

Pharmacogenomics

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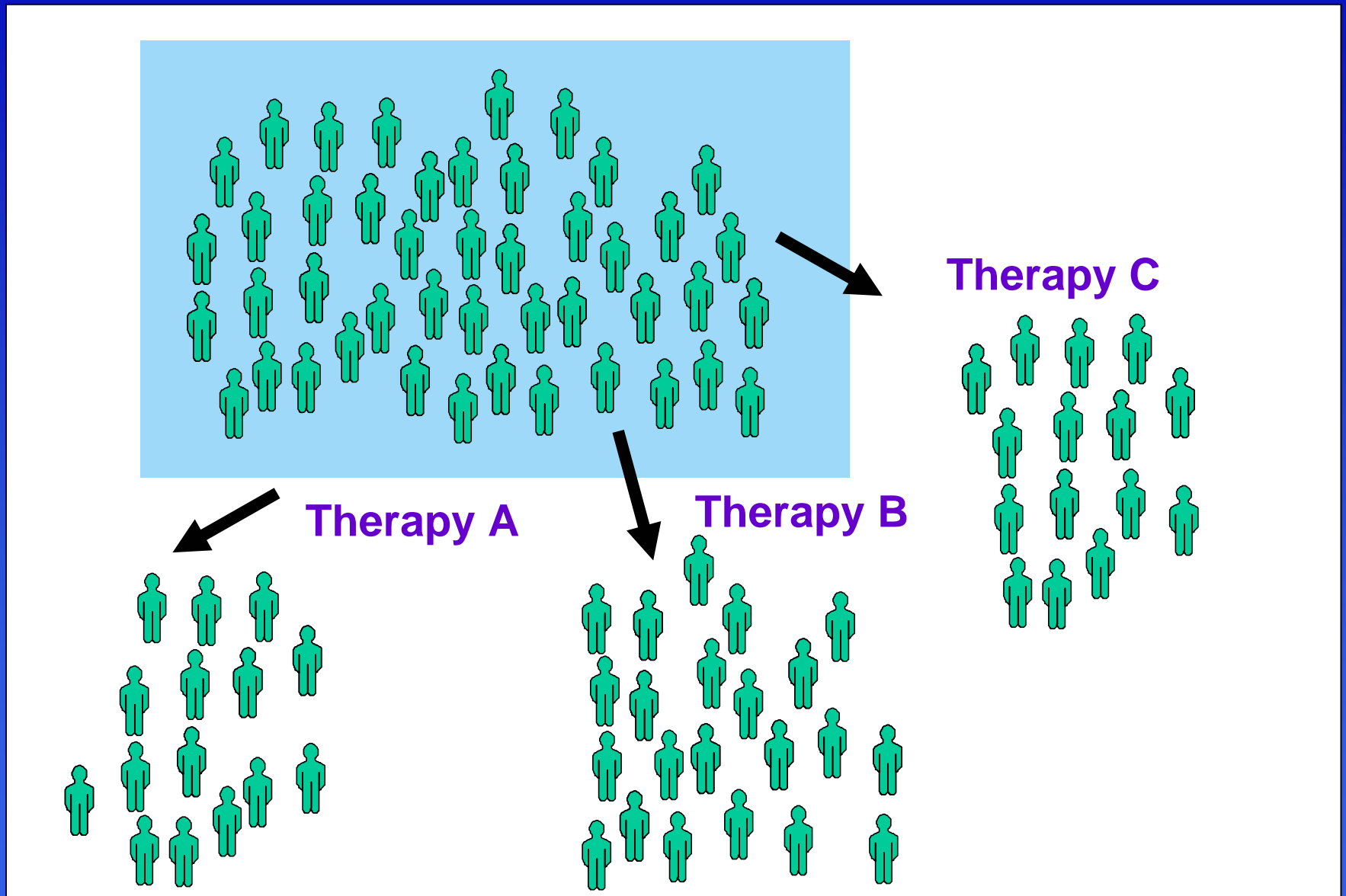
The clinical problem

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

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With choice comes decision

Hypothesis generation: **Is genotype-guided therapy likely to work?**



Drug effect can be heritable

Elliot Vesell *Advances in Pharmacogenetics and Pharmacogenomics*. *J Clin Pharmacol* 2000;40:930-938

