PHARMACOGENOMICS: 2016

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JOHNS HOPKINS
MEDICINE
CONTINUING MEDICAL EDUCATION

Current Topics in Genome Analysis 2016

Howard McLeod

Cancer Genetics Inc

Paid Member of Board

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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

Probabalistic data is enough

Many clinical interventions are based on increased probability of a problem occurring

- Insulin/oral diabetes drugs
- Statins
- antihypertensives

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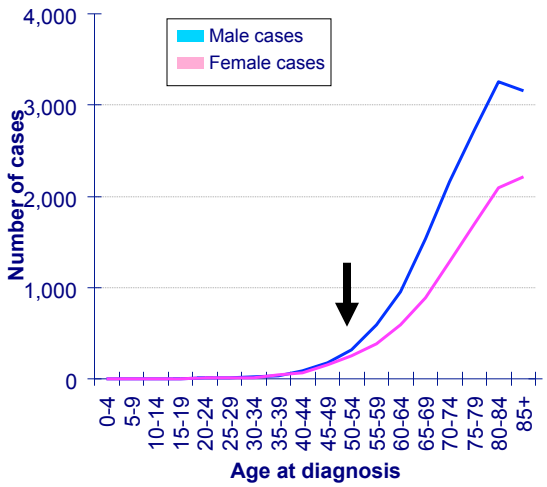
Increase risk = intervention Colon cancer screening



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Why focus on drugs?

- Adverse drug events are 5th leading cause of death in USA
  - Adverse drug events are heavily litigated
  - Many adverse drug events are predictable
- Modern treatments are expensive
- Opportunities to improve 'value'

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Adverse Drug Events
Potential for Pharmacogenomics to Decrease Risk

- An estimated **2 to 4 million** persons suffer from a serious, disabling, or fatal adverse drug event each year
- In the United States, adverse drug events cause over **700,000** emergency room visits each year
- Over **120,000** of those emergency room visits result in further hospitalization
- Approximately **100,000 deaths** per year attributed to adverse drug events

Institute for safe medication practices Quarter Watch 2012
Institute for safe medication practices Quarter Watch 2013
http://www.cdc.gov/MedicationSafety/Adult_AdverseDrugEvents.html

Emergency Department Visits by Adults for Psychiatric Medication Adverse Events

JAMA Psychiatry

Medication Category and Class[a]	ED Visits for Adverse Drug Events[b]				Estimated Annual ED Visits per 10 000 Outpatient Prescription Visits, No. (95% CI)[c]
	No. of Cases	Estimated Annual No. of Visits	% Proportion of Category Visits	% Hospitalization Rate	
Sedatives and anxiolytics	1371	30 707	NA	23.5	3.6 (3.2-4.1)
Antidepressants	1076	25 377	NA	12.4	2.4 (2.1-2.7)
Antipsychotics	1055	21 578	NA	15.3	11.7 (10.1-13.2)
Lithium salts	197	3620	NA	53.6	16.4 (13.0-19.9)

Estimated that ~ 90,000 patients visit ED each year due to psychiatric drug-induced adverse events

Hampton et al, *JAMA Psychiatry* 71(9); 2014

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THE PRECISION MEDICINE INITIATIVE

- Advance **pharmacogenomics,** the right drug for the right patient at the right dose
- Identify new targets for **treatment and prevention**
- Test whether **mobile devices** can encourage healthy behaviors
- Lay **scientific foundation** for precision medicine for **many diseases**

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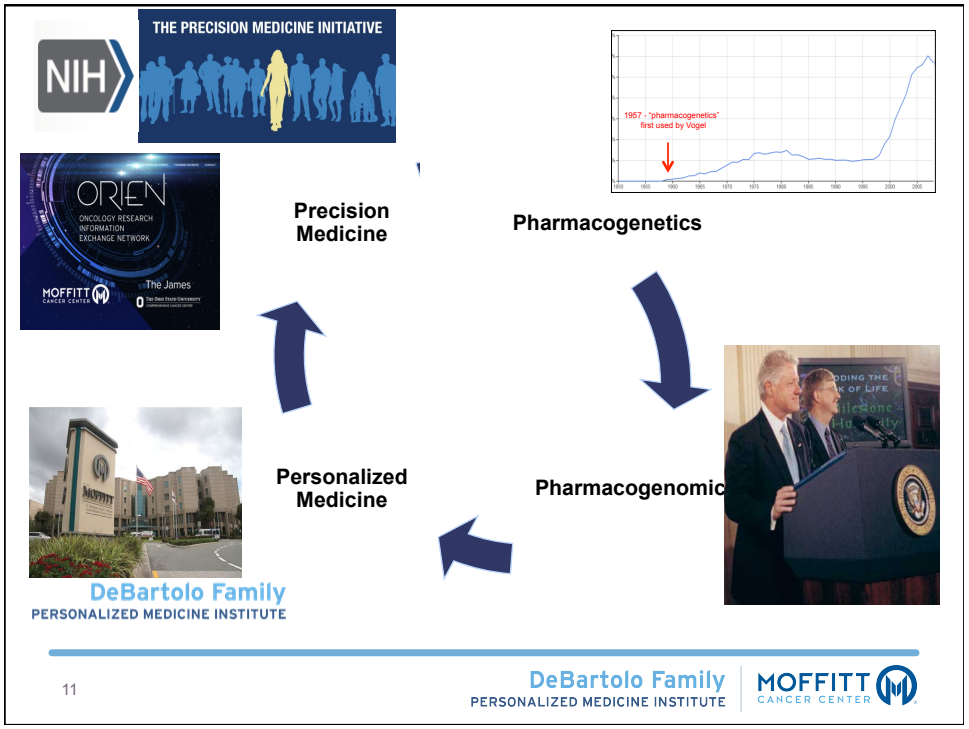

PERSONALIZED MEDICINE, SCHMERSONALIZED MEDICINE!

- Medicine has always been personalized
- Medicine is moving toward greater 'customer accountability'
- Medicine will never be personalized
- it is a change in expectation as well as some practical, process changes

Drivers of Precision Medicine

- Technology
  - Significant new opportunities over the past 5 years
- Patient financial burden
  - When you are paying more, you want more say
- Less personal care
  - Who will be my 'doctor' today?
- Cost of care
  - Even the USA can't afford treating 100% to benefit 20%

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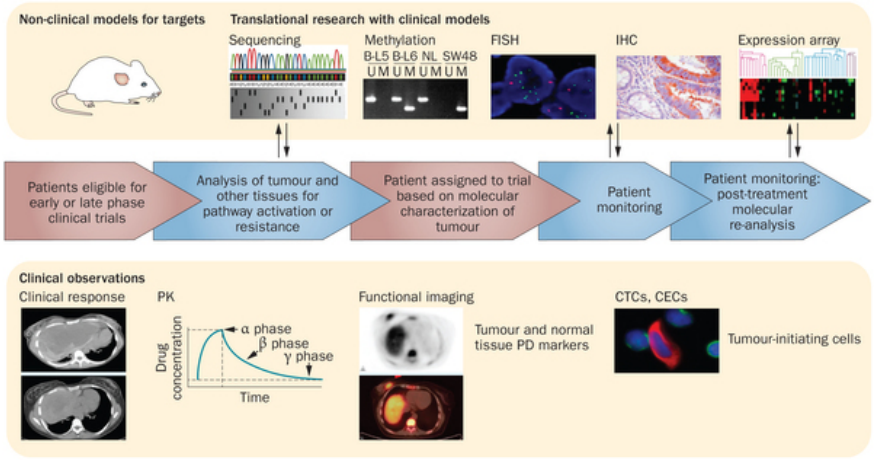

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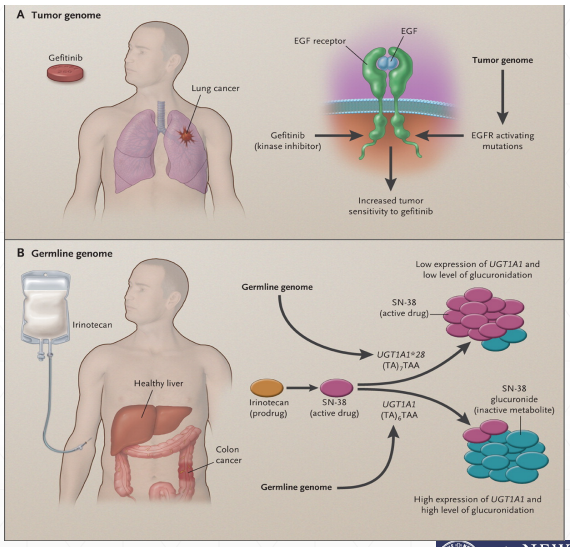
Cancer Pharmacogenomics and Tumor and Germline Genomes.



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

The NEW ENGLAND JOURNAL of MEDICINE

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Pharmacogenomic examples-2016

- *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
- ROS-1_Crizotinib
- TPMT-mercaptopurine a
- UGT1A1-irinotecan**
- CYP2C9/VKORC1-warfa
- HLA-B*5701-abacavir *
- HLA-B*1502-carbamaze
- IL28B-interferon
- CFTR-ivacaftor
- CYP2C19-clopidogrel, v
- CYP2D6-5-HT3 recepto and codeine derivatives*

Pain control
Antiemetics
Antidepressants
ADHD drugs
Anticoagulants
Not just tumor markers!!

