Educational Symposium

The Promise of Personalized Medicine: “Getting it Right the First Time”

Tuesday May 21 2013 | 7:15 AM – 8:15 AM
Sponsored by Xcenda

Speakers and Moderator

Ken Redekop, PhD
Clinical Epidemiologist and HTA Researcher, Institute for Medical Technology Assessment, Erasmus University Rotterdam

Steven Hass
Senior Director of Neuroscience and Hormones, Global HEOR, AbbVie

Amy Grogg, PharmD
President, AmerisourceBergen Consulting Services
Amy.Grogg@absg.com

Tommy Bramley RPh, PhD
Senior Vice President, Scientific Consulting, Xcenda
Tommy.Bramley@xcenda.com
Symposium Overview

• Definitions of Personalized Medicine and Linkage to Clinical Decisions
• Economic Considerations in Personalized Medicine
• Payer Perspectives on Personalized Medicine

Definitions of Personalized Medicine and Linkage to Clinical Decisions

Ken Redekop, PhD
Clinical Epidemiologist and HTA Researcher, Institute for Medical Technology Assessment, Erasmus University Rotterdam
Rotterdam, The Netherlands
redekop@bmg.eur.nl

Based on paper with Dee Dee Mladsi to appear in Value in Health (special issue on Personalized Medicine)
**Personalized Medicine: Definition 1**

“A medical model that proposes the customization of healthcare, with decisions and practices being tailored to the individual patient by use of genetic or other information.”

**Personalized Medicine: Definition 2**

“The tailoring of medical treatment to the specific characteristics of each patient. [It] does not literally mean the creation of drugs or medical devices that are unique to a patient. Rather, it involves the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment.”
Personalized Medicine: Definition 3

“A form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.”

• Which definition do you prefer?
• What definition do you use?
One Size Does Not Fit All

PERCENTAGE OF THE PATIENT POPULATION FOR WHICH A PARTICULAR DRUG IS INEFFECTIVE, ON AVERAGE

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-depressants (SSRIs)</td>
<td>38%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes Drugs</td>
<td>43%</td>
</tr>
<tr>
<td>Arthritis Drugs</td>
<td>50%</td>
</tr>
<tr>
<td>Alzheimer's Drugs</td>
<td>70%</td>
</tr>
<tr>
<td>Cancer Drugs</td>
<td>75%</td>
</tr>
</tbody>
</table>

Source of data: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff. “Clinical Trends in Molecular Medicine,” Volume 7, Issues 5, 1 May 2001, Pages 201-204

Complexities of PM in EGFR-based Therapy in Metastatic Colorectal Cancer
Choosing Amongst PM Definitions?

• How can we determine what personalized medicine is or is not?

• **One option:** to examine some basic elements in medical decision-making
  - Questions
  - Methods to gather information to answer them
  - Treatment decisions

• Which questions, methods and decisions relate to PM?

Some FAQs in Medicine

• **Disease susceptibility:** what is the risk of getting a specific disease in the future?

• **Disease screening:** does a person have the disease?

• **Diagnosis:** what is the diagnosis?

• **Prognosis:** what is the prognosis?

• **Companion diagnostic:** will a patient respond well to a particular treatment?

• **Monitoring:** should treatment continue or be changed?

• **Disease surveillance:** has the disease recurred in one form or another?
Ways to Answer the Questions

- Demographics, medical history, lifestyle, family history
- Physical examination
- Histology
- Clinical chemistry
- Imaging
- Genetics and "-omics" technologies (eg, genomics, proteomics, metabolomics)
- Other
- Combination of any of the above

Decisions to be made

1. Decision about drug use:
   a. Decision about one particular drug (YES/NO)
      i. who will respond well?
      ii. who will respond poorly?
   b. Decision about drug dosage (HOW MUCH?)
   c. Decision between drugs (WHICH?)

2. Decision amongst different medical treatments (eg, drugs, surgery, etc.)
A Matrix of Possibilities

**QUESTIONS**
- Disease susceptibility increased risk of disease?
- Prognosis future course of disease?
- Companion diagnostic treatment response to a particular medicine?

**METHODS**
- Demographics, history, etc.
- Physical examination
- Histology
- Clinical chemistry
- Genetics and “-omics”
- Other
- Combination

**DECISIONS**
- Decision to use a drug (effectiveness)
- Decision not to use a drug (lack of safety)
- Decision about drug dosage
- Decision amongst drugs
- Decision about which treatment (e.g., drugs, surgery, etc.)

