Co-Development of Drugs and Diagnostics: Case Studies

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Pharmacogenetics

The Basic Science of “Personalized Medicine”
Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers... of P4502D6 exhibiting 2-3 fold higher plasma concentrations.
Personalized Medicine is stalled. Example: Capecitabine Marketed in 1998

February 7, 2000

Roche Developing Diagnostic Assay To Predict Xeloda Response

Roche is developing a tumor-specific assay to target the metastatic breast cancer therapy Xeloda (capecitabine) to patients more likely to respond.

The investigational diagnostic identifies biomarkers for three enzymes (and associated genes) that play a role in metabolizing Xeloda, the company said.

Xeloda is converted to the active drug 5-fluorouracil at the site of the tumor. The enzyme thymidine phosphorylase is responsible for the last stage of conversion and dihydrouracil de-hydrogenase is necessary to break down 5-FU. Thymidylate synthase is an enzyme inhibited by 5-FU.

A combination of a high TP/DPD ratio and a low TS concentration may augur a positive response by the patient. On the other hand, a small percentage of patients with practitioners as part of Roche’s flu surveillance program. However, Roche indicated that it is developing the test as a potential OTC diagnostic, where it could be useful in helping consumers determine whether to seek medical treatment.

“When with Tamiflu, we have... a synergistic action of both the diagnostic and the therapeutic,” Roche VP-Genetics Klaus Lindpaintner, PhD, told the European Center for Pharmaceutical Information annual pharmacogenomics meeting Jan. 19 in London.

The focus of the conference was on how collecting data on single nucleotide polymorphisms could lead to development of better-targeted therapeutics.

Roche pioneered one of the first targeted therapies through its marketing of its Genetech

SNP-based targeting will first be applied to adverse event screening, former SB exec Poste says.
Recent example: Irinotecan

All Patients with Same Diagnosis (10% risk)

PGx profile for high risk (50%): treat with alternative drug or dose

PGx Profile for moderate risk (12.5%): treat with alternative drug or dose

PGx Profile for low risk (0%): treat with conventional dose
FDA Clears Genetic Test That Advances Personalized Medicine
Test Helps Determine Safety of Drug Therapy

August 22, 2005
Genotyping

Affymetrix AmpliChip
Order Your Genotype

Ordering Tests
Now you can add another dimension to providing safer and more efficacious care to your patients by ordering DNA Drug Reaction Profiles for them. Each pharmacogenetic test is only $250.00, $600 for a standard panel that includes 2D6, 2C9, and 2C19, or $1000 for all five. Five-day stat testing is available for an additional $100. The process couldn’t be simpler, we provide you with a cheek swab collection kit and prepaid shipping to return samples to our laboratory. Call 800 523-3080 for more information or to obtain collection kits.

Researchers using CYP2C9 genotyping in a major anticoagulation clinic reached the following conclusions relative to patients carrying one or two of the CYP2C9 variant alleles. (JAMA 287,1690-1692 2002)

- Time to a stable dose is increased 95 days for variant carriers.
- Risk of a serious or life threatening event hazard ratio 2.99 for variants.
- The incidence rate/100 pt years of serious events is 10.92 for variants and 4.89 for wild type individuals.
- The rate for life threatening events is 1.96 for variants and 0.70 for wild type/100 pt years.

Thrombosis & Haemostasis 91,87 2004

CYP2C9 is the most important warfarin detoxification enzyme in the body. It is highly polymorphic, with up to a tenfold reduction in activity based on genotype. Approximately 35% of the population are carriers and 7% homozygous for reduced activity alleles.

Examples of common drugs, foods and herbas that interfere with warfarin metabolism include:

Increase INR
- amiodarone, erythromycin, fluconazole,
- Bacitracin, NSAIDS some statins, Vit K, Dong
But .... Not Reimbursed

Coverage Position

CIGNA HealthCare does not cover AmpliChip Cytochrome P450 Genotyping test because its use in clinical practice is considered experimental, investigational or unproven.

I. Aetna considers genotyping for cytochrome P450 polymorphism (diagnostic tests to identify specific genetic variations that may be linked to reduced/enhanced effect or severe side effects of drugs metabolized by the cytochrome P450 system) experimental and investigational because the clinical value of this type of genetic testing has not been established.

II. Aetna considers the Invader UGT1A1 molecular assay (a screening test for determining the proper dosage of irinotecan for persons with colorectal cancer) experimental and investigational because its clinical value has not been established.
What has delayed the advent of “personalized medicine”?
The Roadblocks for Personalized Medicine

FDA
FDA Medical Product Review 2007

Drugs
Devices
Diagnostics
The Roadblocks for Personalized Medicine Marketplace
10 year Trend in Biomedical R&D Spending

- US Pharmaceutical R&D
- Total NIH Budget
10 year Trend in New Applications to FDA

- Total NMEs Rec'd by FDA
- Original BLAs

New Drug Applications
New Biological Applications
Success Rates 2004: 11% Overall

Nature Reviews: Drug Discovery, 3 (8): 711, 2004
Drug Development 2007
Major Threats to the Industry