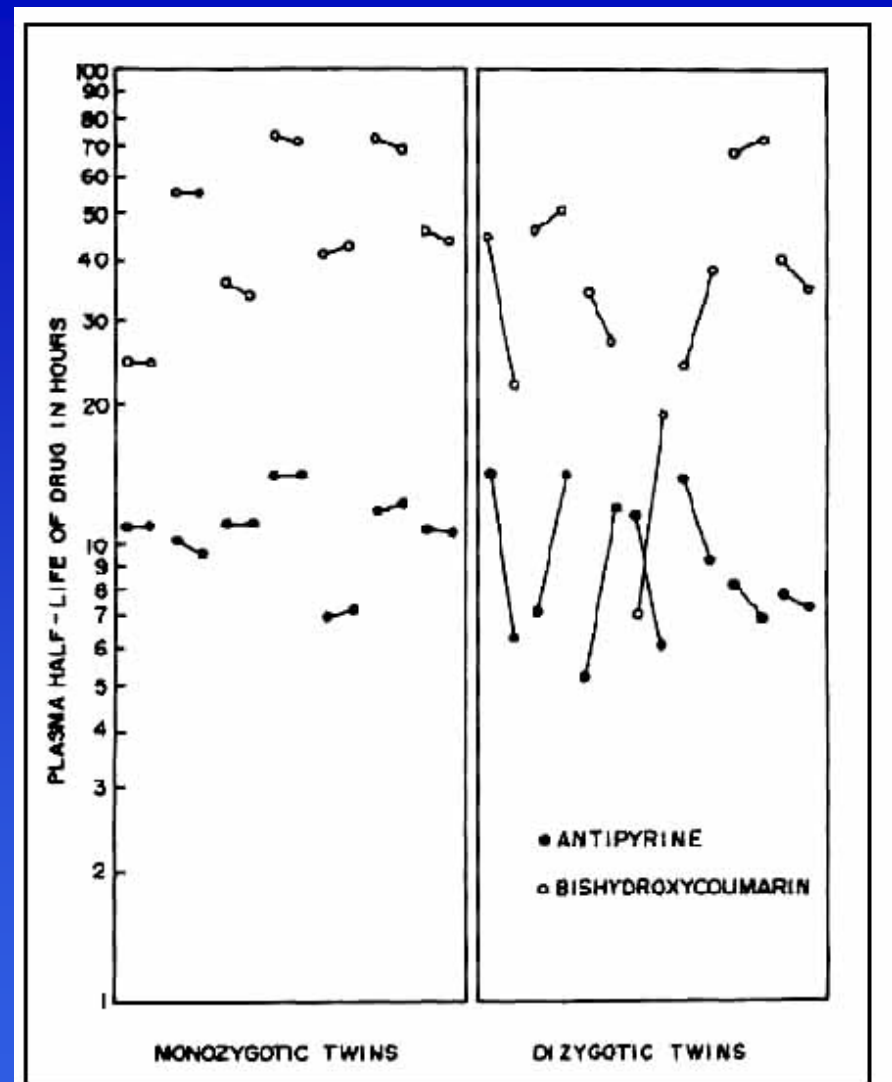


Figure 1 Plasma half-lives of bishydroxycoumarin (open circles) and antipyrine (filled circles) were measured in monozygotic and dizygotic twins after a single dose of each drug. An interval of 6 months separated administration of bishydroxycoumarin and antipyrine. A solid line joins values within each twinship.

Pharmacogenomic examples-2004

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- Thiopurine S-methyltransferase—mercaptopurine and azathioprine

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Research Sites:

Brigham and
Women's Hosp.
Children's Hosp.
Oakland
Indiana Univ.
Mayo Foundation
Stanford Univ.
UCSF X 2
Univ. of Chicago
Univ of Florida
Univ of Maryland
Univ of N Carolina
Vanderbilt Univ.
Washington Univ.

