Personalized Medicine: Current and Future Perspectives

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Why Personalized Medicines

• Using an individual’s genetic profile to predict response to certain drugs
• Clinical goal is to enable better drug treatment decisions and safer medical care
• Pharmaceutical industry goal is to develop more predictable and more effective drugs
• Genetic tests already in use to predict patient response to therapy in the fields of cancer and infectious disease
• Pharmacogenomics (PGx) has the potential to revolutionize how drugs are developed and prescribed in the future
• Faces fewest hurdles to clinical integration because it does not require major healthcare delivery system redesign
**Overall Goals**

- Improve pts outcomes
  - Disease care
  - Health care
- Reduce HC costs

**Disease care**
- **Target medicines precisely** (“pharmacogenomics”)
- **Administer medicines safely** (“toxicogenomics”)

**Health care**
- **Predict disease susceptibility**
  - Prevent disease
- **Detect early onset of disease**
  - Prevent disease progression

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### Examples in Oncology (Taiwan situation)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Bio-marker</th>
<th>Drug Reimbursed</th>
<th>Annually Cost</th>
<th>Test Reimbursed</th>
<th>Test Cost</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>BC</td>
<td>ER</td>
<td>Y</td>
<td><strong>NT$ 2,526</strong></td>
<td>Estrogen receptor (ER)</td>
<td><strong>NT$ 2250</strong></td>
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<td>ER</td>
<td>Y</td>
<td><strong>49,275</strong></td>
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<td>1. Aromasin</td>
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<td>Y</td>
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<td>2. Arimidex</td>
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<td>ER</td>
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<td>3. Femara</td>
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<td>ER</td>
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<td>Herceptin</td>
<td>BC</td>
<td>HER2</td>
<td>Y</td>
<td><strong>750,000</strong></td>
<td>Immunohistochemical (IHC) stains, each antibody or Her-2/neu fluorescence in situ hybridization (FISH)</td>
<td><strong>1354/10400</strong></td>
</tr>
<tr>
<td>Erbitux</td>
<td>Colorectal</td>
<td>EGFR/KRAS</td>
<td>Y</td>
<td><strong>1,610,128</strong></td>
<td>Pay by Industry</td>
<td><strong>6500</strong></td>
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<td>EGFR</td>
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<td>GIST</td>
<td>C-KIT / PDGFR bor-abl mutation</td>
<td>Y</td>
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<td>Pay by Industry</td>
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<td>BC</td>
<td>HER2</td>
<td>N</td>
<td><strong>US$:NT$ = 1:30</strong></td>
<td>Immunohistochemical (IHC) stains, each antibody or Her-2/neu fluorescence in situ hybridization (FISH)</td>
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<td>EGFR/KRAS</td>
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What are potential disadvantages?

- Greater costs of diagnostics/biomarkers
- Smaller patient markets for therapeutics
- Need to track individual health information
- Necessity for accelerated Health Information Technology (HIT)
- Diagnoses without treatments
- Re-education of healthcare professionals
- Distraction from other $ saving opportunities

PM requires coordination across multiple stakeholders

- Government & Universities
- Biopharmaceutical Co's
- Diagnostic Companies
- Genetics Companies (data miners, technology co's, etc.)
- Producers
- Users
- Patients and Health Care consumers
- Managed Care
- Managed Care Professionals
- Payers
- Ethicists, Legislators
Payer perspective: what will be the impact of pharmacogenomics on total healthcare costs?

**Increase healthcare costs**
- Higher drug prices
- Expanded patient populations for testings
- Enforcement of privacy safeguards
- Extended patent protection
- Diagnostic tests required

**Decrease healthcare costs**
- Avoid use of expensive drugs in non-responders
- Save patients avoidable adverse effects
- Improve adherence
- Improved health outcomes
- Reduced hospitalizations

Payer perspective:
- Poor understanding of genomics;
- Poor and inconsistent technology assessment
- Apprehensive about specialty drug prices
- Most don’t see the business case yet
- Needs to assess proportional value for diagnostic health information
- Some are more prepared for PGx than predictive testing
Providers, Physicians perspective

• Lack of genetics literacy
• Intensifying payer pressures for evidence-based practice and the lag in Genomics R&D
• Lack of IT designed for doctors on “how to deliver” genomics. Specialist or GP?
• Still problematic in economic evaluation of personalized medicine. Will reimbursement match the time it takes to treatment target?