Which combinations relate to personalized medicine?

**Possible Examples of Personalized Medicine**

<table>
<thead>
<tr>
<th>TYPE OF TEST</th>
<th>DISEASE</th>
<th>TEST</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease susceptibility test</td>
<td>Breast cancer</td>
<td>BRCA1</td>
<td>Increased risk of breast and ovarian cancer</td>
</tr>
<tr>
<td>Prognostic test</td>
<td>Breast cancer</td>
<td>Mammaprint</td>
<td>Predicts risk of cancer recurrence</td>
</tr>
<tr>
<td>Companion diagnostic - effectiveness-oriented</td>
<td>Breast cancer</td>
<td>HER2</td>
<td>Trastuzumab (Herceptin) more beneficial for tumors with an HER2 overexpression</td>
</tr>
<tr>
<td>Companion diagnostic - safety-oriented</td>
<td>Epilepsy and other indications for carbamazepine</td>
<td>HLA-B*1502</td>
<td>Patients are more likely to have dangerous skin reactions following carbamazepine therapy</td>
</tr>
<tr>
<td>Companion diagnostic - dosage-oriented</td>
<td>Atrial fibrillation and other indications for warfarin</td>
<td>CYP2C9, VKORC1</td>
<td>Optimal warfarin dose is partly dependent on CYP2C9 and VKORC1 genotypes</td>
</tr>
</tbody>
</table>
HER2 and trastuzumab (Herceptin)

**QUESTIONS**
- Disease susceptibility: increased risk of disease?
- Prognosis: future course of disease?
- Companion diagnostic: treatment response to a particular medicine?

**METHODS**
- Demographics, history, etc.
- Physical examination
- Histology
- Clinical chemistry
- Genetics and “-omics”
- Other
- Combination

**DECISIONS**
- Decision to use a drug (effectiveness)
- Decision not to use a drug (lack of safety)
- Decision about drug dosage
- Decision amongst drugs
- Decision about which treatment (eg, drugs, surgery, etc.)

Warfarin (anticoagulation) treatment

**QUESTIONS**
- Disease susceptibility: increased risk of disease?
- Prognosis: future course of disease?
- Companion diagnostic: treatment response to a particular medicine?

**METHODS**
- Demographics, history, etc.
- Physical examination
- Histology
- Clinical chemistry
- Genetics and “-omics”
- Other
- Combination

**DECISIONS**
- Decision to use a drug (effectiveness)
- Decision not to use a drug (lack of safety)
- Decision about drug dosage
- Decision amongst drugs
- Decision about which treatment (eg, drugs, surgery, etc.)
# Oncotype Dx or Mammaprint

## QUESTIONS
- Disease susceptibility increased risk of disease?
- Prognosis future course of disease?
- Companion diagnostic treatment response to a particular medicine?

## METHODS
- Demographics, history, etc.
- Physical examination
- Histology
- Clinical chemistry
- Genetics and “-omics”
- Other
- Combination

## DECISIONS
- Decision to use a drug (effectiveness)
- Decision not to use a drug (lack of safety)
- Decision about drug dosage
- Decision amongst drugs
- Decision about which treatment (eg, drugs, surgery, etc.)

---

# BRCA1 Tests

## QUESTIONS
- Disease susceptibility increased risk of disease?
- Prognosis future course of disease?
- Companion diagnostic treatment response to a particular medicine?

## METHODS
- Demographics, history, etc.
- Physical examination
- Histology
- Clinical chemistry
- Genetics and “-omics”
- Other
- Combination

## DECISIONS
- Decision to use a drug (effectiveness)
- Decision not to use a drug (lack of safety)
- Decision about drug dosage
- Decision amongst drugs
- Decision about which treatment (eg, drugs, surgery, etc.)
Disagreements About Personalized Medicine (PM)

**Questions:** Which questions does PM really deal with?

**Methods:** Is PM only about genetics and –omics?

**Decisions:** Does PM only relate to drug decisions?

- **Scope:** Is PM really about personalized medicine or is it really just stratified (or subgroup) medicine?
- **Agree to disagree?** As long as we understand each other
- **Content is more important than definitions**

Economic Considerations in Personalized Medicine

Steven Hass
Senior Director of Neuroscience and Hormones, Global HEOR
Abbott Laboratories
Economic Drivers for Personalized Medicine

- Global economy
  - Increased pressure on healthcare costs
- Crowded therapeutic space
  - Niche markets have greater relative appeal
- Increased cost of development

