Does comparative-effectiveness research threaten personalized medicine?

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Accessibility
Does Comparative-Effectiveness Research Threaten Personalized Medicine?

Alan M. Garber, M.D., Ph.D., and Sean R. Tunis, M.D.

The American Reinvestment and Recovery Act gives comparative-effectiveness research (CER) a large boost in funding over the next 2 years. Despite a consensus that better information about the relative effectiveness of different medical interventions is needed to improve the quality and value of care, some view CER with skepticism. Recently, the Partnership to Improve Patient Care, a coalition of 36 industry, patient-advocacy, and clinician organizations, raised concerns that CER will not take adequate account of individual patient differences and may impede the development and adoption of improvements in medical care and “stymie progress in personalized medicine.”

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...
approaches — for example, by
often championed personalized
genomic tests. But payers have
riers before agreeing to pay for
unrealistically high evidence bar-
ters before the Food and Drug Ad-
tio. The real bottleneck is
often the science itself: progress
identifying clinically important
genetic variants has been slow,
since seldom does the presence
of a common variant greatly in-
crease the relative risk of a seri-
sous disease or of severe harm
from treatment. Moreover, only
some genomic tests provide clin-
ically important information. For
example, although the FDA en-
dorsed the use of genomic tests
to identify persons with warfa-
rin sensitivity, comparative trials
showed that the tests added little
value over careful monitoring of
the international normalized ra-
tio. 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 ap-
proaches such as genomic testing,
ever, is the lack of adequately
designed studies assessing their
clinical utility. Often there is lit-
tle 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 ad-
dress. As the leaders of the Na-
tional Heart, Lung, and Blood
Institute recently argued, once as-
ociations between genotype and
drug sensitivity have been identi-
fied, studies assessing the clinical
benefits of gene-guided manage-
ment strategies will be needed.4
Without knowing how well these
strategies work, physicians can’t
easily apply them or convince pa-
tients 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 tamox-
ifen, a misleading result could
lead either to unnecessary ex-
sure to side effects or a failure to
reduce an elevated risk of can-
cer. Appropriately designed stud-
ies could reveal that a genomic
test adds little useful information
or, conversely, that the personal-
ized approach works better.

Physicians, recognizing that pa-
tients’ 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 bal-
ance the findings of formal stud-
es with clinical judgment: with-
out 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 treat-
ment, or the patient or the treat-
ment being considered may differ
in important ways from those
already studied.

For many years, clinical epide-
miology and related fields have
sought to improve our understand-
ing of treatment effects at the indi-
vidual level by analyzing subgroup
effects and developing clinical pre-
diction rules. Yet with too few ap-
propriately designed studies, phy-
sicians, 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 pa-
tients.

Although CER’s methods are
not entirely new, the federal ini-
tiative will support research that
is both more comprehensive —
embracing many more treat-
ments and conditions, as well as
more complete outcome measures
— and more relevant to real-world
clinical decisions than tradition-
al 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 ther-
apy. A recent study showed that
mortality was similar overall for
patients with coronary disease
whether treated with percutaneous
coronary intervention (PCI) or cor-
onary-artery bypass surgery. How-
ever, 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 informa-
tion is important not only for pa-

**Selected Genomic Biomarkers.**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Disease</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-kit</td>
<td>Gastrointestinal stromal tumor</td>
<td>Imatinib mesylate</td>
</tr>
<tr>
<td>CCR5</td>
<td>Human immunodeficiency virus</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Cytochrome P-450 variants</td>
<td>Various disorders</td>
<td>Warfarin, voriconazole</td>
</tr>
<tr>
<td>EGFR</td>
<td>Non–small-cell lung cancer</td>
<td>Erlotinib</td>
</tr>
</tbody>
</table>
tients with varying risk characteristics and coexisting conditions but for women, members of minority groups, and others who have historically been underrepresented in clinical trials. Current CER efforts aim to ensure that much more useful data will be collected and that better methods will be developed for understanding differences in effectiveness among different patient groups.

As CER guides individual patient care, it will also guide and promote innovation. In some cases, federal support of the research will reduce the development costs of new medical technologies. Emerging CER methods promise to be more rapid, relevant, and efficient. Furthermore, the development of explicit standards for CER methodology will help to clarify which forms of evidence are sufficiently informative for health care decision makers—an advance that will be particularly important for the most novel personalized approaches, such as the creation of monoclonal antibodies directed against a cancer in a specific patient. Such exciting prospects do not obviate the need for evaluation; they change the kind of evaluation that is needed. CER may well require innovative approaches to clinical trials—such as adaptive, pragmatic, or other novel trial designs. Individualized therapies might be evaluated through the random assignment of patients to tailored therapy or a conventional alternative; such an approach would neither disadvantage the personalized therapy nor presume its superiority.

The deepest concern about CER is that it will be misused, which is why some legislators seek to prohibit information on comparative effectiveness from influencing coverage policy and payment decisions. But surely these decisions will not be improved by discouraging the use of the most relevant and valid information about what works and in whom. CER is not a panacea, but it is a key to individualized care and innovation, not a threat. An initiative to advance our knowledge about the effectiveness of clinical strategies can hasten the day when personalized medicine transforms health care.

Dr. Garber and Dr. Tunis report serving on the Institute of Medicine (IOM) Committee on Priorities for Comparative Effectiveness Research. Dr. Garber reports receiving lecture fees from De Novo Ventures, Express Scripts, and Covidien and consulting fees from McKinsey and Co. and Perlegen, a genomics company. Dr. Tunis also reports serving as director of the Center for Medical Technology Policy, which receives unrestricted funding from a number of foundations, government grants, as well as health plans and life sciences companies. No other potential conflict of interest relevant to this article was reported.

The views expressed in this article are those of the authors and do not necessarily represent those of the IOM, the IOM Committee on Priorities for Comparative Effectiveness Research, the Department of Veterans Affairs, or Stanford University.

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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 it 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...