

Personalized Medicine and Pharmacogenomics: Moving from the Laboratory to Clinic

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Disclosure

I work for the US Government – so I have nothing to disclose, nor any conflicts of interest

Learning Objectives

Understand the differences between genetic polymorphisms and somatic mutations

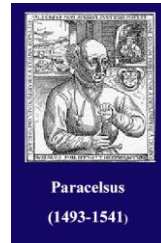
Discuss when pharmacogenetics strategies are most likely to have an impact

Review the 25 drugs that have some form of FDA recommendation or they have been incorporated into standard of clinical care utilizing personalized genotyping (pharmacogenetics)

Review the differences between candidate gene analysis and high-Throughput analysis of drug metabolism and transport genes

Understand the barriers to implementing pharmacogenetic strategies into clinical care

“All things are poison, *only the dose permits something not to be poisonous*”



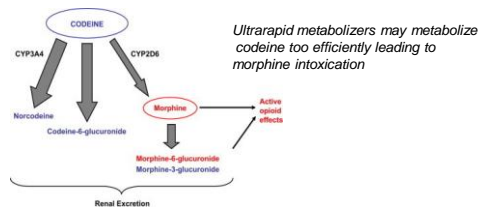
...well that and inter-individual genetic variation...

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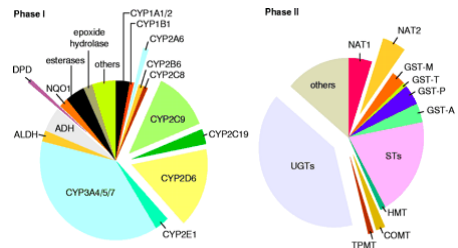
Case report: Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

Healthy 2-yo boy, underwent outpatient elective adenotonsillectomy;
 After surgery, instructions to take 10-12.5mg of codeine + 120 mg APAP q 4-6 hr prn; 2 days post surgery, child died
 Autopsy results: Codeine (0.70 mg/L) & morphine (32 ng/ml) → toxic levels
 CYP2D6 genotyping → 3 copies of CYP2D6 allele → ultrarapid-metabolizer phenotype



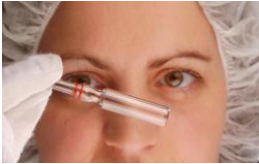
Polymorphic Drug Metabolizing Enzymes

Relative contribution of known variants



(Evans and Rolling, Science 286: 487-91, 1999)

What are the Reasons the Development of a new Drug is Halted?



Four Main Reasons the Development of a Drug is Halted

- Lack of Efficacy
- Side Effects
- Pharmacokinetics
- Pharmacogenetic Profile

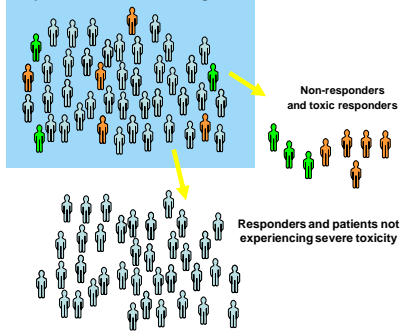
34 FDA approved Agents have been Removed from the Market since 1990

- Annual economic value at the time of removal - \$31 billion

34 FDA approved Agents have been Removed from the Market since 1990

- Annual economic value at the time of removal - \$31 billion
- Twenty of these might have been saved or not developed if we had fully understood the pharmacogenetics

All patients with same diagnosis



Pharmacogenomics and FDA

“Pharmacogenomics holds great promise to shed scientific light on the often risky and costly process of drug development, and to provide greater confidence about the risks and benefits of drugs in specific populations. Pharmacogenomics is a new field, but we intend to do all we can to use it to promote the development of medicines.”