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CPIC: Clinical Pharmacogenetics Implementation Consortium

- **The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a shared project between PharmGKB and the Pharmacogenomics Research Network**
- **CPIC guidelines are designed to help clinicians understand HOW genetic test results should be used to optimize drug therapy**
- **Once published the guidelines are updated periodically**
  http://www.pharmgkb.org

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

Relling and Klein, *Clin Pharmacol Ther.* 89(3): 464-7; 2011

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CPIC Guidelines on PharmGKB

Drug	Guidelines
abacavir	CPIC Dosing Guideline for abacavir and HLA-B
allopurinol	CPIC Dosing Guideline for allopurinol and HLA-B
amitriptyline	CPIC Dosing Guideline for amitriptyline and CYP2C19, CYP2D6
azathioprine	CPIC Dosing Guideline for azathioprine and TPMT
capecitabine	CPIC Dosing Guideline for capecitabine, fluorouracil, tegafur and DPYD
carbamazepine	CPIC Dosing Guideline for carbamazepine and HLA-B
clomipramine	CPIC Dosing Guideline for clomipramine and CYP2C19, CYP2D6
clopidogrel	CPIC Dosing Guideline for clopidogrel and CYP2C19
codeine	CPIC Dosing Guideline for codeine and CYP2D6
desipramine	CPIC Dosing Guideline for desipramine and CYP2D6
doxepin	CPIC Dosing Guideline for doxepin and CYP2C19, CYP2D6
fluorouracil	CPIC Dosing Guideline for capecitabine, fluorouracil, tegafur and DPYD
imipramine	CPIC Dosing Guideline for imipramine and CYP2C19, CYP2D6
mercaptopurine	CPIC Dosing Guideline for mercaptopurine and TPMT
nortriptyline	CPIC Dosing Guideline for nortriptyline and CYP2D6
peginterferon alfa-2a	CPIC Dosing Guideline for peginterferon alfa-2a, peginterferon alfa-2b, ribavirin and IFNL3
peginterferon alfa-2b	CPIC Dosing Guideline for peginterferon alfa-2a, peginterferon alfa-2b, ribavirin and IFNL3
ribavirin	CPIC Dosing Guideline for peginterferon alfa-2a, peginterferon alfa-2b, ribavirin and IFNL3
simvastatin	CPIC Dosing Guideline for simvastatin and SLCO1B1
tegafur	CPIC Dosing Guideline for capecitabine, fluorouracil, tegafur and DPYD
thioguanine	CPIC Dosing Guideline for thioguanine and TPMT
trimipramine	CPIC Dosing Guideline for trimipramine and CYP2C19, CYP2D6
warfarin	CPIC Dosing Guideline for warfarin and CYP2C9, VKORC1

REASONS FOR PRECISION MEDICINE

- Testing for avoidance
- Testing for inclusion
- Testing for stratification
- Testing for explanation

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Opiate Pharmacogenomics

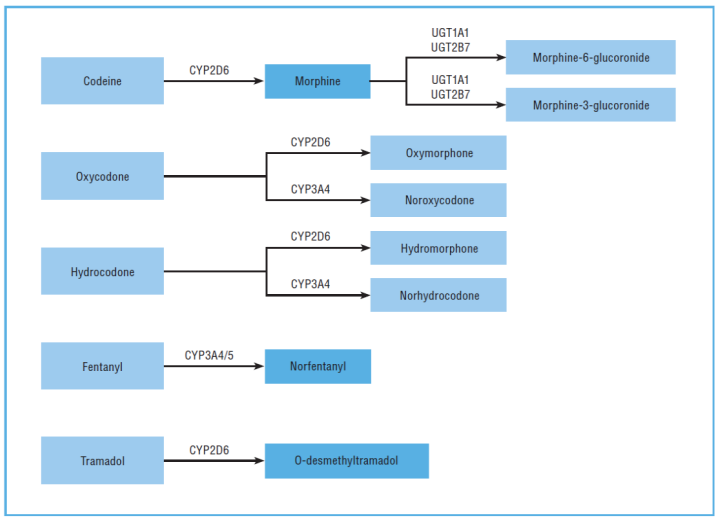

Fig. — Metabolic pathways of commonly used opioids.

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5-HT3 Receptor Antagonists

	Primary pathway	Secondary pathway
Hydrodolasetron (active metabolite of dolasetron)	CYP2D6	CYP3A
Granisetron	CYP3A	
Ondansetron	CYP3A4	CYP1A2 CYP2D6 CYP2E1
Palonosetron	CYP2D6	CYP3A CYP1A1/2
Tropisetron	CYP2D6	CYP3A4

Ho K and Tong JG. *Current Opinion in Anaesthesiology* 2006, 19:606–611

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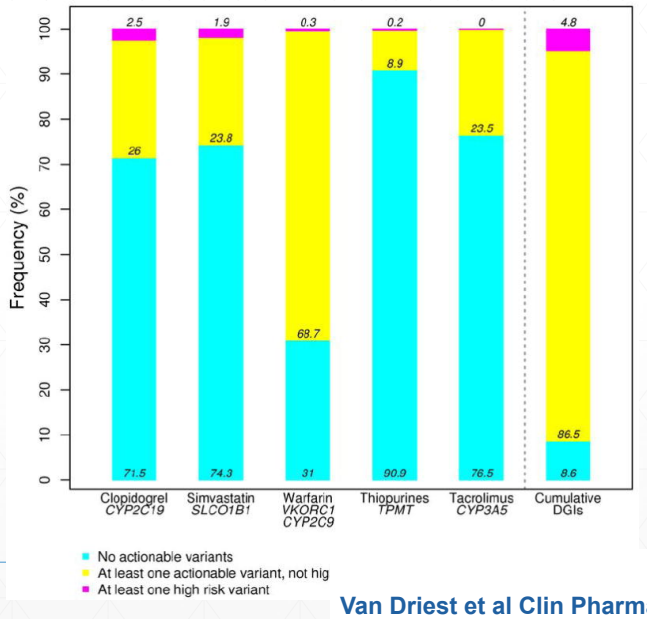
Something for most everyone



Van Driest et al Clin Pharmacol Ther 2014

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More discovery needed

- Relatively few precision medicine GWAS or NGS
- Replication data sets are difficult to obtain
- Team science is required
- Can't ignore cost

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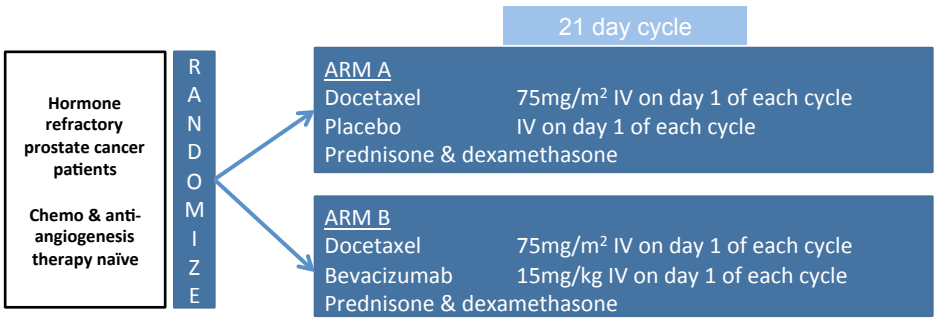
CALGB 90401

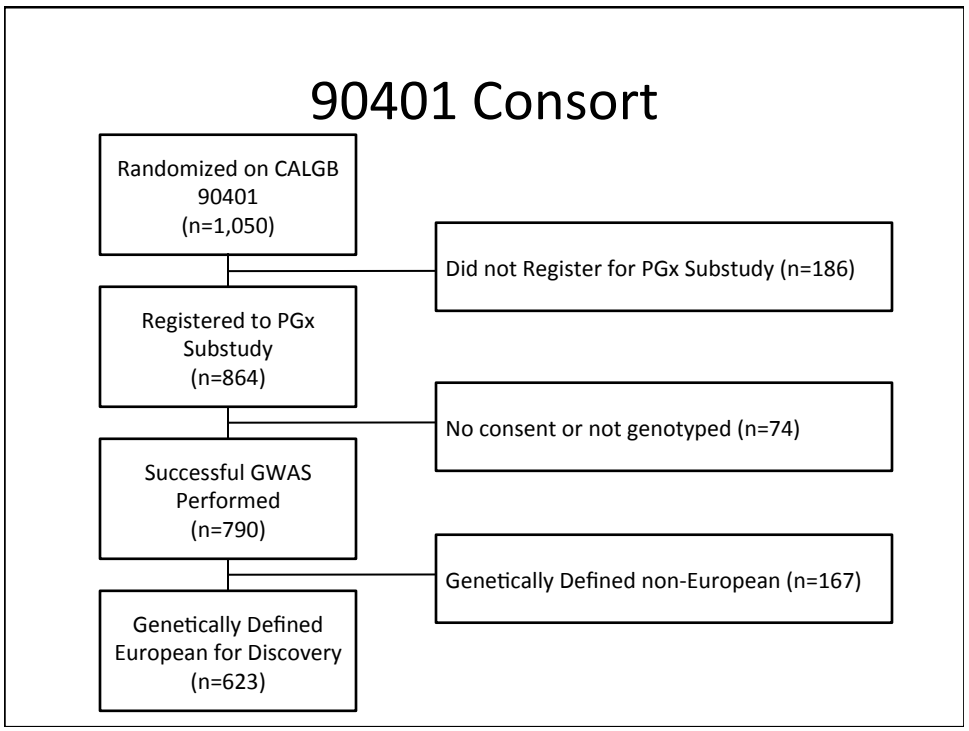
Randomized Double-Blinded Placebo-Controlled Phase III Trial Comparing Docetaxel and Prednisone with and without Bevacizumab in Men with Hormone Refractory Prostate Cancer

