Pharmacogenomics

March 23, 2010

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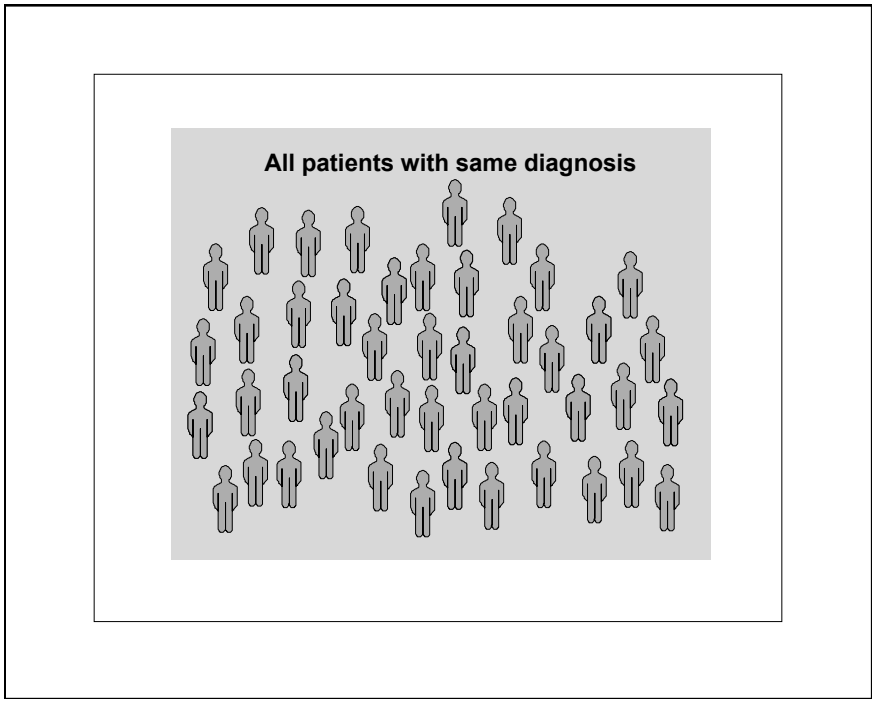
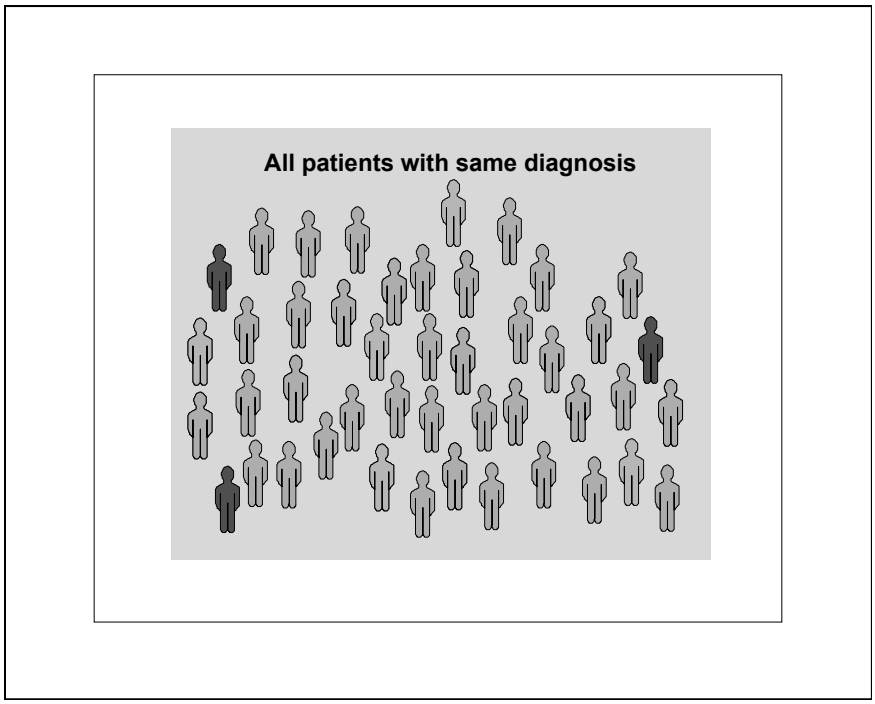
"A surgeon who uses the wrong side of the scalpel cuts her own fingers and not the patient;

if the same applied to drugs they would have been investigated very carefully a long time ago"

Rudolph Bucheim
Beitrage zur Arzneimittellehre, 1849


All patients with same diagnosis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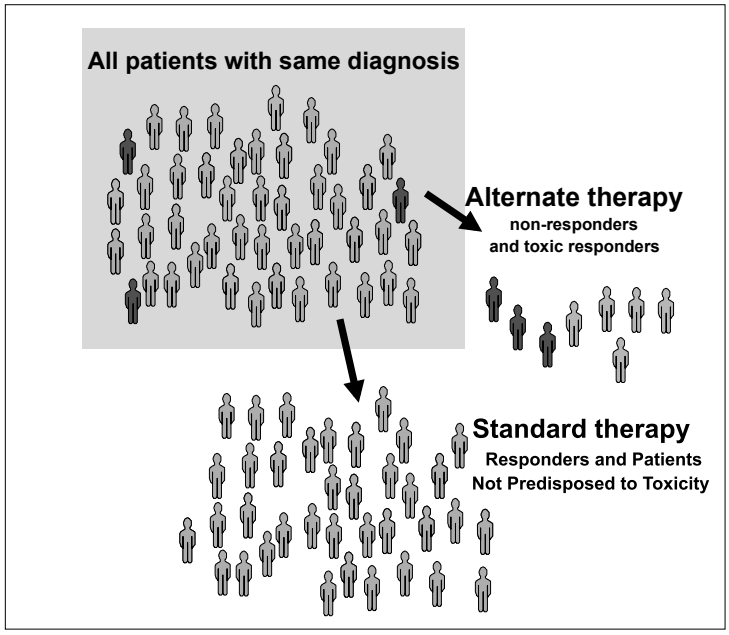
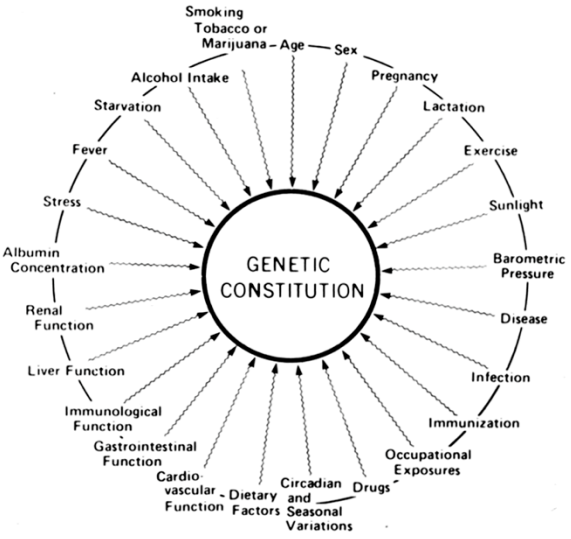