Bio-Pharmaceutical Industry perspective

• Need to make the business case payers won’t make for them;
• Need to work out relationships between drug and diagnostic testing;
• Prove value for money;
• Participate vigorously in policy for technology assessment and regulatory model development.
Ethical, legal, political (ELP) issues

• Marketplace introduction of PGx testing without adequate validation
  – Lack appropriate regulatory framework
  – Failure to define a clinically and economically relevant evidence base for PGx tests and test-drug combinations

• Suboptimal access to and use of PGx testing
  – Professional and payer knowledge gaps about genetics
  – Defining physician obligations to offer a PGx test and obligations to follow PGx test results

• Liability
  – Physicians, pharmacists, pharmaceutical companies

• Testing without adequate consent

• Inappropriate uses of PGx testing as a result of direct marketing (DTC advertising)

• Higher drug costs leading to barriers to access

Rapid and unmanaged introduction of genetic tests into marketplace

• Inappropriately induces demand for services

• Predictive values of PGx tests may be too low to be clinically useful
  – Shift public and private resources away from more effective ways of improving public health

• Lack of information about PGx tests may lead to real harms to patients by physicians and payers
  – Inaccurate test results
  – Poor counseling from physicians (unable to accurately interpret test results)
  – Coverage policies that are not justified by the science

As the train is leaving the station...

Does Taiwan Government have a role

In the "Personalized Medicine Rush"?

If yes, what role?

• Support economic development of industries
• Gain public trust
• Promote thoughtful policy and legislation
• Promote Health Information Technology (HIT) and data sharing
• Encourage continued innovation
• Foster training & education
Encouragement?

- **Economics studies & reimbursement decision**
  - Conduct micro-economics to prove Value for Money
  - Conduct macro-economics (Propose pilot studies to determine economic impact on healthcare in Taiwan)

- **Regulation & Policy development**
  - Propose guiding principles with rational adjudication (HTA)
  - Enable tracking individual outcomes
  - Promote disease prevention
  - Mitigate impediments to innovation

- **Health Information Technology**, to enable
  - Validating biomarkers
  - Tracking individual information & outcomes
  - Integration, implementation, archiving and sharing
  - Training & education

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New version of the Pricing and Reimbursement Guideline

Published at Sep.22, 2009  By BNI

「全民健康保險藥價基準」

- **Chapter 3, article 3**: Have efficacy and safety clinical trial in Taiwan with a reasonable scale, **markup 10%**.
- **2A new drug**: Have pharmacoeconomic study in Taiwan, **add the maximum of 10% premium**.
- **Chapter 3, 貳、 四、**: Manufacturer could submit **Coverage with Evidence Development or Pay-for-Performance proposal** for high cost new drug products.
Attitude: Bureau of National Health Insurance (BNHI) in Taiwan

- The door is open, provide incentives
- Welcome new innovative proposal for reimbursement
- Training and educations are encouraged
- Cases and experiences need to be shared
- A separate reimbursement dossier submission for diagnostic is required

Applying Health Economics and Outcomes Research in Personalized Medicine: Methodological and Policy Challenges

Pfizer Symposium on
Health Economics and Outcomes Research in Personalized Medicine
September 2, 2012
ISPOR 5th Asia-Pacific Conference
Taipei, Taiwan

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- Diego Ossa (Novartis), James Creeden (Roche), Laura Housman (Novartis), and Finley Austin (AstraZeneca)

The Promise

- The remarkable scientific achievement represented by the completion of sequencing of the human genome in 2001 was understandably heralded as the dawn of a new era.

A View from the year 2000:
- “In the next five to seven years, we should identify the genetic susceptibility factors for virtually all common diseases—cancer, diabetes, heart disease, the major mental illnesses—on down that list.” (Francis Collins)
Questions—10 Years After the Genome

The New York Times

June 15, 2010
THE GENOME AT 10: Awaiting the Genome Payoff
By ANDREW POLLACK

NORTH W\n plates center
Assisted by human gene
It is a major
_however,
from assumed.

A Decade Later, Genetic Map Yields Few New Cures
by NICOLAS RANCE

Five years after President Bill Clinton announced that the first draft of the human genome was complete, medicine has yet to see any large
part of the promised benefits.
For biologists, the genome has yielded one insightful surprise after another. But the primary goal of the $3 billion Human Genome
Project — to sort out the genetic roots of common diseases like cancer and Alzheimer's and then generate treatments — remains largely
elusive. Indeed, after 20 years of effort, geneticists are almost back to square one in knowing where to look for the roots of common
disease.

At a news conference, Francis Collins, then the director of the genome agency at the National Institutes of Health, said that genetic
diagnostics of disease would be accomplished in 10 years and that treatments would start to roll out perhaps five years after that.
"Over the longer term, perhaps in another 15 or 20 years," he added, "you will see a complete transformation in therapeutic medicine."

The Growing Perception of the Challenge—as Early as 2004-5

In a review article, Webster and colleagues (2004) conclude:

• “Pharmacogenomics is on the threshold of making a major impact in commercial labs and in the clinic. But, despite its promise and the heavy
investment made in the technology, many companies still question whether there is a coherent business, health policy, or regulatory model
emerging to shape the future development of pharmacogenomics.”