Dan Hertz, Jai Patel, Kouros Owzar, Susan Dorsey, Eileen Dolan, Michael Morris, Kevin Kelly, 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



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

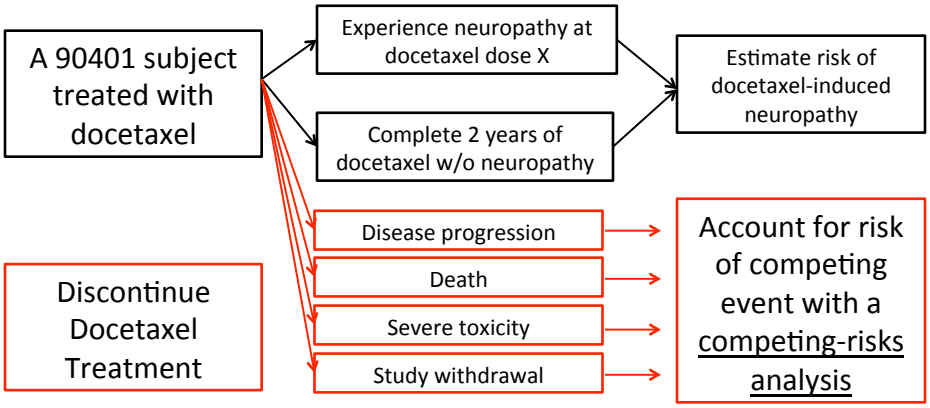
Phenotype Cleaning for Competing Risks Analysis

- 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

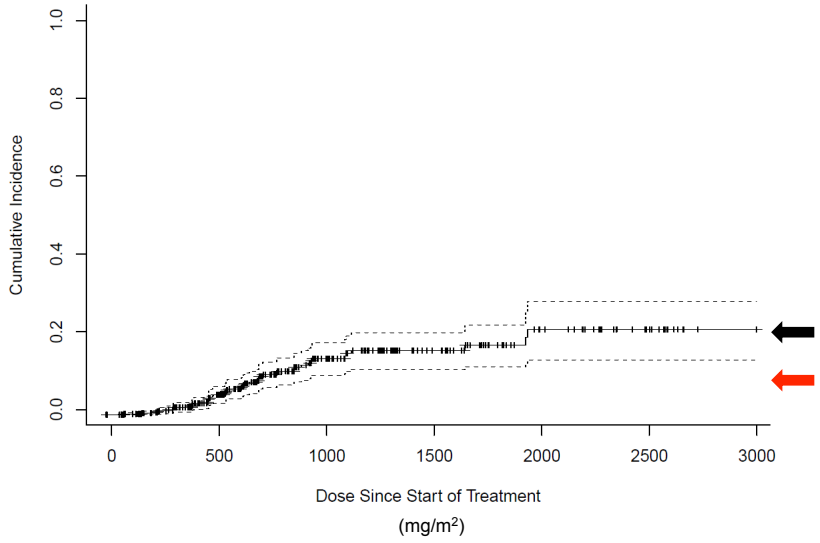
CALGB 90401 Pharmacogenomic Substudy

- 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)

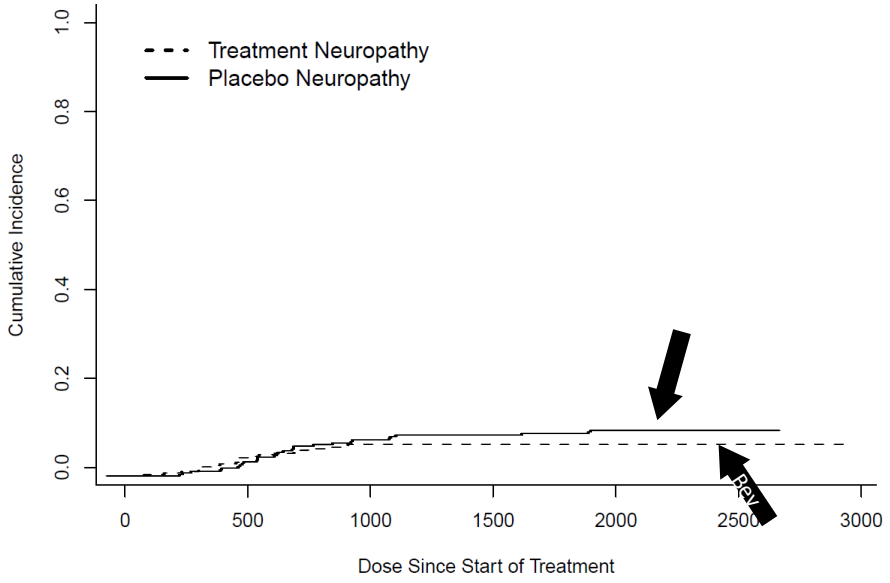
Competing Risks Analysis



Cumulative Incidence of Neuropathy

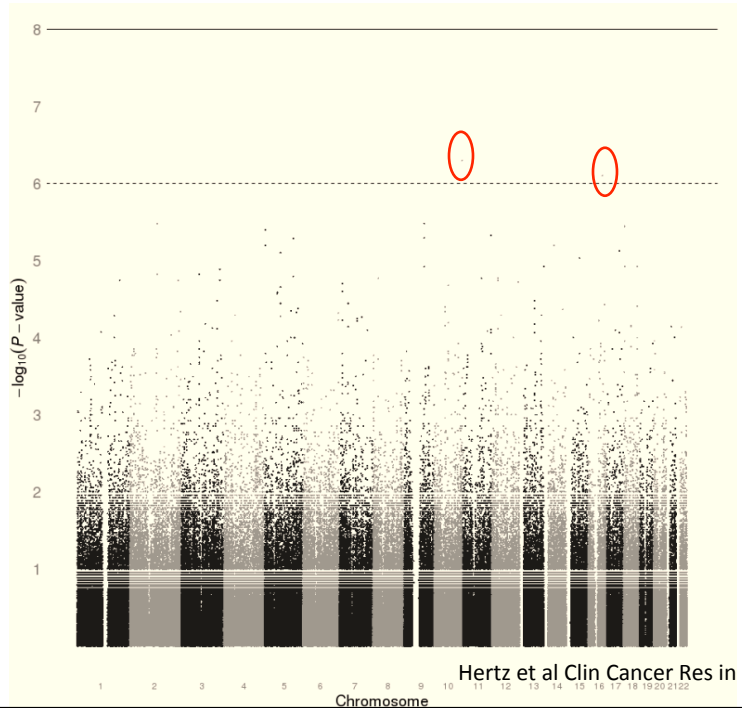


Cumulative Incidence Stratified by Arm



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



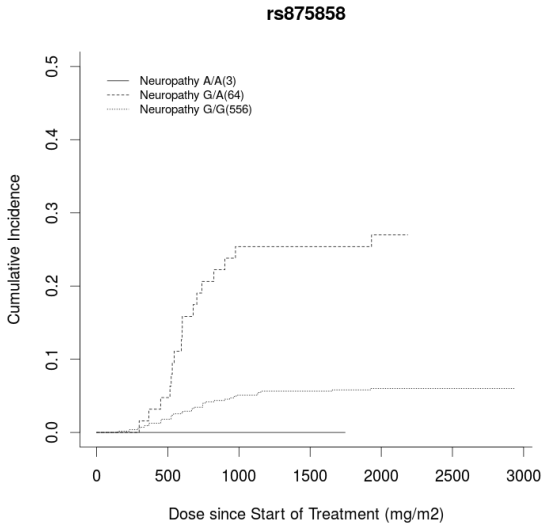
Hertz et al Clin Cancer Res in press

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)

