DOES HEALTH ECONOMICS HAVE A ROLE IN THE NEW ERA OF PERSONALIZED MEDICINE?

ISPOR 19th Annual International Meeting
Montreal, Canada
2014

Speakers

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Personalized Medicine

- A form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease, or to make a prognosis
- Also called precision medicine


Biomarkers: Personalized medicine
Examples of personalized medicine

- Using targeted therapies to treat specific types of cancer cells, such as HER2-positive breast cancer cells
- Using tumor marker testing to help diagnose cancer

Key Policy Issues

- Evidence gaps
  - Most tests come to market without FDA review/approval

- Variable use in practice
  - Tests diffuse into practice unevenly
    - Many patients who could benefit are not offered the test
    - “Off-indication” use is common
Key Policy Issues

• Uneven and uncertain payment structure
  – Test-specific billing codes are often unavailable
  – Insurer policies towards reimbursement can vary widely

• Lack of evidence of cost-effectiveness
  – Models, when they exist, often rely on registration data even though real world use may be very different from ideal use.

Cost-Effectiveness Analysis and Personalized Medicine: Not a good combination

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Traditional health economic approaches to framing and assessing PM have had limited success addressing these issues

1. Uncertainty in economic analyses of PM applications precludes effective use by policymakers
2. Inherent value of PM information to patients – personal utility – is not explicitly evaluated
3. Influence of PM attributes on uptake – and thus population impact – is not captured
4. CEA too dang slow!

Example 1: Warfarin PGx

- **CYP2C9** (Cytochrome P450 2C9)
  - Involved in warfarin metabolism (half life)
  - *CYP2C9* (*2 and *3) variants require lower warfarin doses vs. wild type (*1), and are at increased risk of major bleeding

- **VKORC1** (vitamin K epoxide reductase complex 1)
  - Involved in synthesis of vitamin K–dependent clotting factors
  - *VKORC1* 1173 variants require lower warfarin doses vs. wild type, and may be at increased risk of major bleeding

- **CYP4F2** (Cytochrome P450 4F2)
  - Mechanism not well established, but likely involved in vitamin K metabolism
  - *CYP4F2* *3 variants require higher warfarin doses vs. wild type, but major bleeding association has not been evaluated

Higashi, JAMA, 2002; Limdi, Pharmacogenomics, 2008; McDonald, Mol Pharmacol, 2009; Caldwell, Blood, 2008
Warfarin PGx CEA’s


Warfarin PGx CEA Uncertainty

Meckley et al (2010)
Warfarin Policy Decisions

• The 8th ACCP Guidelines state, “...without evidence from randomized trials, we suggest against the use of pharmacogenetics-based initial dosing.”
Example 2: FVL testing in pregnancy

A risk–benefit analysis of factor V Leiden testing to improve pregnancy outcomes: a case study of the capabilities of decision modeling in genomics

Preeti S. Bajaj, BS¹ and David L. Veenstra, PharmD, PhD¹

Conclusion: Factor V Leiden testing involves tradeoffs between clinical and personal utility, and additional effectiveness data are needed for heparin use to prevent pregnancy loss. Decision-analytic methods offer somewhat limited value in assessing these tradeoffs, suggesting that evaluation of complex outcomes will require novel approaches to appropriately capture patient-centered outcomes.
Example 3: Whole Genome Sequencing and Incidental Findings

Moore’s Law broken
Key Challenges

• ACMG recommendations: 56 different potential incidental findings
  – LOTS of potential outcomes!

• Poor evidence in many cases
  – “We recognize that there are insufficient data on penetrance and clinical utility to fully support these recommendations…” -ACMG Guidance

• Evidence from selected, high-risk populations
CEA - PM ‘Drug’ Interaction

• Grade 3/4 adverse effects
  – headache
  – confusion
  – frustration
  – poor decision making

Future Needs

1. Develop a better understanding of optimal research investment opportunities in PM
2. Achieve a clearer understanding of societal, provider, and patient preferences for PM
3. Develop a consistent and consensus-based approach for evaluating evidence uncertainty
4. Speed it up
• Yes, CEA is useful for PM, but it has serious limitations
• Let’s think outside the box

Personalized Medicine:
Outcomes Evidence Payers Need

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Personalized Medicine and Managed Care

• Evidence-based personalized medicine
  – Is PM a “micro” version of EBM?
  – What evidence should payers require?
• Payer challenges in evaluating evidence
  – Small patient numbers/need companion diagnostics
  – New methodologies (e.g., WGS)
  – Pricing and affordability
  – How much can we generalize results?
  – How to demonstrate clinical utility?

