Personalized Medicine
Challenges in Alzheimer’s Disease

2nd Biomarker Europe Summit
Abridged Materials from Neurological Biomarkers Session
Presenter: Avi Kulkarni
What is Personalized Medicine (PMx)?

- **Definition**: a medical model emphasizing the customization of healthcare, in which decisions are tailored to the characteristics of each patient.

- “The right treatment for the right patient at the right time”

- Also called Tailored Therapeutics, Precision Medicine, and Dx-Rx
We wish the Personalized Medicine story in CNS, particularly Alzheimer’s Disease, were similar to the success stories in Oncology.

Case History: The first PMx success story

### Applicability of Herceptin in Breast Cancer Patients

**Overexpression of HER2 protein & amplification of HER2 gene?**

- ~70-75% No
- ~25-30% Yes
- Other Treatment
- Herceptin

### Herceptin Sales (2000-2011, in CHF bn)

<table>
<thead>
<tr>
<th>Year</th>
<th>Sales (in CHF bn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>0.5</td>
</tr>
<tr>
<td>2002</td>
<td>1.0</td>
</tr>
<tr>
<td>2004</td>
<td>1.4</td>
</tr>
<tr>
<td>2006</td>
<td>3.9</td>
</tr>
<tr>
<td>2008</td>
<td>5.1</td>
</tr>
<tr>
<td>2010</td>
<td>5.4</td>
</tr>
<tr>
<td>2011</td>
<td>5.7</td>
</tr>
</tbody>
</table>

**CAGR +24%**

### Performance

Herceptin demonstrates strong performance today:

- ~90% market share in Japan across Herceptin’s breast cancer indications (2010)
- ~75% penetration in adjuvant breast cancer treatment in top 5 European markets (2008)

### Diagnostic Options

**Immunohistochemistry (IHC):** Usage of antibodies to determine level of HER2 protein expression

**In situ hybridization (ISH):** Usage of DNA probes to determine the level of HER2 gene amplification

### Herceptin MoA & Benefits

**Recombinant humanized monoclonal antibody against HER2** leading to activation of the immune system and suppression of HER2

Sources: Media reports, Booz & Company analysis
There are many reasons for wishing for successes similar to Herceptin/Her-2neu in Alzheimer’s Disease

**Why does PMx matter in Alzheimer’s Disease?**

- Size of the patient population: Prevalence estimates are 35.6 million globally and 5.1 million US
  - The disease incidence is rising in line with the aging population (Ages: 60 = 7%; 71 = 14%)
  - Alzheimer's disease is not a normal part of aging, but the risk of developing the illness rises with advanced age
  - It is estimated that about a half million Americans younger than age 65 have some form of dementia, including Alzheimer's disease (referred to as young onset or early onset)

- High lifetime cost to individuals, care-givers and to society (US economic burden = $148B)

- Poor/ineffective treatments – 30% of patients receiving therapies for Alzheimer’s show any response to medication

Personalized Medicine in Alzheimer’s faces many challenges

*Types of Challenges in Alzheimer’s PMx*

I. Common challenges – PMx program complexity

II. Common challenges – errors and problems in biomarker development

III. Problems specific to Alzheimer’s Disease
Personalized Medicine program complexity makes it hard to convert concepts to practice

1. Identify unmet medical needs: Patient-Journey is critical for developing Tailoring hypothesis

Example: Treatment for MDS non-del (5q) patients

Bone marrow and blood analysis done on potential Hem Onc patient

If IVD: Sale of Kit to Lab

Services Providers

If CLIA validated: Offer test through clinical lab

Education of Physician on Test Availability and Value

2. Stratify patients: Biomarkers or CDx for segmentation of patients with similar disease-biology

Diagnostic Development Process

Biomarker Discovery

Assay (Analytical) Development

Assay (Clinical) Development

Regulatory Approval

Commercialization

If IVD: Sale of Kit to Lab Services Providers

If CLIA validated: Offer test through clinical lab

Education of Physician on Test Availability and Value

3. Develop Rx or Tx solutions: Modify Rx development processes and Rx selection & application

Most patients get Drug X

Minority

Patient only treated with GFs/ ESAs/ Transfusion

Patients may still get supportive care based on the risk profile

Supportive Care?

