Global Implementation of Genomic Medicine

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Impact of Pharmaceuticals

Major public health benefit

- Drugs improve quality of life and prolong life span
- Assess to medications as a human right – WHO

Global Impact

- Efforts of the WHO to ensure global population has access to medicines. Essential Medicines List

United States

- United States 47.9% used at least one prescription drug during the past month (2005-2008)
- Pharmaceuticals are approved for marketing and sale by the Food and Drug Administration

Why focus on drugs?

- Adverse drug events are a leading cause of death in USA, UK, and most countries
  - Adverse drug events are heavily litigated
  - Many adverse drug events are predictable
- Modern treatments are expensive
- Opportunities to improve ‘value’

Medications for all?

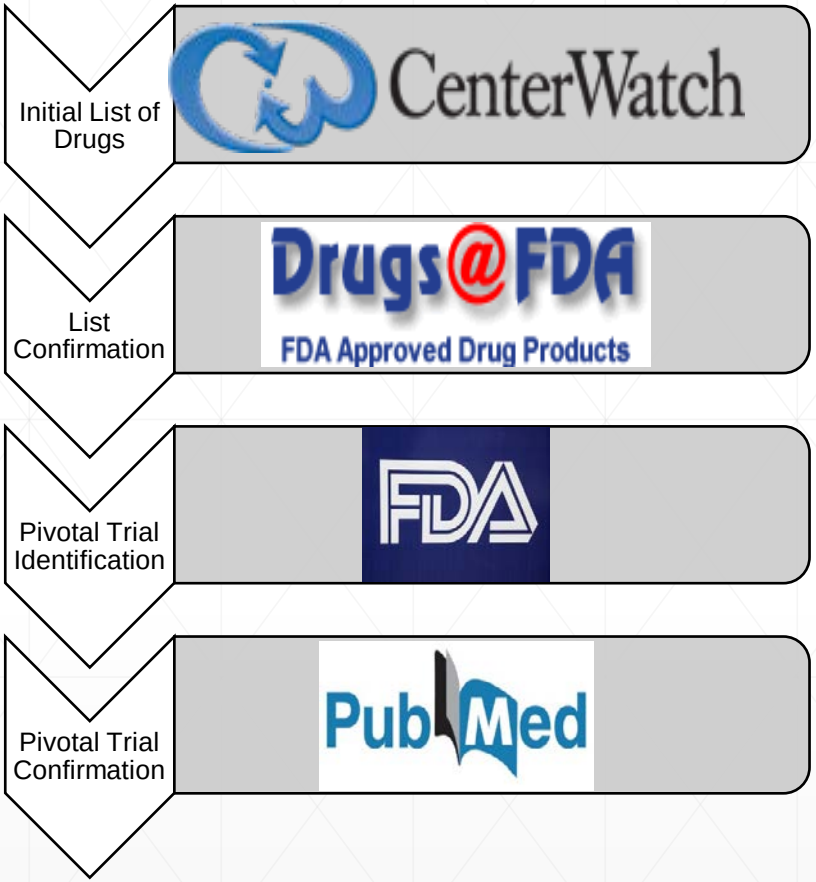
- Where are drugs developed?
- Who participates in the pivotal studies?
- Safety and dosing well characterized?

Data Sources

Clinical Areas

- Cardiovascular Disease
- Central Nervous System
- Oncology

1997 → 2004 → 2009 → 2012



Included Approvals and Pivotal Trials

Approvals

Included

- Identified clinical area
- Identified year of interest
- NDA Chemical Types
  - 1 – NME
  - 4 – New Combination
  - BLA

Excluded

- Does not meet criteria above
  - New ingredient, new dosage form, new formulation, new indication, drug already marketed, OTC switch

Pivotal Trials

Included

- Identified as pivotal per FDA label and/or medical review
- Initial approved NDA

Excluded

- Does not meet criteria above

NDAs Included

1997

CNS
- pramipexole
- quetiapine
- ropinirole
- tiagabine
- zolmitriptan

CV
- arbutamine
- cerivastatin
- clopidogrel
- eprosartan
- fenoldopam
- irbesartan +/- HCTZ

Oncology
- dolasetron
- IL-11
- letrozole
- rituximab
- samarium SM-153
- toremifene

2004

CNS
- apomorphine
- duloxetine
- eszopiclone
- natalizumab
- pregabilin
- zicotinamide

CV
- amlodipine/ atorvastatin
- ezetimibe/ simvastatin
- iloprost
- omega-3-acid

Oncology
- azacitidine
- bevacizumab
- cetuximab
- clofaribine
- erlotinib
- palifermin
- pemetrexed

2009

CNS
- asenapine
- iloperidone
- milnaciprin

CV
- aliskiren/valsartan
- amlodipine/valsartan/HCTZ
- dronedarone
- ecallantide
- pitavastatin
- prasugrel
- recombinant human antithrombin
- talvaptan
- telmisartan/ amlodipine

Oncology
- everolimus
- ofatumumab
- pazopanib
- pralatrexate
- romidepsin

2012

CNS
- florbetapir
- perampanel
- teriflunomide

CV
- apixaban
- ethyl eicosapentaenoic acid
- lomitapide
- peginesatide

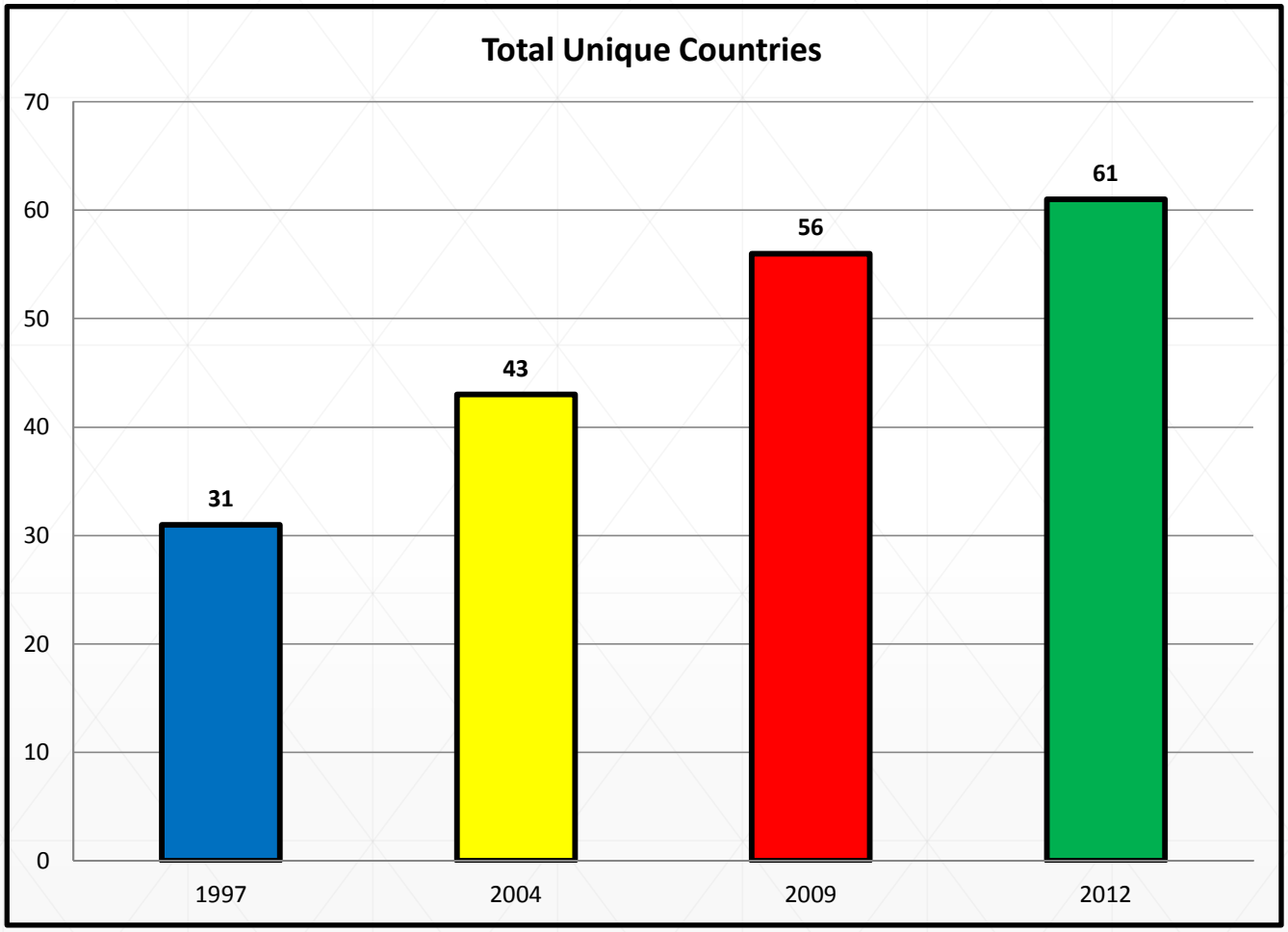
Oncology
- aflibercept
- axitinib
- bosutinib
- cabozantinib
- carfilzomib
- enzalutamide
- omacetaxine mepesuccinate
- pertuzumab
- ponatinib
- regorafenib
- TBO-filgrastim
- vismodegib