Example: Ivacaftor (Kalydeco)

• CFTR protein
  – ATP-gated chloride channel
  – Mutations prevent function causing cystic fibrosis
• Ivacaftor
  – Alters CFTR conformation to open the channel
    • FDA approved only for G551D mutation
    • Several similar mutations may possibly benefit
    • Do we need specific evidence for every mutation?
  – Costs:
    • Ivacaftor costs $300,000 per patient per year
    • Mutation testing costs $500
What Evidence Do We Need?

- Payers’ wish list:
  - Clinical utility of tests and companion drugs
  - Cost-effectiveness of different testing strategies
- Reality:
  - Trials may take 10 years or more to get results
  - Results have different meaning to different people:
    - Personal utility – what do patients want to know?
    - Providers want to identify most effective treatment
    - Payers want to maximize value and minimize overall cost of care

AMCP Format
Framework for Evaluation

2.3 Evidence for Pharmacogenomic Tests and Drugs

Analytic Validity
- Accuracy with which a particular genetic characteristic can be identified using a genetic test in relation to professional standards and federal regulation requirements.

Clinical Validity
- Strength of the association between the genetic variant(s) and clinical outcome(s) (e.g., efficacy, adverse drug reaction)
- Expected prevalence of genetic variant(s) in target population; positive predictive value (PPV) and negative predictive value (NPV) of test

Clinical Utility
- Effectiveness and safety of the clinical intervention implemented as a result of the genetic test, as per Sections 3.1-3.3 of the Format; consider inclusion of quantitative risk-benefit decision analytic modeling (Section 4.1.1 of the Format).

Cost Effectiveness
- Expected difference in costs and outcomes with pharmacogenomic testing compared to usual care, as per Section 4.2.3 of the Format, including cost offsets from changes in drug utilization and health outcomes.

Predicting Breast Cancer Recurrence

*Oncotype DX is a Gene expression panel. Using it may increase or decrease a patient’s recurrence risk estimate.*

- **Payer questions:**
  - Will it change physician’s recommendation?
  - Will it impact patient’s chemotherapy decision?
  - Will it lead to improved outcomes?
  - Will it decrease drug costs?
  - How will it impact overall cost of care?

Companion Diagnostics That Make Sense

- Identify appropriate target patients for a drug
  - Reduce NNT
  - Improve incremental cost-effectiveness
- Test cost is small compared to treatment cost
  - **Favorable:** High drug cost/test cost ratio:
    - BRAF V600 mutations in metastatic melanoma
    - EGFR and ALK testing in NSCLC
  - **Unfavorable:** Low drug cost/test cost ratio:
    - CYP 450 2D6 testing before *H. pylori* treatment
    - Antidepressant metabolism
Example: Metastatic Melanoma

Vemurafenib and Cobas® 4800 BRAF V600 Mutation Test

- Does this demonstrate clinical validity of the diagnostic test?
- Does this demonstrate clinical utility of the test? Of the Drug?
- Does this reduce NNT, eliminate waste and lower cost?
- Are the results generalizable to other V600 mutation tests?

Summary

- CEA is relevant and important
  - Not all biomarker tests are worth doing
  - Need to manage efficient use of this technology
  - Answers are not always straightforward

- Efficiency is achieved when:
  - The drug is narrowly targeted (benefits only a small subset of potential patients)
  - Test results are actionable to providers and patients
  - Testing substantially improves clinical outcomes
  - Drug cost is large compared to diagnostic cost
Health Economics in the Context of Personalized Medicine

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Role of Health Economics

• Two main contribution of microeconomics
  – Optimal allocation of resources under constraints
  – Self-selection behavior
• Personalized medicine embodies these issues at different stakeholder levels
  – uncertainty in economic analyses of PM applications
  – inherent value of PM information to patients
  – influence of PM attributes on uptake
Valuing Personalized Medicine

- Expected Value of Individualized Care (EVIC*) estimates the incremental value of using a perfect test (100% specificity, 100% sensitivity) over current treatment allocation rules.
  - Maximal upper bound on the expected incremental benefits of delivering individualized care
  - \[ \text{EVIC} = [\text{INB}(A-B) \mid \text{Test}] - [\text{INB}(A-B)] \]
  - Different from other VOI concepts (e.g. EVPI, EVSI etc).

