Pharmacogenetics in Medicine: Barriers, Critical Factors, and a Framework for Dialogue

University of Michigan Center for Statistical Genetics/GSK
Statistical & Genomic Challenges for Clinical Studies & Practice
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Office of Clinical Pharmacology, U.S. FDA
October 1st in History

1908 - Ford puts Model T on the market for $825
Overview

• An N of One: How Personal is Personal?
• The Environment: 30,000 ft and Climbing
• What are the barriers to translation?
• What are the critical factors for uptake?
• Questions for consideration
• [Won’t address FDA infrastructure but happy to]

Disclaimer: The views expressed are those of the speaker and do not necessarily reflect the official policy of the FDA. No official endorsement is intended or should be inferred.
An N of One

• 33 yo Caucasian woman
• April 2008: Pelvic US due to ~ 1 yr h/o heavy and prolonged (7-10 days) menstruation, weight loss.
• Diagnosed with fibroid. No atypical pap test. OC seen as an option, but in the setting of intolerance to bleeding (QOL).
• Nov 2008: 2nd pelvic US conducted because of continued symptoms. Fibroid has possibly grown, but unclear if technical. Pt asked for fibroid to be removed.
• Feb 2009: Annual pap test/pre-op. Atypical. D&C done 2 weeks later.
• Dx: Endometrial carcinoma
  • Lowest 5% ile for age
  • Presents screening issues
  • Presents unique treatment dilemma
• Total abdominal hysterectomy and bilateral oophorectomy
How Personal is Personal?

- Stage IA: megestrol acetate (MA) 80 mg QID x 3-4 mos → D&C to see response → MA x 3-4 mos
- Meeting with repro and oncology
- Hysterectomy eventual
- Personalized medicine: patient-specific and appropriate treatment decision based on imperfect data

27 articles
81 patients
76% initial response rate
Median TTR: 12 wks
20 patients pregnant ≥1 s/p tx
0 % mortality

Ramirez et al 2004 [PMID 15385122]
How Personal is Personal?
The Environment: 30,000 Feet

References to “Personalized Medicine”

MONTHLY 2005-08

<table>
<thead>
<tr>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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And Climbing: Shift in the Classic Thinking

Piquette-Miller and Grant 2007 [PMID 17339856]
And Climbing: Pgx Recontextualized

Systems biology approaches

<table>
<thead>
<tr>
<th>Genome</th>
<th>Transcriptome</th>
<th>Proteome</th>
<th>Metabolome</th>
</tr>
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<tbody>
<tr>
<td>DNA</td>
<td>mRNA</td>
<td>Proteins</td>
<td>Metabolites</td>
</tr>
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</table>

Genotyping assays: Microarray, QRT–PCR

Proteomics: LC–MS/MS, NMR, MALDI–MS/MS, 2D gels–MS

Metabolomics: NMR, GC–MS, LC–MS, FT–IR

Orr et al. 2007 [PMID 17259954]
Cancer-drug refund scheme backed

A watchdog has endorsed a new scheme under which a bone marrow-cancer drug's manufacturers would refund the NHS if a patient did not respond to treatment.

The National Institute for Health and Clinical Excellence is recommending multiple myeloma patients in Wales and England should get Velcade on the NHS.

But it said the NHS should pay for the drug, which costs about £18,000 per patient, only when it worked.
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Barriers to Translation

1. The evidence conundrum
2. Uncertainty re: clinical course of action (use/interpretation)
3. Limited incorporation into clinical guidelines
4. The abuse of “clinical utility”
5. Assay validity
6. Time to results
7. Cost

4 Ps (Patient/provider/payer perspective)
Education
Exploratory Biomarkers

“Valid” Biomarkers

Adapted from F. Goodsaid
Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

Eric Van Cutsem, M.D., Ph.D., Claus-Henning Köhne, M.D.,
Erika Hitre, M.D., Ph.D., Jerzy Zaluski, M.D., Chung-Rong Chang Chien, M.D.,
Anatoly Makhson, M.D., Ph.D., Geert D’Haens, M.D., Ph.D., Tamás Pintér, M.D.,
Robert Lim, M.B., Ch.B., György Bodoky, M.D., Ph.D.,
Jae Kyung Roh, M.D., Ph.D., Gunnar Fölprecht, M.D., Paul Ruff, M.D.,
Christopher Stroh, Ph.D., Sabine Tejpar, M.D., Ph.D.,
Michael Schlichting, Dipl.-Stat., Johannes Nipppen, M.D.,
and Philippe Rougier, M.D., Ph.D.

