Integrating pharmacogenetics into national formularies: setting an international research agenda

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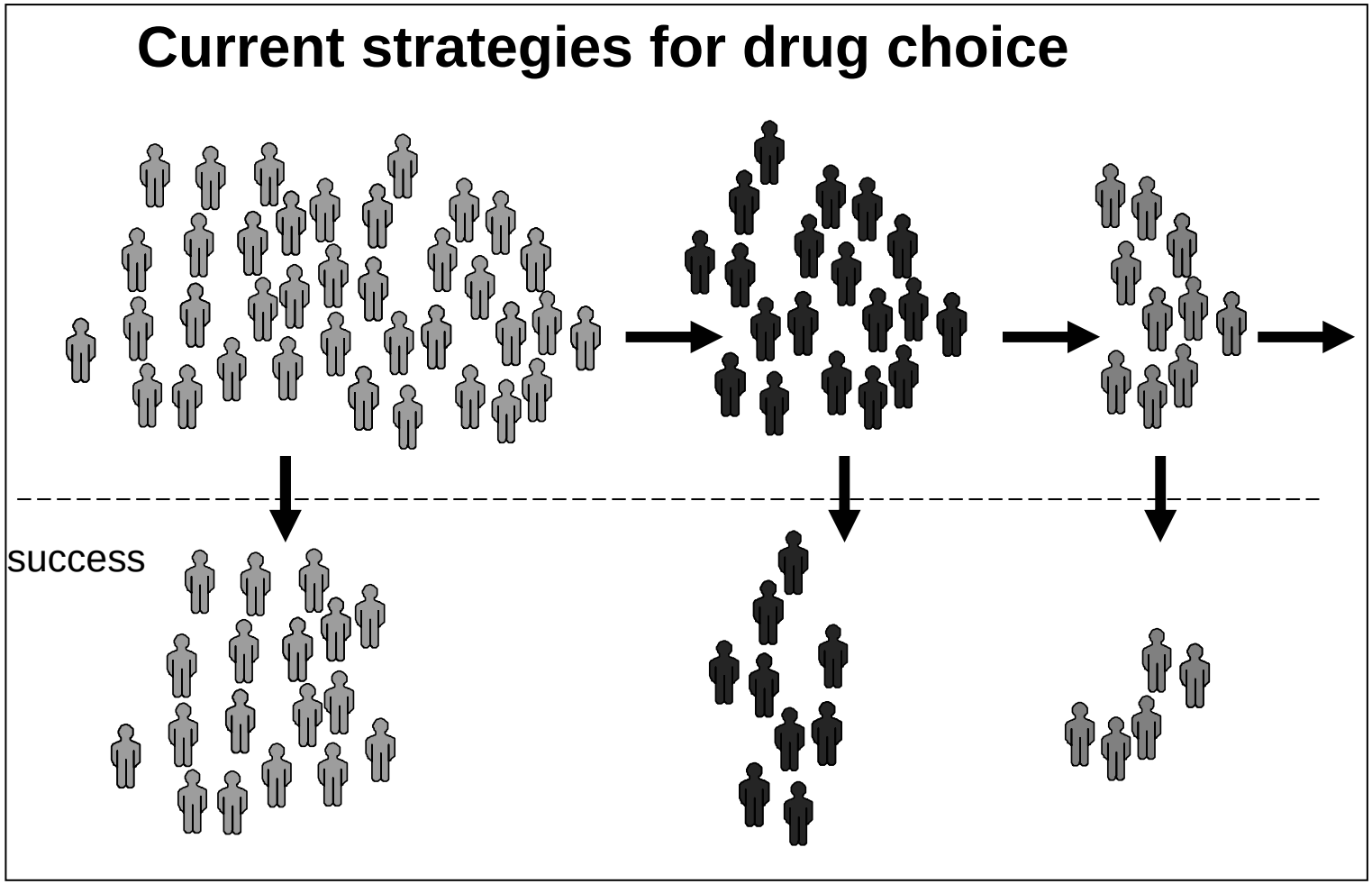
PGENI
PharmacoGenetics for Every Nation Initiative

Background: our current approach to therapy selection is successful in controlling the disease or symptoms of interest in <50% of patients.

Surely we can do better!!



Background: Current source of drug dosing, toxicity data, and efficacy information

•Drugs are primarily developed in White European patients (USA, Europe, Canada, Australia/New Zealand)

-source of global safety and dosing information

•Very little thought to how drugs will be used throughout the world

•Most ‘ethnic differences’ are based on anecdote (example, drug 'x' doesn't seem to work for Ghanaians)

-often based on 1-2 patients, but has wide influence

Background: The human genome project promise

The genetic code will lead to better diagnosis of disease and selection of therapy

•Significant data exists for DNA changes that are predictive for risk of toxicity or lack of effectiveness for commonly used medications

•Genome-guided therapy is starting to be introduced in Western countries

•What about most of the world?

