Issue Brief

21st Century Science: - Comparative Effectiveness Research and - Personalized Medicine -

ISSUE BRIEF

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Modern medicine is at the brink of the next revolution in healthcare due to emerging scientific advances that apply genetic and molecular tools to patient care. Knowledge of an individual's genetic and molecular profile can predict predisposition to certain diseases, and it can guide disease prevention strategies and facilitate the smarter use of therapies—that is, selecting treatments that are more likely to be effective and less likely to be dangerous based on someone's genetic characteristics. Often called "personalized medicine," this approach to clinical care has the potential to enhance preventive medicine and reduce the use of a "one-size-fits-all" approach to disease management. At the same time, it will increase the volume of information available to be processed and used by patients and their healthcare providers.

Personalized medicine (PM) has emerged along with a renewed focus on comparative effectiveness research (CER). Comparative effectiveness research—evaluating two or more healthcare interventions to determine which are most effective for patients in "real-world" settings—holds promise in improving patient care and supporting personalized medicine. At the same time, there is growing recognition of the need to ensure that proposals for comparative effectiveness research are in step with the emerging science of personalized medicine. Dana Farber CEO Ed Benz stated in March 2009 that "wise policy" is needed to make sure PM and CER work together.[1]

A new paper written by the Lewin Group for the Personalized Medicine Coalition systematically examines the intersection of CER and PM and defines key issues to address in developing this "wise policy" to advance the two together.

Background

The Lewin paper, "Comparative Effectiveness Research and Personalized Medicine: From Contradiction to Synergy" explains the central challenge of aligning CER and PM, noting that while the purpose of CER is to determine which healthcare intervention works best for a given healthcare problem, the purpose of PM is to ensure that healthcare delivers "the right treatment to the right patient at the right time." Both are intended to support high-quality, evidence-based decisions for optimal patient care. However, while CER is usually oriented toward evaluating treatment effects across study populations, PM focuses on using individuals' genomic information and other personal traits to inform decisions about their healthcare.

Like most other methods used to evaluate healthcare interventions, CER generally focuses on identifying interventions that are effective, on average, across a given patient population. However, interventions that have a statistically significant average treatment effect across a study population do not necessarily work for all treated patients; they may be ineffective for

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[1] *The RPM Report*, April 1, 2009, "Wise Policy" Needed To Link Comparative Effectiveness with Individualized Medicine.

some patients and potentially harmful for others. Other interventions that do not yield a statistically significant treatment effect across a study population—that also may be dismissed as ineffective—may work for certain subgroups of the population. Said another way, CER usually asks, "what works best for the most," while personalized medicine asks, "what works best for whom."

The paper explains that if CER does not investigate potentially important differences in patient response to interventions—for example, whether patient response to a cancer drug varies by certain genetic characteristics—its findings may be inadequate or misleading for patient care. If such findings are incorporated into product labeling, clinical practice guidelines, reimbursement policies, or utilization management, it could hinder the application of optimal care of the individual and discourage the emergence of personalized medicine. However, if analyses of how well diagnostics and treatments work in particular patient subgroups are incorporated into CER, the resulting evidence can be used in more flexible, adaptive guidelines and policies that would better enable PM. This level of investigation is especially important in cases where the more common treatment does not work for a particular individual.

Aligning CER and PM

The paper notes that population-based evidence derived from CER, personalized evidence derived from PGx, and other research should not be considered alone. Rather, research priorities, the design and conduct of data collection, reporting of results, and translation of CER and PM into practice and policy should be fully integrated. The report identifies issues in several broad areas that are important for policy-makers to address in aligning CER and PM:

1. - *Defining research priorities across a range of interventions related to medical technology and their use to support personalized medicine.*

   CER will provide optimal support for PM when it examines all of the elements of care relevant to high-quality, personalized healthcare. Systems of care include diagnostic tests and therapies, disease prevention, care management protocols, and approaches to healthcare delivery and benefit design. For example, CER that identifies optimal approaches to care coordination among physicians and other providers, examines interventions for prevention and disease management, or evaluates different formulary designs can help define approaches that are supportive of personalized medicine.

   This integrative approach to CER is consistent with the definition of CER adopted by the Federal Coordinating Council for Comparative Effectiveness Research (FCC-CER). According to the FCC-CER definition, CER should encompass "medications, procedures, medical and assistive devices and technologies, diagnostic testing, behavioral change, and delivery system strategies."

   The Lewin report notes that a top tier national CER priority recommended to the Department of Health and Human Services (HHS) by the Institute of Medicine (IOM) includes comparative effectiveness of genetic and biomarker testing. CER also offers the opportunity to advance PM by expanding the evidence base for genetic and other individual-based tests. "Much work is needed to begin to overcome the lack of evidence on the clinical utility of these technologies," the paper states.

As noted by Khoury et al., "CER can be an important tool to assess both the clinical validity and utility of tests that identify genetic variations. Because most genomic applications will be competing with current clinical practice using other tests, evidence is needed to show whether genomic tests provide clinically meaningful incremental benefits in real-world settings."[2]

2. - *Selecting study methods and study designs in CER to recognize and support personalized medicine.*

The ability of population-based evidence to inform healthcare decisions for specific individuals depends not only on how well the study population represents those individuals but also 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.

CER can most fully contribute to PM, the Lewin paper says, if CER "emphasizes study designs." Study designs should account for individuals' genetic, behavioral, environmental, and other personal traits that mediate the impact of screening, diagnostic, therapeutic, and other interventions on patient outcomes.

The Lewin paper describes the range of available study methods (clinical trials, observational studies, and syntheses of existing evidence) as well as their strengths and limitations for conducting CER that supports PM.