Economic Premise for Personalized Medicine

- Offers information relevant to clinical interactions
- Attributes of companion diagnostic will encourage use in clinical practice
- Will offer value proposition relevant to all players

- Patient
- Clinician
- Diagnostic company
- Pharmaceutical company
- Payer
Patient: Economic Considerations

• Benefits
  – Reduced investment in alternative therapies
  – ↓ symptom burden = ↑ productivity
  – ↓ adverse event risk and associated costs

• Costs
  – Out-of-pocket cost of diagnostic and therapy
  – Additional office visits for monitoring
  – “Externalities”: time away from paid employment or significant travel costs

Clinician: Economic Considerations

• Benefits
  – Reimbursement opportunity
  – Reduced cost of care for those at risk for patient HCRU

• Costs
  – Investment in technology
  – Disruption to the clinical encounter and patient flow
Diagnostic Developer: Economic Considerations

- **Benefits**
  - Cost of development shared with partner
  - Increased potential for reimbursement and market success

- **Costs**
  - Failure of therapy could delay or prevent launch of diagnostic

Pharmaceutical Company: Economic Considerations

- **Benefits**
  - “Enriched” trials
    - Reduced cost of trials due to ↓ sample size, ↓ enrollment period
  - Improved probability of clinical success
  - Improved probability of regulatory success

- **Cost**
  - Small target subpopulation can wipe out enrichment benefit
  - If viability of product is dependent on diagnostic, potential program failure due to either
  - Delayed launch if diagnostic registrational pathway encounters problems
  - Investment in infrastructure required to support commercialization of product:diagnostic
Structuring the Economic Analysis

Evolution from “treat to test”...

Structuring the Economic Analysis

...to “test to treat”
Payer:
Economic Considerations

• Benefits
  – More efficient use of scarce financial resources
  – Reduced societal burden of disease

• Cost
  – Increasing number of “orphan” indications
    • Required to cover under Medicare Part D
  – Additional patients who are candidates for therapy

Personalized Medicine:
US Payer Perspectives

Amy Grogg, PharmD
President
AmerisourceBergen Consulting Services
March 23, 2010: President Obama Signed the Patient Protection and Affordable Care Act

- Three Predominant Goals of ACA:
  - Expand access to health insurance coverage
  - Improve affordability and sustainability for those who have healthcare insurance
  - Control the rising costs of healthcare while improving quality

The Promise of Diagnostics in Personalized Medicine

- Government belt-tightening hasn't been easy on pharma's pricing power, but it will be a boon for targeted drugs…On the heels of targeted melanoma drug's FDA approval—<manufacturers> are expecting similar meds, and the tests required to target them, to gain importance for cash-strapped payer.

- "No country is going to be able to afford to increase the percentage of GDP spent on healthcare," Roche Diagnostics COO Daniel O'Day told Bloomberg. "What they're all looking for now is how we can take this certain pie we have for healthcare and better leverage it for society."

- And that leverage can be provided by smarter spending on drugs. With diagnostic-and-drug combinations, governments can be more efficient in their spending, O'Day said. Diagnostics will be "solutions for how the countries divide the pies more efficiently,"
Payer Concerns with Personalized Medicine

1. Inability to easily identify which tests actually reduce costs
2. Difficulty in tracking the use of molecular tests resulting in high overall costs from indiscriminate use
3. Difficulty of enforcing protocols to ensure physicians provide appropriate care based on test results
4. Potential for misuse of information
5. Lack of longitudinal accounting to allow for long-term savings from near-term testing due to patient turnover

“Generating high-quality health economic evidence will provide reimbursement confidence that will allow payers to more rapidly adopt tests and align physician incentives with patient care and outcomes, rather than procedures” – Davis et al


Snapshot of the Personalized Medicine Market

- Compounds in late clinical development (phase 2b onward) that have associated companion diagnostic: 10%
- Companies investing in personalized medicine: 94%
- Requires all compounds in development to have an associated biomarker: 30%
- Discovery strategy includes biomarker and/or targeted therapies: 100%

Percentage of Pharmaceutical Companies

Select Biosciences Market Research Report, August 2012.
Current Personalized Medicine Test Distribution by Therapeutic Class

- Cancer: 70%
- Cardiovascular Disease: 13%
- Central Nervous System Disease: 5%
- Infectious Disease: 7%
- Other Classes: 5%

- There are 57 total personalized medicine tests wherein some association with prescription drug entities is present or documented.
- Oncology is the leader in this space with 70% current market share.
- Numbers in this chart refer to number of tests in a given disease class.

