Successes and Challenges in Pharmacogenomics

1st Latin American Pharmacogenomics Congress
San Juan, Puerto Rico
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Food and Drug Administration
Biodiversity: Positive Measure of the Health of Biological Systems

2010 has been declared the International Year of Biodiversity

Genes and the environment frequently underlie the differential susceptibility of humans to diseases and their sensitivity to drugs.

Genetic variability – and uncertainty – in drug response has driven increasing interest in PGx and personalized medicine.
People of Puerto Rico -- from the South American Archaic Indians, later known as the indigenous Taino Indians, on to the first Spanish settlers, and together with subsequent African and American influences – which shaped the unique heritage and charismatic culture of the Island ...........and the Ancestral Genetic Admixture typical of many Latin American Populations
Latin Americans: Who Are They?

- Genetically-diverse, heterogeneous population of over 600 million people
- Broadly includes people of English-speaking countries south of US in the Caribbean

**Hispanic or Latino:** People of Cuban, Mexican, Puerto Rican, South or Central American ancestry or from other Spanish cultures or origin regardless of race

**Ethnicity:** Two categories, Hispanic/Latino and non Hispanic/Latino; includes differences among people in nationality, culture, beliefs and ancestry

**Race:** Associated with people’s appearance determined biologically by genetic traits and shared ancestry

Problem Statement I: Limitations of Preapproval Clinical Trials

1. RCTs are an important – often primary – source of efficacy and safety data about a new medicine

2. Increasing number of RCTs submitted to regulatory agencies are conducted outside region of jurisdiction

3. Results from RCTs often not *generalizable* to the larger population that will consume the drug post-approval

4. Assuming subjects in RCTs are *comparable* based on phenotypic variables masks interpatient variability
Problem Statement II: Trend to Off-Shoring To Reduce Costs of RCTs

Overall Indexed Clinical Trial Costs

Within the next 3 years, up to 65% of FDA regulated clinical studies will be conducted outside the US

RCT results depend on:
-- drug
-- study design
-- study conduct
-- subgroups
-- local culture

Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)
An Example of the Type of Problem That Off-Shoring Can Render

**Antiviral Agent**: Pivotal clinical trial enrolled primarily Asians. At baseline, patients had HBV of either genotype B (26%) or genotype C (51%). Viral genotype plays a major role in treatment response. Genotype A is the major genotype in Caucasians.

**Comparability**: what are the differences in response among Asians within the RCT assuming them to be identical?

**Generalizability**: can the efficacy in Asians be extrapolated to Latin Americans or non-Hispanics who were not enrolled in the RCT?

*Fung et al, Hepatology 2004;40:790-792*
Perceived Strength of RCT Evidence Related to Experience of PIs

Annual Growth in Clinical Investigators by Country

41% of FDA-regulated principal investigators were based outside the US in 2007; CROs

Regional differences, familiarity with ICH guidelines, country of training, strong regulations

Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)
Trends in Globalization of Clinical Trials: Spain and Latin American Countries

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th># of Sites</th>
<th>Share (%)</th>
<th>Growth Rate (%)</th>
<th>Trial Capacity</th>
<th>Trial Density</th>
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<tbody>
<tr>
<td>1</td>
<td>US</td>
<td>36,300</td>
<td>49</td>
<td>-7</td>
<td>44</td>
<td>120</td>
</tr>
<tr>
<td>5</td>
<td>Spain</td>
<td>2100</td>
<td>3</td>
<td>15</td>
<td>7</td>
<td>46</td>
</tr>
<tr>
<td>15</td>
<td>Argentina</td>
<td>757</td>
<td>1</td>
<td>27</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>17</td>
<td>Brazil</td>
<td>754</td>
<td>1</td>
<td>16</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>Mexico</td>
<td>683</td>
<td>1</td>
<td>22</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

- LAC, as a group, becoming a major player beyond top 4 countries
- Growth rates suggest huge potential to grow into major player
- Well-established regulations govern conduct of clinical trials
- Access to 500 million potential patients concentration in urban areas
- Large fraction of population are treatment-naïve
- Complex ancestry – Hispanic/Latino, European, AA and Asian

Adapted from Nature Rev Drug Discovery, 17: January 2008
Opportunity

Scientific advances resulting from genomics can provide solutions to the RCT concerns of *generalizability* and *comparability*.