NIH Pharmacogenetics Research Network



www.nigms.nih.gov/pharmacogenetics

www.pharmgkb.org

Pharmacogenomic examples-2007

- *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*5101*-carbamazepine**
- Cytochrome P-450 (CYP) 2D6—5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives, tamoxifen*

*-FDA package insert information

*-FDA-approved device



HEALTH & DNA



Drug Reaction Testing

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TABLE OF COMMONLY USED DRUGS: ARRANGED AS P450 CYTOCHROME SUBSTRATES, INDUCERS AND INHIBITORS

Genelex currently offers DNA Prescription Drug Reaction Profiles that test 2D6, 2C9, 1A2 and 2C19 functionality. The table below lists many commonly prescribed drugs that are metabolized through these and other pathways in the Cytochrome P-450 system. This is an abridged chart and not all pathways may be listed for all medications. If your medication is not on the list, or to obtain the most thorough information on drug metabolism, enter the medication into www.genemedrx.com.

Order DNA Prescription Drug Reaction Testing

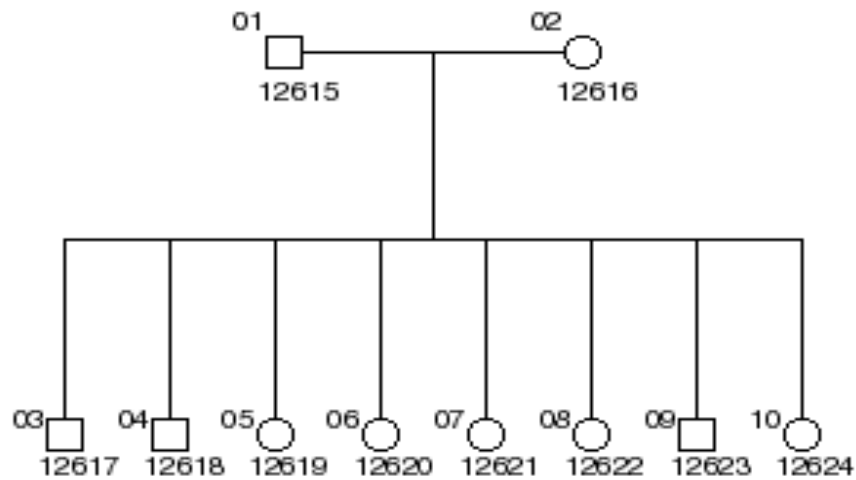
What needs to be done to determine hope vs hype?

- Find the 'right' biomarkers
 - No published GWAS
- Validate in robust datasets
- Apply them!
- Great need for 'real' translation

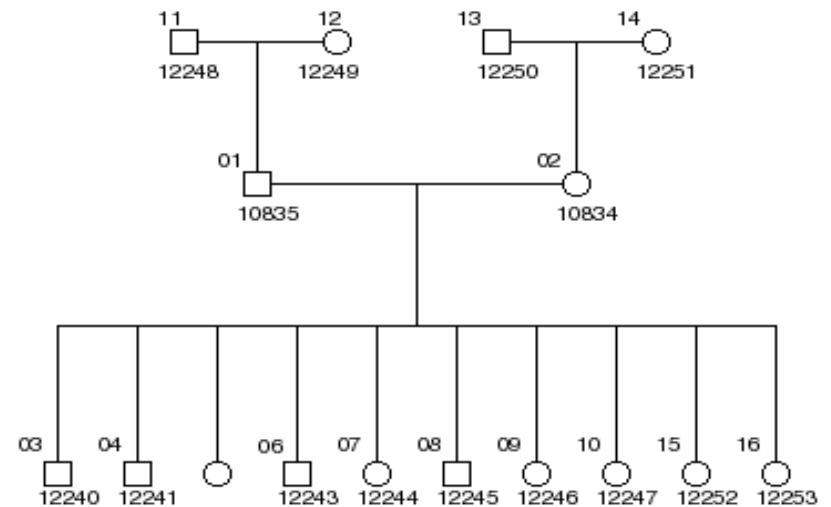
Centre d' Etude du Polymorphisme Human (CEPH) Cell lines