CER offers an evolving portfolio of methods with great potential for meeting the needs of PM, including those arising from CER methods in development that are being supported by the Agency for Healthcare Research and Quality and ongoing work in the public and private sectors on data mining and analysis of claims and other administrative and observational data. Adaptive clinical trials design and other variations on clinical trials that focus on deriving evidence efficiently for responsive versus nonresponsive patient subgroups are particularly promising for PM.

3. - *The development of robust health information technology infrastructures will play an important role in advancing CER that supports PM.*

Full incorporation of PM in CER depends on the adoption of health information technology (HIT), according to the Lewin paper. HIT can enable the contribution of CER to PM in two ways. At the front end of CER, electronic health records (EHRs) can capture patients' genetic and other health information in the course of routine healthcare, clinical trials, and other studies to support the conduct of CER. To support research on relationships among personal traits, interventions, and outcomes, secure ongoing collection of gene-based and other molecular test data from EHRs and clinical research can be linked with population-focused patient registries. At the delivery end of CER, HIT can ensure that evidence pertaining to PM is present and actionable at the point of decision-making, enabling patients and their

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[2] Khoury MJ, Rich EC, Randhawa G, Teutsch SM, Niederhuber J. Comparative effectiveness research and genomic medicine: an evolving partnership for 21st century medicine. *Genet Med*. 2009 Oct;11(10):707-11.

physicians to consider patients' personal traits when weighing the risks and benefits of alternative treatment options. Through computerized clinical alerts and reminders and ready access to relevant clinical practice guidelines, quality standards, and research findings, appropriately designed clinical decision support systems can help clinicians identify interventions or regimens that are more likely to benefit patients with particular characteristics.[3]

4. *Communicating CER results in ways that reflect the emergence of PM.*

   As noted in the Lewin paper, the absence of PM considerations in CER could be suboptimal for patient interests, particularly to the extent that CER findings are used to support gate keeping 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.

   As CER further adapts to reflect the heterogeneity of treatment effects (HTE) and other individual factors, communication and application of findings must adapt as well. Treatment decisions will present more options, and there may be a greater need for communication between clinicians and patients and more considerations for flexibility in payment, utilization management, and other administrative functions.

   Beyond clinical and healthcare management and administration settings, CER findings must be communicated to the public in an accurate, comprehensible manner and include study limitations. If not communicated properly, public information regarding clinical interventions, including emerging findings from CER and PM, can be confusing, if not contradictory.

   The American Medical Association has underscored the importance of effective communication of CER findings, stating, "CER evidence cannot adequately address the wide array of patients with their unique clinical characteristics, co-morbidities, and certain genetic characteristics. In addition, patient autonomy and choice may play a significant role in both CER findings and diagnostic/treatment planning in the clinical setting. As a result, sufficient information must be included concerning the limitations and exceptions of CER studies so that physicians who are making individualized treatment plans will be able to differentiate patients to whom the study findings apply from those for whom the study is not representative."[4]

5. *Applying CER results in ways that reflect the emergence of personalized medicine.*

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[3] Clinical decision support encompasses, e.g., computerized alerts and reminders, means to bring care into compliance with clinical guidelines, generation of order sets and patient data reports, advice to promote accurate and timely diagnoses, and tools that enhance clinical workflow. See: Osheroff JA, et al. A roadmap for national action on clinical decision support. *J Am Med Inform Assoc* 2007;14:141-5.

[4] Michael D. Maves, M.D., MBA, Executive Vice President, CEO of the American Medical Association, Sept. 23 letter to Sens. Max Baucus and Kent Conrad.

Coverage and payment policies, which tend to reflect population-based findings and standardize patterns of care, will need to evolve to reflect a growing understanding of individual and subgroup differences within broad populations. According to the Lewin paper, "Health technology assessment, clinical practice guidelines, and payment policies must adapt to more differentiated bodies of evidence, particularly for making distinctions between average effects and HTEs."

Similarly, Princeton University professor Uwe Reinhardt notes that our increasing knowledge about the influence of genetic factors on patient response to drugs "will make the task of establishing one-drug-fits-all formularies or therapeutic groupings much more complicated."[5]

In the future, coverage and payment policies as well as performance incentives must allow for sufficient flexibility for providers to tailor average treatment to the known determinants of individual patients.

How CER and PM will work together depends on how policymakers and researchers resolve key issues such as those described above. Although they originated with different orientations, CER and PM offer complementary advantages with great potential for advancing patient care. In a stressed healthcare system poised for reform, a continued, concerted effort is necessary to ensure that this potential is realized in order for patients to receive a higher quality of healthcare.

The paper identifies some encouraging developments in the adaptation of CER for PM and policy makers' commitment to ensure that PM is integrated into CER. Recent CER priority setting reports of the FCC-CER and the IOM and also pending legislation emphasize the need to close evidence gaps across the healthcare system as well the importance of subgroup analyses and consideration of patient-level attributes.

The Lewin paper also notes encouraging signs of CER and PM alignment in the private sector. For example, led by global pharmaceutical and biotechnology companies that have been responding to evolving evidence requirements in international markets, many in industry are incorporating both CER and PM considerations into their research and development activities.

Achieving "wise policy" to align CER and PM requires national leadership, a shared vision, and commitment from a broad range of stakeholders. To realize this potential, it will be important to establish policies that support these mutually reinforcing disciplines to ensure that care is both evidence-based and patient-centered.

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[5] U Reinhardt. 2001. Perspectives on the Pharmaceutical Industry. *Health Affairs*, Sep-Oct;20(5):136-149.