Personalized Medicine - Quo Vadis?

Conference on Personalized Medicine: Breaking Down the Barriers and Achieving Results

Harvard Medical School
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Felix W. Frueh, PhD
Office of Clinical Pharmacology
CDER/ FDA
Outline

- Personalized Medicine – what is it?
- Then and now – what we can do today that we couldn’t do before
- Biomarkers and (genetic) testing
- Dose and drug selection – some key points to consider
- Drug-test co-development – a paradigm change?
- Other considerations on the quest to get medicine less impersonal

**Theme:** Evidence and Benefit – Risk considerations
IV. Definition of Personalized Medicine

Personalized medicine means different things to different people. Some have suggested that personalized medicine is the application of genomic data to better target the delivery of medical interventions. Others have suggested that it is a crucial tool in the discovery and clinical testing of new products. And others have suggested that it involves the application of sophisticated, clinically useful diagnostic tools that may help determine a patient’s predisposition to a particular disease or condition. In fact, personalized medicine can encompass all of these concepts.

In theory, personalized medicine is the management of a patient’s disease or disease predisposition, by using molecular analysis to achieve the optimal medical outcomes for that individual — thereby improving the quality of life and health, and potentially reducing overall healthcare costs.

In practice, personalized medicine is a comprehensive approach utilizing:

- Molecular analysis of both patients and healthy individuals to guide decisions throughout all stages of the discovery and development of pharmaceuticals and diagnostics; and
- Applying this knowledge in clinical practice for a more efficient delivery of accurate and quality healthcare through improved prevention, diagnosis, treatment, and monitoring methods.

V. Public Policy Issues Impacting Personalized Medicine

Several clusters of significant public policy issues mark the pathway to the growth and acceptance of personalized medicine. While none of these issues is unique to personalized medicine, government regulation of clinical trials, intellectual property rights, licensing practices, healthcare reimbursement, and privacy are among the areas that may need to be re-examined.
Personalized Drug Therapy: The Right Drug ...
at the Right Dose ...

... for the Right Patient ...
... at the Right Time.
(Personalized) Medicine: Then and Now
(Personalized) Medicine: Then and Now
### Example:
**Leukemia and Lymphoma**

<table>
<thead>
<tr>
<th>Year</th>
<th>Leukemia Types</th>
<th>Lymphoma Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>“Disease of the Blood”</td>
<td></td>
</tr>
<tr>
<td>1960</td>
<td>Leukemia</td>
<td>Lymphoma</td>
</tr>
</tbody>
</table>
| 1970 | Chronic Leukemia  
    Acute Leukemia  
    Preleukemia | Indolent Lymphoma  
    Aggressive Lymphoma |
| 2007 | ~38 Leukemia types identified:  
    - Acute myeloid leukemia (~12 types)  
    - Acute lymphoblastic leukemia (2 types)  
    - Acute promyelocytic leukemia (2 types)  
    - Acute monocytic leukemia (2 types)  
    - Acute erythroid leukemia (2 types)  
    - Acute megakaryoblastic leukemia  
    - Acute myelomonocytic leukemia (2 types)  
    - Chronic myeloid leukemia  
    - Chronic myeloproliferative disorders (5 types)  
    - Myelodysplastic syndromes (6 types)  
    - Mixed myeloproliferative/myelodysplastic syndromes (3 types) | ~51 Lymphomas identified:  
    - Mature B-cell lymphomas (~14 types)  
    - Mature T-cell lymphomas (15 types)  
    - Plasma cell neoplasm (3 types)  
    - Immature (precursor) lymphomas (2 types)  
    - Hodgkin’s lymphoma (5 types)  
    - Immunodeficiency associated lymphomas (~5 types)  
    - Other hematolymphoid neoplasms (~7 types) |

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After Mara Aspinall, Genzyme Genetics (modified)
Idea: Use Molecular Markers to Make Better Treatment Decisions

Gene expression

Imaging

Family history

Clinical data

Information integration

Was the outcome predicted accurately?