The clinical problem

- Multiple active regimens for the treatment of most diseases
- Variation in response to therapy
- Unpredictable toxicity

$$$$$$$$$$$$

With choice comes decision



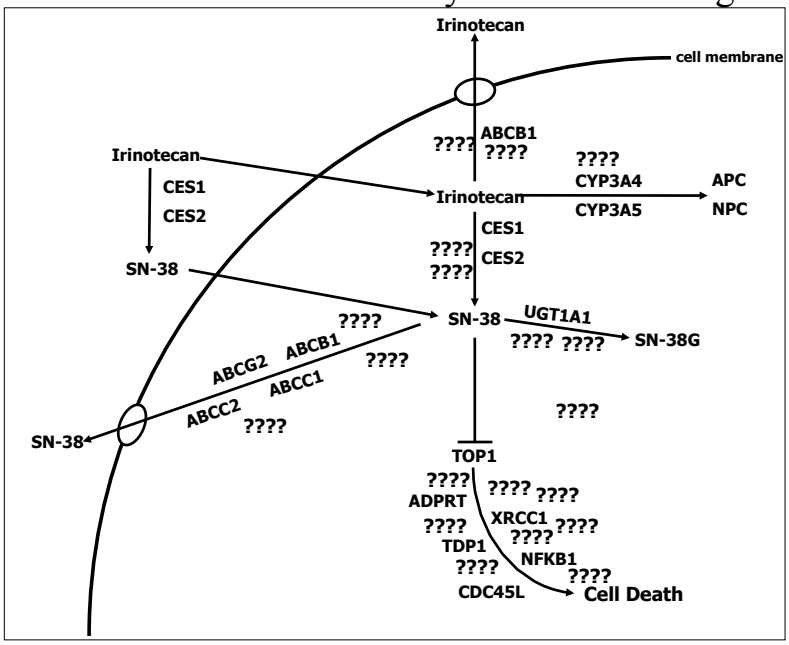
Pharmacogenomic examples-2010

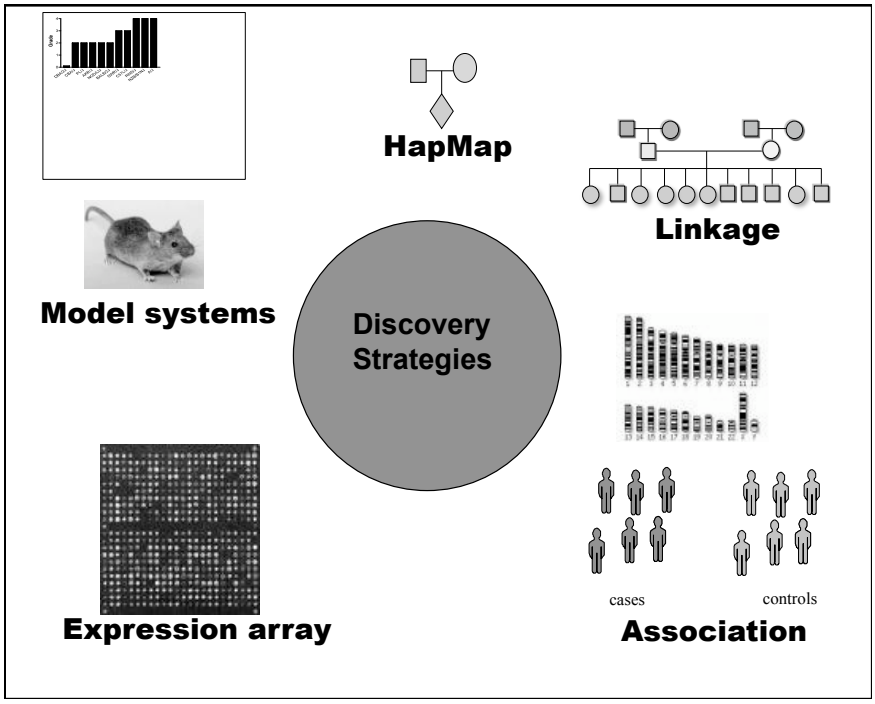
- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib
- Thiopurine S-methyltransferase—mercaptopurine and azathioprine*
- UGT1A1-irinotecan**
- CYP2D9/VKORC1-warfarin*
- HLA-B*5701-abacavir *
- HLA-B*1502-carbamazepine *
- CYP2C19-clopidogrel
- Cytochrome P-450 (CYP) 2D6—5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives, tamoxifen*

What needs to be done to determine hope vs hype?

- Find the 'right' biomarkers
- Validate in robust datasets
- Apply them!

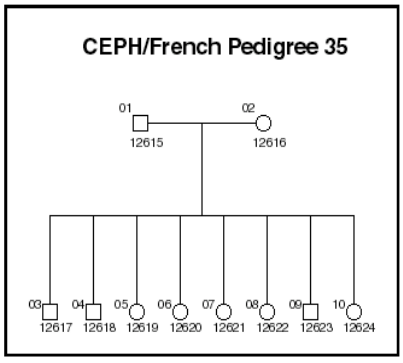
We do not know very much about drugs

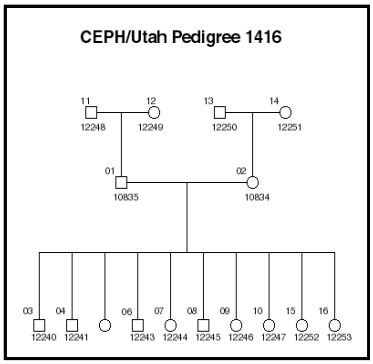




Centre d' Etude du Polymorphisme Human (CEPH) Cell lines

- Large, multigeneration pedigrees widely studied
- Immortalized lymphoblastoid cell lines



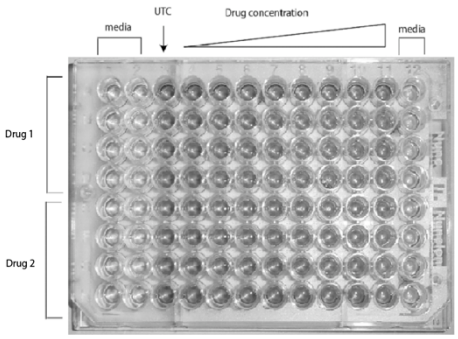


Methodology

Cells counted, plated at 1 x 10^4 / well

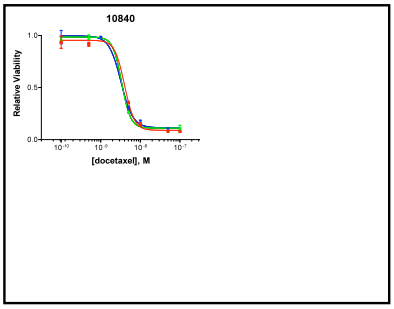
Cells incubated with increasing concentrations of drug

