung transplantation: could *ABCB1* haplotypes have a role?



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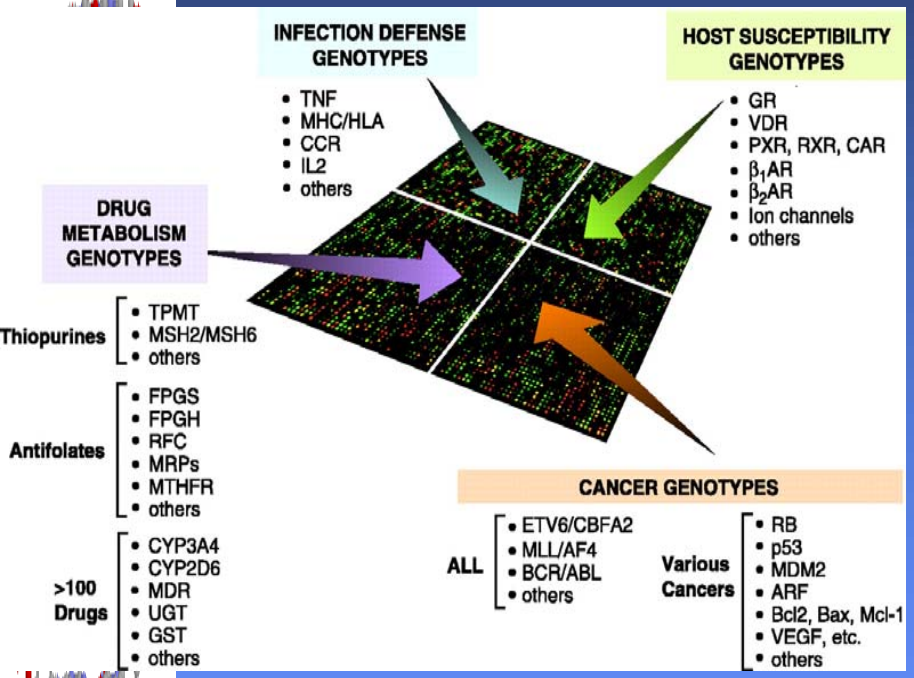
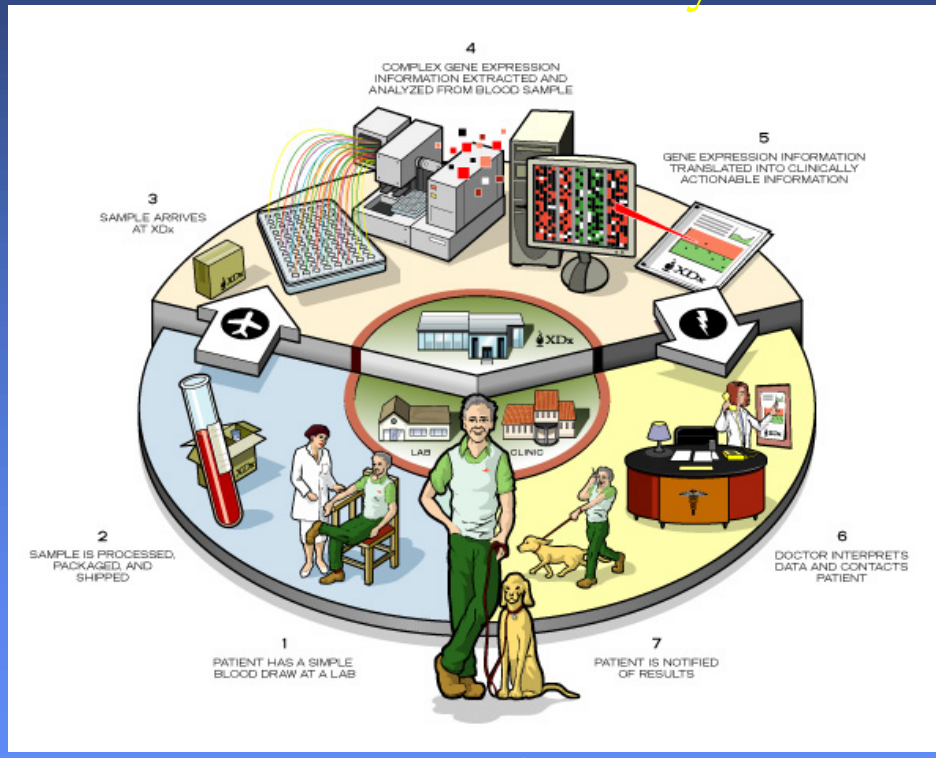
Therapeutic Drug Monitoring in the future