Mark McClennan, M.D.
FDA Commissioner Nov, 2003

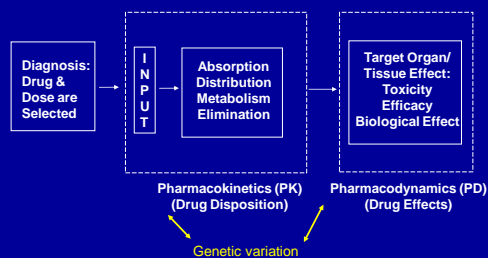
Introduction - Pharmacogenetics

- Genetic polymorphisms in proteins involved in drug metabolism or transport might be of clinical relevance
- Variation in genes encoding for drug target proteins (e.g., receptors) may result in differences in efficacy
- The most commonly observed variants are single-nucleotide polymorphisms (SNPs; i.e., a variant with a population frequency of >1%)
- SNPs are responsible for >90% of all genetic variation in the human genome
- Goal of pharmacogenetics is to aid in individualized treatment with drugs

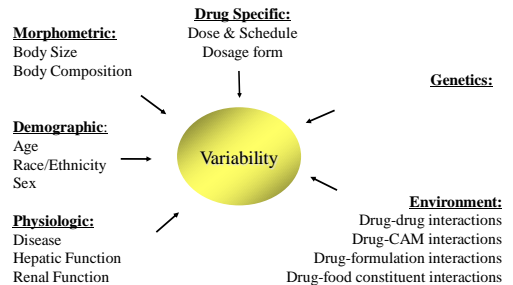
Introduction - Pharmacogenetics

Remember – this is germline DNA, not somatic mutations

Drug Exposure-Effect Relationship



Sources of Pharmacokinetic and Pharmacodynamic Variability



Pharmacogenomics and Oncology

Pharmacogenomic Strategies Most Relevant When:

- Narrow therapeutic indices
- High degree of inter-individual variability in response
- Little or no available methods to monitor safety or efficacy
- Few alternative treatment options

Flowers and Veenstra 2004

Pharmacogenomics and Oncology

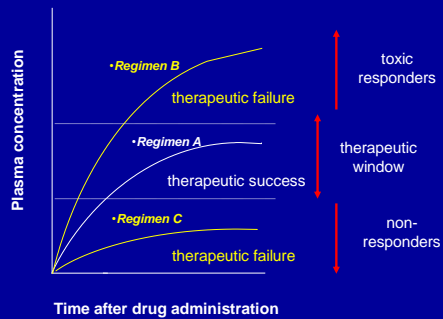
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Flowers and Veenstra 2004

Anticancer agents meet all of these criteria

Therapeutic Window



Pharmacogenetics

Implications of polymorphisms on Pharmacokinetics

- Drug Absorption
- Drug Metabolism
- Drug Elimination
- Drug Distribution
- Drug Activation

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Implications of polymorphisms on Drug Effect (Response and Toxicity)

- Receptors
- Target Proteins
- Resistant
- Toxicity

Genotyping Strategies in Medical Oncology

Example of anticancer drug metabolism by polymorphic enzymes

Drug	Pathway	Variability in CL
Amonafide	N-acetyl transferase (NAT)	>3-fold
Busulfan	Glutathione S-transferase (GST)	10-fold
Docetaxel	Cytochrome P-450 (CYP) 3A4 and 3A5	4 to 9-fold
5-Fluorouracil	Dihydropyrimidine dehydrogenase (DPD)	10-fold
Irinotecan	UDP glucuronosyltransferase (UGT)	50-fold
6-Mercaptopurine	Thiopurine methyltransferase (TPMT)	>30-fold

Evans and Relling, *Science* 286: 487-91, 1999

Genotyping Strategies in Medical Oncology

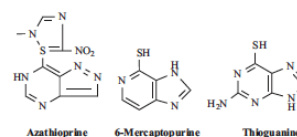
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TPMT and 6-Mercaptopurine

- 6-MP is administered to children with acute lymphoblastic leukemia (ALL), while related compounds (6-thioguanine and azathioprine) are also administered to individuals with ALL, inflammatory bowel disease, organ transplant and autoimmune disorders.
- MP drugs incorporate cytotoxic thioguanine nucleotides into DNA as their primary mechanism of action. May also inhibit *de novo* purine synthesis.