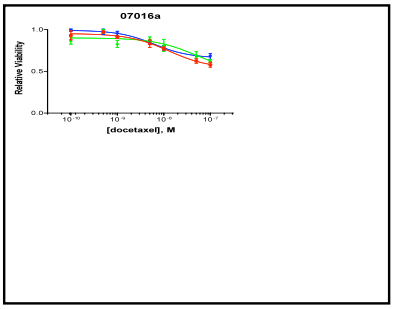
Alamar blue vital dye indicator added



Viability relative to untreated control calculated by spectrophotometry

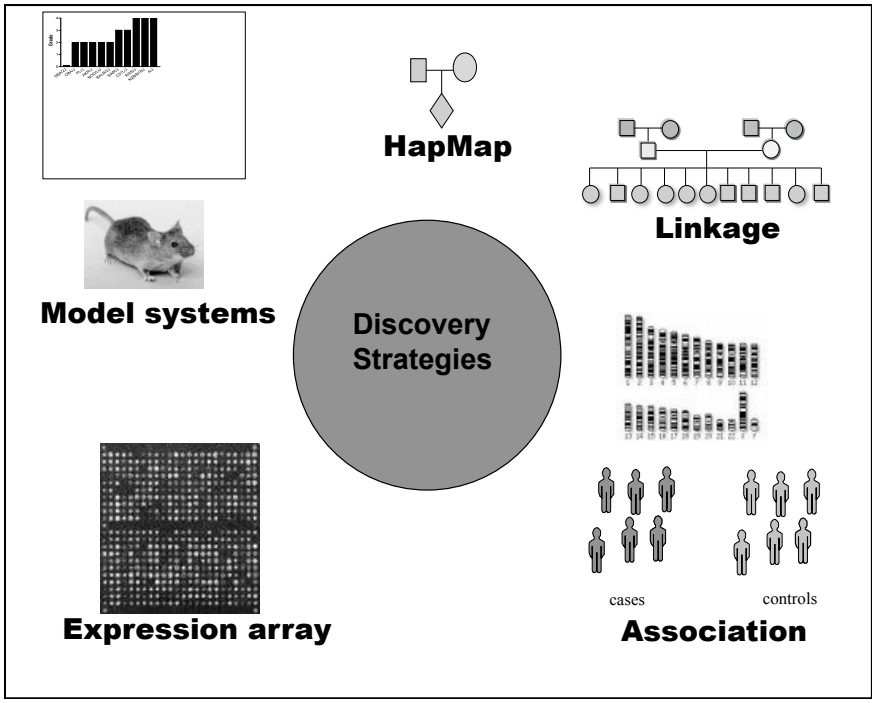
Significant Variation in Cellular Sensitivity to Docetaxel





'CE-PH/F-DA' project

- 126 CEPH cell lines from 14 nuclear families
- All FDA approved cytotoxic drugs + new kinase inhibitors/MTOR/demethylation
- No antiestrogen or vitamin A analogues
- Evaluate degree of heritability, presence of QTL(s), and evidence for correlations between drug sensitivity patterns.



Genetic dissection of complex and quantitative traits: from fantasy to reality via a community effort

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[1]Department of Genetics, CB#7264, Lineberger Comprehensive Cancer Center, Rm 11-109, University of North Carolina, Chapel Hill, North Carolina 27599, USA
[2]Laboratory of Population Genetics, DCEG/NCI/NIH, Bldg 41, Rm 702, 41 Library Drive, Bethesda, Maryland 20892, USA
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Received: 29 November 2001 / Accepted: 17 December 2001

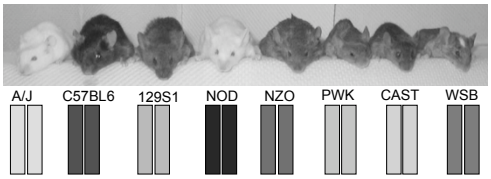
Mammalian Genome 13:175, 2002

The Collaborative Cross, a community resource for the genetic analysis of complex traits

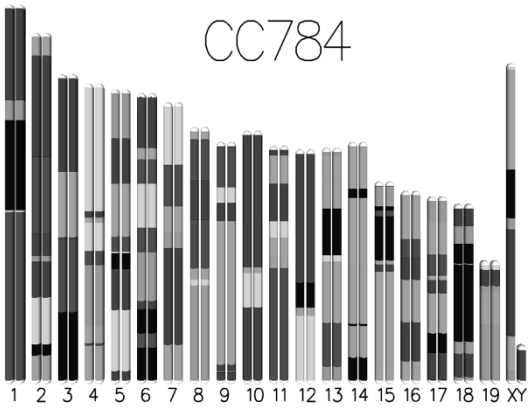
The Complex Trait Consortium*

The goal of the Complex Trait Consortium is to promote the development of resources that can be used to understand, treat and ultimately prevent pervasive human diseases. Existing and proposed mouse resources that are optimized to study the actions of isolated genetic loci on a fixed background are less effective for studying intact polygenic networks and interactions among genes, environments, pathogens and other factors. The Collaborative Cross will provide a common reference panel specifically designed for the integrative analysis of complex systems and will change the way we approach human health and disease.

Nature Genetics 36:1133, 2004



Representative CC genome



What needs to be done to determine hope vs hype?