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

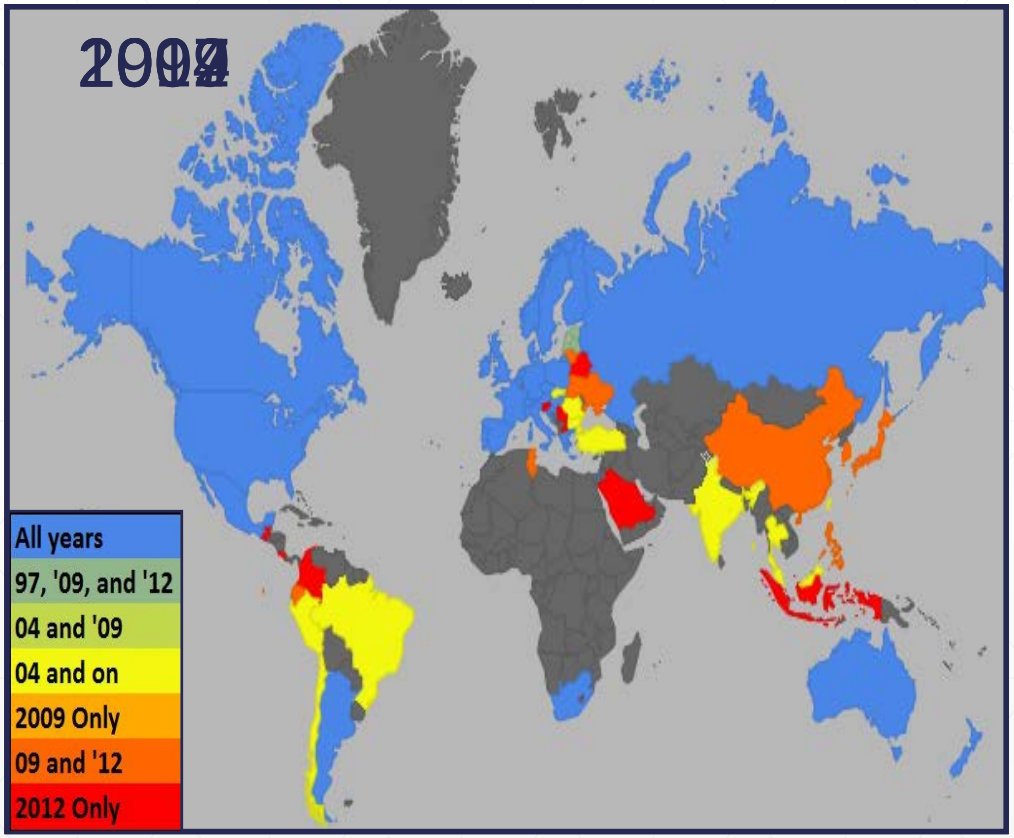
How has the number of countries hosting investigator sites changed?



n = 17 n = 17 n = 17 n = 19

Knepper et al, unpublished

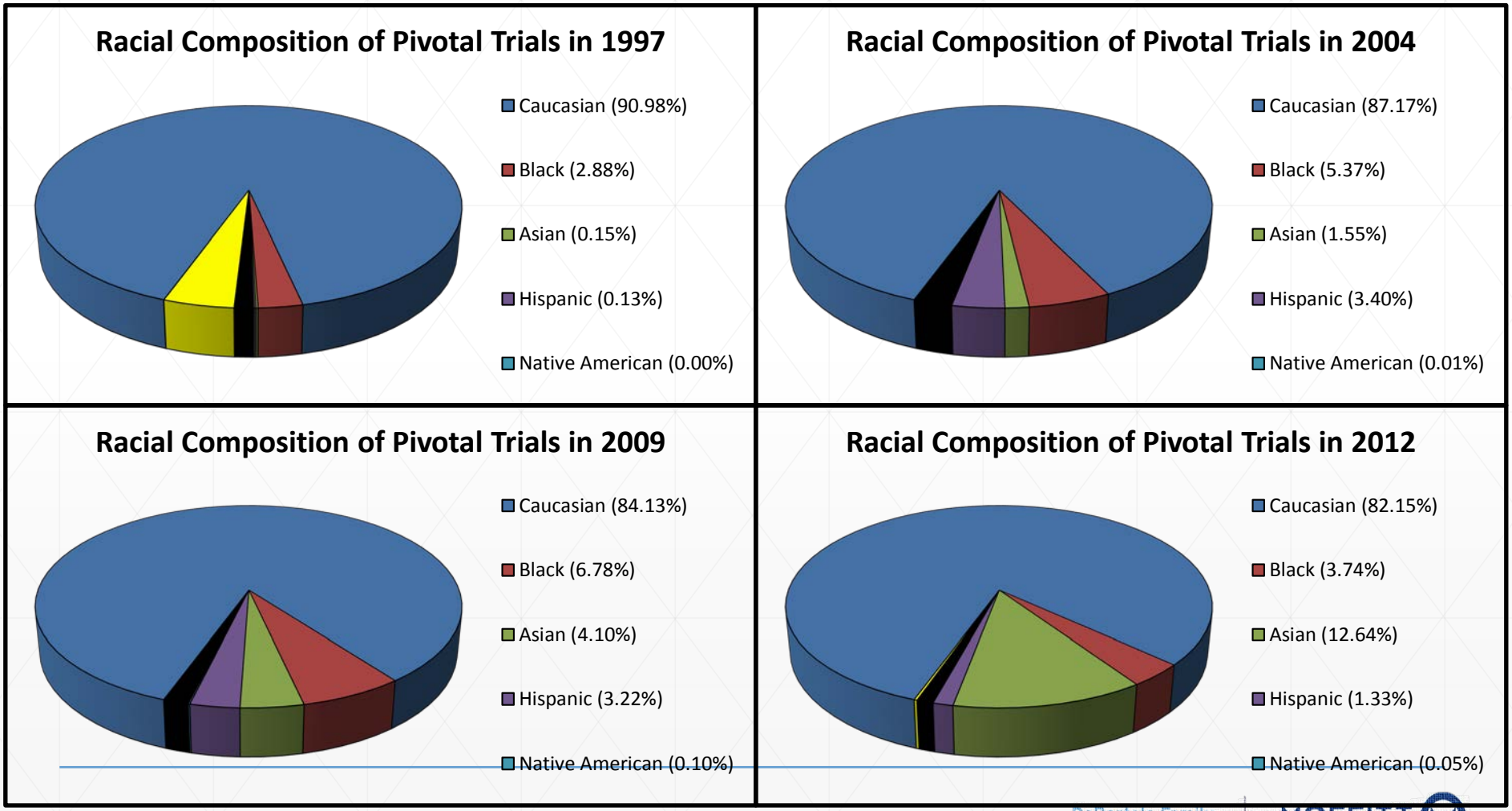
World Maps



	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

Racial Composition of Approvals from All Clinical Areas



Knepper et al, unpublished

Notable Trends in Racial Data

- Despite a downward trend, **Caucasians remain overrepresented** on pivotal trials in the clinical areas of CNS, CV, and oncology
- Representation of **black** patients on pivotal trials **remains stagnant** and underrepresented relative to the US population and global population
- **Asian patients** on pivotal trials **emerged** from obscurity in 1997 to over 10% of the pivotal trial population in 2012

