Economic Incentives for Genetic and Genomic Strategies: Stratified Medicines

PRESENTATION AT IOM WORKSHOP
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PFIZER, INC.
Potential & Current Impact
Major Drugs Ineffective for Many

**Hypertension Drugs 10-30%**
ACE Inhibitors

**Heart Failure Drugs 15-25%**
Beta Blockers

**Anti Depressants 20-50%**
SSRIs

**Cholesterol Drugs 30-70%**
Statins

**Asthma Drugs 40-70%**
Beta-2-agonists

Ineffective Therapies Can Cause Harm

Adverse Events

- Estimated 100,000 deaths per year (in 1994; Lazarou et al 1998)
- 6th leading cause of death in the US
- Experienced by approximately 7% of patients (2.2 million) per year
- Medication-related health problems account for an estimated 3% to 7% of hospital admissions (Pirmohamed M, et al 2004)
- During their hospital stay, 15% of patients experienced adverse drug reactions (Davies, et al 2009)
- Increased patient non-compliance
Stratified Medicine Provides Opportunities for All Participants

- Stratified Medicine: A therapeutic combined with a companion diagnostic that targets a patient subpopulation for treatment.

More Products and Profits

- Higher health
- Less spend on ineffective therapy

More, and more effective, treatment options

Better Benefit/Risk

Trusheim: Economic Incentives for Genetic/Genomic Strategies
Stratified Medicine Provides Challenges for All Participants

Unclear benefit & value
Higher spending

More confusing choices
Cost/reimbursement concerns

Longer dual development,
Smaller markets,
Dual product risk

Dual approvals
Evidence standards
Workload

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Examples of Positive and Negative Economic Impacts

- **Positive Prospectively Stratified Medicines:** Xalkori/ALK-EML4 Fusion, BRAF inhibitors, HER2

- **Positive Diagnostics:** OncotypeDx Value to payers, patients, less clear to company

- **Mixed Impact:**
  - Retrospectively Stratified EGFR inhibitors: Value to provider/payer, likely negative to developer
  - Retrospective dose optimization: Warfarin

- **Failure to Find:** Avastin, 100+ candidate stratifiers, none demonstrated so far
Economic Incentive Dynamics
Recognize the Market Size Dynamics

Linking Biomarkers to Markets: Ideal Case

A Biomodal Marker

- # of Patients
- Biomarker Value
- % Responding
- Incidence / Prevalence
- Market Size ($)
- Time
- Plus Diagnostics Revenue

Critical relationship:
Clinical performance drives commercial performance

Leads to Rapid “Niche Buster”

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Ambiguous Biomarker Threshold Introduces Incentive Uncertainties

Overlapping Populations

Economic Choice is Case Dependent

Case: Larger # of Responders
- High Biomarker Cut-off
- Low Biomarker Cut-off

Case: Smaller # of Responders
- Low Biomarker Cut-off
- High Biomarker Cut-off

Herceptin, switching curves? New life cycle mgmt approach?

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Even Genetic Markers Provide Biomarker Threshold Flexibility

- Many alternative mutations usually exist: EGFR

Stratified Medicines Face Competition even in Small Markets – Monopolistic Power Unlikely

In Oncology often more than 5 Competitors per Molecular Target

Source: PharmaProjects, June 2010. All oncology products and programs with identified mechanisms/targets
Stratified Medicines: Development Cost Impact

- Benefit: Reduced clinical trial sizes & number of trials, but may be off-set by safety database requirements and biomarker negative studies.

- Cost: Need to discover, develop and validate biomarker into a companion diagnostic.

- Cost: Need to recruit enriched patient pool could entail need for more sites.
Examples of Quantifying Positive and Negative Impacts
Thanks to Consortium Collaborators & Colleagues

- A wide range of organizations
  - Adaptive Pharmacogenomics
  - Bristol-Myers Squibb
  - CMS
  - Eli Lilly and Company
  - FDA
  - Genzyme
  - Glaxo SmithKline
  - IMS Health
  - Merck
  - MIT
  - Monogram Biosciences
  - Novartis
  - Roche
  - Van Andel Research Institute

- And MIT Colleagues
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  - Lindsay Johnson
  - Brian Newkirk
  - Samir Sabir
  - Joe Sterk
  - Anushree Subramaniam
  - Heather Vitale

Analysis feature
Quantifying factors for the success of stratified medicine
November 2011
Effort Linked Multiple Tools to Quantitatively Analyze Incentives

