Comparative Effectiveness Research and Personalized Medicine: Policy, Science and Business

Setting the Stage

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Comparative Effectiveness Research and Personalized Medicine: From Contradiction to Synergy

Prepared for: Personalized Medicine Coalition
The Lewin Group Center for Comparative Effectiveness Research

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Timeline: Getting to CER

1. **RCT of streptomycin for pulmonary tuberculosis, sponsored by Medical Research Council (UK): 1948**
3. **Patient Outcomes Assessment Research Program (later, PORTs) initiated by NCHSR (later renamed AHCPR; now AHRQ) in 1986 (“promote research with respect to patient outcomes of selected medical treatments and surgical procedures for the purpose of assessing their appropriateness, necessity and effectiveness“)**
4. **HCFA (later renamed CMS) Effectiveness Initiative: 1988**
5. **Early published appearance of “pharmacoeconomics”: Bootman et al. 1989**
8. **CMS draft guidance in 2005; formalized in 2006. Medicare and other payers began linking coverage to clinical research in 1990s**

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Timeline: Getting to PM, Too

1950
DNA Structure Described (1953)

1960
Genetic Code Cracked (1967)

1970
CYP450 Metabolic Enzymes Identified (1977)

1980
Effectiveness Research (1988)

1990
Pharmacoeconomics (1989)

CED (2006)

2000
Human Genome Sequenced (2003)

2010
CER (2003, 2009)

1948
1st RCT

1959
“Pharmacogenetics”

1974
HTA

1986
Outcomes Research

1989
Pharmacoeconomics

1990
EBM

Source: C. Goodman © 2009 The Lewin Group
CER Attributes (1)

No standard definition. Generally common attributes:

- Direct comparisons of alternative interventions (as opposed to comparison with placebo or indirect comparisons)

- Applies to all types of interventions
  - pharma, biotech, devices/equip’t, medical and surgical procedures; organization, delivery, management, financing

- Effectiveness (in realistic health care settings) rather than efficacy (in ideal circumstances)

- Health care outcomes (e.g., morbidity, mortality, QoL, adverse events, and symptoms) rather than surrogates or other intermediate endpoints
CER Attributes (2)

• Primary and secondary data collection
  ➢ Preferred: head-to-head RCTs/PCTs that meet req’ts for effectiveness research, where feasible
  ➢ Observational studies, including registries, claims data, epidemiological; use of EHRs
  ➢ Systematic reviews (may include meta-analyses) of head-to-head comparisons (direct preferred over indirect; “comparative effectiveness reviews)

• No consensus regarding incorporation of cost-effectiveness analysis or other economic analysis
Defining CER

[T]he generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels. CER’s distinguishing characteristics include informing a specific clinical or policy decision, comparing at least two approaches or interventions, describing results at the subgroup level, measuring benefits in real-world populations, and applying appropriate methods and data sources. — Institute of Medicine 2009
Defining PM

“Personalized medicine” refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.” — President’s Council of Advisors on Science and Technology 2008
CER and PM: Contradiction?

1. CER has been largely oriented toward population-based evaluations and applications. In contrast, PM focuses on using individuals’ genomic information and other personal traits to inform their health care decisions.
2. Like other forms of evaluation of health care interventions, CER generally has focused on identifying interventions that are effective, on average, across a broad patient population.

- Interventions that yield a statistically significant treatment effect across a study population may not necessarily work for all treated patients; they may be ineffective for some patients and harmful for others.

- Interventions that do not yield a statistically significant treatment effect across a study population—and that may be dismissed as ineffective—may work for certain subsets of the population.
Could Mislead Gatekeeping Function

3. The absence of PM considerations in CER could be suboptimal for patient interests, particularly to the extent that CER findings are used to support gatekeeping or other authoritative functions, such as product labeling, clinical practice guidelines, coverage policies, and quality measures and criteria.

• To the extent that PM is incorporated into CER, the resulting evidence will be more relevant and useful for these same functions.
Incorporating PM into CER

4. For CER to contribute to PM, it will have to emphasize priorities and study designs that account for individuals’ genetic, behavioral, environmental, and other personal traits that mediate the impact of screening, diagnostic, therapeutic, and other interventions on patient outcomes.