Summary

Race

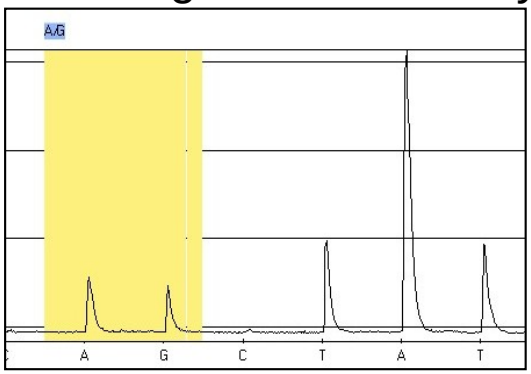
- **Racial and ethnic differences** impact the applicability of foreign clinical data to domestic populations
- Racial composition of pivotal trials is **not well aligned** with the racial composition of the United States as:
  - Caucasians are overrepresented
  - Blacks are underrepresented
  - Asians are emerging and recently exceeded their share of the population
- Increased participants of Asian ancestry on trials in correlated with increased participation of Asian countries on pivotal trials

Globalization

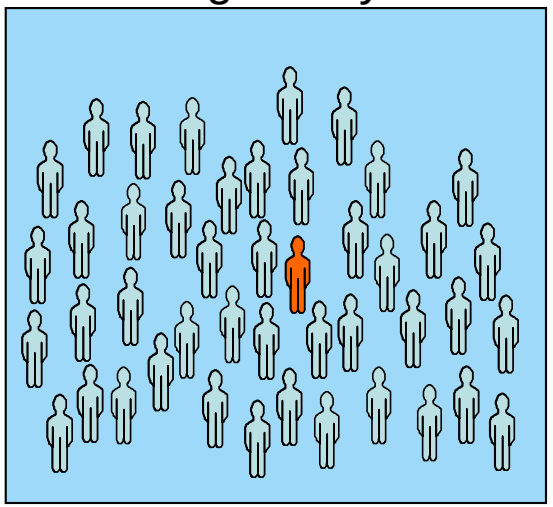
- The **number of countries** hosting investigator sites and the number of countries involved per approval on average has **increased consistently**
- **Developing regions** in Asia, Eastern Europe, and South America are becoming **increasingly involved** in pivotal trials

Pharmacogenomics: what is your intent?

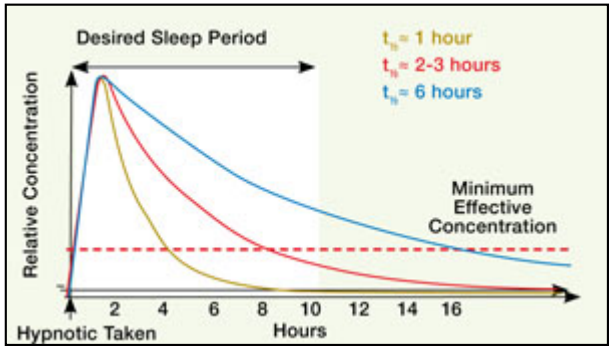
Human genetic discovery



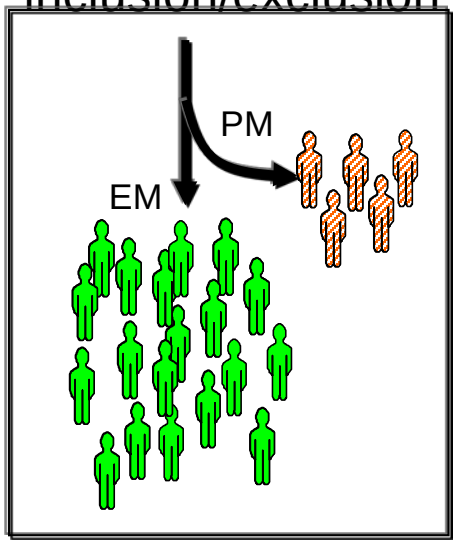
Drug Safety



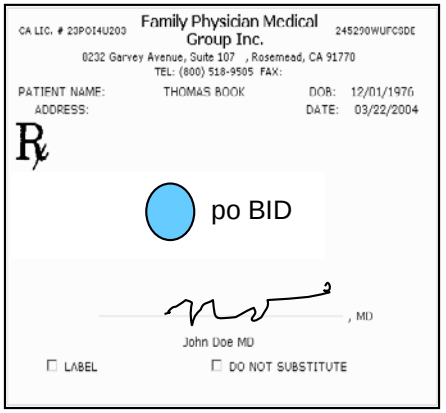
Explain variation in phenotype



Clinical trial inclusion/exclusion



Clinical practice



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)

- What about the rest of the world?

- 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

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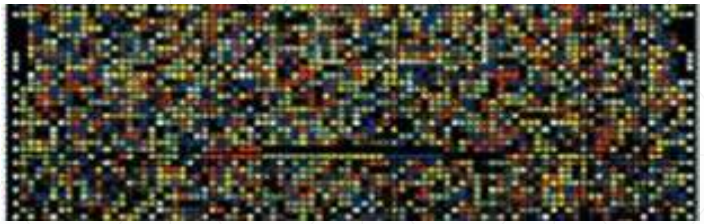
Selection of drugs and genes

- 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

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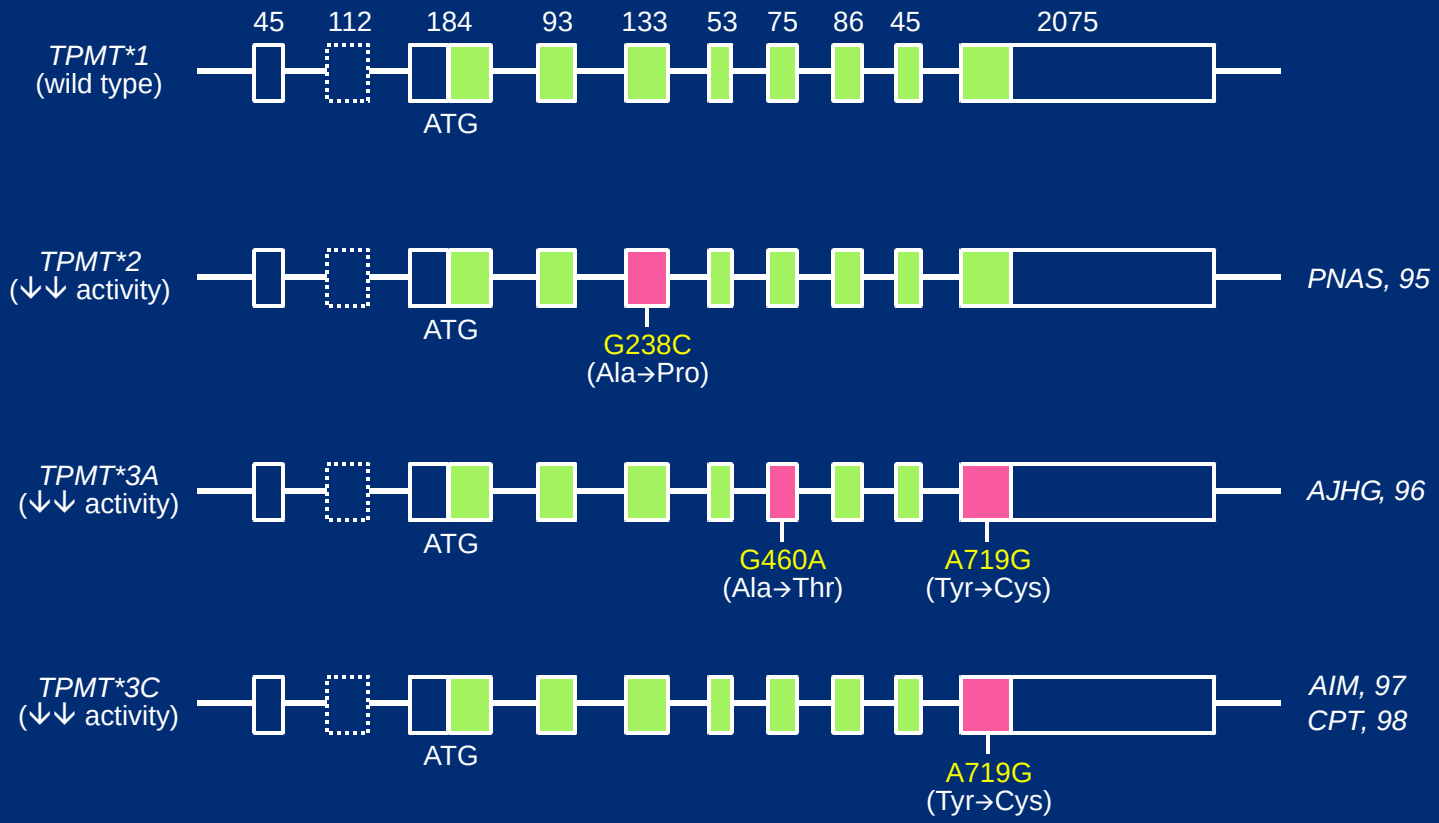
Pharmacogenomic examples-2017