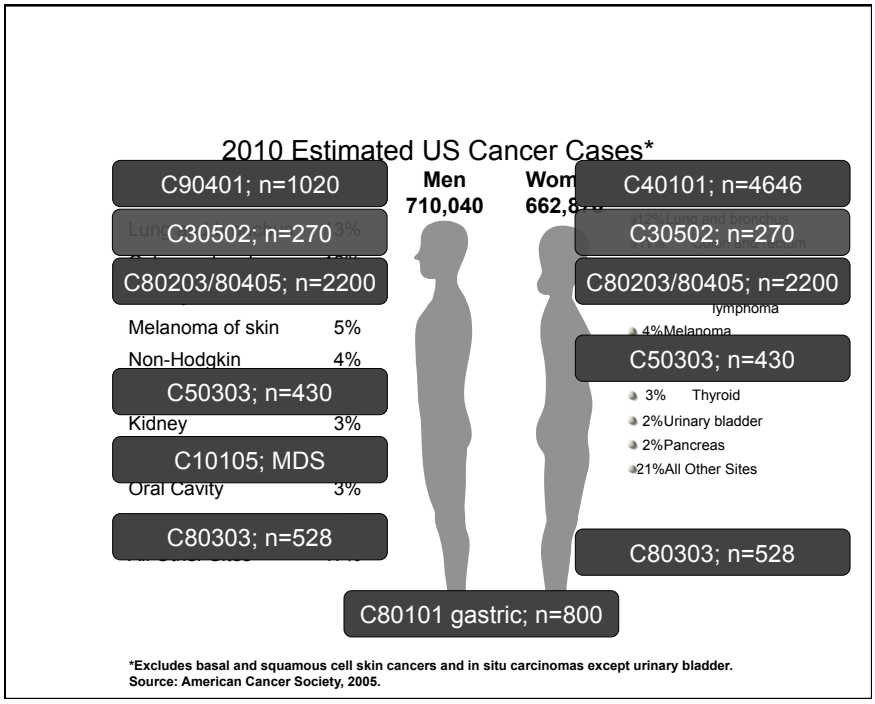
•Find the 'right' biomarkers

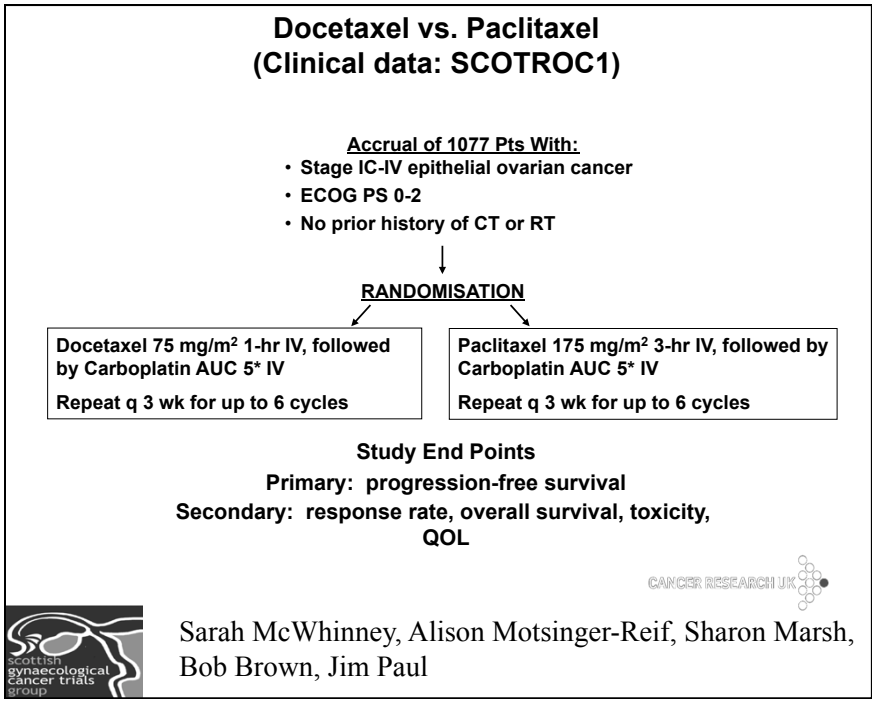
•Validate in robust datasets

•Apply them!

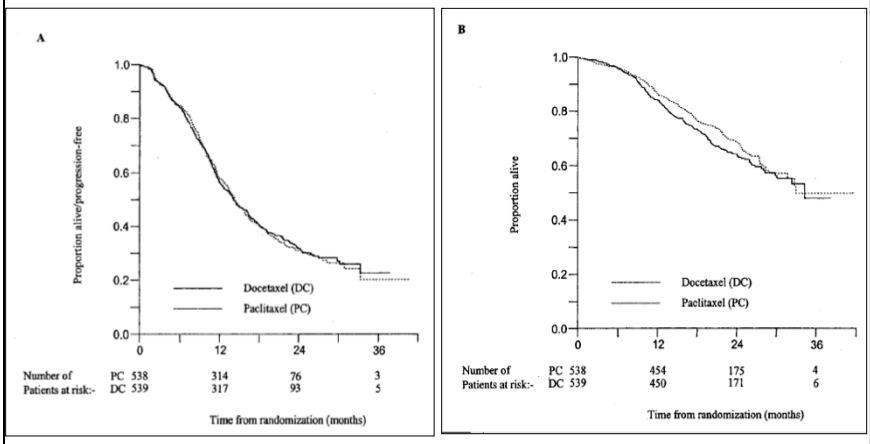
Correlative science: business as usual

Phase I	→	Phase II	→	Phase III
In vivo Mechanism		Biomarker assessment		Biomarker validation


2010 Estimated US Cancer Cases*
Men
710,040
C90401; n=1020
C30502; n=270
C80203/80405; n=2200
Melanoma of skin 5%
Non-Hodgkin 4%
C50303; n=430
Kidney 3%
C10105; MDS
Oral Cavity 3%
C80303; n=528
C40101; n=4646
C30502; n=270
C80203/80405; n=2200
lymphoma
4%Melanoma
C50303; n=430
3% Thyroid
2%Urinary bladder
2%Pancreas
21%All Other Sites
C80303; n=528
C80101 gastric; n=800
*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2005.


Docetaxel vs. Paclitaxel
(Clinical data: SCOTROC1)
Accrual of 1077 Pts With:
• Stage IC-IV epithelial ovarian cancer
• ECOG PS 0-2
• No prior history of CT or RT
RANDOMISATION
Docetaxel 75 mg/m2 1-hr IV, followed by Carboplatin AUC 5* IV
Repeat q 3 wk for up to 6 cycles
Paclitaxel 175 mg/m2 3-hr IV, followed by Carboplatin AUC 5* IV
Repeat q 3 wk for up to 6 cycles
Study End Points
Primary: progression-free survival
Secondary: response rate, overall survival, toxicity, QOL
CANCER RESEARCH UK
scottish gynaecological cancer trials group
Sarah McWhinney, Alison Motsinger-Reif, Sharon Marsh, Bob Brown, Jim Paul

Docetaxel vs. Paclitaxel (Clinical data: SCOTROC1)



Progression-free survival

Overall survival

Vasey et al JNCI 2004

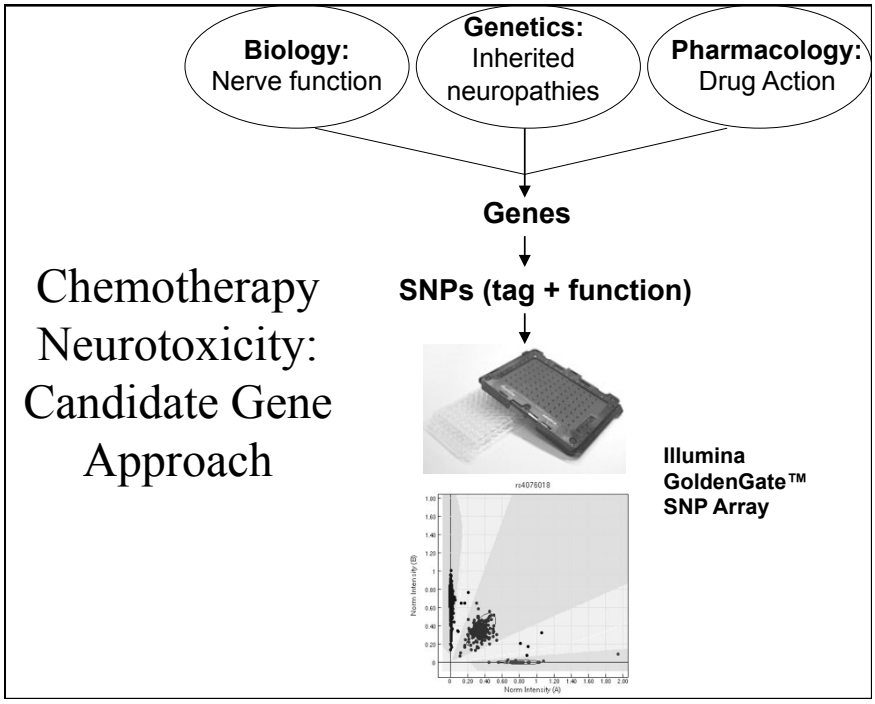
Docetaxel vs. Paclitaxel (Clinical data: SCOTROC1)

Table 5. NCI–CTC neurotoxicity in the Scottish Randomised Trial in Ovarian Cancer 1*

Grade	% of patients: Docetaxel–carboplatin arm (n = 537)†	% of patients: Paclitaxel–carboplatin arm (n = 532)‡	*P*
Sensory‖			
1	35	48	
2	9	22	
3	2	8	<.001‖
4	0	0	
Total	45	78	<.001¶
Motor¶			
1	6	9	
2	2	5	
3	1	2	.005‖
4	0	0	
Total	9	16	.001¶

*NCI–CTC = National Cancer Institute–Common Toxicity Criteria.
†Not available for two patients who died after one cycle.
‡Not available for one patient who died after one cycle.
§All statistical tests were two-sided. *P* value from Mann–Whitney *U* test.
‖Grades 1–4.
¶Total.