The genome may offer a way to better integrate medications into national formularies in a safe and effective manner

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Background: Source of data for patient therapy selection

Best option: individual

Good: relevant geographic/
ethnic/racial population

Worst: inferred world population

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Washington University in St. Louis
School of Medicine

Purpose

•Promote the integration of genetic information into public health decision making process

•Enhance the understanding of pharmacogenetics in developing world

•Provide guidelines for medication prioritization for individual countries, using pharmacogenetic information

•Help build local infrastructure for future pharmacogenetic research studies

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PGENI Project Details

Countries

PGENI ultimately seeks the participation of 104 countries. Click here for the specific guidelines used in selecting PGENI countries.

Genes

The PGENI gene list currently contains 150 "essential genes" that have been associated with known medications.

Drugs

The initial drug list used in this initiative represents the WHO essential medicines list. Additional medications are added, as per clinical usage by PGENI countries. In total, 58 drug groups are represented in PGENI.

Diseases

The disease classes used in this initiative were categorized from the WHO. There are 34 disease classes consisting of 303 diseases.

Recommendations

Selection and/or prioritization of the treatment of each disease class are produced for each participating country following completion of the pharmacogenetic analysis in the populations under evaluation.

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104 PGENI countries; 78% of world population

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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	99%
Jola	10%	(Egyptians, Bedouin,	
Mandinka	42%	and Berbers)	
Wolof	16%		

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
  >200,000 articles reviewed
- Mined literature for allele frequencies of key SNPs in key genes

316 drugs > 132 systemic (oral / IV)

↓

Text mining

↓

150 Essential Genes

Disease: Malaria

Disease Description

Four species of protozoan parasite of the plasmodium genus - P. falciparum, P. vivax, P. ovale, and P. malariae - cause malaria in humans. Though malaria brought on by P.vivax is the most common, it is, however, malaria caused by P. falciparum that is most lethal. The clinical features of malaria vary. The classic symptoms include persistant fever, shivering, joint pains, and headaches and repeated vomiting. Severe and complicated malaria causing renal failure, hypoglycemia, anemia, pulmonary edema, shock and coma can have fatal consequences, leading to death. Malaria can be cured if promptly diagnosed and adequately treated. *Source: WHO*

Disease Groups

Malaria

Medications used in treatment

amodiaquine
artemether
artesunate
chloroquine
doxycycline
lumefantrine
mefloquine
primaquine
proguanil
quinine
sulfadoxine

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ABCB1

Gene Information

Symbols: ABCB1
Unigene: Hs.21330
Entrez Gene: 5243
OMIM: 171050
Chromosomal Location: 7q21.1
Refseq: NM_000927
Names: ATP Binding Cassette, subfamily B, member 1

Gene Length: 115942
Click here for expansion. Click here for sequence.

Public Database Polymorphisms

PGENI mines 3 public databases (dbSNP, JSNP, and CGAP) for variant information. Variant classification defintion can be found here.

5'FR (16)
5'UTR (2)
Intron (274)
Nonsynonymous SNP (10)
Synonymous SNP (8)
3'UTR (3)
3'FR (3)
ALL (316)