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib, afitinib
- 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
- CYP2D6-5-HT3 receptor antagonists, antidepressants, ADHD drugs, and codeine derivatives*

Human TPMT Gene and Mutant Alleles



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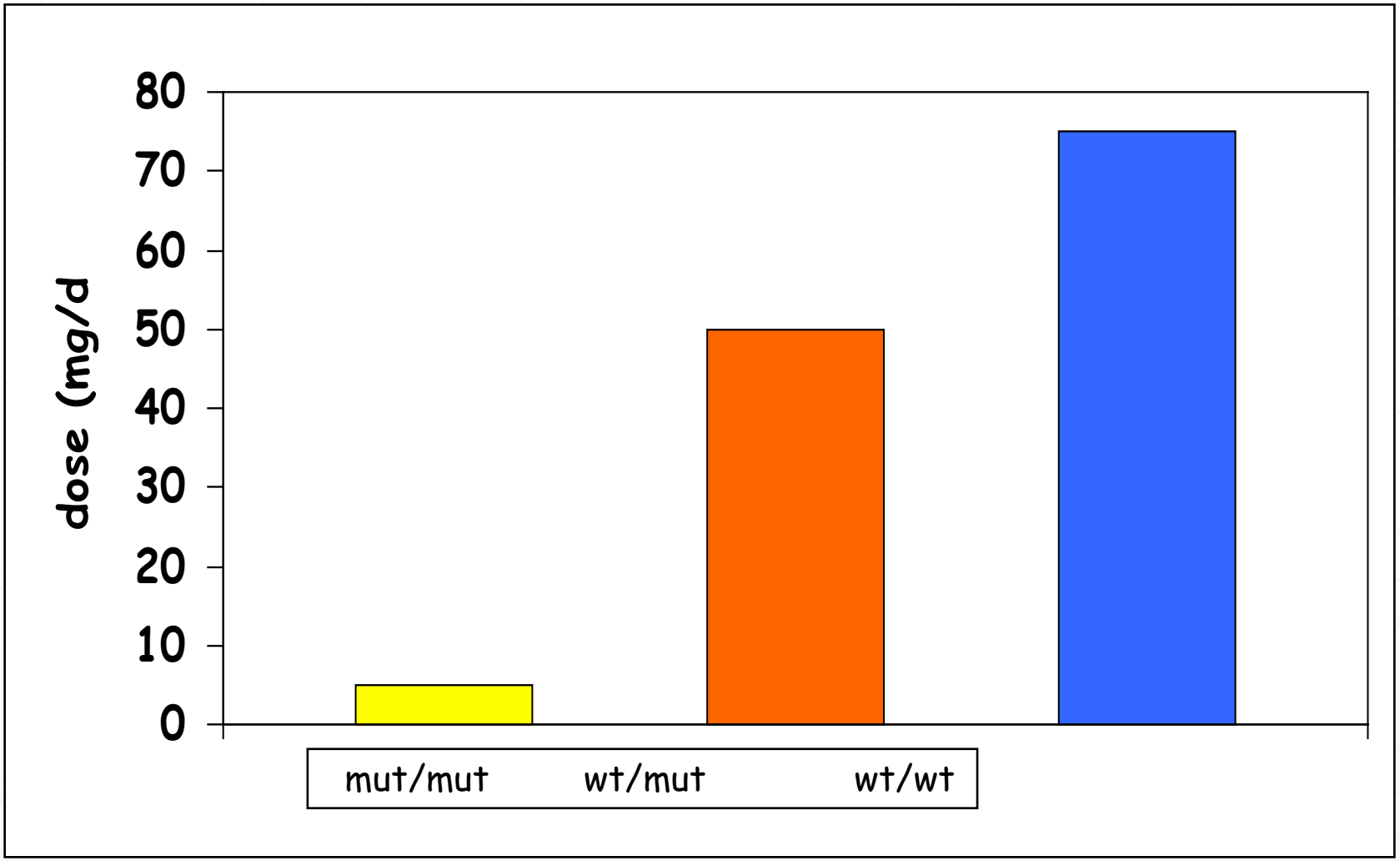
Optimal dose for each patient differs by TPMT genotype



Relling et al JNCI, 1999

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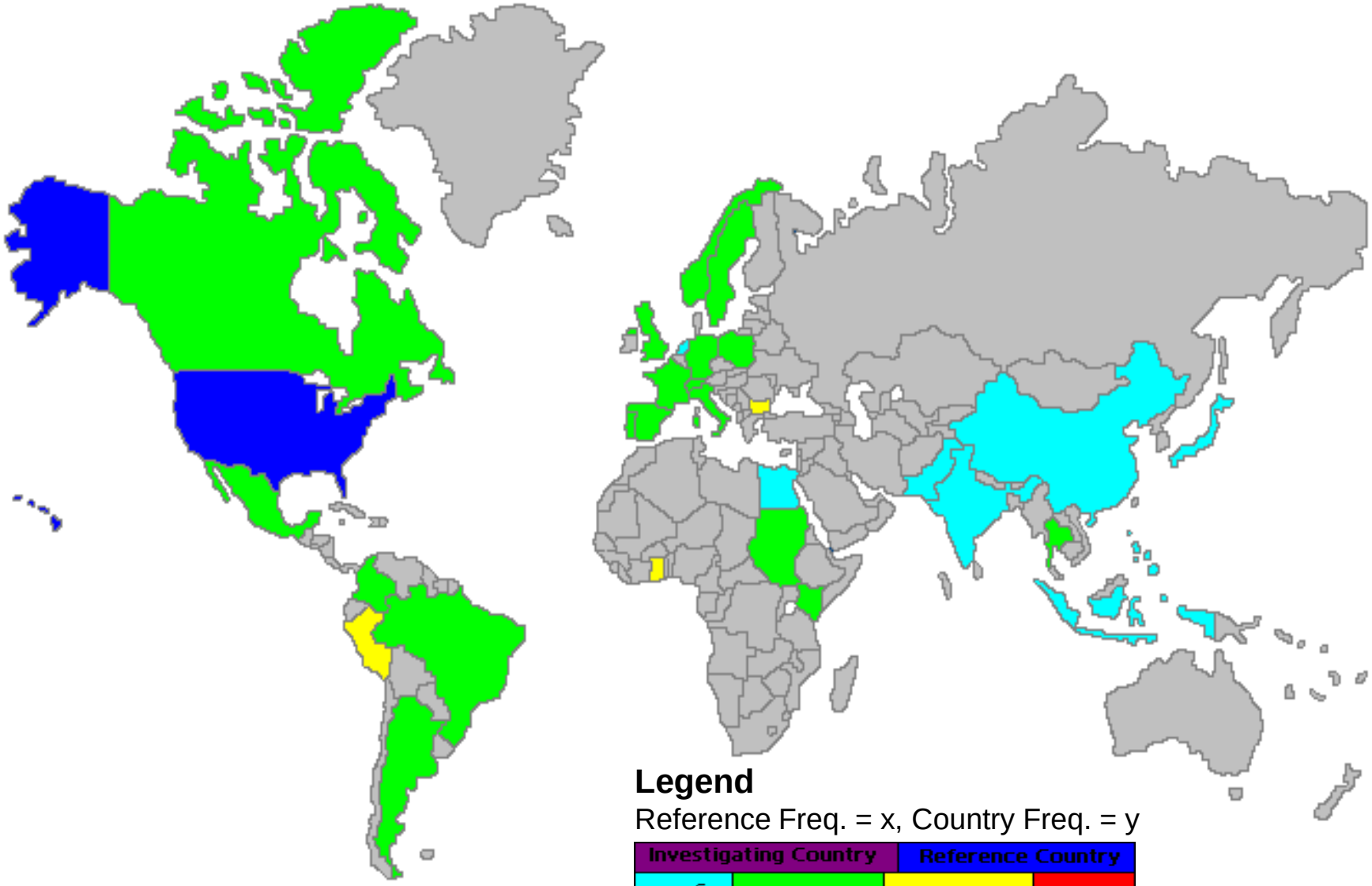