Real Outcome

Outcome Prediction

Treatment decision

Proteomics

Metabolomics

SNPs

Proteomics

Imaging

Gene expression
In Milestone, FDA Pushes Genetic Tests Tied to Drug

Agency Seeks to Tame Risks of Blood Thinner; Some Doctors Protest

Genetic Test Approved for Sensitivity to Blood Thinner

Some people who take Coumadin at higher risk of bleeding

The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR responses to COUMADIN (see CLINICAL PHARMACOLOGY and PRECAUTIONS).
CYP2C9 and VKORC1 Testing - Better Estimation of Warfarin Starting Dose

Genetics and other clinical factors can help to assess approx. 60 percent of the variability in warfarin dose.
KEY POINTS TO KEEP IN MIND…

• Genetic tests not required
• Encourage doctors to consider genetics in initial warfarin doses
• Genetic tests are available
• Prevalence of genetic variants in different ethnic/racial groups
• Non-genetic factors also important
• INR monitoring is still essential
Tamoxifen Metabolic Pathway

Conclusion

- In this trial, CYP2D6 metabolism was an independent predictor of clinical outcome in postmenopausal women with ER positive early breast cancer.
- The effect of impaired metabolism was most marked in poor metabolizers.
- Consistent with clinical data that tamoxifen activation to endoxifen is dependent upon CYP2D6.
- These data suggest that determination of CYP2D6 genotype may be of value in selecting adjuvant hormonal therapy and moderate/potent CYP2D6 inhibitors should not be co-administered with tamoxifen.
Useful, because alternatives exist: Hormonal Therapies of Breast Cancer

- Selective Estrogen Receptor Modulator
  - Tamoxifen

- Aromatase Inhibitors
  - Anastrazole (Arimidex)
  - Letrozole (Femara)
  - Exemestane (Aromasin)
Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA. A significant increase in labels containing such information has been observed over the last decade. In order to provide a reference for pharmacogenomic 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.

The table includes:

- Context-specific biomarker (column 1)
- Reference drug label information about the biomarker context within which the drug was approved (column 2 subsection 1)
- Test criteria (column 2 subsection 2)
- Prototype drug associated with the label information defining the biomarker context (column 2 subsection 3)
- Other drugs in a similar context (column 3)
- Pertinent references (column 4)

Drugs sharing the context of a specific biomarker in their labels have had their pharmacogenomic information extracted into this table. This information can be accessed by placing the mouse over the symbol under the right side of the drug name. All approved drugs in this table are linked to labels at Drugs@FDA which can be accessed by clicking over symbols under the left side of the drug name. The table will be updated on a quarterly basis.

The information provided in "label context" is taken from different sections of the actual drug labels.

The term "valid" biomarker has been defined in the "Guidance for Industry: Pharmacogenomic Data Submissions". Therein, a valid biomarker is described as a "biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that establishes the physiologic, toxicologic, pharmacologic, or clinical significance of the test results."

The classification of biomarkers is context specific.

A critical aspect of many of these drugs is the role they play in drug-drug interactions. This list does not address drug-drug interactions. More information on drug-drug interactions, please see Drug Development and Drug Interactions.

Reference is made to the requirement of testing for the biomarker:
1 = test required,
2 = test recommended,
3 = information only.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Label Context</th>
<th>Examples of other</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker</td>
<td>Representative Label</td>
<td>Label Context</td>
<td>Test</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------</td>
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</tr>
<tr>
<td>C-KIT expression</td>
<td>Gastrointestinal stromal tumor c-Kit expression</td>
<td><em>In vitro</em>, imatinib inhibits proliferation and induces apoptosis in gastro-intestinal stromal tumor (GIST) cells, which express an activating c-Kit mutation. Gefitinib is also indicated for the treatment of patients with c-Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).</td>
<td>3</td>
</tr>
<tr>
<td>CYP2C19 Variants</td>
<td>CYP2C19 Variants (Poor Metabolizers-PM and Extensive Metabolizers-EM) with genetic defect leads to change in drug exposure.</td>
<td><em>In vivo</em> studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.</td>
<td>3</td>
</tr>
<tr>
<td>CYP2C9 Variants</td>
<td>CYP2C9 Variants PM and EM genotypes and drug exposure.</td>
<td>Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.</td>
<td>3</td>
</tr>
<tr>
<td>CYP2D6 Variants</td>
<td>CYP2D6 Variants</td>
<td>Atorvastatin is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atorvastatin compared with people with normal activity (EMs).</td>
<td>3</td>
</tr>
<tr>
<td>CYP2D6 with alternate Context</td>
<td>CYP2D6 Variants</td>
<td>CYP2D6 PM and EM variants and drug exposure and risk.</td>
<td>3</td>
</tr>
</tbody>
</table>

