PHARMACOGENOMICS: 2014

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TOTAL CANCER CARE™

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MEDICINE
CONTINUING MEDICAL EDUCATION

Current Topics in Genome Analysis 2014

Howard McLeod

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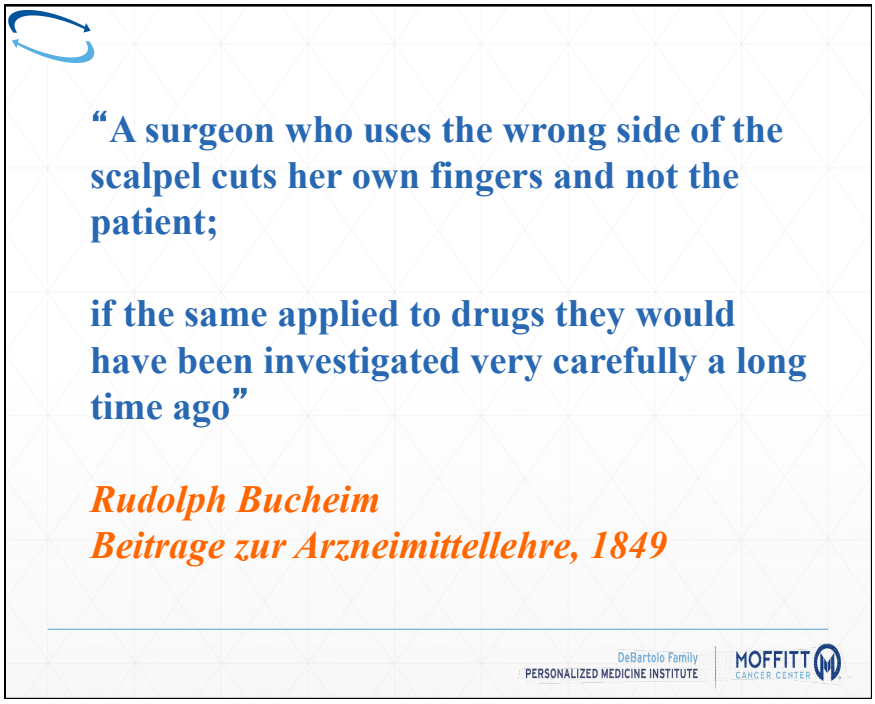
NATIONAL HUMAN GENOME RESEARCH INSTITUTE
Division of Intramural Research


"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
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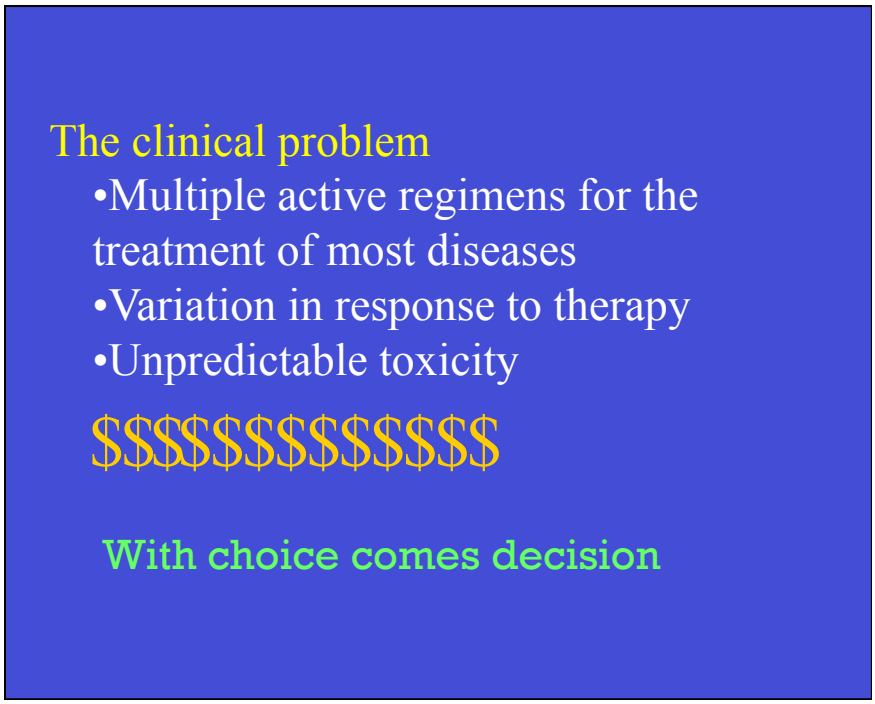
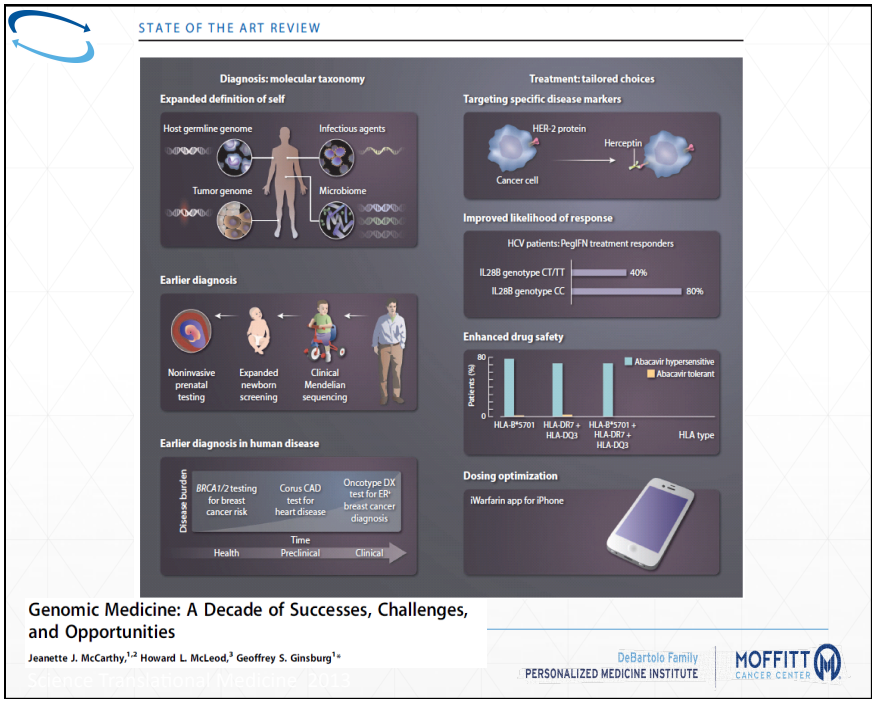

The clinical problem
•Multiple active regimens for the treatment of most diseases
•Variation in response to therapy
•Unpredictable toxicity
$$$$$$$$$$$$
With choice comes decision


STATE OF THE ART REVIEW
Diagnosis: molecular taxonomy
Expanded definition of self
Host germline genome
Infectious agents
Tumor genome
Microbiome
Earlier diagnosis
Noninvasive prenatal testing
Expanded newborn screening
Clinical Mendelian sequencing
Earlier diagnosis in human disease
Disease burden
BRCA1/2 testing for breast cancer risk
Corus CAD test for heart disease
Oncotype DX test for ER+ breast cancer diagnosis
Time
Health
Preclinical
Clinical
Treatment: tailored choices
Targeting specific disease markers
HER-2 protein
Herceptin
Cancer cell
Improved likelihood of response
HCV patients: PegIFN treatment responders
IL28B genotype CT/TT
40%
IL28B genotype CC
80%
Enhanced drug safety
Patients (%)
Abacavir hypersensitive
Abacavir tolerant
HLA-B*5701
HLA-DR7 + HLA-DQ3
HLA-B*5701 + HLA-DR7 + HLA-DQ3
HLA type
Dosing optimization
iWarfarin app for iPhone
Genomic Medicine: A Decade of Successes, Challenges, and Opportunities
Jeanette J. McCarthy,[1,2] Howard L. McLeod,[3] Geoffrey S. Ginsburg[1]*
Science Translational Medicine 2013
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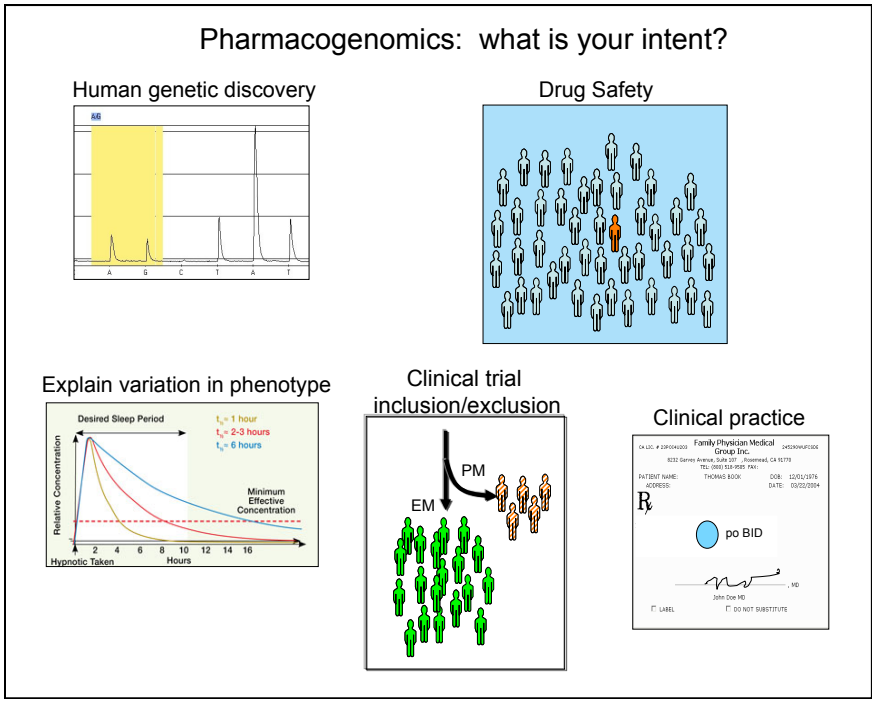
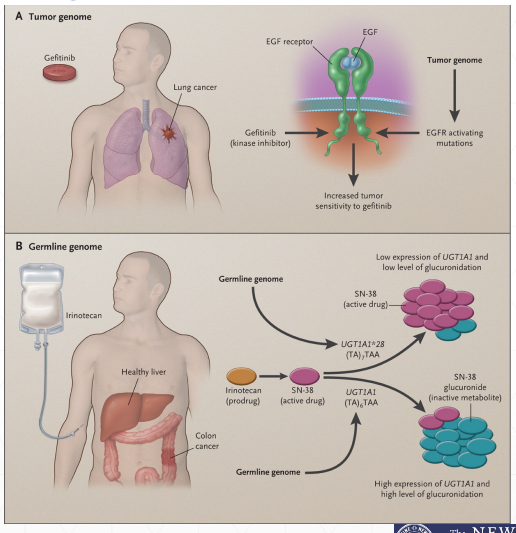

Pharmacogenomics: what is your intent?
Human genetic discovery
Drug Safety
Explain variation in phenotype
Desired Sleep Period
Relative Concentration
Minimum Effective Concentration
Hypnotic Taken
Hours
Clinical trial inclusion/exclusion
PM
EM
Clinical practice
Family Physician Medical Group Inc.
po BID

Cancer Pharmacogenomics and Tumor and Germline Genomes.



Wang L et al. N Engl J Med 2011;364:1144-1153.

The NEW ENGLAND JOURNAL of MEDICINE

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Applications of pharmacogenetics

- Explanation for untoward event (DPYD, CYP2D6)
- Required for insurance coverage (KRAS, EGFR, ABL)
- Identify low utility (KRAS)
- Dose selection (CYP2C9, CYP2C19)
- Therapy selection (CYP2C19)
- Preemptive prediction (HLA-B*5701)

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Pharmacogenomic examples-2014

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib
- BRAF-vemurafenib
- ALK-Crizotinib
- TPMT-mercaptopurine and azathioprine*
- UGT1A1-irinotecan**
- CYP2C9/VKORC1-warfarin*
- HLA-B*5701-abacavir *
- HLA-B*1502-carbamazepine *
- IL28B-interferon
- CFTR-ivacaftor
- CYP2C19-clopidogrel, voriconazole
- CYP2D6-5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives*

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What needs to be done to determine hope vs hype?

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

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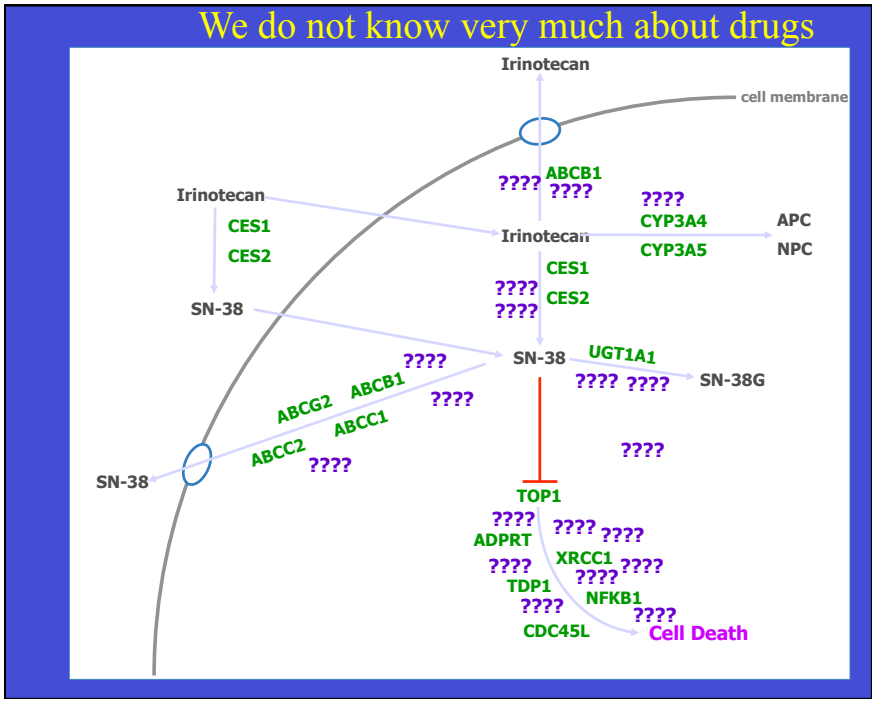
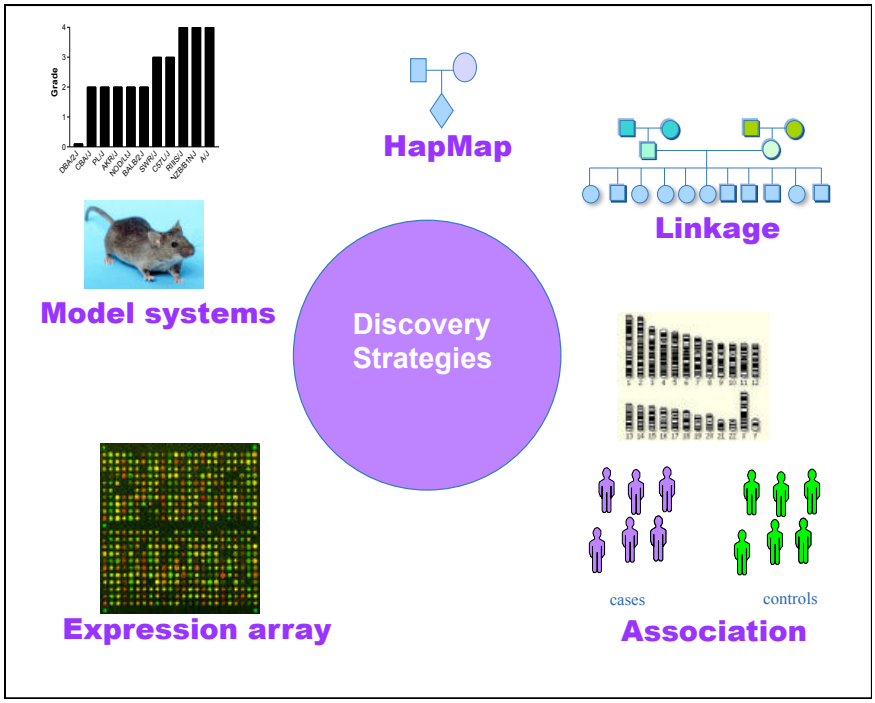

We do not know very much about drugs
Irinotecan
cell membrane
Irinotecan
CES1
CES2
SN-38
????
ABCB1
????
????
CYP3A4
CYP3A5
APC
NPC
Irinotecan
CES1
????
CES2
????
SN-38
UGT1A1
????
????
SN-38G
????
ABCG2
ABCB1
????
ABCC1
ABCC2
????
SN-38
????
TOP1
????
????
????
ADPRT
XRCC1
????
????
????
TDP1
NFKB1
????
????
CDC45L
Cell Death


Grade
HapMap
Linkage
Model systems
Discovery Strategies
Expression array
cases
controls
Association

We are only beginning to try!

