PRECISION MEDICINE: THE END OF OUTCOMES RESEARCH?

An ISPOR Issue Panel by the Precision Medicine: Assessing the Value Working Group of the Precision/Personalized Medicine Special Interest Group
Wednesday, May 25

Surrey Walton, PhD, Associate Professor, Department of Pharmacy Systems Outcomes and Policy, UIC, USA

Susan Snyder, PhD, BS, MBA, Research Investigator / Health Economist, Geisinger Center for Health Research, USA

John Watkins, PharmD, MPH, BCPS Pharmacy Manager, Formulary Development, Premera Blue Cross, USA
Precision Medicine: Assessing the Value Working Group

Co-chairs

Fadia T. Shaya, PhD, MPH, Professor, Vice-Chair, Director of Research, University of Maryland School of Pharmacy & Medicine, Baltimore, USA

Katherine Payne, PhD, MSc, Professor of Health Economics, Manchester Centre for Health Economics, Institute of Population Health, University of Manchester, Manchester, UK

Leadership:

Bhagwan Aggarwal, PhD, MBA, MSc, BSc, Mphil, Assistant Director, NIOH/ICMR, India
Charles Barr, PhD, MD, MPH, Head of Evidence Science & Innovation, Genentech, USA
Eman Biltaji, MS, BSc, Graduate Student/Research Assistant, University of Utah, Pharmacotherapy Outcomes Research Center, USA
Diana Brixner, PhD, RPh, Professor, University of Utah, College of Pharmacy, USA

Vivek Chaudhari, MS, Graduate Research Assistant, University of the Sciences in Philadelphia, USA
Eric Faulkner, MPH, Vice President, Precision and Transformative Technology Solutions, Value Demonstration, Access and Commercial, Evidera; Assistant Professor, Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, USA
Anke-Peggy Holtorf, PhD, MBA, Managing Director, Health Outcomes Strategies, GmbH, Switzerland
Maarten Ijzerman, PhD, MSc, Professor, Chair, Department of Health Technology & Services Research, University of Twente, the Netherlands
James Jackson, PharmD, MPH, Vice President, Xcenda, LLC., USA
Wee Hwee Lin, Assistant Professor, Department of Pharmacy, Faculty of Science, National University of Singapore
Emelline Liu, MSPH, Health Economist, Cepheid, USA
Goal:
• To develop good practices for outcomes research in the study design and utilization of genomics involved in personalized/precision medicine.

Objective:
• Provide a definition of the three key terms used: precision medicine, personalized medicine, and stratified medicine
• Describe the role of health economic and outcomes research (HEOR) in the context of providing an evidence base to support the use of precision medicine
• Identify key research recommendations for applied research and methodological developments to provide an evidence base to support the use of precision medicine
PRECISION MEDICINE: Promise or Reality? A Payer Perspective

John Watkins, PharmD, MPH, BCPS
Pharmacy Manager, Formulary Development, Premera Blue Cross, USA

REALLY???
Specific Terminology

- **PM** = precision medicine, personalized medicine (NOT the same thing!)
- **Genetic test** = single gene, single polymorphism (SNP)
- **Genomic test** = multiple genes, signature
- **NGS** = next generation sequencing
- **WGS** = whole genome sequencing
- **GWAS** = genome-wide association study
- **LDT** = laboratory developed test (FDA designation)
- **RAV** = resistance-associated variant
- **VUS** = variant of unknown significance

Not All Genetic Variants are Equal

Evidence Hierarchy:

- Mutations **known to cause** specific diseases
- Variants **associated** with clinical outcomes
  - Prognostic (disease risk or outcome)
  - Predictive (treatment response)
  - May or may not be the direct cause
- Variants of **unknown significance** (VUS)
  - Insufficient data to correlate with outcome
  - Possible future value
  - If misinterpreted, inappropriate diagnosis/treatment
A Payer’s View of Precision Medicine

<table>
<thead>
<tr>
<th>PROMISES</th>
<th>CHALLENGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Address heterogeneity</td>
<td>• High test cost</td>
</tr>
<tr>
<td>• Target treatment</td>
<td>• Unpredictable variation</td>
</tr>
<tr>
<td>• Efficiency/reduce cost</td>
<td>• Incidental findings</td>
</tr>
<tr>
<td>• Value-based payment</td>
<td>• Diagnostic cascade</td>
</tr>
<tr>
<td>• Understand diseases</td>
<td>• Anxiety, harm and cost</td>
</tr>
<tr>
<td>• Use efficient NGS methods</td>
<td>• Privacy issues</td>
</tr>
<tr>
<td>• Better patient decisions</td>
<td>• Misunderstood results</td>
</tr>
</tbody>
</table>

