Does comparative-effectiveness research threaten personalized medicine?

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The controversy stems in part from a perceived contradiction between the concepts of CER and personalized medicine. In CER, groups of patients are analyzed to compare the effectiveness of alternative medical strategies, with the intent of informing clinical decisions and policies affecting health care. The very name “personalized medicine” suggests an approach to care that is based on individuals rather than groups. The term has been used to describe the consideration of characteristics such as age, coexisting conditions, preferences, and beliefs in crafting an individual management strategy; the use of advanced individual genomic information in choosing an expensive biologic agent; and the development of therapies biologically tailored to patient needs, such as customized monoclonal antibodies and vaccines. But far from impeding personalized medicine, CER offers a way to hasten the discovery of the best approaches to personalization, providing more and better information with which to craft a management strategy for each individual patient.

Perhaps the most prominent examples of modern personalized medicine are genomic tests designed to guide treatment choices (see table). Some are widely recognized as useful, such as testing for human epidermal growth factor receptor type 2 (HER2, also referred to as HER2/neu) to select patients with breast cancer who will benefit from trastuzumab and of testing for the KRAS mutation to determine who is likely to benefit from therapies inhibiting the epidermal growth factor receptor. Genomic medicine, however, has had little impact to date in most areas of care — a fact that some critics blame on payers, claiming that they impose...
unrealistically high evidence barriers before agreeing to pay for genomic tests. But payers have often championed personalized approaches — for example, by reimbursing for KRAS testing before the Food and Drug Administration (FDA) has fully embraced it. The real bottleneck is often the science itself: progress in identifying clinically important genetic variants has been slow, since seldom does the presence of a common variant greatly increase the relative risk of a serious disease or of severe harm from treatment. Moreover, only some genomic tests provide clinically important information. For example, although the FDA endorsed the use of genomic tests to identify persons with warfarin sensitivity, comparative trials showed that the tests added little value over careful monitoring of the international normalized ratio.\(^2\) Chromosomal mutation 9p21.3 is associated with increased risk of cardiovascular disease in women, but a recent study showed that knowledge of its presence adds no additional predictive power to the standard information on risk.\(^3\)

The greatest obstacle to the adoption of personalized approaches such as genomic testing, however, is the lack of adequately designed studies assessing their clinical utility. Often there is little consensus about the best way to design and implement such studies. We may know very little about how a test might improve health in typical clinical settings. These are precisely the kinds of issues that CER is designed to address. As the leaders of the National Heart, Lung, and Blood Institute recently argued, once associations between genotype and drug sensitivity have been identified, studies assessing the clinical benefits of gene-guided management strategies will be needed.\(^4\)

Without knowing how well these strategies work, physicians can’t easily apply them or convince patients that a test is worth the out-of-pocket cost. In the case of tests that determine whether a patient is likely to benefit from a cancer-preventive, such as tamoxifen, a misleading result could lead either to unnecessary exposure to side effects or a failure to reduce an elevated risk of cancer. Appropriately designed studies could reveal that a genomic test adds little useful information or, conversely, that the personalized approach works better.

Physicians, recognizing that patients’ responses to treatment vary, have long tried to make treatment decisions that are as relevant to the individual patient as possible. In doing so, they have had to balance the findings of formal studies with clinical judgment: without the guidance of well-designed studies, physicians’ hunches about the effectiveness of treatments are frequently wrong, but the right kinds of studies have not always been available. There may be no high-quality studies of a treatment, or the patient or the treatment being considered may differ in important ways from those already studied.

For many years, clinical epidemiology and related fields have sought to improve our understanding of treatment effects at the individual level by analyzing subgroup effects and developing clinical prediction rules. Yet with too few appropriately designed studies, physicians, patients, and families have often had little guidance about which patients were most likely to benefit from a clinical strategy. Perhaps the most important goal of CER is to broaden and deepen such information, providing tools for matching medical care much more precisely to individual patients.

Although CER’s methods are not entirely new, the federal initiative will support research that is both more comprehensive — encompassing many more treatments and conditions, as well as more complete outcome measures — and more relevant to real-world clinical decisions than traditional clinical research. For example, large observational databases and pooled trial results can be used to learn more about the subgroups of patients who benefit from therapy. A recent study showed that mortality was similar overall for patients with coronary disease whether treated with percutaneous coronary intervention (PCI) or coronary-artery bypass surgery. However, the results varied strikingly with age: mortality was much lower with surgery among patients 65 years of age or older and lower with PCI among those 55 years of age or younger.\(^5\) Such information is important not only for pa-
Debate about Funding Comparative-Effectiveness Research

Jerry Avorn, M.D.

The proposal to include $1.1 billion for comparative-effectiveness research (CER) in the federal stimulus package encountered a vigorous and well-coordinated backlash. The campaign to gut this funding ultimately failed, but the debate engendered and the resonance of the opposition’s arguments in both lay and policy circles reveal much about the issues that will surround such research and its application in the coming years.

The contested provisions were designed to support studies comparing the efficacy and safety (and, by extension, the cost-effectiveness) of alternative ways of addressing common clinical problems. Interventions to be evaluated will include pharmaceuticals, devices, procedures, and diagnostic approaches, such as imaging studies. This research will fill important information gaps facing clinicians, patients, and payers concerning what works best. Currently, the Food and Drug Administration (FDA) often approves new...