As of 5/6/14

Drug-related phenotypes represented

73/2228 GWA studies (3.3%)

18/73 had ≥ 500 'cases'

22/73 (30%) found no significant 'hits'

37/73 PGx studies had a replication cohort

11 contributed to changes in FDA 'package insert'

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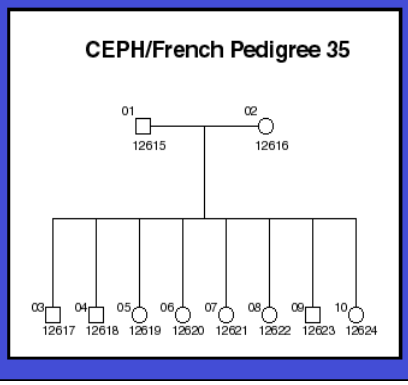
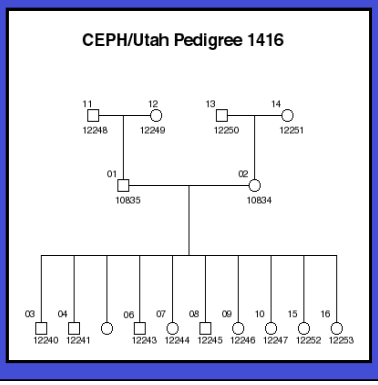
Centre d'Etude du Polymorphisme Human (CEPH) Cell lines

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



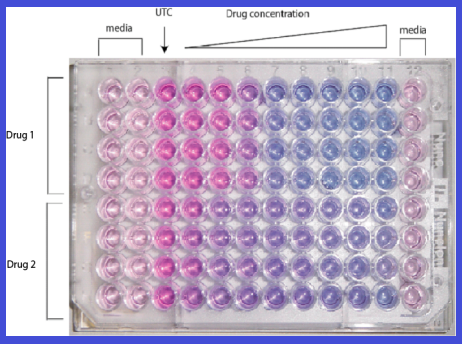


Methodology

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

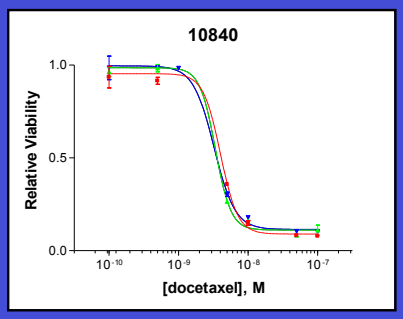
Cells incubated with increasing concentrations of drug

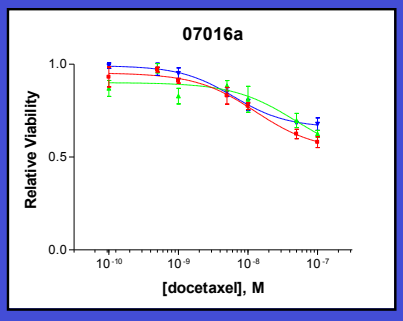
Alamar blue vital dye indicator added



Viability relative to untreated control calculated by spectrophotometry

Significant Variation in Cellular Sensitivity to Docetaxel



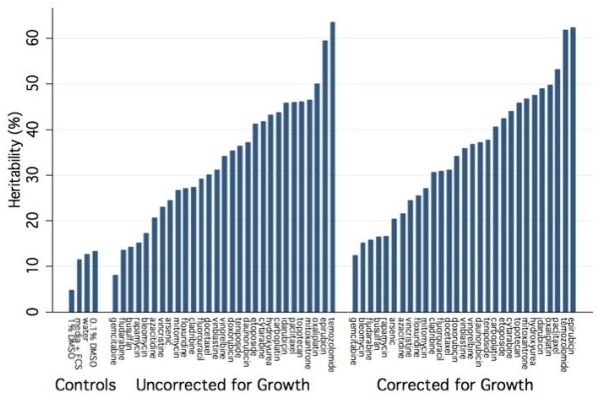


'CE-PH/F-DA' project

- 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.

Maximum heritability over all doses

Drug	Dose	h^2
Temo	4	63.51
Epi	1	59.48
Oxal	1	50.03
Mitox	1	46.46
Topo	1	46.12
Pac	1	45.91
Ida	1	45.83
Carbo	2	43.8
Hydrox	2	43.22
Cytar	1	41.74
Etop	1	41.26
Daun	1	37.14
Ace	1	36.98
Teni	3	36.37
Dox	1	35.3
Vino	1	34.13
Vinb	4	31.17
Doc	3	30.11



Peters et al 2011

Tammy Havener, Alison Motsinger-Reif, Eric Peters, Chad Brown

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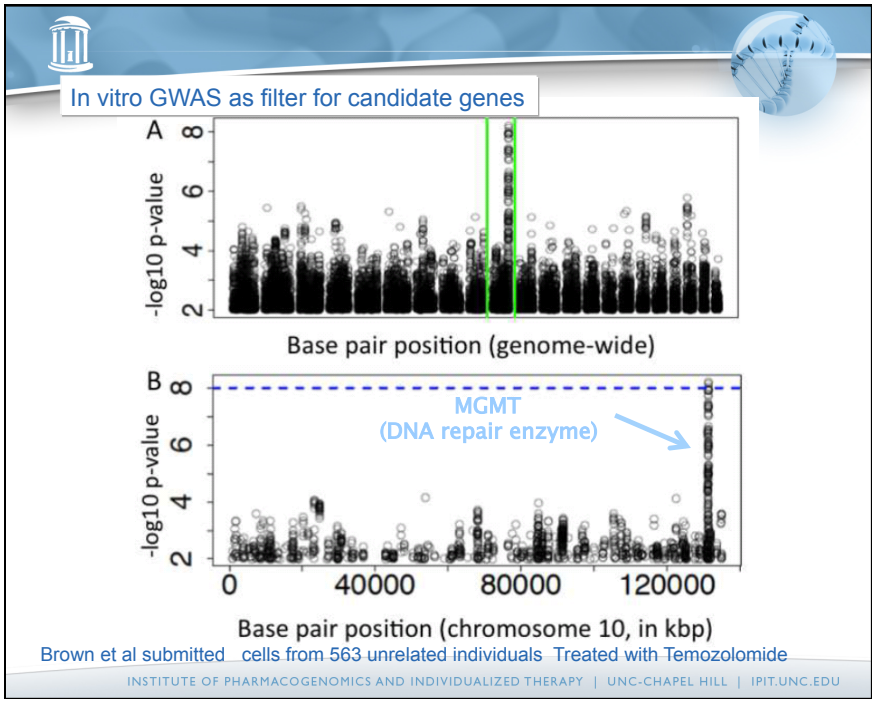
In vitro GWAS as filter for candidate genes
A
-log10 p-value
Base pair position (genome-wide)
B
MGMT
(DNA repair enzyme)
-log10 p-value
0
40000
80000
120000
Base pair position (chromosome 10, in kbp)
Brown et al submitted cells from 563 unrelated individuals Treated with Temozolomide
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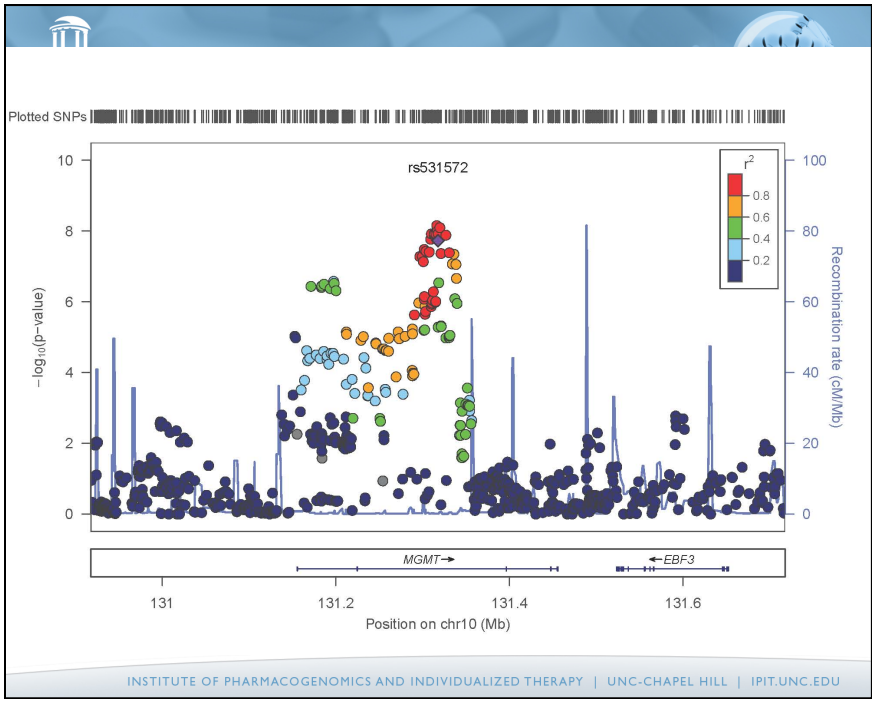
Plotted SNPs
rs531572
r2
0.8
0.6
0.4
0.2
Recombination rate (cM/Mb)
MGMT
EBF3
131
131.2
131.4
131.6
Position on chr10 (Mb)
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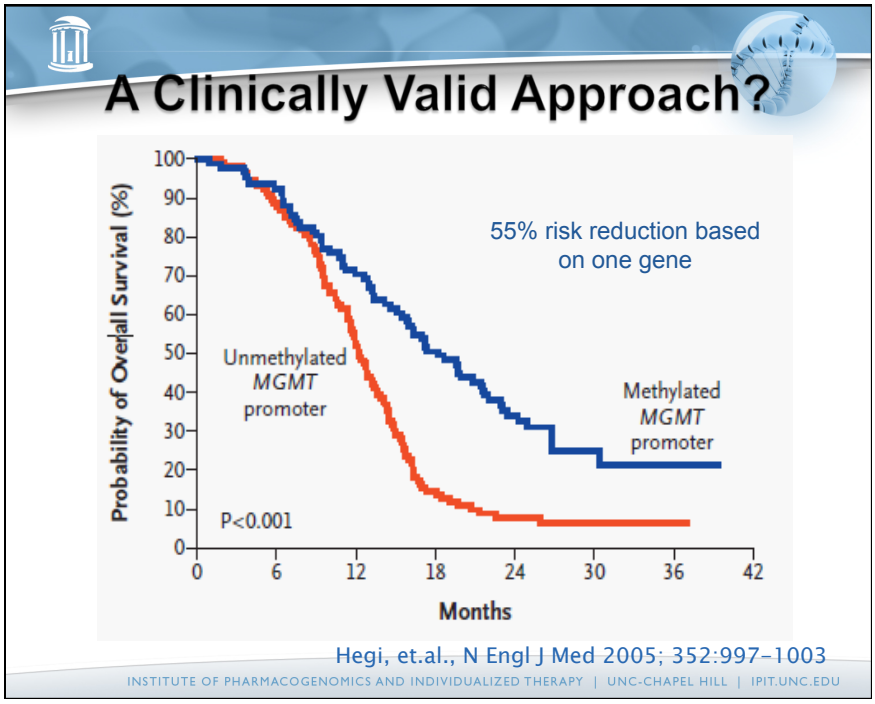
A Clinically Valid Approach?
Probability of Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
Months
55% risk reduction based on one gene
Unmethylated MGMT promoter
Methylated MGMT promoter
P<0.001
Hegi, et.al., N Engl J Med 2005; 352:997-1003
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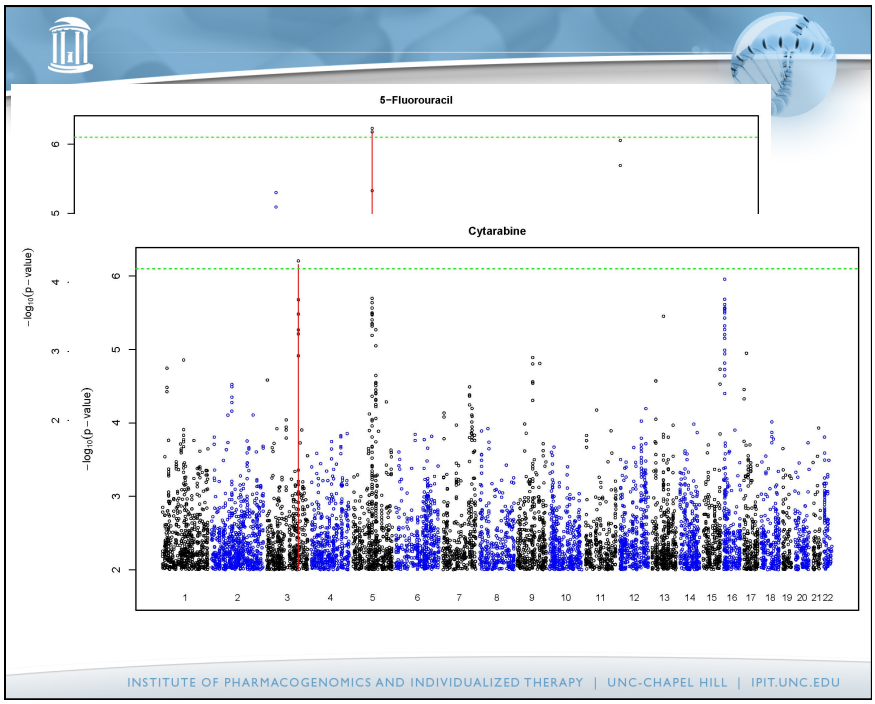
5-Fluorouracil
Cytarabine
−log10(p-value)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
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What needs to be done to determine hope vs hype?

