

## Issues Brief

### *21st Century Medicine: Personalized and Evidence-Based*

### September 18-19, 2007

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Modern medicine is at the brink of the next revolution in health care due to emerging scientific advances that apply genetic and molecular tools to tailored 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 preventative medicine and reduce the use of a “one-size-fits-all” approach to patient management. At the same time, it will increase the volume of information available to be processed and used by patients and their health care providers.

Growth in the area of molecular diagnostics and personalized medicine also means that health care providers must become proficient in the application of a large assortment of molecular tests and their accompanying predictive or therapeutic abilities. Thus, the very nature of “clinical evidence” and its processing and application to patient care will change. A new model for health care will evolve based on improving quality of care and outcomes, built on a foundation of mounting evidence about the interrelationships between genetics and response to disease, prevention, treatment, and patient outcomes.

The science of personalized health care is coming to fruition at a time of growing interest in the use of evidence-based medicine (EBM) as a solution to the challenges of gaps in the quality of care received by patients and rising health care costs. In particular, policy makers are focusing on development and use of comparative effectiveness research as an EBM tool. Together, these two trends — personalized health care and EBM — hold promise in meeting our biggest health care challenges, and thought leaders increasingly recognize the importance of advancing personalized health care and evidence-based medicine in ways that are mutually reinforcing. To realize this potential, it will be critically important to establish policies that support both disciplines to ensure that care is both evidence-based and patient-centered.

Achieving these goals raises several important issues. For example, as the evidence base expands through new research and scientific knowledge, how can this knowledge be delivered effectively to providers to improve the quality of care? How should approaches to conducting, interpreting, and applying research evolve to expand our understanding of the role of genetics in medicine and incorporate this understanding?

## Definitions and Terminology

**Personalized health care** is the segmentation of patient populations by any means, including genetic, imaging, or informatic techniques, to increase the benefit of a therapeutic approach to the patient.

**Personalized medicine** may include testing for variations in genes, gene expression, proteins, and metabolites. Test results are correlated with drug response, disease state, prevention, or treatment prognosis, and they help physicians individualize treatment for each patient with greater precision.

**Pharmacogenomics** is often used interchangeably with personalized medicine. In fact, its meaning is narrower and more specific, referring to the use of genetic information to individualize drug therapies. It is an important component of personalized medicine.

**Evidence-based medicine**, according to David Sackett's well-known and widely accepted definition, is described as follows:

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.<sup>1</sup>

Best available external clinical evidence is obtained from the “basic sciences of medicine, but especially from patient-centered clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens.”<sup>2</sup>

**Comparative effectiveness** studies involve research that compares the clinical or patient outcomes of two or more interventions (including treatments, tests, procedures, and approaches to care management and benefit design). EBM and comparative effectiveness studies generally are conducted at the group or subpopulation level, generating averages and means, rather than at the individual level. “Effectiveness assessments generally describe ‘average’ population effects and often cannot capture individual differences such as side effects, intolerance, noncompliance, and clinical effectiveness.”<sup>3</sup>

## Key Issues

Personalized health care holds great promise for improving patient care and helping to control rising health care costs. However, development and adoption of personalized health care technologies and approaches to care management will be challenged by growing demands for evidence. And, “Some experts predict that the entire foundation for evidence-based medicine and clinical trial design of one-size-fits-all is likely to be proven illogical in an era of personalized medicine.”<sup>4</sup>

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<sup>1</sup> DL Sackett, WMC Rosenberg, JAM Gray, RB Haynes, WS Richardson. 1996. Evidence based medicine: What it is and what it isn't *BMJ*;312:71-72.

<sup>2</sup> Ibid.

<sup>3</sup> K Buto and P Juhn. 2006. Can a Center for Comparative Effectiveness Information Succeed? Perspectives from a Health Care Company. *Health Affairs* Nov-Dec;25(6):w586-8. Epub 2006 Nov 7.

<sup>4</sup> H Belden. 2006. Getting Personal. *Drug Topics*, Sept. 18.

