Biomarkers in Clinical Development: Implications for Personalized Medicine and Streamlining R&D in the UK and EU region

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Biomarker Applications Overview

Biomarkers in Early Diagnosis

Biomarkers in Drug Safety

Biomarkers for Targeted Therapies

Potential Drug Rescue Application

Regulatory Issues

Conclusions
Pharmaceutical Biomarkers Applications

Pharma R & D Biomarkers Applications

- Prognostic/Diagnostic
  - Disease Progression
- Safety/Toxicity
  - Efficacy
- Responder/Non-Responder
  - Safety/Efficacy

Discovery
- Pathway Elucidation
- Animal Model Validation

Pre-Clinical Development
- Mechanism of Action
- Product Decision

Clinical Development
- Target Identification / Characterization / Prioritization
Biomarker information needed

- to choose logical targets
- to understand disease complexity
- to select lead compounds
- to optimise drug design
- to determine effective dose
- to reduce trial failure
- to reclassify disease
Biomarkers in Early & Accurate Diagnosis

- Diagnosis of disease through biomarkers - earlier detection than conventional methods (pre-clinical symptoms)
- This allows preventative routine screening as well as faster acute diagnosis
- Early detection allows early treatment regimes and improved survival rates
- Early clinical intervention is proven to be up to 10x more effective at combating the disease than later treatments

Figure 1: Relative survival (5 year or 10 year) among cancer cases diagnosed with distant, regional or distant, and localized disease by year of diagnosis. a) Breast cancer; b) Colorectal cancer; c) Lung cancer; d) Prostate cancer. Source: Surveillance, Epidemiology, and End Results (SEER) 1973-1993, 1999-2002, Stage I-IV, 1973-2002.

Source: Etzioni et al. 2003, Nature Reviews Cancer
Biomarkers / Pharmaco “omics” in Drug Safety

Pharmacology Models → Lead Candidate Selection → Short term regulatory toxicology → Phase I/II A clinical trials

Elucidation of toxic mechanisms

Protocol refinement
- earlier detection
- lower / optimal dosing

Biomarkers of efficacy / toxicity

Improved predictivity
Annual cost to the NHS of drug interactions is £ 466 M

10% of this could be saved by testing for single nucleotide polymorphisms (SNPs) in the coumarin gene alone

In 2004 the NHS Modernisation Agency put forward ten high impact patient-centred changes for the service improvement and delivery of the NHS.

- Improvement of patient flow across the whole NHS system by improving access to key diagnostic tests

Suggested benefits:

- Improved personalized, appropriate, timely and streamlined care delivery
- Substantial saving of costs, clinician hours and hospital bed days and elimination of waiting lists.

More cost and time effective diagnosis has been recognized as a key bottleneck that prevents smooth patient flow as well as a need to better segment patients according to their specific needs.
Biomarkers for Targeted Therapies – Example Herceptin

- Improve disease management
- Provide a tool for clinical decision making
- Provide patient screening and monitoring value
- Help rule in and out a diagnosis
- Allow patient stratification or patient selection
- Provide information to start / change or stop therapy
Biomarkers for Targeted Therapies – Example Herceptin

- Herceptin (Trastuzumab) in a monoclonal Antibody against the her2/neu receptor
  - HER 2 overexpressed in 25% - 30% of all breast cancer
  - Herceptin is efficacious in ~20% of HER-2 positive patients
  - Overall response rate ~5%

- Three diagnostic tests FDA approved (costs < $100)
  - Normal cut off for serum HER 2 established at 15 ng/ml
  - Est. treatment costs are $7000 per patient
  - Screening valuable until >1.5% responders

- Changes in HER 2 serum levels parallel the clinical course of disease with an 88.6% sensitivity in metastatic breast cancer
  - Increase – disease progression
  - Decrease – response to therapy
Biomarkers for Targeted Therapies – Example Herceptin: Clinical Decision Making

Serum HER-2/neu Levels and Overall Survival


Probability of survival

HER2 ECD < 15 µg/L
p < 0.001

HER2 ECD > 15 µg/L

months
Biomarkers for Targeted Therapies – Example Herceptin: Disease Management

Serum Levels and Clinical Course of Disease

-](Chemotherapy)
- Pre-treatment
- CT Scan Progression
- Chest X-ray Progression
- Responding
- Stable