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

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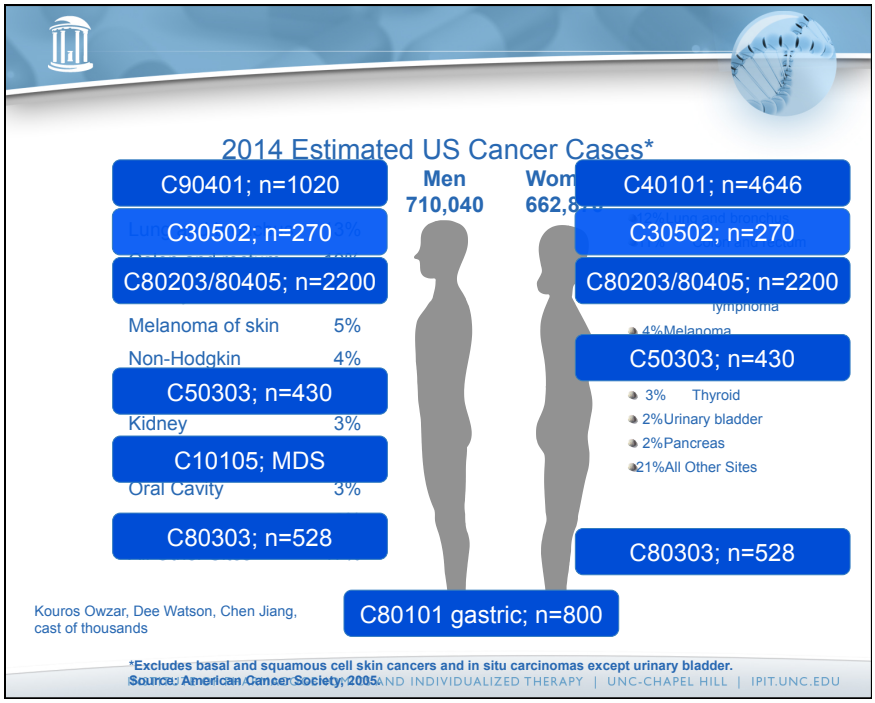
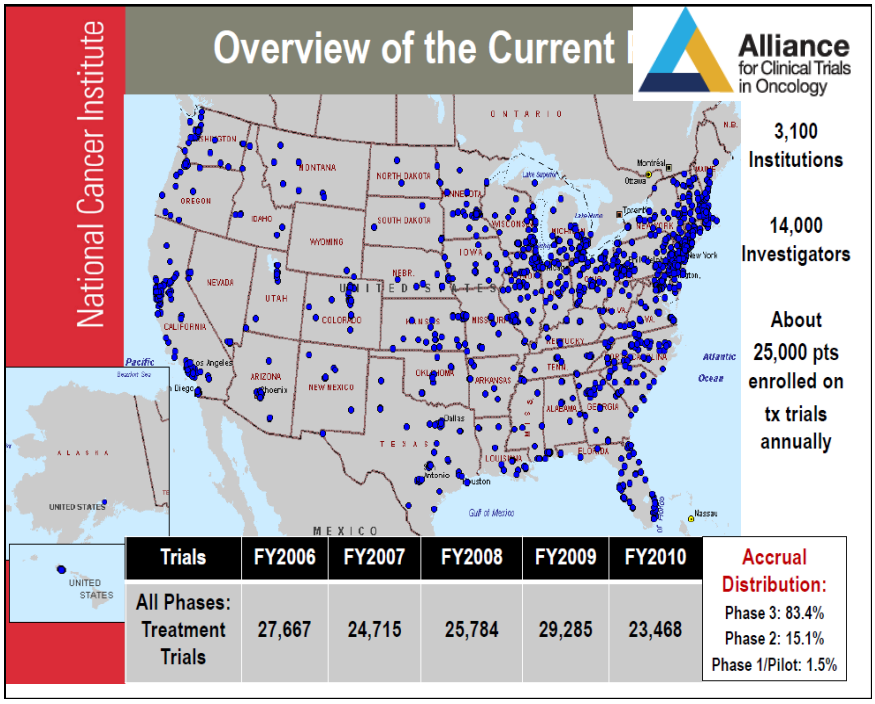




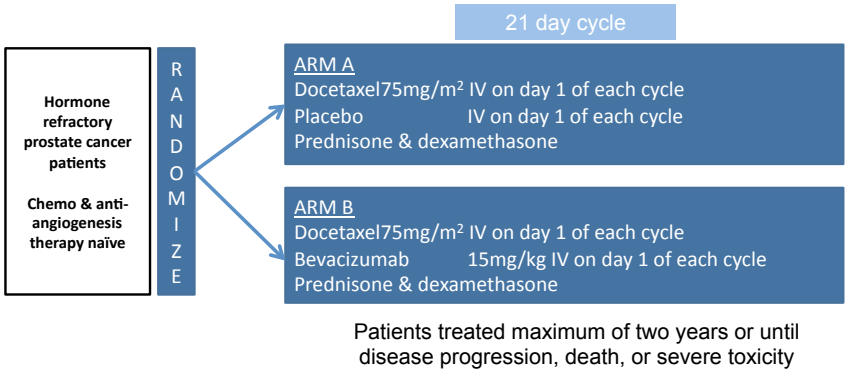
CTC AE V3.0 Toxicity Grading

	Grade 2	Grade 3	Grade 4
Neutropenia	<1500-1000/mm^3	1000-500/mm^3	<500/mm^3
Neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Interfering with function but no activities of daily living	Interfering with activities of daily living
Hypertension	Asymptomatic, transient increase by >20 mmHg (diastolic) or to >150/100 if previously WNL	Symptomatic or persistent increase by >20 mmHg (diastolic) or to >150/100 if previously WNL	Requiring more than one drug or more intensive therapy than previously
Proteinuria	2+ to 3+ or >1.0-3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nephrotic syndrome
Thrombosis	intervention not indicated	Intervention indicated	Embolic event or life-threatening thrombus
Hemorrhage	Gross bleeding or medical intervention necessary	Transfusion or operative intervention indicated	Life-threatening consequences; major urgent intervention

CALGB 90401

Randomized Double-Blinded Placebo-Controlled Phase III Trial Comparing Docetaxel and Prednisone with and without Bevacizumab in Men with Hormone Refractory Prostate Cancer

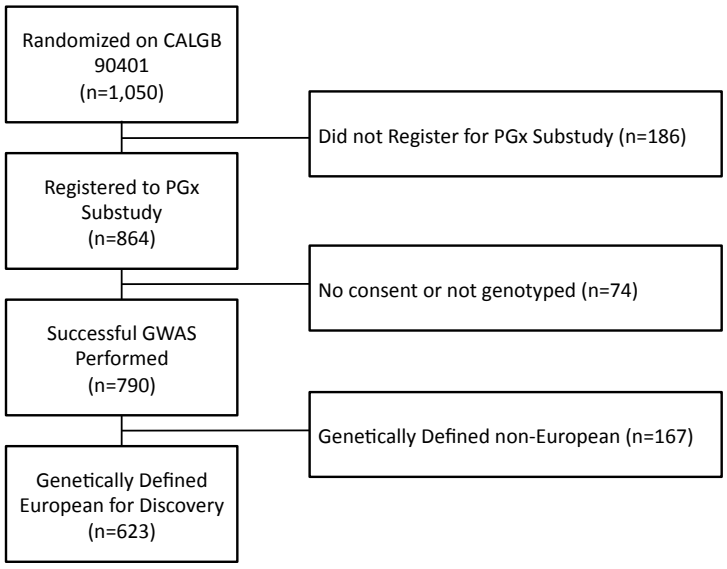
Dan Hertz, Jai Patel, Kouros Owzar, Michael Morris, Kevin Kelly, Susan Halabi, Mark Ratain, Howard McLeod



Patients treated maximum of two years or until disease progression, death, or severe toxicity

Kelly et al. J Clin Oncol 2012

90401 Consort



Toxicity Endpoints and Competing Risks in 90401 cohort (n=810)

	Docetaxel Toxicities				Bevacizumab Toxicities									
	Neutropenia				Neuro-pathy	Hypertension		Proteinuria		Thrombosis		Hemorr-hage		
	3+		4+		3+	2+	3+	2+	3+	2+	3+	2+		
Toxicity Endpoint	285	36%	161	20%	57 7%	86 11%	34 4%	44 6%	10 1%	53 7%	49 6%	79 10%		
Completed tx w/o toxicity	2%		3%		4%	3%	3%	3%	4%	3%	3%	3%		
Death/ Progres.	31%		37%		40%	36%	38%	38%	39%	38%	39%	39%		
Tx Terminating Adverse Event	19%		26%		32%	34%	37%	36%	38%	34%	35%	31%		
Withdrew/ other	12%		14%		17%	16%	18%	17%	18%	18%	18%	18%		

- Prioritize GWAS by:
  - Clinical relevance of toxicity
  - Toxicity event rate
    - Note: half of patients received bevacizumab
  - Likelihood of genetic causal factor
  - Absence of strong confounding

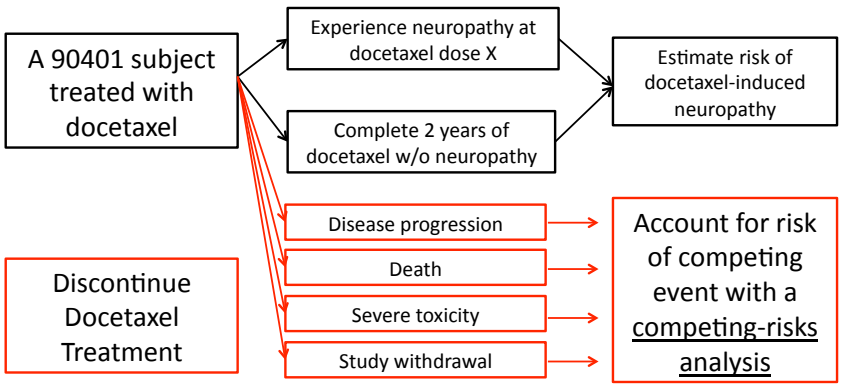
Phenotype Cleaning for Competing Risks Analysis

- Distinct dataset for each toxicity endpoint GWAS
  - Categorize patients for toxicity of interest or treatment completion
  - Patients who discontinued treatment without experiencing toxicity endpoint categorized by reason for discontinuation (competing risk)
    - Death or progression
    - Treatment terminating adverse event (TTAE)
    - Withdrawal/other
- Each toxicity or competing risk assigned dose-at-event

CALGB 90401 Pharmacogenomic Substudy

- Aim
  - Discover loci that modulate toxicity risk in prostate cancer patients treated with docetaxel ± bevacizumab
- Separate GWAS for each toxicity of interest
  - Docetaxel: neuropathy, neutropenia
  - Bevacizumab: hypertension, proteinuria, hemorrhage, thrombosis
- Use dose-to-event Cox proportional hazards model for subdistributions
  - Cumulative docetaxel dose (mg/m^2) at grade 3+ sensory neuropathy occurrence
  - Adjust for relevant clinical covariates
    - Age (continuous)
    - Diabetes (yes vs. no)
    - BMI (>30 kg/m^2 vs. other)
    - Treatment arm (bevacizumab vs. placebo)

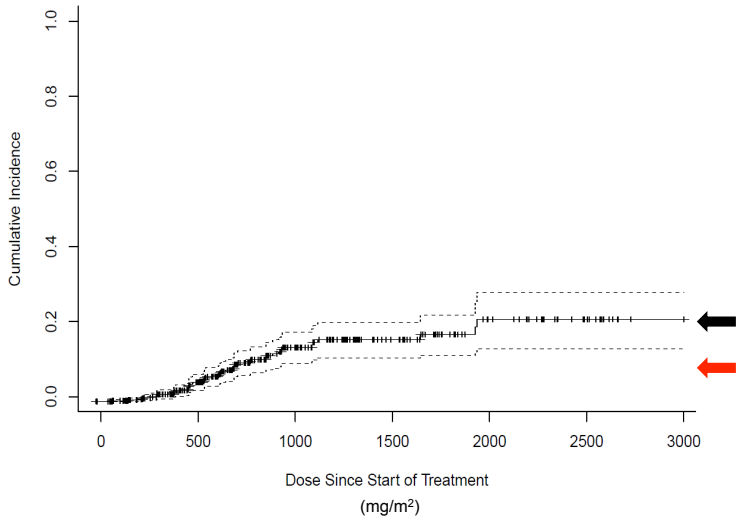
Competing Risks Analysis



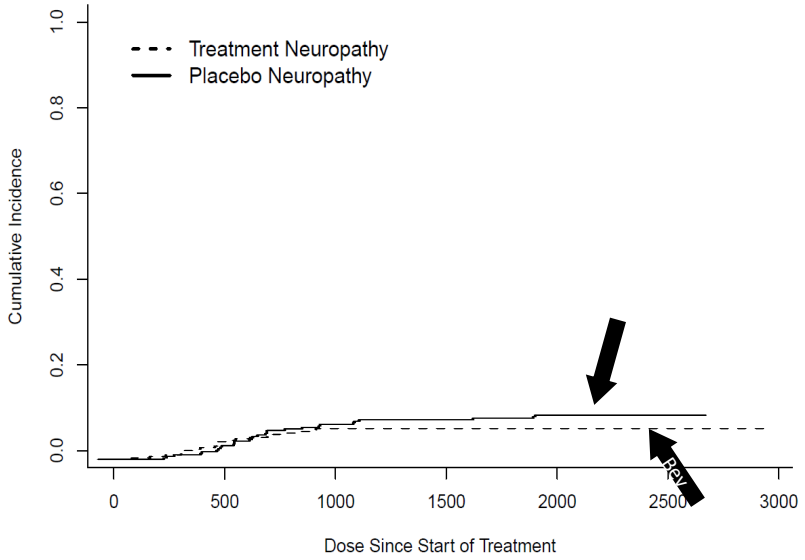
Phenotype Cleaning for Competing Risks Analysis

- Distinct dataset for each toxicity GWAS
  - Categorize every patient by toxicity of interest or competing risk
- Neuropathy GWAS
  - Any patient who experienced neuropathy assigned a 1
  - Any patient who finished treatment w/o neuropathy assigned a 0
- Categorize remaining patients by reason for treatment discontinuation (discontinued treatment before 2 years without neuropathy)
  - Death or progression: 2
  - Treatment terminating adverse event (TTAE): 3
  - Withdrawal/other: 4
  - 2-4 are 'competing risks'
- Each toxicity or competing risk is assigned a dose (or time) at event