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

CEPH/French Pedigree 35



CEPH/Utah Pedigree 1416

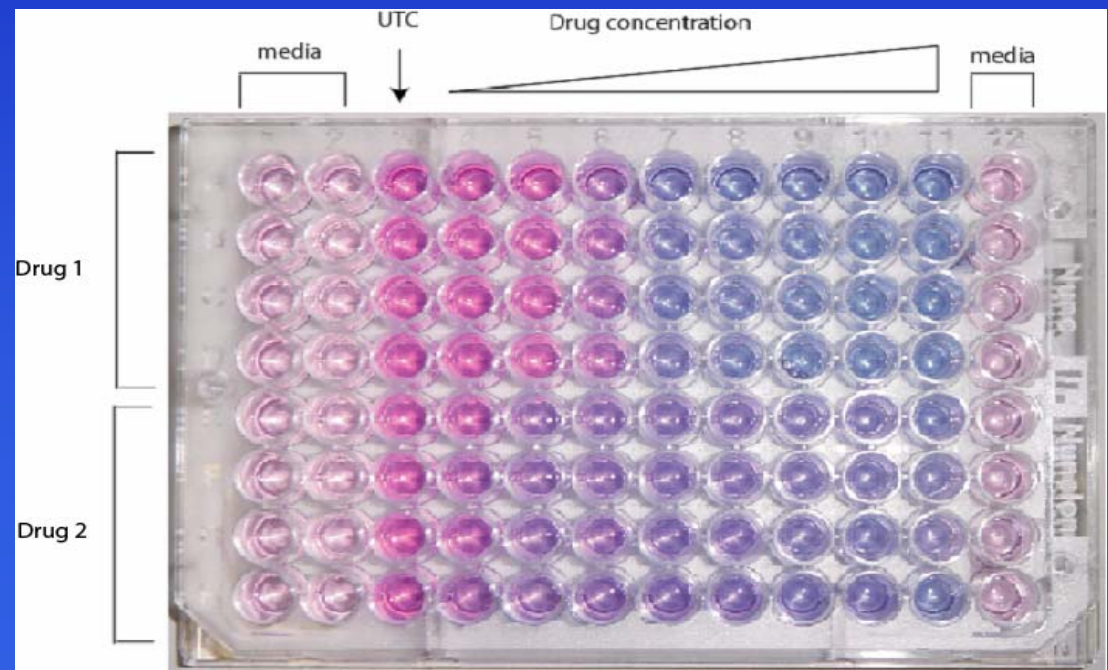


Methodology

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

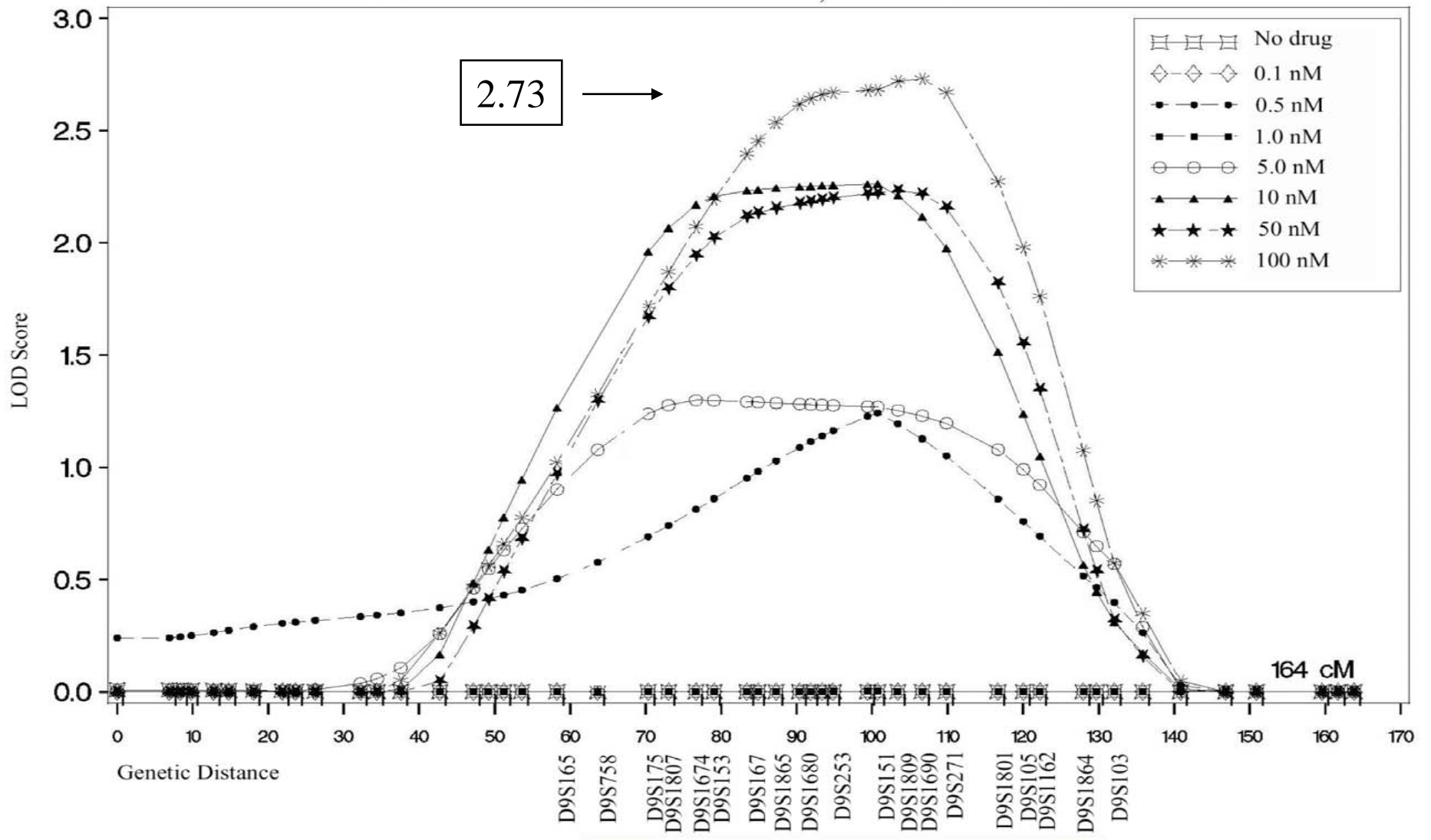
Cells incubated with increasing concentrations of drug

Alamar blue vital dye indicator added



Viability relative to untreated control calculated by spectrophotometry

Chromosome 9, docetaxel



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 - Many NIH studies have no blood sampling (unlike industry)
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U.S. Cooperative Groups

Consortia of institutions that conduct research in cancer treatment, prevention, biology and health outcomes.

<i>ACTIVE Studies</i>			
Tx Study #	N	Short Title	PET Chair/PG
10105	270	PTK787 in MDS	60404/PG/McLeod
40101	4600	CA vs Taxol in node - breast	60202/Kroetz/PG