TPMT and 6-Mercaptopurine

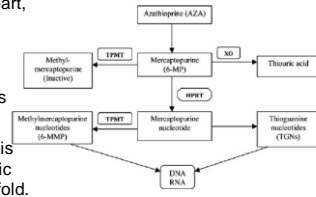
TPMT is expressed in heart, blood cells, pancreas, and intestine.

TPMT methylates mercaptopurine drugs, thus inactivating them.

Metabolism of MP drugs is decreased with polymorphic TPMT variation up to 200-fold.

Rapid metabolizers require higher dosing

Slow metabolizers are at high risk for developing fatal neutropenia and require 7-15% of the normal dose of 6-MP due to accumulation of excessive thioguanine nucleotides in hematopoietic cells. Also risk secondary malignancies (i.e. brain tumors, and AML).



TPMT and 6-Mercaptopurine



Rapid metabolizers ("wild-type" individuals) - require highest doses for efficacy (~ 80-98% of the population)



Intermediate metabolizers (carry one copy of TPMT*2A, *3A, *3C) - require ~65% of normal dose, but have highest cure rate (~ 2-20% of the population)



Slow metabolizers (carry two copies of TPMT*2A, *3A, *3C) - require 7-15% of original dose, and are at risk for secondary malignancies (~0.01 - 1% of the population)

Genetic variation in TPMT explains 95% of phenotype

Pharmacogenetics

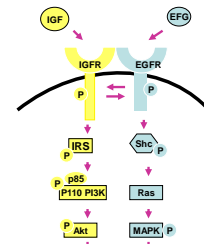
Implications of polymorphisms on Pharmacokinetics

- Drug Absorption
- Drug Metabolism
- Drug Elimination
- Drug Distribution
- Drug Activation

Implications of polymorphisms on Drug Effect

- Receptors (somatic)
- Target Proteins
- Resistant
- Toxicity

IGF and EGF Signaling Pathways



Cell proliferation
Angiogenesis
Invasion/metastasis

Response to Gefitinib (Iressa®)

- Somatic mutations identified in the tyrosine kinase domain of the EGFR gene in 8 of 9 patients with lung cancer responding to gefitinib
- No somatic mutations were identified in 7 patients not responding to gefitinib

Lynch et al. NEJM 2004; 350:2129

Tumors with a Major Clinical Response to EGFR Inhibitors

- ~ 10%–20% of tumors have a major response (dramatic shrinkage) to EGFR inhibitor
- Majority of responders have mutations in EGFR tyrosine kinase domain (exon 19 deletion, point mutation)
- Mutation led to constitutive activation of EGFR and increased sensitivity to EGFR inhibition
- Amplification of EGFR may also increase sensitivity
- Never smokers and patients of Asian origin had a high frequency of EGFR mutations

(Paez et al, Science 2003; Lynch et al, NEJM 2003; Tsao et al, NEJM 2005)

Pharmacogenetics

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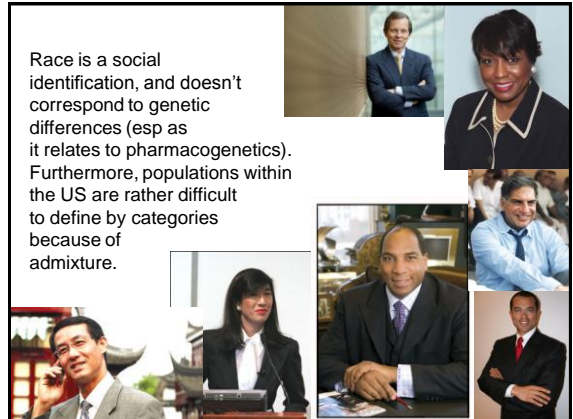
ABCG2 (BCRP, ATP-binding cassette)

- Involved in intrinsic or acquired multidrug resistance (MDR) phenotype of tumor cells
- **ABCG2** encodes a half transporter
- Located on chromosome 4q-22
- 66 kb; 16 exons; 15 introns
- 69 Known genetic polymorphisms including 65 SNPs; 13 SNPs in exons; 7 SNPs cause amino acid substitutions

ABCG2 421 C>A Genotype Frequencies

Population	WT	C/A	A/A
Caucasian	77%	22%	1%
African Am	90%	9%	1%
African	98.4%	1.5%	0.1%
Chinese	43%	45%	12%

Race is a social identification, and doesn't correspond to genetic differences (esp as it relates to pharmacogenetics). Furthermore, populations within the US are rather difficult to define by categories because of admixture.