Vasey et al JNCI 2004



The filtering of Neuro-risk genotypes

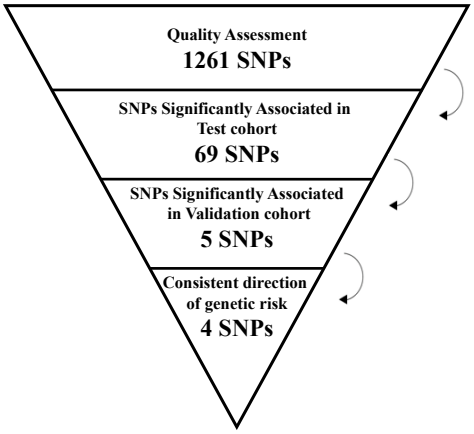
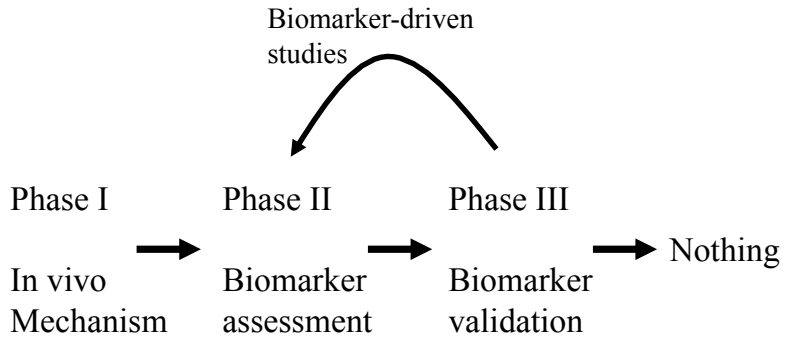
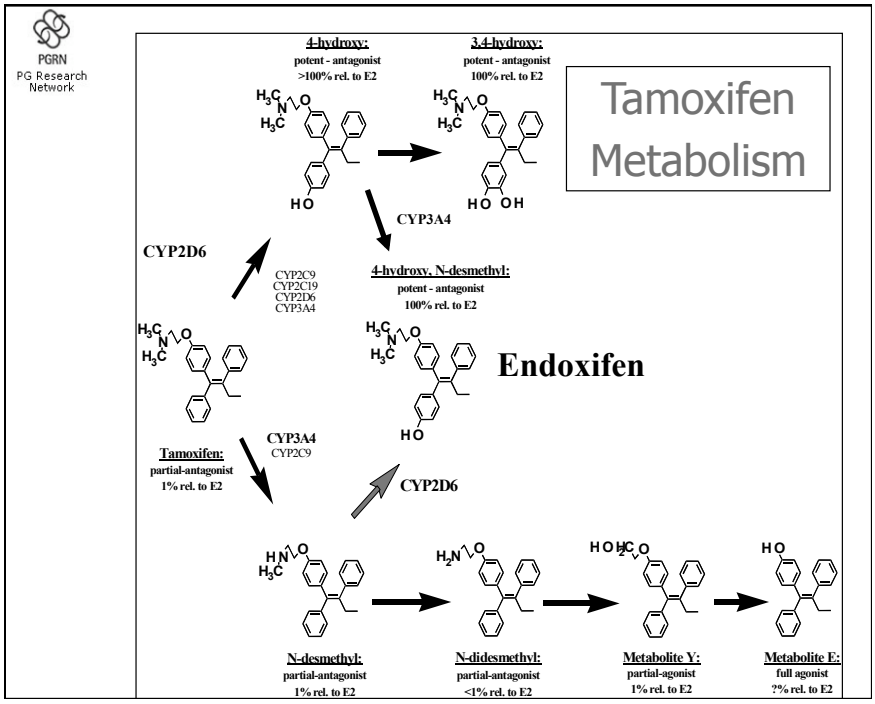


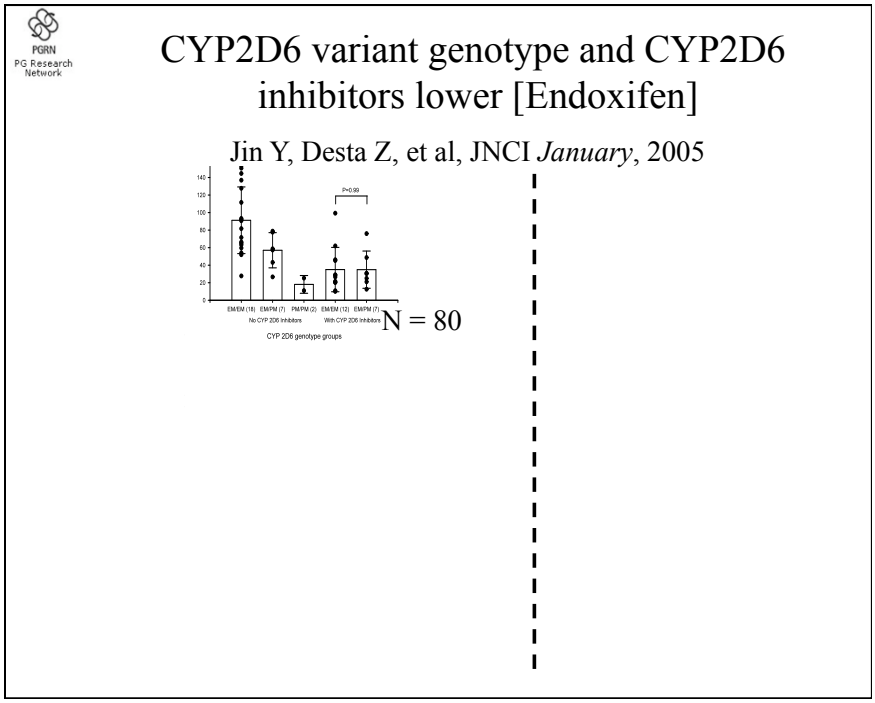
Figure 1: The workflow of the data analysis, represented by the narrowing number of SNPs at each stage of the analysis.

What needs to be done to determine hope vs hype?

- Find the 'right' biomarkers
- Validate in robust datasets
- Apply them!