References (PubMed ID):
**In the Works**

- *New guidance* for industry on “Clinical Pharmacogenomics in early drug development”
- Related to PK/PD and Pharmacogenomics (e.g. what should we do with pharmacogenomics and drug metabolism genotypes)
- Determine:
  - Details on "what are the questions" (i.e., the goals of a PGx study)
  - How to go about getting results that matter (i.e., study designs and the use of M/S to design adequate studies)
  - What to do with the results of PGx studies (i.e., data analysis and labeling)
- *Planned to have a draft ready in early 2008*
The Right Drug for the Wrong Patient?

The response rate to current medicines is often unacceptably low:

After Spear et al. TRENDS in Molecular Medicine Vol.7 No.5 May 2001
**Trastuzumab (Herceptin®)**

In a normal breast tissue cell, the Her-2 gene is expressing cell surface receptor required for normal cell growth.

In certain types of breast cancers, the Her-2 gene is over-expressing this cell surface receptor, contributing to cancerous cell growth. This is the case in ~30% of breast cancers.

**Herceptin (trastuzumab)** is an antibody that blocks the cell surface receptor and thereby prevents further growth. As a result, disease progression is slowed down.
Gefitinib (Iressa)

- Selective inhibitor of EGFR tyrosine kinase domain
- Approved under sub-part H (accelerated approval) for treatment of NSCLC in 2004
- In Dec 2004, pivotal trial (ISEL) did not show survival benefit over placebo
- Nevertheless a subset of patient (~10%) showed significant improvements
- Market withdrawal and access program put in place in 2005
- Current indication: IRESSA is indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from IRESSA
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.
Gefitinib (Iressa), cont’d

- New *exploratory* biomarkers for prediction of response to gefitinib have been identified:

  - **Genetic variations in tumor**
    - Positive results of (small) prospective trials
      - Example: results published at ASCO 2007; abstract #7504, Sequist et al; 31 patients with genetic variations in EGFR treated; RR 58% - problem is, that there are no matched controls, i.e. we don’t know how a patient with the same genetic variation would progress without treatment

- **EGFR gene copy number**
  - In same study, 71% of treated patients had also gene amplification or polysomy
  - Several other reports illustrate that gene copy number (FISH) could be an important predictive factor for gefitinib therapy
Some Key Questions About Getting This Evidence and Consequences

- At what point is retrospective data good enough?
  - E.g., recent warfarin study results confirm conclusions reached two years ago based on retrospective data
  - How can we better use existing data sources?

- When are randomized controlled trials to create the evidence for genetic testing really needed?
  - E.g., warfarin trial: when should genetic test be performed?

- But: multivariate problem with highly complex tests: how to avoid random and meaningless associations?
Breaking Down the Barriers

... two fundamental aspects of personalized medicine that don’t fit our current paradigm of drug development and approval:

- “Superiority” on a population basis does not necessarily reflect the best choice for an individual
  
  (A treatment with a 10% advantage over a comparator may still be the wrong treatment for a lot of people)

- “Low efficacy” can still mean that a subset of patients has a dramatic response – how can we ensure that these patients are identified and the drug is being developed?

