Personalized Medicine and Targeted Therapy – Who Will Pay for Advances in Cancer Care?

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THE MEDICAL AND ECONOMIC CHALLENGES OF TARGETED THERAPY

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Karolinska Institutet, Stockholm, Sweden
ISPOR, Athens, November 11, 2008.

in collaboration with
Professor Bengt Jönsson SSE and i3 Innovus
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THE MEDICAL AND ECONOMIC CHALLENGES OF TARGETED THERAPY

• Is the target a general cancer cell target?

• Is the target functioning i.e. is the signaling pathway intact?

• Is targeted therapy active by itself or (just) in combination with conventional therapy?

• If only in combination, what do we do with progressive disease?
  – Continue or discontinue with the targeted therapy

• Can/should we treat with multiple targeted agents?

Trastuzumab in HER2 positive breast cancer.
Examples of the challenges in targeted therapy.
Targets and therapy in cancer

- Angiogenesis
  - VEGF inhibition, bevacizumab, sunitinib etc
- Apoptosis
  - TRAIL (TNFα-related apoptosis-inducing ligand death receptor) molecules
- Endless replication
  - Chemotherapy
- Invasion/metastasis
  - MMPs/VEGF inhibition
- Self sufficient growth signals
  - TKIs
- Insensitive to anti-growth signals
  - TKIs

- Estrogen receptor
  - Tamoxifen
  - Aromatase inhibitors
  - Fulvestrant
- HER2
  - Trastuzumab
  - Lapatinib
  - Pertuzumab
- EGFr
  - Cetuximab
  - Panitumumab
  - Erlotinib
  - Gefitinib

Hypothetical survival curves for a chemotherapy agent and a targeted drug.
What impacts outcome in cancer?
How do we measure progress?

- Organization
- Prevention
- Early detection
- Treatment
  - Surgery
  - Radiation
  - Drugs
- Data on incidence, mortality and survival
  - Outdated?
  - Scattered
  - Non-consistant
- Desperate need for on-line information
- What are the end points?
  - Survival
  - Recurrence/progression free survival
- Will improvements in metastatic disease translate into the adjuvant situation?

Does access to cancer drugs impact outcome?

Discussion to be continued……..

but breast cancer mortality <70 y down 50% due to screening, tamoxifen and chemotherapy.

CML, NHL and multiple myeloma…. 
5 year survival in %.

<table>
<thead>
<tr>
<th></th>
<th>Eurocare-4 mean</th>
<th>SEERS USA</th>
<th>England</th>
<th>Sweden</th>
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</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>47.3</td>
<td>66.3</td>
<td>44.8</td>
<td>60.3</td>
</tr>
<tr>
<td>Women</td>
<td>55.8</td>
<td>62.9</td>
<td>52.7</td>
<td>61.7</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
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<tr>
<td></td>
<td>79.0</td>
<td>90.1</td>
<td>77.8</td>
<td>86.3</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>56.2</td>
<td>65.5</td>
<td>51.8</td>
<td>59.8</td>
</tr>
<tr>
<td><strong>Lung cancer</strong></td>
<td>10.9</td>
<td>15.7</td>
<td>8.4</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Use of docetaxel, Taxotere® (mg per case of breast cancer) in E13, France, Germany, Italy, Spain and the UK.
Recent trends in long-term survival of patients with chronic myelocytic leukemia: disclosing the impact of advances in therapy on the population level.

Brenner H, Gondos A, Pulte D

- Overall, 5-year relative survival increased from 27 to 49%, and 10-year relative survival increased from 9.5 to 34% between 1990-92 and 2002-04.

- The analysis discloses a dramatic recent increase in long-term survival of younger patients with CML which most likely reflects rapid dissemination of advances in therapy on the population level.
Use of imatinib, Glivec® (mg per case of leukemia) in E13, France, Germany, Italy, Spain and the UK.

Use of bevacizumab, Avastin® (mg per case of colorectal cancer) in E13, France, Germany, Italy, Spain and the UK.
Total sales of cancer drugs (L1+L2 A and B) in Europe 1998-2007.
Different colors of the bars indicate first year of sales.

Sales

Sales of cancer drugs per 100 000 inhabitants in E13 (Wester European average), France, Germany, Italy, Spain and the UK in 2007.
Conclusions

- Cancer drug development is the focus of academia and pharma.
- Access to cancer drugs have an impact on outcome, but are we getting value for money?
Biomarkers—Definition and Implications

*Biomarkers are measurable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans.*

- FDA Critical Path Opportunities

- Much broader than just genomics.
  - Any tool that could be used to stratify or segment the indicated population.

- But from an economic perspective, the drug development and pricing issues are the same for genomic and other biomarkers.
Three Sets of Challenges

• Basic science challenges
• Translational challenges
• Incentive/economic challenges

Conventional Drug Development “Social Contract”: Prices Are More Than Short-Run Marginal Costs

• Blockbuster financing model for R&D.
  » Intellectual property
  » Little relationship between short-run marginal cost and price.