Legend

Reference Freq. = x, Country Freq. = y

Investigating Country		Reference Country	
y < .5x	.5x < y < 2x	2x < y < 4x	y > 4x

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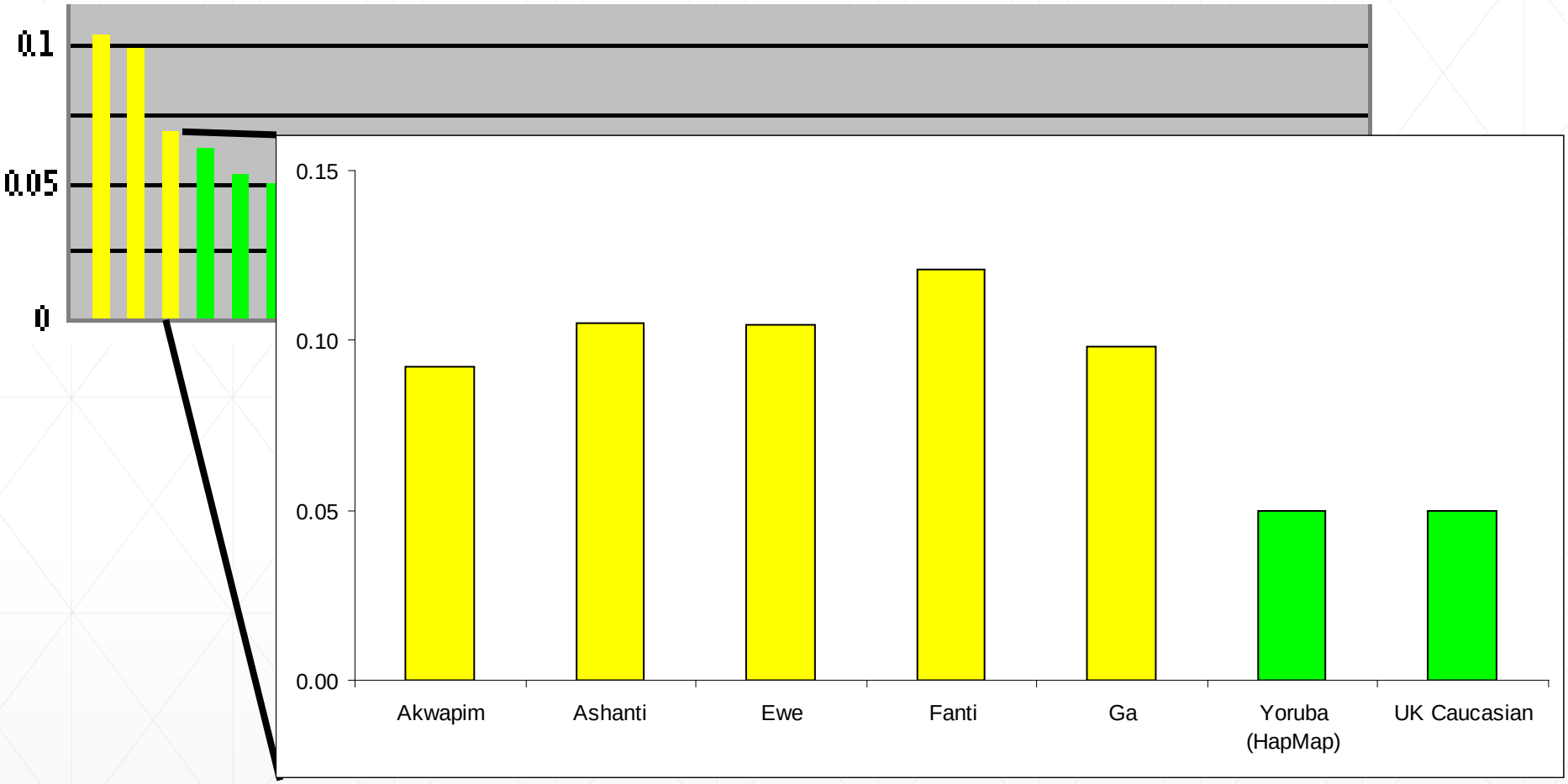

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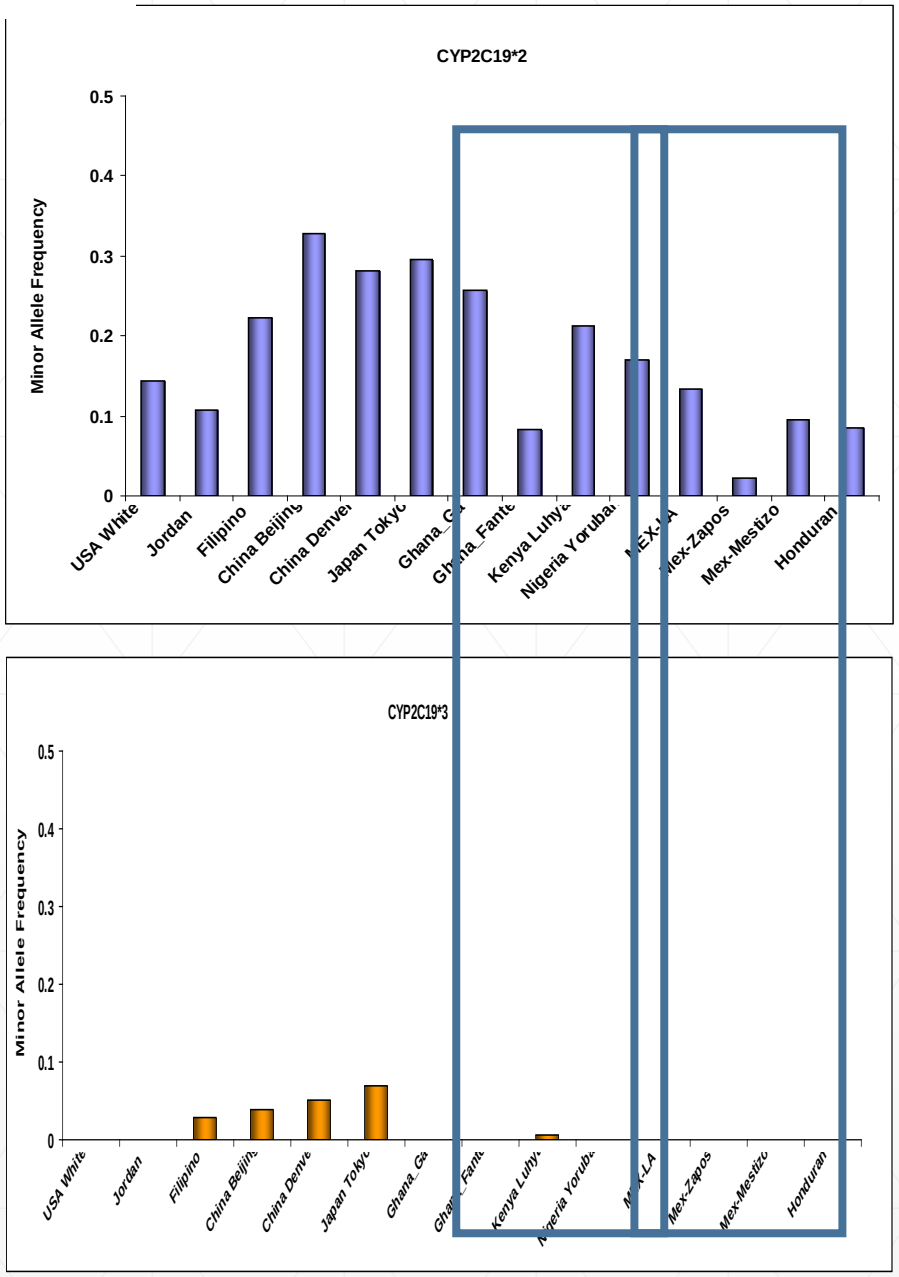
CYP2C19 allele frequency