Study Using Pharmacogenetics to Select Treatment for Head and Neck Cancer (PGx-SELECT)

This study is not yet open for participant recruitment.
Verified by Georgetown University, April 2009

First Received: April 13, 2009  Last Updated: April 14, 2009  History of Changes

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<tr>
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The Human Genome And Translational Research: How Much Evidence Is Enough?

Given the lack of a robust translational infrastructure, conflict between those developing new technologies and those who must use or pay for them seems inevitable.

by Janet Woodcock

ABSTRACT: Multiple new genomic diagnostic tests are currently under development. Given the lack of an efficient translational infrastructure, it is not clear how, or whether, robust evidence for their clinical value will be generated. [Health Affairs 27, no. 6 (2008): 1616–1618; 10.1377/hlthaff.27.6.1616]
Conceptual Risk Assessment for Evidentiary Standards

Modified from L. Lesko
The Pgx Pyramid:
Assessing the Likelihood for Uptake

Clinical Situation/Need
Marker Association
Clinical Variables
Clinical Course
$ 

Magnitude and significance
Replication
Biological plausibility
Functionality, mechanistic support
Gene-dose effect
Support by analogy

Limited Incorporation into Clinical Guidelines

• Pre-requisite for pushing Pgx into practice
• “Epitome of evidence-based medicine”
• In cardiology:
  - 11% level A (multiple randomized trials or meta-analyses)
  - 41% level B (a single randomized trial or nonrandomized studies)
  - 48% level C (expert opinion, case studies, or standards of care)
• Of class I recommendations (procedure/treatment is useful or effective)
  - 19% level A

Califf et al 2009 [PMID 19244190]
The Abuse of “Clinical Utility”

Guilty Parties
Researchers
MDs
Pharmacists
Regulators
Payers

Recommendations from the EGAPP Working Group:
Can tumor gene expression profiling improve outcomes in patients with breast cancer?

EGAPP Recommendation Statement

December 2007 · Vc

Recommend
Testing for
adults selectiv
Evaluation of Ge
### Actionable Pharmacogenetics

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Tumour type</th>
<th>Prognostic value</th>
<th>Predictive value</th>
<th>Therapy</th>
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<tr>
<td></td>
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<td>LOE</td>
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</tr>
<tr>
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<td>Yes</td>
<td>I</td>
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<tr>
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<td>GIST</td>
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<td>Yes, subgroup&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>NSCLC</td>
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<td>Yes, subgroup&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
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<tr>
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<tr>
<td>VEGF</td>
<td>RCC</td>
<td>Yes</td>
<td>No</td>
<td>II</td>
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</tbody>
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LOE: level of evidence; ER: oestrogen receptor; PR: progesterone receptor; BRCA: breast cancer; GIST: gastrointestinal stromal tumours; EGFR1: epidermal growth factor receptor 1; NSCLC: non-small cell lung cancer; CRC: colorectal cancer; TRAIL: tumour necrosis factor (TNF)-related apoptosis-inducing ligand; NK: not known; VEGF: vascular endothelial growth factor; RCC: renal cell carcinoma.

<sup>a</sup> c-KIT exon 11 mutation.
<sup>b</sup> c-KIT exon 9 mutation.
<sup>c</sup> EGFR1 exon 18, 19 or 21 mutation.

Oldenhuis et al 2008 [PMID 18396036]
Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA. A significant increase of labels containing such information has been observed over the last decade. In order to provide a reference for genomic biomarkers in labels of FDA-approved drug products, we created the table shown below. Genomic biomarkers can play an important role in identifying responders and non-responders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. In the context of drug labels, these genomic biomarkers can be classified on the basis of their specific use, for example:

- Clinical response and differentiation,
- Risk identification,
- Dose selection guidance,
- Susceptibility, resistance and differential disease diagnosis,
- Polymorphic drug targets.