Cancer Poses Additional Problems

- **Complexity**
  - Multiple clonal lines, biopsy sample variation
  - Possible erroneous conclusions
- **Instability**
  - Additional mutations over time
  - DNA repair mechanisms nonfunctioning
- **Implications**
  - Diagnostic errors
  - Periodic re-testing for changes

*Whole genome sequencing in cancer offers much promise but even more uncertainty!*
Evaluating Coverage: Payer Perspective

- Is the test analytically and clinically **valid**?
- Is it **actionable**?
- Will providers **act** on the results?
- Will it **improve outcomes**?
- Will it **reduce** overall **cost**?
- Is there a population level **testing strategy**?
- Will it **improve population health** (clinical utility)?
- Is it **cost-effective**? Is it **affordable**?
- Can we get the information **some other way**?
- Will testing people **add** to our **knowledge** base?
- Will it **improve member satisfaction**?

Example: BCR-ABL Kinase Inhibitor RAVs

Evaluating Coverage: Patient Perspective

- What is my **condition**?
- What must I **decide**?
- What do I **need to know**?
- **Which tests** are available? What will I learn?
  - Can I believe them?
  - Will I learn something new?
  - Is there a risk?
- **Will I use** the results?
- What is it **worth to me**?
  - Will I get better?
  - Will I have peace of mind?
  - Will it save me money?

Evaluating Coverage: Ethicist Perspective

- **Data privacy**
- impact on **relatives**
- **Underserved** populations
- **Emerging** healthcare systems
- “Unknown **unknowns”**
- **Moral** implications; “responsible innovation”
- Increasing number of **orphan** populations
- **Untreatable** conditions

“[P]ersonalised medicine is exemplary of what medicine aspires to be: exact, rigorous, specific, and able to control both disease and the very possibility of death. The diagnosis and treatment of breast cancer provides an example of the therapeutic, normative, and heuristic power of genetics in medicine.”

How will PM Change Outcomes Research?

• Unique **rewards**?
  • Increase use of EBM
  • Eliminate trial and error
  • Avoid idiosyncratic drug reactions

• Unique **challenges**!
  • Much raw data, but small subgroups
  • Observational studies, confounding
  • Yet undiscovered genes
  • Over-generalizing results

• New designs and evaluation strategies needed

Less Emphasis on RCT Evidence

• Causal inference is not required
  • Prognostic/predictive accuracy matters
  • Knowing cause helps understand disease
  • But is not critical for treatment decision

• Indirect evidence is often sufficient
  • Requires an analytic framework

• Observational data are plentiful
  • Byproduct of routine care
  • Low data acquisition costs
  • Tissue banking
  • Complements RCTs
New Models Are Needed

- Project long-term outcomes from limited data
  - Clinical outcomes
  - ICER
  - Value of information
- Overall budget impact
  - Added cost and savings
  - Upfront investment
  - ROI
- Create new paradigms for oncology
  - Find the “long tail”
  - Tumor targets ➔ molecular targets
  - Use machine intelligence
- Other ideas??

Will Pharmacogenomics Save Money?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Targets the right patients</td>
<td>• Some tests are expensive (&gt;5000)</td>
</tr>
<tr>
<td>• Reduces NNT</td>
<td>• False positives drive unnecessary treatment</td>
</tr>
<tr>
<td>• Avoids unnecessary treatment</td>
<td>• False negatives drive downstream cost</td>
</tr>
<tr>
<td>• Prevents avoidable adverse events</td>
<td>• Misinterpreted results</td>
</tr>
<tr>
<td>• Clinical validity can be validated</td>
<td>• Incidental findings</td>
</tr>
<tr>
<td>• Clinical utility is rarely demonstrated</td>
<td></td>
</tr>
</tbody>
</table>
Will PM Result in Health Care Rationing?

- **Resource Allocation:**
  - Process of distributing limited resources
  - Necessary when there is scarcity

- **Restriction:**
  - Treatment **NOT likely to benefit** patient and may cause harm
  - Withholding unnecessary treatment is in patient’s best interest

- **Rationing:**
  - Treatment **IS expected to benefit** patient
  - Benefits someone else, usually other patients

*If PM helps us restrict more intelligently, it may improve efficiency. If so, it could actually reduce the need for rationing.*

In Conclusion:

- “Precision medicine holds promise to solve the conundrums of clinical care. Foremost is the well-known but vexing problem of heterogeneity and the tyranny of the mean. Who will respond to a treatment? How can patients avoid the harms of treatments that will not work for them? And if we know who to treat, will that make care more efficient and less costly?”