PGRN
PG Research Network
Tamoxifen Metabolism
4-hydroxy:
potent - antagonist
>100% rel. to E2
3,4-hydroxy:
potent - antagonist
100% rel. to E2
CYP3A4
CYP2D6
CYP2C9
CYP2C19
CYP2D6
CYP3A4
4-hydroxy, N-desmethyl:
potent - antagonist
100% rel. to E2
Endoxifen
Tamoxifen:
partial-antagonist
1% rel. to E2
CYP3A4
CYP2C9
CYP2D6
N-desmethyl:
partial-antagonist
1% rel. to E2
N-didesmethyl:
partial-antagonist
<1% rel. to E2
Metabolite Y:
partial-agonist
1% rel. to E2
Metabolite E:
full agonist
?% rel. to E2

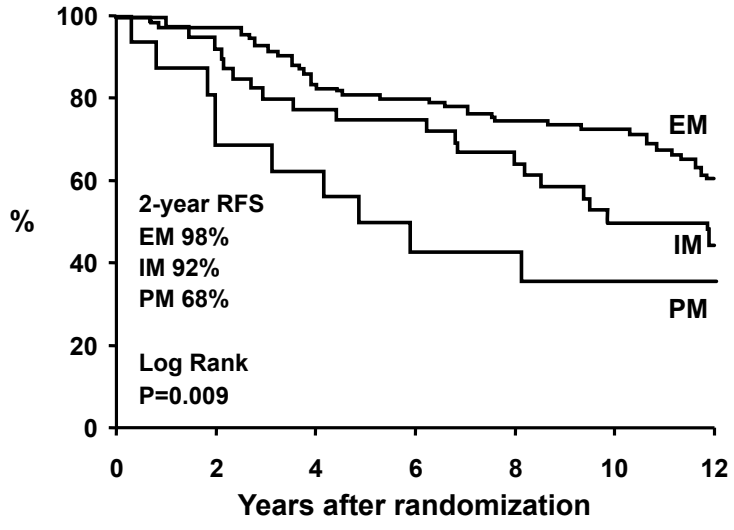

PGRN
PG Research Network
CYP2D6 variant genotype and CYP2D6 inhibitors lower [Endoxifen]
Jin Y, Desta Z, et al, JNCI *January*, 2005
N = 80

Adjuvant Tamoxifen and CYP2D6

- **CYP2D6 associated with recurrence**
  - **Goetz et al. 2005, 2007 (USA)**
  - **Schroth et al. 2007 (Germany)**
  - **Kiyotani et al. 2008 (Japan)**
  - **Newman et al. 2008 (UK)**
  - **Xu et al. 2008 (China)**
  - **Okishiro et al. 2009 (Japan)**
  - **Ramon et al. 2009 (Spain)**
  - **Bijl et al. 2009 (Netherlands)**
- **CYP2D6 not associated with recurrence**
  - **Wegman et al. 2005, 2007 (Sweden)**
  - **Nowell et al. 2005 (USA)**

PGRN
PG Research Network

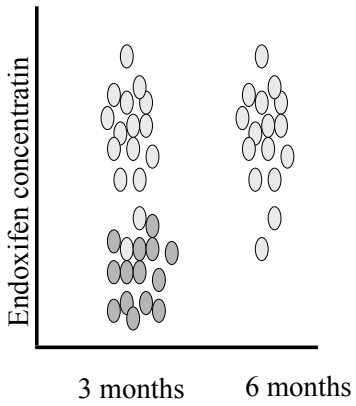
Relapse-free Survival



Goetz et al. Breast Cancer Res Treat. 2007

CP1229323-16

Hypothesis: Increasing tamoxifen dose will 'overcome' metabolic resistance



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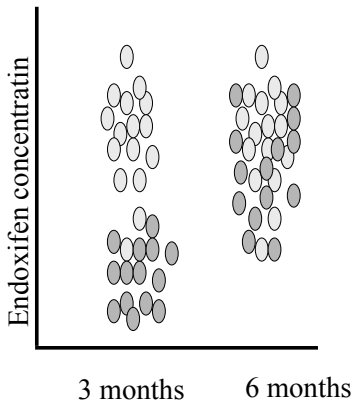
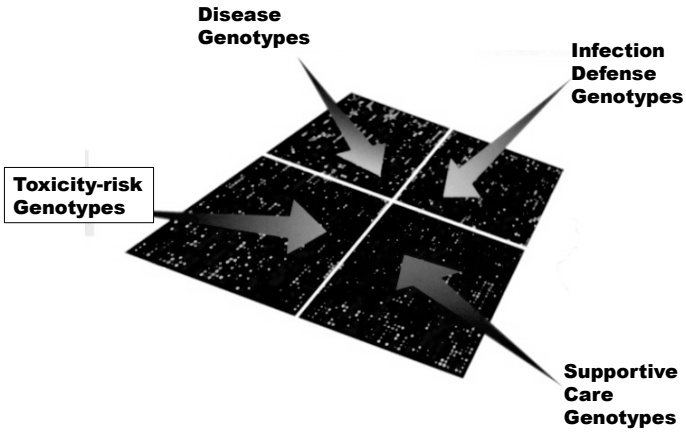


5 Stages of pharmacogenetics progress

Denial (and Isolation)
Anger
Bargaining
Depression
Acceptance

Apologies to Elizabeth KUBLER-ROSS, MD
On Death and Dying (1969)

Comprehensive optimization of patient care



PGENI

Background: The human genome project promise

The genetic code will lead to better diagnosis of disease and selection of therapy

•Significant data exists for DNA changes that are predictive for risk of toxicity or lack of effectiveness for commonly used medications

•Genome-guided therapy is starting to be introduced in Western countries

•What about most of the world?

The genome may offer a way to better integrate medications into national formularies in a safe and effective manner

PGENI

Background: Source of data for patient therapy selection

Best option: individual

Good: relevant geographic/ ethnic/racial population

Worst: inferred world population

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Voltaire

- **"The best is the enemy of good."**,

PGENI

Selection of drugs and genes

- Focused on systemic drugs from WHO Essential Medicines List (http://www.who.int/)
- Conducted text mining for metabolism, transport and drug target proteins
  >300,000 articles reviewed
- Mined literature for allele frequencies of key SNPs in key genes

316 drugs > 206 systemic (oral / IV)