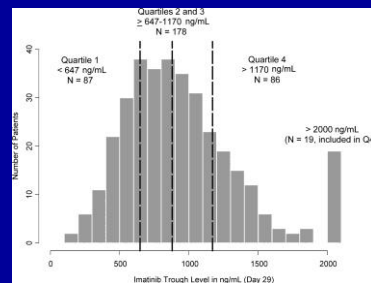
Efficacy of Imatinib in Chronic Myelogenous Leukemia (CML)

(Druker et al, NEJM 2001)

- Imatinib inhibits BCR-ABL
- Of 54 patients treated with imatinib who had failed interferon-alpha (300 mg or higher bid), 53 complete hematological responses

Imatinib $C_{ss,min}$ is highly variable in CML

351 patients receiving 400 mg daily on IRIS study



26-fold variation

RA Larson et al. Blood 2008

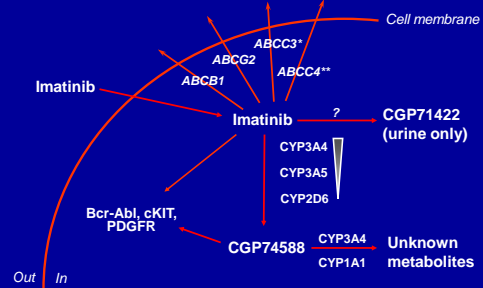
Higher Imatinib Concentrations are associated with adverse events*

Adverse Event	Q1 (N=87)	Q2 & Q3 (N=179)	Q4 (N=86)
Fluid retention	53 (2.3)	62 (3.4)	76 (3.5)
Rash	32 (3.4)	39 (2.2)	51 (1.2)
Myalgia	20 (0)	25 (2.2)	30 (1.2)
Anemia	8.0 (0)	12 (2.4)	20 (7.0)

*data are % of toxicity in the Q (% of grade 3/4 toxicity in the Q); significant association with adverse events within 3 months and 5 years (shown)

RA Larson et al. *Blood* 2008

Selection of Appropriate Genes



* Identified as one of the genes with expression features unique to imatinib relapsers in CML (Radich et al. *PNAS* 2006); ** S Hu et al. *CCR* 2008

Pharmacogenetics

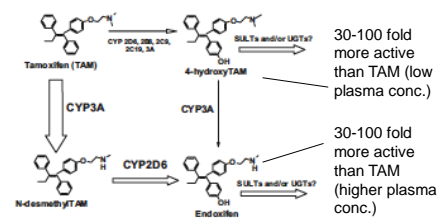
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CYP2D6 and Tamoxifen



CYP2D6 catalyzes the formation of the major active metabolite of tamoxifen - endoxifen

CYP2D6 and Tamoxifen

CYP2D6 is highly polymorphic

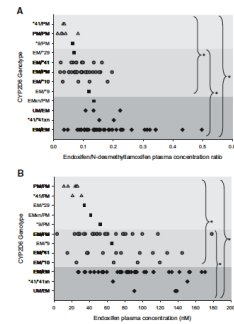
Combinations of multiple SNPs in haplotypes, and knowing the diplotype allows for more effective prediction

This table arranges the SNPs from slow metabolizers (top) to rapid metabolizers (bottom)

