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

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
<table>
<thead>
<tr>
<th>Year</th>
<th>CNS</th>
<th>CV</th>
<th>Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>pramipexole, quetiapine, ropinirole, tiagabine, zolmitriptan</td>
<td>arbutamine, cerivastatin, clopidogrel, eprosartan, fenoldopam, irbesartan +/- HCTZ</td>
<td>dolasetron, IL-11, letrozole, rituximab, samarium SM-153, toremifene</td>
</tr>
<tr>
<td>2004</td>
<td>apomorphine, duloxetine, eszopiclone, natalizumab, pregabalin, zicotinamide</td>
<td>amlodipine/atorvastatin, ezetimibe/simvastatin, iloprost, omega-3-acid</td>
<td>azacitidine, bevacizumab, cetuximab, clofaribine, erlotinib, palifermin, pemetrexed</td>
</tr>
<tr>
<td>2009</td>
<td>asenapine, iloperidone, milnacipran</td>
<td>aliskiren/valsartan, amlodipine/valsartan/HCTZ, dronedarone, ecallantide, pitavastatin, prasugrel, recombinant human antithrombin, telavaptan, telmisartan/amlopidine</td>
<td>everolimus, ofatumumab, pazopanib, palifermin, pralatrexate, romidepsin</td>
</tr>
<tr>
<td>2012</td>
<td>florbetapir, perampanel, teriflunomide</td>
<td>apixaban, ethyl eicosapentaenoic acid, lomitapide, peginesatide</td>
<td>aflibercept, axitinib, bosutinib, cabozantinib, carfilzomib, enzalutamide, omacetaxine mepesuccinate, pertuzumab, ponatinib, regorafenib, TBO-filgrastim, vismodegib</td>
</tr>
</tbody>
</table>
### Number of Participants and Approvals Captured with Racial Data

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

Knepper et al, unpublished
How has the number of countries hosting investigator sites changed?

Knepper et al, unpublished
Knepper et al, unpublished
Racial Composition of Approvals from All Clinical Areas

Racial Composition of Pivotal Trials in 1997
- Caucasian (90.98%)
- Black (2.88%)
- Asian (0.15%)
- Hispanic (0.13%)
- Native American (0.00%)

Racial Composition of Pivotal Trials in 2004
- Caucasian (87.17%)
- Black (5.37%)
- Asian (1.55%)
- Hispanic (3.40%)
- Native American (0.01%)

Racial Composition of Pivotal Trials in 2009
- Caucasian (84.13%)
- Black (6.78%)
- Asian (4.10%)
- Hispanic (3.22%)
- Native American (0.10%)

Racial Composition of Pivotal Trials in 2012
- Caucasian (82.15%)
- Black (3.74%)
- Asian (12.64%)
- Hispanic (1.33%)
- Native American (0.05%)

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
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
Pharmacogenomic examples-2017

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kiot mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib, afitinib
- BRAF—vemurafenib
- ALK—Crizotinib
- TPMT—mercaptopyrline 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

**TPMT*1** (wild type)

**TPMT*2** (↓↓ activity)

**TPMT*3A** (↓↓ activity)

**TPMT*3C** (↓↓ activity)

PNAS, 95

AJHG, 96

AIM, 97

CPT, 98
Optimal dose for each patient differs by TPMT genotype.
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
# PGEni Surveillance Example: Tuberculosis

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

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**PGEni**

Treating the Population. Impacting the World.
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
First Line Therapy
Methotrexate (MTX)

Second Line Therapy
Azathioprine (AZA) vs Sulfasalazine (SSZ)

RA patient

MTX + corticosteroids

TYMS *3/*3
TYMS *2/*2 and *2/*3

MTX

MTX + corticosteroids

TYMS
MTHFR 677T
MTHFR 677C

Add post treatment folic acid

MTX

MTX + corticosteroids

Therapeutic options

NAT2 variant
TPMT*1
Risk of SSZ induced neutropenia
AZA

TPMT variant
NAT2*4
Risk of AZA induced neutropenia
SSZ

No genetic risk for AZA or SSZ toxicities
AZA OR SSZ

Increased risk of treatment failure
Increased risk of toxicity

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

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First Line Therapy
Methotrexate (MTX)

Add post treatment folic acid

MTX+ corticosteroids

RA patient

TYMS *3/*3

MTHFR 677T

Increased risk of treatment failure
Increased risk of toxicity

Risk of SSZ induced neutropenia

Second Line Therapy
Azathioprine (AZA)
Sulfasalazine (SSZ)

NAT2 variant
TPMT*1

Therapeutic options

AZA
Rheumatoid arthritis example

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.
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>
<thead>
<tr>
<th>Variable</th>
<th>Derivation Cohort (N=4043)</th>
<th>Validation Cohort (N=1009)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height — m</td>
<td>1.68</td>
<td>1.68</td>
<td>0.79</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1.60–1.76</td>
<td>1.60–1.76</td>
<td></td>
</tr>
<tr>
<td>Weight — kg</td>
<td>75.3</td>
<td>75.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>62.0–89.4</td>
<td>61.0–90.0</td>
<td></td>
</tr>
<tr>
<td>Race — no. (%)‡‡</td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>White</td>
<td>2233 (55.2)</td>
<td>562 (55.7)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1229 (30.4)</td>
<td>300 (29.7)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>353 (8.7)</td>
<td>97 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Mixed, or missing data</td>
<td>228 (5.6)</td>
<td>50 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Use of enzyme inducers — no. (%)‡‡</td>
<td>41 (1.0)</td>
<td>7 (0.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Use of amiodarone — no. (%)</td>
<td>176 (4.4)</td>
<td>56 (5.6)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
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)

- And so much more!!