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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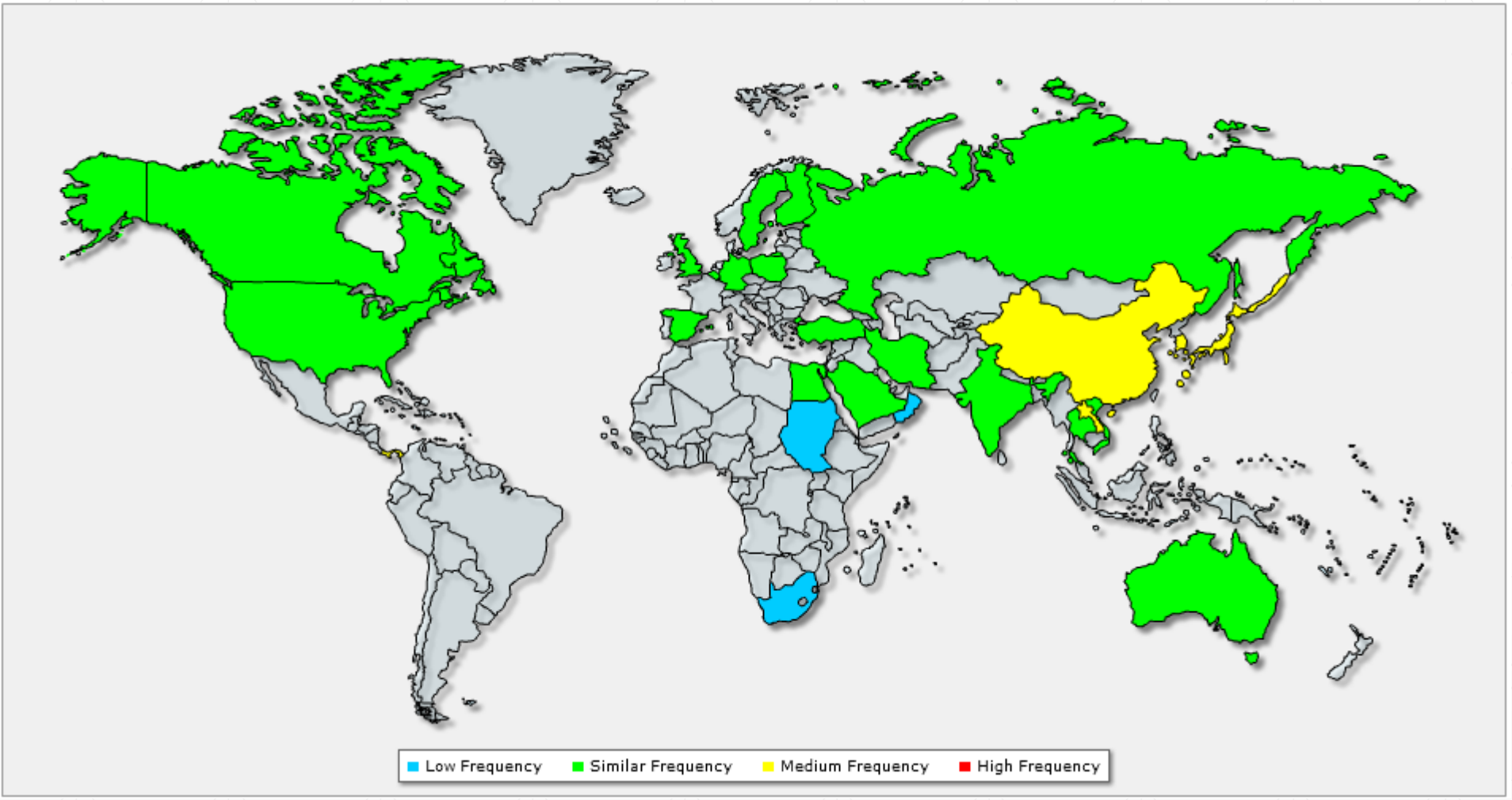
NAT2 *4



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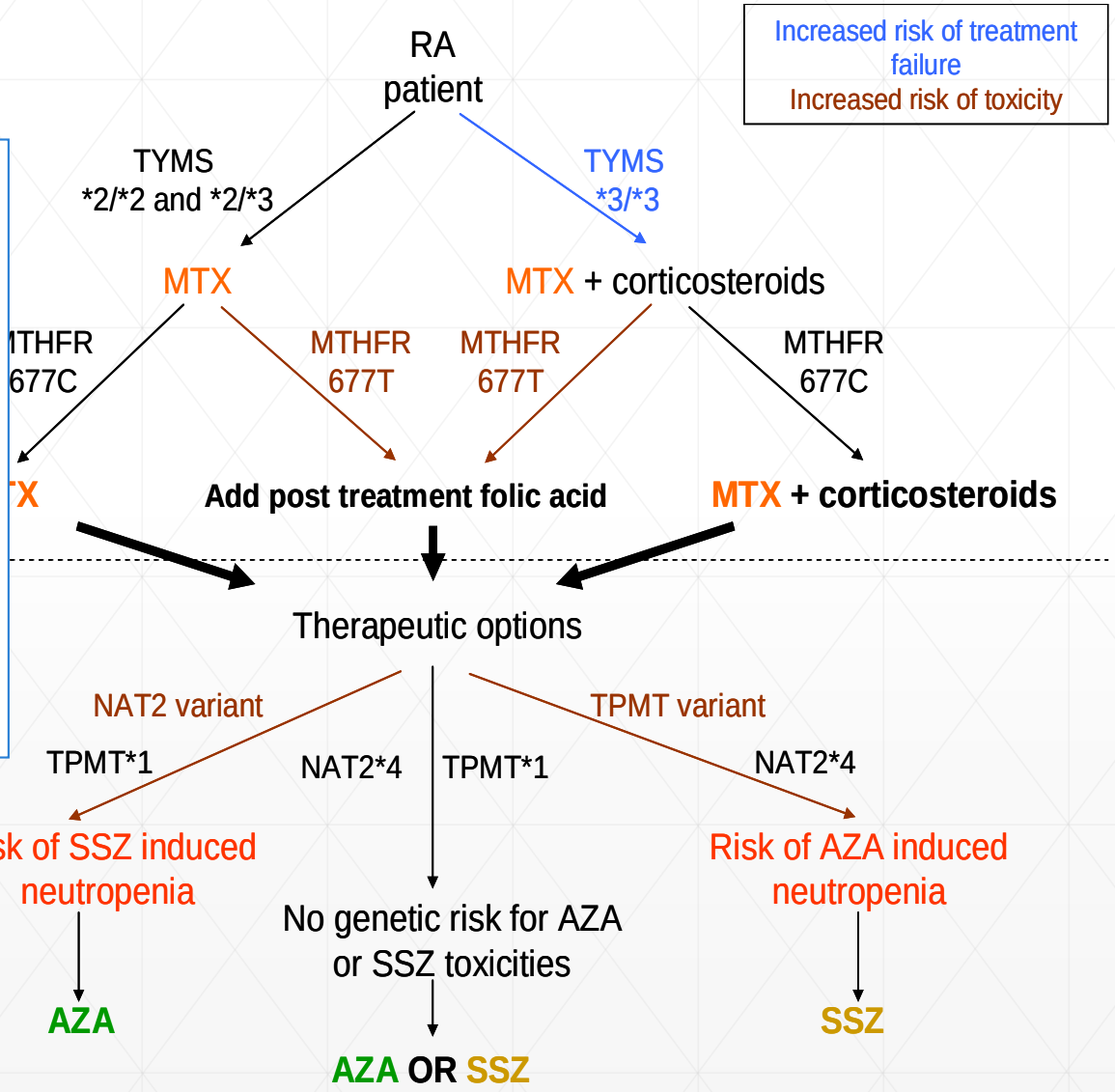
Rheumatoid arthritis example