PGENI Featured Variants with Data

+3435

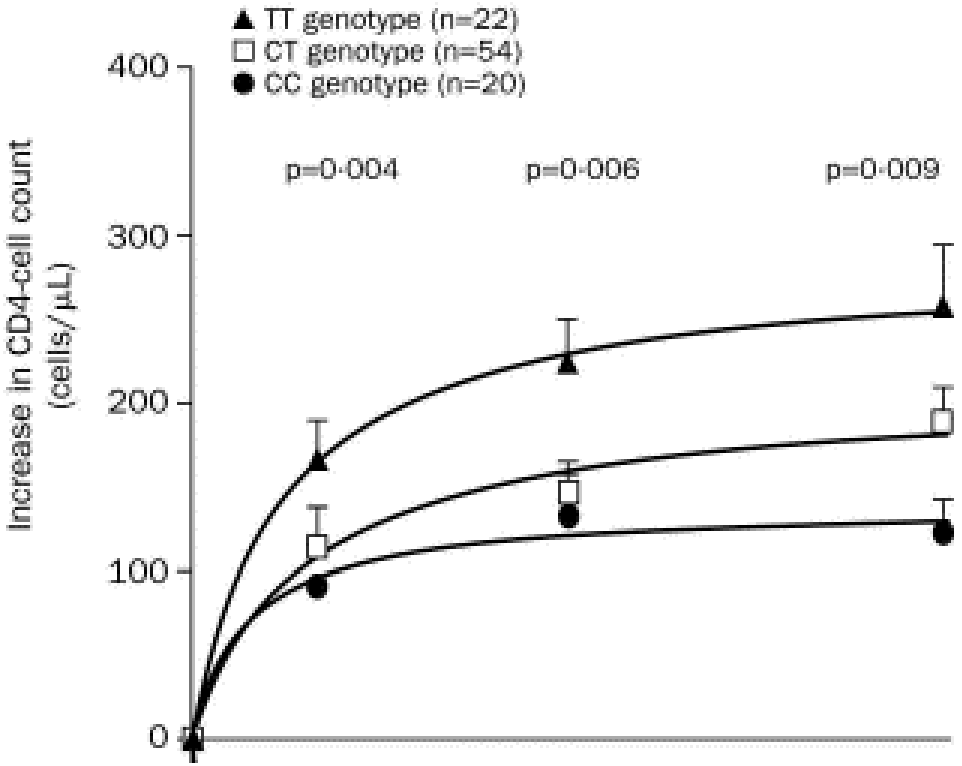
Drug Associations

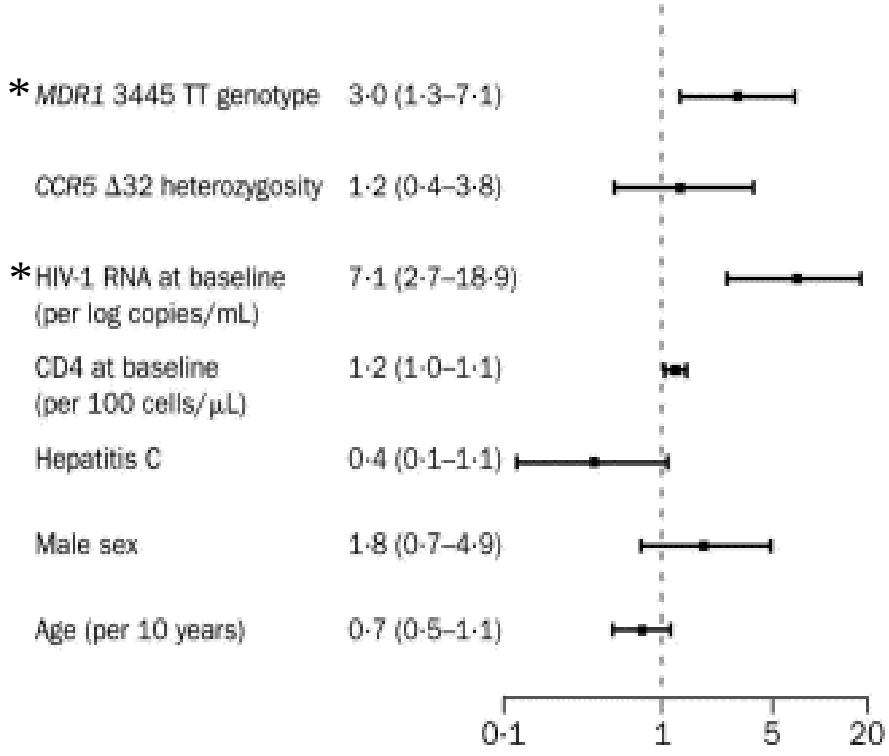
Drug Associations

For a definition of association type click here.
Reference Key: GG - Goodman and Gillman's 10 Ed., TOPC - Textbook of Organic and Pharmaceutical Chemistry 10 Ed.
To suggest another drug association or comment on existing associations click here.

Drug Name	Association	Pubmed Reference	Cited by
azithromycin	Transport	11185676	PGENI
chlorambucil	Transport	11114132	PGENI
ciclosporin	Transport	12545142	PGENI
clofazimine	Transport	11561677	PGENI
colchicine	Transport	2568832	PharmGKB
cytarabine	Transport	7628594	PGENI
dactinomycin	Transport	7908518	PGENI
daunorubicin	Transport	14713364	PGENI
dexamethasone	Transport	10666173	PGENI
dicloxacillin	Transport	12033380	PGENI
digoxin	Transport	12189368	PharmGKB
digoxin	Transport	10716719	PharmGKB
doxorubicin	Transport	12174904	PGENI
efavirenz	Transport	11809184	PharmGKB
erythromycin	Transport	12426516	PGENI
etoposide	Transport	9864272	PGENI
lopinavir	Transport	11919490	PGENI
medroxyprogesterone acetate	Transport	7645952	PGENI
mefloquine	Transport	11683248	PGENI
methotrexate	Transport	8598312	PGENI

ABCB1 3435 C>T in HIV Therapy





Fellay et al, Lancet 2002

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Global distribution of ABCB1 3435CC genotype