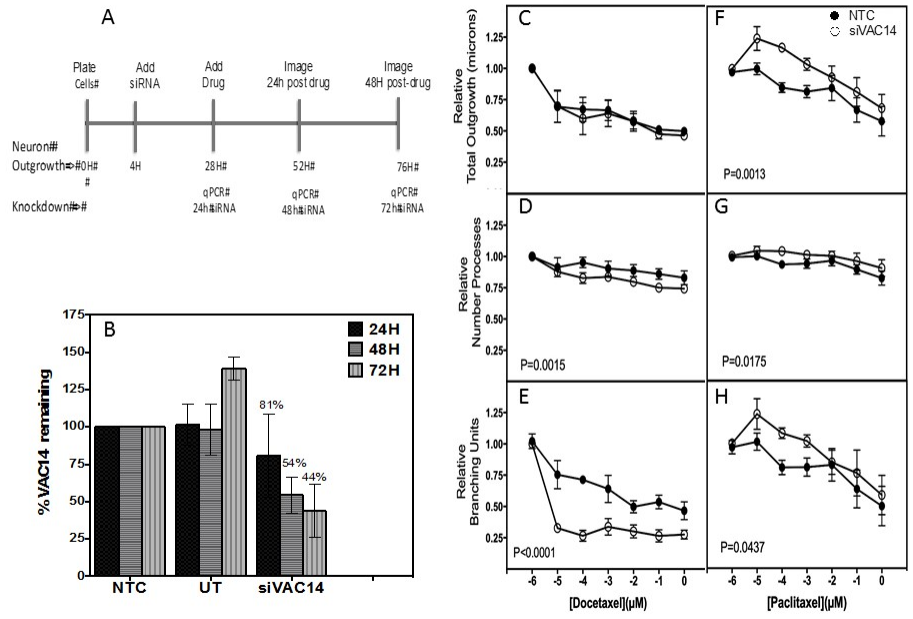
Hertz et al Clin Cancer Res in press

Assessing the VAC14 'hit'



Hertz et al Clin Cancer Res in press

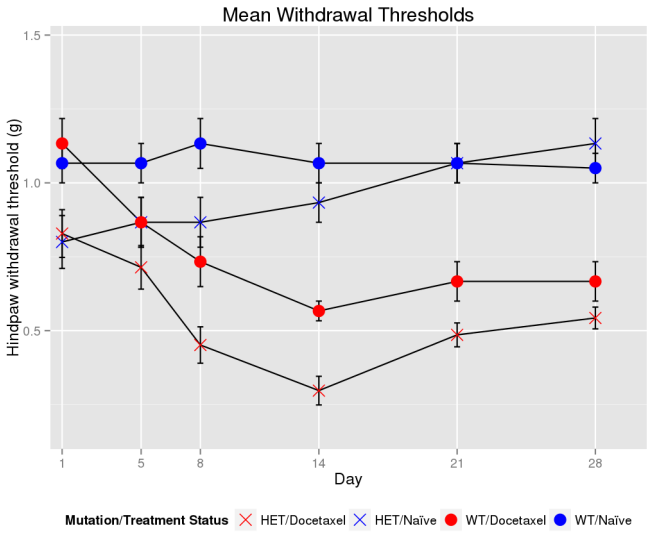
Assessing the VAC14 'hit'



Eileen Dolan iPS cells > peripheral nerve

Hertz et al Clin Cancer Res in press

Assessing the VAC14 'hit'



VAC14 +/- mice

Hertz et al Clin Cancer Res in press

More discovery needed

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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/m^2 1-hr IV, followed by Carboplatin AUC 5* IV	Paclitaxel 175 mg/m^2 3-hr IV, followed by Carboplatin AUC 5* IV
Repeat q 3 wk for up to 6 cycles	Repeat q 3 wk for up to 6 cycles

Study End Points

Primary: progression-free survival

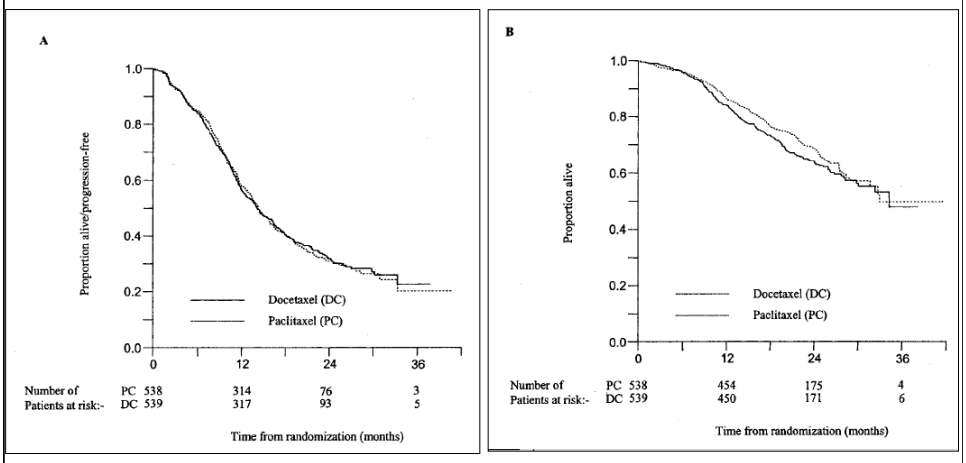
Secondary: response rate, overall survival, toxicity, QOL

CANCER RESEARCH UK

scottish gynaecological cancer trials group

Sarah Glass, Alison Motsinger-Reif, Sharon Marsh, Bob Brown, Jim Paul

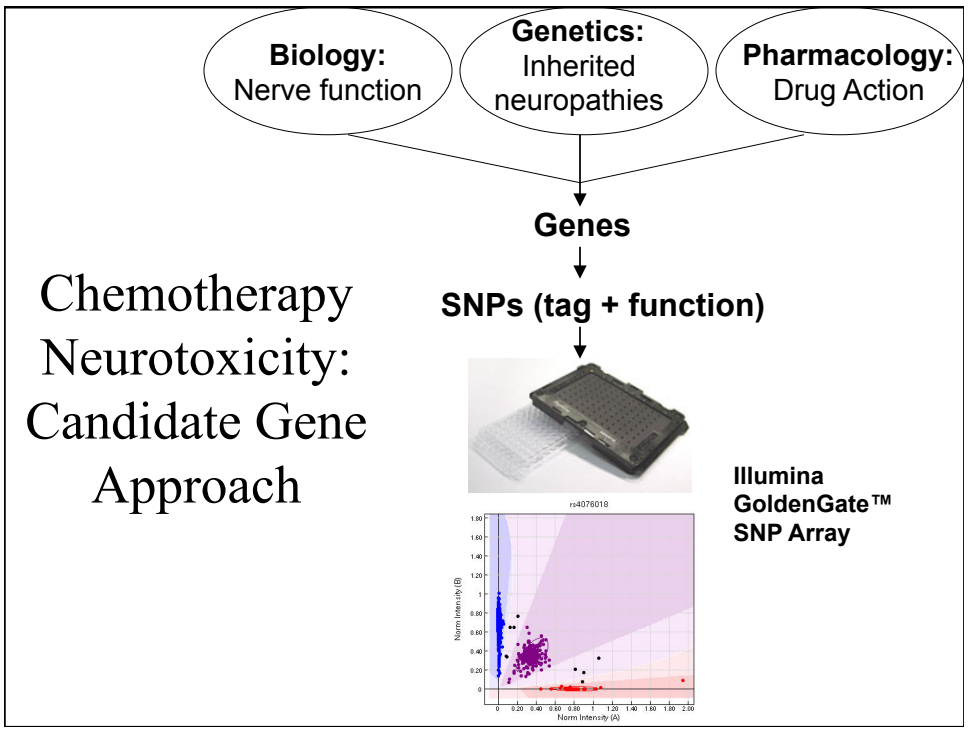
Docetaxel vs. Paclitaxel (Clinical data: SCOTROC1)



Progression-free survival

Overall survival

Vasey et al JNCI 2004



The filtering of Neuro-risk genotypes

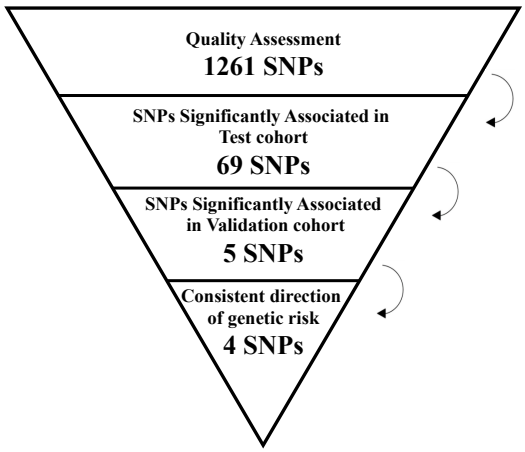


Figure 1: The workflow of the data analysis, represented by the narrowing number of SNPs at each stage of the analysis.