Cumulative Incidence of Neuropathy

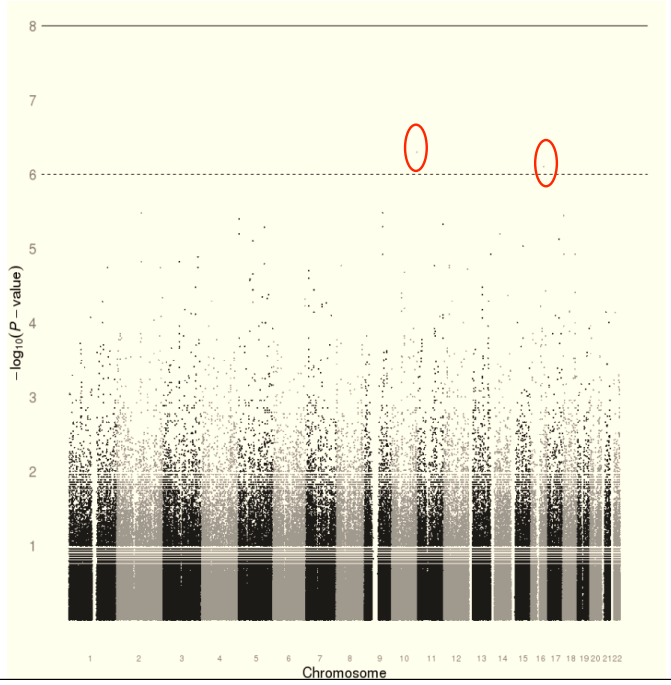


Cumulative Incidence Stratified by Arm



Neuropathy GWAS

- 810 Subjects consented and genotyped on Illumina 610 quad
  - Discovery in 623 genetically defined European patients
  - 187 patient replication cohort (genetically defined non-European)
- No SNP reached genome-wide significance before adjustment
- Created priority SNP list based on:
  - P-value/rank
  - Biological plausibility
    - Previously reported associations
    - Gene function
    - LD with functional variant
    - Regulation of gene expression
    - Encode data



Neuropathy GWAS Priority SNPs

Rank	rsID	Gene	MAF	P-value	Adj p-val	HR	Plausible Biological Mechanism
1	rs11017056	-	0.22	4.7E-7	7.2E-8	2.83	-
2	rs875858	*VAC14*	0.06	7.7E-7	1.6E-6	3.43	Stabilizes FIG4 → causes CMT
3	rs10761189	*FGD3*	0.40	3.1E-6	5.3E-6	2.32	Functionally related to FGD4 (40101)
7	rs1027796	*OPCML*	0.30	4.8E-6	8.3E-6	2.29	Neuronal outgrowth & connectivity (CNS)
15	rs17185211	*DOK 6*	0.23	1.1E-5	3.4E-5	2.30	Highly expressed in the developing CNS
26	rs478472	*NAV1*	0.08	1.7E-5	2.2E-5	3.25	Relevant to neuronal development
72	rs12805206	*OPCML*	0.22	7.6E-5	1.3E-4	2.33	Neuronal outgrowth & connectivity (CNS)

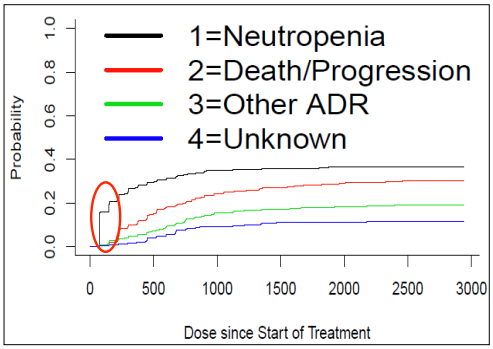
Toxicity Endpoints in 90401 (n=810)

	Docetaxel Toxicities			Bevacizumab Toxicities						
	Neutropenia		Neuro-pathy	Hypertension		Proteinuria		Thrombosis		Hemorr-hage
	3+	4+	3+	2+	3+	2+	3+	2+	3+	2+
Toxicity Endpoint	**285 36%**	**161 20%**	**57 7%**	**86 11%**	**34 4%**	**44 6%**	**10 1%**	**53 7%**	**49 6%**	**79 10%**
Completed tx w/o toxicity	**2%**	**3%**	**4%**	**3%**	**3%**	**3%**	**4%**	**3%**	**3%**	**3%**
Death/ Progres.	**31%**	**37%**	**40%**	**36%**	**38%**	**38%**	**39%**	**38%**	**39%**	**39%**
Tx Terminating Adverse Event	**19%**	**26%**	**32%**	**34%**	**37%**	**36%**	**38%**	**34%**	**35%**	**31%**
Withdrew/ other	**12%**	**14%**	**17%**	**16%**	**18%**	**17%**	**18%**	**18%**	**18%**	**18%**

Prioritize GWAS by:

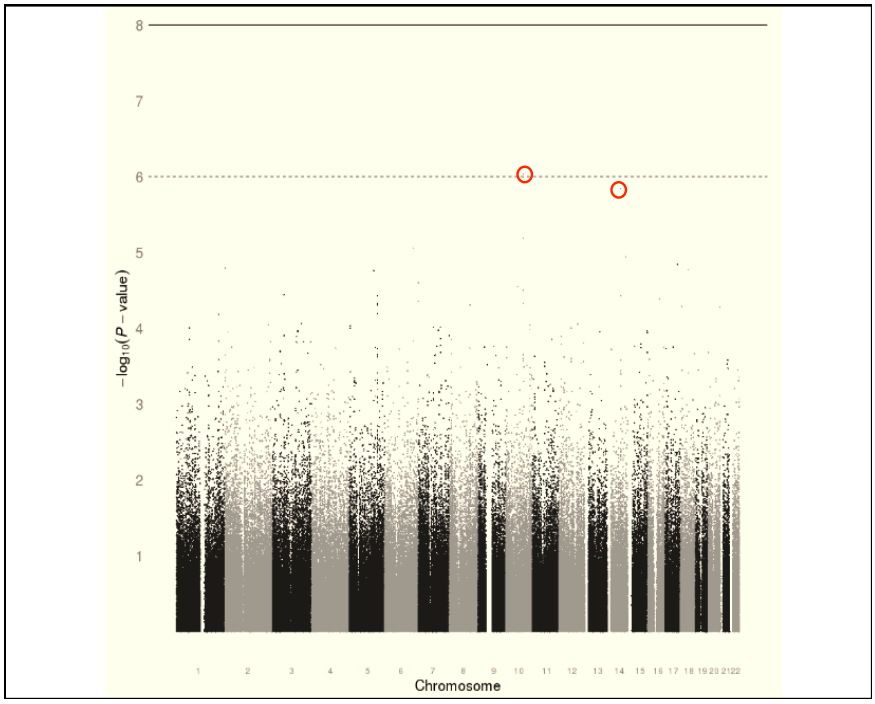
- Clinical relevance of toxicity
- Toxicity event rate
- Likelihood of genetic causal factor
- Absence of strong confounding

Neutropenia Event Rates



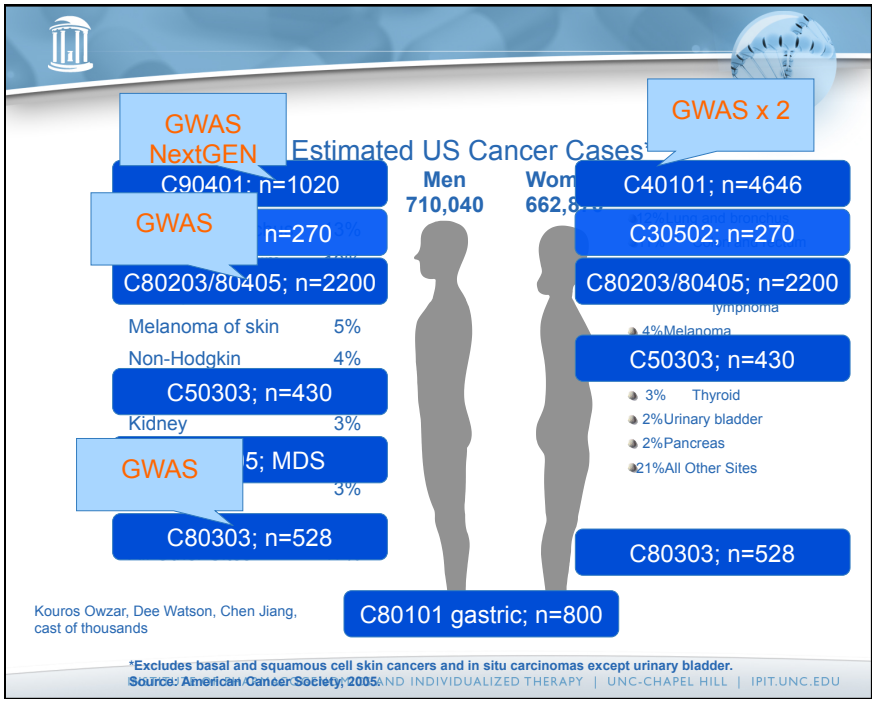
Cycle	G3+ Neut	%	Cum. %
1	124	44%	124 (44%)
2	39	14%	163 (58%)
3	24	8%	187 (66%)
4	19	7%	206 (73%)
5	11	4%	217 (77%)
6	9	3%	226 (80%)
7+	59	21%	285 (100%)

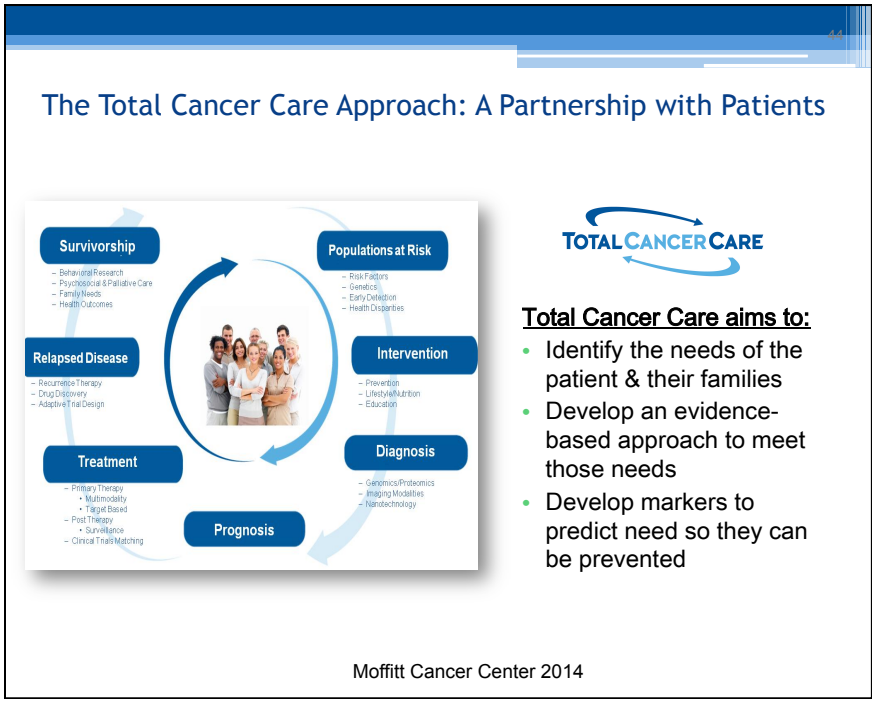
- Neutropenia groups for analysis
  - Case: grade 3+ neutropenia in cycles 1 or 2
  - Control: completed 2 full cycles without G3+ neutropenia
  - Excluded: treatment discontinued or reduced after cycle 1



Neutropenia GWAS Top 10 SNPs

Rank	rsID	Gene	MAF	B-Coeff	P-val	Biological Function or Associations
1	rs533722	RNLS	0.22	0.79	9.19E-07	Amine oxidase relevant to hypertension
2	rs12431732	ACTN1	0.07	1.14	1.42E-06	Congenital macrothrombocytopenia
3	rs1943987	RNLS	0.18	0.74	6.46E-06	LD with #1 (D'=0.98)
4	rs362895	GRM1	0.19	-1.03	8.91E-06	CNS neurotransmission
5	rs926788	SERPINA5	0.30	0.69	1.15E-05	Hemostasis and risk of melanoma
6	rs1318	PITPNC1	0.20	-0.98	1.43E-05	Cell signaling and lipid metabolism
7	rs12618922	TSSC1	0.30	0.66	1.59E-05	Tumor suppressor
8	rs2385427	TSSC1	0.28	0.67	1.62E-05	LD with #7 (D'=0.98)
9	rs16978131	KRT8P5	0.16	-1.15	1.68E-05	Pseudogene
10	rs11241793	ZNF608	0.12	0.88	1.74E-05	Associations with radiation sensitivity, cognitive impairment, & body weight


GWAS NextGEN
GWAS x 2
Estimated US Cancer Cases
Men
710,040
C90401; n=1020
C40101; n=4646
GWAS
n=270
C30502; n=270
C80203/80405; n=2200
C80203/80405; n=2200
Melanoma of skin 5%
Non-Hodgkin 4%
C50303; n=430
C50303; n=430
Kidney 3%
GWAS
5; MDS
3%
C80303; n=528
C80303; n=528
Kouros Owzar, Dee Watson, Chen Jiang, cast of thousands
C80101 gastric; n=800
*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2005.
UNC-CHAPEL HILL | IPIT.UNC.EDU


The Total Cancer Care Approach: A Partnership with Patients
Survivorship
Populations at Risk
Relapsed Disease
Intervention
Treatment
Diagnosis
Prognosis
TOTAL CANCER CARE
Total Cancer Care aims to:
Identify the needs of the patient & their families
Develop an evidence-based approach to meet those needs
Develop markers to predict need so they can be prevented
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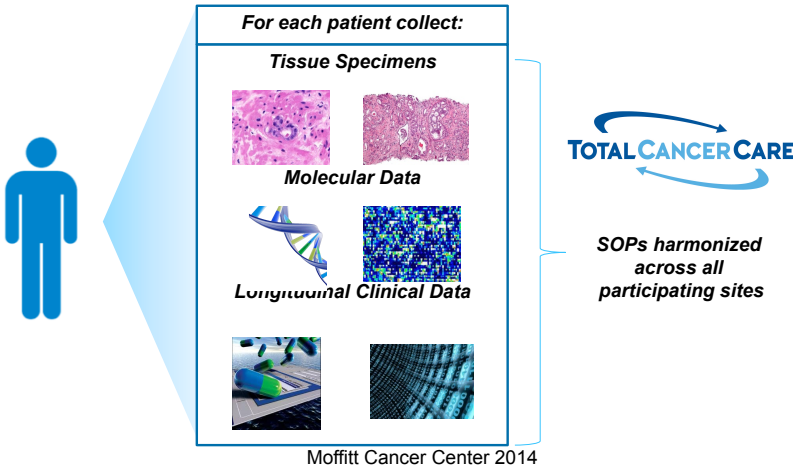
The TCC Protocol: Patient Tissue, Clinical and Molecular Data

The success of TCC to date has been a result of the harmonization of tissue and data SOPs across many different sites.



