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Regulation, Reimbursement, and the Long Road of Implementation of Personalized Medicine—A Perspective from the United States

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ABSTRACT

There is undisputed evidence that personalized medicine, that is, a more precise assessment of which medical intervention might best serve an individual patient on the basis of novel technology, such as molecular profiling, can have a significant impact on clinical outcomes. The field, however, is still new, and the demonstration of improved effectiveness compared with standard of care comes at a cost. How can we be sure that personalized medicine indeed provides a measurable clinical benefit, that we will be able to afford it, and that we can provide adequate access? The risk-benefit evaluation that accompanies each medical decision requires not only good clinical data but also an assessment of cost and infrastructure needed to provide access to technology. Several examples from the last decade illustrate which types of personalized medicines and diagnostic tests are easily being taken up in clinical practice and which types are more difficult to introduce. And

as regulators and payers in the United States and elsewhere are taking on personalized medicine, an interesting convergence can be observed: better, more complete information for both approval and coverage decisions could be gained from a coordination of regulatory and reimbursement questions. Health economics and outcomes research (HEOR) emerges as an approach that can satisfy both needs. Although HEOR represents a well-established approach to demonstrate the effectiveness of interventions in many areas of medical practice, few HEOR studies exist in the field of personalized medicine today. It is reasonable to expect that this will change over the next few years.

Keywords: health economics, outcomes research, personalized medicine, regulatory, reimbursement.

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A brief search in PubMed [1] for “personalized medicine” reveals 10,249 hits, a search for “health economics and outcomes research” reveals 15,409 hits, and a combination of both search terms reveals a mere 48 hits. By combining “personalized medicine” with “economics,” one finds 519 articles; by combining “personalized medicine” with “outcomes,” one finds 989 articles. Clearly, the intersection of personalized medicine with outcome- or economic-oriented research is poorly investigated. Also, the increase (as small as the sample size may be) during the last 3 years is interesting: 5 articles in 2009, 6 in 2010, and 12 in 2011 compared with an average of 1 per year for the last decade. Have we just realized that outcomes and cost matter for the implementation of personalized medicine?

Ten years ago, Lesko and Woodcock [2] described in a seminal article how the Food and Drug Administration (FDA) envisions pharmacogenetics to help guide drug development: it was becoming increasingly apparent that the regulatory body will get exposed to such information and that a regulatory path needs to be developed to appropriately and accurately review the data. Moreover, the FDA, which sees trends in drug development long before the final products are used in routine clinical practice, highlighted the advent of a new era in which patients will be treated and taken care of on the basis of their own molecular profile. After the release of the final “Guidance for industry: pharmacogenomic data submissions” [3] in 2004 (the 2003 draft

guidance was extensively discussed and many public comments have been incorporated in the final guidance), a rapid increase in pharmacogenetic- and other biomarker-driven drug development data submitted to the FDA was observed [4,5]. Assuming an average of 5-year delay from the time of submission to reaching the market, we indeed arrive at the 2009 upswing of publications on outcomes and cost in the field of personalized medicine. Considering that pharmacogenetic information was part of drug labels for a much longer period of time [6], it is still surprising that not much emphasis has been put on evaluating changes in clinical outcomes and determining cost associated with this field. Several possible explanations for the paucity of such data exist.

Most of the early pharmacologically relevant biomarkers used in personalized medicine (or “pharmacogenetics”; the term “personalized medicine” was in fact introduced much later) were pharmacokinetic markers, such as variations in cytochrome P450 (CYP450) enzymes. In those early days, associations between a marker and a clinical outcome, particularly one that then could be affected, for example, via dose adjustment, were identified after the drug had already reached the market (a notable exception marks Her2/neu, a pharmacodynamic marker that was essential for the development of trastuzumab introduced to the US market in 1998). Because these markers were not discovered within the context of the actual drug development effort, the nature of the studies demonstrating the potential