CYP2D6 genotype group	CYP2D6 genotype	n (%)
PMPM (4.4%)	*2/*4	74.0
	*1/*4	21.2
	*1/*2	10.6
	*1/*3	10.6
	*1/*46	10.6
IMPM (3.8%)	*2/*1	10.6
	*2/*2	10.6
	*2/*3	10.6
	*2/*4	10.6
	*2/*46	10.6
EMPM (26.6%)	*1/*1	10.6
	*1/*2	2615.8
	*1/*3	53.1
	*1/*4	31.8
	*1/*46	21.2
EMEM (17.7%)	*1/*5	10.6
	*1/*6	10.6
	*1/*7	159.5
	*1/*10	42.5
	*1/*11	31.8
EMEMx (0.6%)	*1/*12	21.2
	*1/*13	10.6
	*1/*14	10.6
	*1/*15	10.6
	*1/*16	10.6
UMPM (0.6%)	*2/*10	10.6
	*2/*11	10.6
	*2/*12	10.6
	*2/*13	10.6
	*2/*14	10.6
UMPM (0.6%)	*2/*15	10.6
	*2/*16	10.6
	*2/*17	10.6
	*2/*18	10.6
	*2/*19	10.6

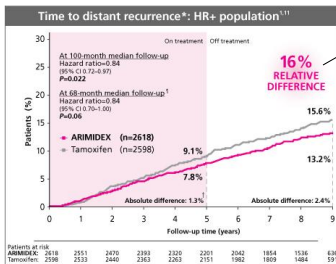
PM, CYP2D6 null allele; IM, CYP2D6 intermediate allele; EM, CYP2D6 normal allele; EMx, 2 or more CYP2D6 functional alleles; UM, 3 or more CYP2D6 functional alleles.

Genotype vs. Endoxifen Conc



* No CYP2D6 inhibitors

Tamoxifen vs. Aromatase Inhibition in Breast Cancer



Sure, but ~12% of the population doesn't make sufficient endoxifen to have efficacy (PMs), and ~40% of the tamoxifen population (EMs) may benefit MUCH more from tamoxifen than anastrozole

Strategies to Dose Warfarin based on Genotype

- From package insert:

"Identification of risk factors for bleeding and certain genetic variations in CYP2C9 and VKORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses."

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes¹

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
Wild type	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
Heterozygous	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
Variant	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

¹Ranges are derived from multiple published clinical studies. Other clinical factors (eg. age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

Abacavir: HLA-B*5701

- Antiretroviral agent
- HLA-B*5701 allele has ~100% predictive value of Abacavir hypersensitivity reaction, which can be fatal.
- Package insert recommends screening for allele.
- Status: Recommended
- Test: TBD

Allopurinol: HLA-B*5801

- Used in treatment of gout and to prevent or treat hyperuricemia from tumor-lysis syndrome.
- HLA-B*5801 a strong predictor of SJS/TEN and allopurinol hypersensitivity reaction.
- Recommended
- Test: TBD

Carbamazepine: HLA-B*1502

- Anti-convulsant
- HLA-B*1502 predicts SJS/TEN.
- FDA recommends testing in Asian populations.
- Recommended
- Test: TBD

Clopidogrel: CYP2C19

- Anti-platelet agent
- CYP2C19 poor metabolizer status predicts non-responsiveness to clopidogrel.
- Higher doses may be useful in poor metabolizers.
- Optional/Available
- Test: DMET

Fluoropyrimidines (i.e. 5-FU, Capecitabine): DPYD

- Chemotherapeutic agent
- DPD deficiency in DPYD mutant heterozygotes and homozygotes at risk of rare but potentially fatal toxicities.
- Recommended
- Test: DMET

Interferon-alpha: IL28B

- Relevant to treatment of Hepatitis C Virus genotype 1 infections.
- One variant in IL28B gene predicts sustained virological response.
- A different variant predicts treatment inefficacy.
- Optional/Available
- Test: LabCorps, others in development

Irinotecan: UGT1A1*28

- Antineoplastic agent
- UGT1A1*28 homozygotes at increased risk of severe neutropenia.
- Package insert recommends lower dose for known mutant homozygotes.
- Recommended
- Test: DMET

Isoniazid: NAT2

- Used to treat tuberculosis.
- N-Acetyltransferase 2 variants confer Acetylator status.
- Slow Acetylator status associated with a 3-fold increase in drug induced liver injury (DILI).
- Optional/Available
- Test: DMET