First Line Therapy
Methotrexate (MTX)

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



Rheumatoid arthritis example

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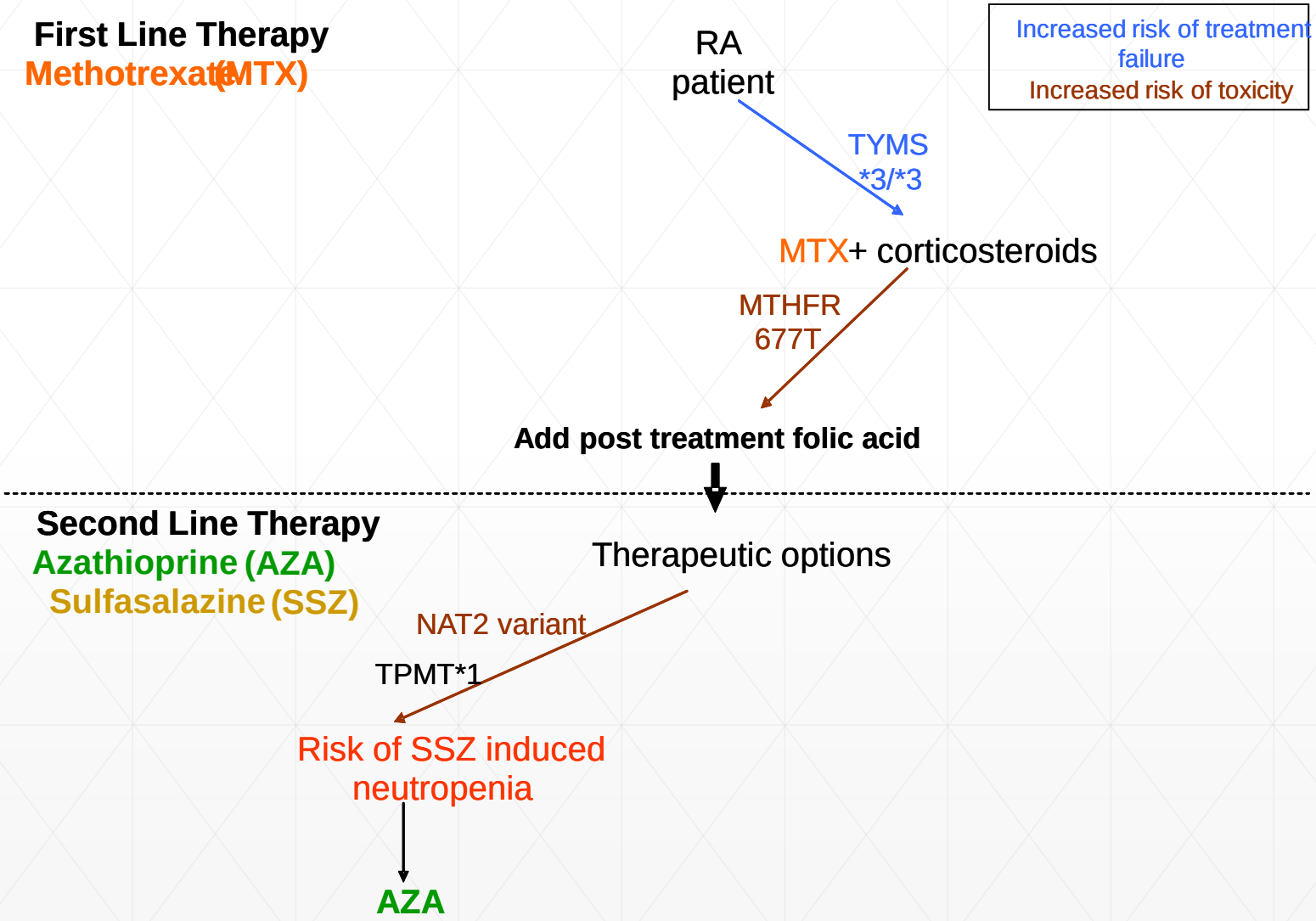

Rheumatoid arthritis example

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PharmacoGenetics for Every Nation Initiative

PGENI Recommendation for China

Country Information

Official Name: People's Republic of China

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

Recommendation

Using US Caucasian population frequency data as a reference, based on genetic variant frequency information, the following therapy strategy is suggested for China:

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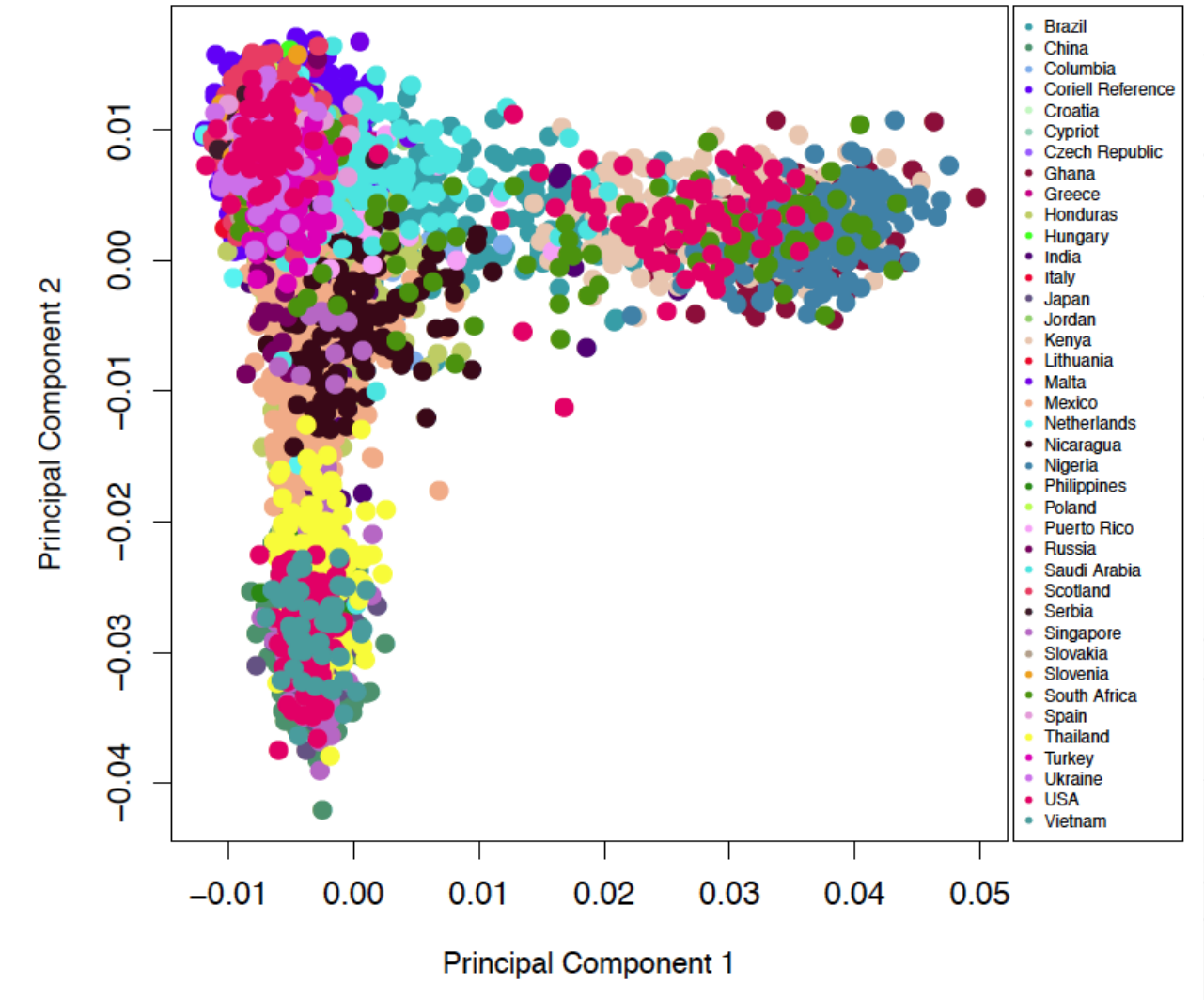

