ISSUES AND CHALLENGES IN THE DEVELOPMENT AND REIMBURSEMENT OF PERSONALIZED MEDICINE:
HOW CAN HEALTH ECONOMICS AND OUTCOMES RESEARCH HELP?

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Health Technology 2010: The Issues

- ↑ Healthcare Spending
- ↓ Cost/Quality Concerns
- ↓ P&R Opportunities
- ↑ Consumerism
- ↓ Placebo Control
- ↓ Physician Control
- ↓ “Blockbuster” Model
- ↑ Value-based Purchasing
- ↑ HTA & EBM Pressures
- ↑ Risk Sharing Approaches
- ↑ Comparative Effectiveness
- ↑ Payer Control
- ↑ Personalized Medicine

Health decision makers are requesting more (and more) clinical and economic evidence on the value of new health technologies. Going forward, it will be important to distinguish “got to have” vs. “nice to know” evidence... What evidence is truly material to informed product use?
Trend: Movement Towards Comparative Effectiveness and Value-based Purchasing

Payers and others ask: Can we get better health value for the dollars we spend?

Trend: Payers Limit or Reject Expensive New Health Technologies


What is Personalized Medicine?

Personalized Medicine:
Use of genetic or other molecular biomarker information to improve the safety, effectiveness and health outcomes of patients via more efficiently targeted risk stratification, prevention and tailored treatment management approaches

Pharmacogenomics:
Use of genomic tests to inform patient treatment selection and dosing by predicting drug response

Several examples thus far...
— HER2/neu: Herceptin
— KRAS/EGFR drugs: Vectibix/Erbilux
— Oncotype DX: breast cancer chemo
— CYP2C19: Plavix

Source: Scientific American 2000 and 2006

How Will Personalized Medicine Evolve? What Potential Influence on Quality & Cost?

Adapted from "The Evolution of Man"

Factors Driving Personalized Medicine Forward

- State of the science and information systems now evolved to enable personalized medicine
- Regulatory agencies have taken steps to integrate biomarkers into drug development
- Payer struggles to balance quality and costs
  - Limit access to responders/subpopulations – † effectiveness & safety
  - ‡ wastage and unnecessary costs
  - Manage increasingly expensive drug categories (e.g., oncologybiologics)
- Aggregate affordability of health services is a significant concern in many nations
- Manufacturers recognize challenging reimbursement landscape and emphasis on PM is one tool to support market access

What is Different About Personalized Medicine?

- Opportunity to † quality via better treatment targeting and may improve cost-effectiveness (but not always)
- Significant patient access & policy implications
  - Responders vs. nonresponders
  - Patients in the "grey zone"
  - Accomplishes similar objectives as emerging risk-sharing approaches
- Diagnostic evidence-assessment methods are still evolving in most major markets…lack of best practices & homogeneity
  - Test developed separately from drug vs. co-development
  - Uncertainty of acceptance of adaptive HEOR approaches
  - Where is the evidence threshold?…moving target problem
  - Challenges defining value & lack of value-based pricing opportunities
- Education, adoption and acceptance barriers differ from traditional pharmaceutical paradigms
Initial Research: Setting the Stage for Future Efforts of the PM SIG

- Initial PM SIG paper will focus on:
  - Characterization of common gaps and challenges associated with personalized medicine
  - Describe perspectives key stakeholders along the continuum of evidence development and technology uptake
  - Consider how health economics and outcomes research (HEOR) methods can help address existing gaps and decision requirements for personalized medicine
- Initial paper focused only on evaluation of these issues as related to pharmacogenomic scenarios

Key Perspectives

- Researcher
  - Clinical
  - HEOR
- Diagnostic Test Developer
- Treatment Developer
- Regulator
- Payer

How Can HEOR Methods Help to Close Gaps and Address Decision Maker Needs?

- Linking personalized medicine challenges to HEOR solutions
- Identifying best practices and closing gaps
- Evaluating practice and policy implications

Role of Diagnostics in Personalizing Health Care:

1. Risk stratification
   - Patient MORE or LESS likely to develop disease/condition?
2. Inform treatment selection
   - Is it safe?
   - Is it effective?
3. Inform dosage
   - Slow metabolizers
   - Rapid metabolizers
4. Prognostic testing
   - How likely is the patient to respond to standard treatments?
5. Treatment monitoring
   - Is it working?
   - Should we switch therapies or treatment strategies?
6. Improve or optimize clinical treatment pathways

(Dan Malone, RPh, PhD)

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Trial sample size and study design challenges