Isoniazid: CYP2E1

- CYP2E1 wild-type homozygotes (with higher CYP2E1 activity) may be at increased risk of liver toxicity, regardless of Acetylator status.
- Optional/Available
- Test: DMET

Phenytoin: CYP2C9

- Anticonvulsant
- CYP2C9 *2 and *3 variants affect toxicity and efficacy.
- Optional/Available
- Test: DMET and others

Phenytoin: HLA-B*1502

- HLA-B*1502 variant is associated with SJS/TEN in Asian populations.
- Package insert recommends avoiding use in HLA-B*1502 positive patients when other therapies are available.
- Recommended
- Test: TBD

Rasburicase: G6PD

- Used in the treatment of hyperuricemia in patients with tumor-lysis syndrome.
- Patients with a G6PD deficiency are at a higher risk of hemolytic anemia.
- Package insert recommends screening patients at high risk (e.g. of African or Mediterranean descent).
- Recommended
- Test: DMET

Statins: SLCO1B1

- SLCO1B1 variant confers risk of statin-induced myopathy.
- Optional/Available
- Test: DMET

HER2 Inhibitors (Trastuzumab, Lapatinib)

- Overexpression of HER2 receptor confers sensitivity to a HER2-inhibiting agent.
- Optional/Available
- Test: Molecular Pathology

BCR-ABL inhibitors (Dasatinib, Nilotinib, Imatinib)

- BCR-ABL is a fusion oncogene in hematologic malignancies.
- BCR-ABL fusion gene is required for sensitivity to a BCR-ABL inhibitor.
- Recommended
- Available in Hematology/Oncology.

Imatinib: KIT

- GIST patients with KIT mutation show sensitivity to Imatinib.
- Patients with a mutation in exon 9 of KIT may experience greater benefit with dose increase.
- Recommended
- Test: Molecular Pathology

BRAF inhibitors (i.e. Sorafenib) and EGFR inhibitors

- BRAF activating mutation predicts sensitivity to BRAF inhibitors.
- BRAF activating mutation associated with poor response to EGFR inhibitors, although a BRAF inhibitor can restore sensitivity.
- Recommended
- Test: Molecular Pathology

RET inhibitors (i.e. Vandetanib)

- RET mutation required for response to RET inhibitors.
- Recommended
- Test: to be available in Molecular Pathology

Alkylating Agents (i.e. Temozolomide, BCNU, Procarbazine): MGMT

- MGMT reverses DNA methylation. Expression may predict resistance in Glioblastoma Multiforme (GBM).
- MGMT promoter methylation (silencing) predicts response.
- Recommended
- Test: Molecular Pathology

One ultimate goal of pharmacogenetics is to provide a patient with individualized therapy ("getting the dose right")

Using candidate gene approach - It will be virtually impossible to assign a patient to an unequivocal phenotype and especially to an unequivocal genotype

Current Genotyping Platforms

Manufacturer	Product	Genes	Total SNPs
Roche	AmpliChip P450	CYP2C19 and 2D6	23
TM Bioscience	P450-2C19 P450-2C9 P450-2D6	CYP2C19	7
		CYP2C9	5
		CYP2D6	14
GE Healthcare	CodeLink P450	CYP2D6, CYP2C9, CYP2C19, CYP1A1, CYP1A2, CYP2E1, CYP3A4, CYP3A5, and CYP1B1	110
Juniab	DrugMEt	CYP2D6, CYP2C9, CYP2C19, CYP3A5, CYP2B6, NAT2, TPMT, and MDR1	27
Affymetrix/ParAllele	DMET	168	1248

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Roche	AmpliChip P450	CYP2C19 and 2D6	23
TM Bioscience	P450-2C19 P450-2C9 P450-2D6	CYP2C19	7
		CYP2C9	5
		CYP2D6	14
GE Healthcare	CodeLink P450	CYP2D6, CYP2C9, CYP2C19, CYP1A1, CYP1A2, CYP2E1, CYP3A4, CYP3A5, and CYP1B1	110
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Affymetrix/ParAllele	DMET	168	1248

DMET Genotyping Platform

1936 variants (actual causative variants) in 235 PK/PD genes.
 Useful for haplotype determination.
 Captures the vast majority of SNPs involved in PK/PD.