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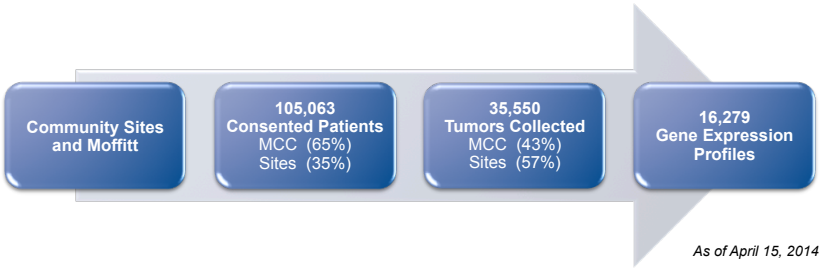
Total Cancer Care to Date



As of April 15, 2014

Data Generated from Specimens	
CEL Files (Gene Expression Data)	16,279 files
Targeted Exome Sequencing	4,016 samples
Whole Exome Sequencing (Ovary, Lung, Colon, Myeloma)	574 samples
Whole Genome Sequencing (Melanoma)	13 samples with normal pairs
SNP/CNV (Lung, Breast, Colon)	559 samples
RNA Sequencing (Breast, Myeloma)	430 samples

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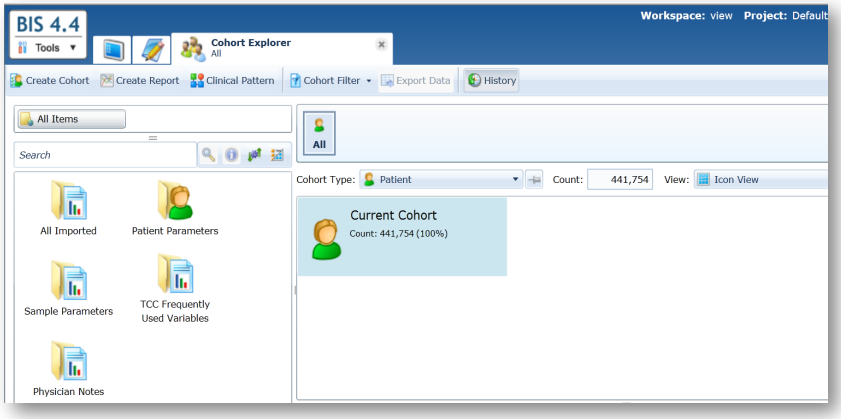
Querying via TransMed



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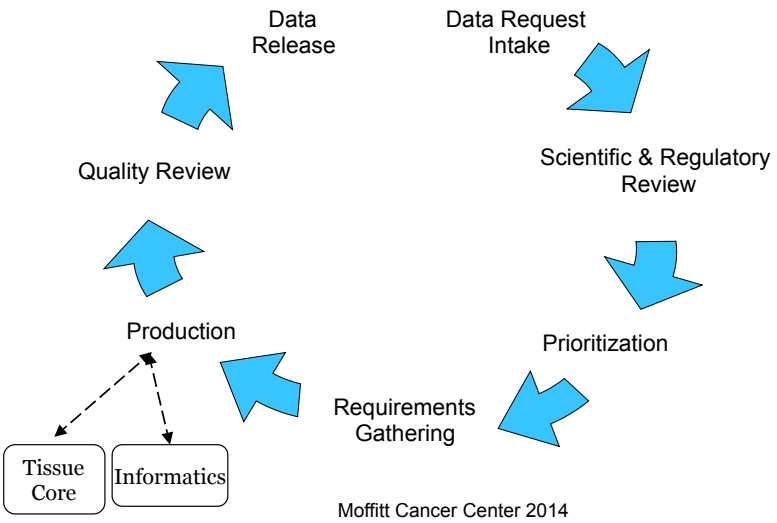
http://transmedprod/bisde_identified/bis.silverlight.shell.aspx

Data Provisioning Process



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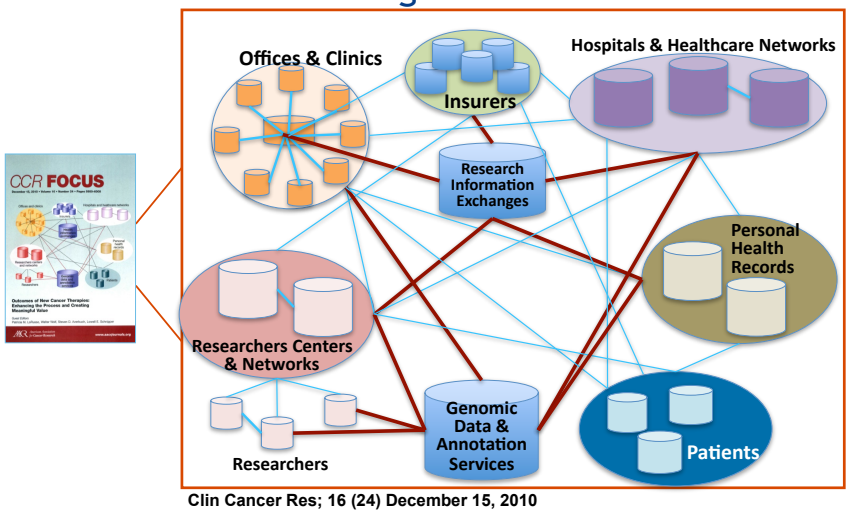
Designing a New Research & Healthcare Network Model for 'Big Data'



Clin Cancer Res; 16 (24) December 15, 2010

What needs to be done to determine hope vs hype?

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

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Pharmacogenomic examples-2014

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib
- BRAF-vemurafenib
- ALK-Crizotinib
- TPMT-mercaptopurine and azathioprine*
- UGT1A1-irinotecan**
- CYP2C9/VKORC1-warfarin*
- HLA-B*5701-abacavir *
- HLA-B*1502-carbamazepine *
- IL28B-interferon
- CFTR-ivacaftor
- CYP2C19-clopidogrel, voriconazole
- CYP2D6-5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives*

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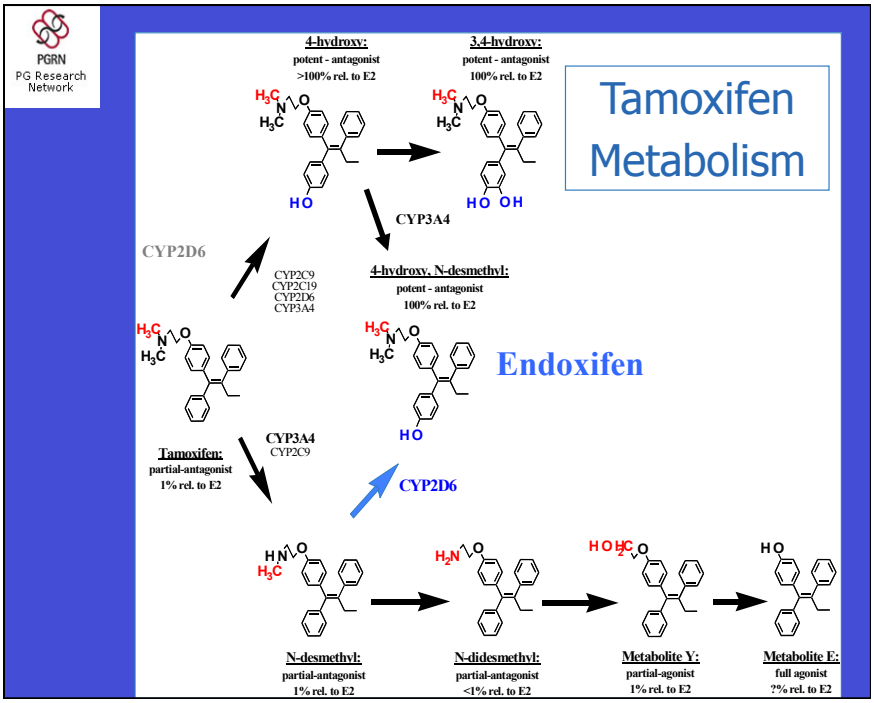
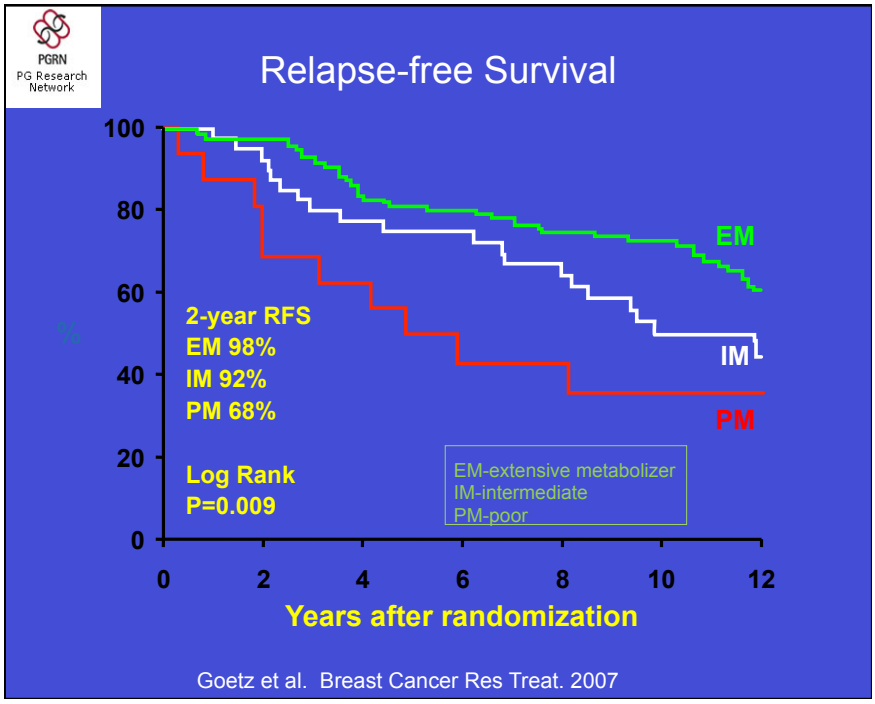
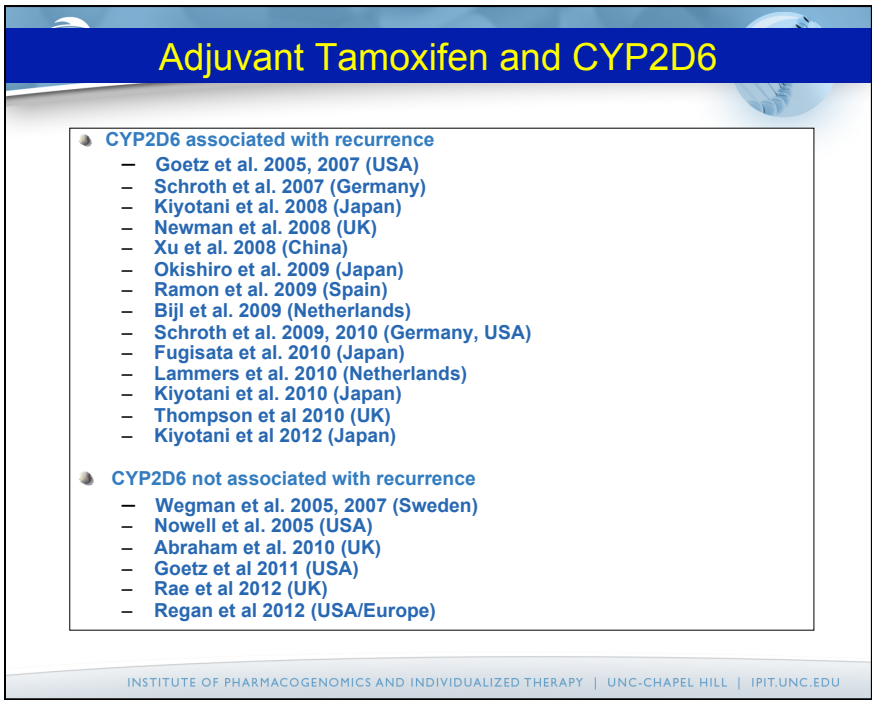
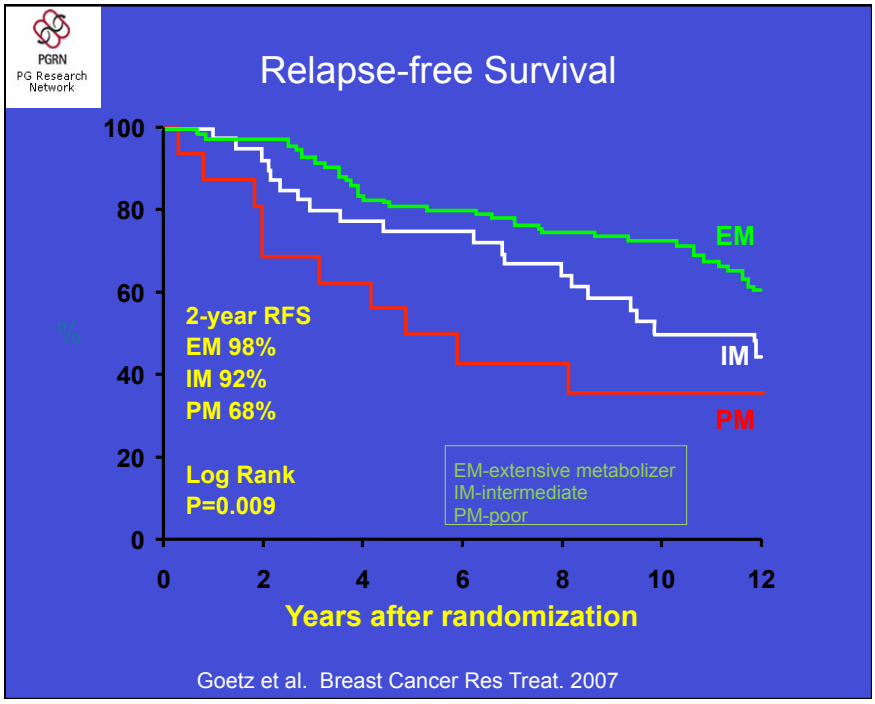
PGRN PG Research Network



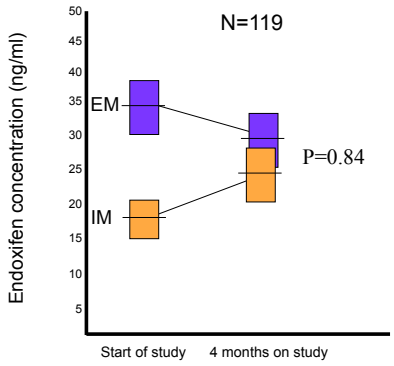

PGRN
PG Research Network
Relapse-free Survival
100
80
60
40
20
0
%
2-year RFS
EM 98%
IM 92%
PM 68%
Log Rank
P=0.009
EM
IM
PM
EM-extensive metabolizer
IM-intermediate
PM-poor
0
2
4
6
8
10
12
Years after randomization
Goetz et al. Breast Cancer Res Treat. 2007


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)
– Schroth et al. 2009, 2010 (Germany, USA)
– Fugisata et al. 2010 (Japan)
– Lammers et al. 2010 (Netherlands)
– Kiyotani et al. 2010 (Japan)
– Thompson et al 2010 (UK)
– Kiyotani et al 2012 (Japan)
CYP2D6 not associated with recurrence
– Wegman et al. 2005, 2007 (Sweden)
– Nowell et al. 2005 (USA)
– Abraham et al. 2010 (UK)
– Goetz et al 2011 (USA)
– Rae et al 2012 (UK)
– Regan et al 2012 (USA/Europe)
INSTITUTE OF PHARMACOGENOMICS AND INDIVIDUALIZED THERAPY | UNC-CHAPEL HILL | IPIT.UNC.EDU



CYP2D6-guided tamoxifen dosing normalizes endoxifen levels in IM patients

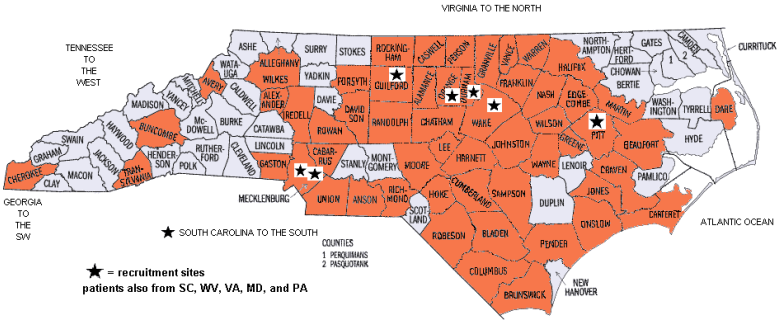
All patients on tamoxifen 20 mg/day for 4 months then
EM-20 mg
IM-change to 40 mg