- Many SNPs are rare
  - Large study sample sizes needed to test associations
  - Inclusion criteria may select for certain patients and may not be generalizable to broader population
- Genomic consortiums
  - Warfarin Pharmacogenetics Consortium
  - Sub issues:
    - Credit for contributing data
    - Access to combined data
  - Common data elements
  - Standards for measurement

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Relationship between genotype and health outcomes can prove challenging

- Effect sizes between health outcomes and genotype are weaker than expected
- Risk ratios: 1.2 to 1.6
- Multiple exposures over time may occur before adverse effects observed
- Relevance to clinical practice must be considered on case-by-case basis

Source: Kelly et al. BMJ 2010;340:c693

Downstream challenges for health outcomes and economics researchers...a short list

- Insufficient coordination between basic/academic research, clinical research & downstream decision maker’s information needs
- Limited or inconsistent data to support outcomes-focused evaluation...including insufficient data systems
- Evolving, inconsistent and non-transparent standards/methods for trial design & modeling for diagnostics and drug-diagnostic combo products
- Lack of implementation research to understand effectiveness of integrating Dx & PM into practice

Drug & Diagnostic Manufacturer Perspective

Goal: Produce a measurement that provides prudentially meaningful information within a defined clinical context
Performance expectations: Risk tolerance often inversely proportional to that of therapy
IP environment: Platform vs. Analyte
Exact duplicates barred during patent period, work-arounds require significant R&D
Regulatory environment: Must go through FDA, acceptability and performance varied in ultimate result for patients

Drugs
- A novel, more effective measure of a disease or condition
- Can provide patient-specific information
- Based on clinical studies
- Can be used as a diagnostic tool

Diagnostics
- A novel, more effective measure of a disease or condition
- Can provide patient-specific information
- Based on clinical studies
- Can be used as a diagnostic tool

Business Considerations for Drug & Diagnostic Manufacturers

Business environment: Producing a SAE drug, meeting FDA and payer demands for evidence requires very large investment.

High acceptance with strong data
- Access/Gate Keepers: Patient presents, physician prescribes, pharmacist fills, payer pays if meets coverage criteria (label, other studies, professional recommendations)
- Flexible pricing reflecting (often) value to patients
- High failure rate, but most successes recoup investment and a few surpass it considerably

Business environment: R&D investment dependent on type of product and route to market but considerably less than drugs.
- Access/Gate Keepers: Patient presents, physician requests, lab performs and reports, payer pays if meets coverage criteria (label, other studies, professional recommendations). DTC testing
- Pricing often administered with little attention to value to patients
- High success rate for incremental improvements to proven measurements; novel analytic success variable
Key Drug Developer Issues

- Is a test needed? When is it known?
  - Hypothesized response variance?
  - Will the test improve the benefit, risk of the drug and outcomes for patients (i.e., will it add clinical value)?
- Clinical evidence, utility
  - Trials design or additional studies necessary to support the targeted use?
- Labeling
  - What will be the intended use in the drug, diagnostic labels?
- Regulatory approval of the test and test parameters
  - FDA (or CE) required or can LDT be used?
  - Availability and accessibility of the test
  - Added costs and potential ROI?

Key Diagnostic Developer Issues

- At what point in the drug lifecycle is test need identified?
  - What if the drug fails? Any stand alone potential?
  - Will the test improve the benefit, risk of the drug and outcomes for patients (i.e., will it add value)?
- Clinical evidence, utility
  - Will the test change the practice of medicine?
- Regulatory approval of the test
  - Test parameters, reliability of the test, transition from RU assay to clinically validated assay, timing?
- Platform, expected reimbursement?
  - Potential for fast followers?
  - Costs including lost opportunity, potential ROI?

Concerns Faced by U.S. Payers

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Payer Perspective: Need for Companion Diagnostics

- Targeted therapies benefit narrowly-defined populations and are priced accordingly
- Efficient use requires diagnostics that identify responders and reduce NNT
- Cost-benefit analysis should capture adverse events avoided by not treating non-responders
- Companion diagnostics will help targeted drug manufacturers develop a solid value proposition

Payer Perspective: Inadequate Procedure Coding

- Tests billed under miscellaneous codes require manual review to identify
- Manual review is not cost-effective for single marker tests usually priced under $250
- Therefore, U.S. payers cannot efficiently preauthorize most genetic tests