Knowledge of the human genome will not address the differences in drug response among Latin Americans unless they are enrolled in clinical trials.
Medicine Is Highly Observational: Problem of Heterogeneity of Treatment Effects

“If it were not for the great variability among individuals, medicine might have well been a science and not an art”

Sir William Osler (1849 – 1919)
The Johns Hopkins University
The Father of Modern Medicine

Primary task of medicine in the 20th century was diagnosis and treatment. Variability in results produced by the same drug in different patients was acceptable because there were no ways to conduct individual or subgroup analysis.
What If We Conducted a RCT in a Famous Hispanic-Latino Population?

Problem: Race or ethnicity is not obvious from the way people look
Problem: Individuals may not know their race/ethnicity or may be wrong
Problem: Genetics may differ greatly within self-identified race/ethnicity
Problem: Average response across dissimilar individuals is not relevant to any one individual → large heterogeneity in drug response
Would the RCT Results in Hispanic-Latino People Be Applicable in Brazil?

Most RCT populations are not representative of people not in the trial who will consume the drug:

- severity of disease
- different demographics
- different organ function
- concomitant medications
- duration of treatment
- gene-related disease biology
- gene-dependent PK and/or PD
RCTs Provide Evidence of Efficacy at the Population Level for 50 Years

Efficacy expressed as *average* drug response. Average effects within a RCT population may be quite different from effects expressed by a given individual.

- Relatively low response rate to existing medicines means that administration of drugs to *nonresponders* is a major public health issue.
- RCTs are basically large efficacy studies with only a small observational safety study built in.

Source: Steven Paul (Lilly); Brian Spear (Abbott); Barbara Evans (U of Houston)
Schematic of Variable Responses Observed in a RCT of Hypothetical New Drug

- Green = Benefit
- Red = Harm
- Yellow = Mixed Benefit and Harm
- Silver = Neither Benefit or Harm

Frequency of various responses in the RCT treated population

- Large Benefit with little harm (10%)
- Mixed Benefit and Harm (30%). Small benefit for most.
- Neither harm or benefit -- Nonresponders (50%)
- Harm Without Benefit (10%)

Adapted from presentation by Dr. Barbara Evans, ASCPT Annual Meeting (2010)
Typical Variability in a Drug Anti-Platelet Response Due to CYP2C19

Asians: 16.7%
African-Americans: 5.4%
Caucasians: 5.0%
Hispanics: 3.2%

What Are The Implications of Preapproval RCT Variability?

- Subgroups in the treated RCT population have different dose-response relationships for benefit and risk
- Drug is destined to have problems postapproval with lack of response or adverse experiences as use widens
- Postapproval studies will always be needed to fill in the knowledge gaps around B/R in the real world
- Future drug therapies for certain diseases will look quite differently because of biomarker stratification of patients
- New regulations or guidelines will empower regulators to ask for data on differences in B/R among subgroups
Paradigm For Dealing With Heterogeneity (Race/Ethnicity) in RCT Population

Comparative systemic exposure and corresponding starting and maintenance doses for rosuvastatin

<table>
<thead>
<tr>
<th>Group</th>
<th>Ethnic factor</th>
<th>Fold change in exposure (AUC)</th>
<th>Initial dose (mg)</th>
<th>Daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>1-fold</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td>2</td>
<td>Hepatic impairment</td>
<td>1.1-fold (mild)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.2-fold (moderate)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td>3</td>
<td>Renal impairment</td>
<td>1-fold (mild)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-fold (moderate)</td>
<td>10–20</td>
<td>5–40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-fold (severe)</td>
<td>5</td>
<td>≤10</td>
</tr>
<tr>
<td>4</td>
<td>Race</td>
<td>2-fold (Asians)</td>
<td>5</td>
<td>5–20</td>
</tr>
<tr>
<td>5</td>
<td>Cyclosporine</td>
<td>7-fold</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Gemfibrozil</td>
<td>1.9-fold</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Lopinavir/ritonavir</td>
<td>5-fold</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

From Huang, S-M and Temple, R, Clin Pharmacol Ther 2008 (September)
Problem: Stone Age Approach to Variability and Not Very Sophisticated

Clinical pharmacology studies provide important knowledge for B/R but they focus only on PK changes and AUC-driven dose adjustments in populations.