Irvin et al J Clin Oncol 2011

Study of 500 patients across NC is completed, with oversampling of African American and Hispanic patient

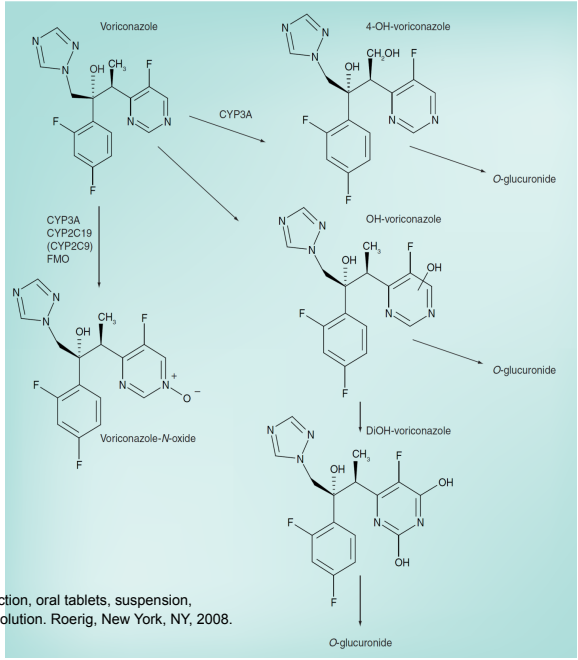
Implementation Science can be conducted where most patients are treated



Voriconazole and CYP2C19: Clinical Implications

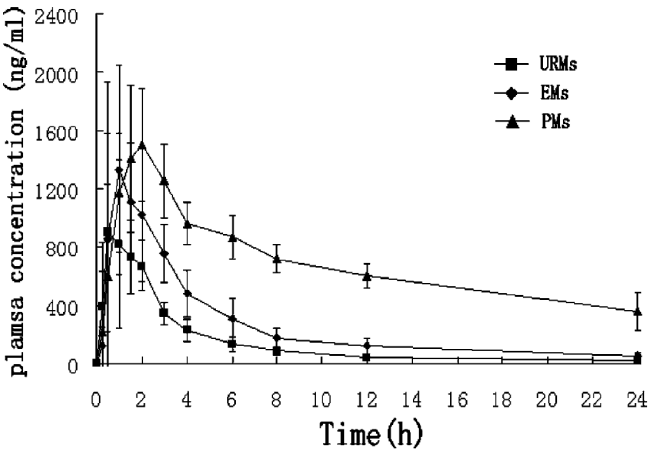
- Used to treat fungal infection
- Used as fungal prophylaxis in myeloid malignancies

- Metabolized by CYP2C19, CYP2C9 and CYP3A4.
- A significant isoenzyme, involved in metabolism, is the CYP2C19, which exhibits polymorphism.
- Studies in caucasian and japanese poor metabolizers demonstrated on average, a 4-fold increase in AUC.
- Patients who are heterozygous extensive metabolizers have a average of a 2-fold higher AUC compared with homozygous extensive metabolizers



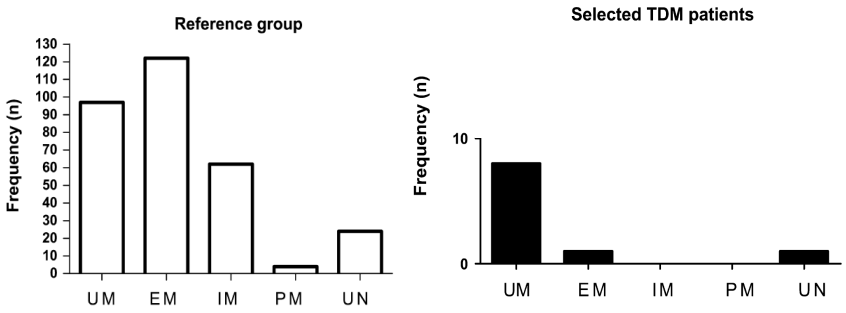
Product Information: VFEND(R) IV injection, oral tablets, suspension, voriconazole IV injection, oral tablets, solution. Roerig, New York, NY, 2008.

Plasma concentration–time curve of voriconazole after an oral dose of 200 mg in volunteers



Wang G, et al. *Eur J Clin Pharmacol.* 2009 Mar;65(3):281-5.

CYP2C19 *17 allele found in 80% of selected patients with low voriconazole trough levels



Hassan A, et al. *Ther Drug Monit*. 2011;33:86–93.

Genotyping for Ultrarapid Metabolizers in Adult BMT and AML Patient Populations Can Save Significant Healthcare Costs

Realistic Case

Cost Savings Model Based on 100 Patients

	# of Patients	Cost of Genotyping	Incremental Savings by Avoiding IFI	Total
Cost of Screening Patients	100	($319.12)	-	($31,912)
Cost Savings from Genotyping	5	-	$29,183	$145,915
Total Cost Savings from CYP2C19 Screening Program				**$114,003**
Total Savings/Patient				**$1,140**

Assumptions:
Estimated # of Patients with CYP2C19*17 = 30
Predicted # of Patients to Develop IFI = 5.4
Estimated Effectiveness of CYP2C19*17 Status Based Intervention = 94%
Estimated # of IFI Cases Avoided by Genotyping = 5.4 x 0.94 = 5

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Genotyping for Ultrarapid Metabolizers in Adult BMT and AML Patient Populations Can Save Significant Healthcare Costs

Conservative Case

Cost Savings Model Based on 100 Patients

	# of Patients	Cost of Genotyping	Incremental Savings by Avoiding IFI	Total
Cost of Screening Patients	100	($319.12)	-	($31,912)
Cost Savings from Genotyping	1.6	-	$29,183	$46,693
Total Cost Savings from CYP2C19 Screening Program				**$14,781**
Total Savings/Patient				**$148**

Assumptions:
Estimated # of Patients with CYP2C19*17 = 1.8
Estimated Effectiveness of Intervention Based on CYP2C19*17 Status = 90%
Estimated # of IFI Cases Avoided by Genotyping = 1.8 X 90% = 1.6

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Genotyping for Ultrarapid Metabolizers in Adult BMT and AML Patient Populations Can Save Significant Healthcare Costs

Aggressive Case

Cost Savings Model Based on 100 Patients

	# of Patients	Cost of Genotyping	Incremental Savings by Avoiding IFI	Total
Cost of Screening Patients	100	($319.12)	-	($31,912)
Cost Savings from Genotyping	30	-	$29,183	$875,490
Total Cost Savings from CYP2C19 Screening Program				**$843,578**
Total Savings/Patient				**$8,436**

Assumptions:
Estimated # of Patients with CYP2C19*17 = 30
Estimated # of IFI Cases Avoided by Genotyping = 5.4 x 0.94 = 30

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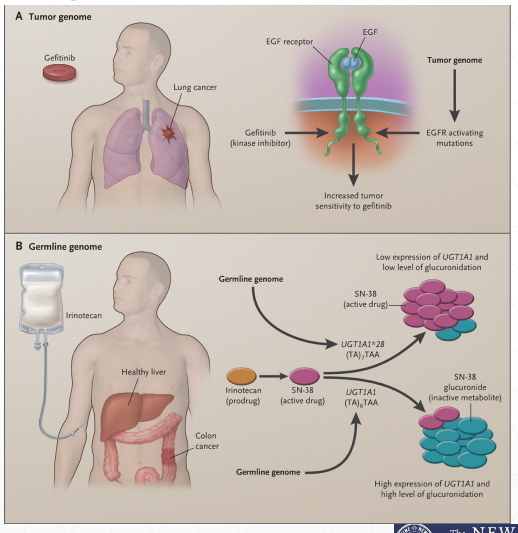
Cancer Pharmacogenomics and Tumor and Germline Genomes.



Wang L et al. N Engl J Med 2011;364:1144-1153.

The NEW ENGLAND JOURNAL of MEDICINE

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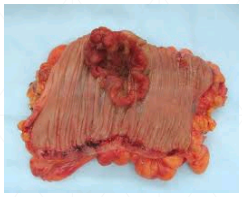
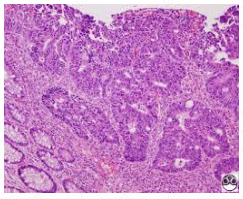
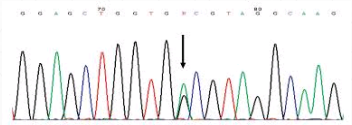
Cancer Care is changing fast: the opportunity and the threat







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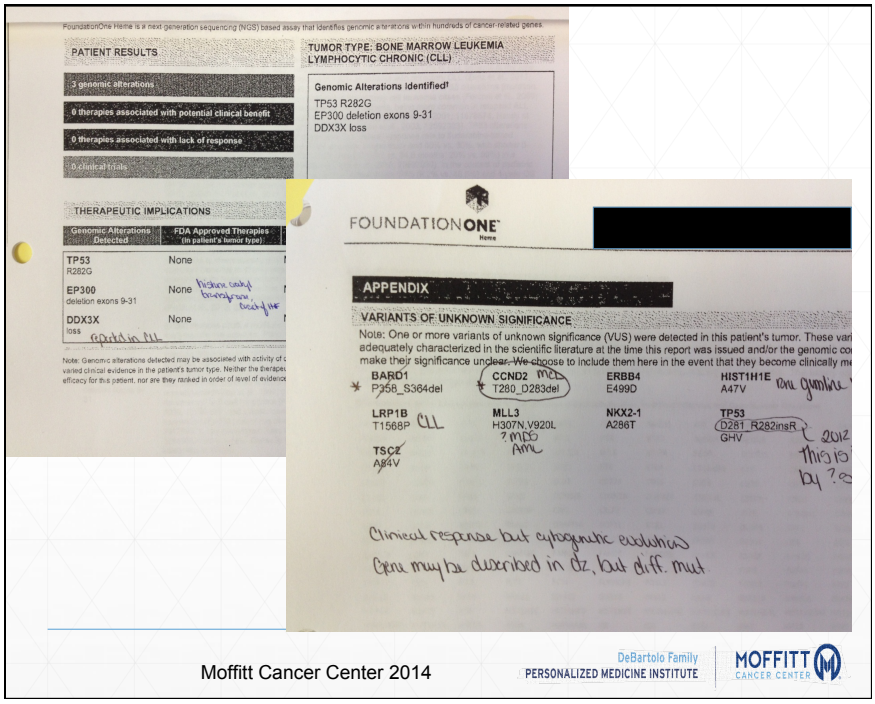


PGENI

- Modern medical therapy is a key component of improved health and a sizeable part of health budgets
- Selection of medications for each indication is a combination of clinical consensus, access/cost of drugs, and familiarity
- Medicine prioritization is a high stakes undertaking for developing countries
- We need to use all available data

Source of data for patient therapy selection

Best option: individual

Good: relevant geographic/ ethnic/racial population

Worst: inferred world population

PGENI Treating the Population. Impacting the World.

Overview of study plan

- Identify common ethnic racial groups (>10%)
- Collect 500 blood samples (250 male; 250 female) from each ethnic group.
  Preference is for healthy volunteers (e.g., blood donors).
  Only gender, ethnicity, and age known for each sample.
- Genotype for variants of interest
- Generate recommendations for medication selection

Africa example

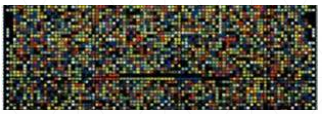
The Gambia:		**Egypt:**	
Fulani	18%	Eastern Hamitic (Egyptians, Bedouin, and Berbers)	99%
Jola	10%		
Mandinka	42%		
Wolof	16%		

PGENI Treating the Population. Impacting the World.

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

PGENI Treating the Population. Impacting the World.

Pharmacogenomic examples-2014

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib
- BRAF-vemurafenib
- ALK-Crizotinib
- TPMT-mercaptopurine and azathioprine*
- UGT1A1-irinotecan**
- CYP2C9/VKORC1-warfarin*
- HLA-B*5701-abacavir *
- HLA-B*1502-carbamazepine *
- IL28B-interferon
- CFTR-ivacaftor
- CYP2C19-clopidogrel, voriconazole
- CYP2D6-5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives*

