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Economic Incentives for Evidence Generation: Promoting an Efficient Path to Personalized Medicine

Adrian Towse, MA, MPhil[1,*], *Louis P. Garrison, Jr., PhD*[2]

[1]*Office of Health Economics, London, UK;* [2]*University of Washington, Seattle, WA, USA*

ABSTRACT

The preceding articles in this volume have identified and discussed a wide range of methodological and practical issues in the development of personalized medicine. This concluding article uses the resulting insights to identify implications for the economic incentives for evidence generation. It argues that promoting an efficient path to personalized medicine is going to require appropriate incentives for evidence generation including: 1) a greater willingness on the part of payers to accept prices that reflect value; 2) consideration of some form of intellectual property protection (e.g., data exclusivity) for diagnostics to incentivize generation of evidence of clinical utility; 3) realistic expectations around the standards for evidence; and 4) public investment in evidence collection to complement the efforts of payers and manufacturers. It concludes that such incentives could build and maintain a balance among: 1) realistic thresholds for evidence and the need for payers to have confidence in the clinical utility of the drugs and tests they use; 2) payment for value, with prices that ensure cost-effectiveness for health systems; and 3) levels of intellectual property protection for evidence generation that provide a return for those financing research and development, while encouraging competition to produce both better and more efficient tests.

Keywords: economic incentives, personalized medicine, pharmacogenetics, stratified medicine.

Introduction

The preceding articles in this volume have identified and discussed a wide range of methodological and practical issues in the development of personalized medicine. As O'Donnell [1] points out in the introduction, they cover three broad topic areas: comparative effectiveness research, drug development, and economic evaluation. In this concluding article, we attempt—from an economic perspective—to identify the insights and implications for the crosscutting theme of economic incentives for evidence generation.

Definitional Issues

We follow Redekop and Mladsi [2] in using the term personalized medicine (PM) in this article, while recognizing that this typically involves stratifying patients into subpopulations and that we are not just using genetic information to "prevent, diagnose and treat." As O'Donnell notes, it is important to avoid "second-order discourse" from distracting us from the "pressing issues at hand" [1]. As Redekop and Mladsi note, most economists would be quick to point out that all medical treatments should be personalized in the sense that the physician (the agent) should advise the patient (the principal) taking into account patient preferences, the evidence base that supports the likely benefits and risks of different treatment choices, and the cost to the payer and to the patient. The important difference in PM is the use of a biomarker-based diagnostic test [3] to further define and identify a subgroup of patients for whom the treatment performs better—in terms of either cost-effectiveness or benefit-risk balance. Thus, we restrict our use of the term PM to refer to this biomarker-based stratification.

The Progress of PM

We share the view of O'Donnell that "there remains a general sense of dissatisfaction about the progress of personalized medicine" [1]. It is not hard to understand how the excessive optimism—even hype—of a decade ago has led to some cynical views about the possibility of realizing the promise that PM holds for the future. In the year 2000, Francis Collins, the current head of the U.S. National Institutes of Health said, "In the next five to seven years, we should identify the genetic susceptibility factors for virtually all common diseases—cancer, diabetes, heart disease, the major mental illnesses—on down that list" [4]. Clearly, this has not happened.

In 2005, a multidisciplinary exercise at the University of Washington—including geneticists, physicians, pharmacists, and economists—reached a less sanguine view about the speed

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* *Address correspondence to:* Adrian Towse, Office of Health Economics, Southside, 7th Floor, 105 Victoria Street, London SW1E 6QT, UK. E-mail: atowse@ohe.org.

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at which this promising future will unfold. In the "most likely" scenario for the year 2015, they predicted:

> By 2015, approximately 10 years from now, a variety of test kits using various biological markers testing will be feasible when rapid test results are needed. Yet, the discovery and validation of pharmacogenomic associations will likely continue at a similar measured pace. A notable development will be the identification of clinically useful pharmacogenomic associations in drug development trials outside of oncology. We expect that 10 to 15 pharmacogenomic tests will be in routine use in clinical practice. Although the majority will continue to be in oncology, evaluating both tumor and patient genetics, several tests outside of oncology will be used by primary care clinicians to guide treatment decisions. [5]

This prediction is arguably still on target. It is clear that several genetic tests are widely used, mainly in oncology [6]; however, the total number in routine clinical use remains fairly limited. The articles here have mentioned a number of examples outside of oncology, including CYP2C19 testing for clopidogrel and HLA-B*5701 testing for abacavir. In relation to drug development also, the picture is mixed. Trastuzumab (Herceptin, Roche) for HER2+ breast cancer has often been cited as the "poster child" of PM. Despite the HER2 target receptor being identified in the mid-1980s, it was not until 1998 that it was first approved by the U.S. Food and Drug Administration for HER2+ metastatic breast cancer, and for HER2+ early breast cancer in 2006. Its impact is still evolving, with evidence of a synergistic effect with pertuzumab, which acts on the HER3 receptor.