Yes

No

Majority

Patient treated with Drug X

New rule-in test for Drug X

Identified Low Risk Hem Onc patient who is Drug X appropriate

Source: Booz & Company analysis
I. PMx program complexity

Complexity of PMx capabilities framework

1) These capabilities are specific to diagnostic product type and varies by target product  2) These capabilities vary by offering and go-to-market approach

Source: Booz & Company analysis
Complexity of overlaying diagnostic development onto drug development process

Rx Process

<table>
<thead>
<tr>
<th>Pre-Clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>Lead Identification</td>
<td>Lead Optimization</td>
<td>Candidate Selection</td>
</tr>
<tr>
<td></td>
<td>First Tox Dose (FTD)</td>
<td>First Human Dose (FHD)</td>
<td>First Efficacy Dose (FED)</td>
</tr>
<tr>
<td></td>
<td>First Registration Dose (FRD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High-Level Dx Process

- Tailoring Hypothesis
- Assay Prototyping
- Assay Design
- Assay Development
- Assay Validation

Details of Dx Process

- Biomarker Discovery, Selection, and Measurement
- Assay and Instrument Development
- Analytical and Clinical Validation
- Regulatory
- Pricing, Reimbursement, and Billing
- Manufacturing and Commercial Ops
- Marketing and Sales

Source: Booz & Company analysis
II. Common challenges, errors and problems in biomarker development

Common challenges, errors and problems in biomarker development

Problems with Biomarker Development

- High biological variance
- Experimental design / choice of healthy controls
- Sample variability (collection and storage)
- Poor adjudication of samples
- Training on discovery specimens
- Inability to detect small, but relevant signals
- Over-fitting multiple markers and/or Bias
- Unable to license marker, no freedom to operate
- Failure to anticipate requirements for regulatory approval

Problems with the Disease / Indication

- Is it real?
- Is it homogeneous?
- Does its epidemiology support the program?
- Is there a “gold standard” for diagnostic adjudication?
- Does the diagnostic point of interest want sensitivity, specificity or both?
- What about cost/benefit?
- Are there other solutions and factors specific to the disease indication (e.g., preference for imaging, power of pathologists, medical practice economics)?

Source: Booz & Company analysis
A continuing challenge for the US market is the choice of dual regulatory paths for approval/commercialization of diagnostics.

Regulatory Agencies & Pathways
United States

CMS
CLIA/HIPAA/Reimbursement

CLIA
Lab Testing Services

CMS has authority over diagnostic services

FDA

Department of Health & Human Services

CDRH
Medical Devices Radiation

FDA has authority over diagnostic products (in vitro diagnostic kits)

Office of In Vitro Diagnostics

Other Agencies:
CBER
CDER

Source: Booz & Company analysis
Ways to overcome the challenges

- Choose projects that are doable
- Line up expert advisors
- Listen to clinical advisors
- Focus on validation from beginning
- Build and implement high-quality licensing & regulatory strategy
- Try and find valid samples
- Avoid over-fitting and bias
- Adjudicate properly

- Collaborate
- Gantt out vital components in parallel
- Make only new mistakes
- Fail fast and move on
- Build products to a hybrid regulatory approach (e.g., take advantages of CLIA in the short term, but build FDA level QSR systems to ensure compliance with potential future FDA enforcement action)

Source: Booz & Company analysis
Challenges specific to Alzheimer’s Disease

- Lack of understanding of disease patho-physiology and dominance of amyloid hypothesis
- Correlating In-vivo (imaging) with In-vitro diagnostics
- Measuring biomarker levels for a disease on the other side of the Blood Brain barrier and dealing with biomarker concentration gradients in brain tissue, versus circulating blood
- History of failed hypothesis; correlation versus causation
- Not enough samples, leave alone longitudinal samples
- Disease progression and cost and complexity of clinical studies, including issues with observational on retrospective banked sample sets, versus prospective studies