Similarly, EBM initiatives (such as current proposals for expanding comparative effectiveness research) can improve the quality and efficiency of health care. When properly understood and applied, such efforts are good for patients and for the health care system. However, current definitions and applications of comparative effectiveness research vary widely. While there is some recognition of the major implications that personalized health care holds for comparative effectiveness research, little work has been done to define approaches to developing and using comparative effectiveness research in ways that support, rather than hinder, the adoption of personalized health care.

As personalized health care advances, it will be critical to find ways to integrate the research methods of individual-based versus population-based studies and to identify what levels of evidence are required for prevention and treatment decisions at all levels. Such approaches should result in evidence that is sub-stratified for particular subpopulations based on genetic, molecular, or subtypes based on imaging, or patients, and that compares effectiveness of diagnostic and treatment options across these groups.

As EBM advances, new approaches are needed for evaluating and communicating comparative effectiveness research in ways that incorporate our expanding knowledge of differences at the individual and subpopulation level. In addition, further research is needed on approaches to care management, delivery, and benefit design that support personalized, evidence-based care.

Regulatory and payment policies represent important intersections between personalized health care and EBM. Some key issues in these areas are described below.

## **Payment Policy Issues**

Current economic incentives, such as intellectual property and reimbursement policies for diagnostics and pharmaceuticals, are generally not structured to reward appropriately and consistently innovative value creation for drugs, diagnostics, and pharmacogenomics-based treatment regimens.

Personalized health care challenges current assumptions made in health care coverage and reimbursement decisions—which are based on population averages—by providing a new type of evidence showing differences in patients and subgroups within populations. New imaging, molecular, and genetic tests may provide more precise information about future susceptibility to disease and response to treatment, but they also may be more costly. Insurers typically do not provide coverage for tests of disease susceptibility. Payers have stressed that prognostic tests would have to be subjected to a rigorous assessment to determine their cost-effectiveness and impact on health outcomes in order to justify coverage.

The emergence of personalized health care will also challenge conventional models for drug coverage and payment. For example, as pharmacogenomics increasingly illustrates the importance of providing physicians with a wide choice of medicines and gives them new diagnostic tools to guide these choices, current drug formulary structures may be challenged. Princeton University researcher Uwe Reinhardt notes, “Within the next two decades it will be discovered that the metabolism of individual patients for many drugs is strongly influenced by a

patient's unique genetic factors. That, of course, will make the task of establishing one-drug-fits-all formularies or therapeutic groupings much more complicated.”<sup>5</sup>

## Regulatory Issues

As evidence of the migration of genomic medicine into mainstream medical care, in August 2007, the U.S. Food and Drug Administration announced that it was bringing to doctors' attention the potential usefulness of getting a patient's genetic profile before prescribing warfarin, a widely used drug in the treatment of various cardiovascular disorders. There were 31 million outpatient prescriptions for the drug in 2004. It can have serious side effects, and variations in the activity of two genes can greatly increase its potency. This is the first time that FDA has provided data on the usefulness of such tests in the label of a therapeutic.

FDA has also demonstrated leadership in developing regulations to support personalized medicine by developing guidance for voluntary pharmacogenetic data submissions (2005, 2007); publishing draft guidance for pharmacogenetic and other genetic tests, including microarrays (2006); publishing a concept paper for co-development of pharmacogenomic drugs and diagnostics (2005); establishing labeling regulations (21 CFR 201.57) that recognize the relationship between genotype and drug response; and establishing a precedent for microarray diagnostics regulation. Industry is awaiting a final guidance on the co-development of pharmaceutical drugs and diagnostics.

However, a number of significant issues remain unresolved. For example, regulators and stakeholders continue to debate the role of FDA in regulating laboratory developed tests that profile multiple biological entities, such as proteins or genes. In addition, FDA is organizing, through its Critical Path Initiative, work across 76 science and regulatory areas to improve product development, especially for gene-oriented drugs and diagnostic tests.