DNA arrays plus mRNA arrays



Wilson et al. *Nature Genetics* 29:265, 2001.



XDx Inc. Web site

= Individualized therapy

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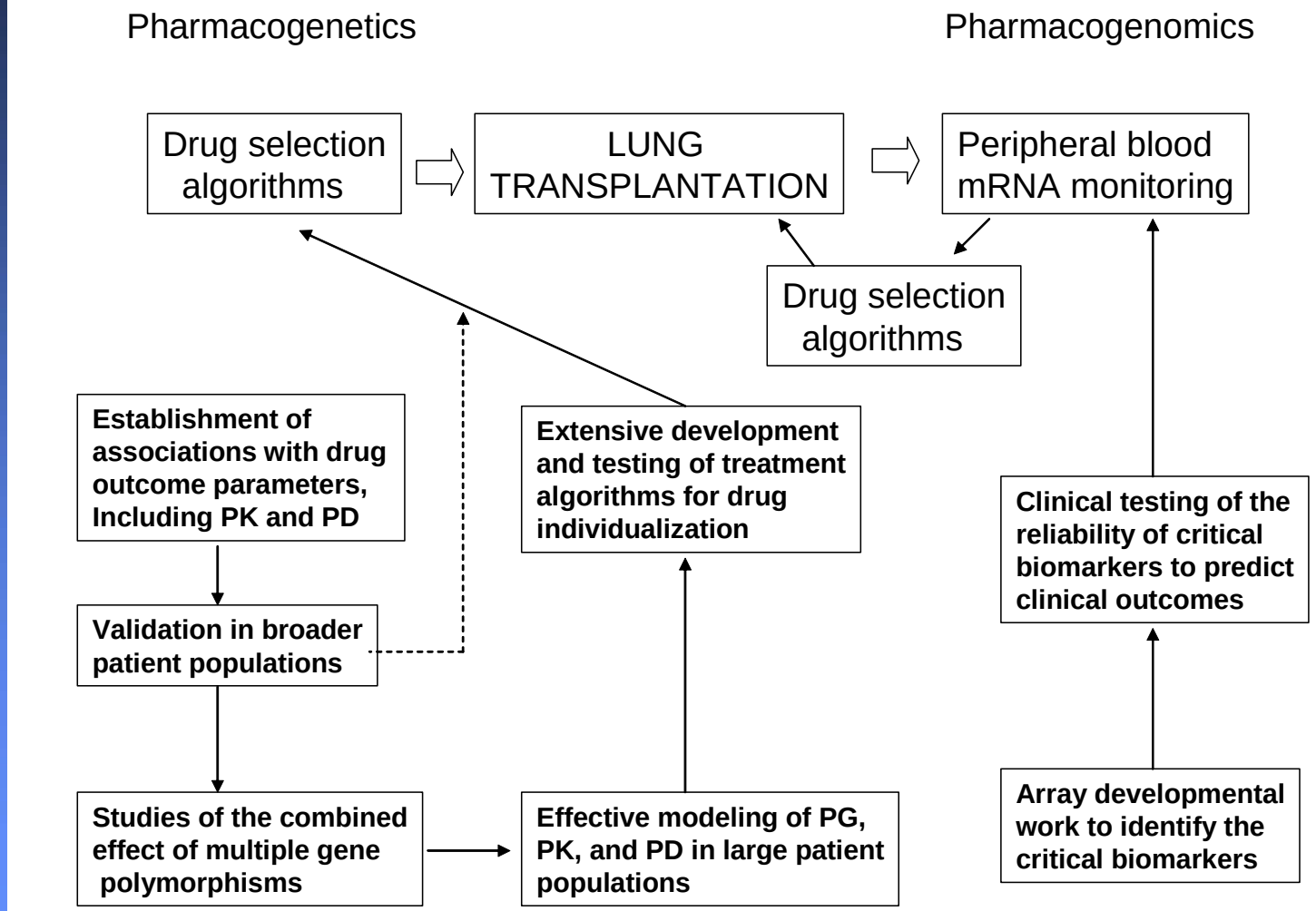
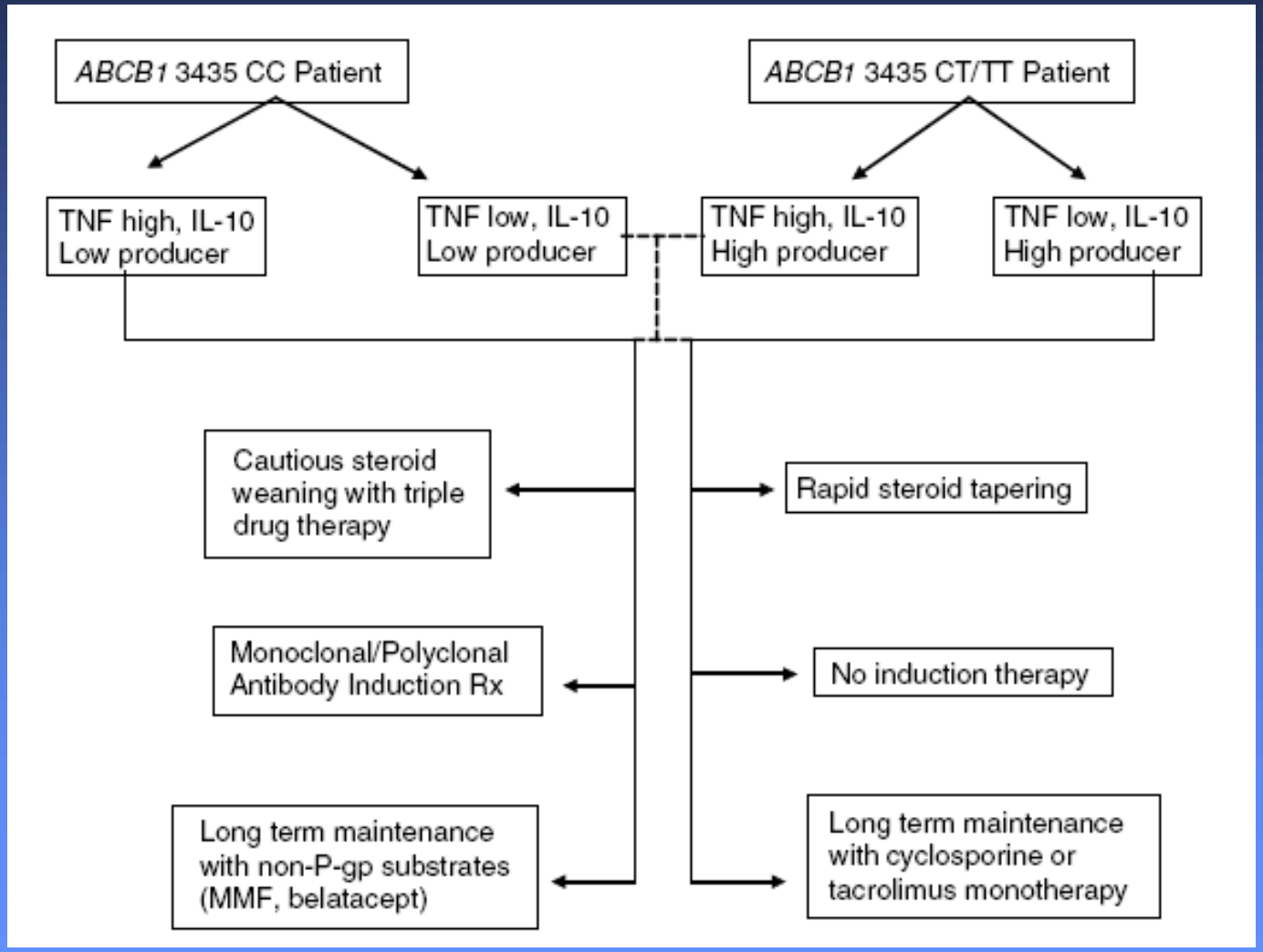
New knowledge requires new approaches to therapeutic drug monitoring