And the 2005 report Personalised Medicine: Hopes and Realities from The Royal Society cautions:

• “Pharmacogenetics is unlikely to revolutionize or personalize medical practice in the immediate future.”
By 2015, approximately 10 years from now, a variety of test kits using various biological markers testing will be feasible when rapid test results are needed. Yet, the discovery and validation of pharmacogenomic associations will likely continue at a similar measured pace. A notable development will be the identification of clinically useful pharmacogenomic associations in drug development trials outside of oncology. We expect that 10 to 15 pharmacogenomic tests will be in routine use in clinical practice. Although the majority will continue to be in oncology, evaluating both tumor and patient genetics, several tests outside of oncology will be used by primary care clinicians to guide treatment decisions.

• 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)
• “Twin studies show that genetic differences account for about a quarter of the variance in adult life span.” (Christensen et al., 2006)
Progress has been slower than many expect but much of the excitement and impact has been in oncology and each of the cases has its own lessons...

- HER2: Herceptin (trastuzumab) for BrCa
- BCR-ABL in CML: Gleevec (imatinib), Sprycel (dasatinib), and Tasigna (nilotinib)
- Gene expression profiling in breast cancer: Oncotype DX/Mammaprint
- EGFR in lung cancer: Tarceva (erlotinib) and Iressa (gefitinib)
- KRAS mutations in colorectal cancer: Erbitux (cetuximab) and Vectibex (panitumumab)
- ALK Inhibitor in lung cancer: Xalkori (crizotinib)
- BRAF mutation in melanoma—Zelboraf (vemurafenib)

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 (LYs),
  3) improvements in quality of life or morbidity (2+3→QALYs)
  4) reduction in uncertainty/value of knowing

This is “QALY-based”: UK NHS value-based pricing aims to broaden this concept of value.
How Can Personalized Medicine Create Value?

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 additional value for patients as they face less uncertainty.

Five Challenges For Personalized Medicine

1. Science
2. Regulatory
3. Evidence
4. Economic Evaluation
5. Reimbursement
Special Challenge #1: Science

- The science is more difficult than many expect.
  - Drug development is risky and difficult.
  - Developing, testing, and validating a biomarker strategy can compound the complexity.

Special Challenge #2: Regulatory

- Regulatory pathways for companion diagnostics are less well-defined
- They are issues around laboratory-developed tests (LDTs) vs. in vitro diagnostics (IVDs).
Special Challenge #3: Evidence

• Diagnostics typically come to market with limited evidence on clinical utility (i.e., effectiveness and benefit-risk balance).
  – Challenge for standalone test (i.e., ex post stratification)
  – There is a need for new clinical trial designs.
  – Public goods/free rider issues can be a barrier.

Special Challenge #4: Economic Evaluation

• “. . . the requirements for the policymaking (appraisal) component of the HTA process are no different for drugs and medical devices. . . . The cost per quality of life in many settings has become that gold standard metric, regardless of whether a policy maker is evaluating a drug, medical device, or any other health-care technology.” (Taylor & Iglesias, 2009)

• Two issues:
  – The cost per QALY metric does not consider the value of reducing uncertainty—i.e., “the value of knowing.”
  – A linked diagnostic-drug combination is a joint product—the attribution of value to either is arbitrary.
Special Challenge #5: Reimbursement

• Oftentimes, companion diagnostics are reimbursed under a cost-based, administered pricing system.
  – This does not reward value creation or incentivize evidence generation to support value demonstration.

The Economics of Personalized Medicine: A Model of Incentives for Value Creation and Capture

Who captures the value created?

With Uncertainty
About Who Responds
(Value of Tx Alone)

$100,000

With Certainty
About Who Responds
(Value of Tx+Dx)

$120,000:
Who Captures This?

Scenario V: Ex ante linked situation;
Tx and Dx price flexibility; IP protection on both.

Key Assumptions:
- Linked Dx-Tx launched at same time
- Tx pricing is flexible and value-based.
- Dx pricing is flexible and value-based.
- Insurer raises premiums in competitive market.

Implications:
- How the value capture is split between Dx and Tx is “arbitrary”—but competitive market conditions could be key determinant.