↓

Text mining

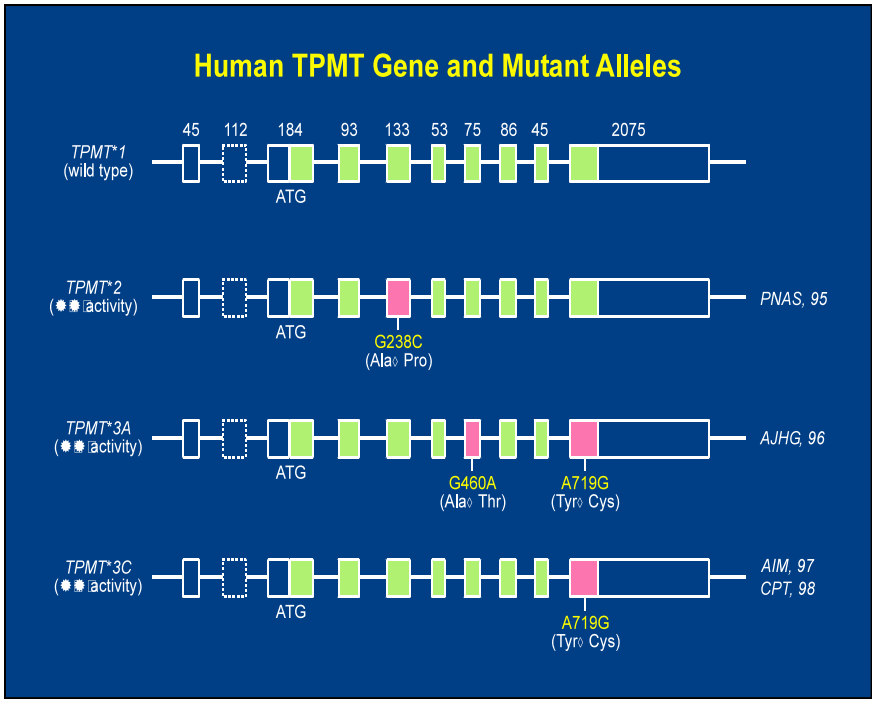
↓

154 Essential Genes* → 230 Essential Variants*

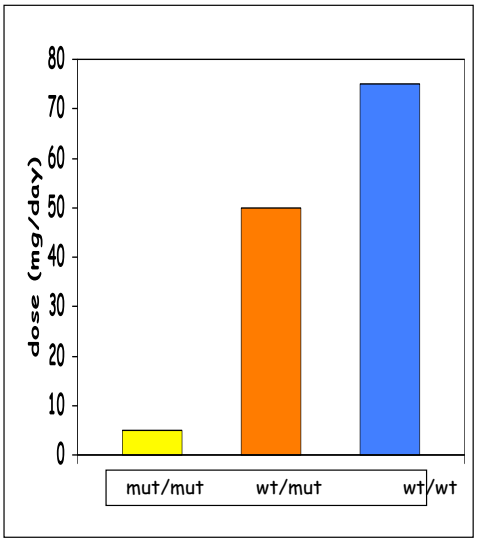
*to date

Pharmacogenomic examples-2009

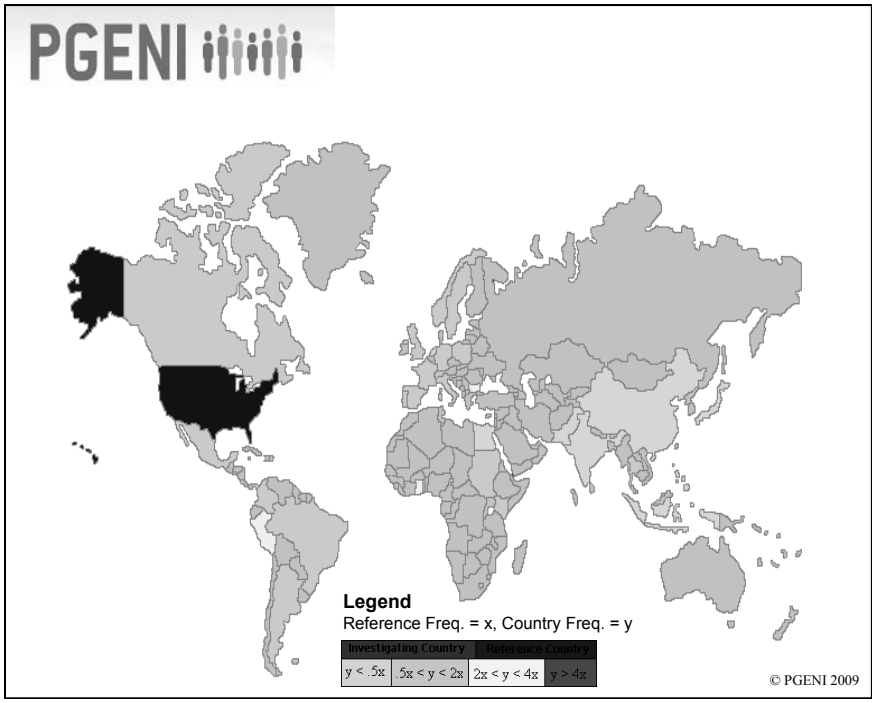
- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib
- Thiopurine S-methyltransferase—mercaptopurine and azathioprine*
- UGT1A1-irinotecan**
- CYP2D9/VKORC1-warfarin **
- Carbamazepine-HLA-B*1502 *
- Abacavir-HLA-B*5701 *
- Clopidogrel-CYP2C19**
- Cytochrome P-450 (CYP) 2D6—5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives, tamoxifen **



Optimal dose for each patient differs by TPMT genotype



Relling et al JNCI, 1999



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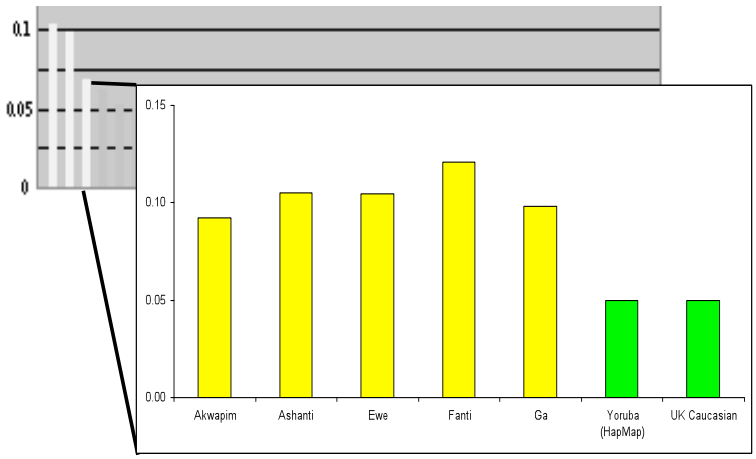

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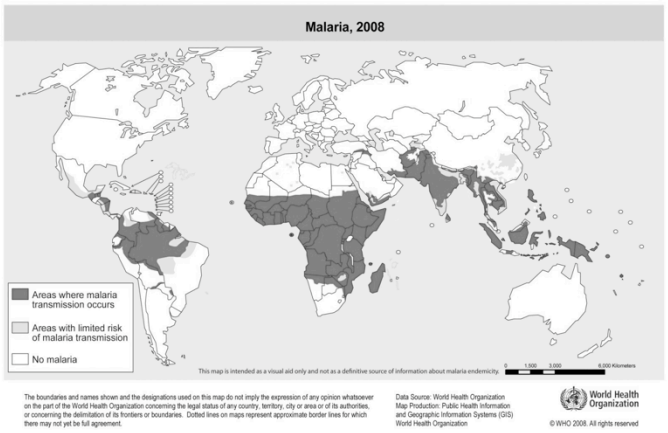
Type of output

Surveillance - identifying population subgroups at higher risk of toxicity or treatment failure

Prioritization - assisting the treatment selection from among WHO recommended therapies

Global Map of Malaria Transmission – WHO 2008



PGENI

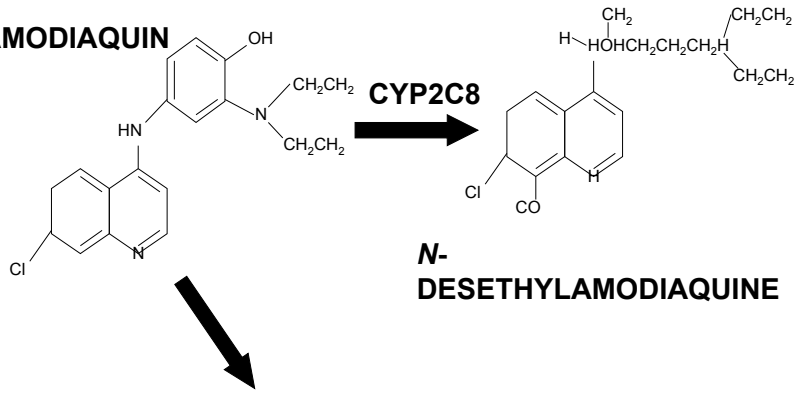
WHO
Malaria Treatment P. falciparum Men and Nonpregnant Women

AS + AQ ↔ **AS + MQ** ↔ **AS + SP** ↔ **AL**

•AS = artesunate; AQ = amodiaquine; MQ = mefloquine; SP = sulfadoxine/pyrimethamine; AL = artemether + lumefantrine