Phase I Enzymes		Phase II Enzymes		Transporters		Other			
CYP1A1	CYP2E2	ADMTA	UGT1	MAOB	ABCB1	SLC15A2	SLC7A5	ABP1	NR3C1
CYP1A2	CYP4F3	ADH1B	DPYD	NAT1	ABCB4	SLC16A1	SLC7A7	AHR	ORM1
CYP1B1	CYP4F8	ADH1C	FMO3	NAT2	ABCB7	SLC19A1	SLC7A8	AKAP9	ORM2
CYP2A6	CYP4F11	ADH4	FMO2	NNMT	ABCB11	SLC22A1	SLCO1A2	ALB	PNMT
CYP2A7	CYP4F12	ADH6	FMO3	NDI1	ABCC1	SLC22A11	SLCO1B1	AOX1	POH1
CYP2A13	CYP4Z1	ADH6	FMO4	TPMT	ABCC2	SLC22A12	SLCO1B3	ARN1	PON2
CYP2B6	CYP7A1	ADH7	FMO5	UGT1A1	ABCC3	SLC22A14	SLCO2B1	ARSA	PON3
CYP2B7	CYP9B1	ALDH1A1	FMO6	UGT1A3	ABCC4	SLC22A2	SLCO3A1	CBR11	POK
CYP2B7P1	CYP9B1	ALDH2	GSTA1	UGT1A4	ABCC5	SLC22A3	SLCO4A1	CBR3	PPARD
CYP2C8	CYP11A1	ALDH3A1	GSTA2	UGT1A6	ABCC6	SLC22A4	SLCO5A1	CCA	PPARG
CYP2C9	CYP11B1	ALDH3A2	GSTA3	UGT1A6	ABCC8	SLC22A5	SULT1A1	CES2	PTGIS
CYP2C18	CYP11B2	CHST1	GSTA4	UGT1A7	ABCC9	SLC22A6	SULT1A2	CROT	RALBP1
CYP2C19	CYP17A1	CHST2	GSTA5	UGT1A8	ABCG1	SLC22A7	SULT1A3	DOX	RPL13
CYP2D6	CYP19A1	CHST3	GSTM1	UGT1A8	ABCG2	SLC22A8	SULT1B1	EPHX1	RARA
CYP2E1	CYP20A1	CHST4	GSTM2	UGT1A9	AT1FA	SLC28A1	SULT1C1	EPHX2	SEC16L1
CYP2F1	CYP21A2	CHST5	GSTM3	UGT2A1	AT1FB	SLC28A2	SULT1C2	FAAH	SERPINA7
CYP2G2	CYP2A41	CHST6	GSTM4	UGT2B4	SCLA13	SLC28A3	SULT1E1	GFPD	SETD4
CYP2S1	CYP26A1	CHST7	GSTM5	UGT2B7	SLC10A1	SLC29A1	SULT2A1	HMGCR	SPG7
CYP3A4	CYP27A1	CHST8	GSTO1	UGT2B11	SLC10A2	SLC29A2	SULT2B1	HMAT	TBAI1
CYP3A5	CYP27B1	CHST9	GSTP1	UGT2B15	SLC13A1	SLC5A6	SULT4A1	MAT1A	TPSG1
CYP3A7	CYP28A1	CHT1B	GSTT1	UGT2B17	SLC15A1	SLC6A6		METTL1	TTMS
CYP3A43	CYP46A1	CHT11	GSTT2	UGT2B28				NR12	VKORC1
CYP4A11	CYP51A1	CHT13	GSTZ1	UGT8				NR13	XDH
CYP4B1			HMOR						

Deeken (Figg) et al. (2009) Pharmacogenomics 1; [epub ahead of print]

Where is Pharmacogenetics Going?



Where is Pharmacogenetics Going?