Burckart GJ et al. The Pharmacogenomics Journal [Nature] 2006; 6:301-310

An Initial Algorithm for Designing a Transplant Therapeutic Regimen Based Upon Gene Polymorphisms



Burckart GJ et al. The Pharmacogenomics Journal [Nature] 2006; 6:301-310

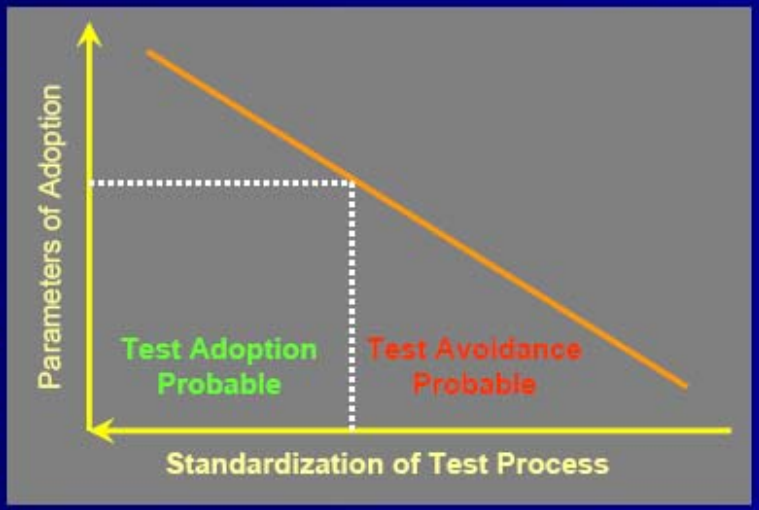
Overcoming the Challenges

- There is always a learning curve
- Clinicians exist in state of information overload
- Do not desire genomics tutorial in patient setting