- “Next generation sequencing is making genetic testing radically cheaper. But the costs of medical tests also include false positive results, incidental findings, and the cascade of follow-up. The affordability of precision medicine is intertwined with the broader issue of affordability of our healthcare system, and will require all stakeholders to assume stewardship for access and sustainability.”

Precision Medicine: Health System Perspective

Value-based, patient-centered healthcare

- Better patient outcomes
- Improved resource utilization and cost avoidance

Evaluate health and economic outcomes of PM testing methods and targeted therapies to facilitate trade-off analysis between alternatives
- Clinically actionable (identified risk → acceptable care strategies)
- Useful for decision making
- Transparent criteria
- Cost-effective
Diagnostic process

- Symptom/complaint or clinical finding
- Generate diagnostic hypotheses to explain the finding
- Test hypotheses
- Pertinent positives and negatives assembled for a working diagnosis
- Genomic testing typically applied late in the diagnostic process
  - Intent of confirming clinical suspicion of a genotype-phenotype correlation

“The successful use of a targeted therapy is intrinsically linked to the ability of a companion diagnostic to correctly identify patients most likely to benefit from treatment.”

Doble et al. 2015

Precision Medicine: Promise or Reality?
Health System Perspective

Promise
Evidence of adequate value in targeted populations is necessary but not sufficient

Reality
Requires translation of evidence into practice using well-designed protocols to reliably implement care/services for high value populations

Achievement
Align care value with health system value
HEALTH SYSTEM PERSPECTIVE
PCSK9 Inhibitors and Familial Hypercholesterolemia

The goal of this report is to evaluate the comparative clinical effectiveness and comparative value of PCSK9 inhibitors as a class for patients with elevated LDL-C.
Familial Hypercholesterolemia (FH)

- FH is a life threatening genetic disorder marked by early coronary artery disease and stroke secondary to premature atherosclerosis resulting in significant lifelong elevations in low density lipoprotein cholesterol (LDL-C).

- To date there are no single internationally accepted criteria for clinical diagnosis of FH, which is diagnosed by high LDL-C levels, a physical exam, and family history.

- The optimal management of patients diagnosed with FH has not been discovered in the new era of approved PCSK9 inhibitor therapy.
Base Case and Clinical Outcomes among Patients with FH (ICER Report 2015)

ICER Summary and Comment

- PCSK9 inhibitors may produce substantial reductions in non-fatal MIs, non-fatal strokes, and cardiovascular deaths over a lifetime analytic horizon.

- NNT for 5 years to avoid one major adverse cardiovascular event) of 28 for PCSK9 inhibitors appears to be relatively low.

- PCSK9 inhibitors generate cost-effectiveness ratios that far exceed commonly-accepted thresholds ($100,000/QALY) which would require price reductions of 60% to 63% compared with current prices.

- Our value-based price benchmark for each PCSK9 inhibitor is $2,177 annually, which represents an 85% reduction from the list price of $14,350.
At Geisinger Health System in Pennsylvania we have a unique opportunity to study PCSK9 inhibitor therapy in our FH population.

MyCode®: Whole exome sequencing (WES) in over 50,000 volunteer participants in our biobank.

Includes 4,262 volunteer participants with LDL-C over 190 mg/dL who as of March 2016.

A preliminary analysis: only 6% of patients with LDL > 190 mg/dL are positive for pathogenic variants in the three genes associated with classic FH (i.e., low density lipoprotein receptors (LDL-R), apolipoprotein B (APOB), and PCSK9).
Familial Hypercholesterolemia
Multidisciplinary Clinic
Draft Protocol for Pharmacologic Management

FH Pharmacologic Management Protocol includes PCSK9

Aligns care value with health system value

Protocol ensures limiting use by patient selection and step therapy

Value can be further increased by effectively reducing pricing
HEALTH SYSTEM POPULATION-BASED PERSONALIZED MEDICINE

Pharmacogenomic testing for Adult Onset Epilepsy
Risk-Stratified Personalized Breast Cancer Screening

Generic Pharmacogenomic Screening Economic Model: Adult Onset Epilepsy
Generic Pharmacogenomic Screening Economic Model: Adult Onset Epilepsy

### Input Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value/Value in Decision Model</th>
<th>Description/Description in Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*1502 screening</td>
<td>Yes if 1 in 10% chance carrier status in adult population; progressive relevance in adult epilepsy</td>
<td>To assess the cost-effectiveness of HLA-B*1502 screening in adult population.</td>
</tr>
</tbody>
</table>