- New and innovative approaches are needed...
Genome-wide SNP Analyses

Genome-wide pharmacogenetic investigation of a hepatic adverse event without clinical signs of immunopathology suggests an underlying immune pathogenesis

One of the major goals of pharmacogenetics is to elucidate mechanisms and identify patients at increased risk of adverse events (AE). To date, however, there have been only a few successful examples of this type of approach. In this paper, we describe a retrospective case-control pharmacogenetic study of an AE of unknown mechanism, characterized by elevated levels of serum alanine aminotransferase (ALT) during long-term treatment with the oral direct thrombin inhibitor ximelagatran. The study was based on 74 cases and 130 treated controls and included both a genome-wide tag single nucleotide polymorphism and large-scale candidate gene analysis. A strong genetic association between elevated ALT and the MHC alleles DRB1*07 and DQA1*02 was discovered and replicated, suggesting a possible immune pathogenesis. Consistent with this hypothesis, immunological studies suggest that ximelagatran may have the ability to act as a contact sensitiser, and hence be able to stimulate an adaptive immune response. The Pharmacogenomics Journal advance online publication, 15 May 2007; doi:10.1038/sj.tpj.6500458

Keywords: pharmacogenetics; pharmacogenomics; adverse event; immune system; liver injury

Introduction

Ximelagatran, marketed as Exanta, was developed for the prevention and treatment of thromboembolism. In patients treated with ximelagatran for more
Whole Genome Scans

“Man, that record came out and was real big in Memphis. They started playing it, and it got real big. Don't know why – the lyrics had no meaning.”

*Elvis Presley*
Genomic signatures to guide the use of chemotherapeutics

Anil Potti\textsuperscript{1,2}, Holly K Dressman\textsuperscript{1,3}, Andrea Bild\textsuperscript{1,3}, Richard F Riedel\textsuperscript{1,2}, Gina Chan\textsuperscript{4}, Robyn Sayer\textsuperscript{4}, Janiel Cragun\textsuperscript{4}, Hope Cottrill\textsuperscript{4}, Michael J Kelley\textsuperscript{2}, Rebecca Petersen\textsuperscript{5}, David Harpole\textsuperscript{5}, Jeffrey Marks\textsuperscript{5}, Andrew Berchuck\textsuperscript{1,6}, Geoffrey S Ginsburg\textsuperscript{1,2}, Phillip Febbo\textsuperscript{1,3}, Johnathan Lancaster\textsuperscript{1} & Joseph R Nevins\textsuperscript{1,3}

Gene expression signatures predict sensitivity to individual chemotherapeutic drugs

Signatures can accurately predict clinical response

When combined, could also predict response to multidrug regimens

“The development of gene expression profiles that can predict response to commonly used cytotoxic agents provides opportunities to better use these drugs, including using them in combination with existing targeted therapies”

→ Useful for drug selection!

But how can we better develop these drugs in the first place?

- Drug-Test Co-Development: making the biomarker an integral part of the drug development process
Consideration of impact on label: Is it a “development only” biomarker or should it be used in the market?
Biomarker and assay development process

Early Assay Development

Clinical Utility and Validation

Possible Need for Platform Change

Analytical Validation

Marker Discovery

Marker and Assay Development

Basic Research

Prototype Design or Discovery

Preclinical Development

Clinical Development

Phase 1

Phase 2

Phase 3

FDA Filing/Approval & Launch

Early Go/No-Go Decision Points (includes decision about use of marker in further development)

Late Go/No-Go Decision Points (other decision points exist, e.g. EOP2a) – main decision points for marker discovery in phase 2
Sponsor – Regulator Interactions

Voluntary Submissions

VXDS

Investigational Phase pre-IDE or IDE Meeting as appropriate

PMA or 510(k) Application

Basic Research

Prototype Design or Discovery

Preclinical Development

Clinical Development

Phase 1

Phase 2

Phase 3

FDA Filing/Approval & Launch

Pre-IND Meeting

Initial IND Submission

Ongoing Submission

End of Phase 2A Meeting

End of Phase 2 Meeting

Pre-BLA or NDA Meeting

Drug Market Application

Early Go/No-Go Decision Points

(includes decision about use of marker in further development)

Late Go/No-Go Decision Points

(other decision points exist, e.g. EOP2a) – main decision points for marker discovery in phase 2
But why stop learning when the drug is on the market?
A proposal to create larger safety and efficacy databases, assess biomarkers

Monitor the first e.g. 100,000 patients that receive the drug, collect samples from patients experiencing an AE and from matched controls, conduct e.g. WGA to identify genetic basis for AE and what could be done to prevent it in future.