Table 1: SNPs significantly associated with severe neurotoxicity in the validation cohort

SNP	Gene	Base Change	Corrected P-value	Odds Ratio	95% CI	Risk Genotype
rs139887	SOX10	C->G	0.001	2.87	(1.4361, 5.7530)	CG
rs2849380	BCL2	A->G	0.013	4.08	(1.5254, 10.8975)	AA
rs544093	OPRM1	A->C	0.015	2.25	(1.2365, 4.0841)	AA
rs879207	TRPV1	A->G	0.002	2.31	(1.4467, 3.6767)	AG

Table 2: Percent PAR for each SNP and joint PAR

	rs139887	rs2849380	rs544093	rs879207	All SNPs
PAR (%)	**45.8**	**9.1**	**50.2**	**38.4**	**84.9**

Neuro-risk genotypes not associated with outcome

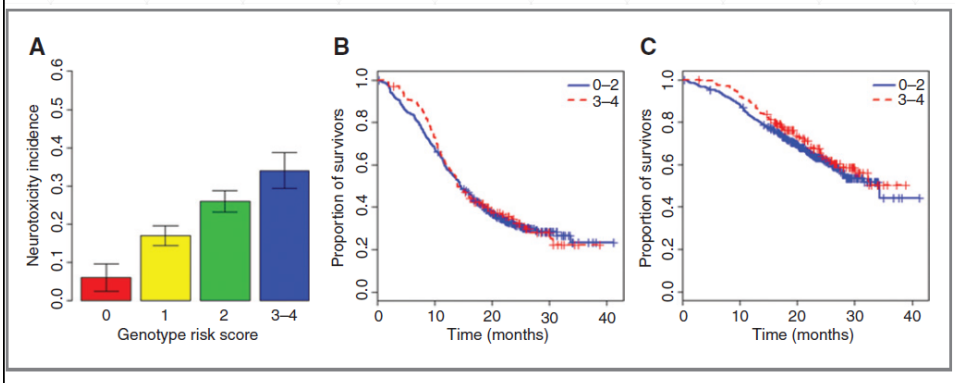


Figure 2. Relationship between genotype risk score (0–2 vs. 3–4). A, incidence of neurotoxicity (±2 SE); B, progression-free survival ($P = 0.75$); or C, overall survival ($P = 0.54$) in the full dataset.

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Peripheral Neuropathy Pharmacogenetics is peripheral neuropathy biology

Published OnlineFirst July 27, 2012; DOI: 10.1158/1078-0432.CCR-12-1590

FGD4, EPHA5, FZD3

Clinical Cancer Research

Predictive Biomarkers and Personalized Medicine

A Genome-Wide Association Study Identifies Novel Loci for Paclitaxel-Induced Sensory Peripheral Neuropathy in CALGB 40101

R. Michael Baldwin[1], Kouros Owzar[5,6], Hitoshi Zembutsu[11], Aparna Chhibber[1], Michiaki Kubo[11], Chen Jiang[6], Dorothy Watson[6], Rachel J. Edov[1], Joel Mefford[2], Howard L. McLeod[7], Paula N. Friedman[8], Clifford A. Hudis[9], Eric P. Winer[10], Eric M. Jorgenson[3,4], John S. Witte[2,4], Lawrence N. Shulman[10], Yusuke Nakamura[11], Mark J. Ratain[6], and Deanna L. Kroetz[1,4]

ARHGEF10, PRX

Sequencing of Charcot–Marie–Tooth Disease Genes in a Toxic Polyneuropathy

Andreas E. Reuter, MD,[1,4] Anna A. Kulbaeva, MD,[1] Rahul Kanwar, MSc,[1] Christopher J. Klein, MD,[2] Tracy M. Thomson, PhD,[3,4] Bai Lin, PhD[3,4]

Published OnlineFirst November 30, 2012; DOI: 10.1158/1078-0432.CCR-12-2618

RXF2

Clinical Cancer Research

Predictive Biomarkers and Personalized Medicine

Integration of Cell Line and Clinical Trial Genome-Wide Analyses Supports a Polygenic Architecture of Paclitaxel-Induced Sensory Peripheral Neuropathy

Heather E. Wheeler[1], Eric R. Gamazon[2], Claudia Wing[1], Uchenna O. Njiaju[1], Chidiamara Njoku[1], Robert Michael Baldwin[3], Kouros Owzar[4], Chen Jiang[4], Dorothy Watson[4], Ivo Shterev[4], Michiaki Kubo[5], Hitoshi Zembutsu[5], Eric P. Winer[6], Clifford A. Hudis[7], Lawrence N. Shulman[6], Yusuke Nakamura[1,5], Mark J. Ratain[1], and Deanna L. Kroetz[1] for the Cancer and Leukemia Group B; Nancy J. Cox[2], and Mary Eileen Dolan[1]

The Pharmacogenomics Journal (2014), 1 –

www.nature.com/tpj

Axon outgrowth genes

ORIGINAL ARTICLE

Polygenic inheritance of paclitaxel-induced sensory peripheral neuropathy driven by axon outgrowth gene sets in CALGB 40101 (Alliance)

A Chhibber[1,2], J Mefford[2,3], EA Stahl[4,5,14], SA Pendergrass[6], RM Baldwin[1,2], K Owzar[7], M Li[1,2], EP Winer[8], CA Hudis[9], H Zembutsu[10], M Kubo[11], Y Nakamura[10,11,12], HL McLeod[13], MJ Ratain[12], LN Shulman[8], MD Ritchie[6], RM Plenge[4,5], JS Witte[2,3] and DL Kroetz[1,2]

More discovery needed

- Relatively few precision medicine GWAS or NGS
- Replication data sets are difficult to obtain
- Team science is required
- Can't ignore cost

VORICONAZOLE AND CYP2C19: CLINICAL IMPLICATIONS

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

TOTAL CANCER CARE™

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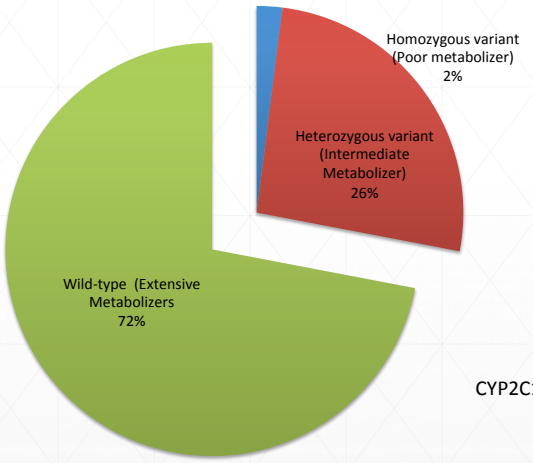
28% of patients with "high-risk" *CYP2C19* genotypes that would require a dose modification or a different medication



CYP2C19 *2, *3, *4, *8

Dr Gillian Bell, Moffitt Cancer Center

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

Neil Mason

Moffitt Cancer Center 2016

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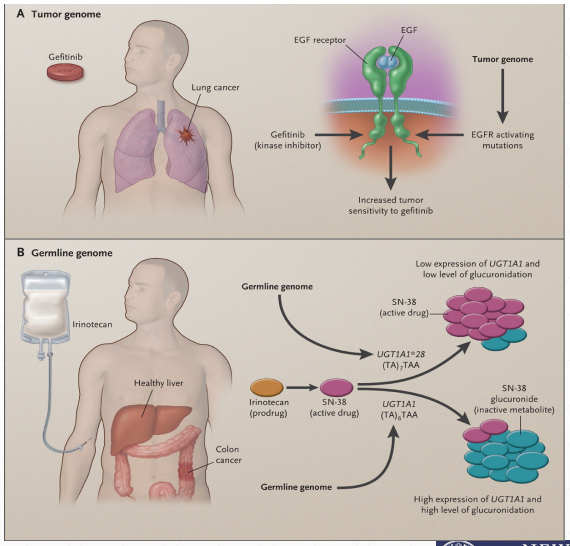
Cancer Pharmacogenomics and Tumor and Germline Genomes.



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

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Practical choices

- Selection from amongst 'equals'
- Clinical trial options, beyond non-specific or anatomical
- 'acceptable'* levels of toxicity

*to the patient, not prescriber

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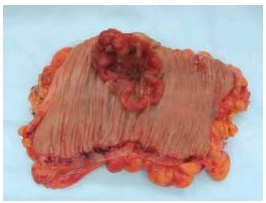
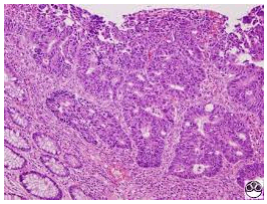
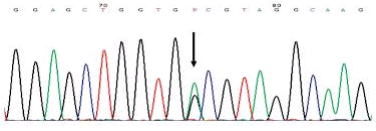
Cancer Care is changing fast: the opportunity and the threat