Medicare Price Negotiations
Direct to Consumer Advertising
Reimportation of drugs
Generic Biologic Drugs
Toxic Drugs - Vioxx, etc
Counterfeit drugs
Pharmaceuticals: The “Kodak Film” of the digital age?
Are we facing the “sunrise” or a “sunset” for medical product development?
Delivering a new drug to the FDA

One drug – One patent – One NDA

15 years and $2 billion
“The FDA of the future should approve solutions to medical problems.”
Laptop Computer: An example of a “Solution”

- LCD Technology
- Modem
- Wireless
- CD/DVD
- Li battery
- Microprocessor
- Software

Over 20,000 patents
FDA Reviews and Approves

Diagnostics
Drugs
Devices
Advertisements
Post-market Safety
FDA Reviews and Approves

- Diagnostics
- Drugs
- Devices
- Advertisements
- Post-market Safety

Solution

27
“Solutions” will require:

- New policies and regulatory pathways within the FDA
- New commercial relationships for diagnostic & pharmaceutical companies”
June 2005 – A new “path” is now being discussed!

Drug-Diagnostic Co-Development Concept Paper

Draft — Not for Implementation
FDA of the Future

Solutions
Targeted Therapies (Personalized Medicine)
Targeted Cancer Treatment

• A call for combined drug/diagnostic/device solution
  – FDA, NCI, CMS
Targeted Lung Cancer Treatment
EGFR Inhibitors

- Tarceva, Iressa
- Effective in only 10-20%

Needed:
A reliable, predictive biomarker
  - To predict who will respond
  - Tailor the right treatment for the patient
C-Path Lung Cancer EGFR Project

- FDA
- NCI
- CMS
- Companies
  - Pharmaceutical
  - Biotechnology
  - Diagnostic
## C-Path EGFR Industry Participants

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<th>Pharma</th>
<th>Diagnostic</th>
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<tr>
<td>Bristol-Myers Squibb</td>
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<td>Cell Signalling</td>
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EGFR Diagnostics

Agreement to focus on

• Pathology - NSCLC
  – Pathology review
  – Tissue management

• Assays
  – Protein expression (IHC)
  – DNA copy number (FISH)
  – Mutation
“Warfarin will be a first step forward toward … a model for how to do it right for other drug-gene combinations.”

-Steve Gutman, M.D.
Director, Office of In Vitro Diagnostics Device Evaluation and Safety,
FDA, April 19, 2006
Warfarin

Manage thrombosis and thromboemboli
Polymorphic Distribution

Number of Subjects

Metabolic Capacity

PM  EM  URM
Warfarin Clearance

Genetic Influence of CYP2C9 *3

![Bar chart showing predicted clearance (ml/min) for different genotypes: WT (*1/*1) with predicted clearance of 625 ml/min, WT/*3 with predicted clearance of 212 ml/min, and *3/*3 with predicted clearance of 66 ml/min.](chart.png)
Warfarin Dosage

N = 185
Higashi, et al, JAMA, 287:1690, 2002

Daily Dose (mg ± S.D.)

*1/*1  5.63
*1/*2  4.88
*1/*3  3.32
*2/*2  4.07
*2/*3  2.34
*3/*3  1.6
Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2
(vitamin K epoxide reductase multiprotein complex)

- Feb 2004  VKORC1 mutations discovered
- May 2005  Warfarin dose related to mutation
- June 2005  Ethnic variation in VKORC1 haplotypes
- Oct 2005  Combined impact of CYP2C9 and VKORC1
## Individual Dose Variance

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<thead>
<tr>
<th>FACTOR</th>
<th>Percent Variance Explained</th>
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<tr>
<td>CYP2C9 (*2, *3)</td>
<td>18.3%</td>
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<tr>
<td>VKORC1 (C1173T)</td>
<td>15.1%</td>
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<tr>
<td>CLINICAL FACTORS (Age, Sex, Weight)</td>
<td>11.4%</td>
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<tr>
<td>FULL REGRESSION MODEL</td>
<td>44.6%</td>
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Warfarin

Impact of Genetics

Gene Variants – (~70% of patients)
retrospective

• Lower final dose
• Longer time to stable dose
• Greater risk of bleeding

Can a prospective study demonstrate:

1. Greater efficacy  \(\downarrow\) Strokes
2. Less toxicity  \(\downarrow\) Bleeding
Collaborative Warfarin GenoDosing Validation Project

Collaboration between

- C-Path
- FDA
- Univ. of Utah
- Diagnostic Companies
Methods
Warfarin

• Standard of care for conventional warfarin Rx
• Rapid genotype for CYP2C9 & VKORC1
• Clinical factors (age, sex, renal function, diet,
• Drug interactions affecting warfarin response
• Prospective evaluation of genotype-based dosage vs conventional dosing regimen
• Outcomes: INR (primary), adverse events and therapeutic response
Technologies Compared

- Idaho Technologies
- Third Wave Technologies
- Affymetrix GeneChip
- Others
In Conclusion....
We believe it is a "Sunrise"

Thank You