Personalized Medicine - Quo Vadis?

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

Harvard Medical School
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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 those 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

Mendel: Experiment 1
Example: Leukemia and Lymphoma

<table>
<thead>
<tr>
<th>Year</th>
<th>Leukemia Types</th>
<th>Lymphoma Types</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1950</strong></td>
<td>“Disease of the Blood”</td>
<td></td>
</tr>
<tr>
<td><strong>1960</strong></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) |

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

- Gene expression
- Imaging
- Family history
- Clinical data
- Proteomics
- Metabolomics
- Information integration

Was the outcome predicted accurately?

Real Outcome

Outcome Prediction

Treatment Decision
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

Tamoxifen (TAM) → CYP2D6
(CYP2B6, CYP2C9, CYP2C19, CYP3A)
→ 4-hydroxyTAM
CYP3A4/5
(CYP2C9 + other CYP isoforms)
→ N-desmethylTAM
CYP2D6
→ Endoxifen

**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.

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Useful, because alternatives exist: Hormonal Therapies of Breast Cancer

- Selective Estrogen Receptor Modulator
  - Tamoxifen

- Aromatase Inhibitors
  - Anastrazole (Arimidex)
  - Letrozole (Femara)
  - Exemestane (Aromasin)
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 in the number 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.

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)
- Prototypic 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 pharmacogenetic 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>
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<tr>
<td><strong>C-KIT expression</strong></td>
<td>Gastrointestinal stromal tumor c-Kit expression</td>
<td><em>In vitro,</em> imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation. <em>Gleevec</em> is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).</td>
<td>3</td>
</tr>
<tr>
<td><strong>CYP2C19 Variants</strong></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><strong>CYP2C9 Variants</strong></td>
<td>CYP2C9 Variants PM and EM genotypes and drug exposure; <em>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.</em></td>
<td>CYP2C9 Variants PM and EM genotypes and drug exposure</td>
<td>3</td>
</tr>
<tr>
<td><strong>CYP2D6 Variants</strong></td>
<td>CYP2D6 Variants <em>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).</em></td>
<td>CYP2D6 Variants</td>
<td>3</td>
</tr>
<tr>
<td><strong>CYP2D6 with alternate context</strong></td>
<td>CYP2D6 PM and EM Variants and drug exposure and risk. <em>Population who are known to have a genetic defect leading to reduced levels of activity of P450 2D6. Therefore, like other agents that are metabolized by the P450IIID6 system and have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving atorvastatin concurrently or has taken it in the previous 5 weeks.</em></td>
<td>CYP2D6 PM and EM Variants and drug exposure and risk</td>
<td>3</td>
</tr>
</tbody>
</table>
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 patients (~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
Gefitinib (Iressa), cont’d

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.
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?
... 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

“Our data further suggest that a biomarker test based on DRB1*07 would have been able to detect patients at risk of the AE with sensitivity of 47% and specificity of 83%.”

What does FDA think?

If at-risk patients can be excluded, a suspected hepatotoxic drug would be potentially approvable, in the context of the overall risk/benefit analysis for the drug.
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*
New gene expression approaches to guide the use of existing chemotherapy

Genomic signatures to guide the use of chemotherapeutics

Anil Potti¹,², Holly K Dressman¹,³, Andrea Bild¹,³, Richard F Riedel¹,², Gina Chan⁴, Robyn Sayer⁴, Janiel Cragun⁴, Hope Cottrill⁴, Michael J Kelley², Rebecca Petersen⁵, David Harpole⁵, Jeffrey Marks⁵, Andrew Berchuck¹,⁶, Geoffrey S Ginsburg¹,², Phillip Febbo¹–³, Johnathan Lancaster¹ & Joseph R Nevins¹–³

Gene expression signatures to guide the use of chemotherapeutics

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
**Drug-Test Co-Development**

- **Characterize and learn about the biology, e.g. identify affected biological pathways**

- **Validation**

- **Basic Research** → **Prototype Design or Discovery** → **Preclinical Development** → **Clinical Development** → **Clinical Development** → **Clinical Development** → **Clinical Development** → **FDA Filing/Approval & Launch**

- **Identification of Disease Targets**
- **Optimizing the Safety Profile**
- **Streamline Clinical Trials (Enrichment, Stratification)**

- **Target Optimization**

- **Drug Label**

  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

Basic Research → Prototype Design or Discovery → Preclinical Development → Clinical Development1 → Clinical Development2 → Clinical Development3 → 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**

[Diagram showing various stages of drug development and regulatory interactions, including Basic Research, Prototype Design or Discovery, Preclinical Development, Clinical Development phases (Phase 1, Phase 2, Phase 3), and FDA Filing/Approval & Launch.]

- **Analytical Validation**
- **Clinical Utility and Validation**
  - Investigational Phase pre-IDE or IDE Meeting as appropriate
- **PMA or 510(k) Application**

**Early Assay Development**

**Voluntary Submissions**

**Marker Discovery**

**VXDS**

**Early Go/ No-Go Decision Points**
- 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 point for Market discovery in phase 2

**Pilot**

**Preclinical Research**

**Basic Research**

**Prototype Design or Discovery**

**Preclinical Development**

**1-Phase Development**

**2-Phase Development**

**3-Phase Development**

**FDA Filing/Approval & Launch**

**Drug Market Application**

- Pre-IND Meeting
- End of Phase 2A Meeting
- Initial IND Submission
- End of Phase 2 Meeting
- Drug Market Application
- FDA Filing/Approval & Launch
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.
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?
Alternative Reimbursement

“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.
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

Ms. Slaughter (for herself, Mrs. Biggert, Ms. Eshoo, Mr. Walden of Oregon, Mr. George Miller of California, Mr. Dingell, Mr. Rahall, Mr. Abercrombie, Mr. Alexander, Mr. Allen, Mr. Bachus, Mr. Baker, Ms. Baldwin, Mr. Bartlett of Maryland, Mr. Bilbray, Mrs. Blackburn, Mr. Broun, Mrs. Brown of Florida, Mr. Burton of Indiana, Mr. Calvert, Mrs. Capito, Mrs. Capps, Mr. Capuano, Mr. Castle, Mr. Chabot, Mr. Chandler, Mr. Cole of
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

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FDA/CDER