50303	580	RCHOP vs EPOCH-R in B-cell lymphoma	60405/McLeod/PG
80101	570	Adj chemo after gastric resect	60201/McLeod/PG
80403	230	ECF-C vs IC-C vs FOLFOX-C in mets colorectal ca	60601/Innocenti/PG
80405	2200	FOLFOX/FOLFIRI + bv, + C225, or + bv/C225 for mets colon ca	60501/McLeod/PG
90401	1020	Est/doc vs Est/doc/bev for HRPC	60404/McLeod/PG
<i>Closed Studies</i>			
80203	200	Ph III CPT-11/5-FU/Leu or Ox/5-FU/Leu +/- C225 in colorectal ca	60304/McLeod/PG
80303	600	Ph III pancreatic ca	60401/Innocenti/PG

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Biomarker-driven
studies

Phase I

Phase II

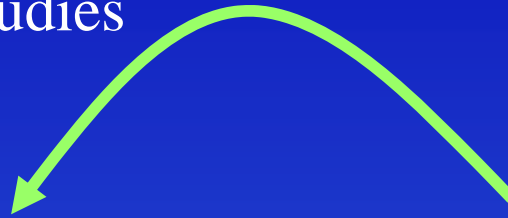
Phase III

Nothing

In vivo
Mechanism

Biomarker
assessment

Biomarker
validation



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- Apply them!
- Great need for 'real' translation
 - What is CYP2D6*4?



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