• At launch--very limited information about real-world effectiveness.

• Individual countries strike different types of deals with manufacturers
  » Range of country environments: negotiated prices < -- > free pricing
  » Ability to adjust prices based on new evidence varies.
    • US—prices can be increased over time.
    • EU and ROW—internal and external reference pricing
    • Incentive for manufacturers to seek highest justifiable
New Product Discovery and Development – A Risky and Expensive Proposition

Compound Success Rates by Stage
- 5,000–10,000 Screened
- 250 Enter Preclinical Testing
- 5 Enter Clinical Testing
- 1 Approved by the FDA

Transition Probabilities by Development Phase (U.S.): Oncology vs. Other Products
(DiMasi and Grabowski, JCO, 2007)
UW PGx Report, 2007
Sponsor: PhRMA

Taxonomy of Potential Applications of Pharmacogenomics [and Biomarkers] (Webster et al., 2004)

Option 1: using PGx to discover better drugs
Option 2: PGx to improve the safety of new drugs in development
Option 3: PGx to improve the efficacy of new drugs in development
Option 4: improving the safety of licensed drugs
Option 5: improving the efficacy of licensed drugs
"Twin studies show that genetic differences account for about a quarter of the variance in adult life span." (Christensen et al., 2006)

- Parental height explains 70-80% variation in children’s height as an adult. (Vaupal)
- But parental life-span explains only 3% of variation in child life-span. (Vaupal)

Pharmacogenomics: 2010 Forecast

- Testing technologies
  - Gene chips capable of evaluating up to 500,000 SNPs will be available for less than $1,000.
  - Several more FDA-approved pharmacogenomic test kits will likely be available, but likely 3-5 rather than greater than 10.

- Pharmacogenomic associations
  - Our understanding of specific pharmacogenomics associations will change as additional studies are performed.
  - It is reasonable to expect that 5-10 clinically relevant pharmacogenomic associations will be validated in the next five years. Many of these associations will be in oncology.

Source: UW PGx Report, 2007
Challenge of the Translational Science

» As with most common diseases, the effect of genetic variation on drug response generally is a result of complex interactions with multiple genes and non-genetic factors, and hence the genetic markers are often only weakly associated with drug treatment outcomes. As a result, the effect of genetic variation on drug response is often subtle and difficult to detect.

» Our knowledge of the role of genes in specific disease processes is generally in its infancy, with multiple gene correlates but little understanding of the underlying biological mechanisms.

Economics of Personalized Medicine: Value Creation and Capture

• Two publications (L Garrison and MJF Austin):

  » “Linking Pharmacogenetics-Based Diagnostics and Drugs for Personalized Medicine” Health Affairs 25 (5), 2006
A Simple Framework and Example: Defining Economic Value

• What is “economic value”?

• “Value” = what fully informed patients would be willing to pay (WTP) for a new Dx or Tx based on:

  1) any cost savings,
  2) life years gained,
  3) improvements in quality of life or morbidity, and
  4) reduction in uncertainty.

Commercial/Economic Rationale

Personalized Medicine—and a linked PGx/Biomarker Dx-Tx--could create additional economic value in at least four ways:

1. As the non-responders or poor responders are removed from the pool of users, their costs (monetary and negative utility) for adverse events are avoided.

2. Better targeting can lead to a greater volume of adoption by good responders (some of whom would not have used the drug previously).

3. Good responders may have improved compliance—and therefore additional net benefits—especially for long-term chronic therapies.

4. The improvement of predictability of outcome creates
**BASE CASE: Only Tx on market; no Dx**

**Key Assumptions:**
- Tx already on market
- No Dx available for targeting.

**Implications:**
- Total value created is $20,000 lower than could be achieved with targeting.

**Value Distribution**

<table>
<thead>
<tr>
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<th>Value</th>
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<tbody>
<tr>
<td>Patient (Direct)</td>
<td>$0</td>
</tr>
<tr>
<td>Insurer N</td>
<td>$0</td>
</tr>
<tr>
<td>T manufact.</td>
<td>$100K</td>
</tr>
<tr>
<td>D Manufactur.</td>
<td>$0</td>
</tr>
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**Scenario I: Ex post situation; new diagnostic; no Tx price flexibility; Dx with administered pricing**

**Key Assumptions:**
- Tx already on market
- T can’t raise price
- D set at cost=charge
- Insurer premiums unchanged

**Implications:**
- Tx price $1000 → -$80K revenues; 80% reduction profit; low incentive
- Dx price $100 → Low profit; normal incentive
- Premium collected $100,000 → Claims paid out $30,000; high incentive.
- Patient gets better value for money spent

**Value Distribution**

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<tr>
<td>T manufact.</td>
<td>$20K</td>
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<tr>
<td>D Manufactur.</td>
<td>$10K</td>
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<tr>
<td>Insurer N</td>
<td>$70K</td>
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<tr>
<td>Patient (Direct)</td>
<td>$20K</td>
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**TOTAL** $120K
Public Policy Implications from a Value Creation Perspective

• Need for flexible and value-based pricing and reimbursement for both diagnostics and drugs.
  → linking pricing and reimbursement for drugs and diagnostics to value creation

• Strong, consistent, predictable IP environment is key.

