Personalized Medicine: Hope, Hype and A Little Statistics

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Drug development focuses on treating diseases of a community of patients (population) rather than in specific patients (individual).

Regulatory approval of drugs is intended to improve the health of a population as a whole. But approved drugs may or may not be the best choice for an individual.
Heterogeneity in Treatment Effects in Populations in a Typical RCT

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

Frequency of various responses in the RCT treated population

Adapted from presentation by Dr. Barbara Evans, ASCPT Annual Meeting (2010)
Efficacy – Effectiveness Gap

% of patient population for which a particular drug is effective on average

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>62%</td>
</tr>
<tr>
<td>Asthma</td>
<td>60%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>50%</td>
</tr>
<tr>
<td>Alzheimer’s</td>
<td>30%</td>
</tr>
<tr>
<td>Cancer</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Spear et al, Trends in Molec Med 7(5), 201-204 (2001)*
### Issue of Unpredictable Adverse Events

<table>
<thead>
<tr>
<th>Setting</th>
<th>ADR Rate</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Care</td>
<td>25.1%</td>
<td>1150</td>
</tr>
<tr>
<td>Inpatient</td>
<td>14.7%</td>
<td>3675</td>
</tr>
<tr>
<td>Hospital Admissions</td>
<td>6.5%</td>
<td>18820</td>
</tr>
<tr>
<td>ER Visits</td>
<td>2.5%</td>
<td>1017</td>
</tr>
</tbody>
</table>

Pirmohamed et al, Br Med J 324 (15), 2004; Images, George Poste
Physician Office Visit for an Individual Patient

- 82% of adults
- General medical exam
- Ave wait time - 21 min
- Ave visit time - 18 min
- Ave cost -- $60 - $240
- Most common Dx - HBP/LDL
- 71% of visits lead to Rx

I’m guessing that most patients assume that personalized medicine is already happening for them

What Patients Really Think When They Take Their Medication

“Life is like a box of chocolates. You never know what you are going to get until you eat one”

Forrest Gump (1994)
Statin Paradox: Primary Prevention of CV Event

**Benefit:** lower LDL cholesterol

**Risk:** myalgia and rhabdomyolysis

**NNT:** average # of patients who need to be treated to prevent one CV event compared to control.

NNT=1, all benefit.......NNT=0, nobody benefits

Greater the NNT, less effective is the therapy
Of 100 patients with high cholesterol... 

Only 3 will develop a stroke or heart attack... 

But we treat 100% of all patients... 

Only 2 will develop a stroke or heart attack... 

98% of all patients get a treatment that they did not need

http://www.medicine.ox.ac.uk/bandolier/booth/cardiac/statascot.html
Safety of Lipitor® (Atorvastatin)

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with LIPITOR in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at (1-800-438-1985 and www.pfizer.com) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Concomitant meds, female, small frame or BW, renal or hepatic impairment, T1 or T2 DM
Biomarkers As a Potential Solution – Especially Genetic Biomarkers

A characteristic that is objectively measured and evaluated as indicator of normal biologic processes, pathogenic processes or pharmacologic response to therapeutic interventions.

Biomarkers Definitions Working Group, Clin Pharmacol Ther 69, 89-95 (2001)
Biomarkers May Make Personalized Medicine More Challenging

**SIMPLE**
- Demographics
  - Family history, age, weight, sex
- Disease
  - Symptoms, severity, comorbidity
- Concomitant Drugs
  - Who prescribes what and for what: Rx, OTC, off-label
- Behavior
  - Who uses what drugs and for what purpose: adherence, diet
- Genetics
  - Germline or somatic differences

**COMPLEX**
Overcoming Sheer Volume and Access to Health Care Data

“I’m sorry. It appears that Dr. Mitchell won’t be accepting any more information today.”

ADOPTION OF GENETIC TESTS
Hype: Vision For Using Genomics

The human genome sequenced and assembled

June 16, 2000

“This set of power tools that the genome project is producing will accelerate this discovery process rather dramatically, and we're going to see the consequences of that in the next three to five years”
Chronic Disease Are Enormously More Complex Than Expected

Like trying to find the one loose wire in this mess of cables
Hope: Example of Success in Treating Leukemia

1949
- Leukemia: an umbrella term for “diseases of the blood”
- Five year survival of 0%

2009
- Leukemia: 38 subtypes have been identified
- Five year survival of 70%

No effective treatments; one size fits all

Tailored therapies, e.g., Gleevec for CML where 5 year survival is 90%

Adapted from a Presentation by Mara Aspinall on “Future Directions in Personalized Medicine” (2007)
Example: Diabetes Where Hypothesis for Treatments Lacking
Problem: Number of Genes Implicated in Type 2 DM

Survey of 16 PhRMA Companies (2003-2008)

All conduct DNA-related research
50% DNA biomarkers, 50% expression biomarkers
Most biomarker validation prospective
25% completed more than 25 studies
Most common reason – explain efficacy variability
Therapeutic areas – oncology, neuro, immuno
Most common barriers
  -- statistical (sample size)
  -- lack of hypothesis
  -- trial feasibility
  -- finding genetic biomarker post-approval

Genomic Biomarkers in FDA Labels

120 Drug Labels (Various Sections)
82 Descriptive (Mostly CYPs)
26 Recommended and Actionable (If Adopted)
12 Required (Mainly in Oncology)

http://www.fda.gov/drugs/sciencereseach/researchareas/pharmacogenetics/ucm083378.htm
Dear FDA Letter

“Companies are hesitant to submit genomic data to the FDA owing to concerns about potential regulatory use of exploratory genomic information.”
The Safe Harbor Concept

Dear Industry Letter:

“Please submit your exploratory genomic data to FDA and we won’t make regulatory decisions when we recognize these data are immature.”