PGENI

AMODIAQUINE



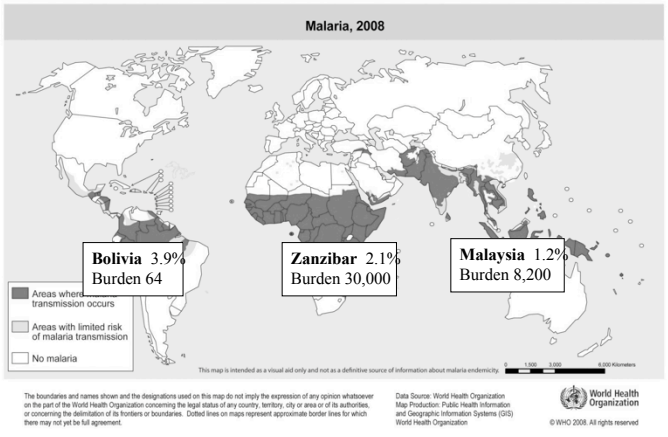
***N*-DESETHYLAMODIAQUINE**

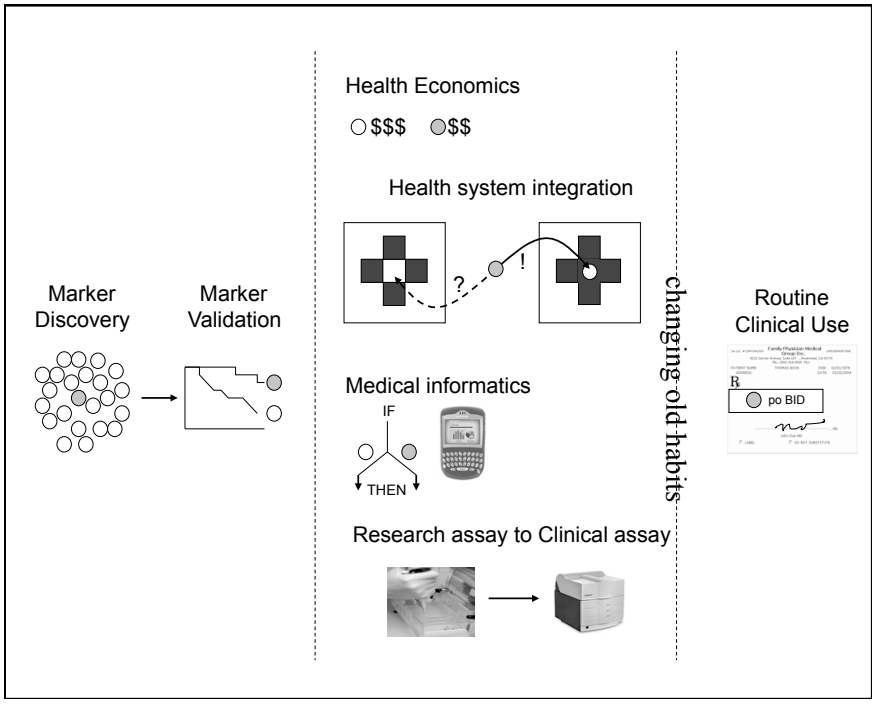
QUINONEIMINE

Toxic metabolite

PGENI

Amodiaquine PG toxicity burden: CYP2C8*3




Health Economics
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Health system integration
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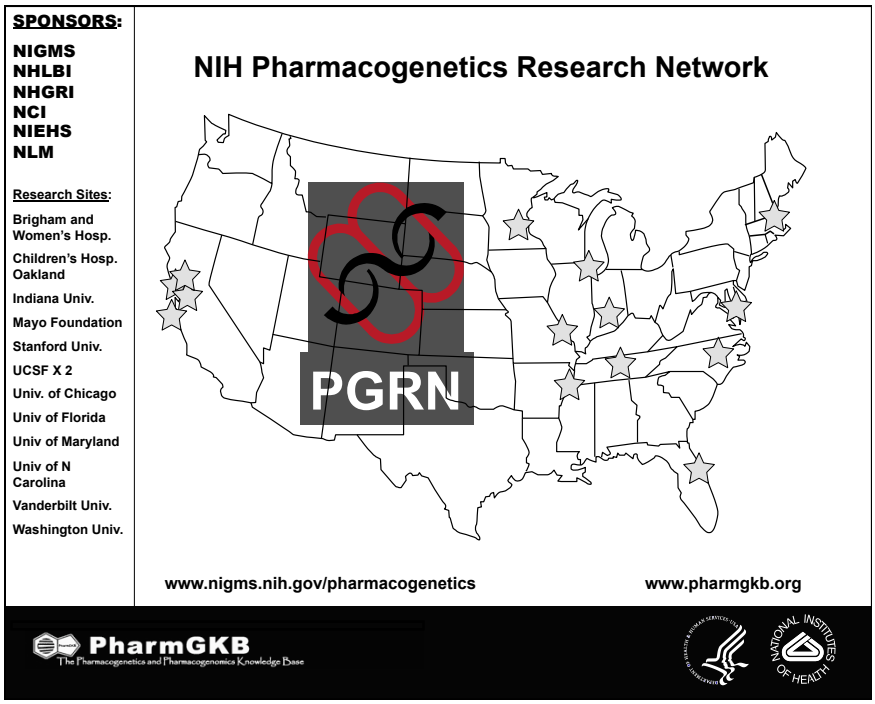
Marker Discovery
Marker Validation
changing old habits
Routine Clinical Use
Medical informatics
IF
THEN
po BID
Research assay to Clinical assay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PharmGKB
The Pharmacogenetics and Pharmacogenomics Knowledge Base
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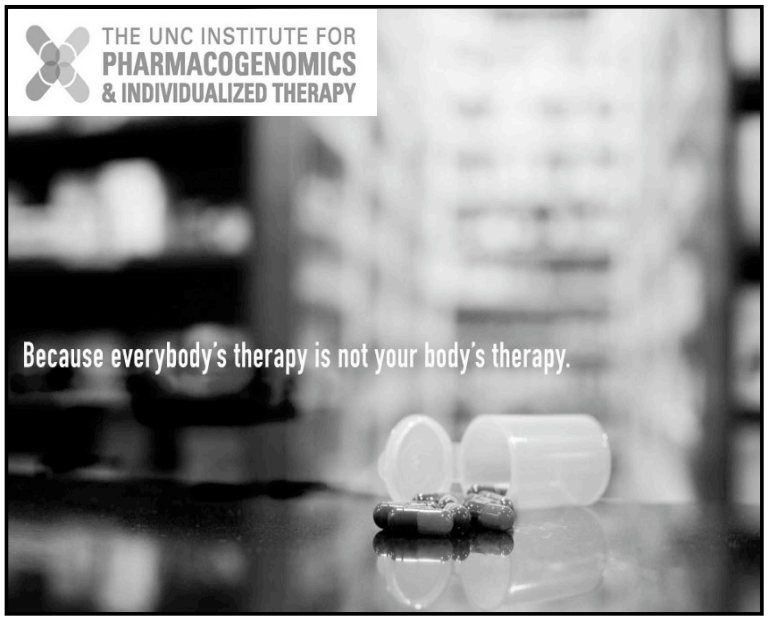
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