• Public policy should NOT focus on PGx technologies, but on biomarkers more generally.

Estimating the potential economic value of trastuzumab in breast cancer from 2000-2020 in five European countries

L.P. Garrick, 1 A. Citrinuone, 2 U. Weisgerber-Kriegl1, D. Veenstra1

1 University of Washington, Seattle, Washington, USA; 2 Hoffmann-La Roche Ltd, Basel, Switzerland

44th ASCO Annual Meeting, Chicago, Illinois, USA, 30 May-3 June 2008
ICERs in Early Breast Cancer and Metastasis
Breast Cancer and combined use 2000-2020, Five Major EU Countries

Estimated annual number of patients treated with trastuzumab for EBC and MBC, 2000-2020, Five Major EU Countries
Cumulative (2000-2020) economic value of trastuzumab over its life cycle in five EU countries: UK, France, Germany, Spain, and Italy

<table>
<thead>
<tr>
<th>Assigned monetary value per QALY gained, €</th>
<th>Cumulative number of QALYs gained</th>
<th>Gross life-cycle value due to QALYs gained, €</th>
<th>Cumulative net cost of trastuzumab-based therapy, €</th>
<th>Net life-cycle value due to QALYs gained, €*</th>
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</thead>
<tbody>
<tr>
<td>50,000</td>
<td>811,000</td>
<td>40.5 billion</td>
<td>14.0 billion</td>
<td>26.1 billion</td>
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<td>100,000</td>
<td>811,000</td>
<td>84.6 billion</td>
<td>14.0 billion</td>
<td>68.7 billion</td>
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<tr>
<td>150,000</td>
<td>811,000</td>
<td>126.9 billion</td>
<td>14.0 billion</td>
<td>109.2 billion</td>
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</table>

*Calculated by subtracting cumulative net cost of trastuzumab-based therapy from gross life-cycle value due to QALYs gained, both discounted to the year 2000 at 3.5% per annum and expressed in 2007 €

Remembering Some Basic Economics—Knowledge and Technology as Public Goods

- Information is a public good (as opposed to a private good):
  - Its consumption is (1) non-rivalrous and (2) non-excludable.
  - There is a tendency toward a “free-rider problem”
  - Private market will not provide the socially optimal amount without interventions (such as patents).

- Knowledge (about medical technology and medical practice) is a global public good.
Static vs. Dynamic Efficiency—
A Global Societal Perspective?

• **Static Efficiency**—optimal use given today’s prices—e.g.,
  by using cost-effectiveness analysis.

• **Dynamic Efficiency**—eliciting the optimal rate of
  innovation over time.

*A final question:*
Do we need to take a *global* societal perspective—
including greater price flexibility for both therapeutics
and diagnostics to reward innovation consistently?

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*Thanks for your attention!*

lgarrisn@u.washington.edu
The Swedish cancer plan
- input from industry

Richard Bergström
Director General
LIF Sweden
Improvements in cancer care

- One person in three will be affected: two thirds will be cured or die from something else
- Mortality in breast cancer has declined with 25% since 1980
- Testicular cancer: more than 90% cured
- 5-year survival (age 15-65) with CML has increased from 15 to 85%
- And the cost is reasonable: cost of cancer care 5-8% of total and constant last 30 years

Cancer is the most research-intensive field in the industry

R&D Global Activity in Main Therapeutic Areas

- Oncology (L1, L2)
- CNS (N3A, N5A, N6A)
- Osteoporosis (M5B, G3H, H4A, H4V)
- HIV antiretrovirals (J5D)
- Oral antidiabetics (A10B)
- Cardiovascular (C8, C9, C10A)
- Epoetins (B3C)
- PPIs (A2B2)
- Anti-platelet inhibs (B1C)
- Oral antidiabetics (A10B)

Source: IMS Management Consulting analysis
Note: * = Growth of value sales
3.5-7% of total sales; 10-15% of direct costs for cancer care

Sales of cancer medicines 2000-2007 and forecast until 2022
Summary

- Targeted therapies will reduce waste
- Many new drugs will replace others
- Patent expiries will create headroom to spend
- Biosimilars will play important role in reducing cost of treatment
- Introduction of new therapies crucial
  - sound HTA has a role to play
  - need to take life cycle perspective
  - early but controlled and precise usage
  - mandatory follow-up
- Part of innovation system
  - translational research
  - you get what you pay for....

DISCUSSION – Q&A

Thank you for attending today’s Educational Symposium

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