Source: Booz & Company analysis
Case Example: Amyvid (Florbetapir F18)

### Description
- Amyvid is a radiolabelled antibody that has high affinity for beta-amyloid plaque
- It is used with a PET scan to show the extent of beta-amyloid neuritic plaque density in the evaluation of Alzheimer’s Disease (AD) and other causes of cognitive decline

### Path to Approval
Lilly’s groundbreaking effort to establish the “first-and-only FDA approved diagnostic” was no easy feat:
- First FDA submission was complicated by an inability to definitively show causality: a high correlation existed between cases (patients with post-mortem confirmation of Alzheimer’s Disease), but what exactly did a positive scan indicate peri-mortem?
- The FDA was also concerned that HCPs would not know how to interpret the scan results
- Despite voting 3-13 against approval of florbetapir without additional data, the AdCom unanimously approved it with the successful implementation of a physician training program and a re-read of the data

### The Bottom Line
The use of Amyvid as a PET imaging agent will facilitate diagnosis of AD and development of disease-modifying drugs

Sources:  http://www.amyvid.com/Pages/home.aspx, Cowen reports
### Commonly analyzed biomarkers in Alzheimer’s Disease

#### Amyloid hypothesis
- Amyloid beta 42 peptide
- Tau / p-tau proteins
  - General agreement that MCI and AD are accompanied by decreased levels of Aβ42 in CSF and an increase in tau/p-tau in CSF
  - The use of Aβ42 and tau in combination can be used to confirm the diagnosis of probable AD based on cognitive decline and can be used to enrich clinical trial populations
  - Attempts to correlate plasma levels of AB and tau with stages of AD have provided inconsistent data, and plasma Aβ42 does not appear to represent a useful supporting biomarker to help the diagnosis of AD

#### Genomic and non-genomic factors
- Gene mutations APP, PS1 and PS2
- Apolipoprotein E
- TOMM40
- Homocysteine
  - Genetic mutations can be used in an accurate predictive manner where a family history of AD exists
  - ApoE cannot be used as a predictive marker since a large number of positive subjects do not develop AD
  - TOMM40 is a protein encoded by the TOMM40 gene; alleles of this gene have been statistically associated with an increased risk of developing late-onset AD
  - Elevated blood homocysteine levels are associated with greater risk of developing AD; reduction of homocysteine levels is accompanied by decreased brain atrophy and improved cognition

#### Other CSF Markers
- Aβ oligomers
- ALZAS protein
- BACE1
- Clusterin
- Isoprostanes
- Proteomic 15/17 panel
- Ubiquitin
  - The list of potential suspects gets longer...

Reasons to be optimistic

- Technology is getting better & cheaper (e.g., Next Gen Sequencing & the $1000 genome)
- People/Practitioners are getting smarter (we are avoiding making the same mistakes)
- More responsive regulatory agencies, e.g., FDA willingness to accept literature bridging & biobanked samples
- Increasing the success stories (e.g., Beta amyloid protein)
- Samples are being collected using multiple collection protocols and stringent storage conditions; and many more longitudinal samples and clinical covariate data are being collected and stored
  - E.g., Samples and studies commissioned by the National Institute on Aging, NIH
  - E.g., Various consortia: Alzheimer’s Association: Global Consortia for Biomarker Standardization

Source: Booz & Company analysis
In Summary

- If the successes in Personalized Medicine and Biomarkers in Oncology represent one end of the spectrum, Alzheimer’s Disease represents the other end.

- While the process of generating clinically validated PMx and CDx has challenges and obstacles, Alzheimer’s Disease development imposes a unique set of additional challenges.

- But it is important to persevere for many reasons (clinical, economic) and the journey has just begun: progress is being made on many fronts (e.g., biobanked longitudinal samples; renewed interest from pharma and biotech companies) and, as the critical elements fall into place, the probability of success is surely increasing.

Source: Booz & Company analysis