In addition, we need more robust means of obtaining the evidence needed to evaluate personalized health care and make good clinical decisions, for example:

- A clinical research infrastructure to evaluate diagnostic/prognostic tests that accommodates the difficulties posed by genetic differences in controlling experiments and extrapolating to populations.
- Databases and analytical capabilities to incorporate large amounts of population data and make inferences on an individual level.
- Alignment of evidence to support market entry and coverage decisions.
- A definitive framework to evaluate highly complex genomic analysis tools and clinical decision support tools.

For regulatory (and reimbursement) purposes, defining the parameters for data quality will be a tremendous challenge. How much evidence is enough? How do we contend with contradictory evidence?

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

## Issues for the Future

### Comparative effectiveness

Proposals for expanding the federal government's role in comparative effectiveness research have gained prominence in recent months as a solution for improving quality and/or containing health care costs. Thought leaders have identified the relationship between the emerging science of personalized health care and the development and use of comparative effectiveness research. However, little work has been done to define approaches to federal comparative effectiveness research that incorporate and encourage continued progress towards personalized health care. As proposals for expanding comparative effectiveness research move forward, it is important to ensure that they take into account the new science of personalized health care.

At a March 2007 conference sponsored by Old Dominion University and the Center for Medicine in the Public Interest, several experts addressed this issue.<sup>6</sup> Andrew Balas, Dean of the College of Health Sciences and Professor of Community Health, Old Dominion University, asked, "Are population-based studies fully relevant to specific individualization of treatment in the emerging area of personalized medicine?" John Bridges, Bloomberg School of Public Health at Johns Hopkins University stated, "If we think about a distribution of people and a distribution of outcomes, no single person in the health care system is the average...And so this is not conducive to issues of personalized medicine."

At the same conference, Peter Elkin, Associate Professor of Medicine and Medical Informatics, Mayo Medical School, discussed the intersection of personalized medicine, comparative effectiveness, and health information technology, stating, "We need to go from a slow diffusion of research data into the practice to a rapid diffusion of innovation toward a healthier America, from group-based practice of medicine to personalized medicine. So in other words, it's not, oh, this patient has a pneumonia, but it's this particular patient's pneumonia, with not only the organism, but the DNA-identified fingerprint and the strain of that organism and the genetic fingerprint for the patient so that we can know exactly what the right treatment is for that patient and that patient's pneumonia, not anybody's pneumonia, and decrease our failure rates in terms of both how we run clinical trials and also how we treat our patients."

Others suggest that comparative effectiveness and personalized health care can work together. In congressional testimony, Congressional Budget Office Director Peter Orszag highlighted the potential for comparative effectiveness research to identify subpopulations to which interventions could be targeted.<sup>7</sup> Carolyn Clancy, Director of the Agency for Healthcare Research and Quality, has also identified personalized health care as one potential framework for advancing comparative effectiveness research. "We're going to start off with issues that no single health care system is going to be able to address on their own," Clancy said at the June 12,

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<sup>6</sup> Improving Healthcare Quality and Value: The Role of Comparative Effectiveness Research. Old Dominion University and The Center for Medicine in the Public Interest. March 29, 2007. The National Press Club, Washington, D.C.

<sup>7</sup> Peter R. Orszag, Congressional Budget Office. Testimony on "Research on the Comparative Effectiveness of Medical Treatments: Options for an Expanded Federal Role" before the House Ways and Means Health Subcommittee. June 12, 2007

2007 hearing. “We’re going to be examining the impact of breakthrough treatments, sometimes referred to as personalized health care....That may be one framework to begin.”<sup>8</sup>

### **Health information technology (HIT)**

Improved health outcomes and increased efficiency will result from evidence-based practice in a patient-centered health system that is powered by interoperable HIT. Widespread adoption of electronic health records will play an important role in the quality-centered transformation of the health care system, and provide patients and physicians with information to make optimal treatment decisions. By improving predictive and preventive care and supporting effective approaches to disease and care management, HIT holds promise to improve the quality and value of health care. This infrastructure should also take into account the unique needs of the basic, clinical, and translational research communities. By recognizing the value of supporting these communities with clinical outcomes information, HIT will accelerate new personalized health care breakthroughs into practice, as well as support consumer and physician access to new medical technologies and information.