The table portrays a view on valid genomic biomarkers in the context of FDA-approved drug labels. It provides a comprehensive list of these markers and links to pharmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provide pharmacogenomic information with no immediate recommendation for a specific action (i.e. genetic testing); however a few labels recommend or require genetic testing thereby specifying the use of these markers for reaching a therapeutic decision.
Barriers to Translation

1. The evidence conundrum
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6. Time to results
7. Cost

4 Ps (Patient/provider/payer perspective)
Education
Critical Factors for Uptake

HLA-B*5701 test orders by Qr 2002-2008

Test orders

1st Qr 02
1st QR 05
2nd Qr 05
3rd Qr 05
4th Qr 05
1st Qr 06
2nd Qr 06
3rd Qr 06
4th Qr 06
1st Qr 07
2nd Qr 07
3rd Qr 07
4th Qr 07
1st Qr 08
2nd Qr 08

Time

FDA drug label update
NEJM Publication
Intl Aids Mtg Presentation
DHHS HIV Guideline Inclusion
HLA Association Published
Clinical Test Introduced

Lai-Goldman and Faruki 2008 [PMID 19092439]
Critical Factors for Uptake

- Medical specialists more apt to be early adopters (treaters and healers of potentially fatal diseases)
- Patients engaged in wanting to know more about their disease and treatments (activists)
- Networked community
- Incorporation into clinical guidelines
- Publication in high impact journals
- Recognition by regulatory agencies
"Right now, as an oncologist, much of what we do is really barely educated guesswork in terms of what therapy is going to be the best for a particular patient," said Dr. Leif Ellisen, a Mass. General breast cancer specialist. "We needed a new way to think about cancer diagnosis and cancer therapy."
Reduction to Practice Requires Practice

- Started with lung tumors
- N=13 genes and 110 variants
- Predict approved or research drugs that would work by molecular subtype rather than location
  - Could be most relevant for rare tumors
- 5,000 to 6,000 patients/yr capability
- Charge about $2,000 a test and will ask insurers to pay as part of basic care
- If not covered, hospital might absorb the cost or seek payment from patients
Response to Change Curve

- Resisters: 5%
- Fence Sitters: 65%
- Change Agents: 20%
- Visionaries: 5%
CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject  Pharmacogenetic Testing for Warfarin Metabolism

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| Effective Date ......................... 11/15/2008 |
| Next Review Date ....................... 11/15/2009 |
| Coverage Policy Number ............... 0484 |

Hyperlink to Related Coverage Policies
Drug Metabolizing Enzyme Genotyping Systems (AmpliChip™, Invader®)
Genotyping for Thiopurine Methyltransferase (TPMT) Deficiency in Individuals with Inflammatory Bowel Disease (IBD)
Prothrombin Time Home Testing Systems
CVS-Google Health pact now includes drugstores

NEW YORK

CVS Caremark Corp. said Monday it expanded its partnership with Google's health service, allowing CVS pharmacy customers to download their prescription and medication histories to Google Health accounts.

Patients who pick up a prescription at a CVS pharmacy will be able to update their online medical histories directly from CVS.com, the company said. CVS says the program will close a gap in the health care system and make patient
Optimizing Drug Knowledge

Demographics  Exposure  Diet  Compliance  Genetics

Unaccounted Variability (%)

Knowledge of B/R

Time
Questions for Consideration

1) How do we begin a realistic dialogue on levels of evidence (i.e., clinical “utility”)?

2) What is the role of guidelines in advancing the practice of pharmacogenetics?

3) How do we get around the chicken-egg quandary of limited clinical experience-limited recommendations?

4) How might IT enable the practice of patient-centric clinical pharmacy (i.e., precision medicine)?

5) How might statistical genetics enable developers, regulators, and clinicians to move towards more personalized medicine?
A surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient.

If the same applied to drugs they would have been investigated very carefully a long time ago.

Rudolph Buccheim
Beiträge zur Arzneimittellehre, 1849