Value Distribution:
- Tx manufacturer: $60K
- Dx manufacturer: $60K
- Insurer N: $0K
- Patient (Direct): $0K
- TOTAL: $120K
HEOR Methodology Challenges in Personalized Medicine

1. Including testing costs and test performance in cost-effectiveness models
2. Valuing and including the valuation of reductions in uncertainty
3. Assessing impact of uptake on aggregate value created
4. Assessing impact of greater predictability of response on compliance and consequent health outcomes

Public Policy Needs from a Value Creation Perspective
(Garrison-Austin, 2007)

1. Flexible and value-based pricing and reimbursement
2. Incentive-oriented reforms--linking pricing and reimbursement for drugs and diagnostics to value creation
3. Strong, consistent, predictable IP environment.
4. Do not focus on PGx technologies alone—consider biomarkers more broadly.
Thanks!
Questions?

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Reimbursement Environment for Personalized Medicine: Issues, Challenges and Ways Forward

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Sept. 2012, Taipei
Background

• Recent advances in biotechnology and improved understanding of cancer biology have led pharmaceutical companies to introduce the concept of personalized treatment of cancer.
  – Involves the use of companion diagnostics (i.e., testing for biomarkers) in selecting optimum therapy with targeted agents.
    • Predictive biomarkers identify patient subpopulations most likely to respond to treatments.
• The ability to identify the patients most likely to benefit from such therapies using companion diagnostics is a major advance in the clinical approach to treatment of cancer.
• Reimbursement of such therapies has become increasingly important due to the costs of such therapies.

Reimbursement for newly launched target treatment
(China as an example)

• Although Iressa (gefitinib) was launched in China six to seven years ago, it is still not listed in National Reimbursement Drug List (NRDL)
• Erlotinib is not reimbursed as well
• Bevacizumab is not indicated in China
• Both erlotinib and gefitinib have patient assistance programs in China, teaming up with China Charity Foundation (CCF)
• However, government realized the need to offer advanced treatment to patients, was trying to open a window to include those highly priced products into NRDL via a negotiation process. The process is currently still being discussed among different Ministries.
• Example: Qingdao city government has recently listed Sutent along with other 8 drugs on its city reimbursement drug list on the negotiation base that government, manufactures, and individual patients will all contribute into the coverage.
Herceptin in China

Indication: HER2+ metastatic Breast cancer / Breast cancer adjuvant treatment

Diagnostic kit: special test of HER2 receptor is needed to decide if the Herceptin can be used for patients

Neither the drug nor the test is reimbursed in China

Patients need to pay for the test in hospital. A local manufactured IHC test costs about 80 RMB, but the result is not very accurate. Roche provides free IHC test kit to some hospitals, hospitals then charge patients 200 RMB for a test. FISH test, which is quite expensive (around 2,000 per test), is not widely used in China

Issues/challenges Related to Reimbursement of Personalized Medicines

• Lack of infrastructure in the hospital laboratories to conduct diagnostic tests.
  – Immunohistochemistry exams, such as those that determine gene mutations using PCR or sequencing techniques, are not available in many countries.

• A separate reimbursement dossier submission for diagnostic is potentially required.
  – The following information could be required in the dossier: patient’s medical history, scientific evidence for the diagnostic test, intended use of the diagnostic test, specificity, sensitivity and predictive value of the test. Bibliography, and patient’s disease state etc.
Issues/challenges Related to Reimbursement of Personalized Medicines

• A relatively small responder population with the requirement of testing a large population (When do we decide to cover?).
• Cost issue of the diagnostic test/drug combination. (Budgetary Impact)
• Traditional sales/marketing strategies might not be applied to PM due to its small population and higher Costs. Creative approaches have to be developed

What Evidence Payers Might Be Searching In Order To Support Reimbursement Decisions (Lesson Learned)
Clinical Endpoint Or Outcome Data To Support Coverage or Reimbursement

- Overall Survival
- Quality of life
- Progression survival
- Response rate/disease control rate
- Adverse Events

Economic Evidence required To Support Coverage or Reimbursement

- Budgetary Impact Analysis
- Cost Effectiveness results
- Reduced hospitalizations (cost offsets)
- Reduced drug treatment costs for adverse events (cost offsets)
Creative Market Access Program To Support Coverage or Reimbursement

• Financial or outcomes based risk sharing agreement to support the acceptance of tests or test-treatment combinations
  • Iressa is approved for first-line use for non-small-cell lung cancer (NSCLC) patients who tested EGFR-mutation positive
  • Drug costs around $4,000 per month per patient
  • Reimbursement coverage details: Manufacture provides the first two months of the drug treatment free. If there is a response to the drug, the National Health Service will pay a £12,200 fixed amount on per patient base disregarding how long the drug is used.
  • If a patient does not show evidence of response to the drug at the end of two months, No payment due at all.

Creative Market Access Program To Support Coverage or Reimbursement

• Patient access program/Net pricing/Capped Pricing
• Subsidizing diagnostic costs to decrease patient financial burden
• Cost-sharing with government /3rd party/patients
Discussions

We are entering a new era and we need creative ideas