1. Interdisciplinary PGx review group (2002)
Biomarker Qualification

Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Shaniece Gathers, 301-796-2600.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical
Nobel Prize: Discoveries of Important Principles of Drug Treatment (1988)

Three scientists jointly received the 1988 Nobel Prize in Physiology or Medicine, “for their discoveries of the important principles of drug treatment”.

Born in Uddingston, Scotland, James Black (figure, left) studied medicine at the University of St Andrews. In 1958, he joined the Pharmaceutical Division of Imperial Chemical Industries. In 1948, American scientist Raymond Alquist had proposed two sets of receptors were present—α and β—that might explain parasympathetic actions of epinephrine, norepinephrine, and acetylcholine. Black and his colleagues attempted to characterise these receptors. Isoproterenol, an analogue of norepinephrine, they synthesised propranolol—a β-receptor antagonist—which became invaluable in the treatment of coronary-artery diseases.

Black moved to Smith, Kline & French Company (now SmithKline Beecham) in 1964 and pursued antihistamine research. Since the antihistamines available then could inhibit nasal secretions, but not gastric acid secretions, Black proposed the existence of a different receptor (H2), akin to the β receptor. Using a carded the old “magic bullet” method and applied the basic principles of biochemistry and physiology. Having found that bacteria needed folic acid and purines for DNA synthesis, they were able to develop 6-mercaptopurine (6 MP), an effective chemotherapeutic agent against leukaemia.

In the same year that 6 MP, Elion and Hitchings were producing a series of 5-fluorouracil, they developed amphotericin B, then cryosurgery, and alloplastic silastic. 1975, they synthesised a powerful antiviral agent, acyclovir, and zidovudine (AZT), the first drug for the treatment of HIV/AIDS.

In chemistry from the New York University, Elion joined Hitchings and remained with him as collaborator for the rest of her career. A compassionate, inspiring, and industrious scientist—she never stopped working until her sudden death in February, 1999. Elion once said, “The Nobel Prize is fine, but the drugs I have developed are rewards in themselves.”

“The most fruitful basis for the discovery of a new drug is to start with an old drug”

- James Black

The Nobel Chronicles

1988: James Black (b 1924), Gertrude Elion (1918-99), and George H Hitchings (1905-98)
Variable Response to Clopidogrel


24 hrs after 300 mg Clopidogrel
N = 96, Elective PCI

“Resistance” = 31%

Δ Platelet aggregation before and after Clopidogrel (%)
Strategies: Biomarkers For Optimal Dosing and Drug Safety

A. Retrofitting new PGx information to old labels

- Mainly CYP enzyme polymorphisms
- Case-control observational trials
- Poor selection of control groups
- Small sample size
- Effect size overestimations
- Incomplete DNA collection

Generally weak statistically so we used the Bradford-Hill criteria for causation to evaluate evidence
Biomarker-Drug Pairs and Their Use as Diagnostic Tests

1. Gene mutations in well-characterized biological processes (CYP2C9*2 SNP resulting in reduced metabolism of warfarin to guide dosing)

2. Gene haplotypes that identify pharmacodynamic response (VKORC1 AA and warfarin anticoagulation)

TPMT/6MP, UGT1A1/irinotecan, CYP2C19/clopidogrel, HLA-B*5701/abacavir, HLA-B*1502/CBZ, boceprevir/IL28B, cisplatin/TPMT, codeine/CYP2D6,
Strategies at FDA: Retrospective Stratification for Benefit or Risk

B. Prospective-retrospective clinical trials

- Suspected or known biomarker hypothesis
- Prognostic or predictive
- Robust trial-ready assay
- Prespecified DNA collection and archival plan
- High ascertainment rate
- Adequate and balanced sample size per arm
- Strong biomarker-clinical endpoint correlation

Generally strong statistically, protocol designed to minimize bias and Type1 errors and statistical plan prespecified, often multiple studies
Major Genetic Test Categories Used As Biomarkers

1. Composite biomarkers in oncology (measure activity in 21 genes in breast cancer for \textit{prognosis})

2. Functional gene variants in common diseases (HMG1A variant in Type2 DM to define \textit{subtype})

3. Negative selection biomarker (KRAS mutations define \textit{non-responders})
Strategies: Integrated Biomarker Throughout Development

C. Co-development of drug and diagnostic

Mainly in oncology but also ID, CR and neuro
Clinical trials may exclude biomarker (-) group
Applications reviewed in CDER and CDRH per SOP
Label requires FDA-approved test
Required testing may appear in different places

*Generally the strongest statistically since clinical trials are designed to provide evidence of efficacy for drug and qualify performance of diagnostic test*
Major Genetic Tests Representing Biomarkers and Their Roles

1. Gene rearrangements that predict efficacy (ALK+ metastatic NSCLC and crizotinib)

2. Gene mutations in monogenic disorders (delta 508 mutation in CTFR gene to diagnose CF and target treatment (G551D mutation and ivacaftor)

3. Gene mutations to identify non-responders (BRAF V600E mutation-negative metastatic melanoma patients)
Regulatory Thinking With Respect to Biomarkers and Personalized Medicine

Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
Document issued on: March 13, 2007

Design Considerations for Pivotal Clinical Investigations for Medical Devices
This guidance document is being distributed for comment purposes only.
Document issued on: August 15, 2011

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications
Document issued on: March 28, 2012

Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm
Thanks for Your Time and Attention

Questions – Comments

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