- **Phase II**: Decision at beginning of Phase II
  - Use biomarker
  - Don't use biomarker

- **Phase III**: Targeted Ph 2
  - Success
  - Failure
  - Phase 2 in all comers
    - Success
    - Failure
  - Targeted Ph 3
    - Success
    - Failure
  - Analysis positive
    - Success
    - Failure
  - Analysis negative
    - Failure

- **Clinical**
  - Targeted Ph 3
    - Analysis positive
    - Analysis negative

- **Regulatory**
  - Retrospective analysis
    - Failure
    - Targeted Ph 3
      - Analysis positive
      - Analysis negative

- **Commercial/Reimburse**

**PCSD**

**IMS Health Personalized Medicine Strategy Analysis Tool**

**MIT Stratified Medicine Model**

**Drivers of Value**

**Impact of**
Stratified Approach Proved Superior in All Cases

- **Oncology**
  - Trastuzumab (Herceptin)
  - Panitumumab (Vectibix)
- **Alzheimer’s Disease**
  - Bapineuzumab

- **Focus**
  - Phase II – therapeutic exclusivity expiry
  - First in class, first indication, first region

Increased eNPV of Stratified Over All Comers Approaches

Trusheim et al. Quantifying factors for the success of stratified medicine. NRDD November 2011
With all uncertainties factored in by the IMS tool, the biomarker strategy dominates all-comers for Herceptin.

**NPV Uncertainty Range for Alternative Strategic Scenarios**

*Monte Carlo Simulation Outputs*

Adapted from Trusheim et al. Quantifying factors for the success of stratified medicine. NRDD November 2011
Landscape & Opportunities in Next 5 Years: Economic Forces at Play
In Personalized Medicine Development, the factors are not just additive, but multiplicative.

$1B$ NPV stratified medicine example

9 factors +/- 25% from development time to clinical adoption speed to market share

Nirvana

Adapted from Trusheim et al. Quantifying factors for the success of stratified medicine. NRDD November 2011
More Poor Futures than Rich Futures

- >500,000 potential futures exist by combining 12 factors
- 36% of cases are negative risk adjusted NPV, 21% 0<x<$100M and only 10%>$1B

Achieving Stratified Medicine’s Potential for Patients Requires Coordinated Action Among All

Adapted from Trusheim et al. Quantifying factors for the success of stratified medicine. NRDD November 2011
Increasing Pressures on Economic Incentives
Moving towards Pharmageddon Scenarios

Regulatory
- CLIA lab restriction
- Multi-variate test guidance
- Rejection of retrospective data

Product Exclusivity
- Biosimilar 7-12 year period
- Diag Patent restrictions
- Unclear Orphan designation

Drug Reimbursement
- Asymmetric post-launch adjustment
- 4th Tier formulary

Provider Adoption
- Poor Adherence to EBM
- Restricted product education/detailing

Diagnostic Reimbursement
- Remains ‘cost plus’ rather than value
- No payer investment in R&D

Academic Research Standard Assymetry
- New biomarker claims often statistically underpowered
- Retrospective, Meta analysis not confirmed prospectively (KRAS)

Economic Feasible Space
## Possible Incentive Actions: Other than Price

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<thead>
<tr>
<th>Traditional Tools</th>
<th>New Tools</th>
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<tr>
<td>• Faster to market (Accelerated approval)</td>
<td>• Sub-populations designated as qualified ‘Orphan’ conditions</td>
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<tr>
<td>• Patent extensions (Pediatric)</td>
<td>• Contingent, staged early regulatory approvals</td>
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<tr>
<td>• Exclusivity periods (Orphan)</td>
<td>• Automatic reimbursement for defined time period</td>
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<tr>
<td>• Guaranteed market (Advance Purchase Agreements)</td>
<td>• Accept advanced trial designs</td>
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<td>• Subsidized development (R&amp;D Tax Credit, SBIR Grants)</td>
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<tr>
<td>• Direct gov’t development (NIH biomarkers, DOD defense program procurement, NASA)</td>
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Conclusion

- **Opposing Forces:** Increasing power of platforms & increasing genomic potential opposed by increasing evidence standards, lower economic returns, higher privacy and sample access hurdles

- **Constrained Funding:** private sector funding constrained by investor returns and constrained public sector funding due to fiscal deficits & constrained foundation/philanthropic funding due to low endowment returns and difficult fund raising environment

- **Incentives Trending Downward:** Incentives high in principle but being lowered by local optimization by stakeholders