Molecular Biology Informing Personalized Prescribing in Cancer Care

- “Personalized prescribing” has always been the preferred paradigm of medical management:
  - Infectious disease management
  - Anticancer therapy
- But aligning preference and practice requires understanding and documenting the core biology driving disease at the level of the individual patient.
- The revolution in molecular biology has allowed us to get closer to making this an everyday occurrence.
Survey Overview and Methodology

- A double-blinded online survey was conducted with payers during the period of September 24 to October 7, 2012
- Survey question content was developed by Xcenda and fielded through Xcenda’s proprietary PayerPulse® survey subscription service

THERE WERE 59 RESPONDENTS representing ~135 million lives

The survey was fielded to Xcenda’s panel of managed care executives, the Managed Care Network (MCN)

50%+ of US Plans Surveyed Are Covering Multiple Tests

MORE THAN HALF OF PLANS INDICATED they are covering 9 of the 15 tests listed.

- 92% Cover HER2
- 86% Cover KRAS mutation testing for metastatic colorectal cancer (pancreatic)
- 75% Cover BRCA 1,2
- 71% Cover Oncotype DX
- 61% Cover BRAF for melanoma
- 54% Cover EGFR expression for lung cancer (Tarceva® [erlotinib])
- 50% Cover UGT1A1 (irinotecan)
- 44% Cover BCR-ABL for leukemia (Gleevec® [imatinib mesylate])
- 36% Cover BRAF for colon cancer
- 25% Cover Mammastrat®, Mammaprint® for breast cancer (chemotherapy)
- 29% Cover BRAF for melanoma
- 18% Cover HER2 (Herceptin®, Tykerb®)
- 15% Cover HER2
- 14% Cover KRAS mutation testing for metastatic colorectal cancer (pancreatic)
- 7% Cover UGT1A1 (irinotecan)
- 7% Cover Mammastrat®, Mammaprint® for breast cancer (chemotherapy)
- 7% Cover KRAS mutation testing for metastatic colorectal cancer (pancreatic)
- 7% Cover Mammastrat®, Mammaprint® for breast cancer (chemotherapy)
- 3% Cover BRAF for colon cancer
- 3% Cover HER2

Other

Significant variation in plan sponsor coverage of tests attributed to the variation in best practice or progressive nature of the body of evidence to support use of personalized testing

Which of the following personalized medicine tests has your health plan agreed to cover as of 2012? Select all that apply. (N=59)
Payer Views: Most Clinically Important Uses of Personalized Medicine

85% consider “prediction of response to an agent” as the most CLINICALLY IMPORTANT uses of personalized medicine, considering the way medicine is practiced in their health plan.

81% consider ‘getting effective therapy the first time’ as the most CLINICALLY IMPORTANT uses of personalized medicine, considering the way medicine is practiced in their health plan.

What would be the most clinically important uses of personalized medicine in terms of the way that medicine is practiced in your health plan? (N=59)

- Prediction of response to an agent: 85%
- Getting effective therapy the first time: 81%
- Managing cost more effectively: 63%
- Dosing guidance: 53%
- Managing to guidelines: 44%
- Prediction of a side effect likelihood: 36%
- Other, please specify: 2%

Other
- Improved outcomes, reduction in add-on or follow-on therapy

Future Impact

80% PREDICT PERSONALIZED MEDICINE WILL HAVE A MODERATE TO EXTREMELY LARGE impact on their plan in the next 10 years

On a scale of 1 to 5, with 1 = no impact at all and 5 = extremely large impact, what do you believe the impact of personalized medicine (composed of pharmacogenomic and genetic predisposition testing) will be on your health plan over the next 10 years? (N=59)

- 1 - No impact at all: 0%
- 2: 7%
- 3 - Neutral: 14%
- 4: 66%
- 5 - Extremely large impact: 14%
New Frontiers in Personalized Medicine: Deep Phenotyping

“We continue to depend primarily on standard disease diagnoses, which are both incomplete and imprecise, as representations of human phenotypes.”

“Our capacity to undertake [genome-wide] projects will probably not be the limiting step in elucidating the genetic basis of common diseases. Instead, we may be held back by our inability to specify precisely the phenotypes… in those individuals whose genomes we investigate.”

“Furthermore, phenotyping is still rooted in clinical traditions, which vary greatly between medical specialties and between different locales; it does not yet have the systematization or throughput to match the worldwide genotyping studies that are envisioned.”

Panel Discussion
Question and Answers