- Biomarker Characterization
- Exploratory (Learn)
- Validation (Confirmatory)
- Modeling and Simulation
- Continuous Interaction with health authorities

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Monitor the first e.g. 100,000 patients that receive the drug, collect samples from patients experiencing an AE and from matched controls, conduct e.g. WGA to identify genetic basis for AE and what could be done to prevent it in future.
What We Could Learn Using this Approach

- Who really benefits from a particular treatment
- Who might be at risk for an adverse event
  - (this is the only strategy that would help us to learn more about the molecular mechanisms of rare adverse events: “retrospective” sample collection approaches do not work)
- If indeed we have the right dose
- Comparative effectiveness
- Clinical utility of testing (reimbursement?)
- Actual response rate and what factors may influence it
- Aspects of compliance
- How to educate physicians about molecular medicine
- ...
Translation into Clinical Practice -

The two Elephants in the Room:
Reimbursement - How Much Evidence Is Needed?
Drug companies like to say that their most expensive products are fully worth their breathtaking prices. Now one company is putting its money where its mouth is — by offering a money-back guarantee.

Johnson & Johnson has proposed that Britain’s national health service pay for the cancer drug Velcade, but only for people who benefit from the medicine, which can cost $48,000 a patient. The company would refund any money spent on patients whose tumors do not shrink sufficiently after a trial treatment.

“I and others suggested a money-back guarantee on a cancer drug looked silly,” said Dr. Tunis, who is now director of the nonprofit Center for Medical Technology Policy.

“ ‘Oh, I’m sorry your grandma died. Here’s your money back.’ ”

Transcription of Genes

During transcription, which occurs in the cell’s nucleus, a messenger RNA (mRNA) strand is synthesized using the gene’s DNA as a template. The double-stranded DNA opens up to expose each single strand.

The strand encoding the gene becomes the template for the synthesis of an mRNA strand.

The mRNA strand is synthesized by sequential addition of nucleotides that are complementary to those on the DNA template strand.

After viewing the animation, click Next to continue.
Pharmacogenomics and Biomarkers in Oncology
by Felix W. Frueh, PhD

Progress in the translation of pharmacogenomic knowledge in drug development and clinical practice has been most rapid in the areas for which we understand, at least to some extent, the molecular mechanisms that lead to pathophysiology and, therefore, can be utilized to explore drug function.

NEWS & EVENTS
01.01.07: Article Introduction
This is an example of a news article. This is the 1st slide.
The articles are short, punchy and can be updated quickly across the entire site.

LEGEND
As you select a slide, this helix shows you which slide you are currently on.
Lastly, New Legislation

For example:
- Genetic Information Nondiscrimination Act (GINA)
- Genomics and Personalized Medicine Act

110TH CONGRESS
1ST SESSION

H. R. 493

To prohibit discrimination on the basis of genetic information with respect to health insurance and employment.

IN THE HOUSE OF REPRESENTATIVES
JANUARY 16, 2007

S. 976

To secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments.

IN THE SENATE OF THE UNITED STATES
MARCH 21, 2007

Mr. Obama, the sponsor of this bill, introduced the following bill, which was read twice and referred to the Committee on Health, Education, Labor, and Pensions:

A BILL
To secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.
This Act may be cited as the "Genomics and Personalized Medicine Act of 2007".
All of the fruits of the tremendous explosion in innovation that’s been occurring in biomedical research — which make the molecular metamorphosis possible — fulfill their purpose only when they are translated into interventions and solutions that are applied to patients.

Dr. A. von Eschenbach, April 6, 2006
THANK YOU!

www.fda.gov/cder/genomics

Felix.Frueh@hhs.fda.gov
Office of Clinical Pharmacology
FDA/CDER