- To date, only a small percentage of published comparative effectiveness studies have focused on treatment effectiveness in patient subgroups.
Most CER Has Not Focused on Subgroups, Even Large, Aggregated Ones

- CRS analysis: only 13% of comparative clinical effectiveness studies published in the peer-reviewed literature Jan. ‘04-Aug. ‘07 focused on effectiveness of treatments in subpopulations other than white middle-age adults (or females for diseases that only occur in females), e.g., children, the elderly, and non-white populations.

- Only about 5% of these CER studies included patients with comorbidities, even though nearly 60% of hospitalized patients have one comorbidity and more than a third have at least two comorbidities.*

Spectrum of CER-PM Alignment

5. Aligning CER and PM depends on several key factors, including:
   • Research questions being addressed
   • Type of interventions being studied
   • Study design and implementation
   • Ways in which findings are communicated to and applied by patients, clinicians, payers, and others
   • Ability of health care organization, delivery, management, and payment to support and enable PM
Study Designs to Detect HTEs*

6. The extent to which population-based evidence can be used to inform health care decisions for specific individuals depends not only on how well the study population represents those individuals …

- It also depends on whether the study designs and analytical methods used are capable of detecting important treatment effects and adverse outcomes for the patient subgroups representing those individuals.

* Heterogeneity of treatment effects
PM Interventions Subject to Evidence Req’ts

7. PM interventions are subject to prevailing requirements for rigorous evidence demonstrating how well they work compared to standard care.

• Increasingly, this means showing that an intervention has some direct, or least demonstrably indirect, favorable impact on health outcomes in real-world practice settings.

• For genetic/genomic testing and other aspects of molecular-based PM, this means demonstrating not only technical accuracy of a test, but further downstream impact on health care decisions and outcomes.
Figure 1. Chain of inquiry for valuation of laboratory tests

Analytic Validity

Definition:
A laboratory test’s ability to measure the analyte (or genotype, in the case of genetic testing) of interest accurately and reliably (i.e., the quality of the measurement)

Key measurements:
- Accuracy
- Analytic sensitivity
- Analytic specificity
- Precision
- Robustness

Clinical Validity

Definition:
A laboratory test’s ability to detect and predict the disorder that is associated with an analyte measurement; a test’s value to clinical decision making.

Key measurements:
- Clinical sensitivity
- Clinical specificity
- Positive predictive value
- Negative predictive value

Clinical Utility

Definition:
Clinical effectiveness; the balance of risks and benefits associated with use of a test in routine clinical practice; usefulness and value of information, positive or negative, to person being tested

Key measurements:
- Intermediate/surrogate outcomes
- Health outcomes (mortality, morbidity, quality of life)
- Adverse effects of diagnostic use
- Adverse effects of treatment

Economic outcomes

Types of economic outcomes measurements:
- Estimates of the economic value relative to investment and may include analyses such as cost per test, patient, treatment and episode of care
- Estimates of the budget impact of a test on a provider, provider organization, health system
- Estimates the tradeoff value between costs and benefits to health are, including cost-effectiveness, cost-utility, and cost-benefit analysis

<table>
<thead>
<tr>
<th>Level</th>
<th>Analytic Validity</th>
<th>Clinical Validity</th>
<th>Clinical Utility</th>
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| 1 (highest) | Collaborative study using a large panel of well-characterized samples  
Summary data from well-designed external proficiency testing schemes or interlaboratory comparison programs | Well-designed longitudinal cohort studies  
Validated clinical decision rule                  | Meta-analysis of RCTs                            |
| 2     | Other data from proficiency testing schemes  
Well-designed peer-reviewed studies (e.g., method comparisons, validation studies)  
Expert panel reviewed FDA summaries                | Well-designed case-control studies                        | A single RCT                                  |
| 3     | Less well designed peer-reviewed studies                                           | Lower quality case-control and cross sectional studies  
Unvalidated clinical decision rule                  | Controlled trial without randomization  
Cohort or case-control study                        |
| 4     | Unpublished and/or non-peer-reviewed research, clinical laboratory, or manufacturer data  
Studies on performance of the same basic methodology, but used to test for a different target | Case series                                           | Case series                                   |
|       |                                                                                 | Unpublished and/or non-peer-reviewed research, clinical laboratory, or manufacturer data  
Consensus guidelines  
Expert opinion                                                 | Unpublished and/or peer-reviewed studies  
Clinical laboratory or manufacturer data  
Consensus guidelines  
Expert opinion                                                  |