#### Selected Currency

- **High**: HLA-B*1502 Testing Cost
- **Low**: Cost of Adult Onset Epilepsy Treatment

<table>
<thead>
<tr>
<th>Cost of HLA-B<em>1502 Screening (for selected HLA-B</em>1502) (in 2019 U.S. dollars)</th>
<th>Cost of Adult Onset Epilepsy Treatment (in 2019 U.S. dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1,200</td>
<td>$10,000</td>
</tr>
</tbody>
</table>

### Result Table 1

#### Baseline (Deterministic/Case)

<table>
<thead>
<tr>
<th>Cost (Selected Currency)</th>
<th>Current practice</th>
<th>HLA-B*1502 screening</th>
<th>No HLA-B*1502 screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life year</td>
<td>85,971.95</td>
<td>120,862.33</td>
<td>322,773.01</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>20.18</td>
<td>20.19</td>
<td>20.19</td>
</tr>
<tr>
<td>Incremental QALY</td>
<td>16.17</td>
<td>16.17</td>
<td>16.17</td>
</tr>
</tbody>
</table>

### Result Table 2

#### Baseline (Probabilistic)

<table>
<thead>
<tr>
<th>Cost (Selected Currency)</th>
<th>Current practice</th>
<th>HLA-B*1502 screening</th>
<th>No HLA-B*1502 screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life year</td>
<td>88,993</td>
<td>129,842</td>
<td>330,883</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>20.04</td>
<td>20.05</td>
<td>20.05</td>
</tr>
<tr>
<td>Incremental QALY</td>
<td>18.92</td>
<td>18.93</td>
<td>18.92</td>
</tr>
</tbody>
</table>

Generic Pharmacogenomic Screening Economic Model: Adult Onset Epilepsy
Breast Cancer Screening: Goals, Benefits and Harms

- **Main Goal**
  - Early detection to reduce breast cancer mortality

- **Early Detection Benefits**
  - Timely treatment
  - Less treatment
  - Less toxic treatment
  - Lower mortality

- **Early Detection Harms**
  - More treatment than necessary
  - No reductions in mortality
  - Overdiagnosis
  - Unnecessary treatment

**Personalized Screening Paradigm**
Evidence-based screening balancing early detection benefits and harms with objective of providing high quality, cost effective care

**Risk-Stratified Approach**
- Aligns individual risk with specific screening strategies
- Appropriate use of imaging modalities tailored to risks and preferences
- Goal: maximizing benefit and minimizing harm (e.g., false positive mammograms)

Personalized Risk Assessment for Breast Cancer: Gaps/Challenges for Accurate Evaluation

- Variation in evidence-based recommendations and low adherence
  - Risk assessment
  - Genetic counseling and testing
  - Mammographic screening
  - Follow-up, surveillance and other preventive care
- Breast density legislation in ~20 states mandating disclosure
- Women typically overestimate breast cancer risk
- Genetic counselor risk assessment focused on hereditary/very high risk population (overuse as first screen)
- Primary care providers not equipped to handle risk assessment

Opportunity to improve care for the majority of women at moderately or slightly increased (non-hereditary) risk
Translation to Evidence-based Practice: Personalized Risk Assessment-based Model

High Risk Breast Clinic (HRBC)

- Started June 2014 in tertiary medical center (extended to other sites)
- Serves all interested women (without active breast problems)
- Participants complete a detailed history questionnaire
- Mid-level providers trained in risk assessment
- Risk Assessment with Hughes Risk Apps
  - Family History
  - Menarche/childbirth history
  - Hormone history
  - Biopsy history

HRBC Risk Assessment

Referral to High Risk Breast Clinic

Personalized Risk Assessment

- Average Risk
- Moderate Risk
- High Risk for Inherited Predisposition
- Dense Breasts

Personalized Care Plan
Risk Assessment-Based Screening Strategy
Moderate Risk and Dense Breasts

In Conclusion:

- Precision medicine can prove its value by providing new information to guide treatment and/or prevention with incremental tangible benefits.

- Most precision medicine interventions will improve outcomes and increase cost, requiring addressing trade-offs with additional information and tools to support decisionmaking and implementation.

- To achieve its promise, precision medicine needs to address the important gaps between science and what is needed in practice.
Sign up as Review Group Member

- Sign up as Review Group Member
- Join ISPOR Special Interest Groups
- Need ISPOR membership number
- Give business card to:
  - Theresa
    ttesoro@ispor.org
  - Clarissa
    ccooblll@ispor.org