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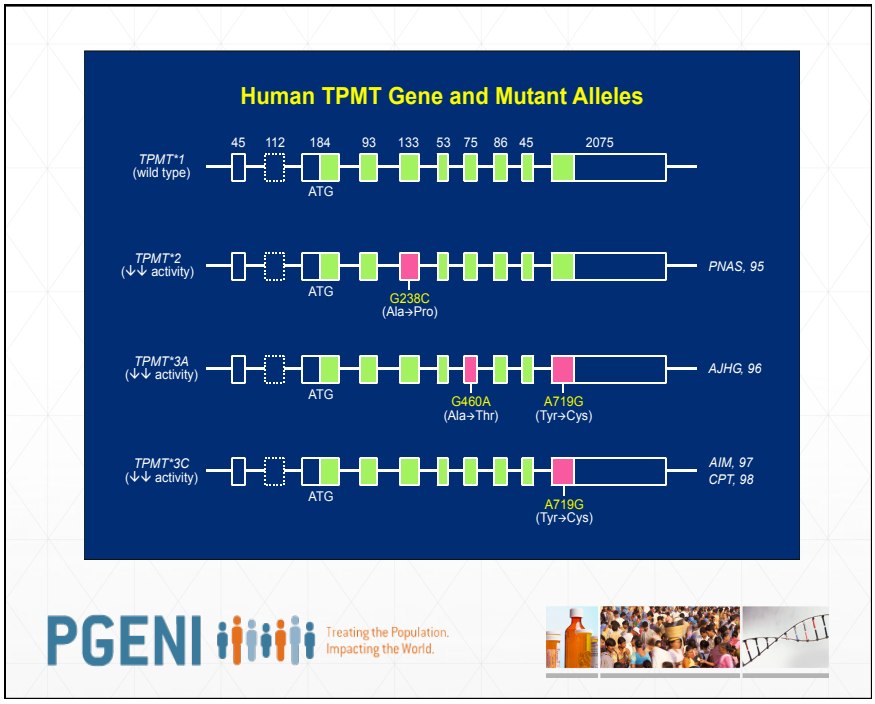
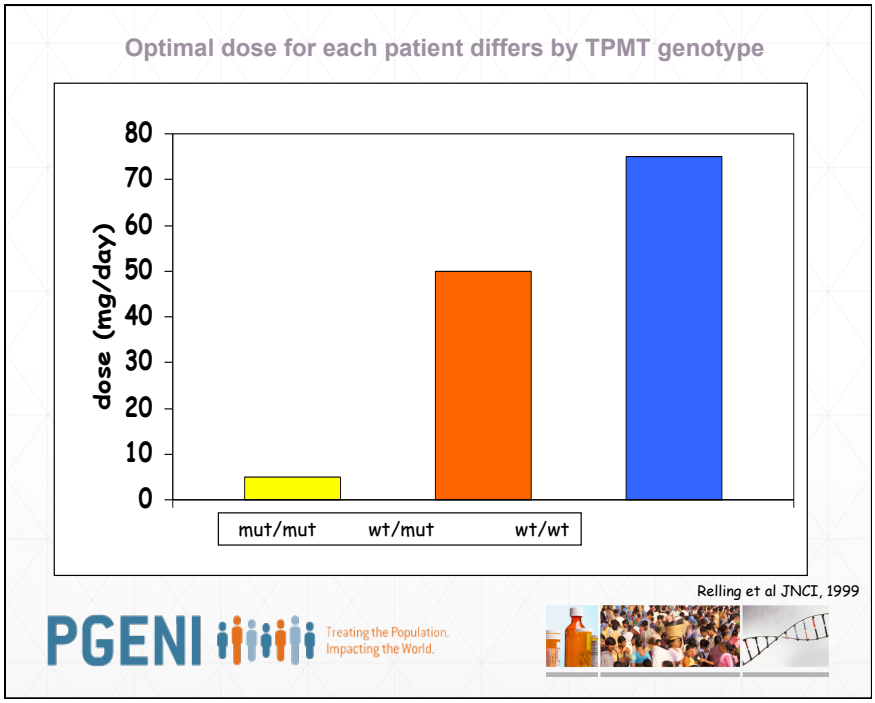
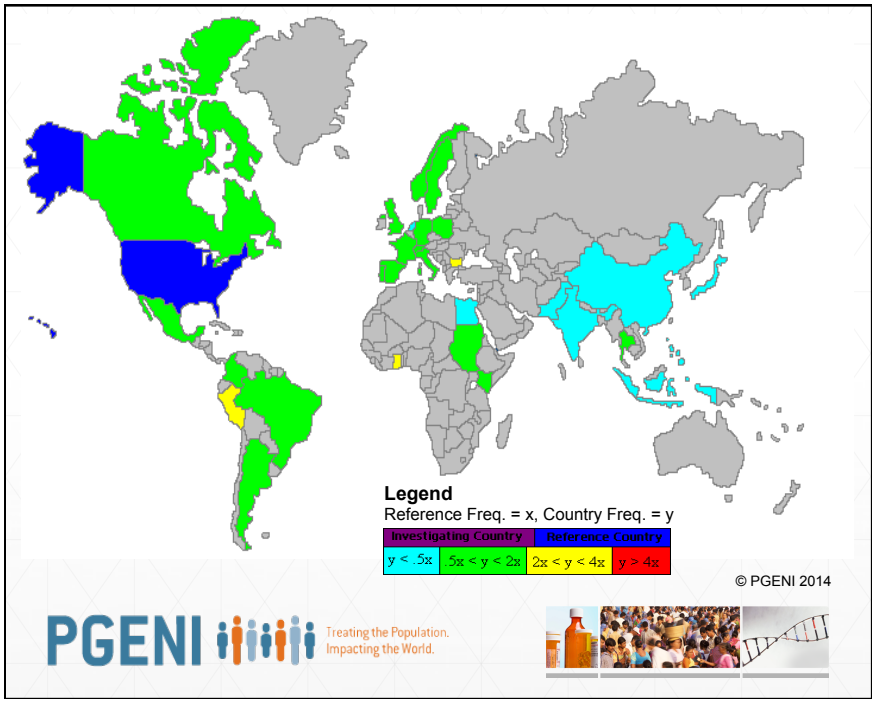

Human TPMT Gene and Mutant Alleles
45 112 184 93 133 53 75 86 45 2075
TPMT*1
(wild type)
ATG
TPMT*2
(↓↓ activity)
ATG
G238C
(Ala→Pro)
PNAS, 95
TPMT*3A
(↓↓ activity)
ATG
G460A
(Ala→Thr)
A719G
(Tyr→Cys)
AJHG, 96
TPMT*3C
(↓↓ activity)
ATG
A719G
(Tyr→Cys)
AIM, 97
CPT, 98
PGENI
Treating the Population.
Impacting the World.


Optimal dose for each patient differs by TPMT genotype
dose (mg/day)
80
70
60
50
40
30
20
10
0
mut/mut
wt/mut
wt/wt
Relling et al JNCI, 1999
PGENI
Treating the Population.
Impacting the World.


Legend
Reference Freq. = x, Country Freq. = y
Investigating Country
Reference Country
y < .5x
.5x < y < 2x
2x < y < 4x
y > 4x
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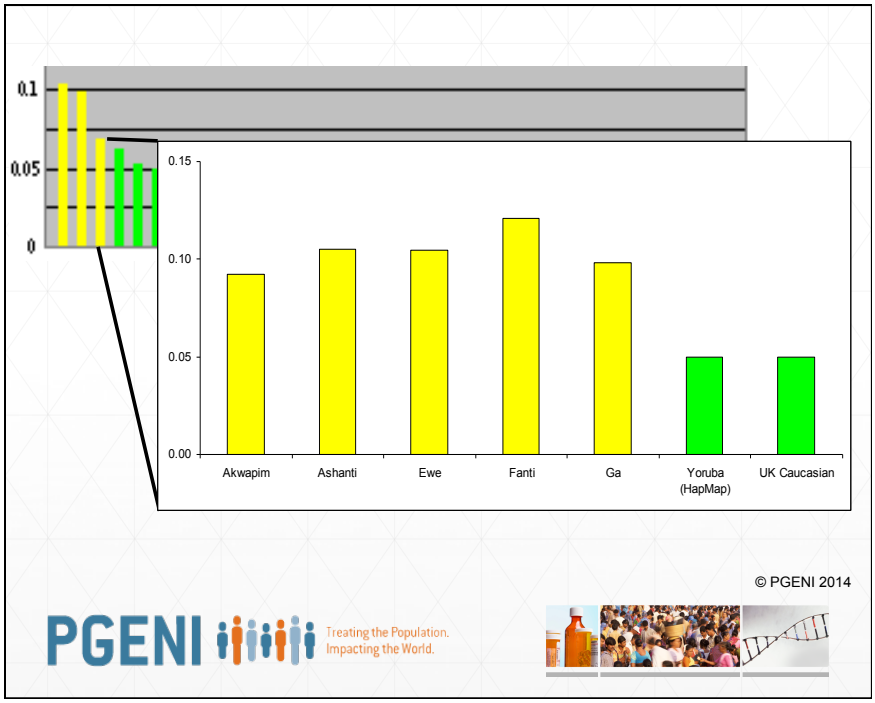
0.1
0.05
0
0.15
0.10
0.05
0.00
Akwapim
Ashanti
Ewe
Fanti
Ga
Yoruba (HapMap)
UK Caucasian
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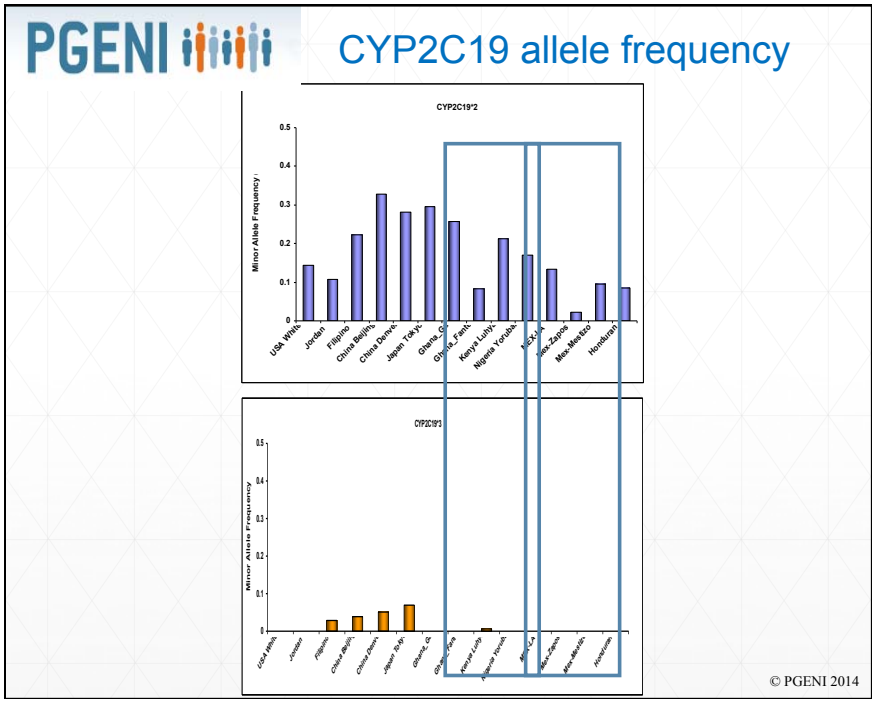

Type of output

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

Prioritization - assisting the treatment selection from among WHO recommended therapies

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PGENI Surveillance example: Tuberculosis

Drug	Gene	Allele	Effect	Associated	Probably Associated	Possibly Associated	Not Associated	No Data Available
Isoniazid	NAT2	*5/*6/*7	Efficacy				X	
			Hepatotoxicity	X				
			Neuropathy		X			
	CYP2E1	*5B	Efficacy					X
			Hepatotoxicity	X				
Rifampicin	ESB		Efficacy					X
			Toxicity					X
Pyrazinamide	XDH		Efficacy					X
			Hepatotoxicity			X		
Ethambutol	MTND4		Efficacy					X
			Optic neuropathy			X		
Streptomycin	MTRNR1		Efficacy					X
			Ototoxicity		X			

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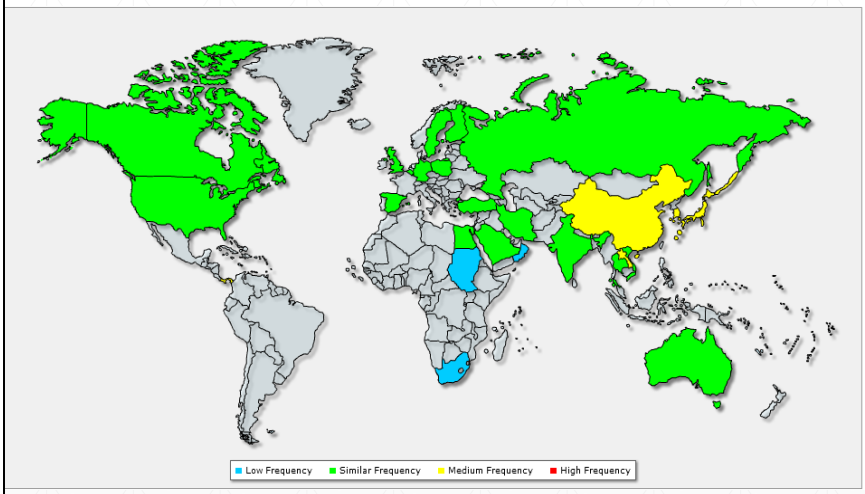
NAT2 *4



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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

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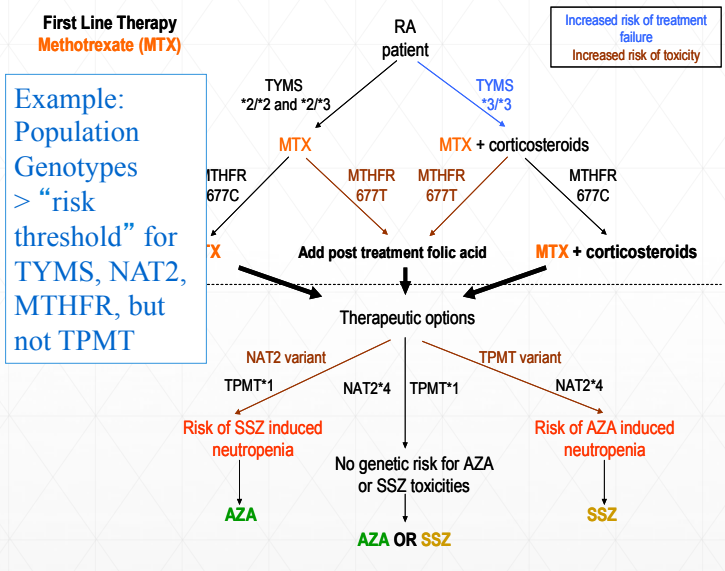
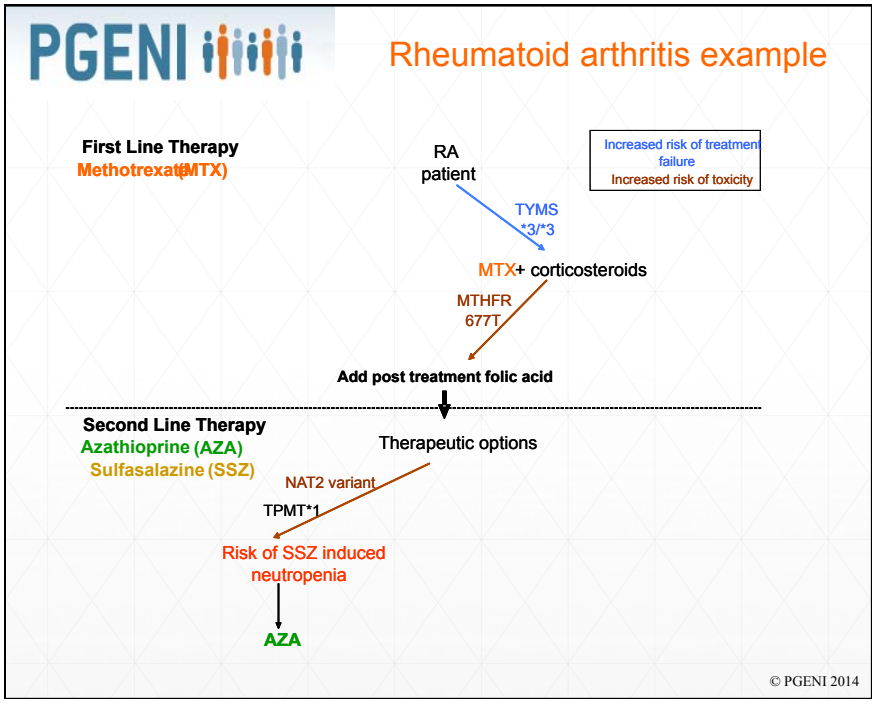
Rheumatoid arthritis example



Example: Population Genotypes > "risk threshold" for TYMS, NAT2, MTHFR, but not TPMT