Unambiguous statements about clinical implications of results

When and how should dosing be adjusted quantitatively

Actionable results important to patient care

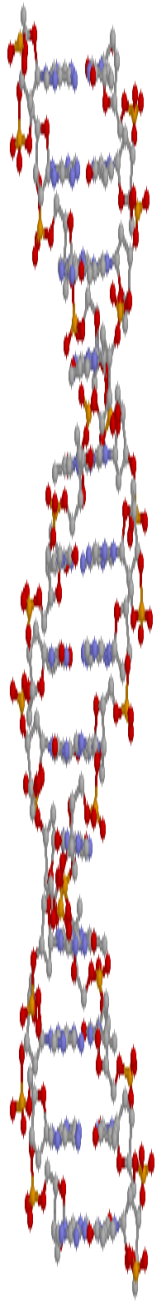


No complexities from blood draw to sample handling to test results

Proximal availability of laboratory assay and rapid turn-around-time

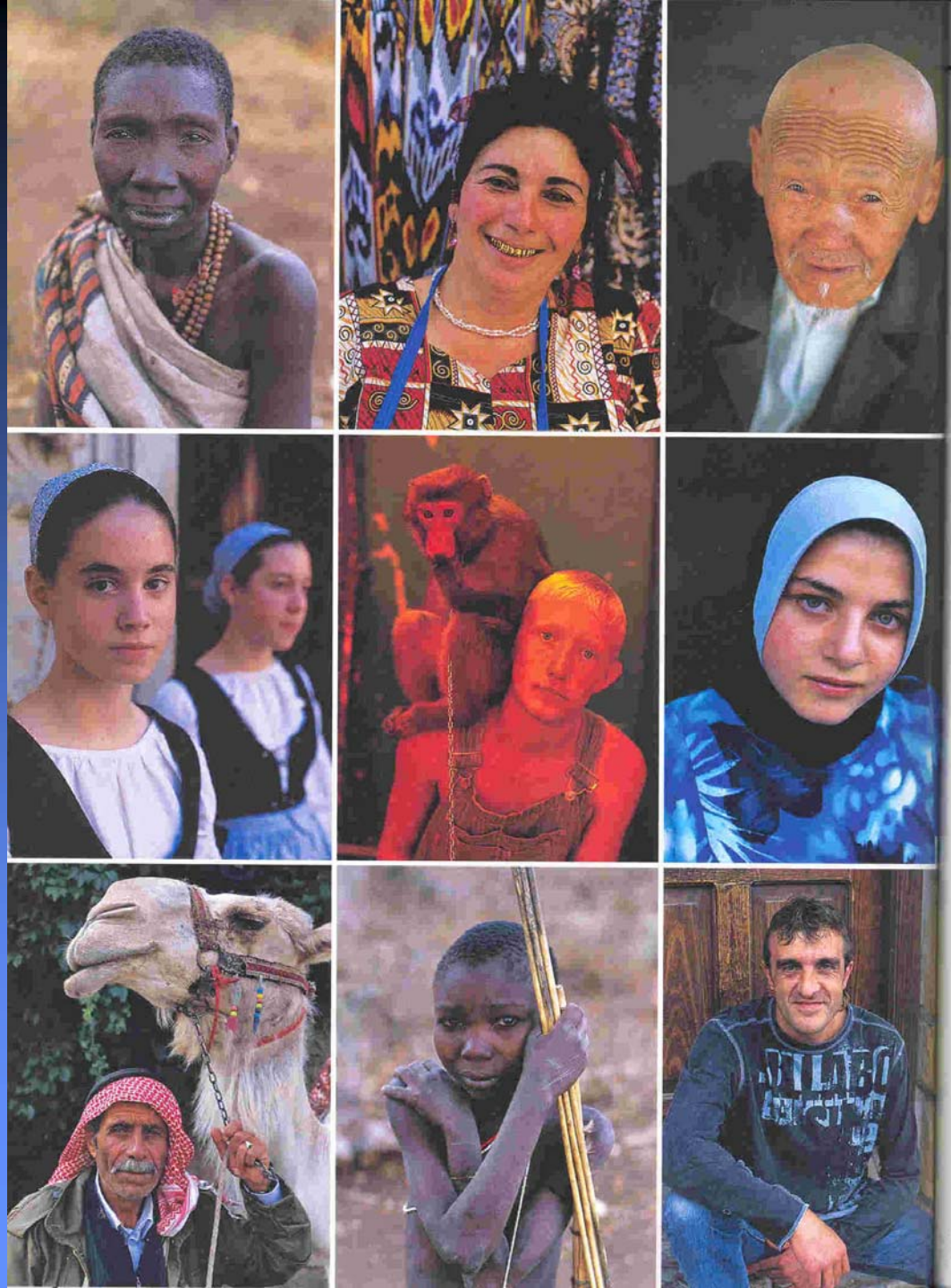
Straightforward billing and reimbursement

Adapted from presentation by Peter Keeling, Diaceutics,2007



Drug responses are as individualized as are the faces that you see here.

Pharm.D.'s should lead the movement to incorporate pharmacogenomics into clinical practice



National Geographic Traveler
22:78, October 2005