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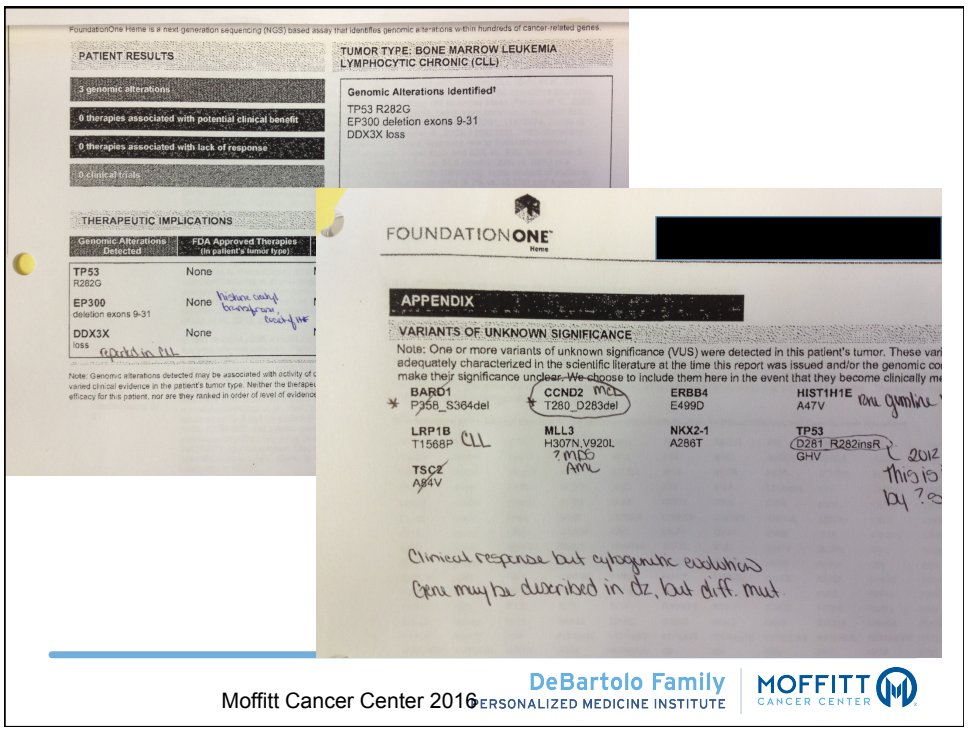
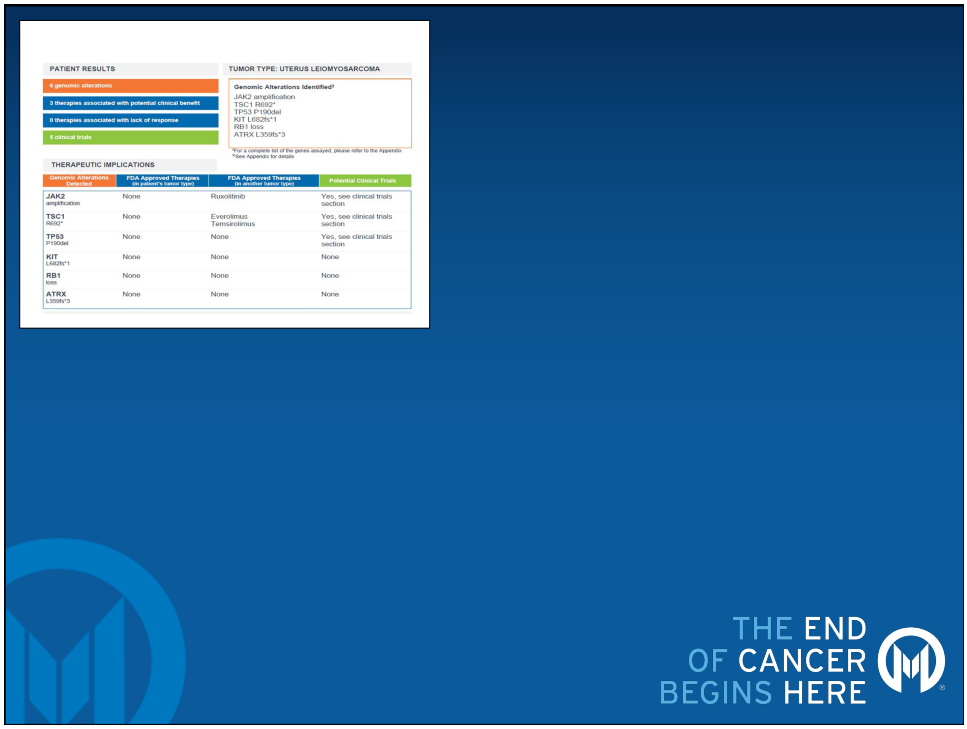
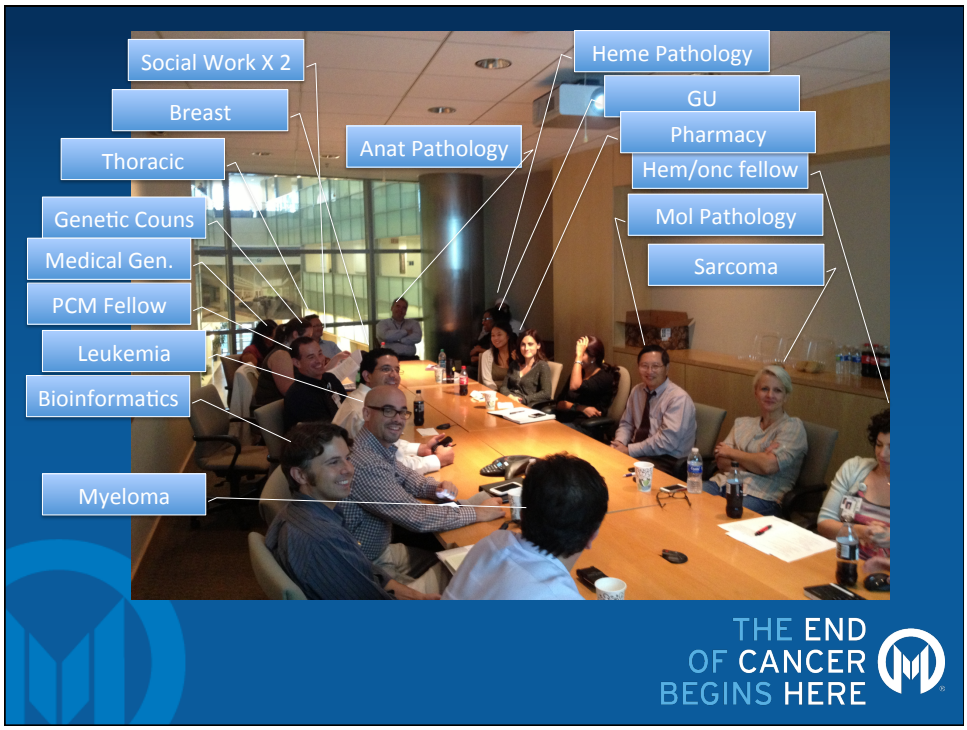


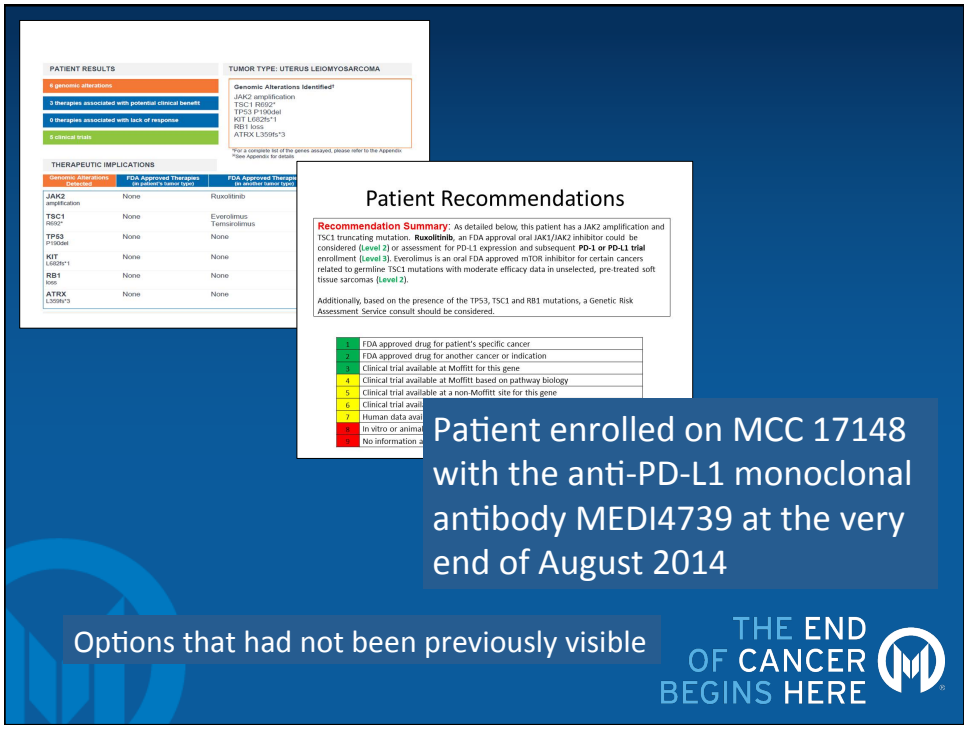
Recent example

55 yo female, Stage IV leiomyosarcoma spread to the lungs
Previous therapy in addition to surgical excision includes:
*Gemcitabine and docetaxel x 3 months then
*Doxorubicin and ifosfamide x 4 months then
*Dacarbazine and gemcitabine x 3 months then
*Pazopanib x 3 months but is no longer working
No clear next steps and patient is fit and wants to keep trying