- Same as reference population
- >2 times reference population
- < 1/2 reference population

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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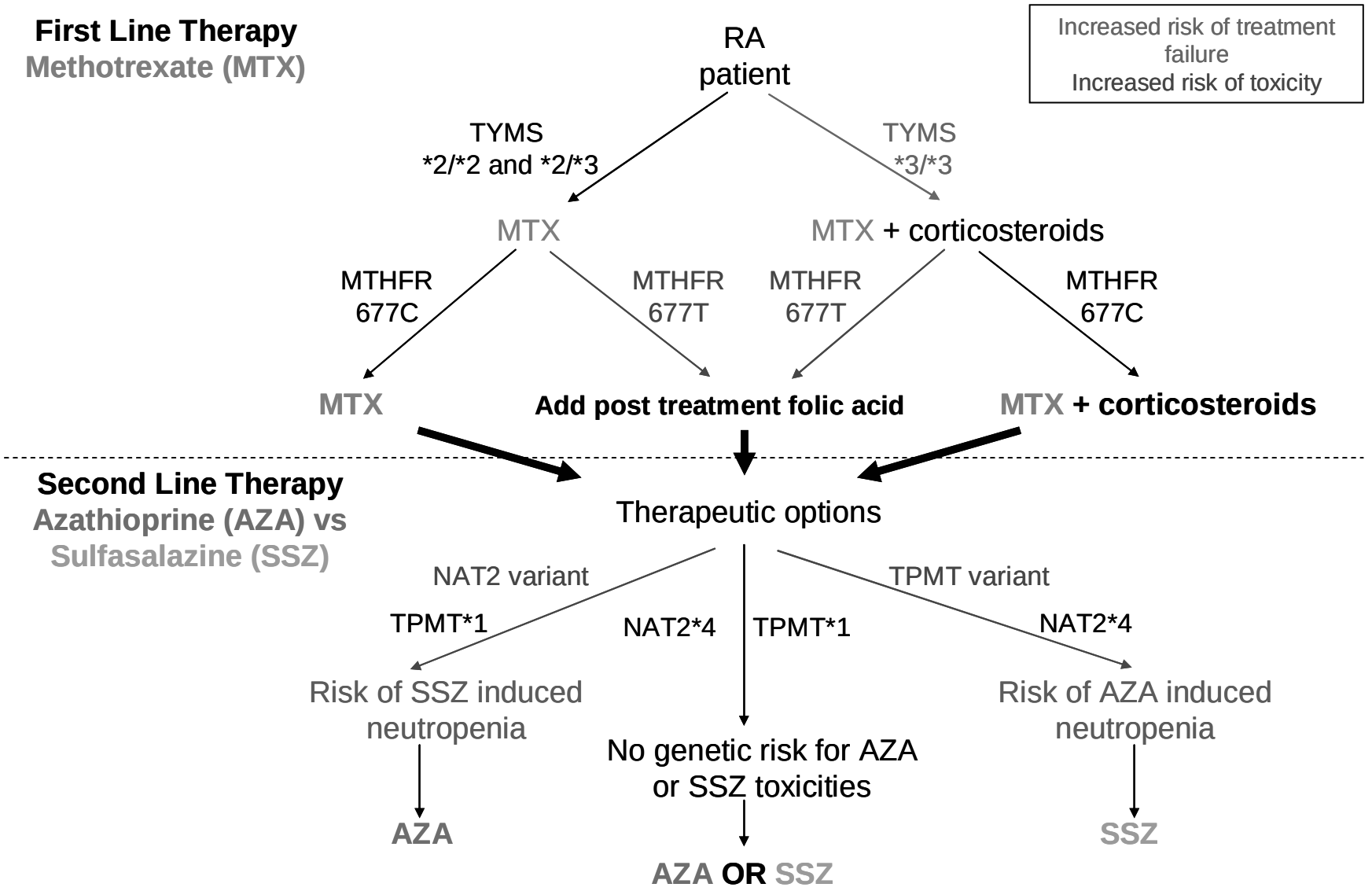

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PGENI Recommendation for China

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

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Ethics of public health pharmacogenetics

- Community consultation
- Clear mechanism for integration of information
- Safeguards for ’genetic orphan’ populations

What is PGENI not doing?

- Population genetics
- Clinical trials
- Gene-outcome (pharmacokinetics, toxicity, efficacy) studies (in the future)

Key elements (thus far)

- **Keep it local**
  -selection of drugs, ethnic/racial groups, ethics approval process
  -early involvement of ministry of health
  -engage local investigators (public health, medicine, pharmacy, government, community leaders)

- **Opportunity for PG to be meaningful now and essential later**