What the studies neglect – especially with regard to race and ethnicity – are differences in C/R relationships and non-PK intrinsic (e.g., disease subtypes) and extrinsic (e.g., culture, lifestyle) factors that contribute to variability.
Empiricism: BiDil (Isosorbide and Hydralazine) For Treatment of Heart Failure

- 2005: 1st drug approved by FDA to treat a disease in patients identified by race
- Sponsor conducted two trials in general populations that failed to show benefit but suggested benefit in black patients
- BiDil studied in pivotal RCT in 1,050 self-identified black patients and reduced mortality by 43% versus placebo
- MOA related to release of nitric oxide by isosorbide and vasodilatation and decrease in nitrate tolerance by hydrazine
- Prospective genetic subset analysis on endothelial nitric oxide synthase (NOS3) gene (Glu298→Asp) was promising
Growing International Recognition of the Importance of Race and Ethnicity

- 1985: 1st regulation (CFR 314.50) specifying analysis of population subsets to support dosage recommendations

- 1988: 1st Guidance for Industry recommending subset analysis of NDA clinical trials to assess B/R

- 1993: 1st Guidance for Industry on Refuse to File if inadequate evaluation of B/R in population subsets

- 1999: Population PK Guidance recommended sparse samples in clinical trials to identify differences in population subsets

- 1999: 1st ICH Guidance on Ethnic Factors in Acceptability of Foreign Clinical Trials (E5)
# Intrinsic and Extrinsic Ethnic Factors in ICH E5 Guideline: Bridging Studies

<table>
<thead>
<tr>
<th>INTRINSIC</th>
<th>EXTRINSIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Disease</td>
<td>Medical Practice, Disease Definition</td>
</tr>
<tr>
<td>Gender</td>
<td>Therapeutic Approach, Adherence</td>
</tr>
<tr>
<td>Race</td>
<td>Clinical Trial Methods and Endpoints</td>
</tr>
<tr>
<td>Genetic Polymorphism of Metabolism</td>
<td>Regulatory Practices</td>
</tr>
<tr>
<td>Age</td>
<td>Smoking and Alcohol Intake</td>
</tr>
<tr>
<td>Liver, Kidney and CV Functions</td>
<td>Food Habits and Stress</td>
</tr>
<tr>
<td>Diseases</td>
<td>Climate, Sunlight and Pollution</td>
</tr>
<tr>
<td>Height</td>
<td>Culture and Socio-economic Factors</td>
</tr>
<tr>
<td>Body Weight</td>
<td>Educational Status</td>
</tr>
<tr>
<td>ADME and Receptor Sensitivity</td>
<td>Language</td>
</tr>
</tbody>
</table>

Racial and Ethnic Groups Have Been Underrepresented in Clinical Trials

Survey of 185 NMEs approved between 1995 and 1999 representing 2581 clinical trials and 493,347 patients

Findings

1. Race/ethnicity was not reported for 47% of NMEs
2. Hispanic/Latino patients represented only 3% of patients
3. 82% of NME labels did not distinguish between racial/ethnic groups
4. 18% of NME labels reported differences but ½ of them were PK
5. No NME had race/ethnicity-based dosing adjustments

What Are the Possible Explanations For Underrepresentation?

- Racial/Ethnic group are not knowingly be excluded
- Reasons for underrepresentation are complex and challenging
  - Overly stringent inclusion/exclusion criteria (co-morbidities)
  - Communication barriers and level of health literacy
  - Cultural and language issues with informed consent
  - Economic constraints and lack of insurance
  - Substandard quality of life
  - Mistrust of research and fear of adverse events
  - Lack of principal investigators from racial/ethnic groups
  - Unawareness of clinical trial opportunities
Significant Gaps in Treatments for Latin Americans That Need to Be Bridged

- Less access to medicines
- Less access to advances in PGx
- Genetic factors influence response
- Uncertainty in optimal doses
- Problem of concomitant diseases
- Cultural and communication issues
- Research is limited

Important to Hispanic/Latino People: Fastest Growing Minority Group in the USA

Demographic data from US Census Bureau (2002)
1 in 8 persons in US is Hispanic/Latino
Projected to be 1 in 4 persons by 2050

From U.S. Census Bureau, Current Population Survey PGP-5. Published March 2002
FDA Amendments Act (FDAAA) of 2007

- Provides regulatory authority to require postmarket evidence development to address individual variability in a drug's efficacy and/or safety, and improve B/R over its life cycle.