Weeks

HER-2/neu (ng/ml)

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Where do Biomarkers Create Value in Drug Development

Core Pharmaceutical Business Goals

- Clinically relevant targets
- Screening / Chemistry
- Decision making markers
- New Medicines

Gene function → Protein expression

- potential impact of Biomarkers
Where do Biomarkers Create Value in Drug Development

- Applying pharmacogenomics and other biomarker will reduce drug development times 1.5 – 2 years

- Benefits:
  - Pharma:
    - Reduce attrition
    - Reduce risk / increased productivity
  - Healthcare provider:
    - Reduce Cost
    - Improve patient outcome

- Goal: To move go/ no go decision from phase II to phase I
Predicted NDA dates for molecular therapies

**Key**
- MAbs
- Vaccines
- Anti-Angiogenesis
- Kinase Inhibitors
- Apoptosis Inducers
- Anti-Sense
- Gene Therapy
# Marketed targeted therapies

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Potential Drug Rescue Applications – Alzheimer’s Disease

- 4.5m Americans already have Alzheimer’s and that number could more than triple by 2050.
- NICE's guidance will lead to a ban on the use of Alzheimer's medicines in the NHS
- Absolute need for new biomarkers to show efficacy or to select subpopulation of patients, that respond better to drug
“omics” Utility for Biomarker Applications

- Pharmagenomics:
  - Disease Risk Factors: Alzheimer’s - Apo E allele
  - Drug sensitivity / efficacy: Infl. - Vioxx; Cancer - Iressa

- Pharmacoproteomics:
  - Disease onset: Alzheimer’ - CSF Tau / Abeta
  - Cancer - Her 2, PSA, AFP
  - Disease management: Her 2
  - Acute toxicity: Cardiotox - Troponin
Biomarker Data Integration & Management
From Discovery to Market

- **DISEASE** - Search the OGAP genes for a particular disease.
- **DRUG TREATMENT & RESPONSE**
- **DIAGNOSIS - DUKE STAGES**
- **OMIM** - Search for OGAP genes within chromosomal locations identified using genetic data by OMIM (Online Mendelian Inheritance in Man).
- **IMAGING - CT - MRI - PET**
- **PROTEIN NAME / DESCRIPTION SEARCH** - Search genes using protein descriptions or protein functional annotations.
- **SAMPLE SEARCH** - Search for OGAP gene products that have been observed in different samples.
- **PATIENT ID** - Search for details of a particular patient.
- **SNP** - Enter the rsSNP ID: [ ]

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Biomarker Data Integration & Management
From Discovery to Market

Normal & Disease

mRNA | Protein | SNPs

OGAP Data Integration

Gene Chip | Protein Chip

Clinical Studies

New diagnostic tools for integrated personalized molecular approach to screening, diagnosis, staging, therapy and monitoring of disease
NHS focus on shifting emphasis towards screening and early detection

Goal to shift population-based treatment towards “fine tuning” individual therapy

Data management and integration vital
Regulatory Issues

- FDA Initiative Aims to Bring Biomarkers To Forefront of Drug Development Process
- FDA guidelines on pharmacogenomics:
  - “The promise of pharmacogenomics lies in its ability to individualize therapy by predicting which individuals have a greater chance of benefit or risk and this can be integrated smoothly into drug development processes.”
  - Guidelines can also be used for pharmacoproteomics
  - Likely to be adopted with some revisions by European Regulatory Agencies
- UK NHS initiative likely to providing leadership within Europe
- Goal to achieve more cost effective drug development and reduce healthcare costs
Conclusions

- Biomarkers are going to play a key role in drug development in the next decade

- Healthcare providers will adopt biomarker for cost effective patient management

- Platforms must be able to monitor biomarker panels because:
  - Most diseases are multifactorial
  - There will be a need to screen for several disease in parallel

- Biomarker applications for clinical development require multiple “omics” platforms:
  - Pharmacogen”omics”
  - Pharmacoprote”omics”
  - Pharmacometabon”omics”

- Effective data management of clinical and experimental data across all “omics” platforms will be key to the success on this exciting endeavour
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Discovering the World of Proteins to Develop Targeted Treatment Solutions for Better Individual Care