* Basu A, Meltzer D. MDM 2007
Valuing Personalized Medicine

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EVIC
(individualization only based on cost-effectiveness)
Three main assumptions under current EVIC framework

1. Patients pay for treatments A versus B.
2. A perfect (100% specificity, 100% sensitivity) PM test is available.
3. The PM test, when available, is always used by the physician, patients and is fully covered by the insurer

**GOAL:** Relax these assumptions and expand the EVIC framework to incorporate empirical estimates of test characteristics, their uncertainties and uptake.

Relax assumptions under current EVIC framework

1. *Insurer fully cover treatments A versus B - patients only care about benefits.*
EVIC
(individualization only based on effectiveness only)

EVIC (Patients) ≥ EVIC (Insurer)
EVIC
(individualization only based on effectiveness only)

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Role of co-payments for treatments

Relax assumptions under current EVIC framework

1. Insurer fully cover treatments A versus B - patients only care about benefits.
2. PM test is imperfect (<100% specificity, <100% sensitivity).

Evic(Patients) ≥ or ≤ EVIC(Insurer)
Relax assumptions under current EVIC framework

1. Insurer fully cover treatments A versus B - patients only care about benefits.
2. *PM test is imperfect* (<100% specificity, <100% sensitivity).

\[ \text{EVIC(Patients)} \geq \text{or} \leq \text{EVIC(Insurer)} \]

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Relax assumptions under current EVIC framework

1. Insurer fully cover treatments A versus B - patients only care about benefits.
2. *PM test is imperfect* (<100% specificity, <100% sensitivity) and *uncertain*.

*For example, Contemplate a RCT aims to establish properties of a PM test:*

- **EVPI** = \( \text{EVIC (without test property uncertainty)} - \text{EVIC (with current test property uncertainty)} \)
- **EVSI** = \( \text{EVIC (with reduced test property uncertainty) - EVIC (with current test property uncertainty)} \)
Relax assumptions under current EVIC framework

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E.g. Contemplate a RCT aims to establish properties of a PM test:

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Relax assumptions under current EVIC framework

1. Insurer fully cover treatments A versus B - patients only care about benefits.
2. PM test is imperfect (<100% specificity, <100% sensitivity) and uncertain.
3. Imperfect Uptake of PM

\[ \text{EVIC} = \text{pr(Test)}*\{[\text{INB(A-B) | Test}] - [\text{INB(A-B)}]\} \]
Relax assumptions under current EVIC framework

1. Insurer fully cover treatments A versus B - patients only care about benefits.
2. PM test is imperfect (<100% specificity, <100% sensitivity) and uncertain.
3. Imperfect Uptake of PM

\[
\text{EVIC} = \text{pr(Test)} \times \{[\text{INB}(A-B) \mid \text{Test}] - [\text{INB}(A-B)]\}
\]

Diffusion of PM

Selection on Gains?
Use of Expanded EVIC

• U01 Goals - Understand how EVIC can be used to
  – prioritize investment decisions by manufacturers,
  – determine coverage decisions by insurers, and
  – determine adoption decision by patients/clinicians
• Go beyond traditional cost-effectiveness ratio
  – Develop a comprehensive return-on-investment framework
• Develop a discrete choice framework that can be used to predict choices at each level of decision making
  – Used to develop prediction models for diffusion of PM.

References

Thanks

NIH Common Fund, NIA
(1U01AG047109-01; Veenstra, Basu, Carlson)
NIH Common Fund, NCI
(1U01CA183081-01; Mandelblatt, Ramsey, Lieu)

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