Payer Perspective: Direct to Consumer Marketing

- Risk panels are marketed to healthy individuals
- Evidence of clinical utility is rarely available
- Interpretation requires sophisticated knowledge
- Erroneous interpretation of results can harm
- We may not cover a test but still pay unnecessary cost of poorly informed treatment decisions
- If a test does not lead to actions that improve the individual’s present or future health, it is difficult to argue its cost-effectiveness
**Payer Perspective: Case Example: CYP450 Testing**
- AmpliChip (Roche Diagnostics) $250 per test
- Probably Cost-effective: Tamoxifen metabolism
  - Test cost = cost of 5-6 months of generic drug
  - Prodrug: poor metabolism \(\rightarrow\) poor response, patient not effectively treated & drug cost wasted
- Probably Not cost-effective: PPI metabolism
  - Rapid PPI metabolizers need high-dose PPI for effective H. pylori eradication
  - Incremental cost to double PPI dose: $20-40
  - Best to high dose everyone

**Does it Improve Care + Result in Savings? Early Assessment from One BCBS Plan**
- Case Study: CareFirst BlueCross BlueShield internal return on investment analysis of Oncotype Dx and KRAS testing
  - Plan had medical & pharmacy data aggregated
  - Evaluated total tests completed X list cost of test vs. actual cost avoidance
- Oncotype DX testing:
  - Test cost $3,900
  - For every $1 spent, the plan estimated $2 in savings
- KRAS testing:
  - Test cost $450
  - For every $1 spent, the plan estimated $18 in savings
  - When considered PTEN + BRAF + KRAS at $2,700 testing cost, ROI was still 1.5

**How Can Health Outcomes & Economics Research Help?**

**Research prioritization using VOI approaches**

**Create a robust research infrastructure to support conduct of observational studies of PM technologies**

**Define an evidentiary framework to support decision-making regarding**

**Strategic decision making in development**
- Early stage modeling
- Test performance thresholds
- Support for value-based reimbursement
  - Cost-effectiveness analyses
  - Pricing models

**How Can HEOR Help?: Diagnostic Test Development**

**How Can HEOR Help?: Drug Development**
- Use early stage modeling to understand potential impact of biomarkers on product efficacy and value
- Facilitate participation in public-private partnerships to improve research infrastructure, methods, evidence framework

Source: David Veenstra, PhD, PharmD, Associate Professor, University of Washington, Seattle, Washington, USA. Member, ISPOR Personalized Medicine Reimbursement & Development Working Group. AMCP Annual Meeting April 2010.
**How Can HEOR Help?: Regulatory Decisions**

- Consider use of quantitative methods for assessing potential benefits and harms of genomic tests
  - Decision modeling
  - Discrete choice experiments

**How Can HEOR Help?: Technology Assessment & Payer Decisions**

- Employ decision models of varying complexity to serve purposes ranging from providing a framework for discussions to projections of events rates to estimation of QALYs
- Develop evidence framework to assist decision makers in developing recommendations and decisions

**Conclusions**

- Novel healthcare technologies offer great promise to improve population health, but identification of optimal strategies and efficient use is challenging
- Personalized medicine is particularly challenging because of the pace of technology advancements, often small effect sizes, and comparatively low regulatory hurdles/ease of patient access

**Conclusions**

- Approaches used in health economics and outcomes research can facilitate prioritization of research topics, strategic development decisions, trial design, guideline development, and reimbursement decisions
- However, many challenges remain, including
  - Transparent approaches to decision modeling acceptable to multiple stakeholders
  - Assessment of patient preferences and "information for information’s sake"
  - Potential misperceptions that there is a tension between comparative effectiveness research and personalized medicine

**Questions**

- How do we identify areas of greatest impact for PM and prioritize what to pursue?
- How can we harmonize methodologies and expectations across markets for diagnostics & personalized medicine?
- What different clinical & economic considerations are relevant in assessing PM technologies? What is currently missing?
- Should all tests be subject to the same evidentiary expectations? If so, what is evidence is appropriate?
- If some tests are subject to different evidence expectations, what approach/criteria should we use to decide/prioritize?
- Can we harmonize...or will system differences prevent common approaches to assessing clinical/economic benefit?
(Potential) Future Directions of the PM SIG

- Evaluation of best practices for diagnostics and personalized medicine
- Clinical & economic evidence development approaches
- Technology assessment
- Decision support approaches
- Evaluation of case scenarios – What’s working/not working?
- Consideration of and input on policy topics
  - Appropriateness of adaptive value characterization
  - Value-based pricing approaches
  - Harmonization of approaches
  - Comparative effectiveness vs. personalized medicine
  - Consumer-driven decision making

Thank You!

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