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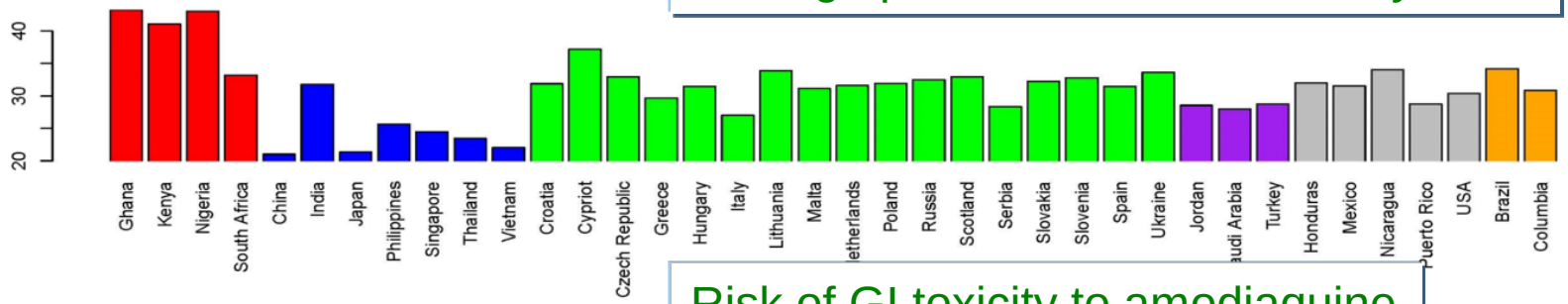
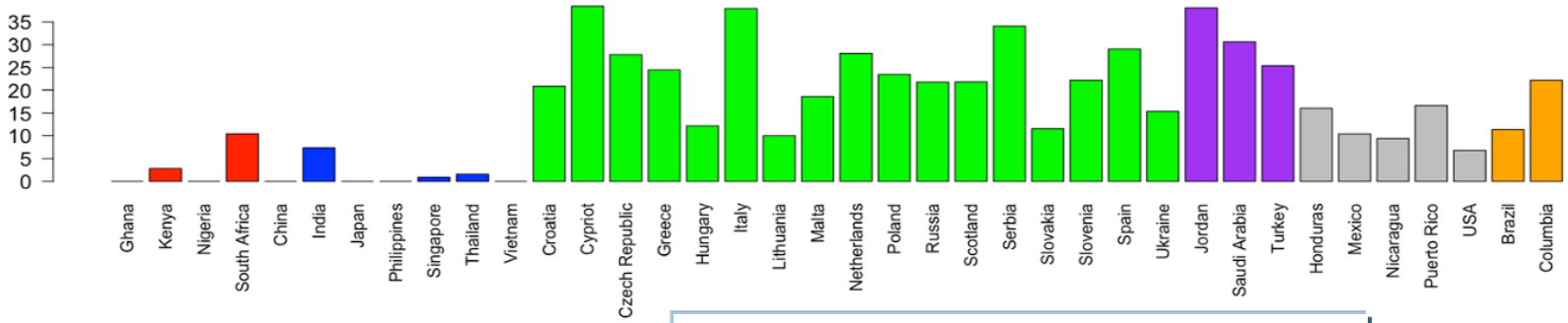
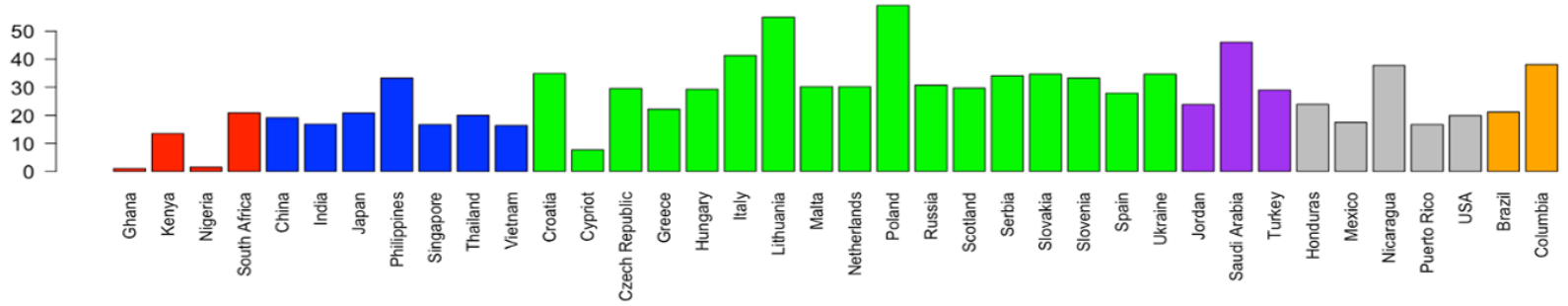
Average predicted warfarin weekly dose



Risk of GI toxicity to amodiaquine



Risk of Simvastatin myotoxicity



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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

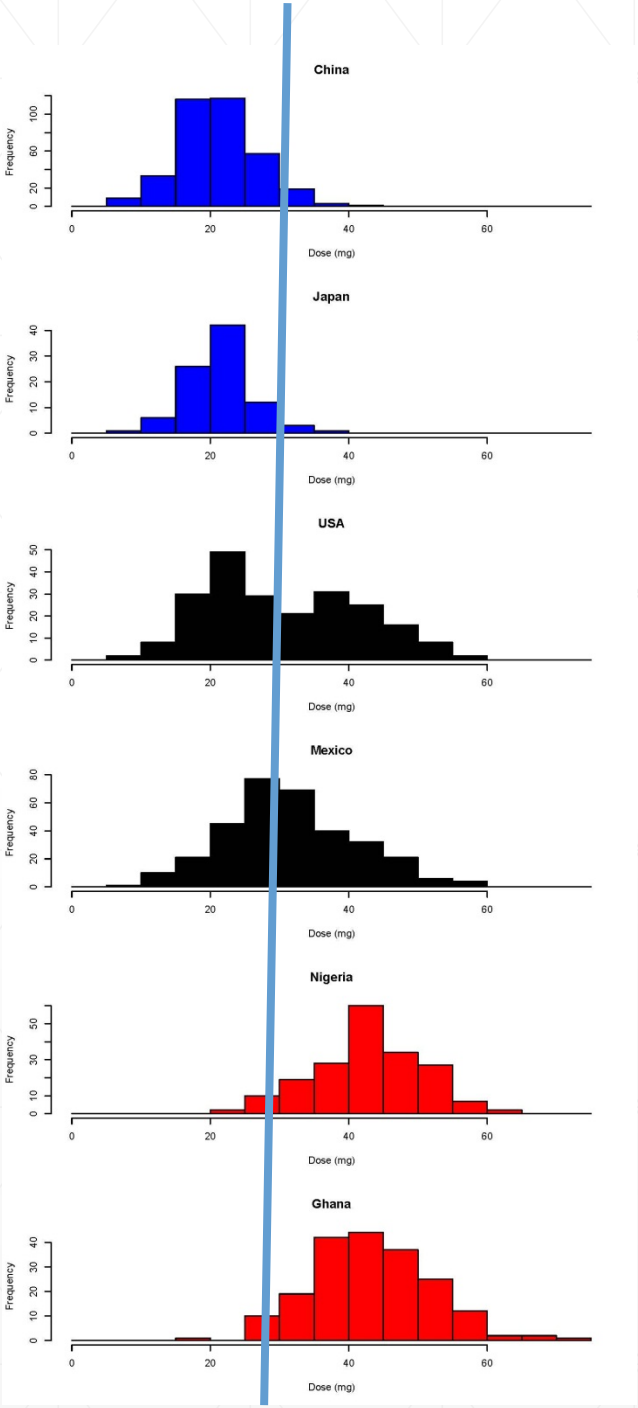
The International Warfarin Pharmacogenetics Consortium*

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



Mexico

Applications of pharmacogenetics

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- **And so much more!!**