I can envision a day in which an infant is genotyped with a PG chip, from that day forward that information can aid in all prescriptions that individual receives



How much would you pay to know this information for your child or grandchild?



Barriers to Pharmacogenomics Progress

- Complexity of finding gene variation that affect drug outcome
- Limited drug alternatives for patients with gene variations that prevent them from using certain drugs
- Disincentives for pharmaceutical companies
- Educating healthcare providers
- Concerns about how personal genetic information would be stored and who would have access to this information

Difficulty Moving from Research to Routine Clinical Practice

Prospective validated data showing a clinical benefit for using PG data in patient care is needed

A cost savings data is needed – decrease hospitalization due to side effects or data showing prolong survival associated with PG testing

Difficulty Moving from Research to Routine Clinical Practice

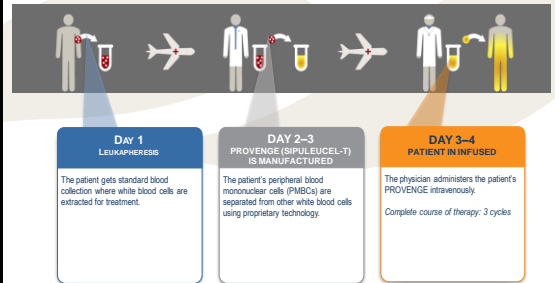
The largest expense won't be the genotyping, but the bioinformatics to handle the data...
Where will the data be housed? Who has access?

The data needs to be accessible for all future physicians who are prescribing a drug to an individual patient that has been genotyped

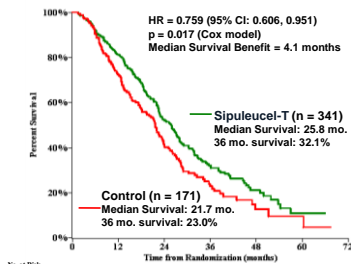
The system needs to quickly determine if a drug is a problem for an individual patient

What about Truly Personalized Medicine?

PROVENGE (sipuleucel-T) Production and Delivery



Study D9902B: Overall Survival Additional Analysis (349 events)



Kantoff, ASCO-GU March 2010

Conclusion

- The era of personalized medicine has arrived – but one needs to understand the difference in target specific therapy, PG driven therapy and individualized therapy
- Pharmacogenetics hold tremendous promising in guiding clinical care, as well as drug development
- Difficult to predict pharmacogenetics based on simply on race
- The PG chip appears to provide important data in the understanding of pharmacogenetics
- The potential for the PG chip goes beyond drug development, to altering the patient care paradigm



Azathioprine, 6MP, 6TG: TPMT

- Purine analog
- Low levels of TPMT enzyme, or homozygous mutant genotype, predict severe myelosuppression.
- Package insert suggests TPMT genotyping or phenotyping of enzyme activity.
- Recommended
- Test: DMET platform

Codeine: CYP2D6

- Opioid
- CYP2D6 genotype determines poor, intermediate, or ultra metabolizer status.
- Poor metabolizers may experience reduced pain relief.
- Ultra metabolizers are at risk of CNS depression and death due to extensive conversion to morphine.
- Optional/Available
- Test: DMET, others

Tamoxifen: CYP2D6

- Used to treat breast cancer.
- CYP2D6 poor metabolizers may experience reduced efficacy and increased rates of recurrence.
- Recommended
- Test: DMET and others

Warfarin: VKORC1, CYP2C9

- Variants of both alleles increases sensitivity to warfarin and can cause over-anticoagulation and bleeding.
- Optional/Available (both)
- Test: DMET and others

EGFR inhibitors (Gefitinib, Erlotinib, Cetuximab, Panitumumab)

- EGFR mutation and copy number are predictors of response to these agents.
 - Recommended; available in Mol. Path.
- Activating KRAS mutations are associated with resistance to these agents.
 - Recommended; available in Mol. Path.
- PIK3CA and PTEN activating mutations may be related to Cetuximab and Panitumumab resistance.
 - Recommended; to be available in Mol. Path.