Multiple Evidence Req’ts for PM Tests Along Clinical Pathway – Direct vs. Indirect Evidence

Essential Role of HIT for CER-PM

8. HIT can help align CER and PM in two main ways:
   • Through EHR capture of genetic and other personal health information in clinical trials and clinical practice, HIT can support CER to augment the evidence base for PM.
   • Clinical decision support systems and other forms of HIT can ensure that evidence pertaining to PM is present and actionable at the point of decision-making by patients and clinicians.
   • Slow adoption of HIT …
Evolving Methods Portfolio Needed

9. CER offers an evolving portfolio of methods with great potential for meeting the needs of PM.
   • CER methods development supported by AHRQ
   • Ongoing work in the public and private sectors on data mining and analysis of claims and other administrative and observational data.
   • Adaptive clinical trial designs, other variations on clinical trials that focus on deriving evidence efficiently for responsive vs. nonresponsive patient subgroups.
CER Methods Portfolio (Evolving)

Clinical Trials
- Randomized clinical trials
- Practical (pragmatic) clinical trials
- Other non-randomized controlled trials
- Adaptive clinical trials and other trial designs
- Other, e.g., randomized consent, regression discontinuity, combined single-subject (“n of 1”) trials

Observational Studies (prospective or retrospective)
- Population-based longitudinal cohort studies
- Patient registries
- Claims databases
- Clinical data networks
- Electronic health record data analyses
- Post-marketing surveillance (passive and active)

Syntheses of Existing Evidence
- Systematic reviews (comparative effectiveness reviews)
- Meta-analyses
- Modeling
Encouraging Policy Developments

10. Encouraging developments in the adaptation of CER for PM and policy makers’ commitment to ensure that PM is integrated into CER.

- CER priorities recommended by Federal Coordinating Council for CER and IOM
- Pending legislation emphasizing need for subgroup analyses and consideration of patient-level attributes
- AHRQ-sponsored analysis of how well CER studies* have accounted for HTEs; findings to be incorporated into methods guidance
- OK … but much work is needed to ensure that these early signs will actually lead to evidence-based PM

* AHRQ, Cochrane Collaboration, OHSU DERP, Australia NHMRC, UK NICE
“In addition, comparative effectiveness should complement the trend in medicine to develop personalized medicine—the ability to customize a drug and dose based on individual patient and disease characteristics. One of the advantages of large comparative effectiveness studies is the power to investigate effects at the sub-group level that often cannot be determined in a randomized trial. This power needs to be harnessed so personalized medicine and comparative effectiveness complement each other.”

IOM Recommended CER Priorities

In top tier:

- Compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancer, and possibly other clinical conditions for which promising biomarkers exist.

Pending Legislation, e.g.:

• “Taking into account potential differences.—Research shall—(i) be designed, as appropriate, to take into account the potential for differences in the effectiveness of health care treatments, services, and items as used with various subpopulations, such as racial and ethnic minorities, women, age, and groups of individuals with different comorbidities, genetic and molecular subtypes, or quality of life preferences; and (ii) include members of such subpopulations as subjects in the research as feasible and appropriate.”

CER Affecting Innovation, Including in PM

11. CER is likely to alter value propositions for innovation in PM. It will provide new opportunities and hasten some shakeouts.

• The need to generate comparative evidence at more discrete levels raises the risk of innovation and forces choices about its direction and sequence. Targeted therapies that can demonstrate comparative effectiveness may gain market advantages.

• Federal support of comparative effectiveness trials, other studies could reduce development costs of some new interventions. Analyses of linked databases may help to identify new genetic determinants of drug response and related biomarkers.
Target Group Translation … and Don’t Forget Limitations

12. As CER further reflects patient risk factors, comorbidities, HTEs, and other individual factors that can affect the use and outcomes of health care interventions, communications and applications of these findings must be more adaptive and targeted to clinicians, patients, payers, public.

• These messages should address limitations of this evidence for decision-making and evidence gaps that are priorities for further CER.
What Will It Be?

• Whether CER and PM will be opposed or aligned—let alone synergistic—is now unfolding. CER and PM offer complementary advantages of great potential. In a stressed health care system poised for reform, a continued, concerted effort is necessary to ensure that this potential is realized.
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