At the other end of the speed-of-development spectrum, however, two highly significant clinical improvements—cures or near cures for some patients—were developed and adopted very quickly: imatinib (Gleevec, Novartis) for Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia and crizotinib (Xalkori, Pfizer) for a small targeted group of non–small cell lung cancer patients with anaplastic lymphoma kinase (ALK) mutations.

The scientific challenges are therefore being met in some cases but clearly remain. They are accompanied by a related set of challenges in terms of evidence, economic evaluation, reimbursement, and regulation. The articles in this volume have touched on all of these. We would like to reiterate and highlight some of these points, placing particular emphasis on how each of these challenges affects or is affected by economic incentives.

Economic Evaluation Challenges and the Value to a Patient of Knowing

In general, the methods of economic evaluation in PM are no different than standard cost-effectiveness analysis (CEA). Besides health gain and cost-offsets captured in the usual CEA for a typical patient, however, we can identify at least three other ways in which PM might create additional value: 1) reducing the patient's uncertainty about the likelihood of successful treatment —the "value of knowing"— and as a result; 2) improving adherence and thus health outcomes for treated patients; and 3) raising overall uptake and utilization at a population level [7].

Annemans et al. [8] very effectively explain, however, how adding a PM test or sequence of tests before the clinical treatment pathway begins creates some new measurement challenges for traditional CEA. For example, where will we get the data on the clinical and economic consequences for false-negative and false-positives? Could they even be identified in most commonly used trial designs? It is hoped that their numbers will be small, yet this makes the measurement of consequences less accurate.

Annemans et al. also allude to the "value of knowing," by placing a "special emphasis on process utility." Information is important. As they put it: "even if a test result will not lead to changing treatment, the actual value of receiving the communication about the results and the associated advice cannot be ignored." Payne and Annemans [9] note that there is evidence to support the "added value from information" for clinicians and patients. Annemans et al. note that contingent valuation approaches have been used to measure and value the benefit of knowing. One example of this is Neumann et al. [10]. Interestingly, they suggest the relevance of "capability" theory and measurement as a research route to explore. They also point out that "a testing strategy does not necessarily lead to more QALYs." In other words, the effect of testing might be to restrict use to a subgroup, reducing the absolute quality-adjusted life-year gains from treatment. This is because although targeting may be cost-effective, it may mean that some patients for whom the drug would have been effective do not receive treatment. This could be because some of the "nonresponders" would actually respond to some degree, and in addition there may be some false negatives, patients misclassified as nonresponders by the test. Thus, efficiency increases but some quality-adjusted life-years are lost. Ex post targeting, where it explicitly involves no longer treating some existing patients, can be seen in this context as a form of disinvestment [11].

Evidence Gaps: The Need for Coverage with Evidence Development and Performance-Based Risk-Sharing Arrangements

Another factor hindering the development and adoption of PM is that the current regulatory and reimbursement systems are not leading to sufficient evidence as to the value of identifying and treating only those predicted to be "responders." Willke et al. [12] frame the PM stratification strategy in terms of "heterogeneity of treatment effect (HTE)." In other words, different subgroups respond differently and PM research seeks to identify and study this variation systematically. It is, however, often difficult to explore this preapproval. They speculate that manufacturers are reluctant to limit market size and (potentially) increase the complexity of trials by looking for HTEs preapproval even though development costs could fall if a genetic response is identified "early enough to reduce trial sizes and increase the probability of success during Phase 3." However, they also note that "over 50% of manufacturers have incorporated pharmacogenomics or pharmacogenetic diagnostics into their clinical development programmes," suggesting that companies are exploring this option. This is because, as Frueh [13] notes, "drug-test co-development . . . poses the least challenge with respect to demonstrating the effectiveness of a personalised medicine approach", and as Danzon and Towse [14] noted, "drug producers will have incentives to do this ... as part of the drug development process rather than wait for others to do it after the drugs reach the market."

The relatively slow evolution of the science, however, means that this may continue to be the exception rather than the rule. Oncology and orphan diseases are areas where the science has advanced most, and a proactive approach to stratification to identify HTE is likely to make sense. It does not, however, make economic sense for companies to routinely invest in extensive HTE analysis preapproval in many other disease areas unless they have a very strong prior view about how to stratify the trial population. We agree with the central point of Willke et al. [12] that, for the time being, most HTE data are going to be collected postapproval, and with their argument for using "risk-sharing agreements and coverage-with-evidence development agreements . . . to incentivise evidence generation and utilisation of HTE."