- Regards efficacy failure as a safety problem – lost opportunity for patient allowing disease to press (Ex: KRAS)

- Allows flexible view of best evidence (not necessarily RCT) on a case-by-case basis depending on the question (Ex: Warfarin)

- Accepts evidence from different sources (not necessarily NDA holder) and different study designs (Ex: Observational)

- Enable attention to be paid to B/R at both population and individual subgroup level even with retrospective data analysis
Warfarin: Use of PGx To Predict Dose Requirements Before Taking 1\textsuperscript{st} Dose

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>African-American</th>
<th>Caucasian</th>
<th>Hispanic</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Dose</td>
<td>5.2 mg/day</td>
<td>4.3 mg/day</td>
<td>4.0 mg/day</td>
<td>2.7 mg/day</td>
</tr>
<tr>
<td>CYP2C9*1</td>
<td>94%</td>
<td>74%</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>CYP 2C9*2</td>
<td>1%</td>
<td>19%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>VKORC1 GG</td>
<td>82%</td>
<td>37%</td>
<td>32%</td>
<td>7%</td>
</tr>
<tr>
<td>VKORC1 AA</td>
<td>6%</td>
<td>18%</td>
<td>27%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

http://www.accessdata.fda.gov; Wu et al, Pharmacogenomics 9(2) 169-178 (2008)
Genetic differences among and between racial and ethnic groups usually reflect differences in the distribution of polymorphic traits, which occur at different frequencies in different populations, rather than a trait unique to a particular race or ethnic group.
Abacavir: Attempt to Compare HLA-Related Risk of HSR by Race/Ethnicity

**Label:** Screening for HLA-B*5701 recommended because patients with allele at high risk for HSR

- Allele most prevalent in Caucasians (4-8%), less so in Hispanics (1-7%), Spaniards (1-4%), Asians (0.9-2%) and African-Americans (0-0.5%)

- Sensitivity and specificity varies significantly across subgroups; PPV from 8% (Hispanics) to 48% (Caucasians) so as to be not clinically useful in Hispanics

- HSR prevalence > HLA-B*5701 frequency in Hispanics suggesting additional at risk alleles

*Hughes et al, Pharmacogenomics 5(2), 203-211 (2004); Rodriguez-Novoa et al, Pharmacogenomics 9(10), 1531-1541 (2008)*
Carbamazepine: Heterogeneity in Risk Among and Between Race/Ethnic Groups

**Label:** Screening for HLA-B*1502 recommended for patients of *Asian ancestry* because patients with allele at high risk for SJS

- Allele most prevalent in Asians (5.1%), least prevalent in Blacks (0.2%), Whites (0%) and *Hispanics* (0%)

- Prevalence among Asians, Singapore (11.6%), Taiwan (10.2%), Malay (8.4%), Thai (6.1%), Filipino (5.3%), India Marathas (1%) and Korean (0.5%)

- Subgroups combined as *Asians* despite heterogeneity because alternative therapies available

_Ferrell and McLeod, Pharmacogenomics 9(10), 1543-1546 (2008)_
Trend Watching: Chronic Hepatitis C Infection in Hispanic/Latino Patients

- Interferon/Ribavirin is treatment of choice
  - Untreated HCV leads to hepatitis, cirrhosis and hepatic cell carcinoma
  - Response rates are African-Americans << Caucasians << Asians (Data on Hispanics/Latinos contradictory)
  - Efficacy ~ sustained virological response at 24 wks (HCV genotype 2 or 3) or 48 wks (HCV genotype 1 or 4)
  - SVR at 24 wks ~ 25% and for genotype 1 ~ 14% in Hispanics/Latinos, well below that for Caucasians

- 52% of patients discontinued treatment by 12 wks for serious AE (infection, neutropenia, depression) and other cultural/socioeconomic reasons

Genetics Is a Major Determinant of Effectiveness of Interferon/Ribavirin

SNPs in IL28B Gene (n = 1671)
- Up-regulated by interferon and RNA virus infection
- Genotypes contribute differentially to viral resistance
- Homozygous CC genotype has best sustained viral response (80%)
- C versions most common in Asians and least common in African-Americans

1. Significant interpatient variability in clinically important response
2. Reliable biomarker to separate high from low responders
3. Prevalence of CC genotype ranges from 16% to 39%

Rumsfeld: Facts About Individual Variability in Treatment Response

There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

Genetics has taken heterogeneity in drug response from the “unknown unknown” category to the “known unknown” category

From Dept of Defense Press Conference on Feb 12, 2002
Summary

1. No complete set of demographic and/or clinical facts will capture the true extent of individual variability in disease and drug response – work the problem harder with genetics

2. Use existing regulatory authority to compel greater inclusion of Latin-Americans in premarket clinical trials – especially for diseases indigenous to Hispanic/Latino people

3. Use new FDAAA authority to render PMR to conduct studies in Hispanic/Latino people where there are expected causal mechanisms for lack of efficacy or adverse experiences

4. Mine electronic databases for drug-event pairs that differentiate efficacy or safety in non-Hispanic whites, Hispanics, Asians and African-Americans
Thanks for your time and attention
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