At the Department of Health and Human Services, the Personalized Health Care Workgroup of the American Health Information Community (AHIC) is developing recommendations to identify HIT standards for including genetic information and analytical tools in electronic health records. AHIC is charged with developing recommendations for establishing or identifying consensus standards to ensure interoperability of electronic health records and for other specific actions.

Proposals for generating and applying comparative effectiveness data must recognize and encourage adoption of personalized health care approaches. HIT systems should facilitate communication of information in ways that allow physicians and patients to consider the risks and benefits of a range of treatment options and understand how these might vary depending on an individual’s genetic profile. Tools that obscure these differences through overly simplistic application of population-based comparative evidence will discourage the evolution of personalized health care.

### **Biomarker validation**

The reality of personalized medicine will depend, in part, on a better molecular understanding of how to optimize drug selection and dosing. This understanding will require integrating more clinically relevant genetic information into the drug development process.<sup>9</sup> In addition, large-scale prospective studies will be needed that measure genetics and other biomarkers over time to better understand the causal relationships among genes and drug responses so that validation of treatment options can occur.

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<sup>8</sup> As reported by K Rawson. 2007. In “Is Comparative Effectiveness Antithetical to Personalized Medicine?” *The RPM Report* 2(9).

<sup>9</sup> LJ Leslo. 2007. Personalized medicine: Elusive Dream or Imminent Reality? *Clin Pharmacol Ther* Jun;81(6):807-16.

Because there may be disincentives to develop a pharmacogenomics predictive test for drugs already on the market, some have argued that there should be incentives in place for co-development of tests and drugs coming to market, with the associations fully proven.<sup>10</sup> Still, business models for drugs and diagnostics traditionally have taken a path of separate development. However, organizations will be reluctant to adapt their business models to the new reality of linked development, and the diagnostic/drug products meant to benefit patients will likely be delayed until FDA clarifies what it expects for combination product clinical trials and regulatory submission.

## National Leadership

Realizing the promise of personalized, evidence-based medicine requires national leadership and a shared vision and commitment from a broad range of stakeholders. To realize this potential, it will be critically important to establish policies that support these mutually reinforcing disciplines to ensure that care is both evidence-based and patient-centered. Work towards this end should be guided by the following principles:

- Broad stakeholder representation and input is needed from public and private sector groups.
- The development of policies and strategies should take place through an open and transparent processes that encourages a shared vision and promotes mutual trust.
- Patient and physician treatment decision-making should be supported through strategies and tools that incorporate knowledge gained from personalized medicine approaches.
- Payment and coverage policies should reflect the emergence of personalized health care by enabling physicians and patients to choose the optimal ways to prevent, diagnose, and treat disease.
- Effective use of HIT is needed to improve quality and efficiency in health care.
- Approaches to health care delivery and care management that foster effective application of personalized health care need to be identified and supported.

Personalized health care offers a new paradigm for the development of drugs and the practice of medicine. We now know a great deal more about the biochemistry of drugs and how they interact with genes and the symptoms of disease. With the tools of genomics, we can know much about the biology of an individual human being. Combined, these tools offer the benefits of personalized health care, including prevention strategies and the development of drugs that are safer and more effective for specific disease populations. However, such benefits cannot be realized until we find a way to gather, analyze, and use the evidence emerging from clinical research and practice. To realize this potential, it will be critically important to establish policies that support the mutually reinforcing disciplines of personalized health care and evidence-based medicine to ensure that care is both evidence-based and patient-centered.

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<sup>10</sup> LP Garrison and MJ Finley Austin. 2006. Linking Pharmacogenetics-Based Diagnostics and Drugs for Personalized Medicine. *Health Affairs* 25(5):1281-1290.