PGENI
Rheumatoid arthritis example
First Line Therapy
Methotrexate (MTX)
RA patient
Increased risk of treatment failure
Increased risk of toxicity
TYMS *3/*3
MTX + corticosteroids
MTHFR 677T
Add post treatment folic acid
Second Line Therapy
Azathioprine (AZA)
Sulfasalazine (SSZ)
Therapeutic options
NAT2 variant
TPMT*1
Risk of SSZ induced neutropenia
AZA
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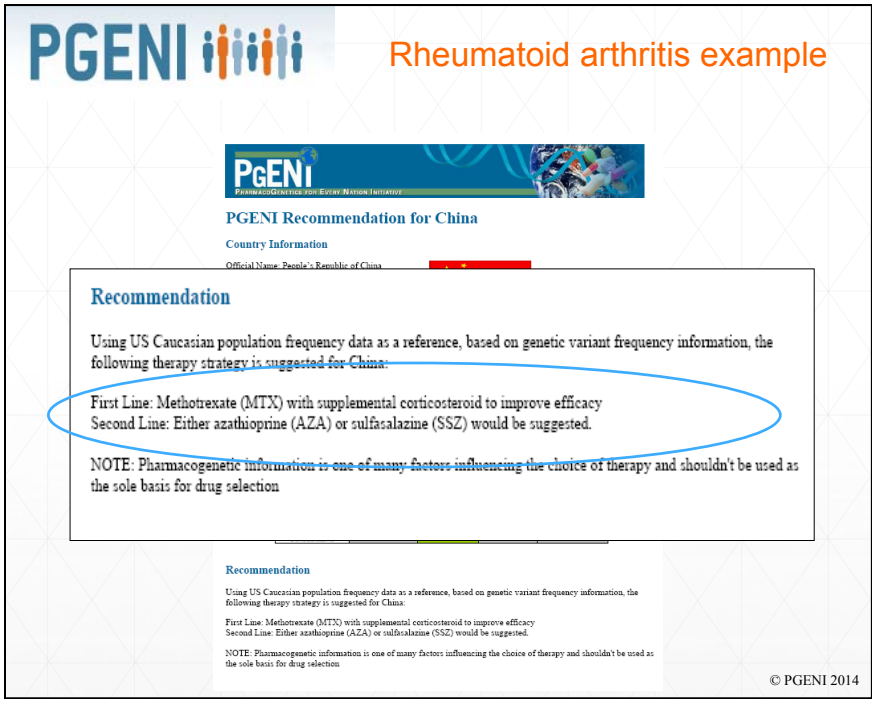
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Rheumatoid arthritis example
PGENI Recommendation for China
Country Information
Recommendation
Using US Caucasian population frequency data as a reference, based on genetic variant frequency information, the following therapy strategy is suggested for China:
First Line: Methotrexate (MTX) with supplemental corticosteroid to improve efficacy
Second Line: Either azathioprine (AZA) or sulfasalazine (SSZ) would be suggested.
NOTE: Pharmacogenetic information is one of many factors influencing the choice of therapy and shouldn't be used as the sole basis for drug selection
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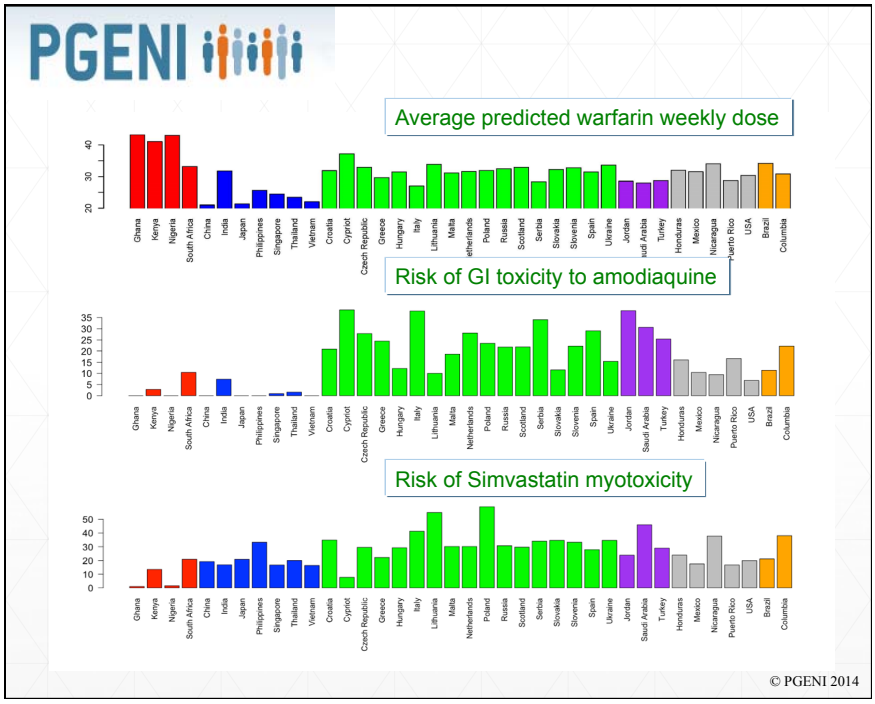
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Average predicted warfarin weekly dose
Risk of GI toxicity to amodiaquine
Risk of Simvastatin myotoxicity
Ghana Kenya Nigeria South Africa China India Japan Philippines Singapore Thailand Vietnam Croatia Cyprus Czech Republic Greece Hungary Italy Lithuania Malta Netherlands Poland Russia Scotland Serbia Slovakia Slovenia Spain Ukraine Jordan Saudi Arabia Turkey Honduras Mexico Nicaragua Puerto Rico USA Brazil Columbia
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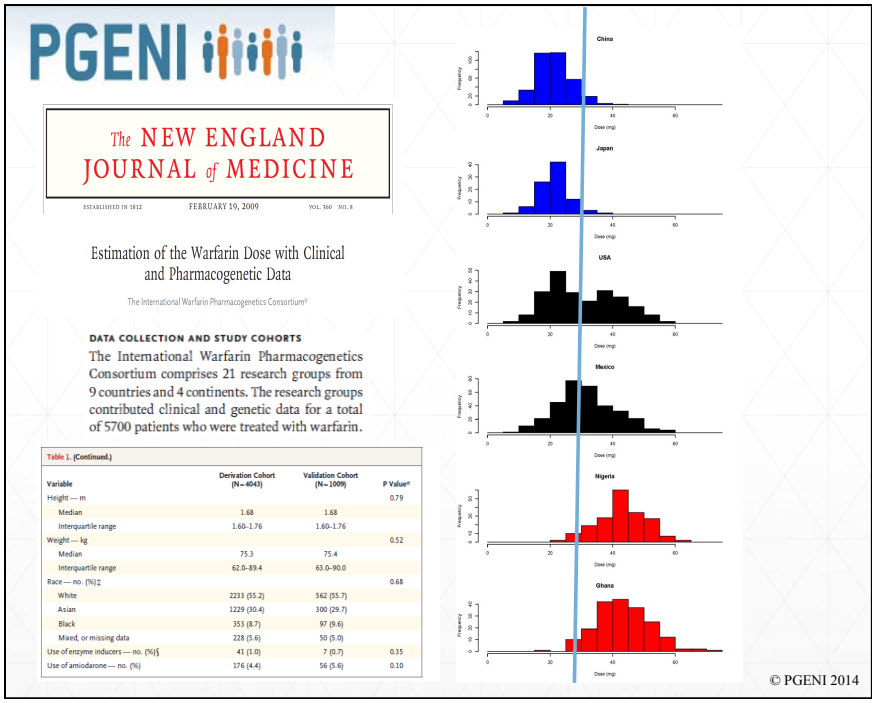
PGENI
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 19, 2009 VOL. 360 NO. 8
Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data
The International Warfarin Pharmacogenetics Consortium*
DATA COLLECTION AND STUDY COHORTS
The International Warfarin Pharmacogenetics Consortium comprises 21 research groups from 9 countries and 4 continents. The research groups contributed clinical and genetic data for a total of 5700 patients who were treated with warfarin.
Table 1. (Continued.)
Variable | Derivation Cohort (N = 4043) | Validation Cohort (N = 1009) | P Value*
Height — m | | | 0.79
Median | 1.68 | 1.68 |
Interquartile range | 1.60–1.76 | 1.60–1.76 |
Weight — kg | | | 0.52
Median | 75.3 | 75.4 |
Interquartile range | 62.0–89.4 | 63.0–90.0 |
Race — no. (%)‡ | | | 0.68
White | 2233 (55.2) | 562 (55.7) |
Asian | 1229 (30.4) | 300 (29.7) |
Black | 353 (8.7) | 97 (9.6) |
Mixed, or missing data | 228 (5.6) | 50 (5.0) |
Use of enzyme inducers — no. (%)§ | 41 (1.0) | 7 (0.7) | 0.35
Use of amiodarone — no. (%) | 176 (4.4) | 56 (5.6) | 0.10
China
Japan
USA
Mexico
Nigeria
Ghana
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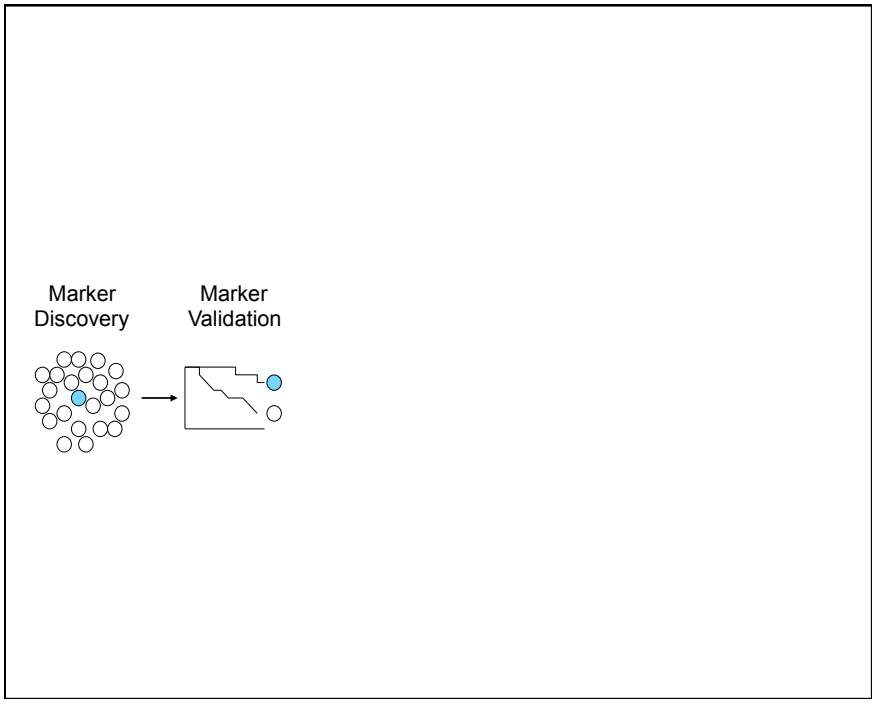
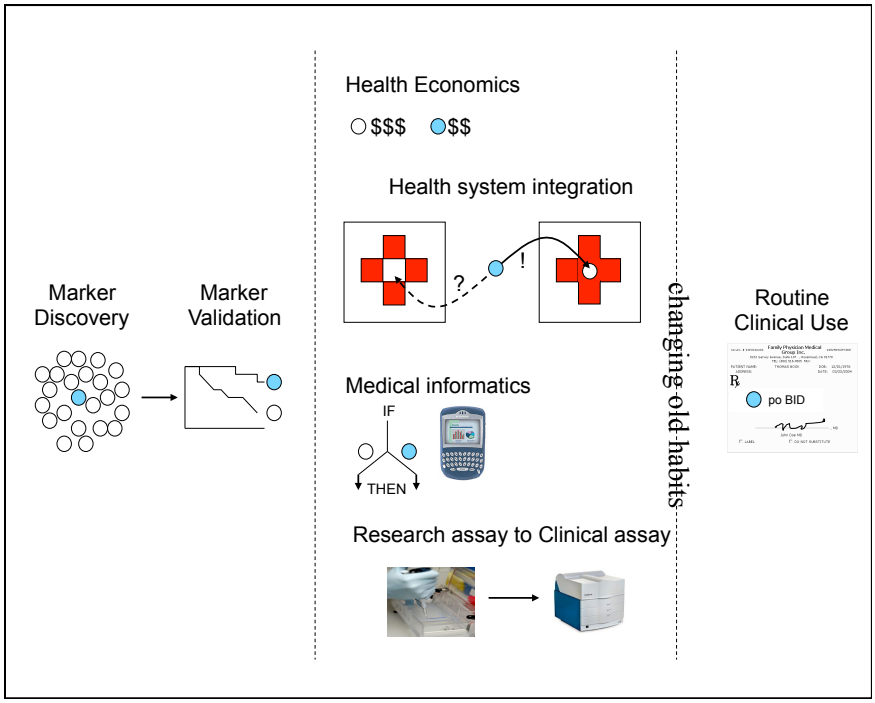
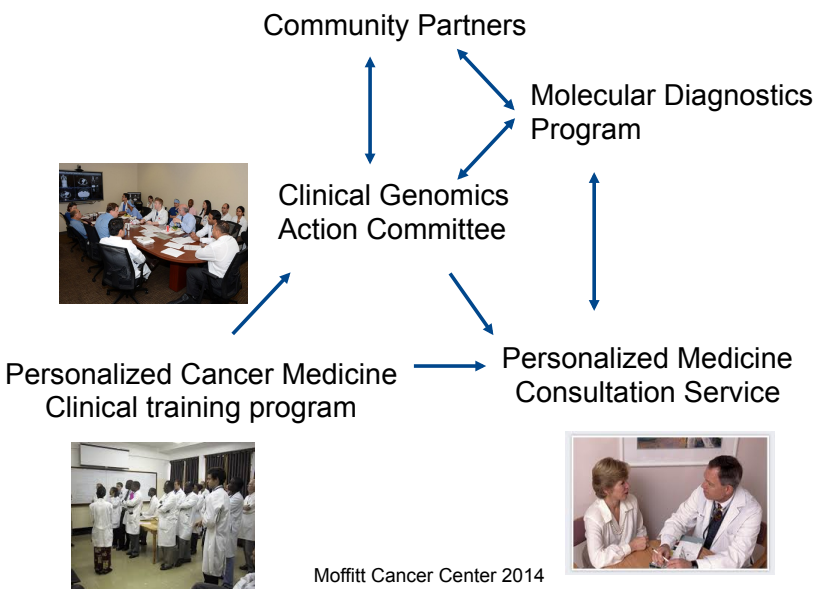

Marker
Discovery
Marker
Validation

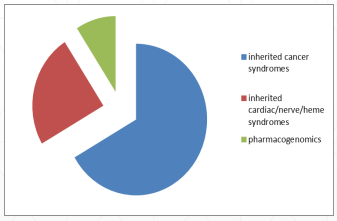

Marker
Discovery
Marker
Validation
Health Economics
$$$
$$
Health system integration
?
!
Medical informatics
IF
THEN
Research assay to Clinical assay
changing old habits
Routine
Clinical Use
po BID

Moffitt Personalized Cancer Medicine



Clinical Risk Panel: easier to test all than some

- Clinical pathway-driven care
- Adhere to cancer risk guidelines
- Identify underlying predisposition to severe toxicity
- Mitigating risk of untoward drug effects



Moffitt Cancer Center 2014

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I have ears, but cannot hear

- 44 year old white male (CSO at a NC biotech)
- AV block 2^0 congenital heart disease
- Presents for placement of epicardial pacemaker
- Tells cardiologist, CT surgeon, anesthesiologist, and admitting team (cardiology fellow, resident, intern) that an executive physical revealed genetic data relevant to pain control and anticoagulation
- Adequate pain control (4/10) in recovery room on MS
- moved to CCU and switch to oxycodone during the night, waking up in severe pain (10/10), ignored x 24 hours
- Student and PharmD recognized CYP2D6 PM and patient was switched to hydromorphone (5/10)

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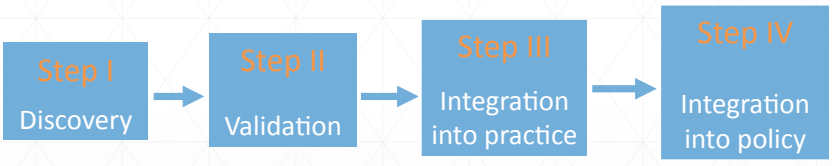
Translational science: The steps to success



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