THE END OF CANCER BEGINS HERE

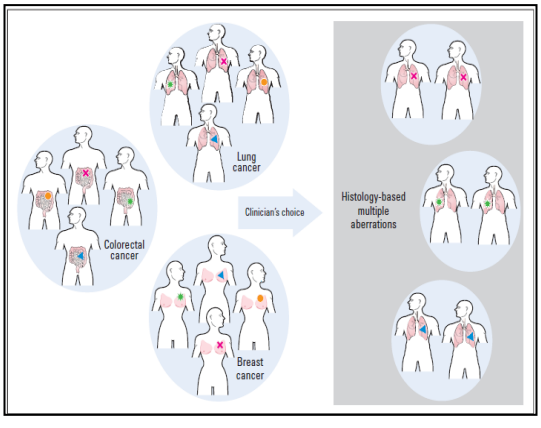

PATIENT RESULTS
6 genomic alterations
3 therapies associated with potential clinical benefit
0 therapies associated with lack of response
5 clinical trials
TUMOR TYPE: UTERUS LEIOMYOSARCOMA
Genomic Alterations Identified†
JAK2 amplification
TSC1 R692*
TP53 P190del
KIT L682fs*1
RB1 loss
ATRX L359fs*3
†For a complete list of the genes assayed, please refer to the Appendix
*See Appendix for details
THERAPEUTIC IMPLICATIONS
Genomic Alterations Detected
FDA Approved Therapies (in patient's tumor type)
FDA Approved Therapies (in another tumor type)
Potential Clinical Trials
JAK2 amplification
None
Ruxolitinib
Yes, see clinical trials section
TSC1 R692*
None
Everolimus
Temsirolimus
Yes, see clinical trials section
TP53 P190del
None
None
Yes, see clinical trials section
KIT L682fs*1
None
None
None
RB1 loss
None
None
None
ATRX L359fs*3
None
None
None
THE END OF CANCER BEGINS HERE


Social Work X 2
Breast
Thoracic
Genetic Couns
Medical Gen.
PCM Fellow
Leukemia
Bioinformatics
Myeloma
Anat Pathology
Heme Pathology
GU
Pharmacy
Hem/onc fellow
Mol Pathology
Sarcoma
THE END OF CANCER BEGINS HERE



HISTOLOGY-BASED CLINICAL TRIAL DESIGN TO EVALUATE MULTIPLE MOLECULAR ABERRATIONS

"Umbrella Trial"



- Variety of targeted agents
- Specific molecular profiles
- Single tumor type

J Clin Oncol. 2013 May 20;31(15):1834-41

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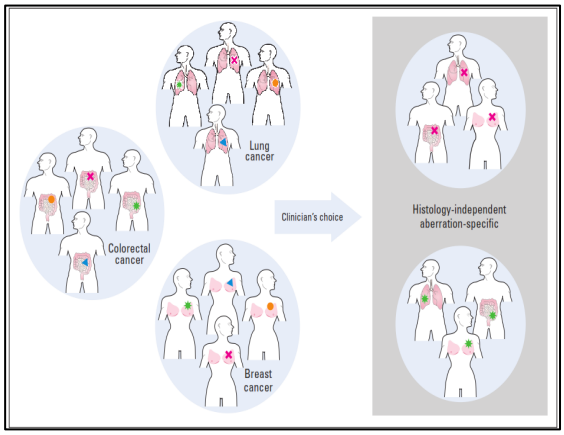
HISTOLOGY-INDEPENDENT, ABERRATION-SPECIFIC CLINICAL TRIAL DESIGN

"Basket Trial"



Eligibility is based on molecular aberrations rather than anatomical origin of a cancer

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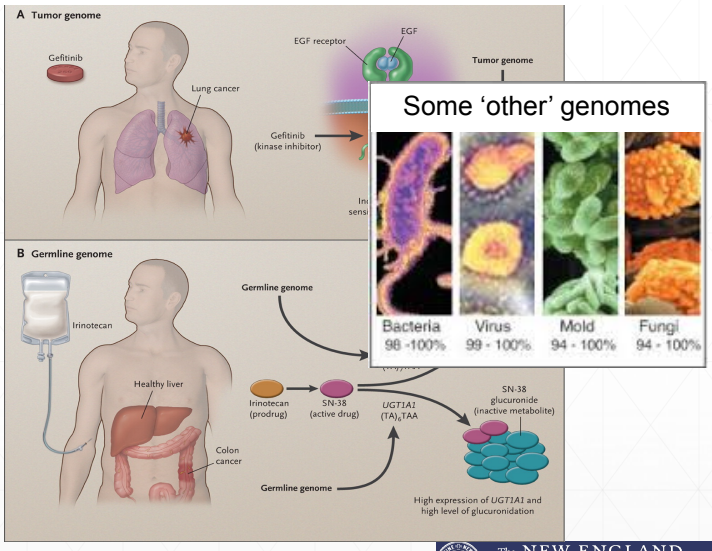
J Clin Oncol. 2013 May 20;31(15):1834-41

Cancer Pharmacogenomics and Tumor and Germline Genomes.



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Melting pot or carton of eggs?

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Number of Participants and Approvals Captured with Racial Data

	1997	2004	2009	2012	TOTAL
CNS	6,902 (5)	6,847 (6)	5,189 (3)	3,810 (3)	**22,748 (17)**
CV	28,031 (6)	5,360 (3)	35,786 (9)	19,702 (4)	**88,879 (22)**
Oncology	3,353 (5)	2,773 (7)	1,310 (5)	6,883 (12)	**14,319 (29)**
TOTAL	**38,286 (16)**	**14,980 (16)**	**42,285 (17)**	**30,395 (19)**	**127,175 (68)**

Knepper et al, unpublished

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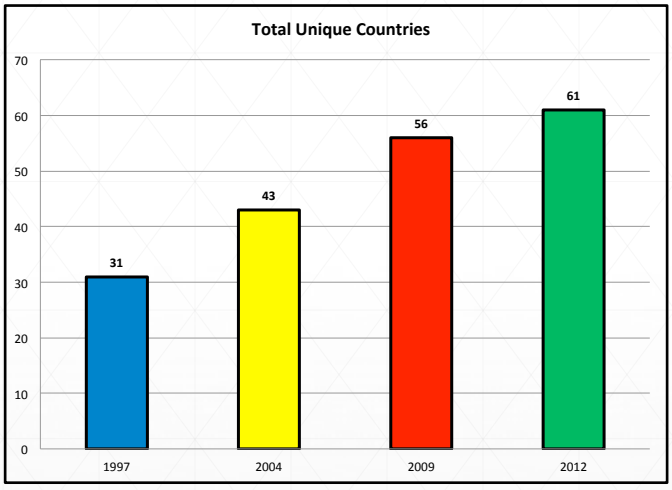
How has the number of countries hosting investigator sites changed?



Knepper et al, unpublished

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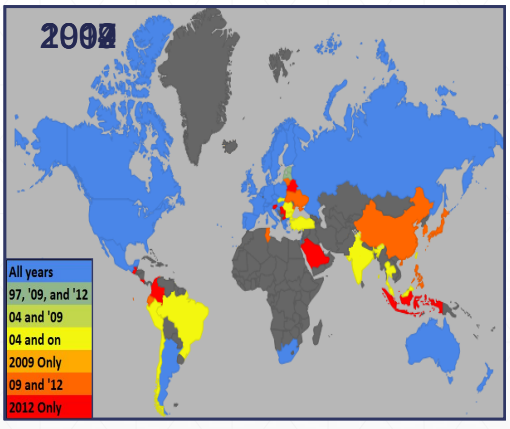
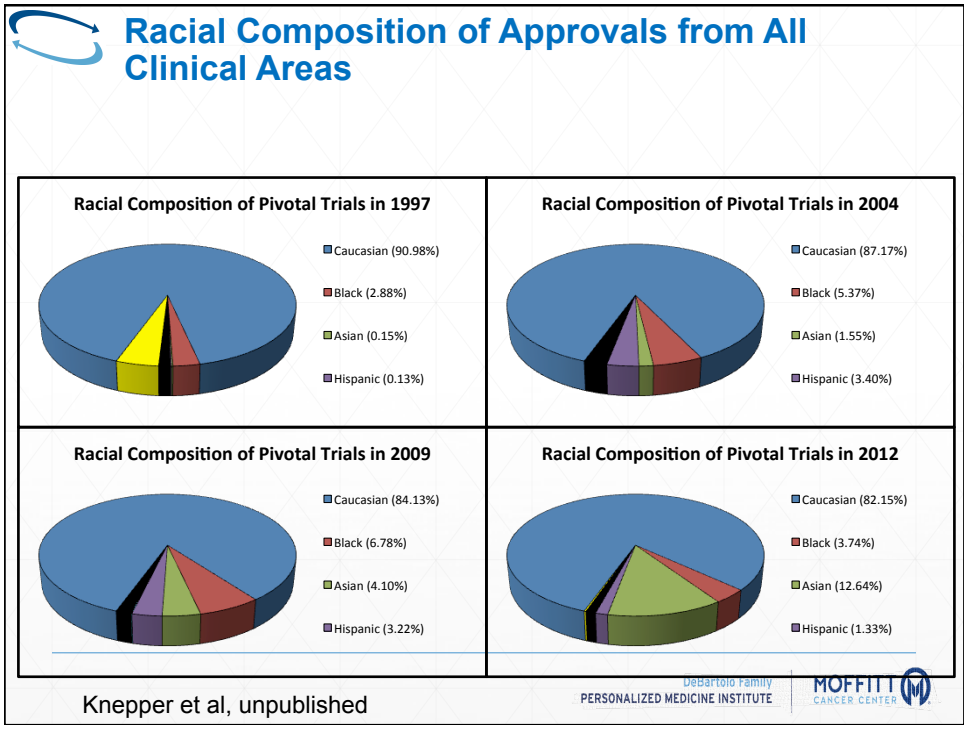
World Maps

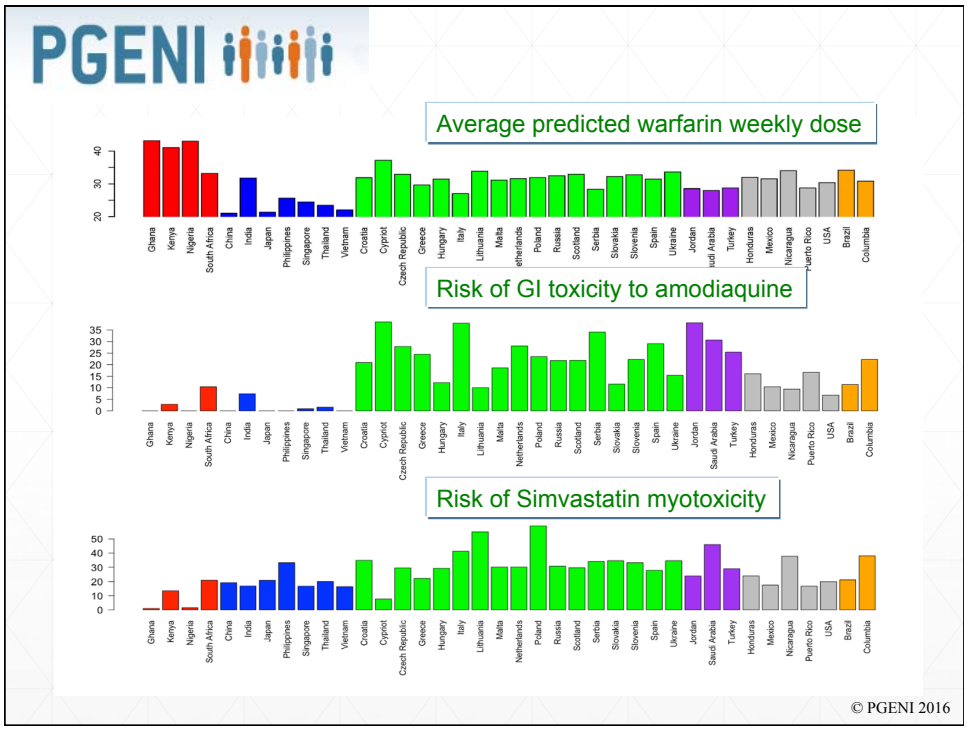


	All Years	All but 2004	2004 and 2009	2004 and on	2009 only	2009 and 2012	2012 only
1	Argentina	Estonia	Venezuela	Brazil	Georgia	China	Belarus
2	Australia	Latvia		Bulgaria	Iceland	Ecuador	Colombia
3	Austria			Chile	Morocco	Japan	Costa Rica
4	Belgium			Hong Kong*	Pakistan	Lithuania	Guatemala
5	Canada			India		Philippines	Indonesia
6	Croatia			Malaysia		South Korea	Macedonia
7	Czech Republic			Peru		Tunisia	Saudi Arabia
8	Denmark			Romania		Ukraine	Serbia
9	Finland			Singapore			Slovenia
10	France			Slovakia			
11	Germany			Taiwan*			
12	Greece			Thailand			
13	Hungary			Turkey			
14	Ireland						
15	Israel						
16	Italy						

Knepper et al, unpublished



Knepper et al, unpublished



PGENI

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ESTABLISHED IN 1812 FEBRUARY 19, 2009 VOL. 360 NO. 8

Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

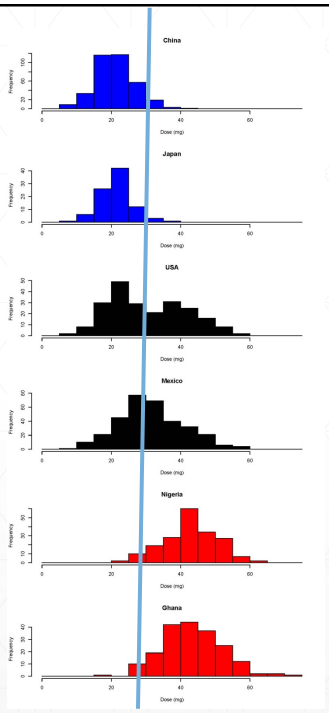
The International Warfarin Pharmacogenetics Consortium*

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



Mexico

Practical choices

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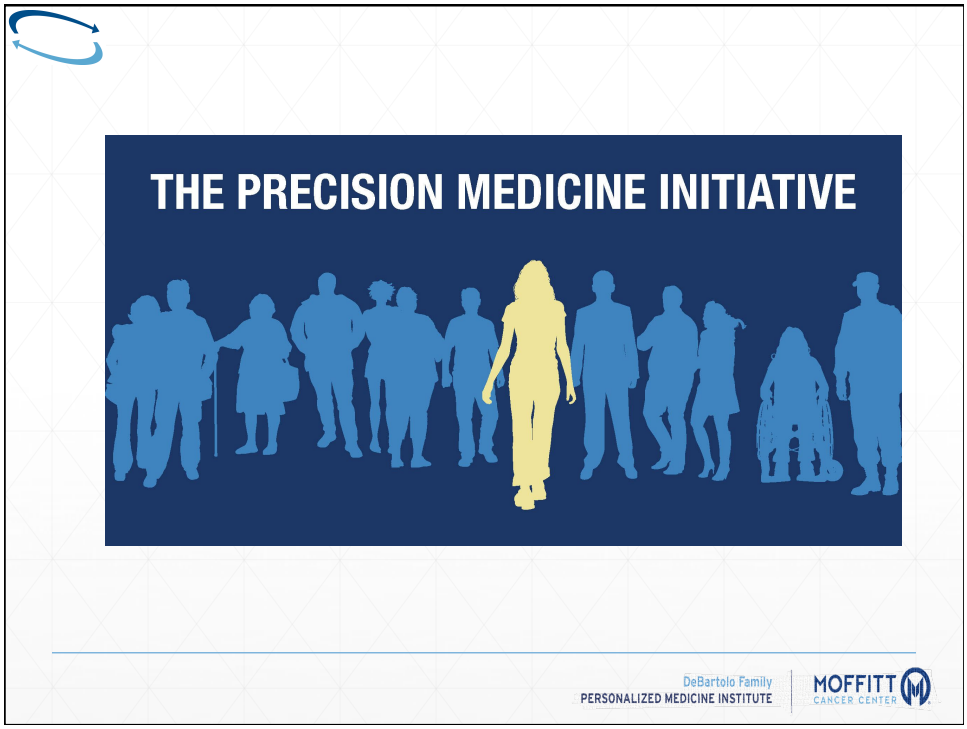
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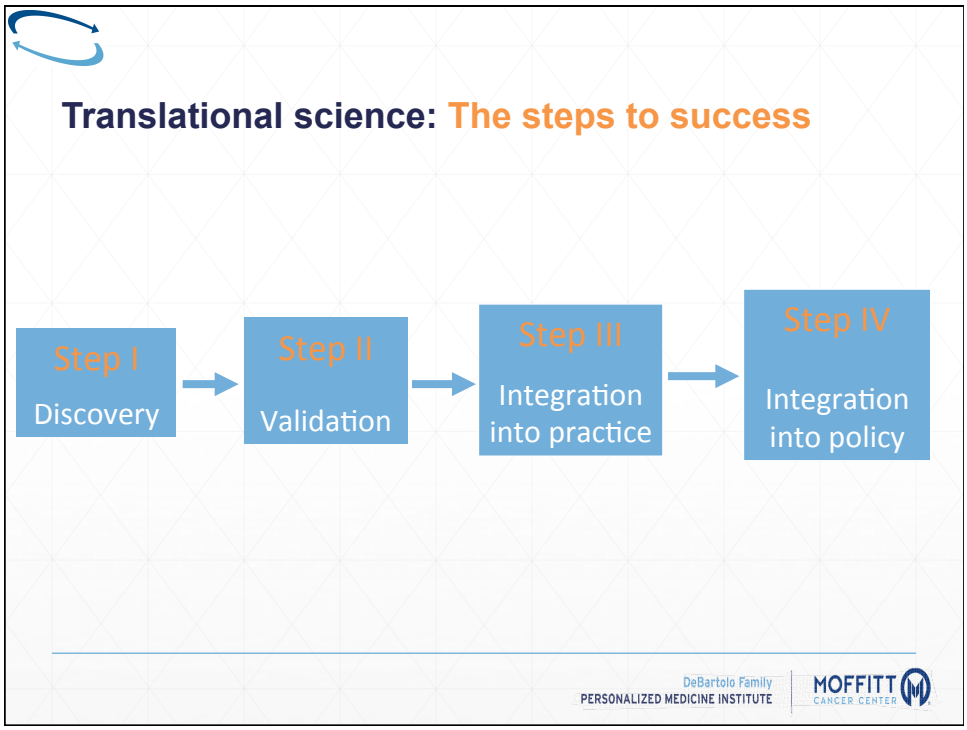
Translational science: The steps to success
Step I
Discovery
Step II
Validation
Step III
Integration into practice
Step IV
Integration into policy
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