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clinical impact of the markers was markedly different from that of studies requiring a marker as an integral part of drug development (and its potentially required use as a diagnostic to guide therapy). To the most part, these studies were limited, with a small *n*, and not oriented toward hard clinical outcomes, but rather using soft or surrogate end points such as pharmacokinetic. Therefore, it was difficult to translate these markers into clinical practice, and in situations in which diagnostics measuring these markers had been developed, uptake was (and continues to be) slow: the lack of convincing studies that focus on relevant clinical outcomes poses a significant hurdle for the acceptance of personalized medicine in the clinic. Studies for newer markers that have been critical or even required for the (co-)approval of a drug associated with the marker of interest, however, are more rigorous, and the demonstration of clinical effectiveness and cost-effectiveness is significantly streamlined (see below). Therefore, many markers that are often cited in the context of personalized medicine have not been studied in pivotal trials, and although exploratory or smaller studies were conducted and may point toward clinical effectiveness and cost-effectiveness, they were not convincing enough to regulators to, for example, update the label of a drug and requiring the use of a test or to payers to cover the payment of a test (or even require a test before authorizing the reimbursement for a drug). Moreover, in situations in which the FDA took the initiative to update the label of a particular drug, for example, warfarin [7], clopidogrel [8], and irinotecan [9], translation into clinical practice occurs slowly and reimbursement for these tests remains fragmented. More recently, in addition to tests that are directly associated with the use of a particular drug, developed either in conjunction of the drug or later [10], a third category of tests that are not associated with a particular drug therapy (although they can inform about appropriate therapies) has emerged. It is interesting to take a closer look at these three categories of personalized medicine tests, and the regulatory and reimbursement pattern they reveal:

1. Tests developed in association with a drug (drug-test codevelopment, e.g., Her2/neu for trastuzumab [11]). This category of tests benefits from the rigor of studies needed to bring the drug to the market, which bears several advantages: the regulatory pathway requires the test and the drug to be approved at the same time, reimbursement usually follows in line with the requirement of the test to demonstrate appropriate use of (or even eligibility to receive) the drug, and if the drug fails to gain approval, the test is likely not needed (at least not in this particular context). Moreover, in clinical practice, there is a significantly lower burden of informing and educating health care professionals about the benefit of the test because in this situation the test will likely be required to gain access to the drug. The onus of demonstrating the impact of the test is not only on the developer of the test but also on the manufacturer of the drug because of the vested interest in making the test available. This category of tests poses the least challenge with respect to demonstrating the effectiveness of a personalized medicine approach: it is inherent to the product (which is a personalized medicine product by definition), and clinical effectiveness and cost-effectiveness data encompass both drug and test simultaneously. If approved by regulators, products in this category are also likely to be covered and reimbursed by payers.
2. Tests developed after the drug has reached the market. The fundamental difference between this and the aforementioned scenario is the state of clinical practice: although the previous example establishes clinical practice for both the test and the drug simultaneously, here the introduction of the test requires an adjustment or change in established clinical practice: this is much harder to achieve. Two different types of tests in this category exist: tests that are developed specifically for one drug product and tests that are of more general use. For the former, tests are developed as either improvements in existing tests already marketed (e.g., fluorescence in situ hybridization testing in lieu of immune histochemistry testing for trastuzumab) or new tests for drugs that were marketed without the need for a specific test (e.g., HLA-B*5701 testing for abacavir). The latter include tests such as assays for drug-metabolizing enzymes (e.g., CYP450s) that are relevant for the use of various drugs [12]. Although all these tests are developed after the drugs they are useful for, there are significant differences with respect to the level of evidence needed for them to be successfully introduced into clinical practice: clinical utility for tests that follow tests already on the market has, by definition, already been established. The characteristics of the new test (in particular sensitivity, specificity, and cost) determine its performance compared with that of its predecessor, and it can be judged relatively easily whether the cost-benefit profile of the new test is superior to that of the existing assay. For tests for which no predicate assays exist, this evaluation is more difficult and includes demonstration of clinical utility. In addition, cost-effectiveness becomes a more critical component: the introduction of a new test will add cost and the demonstration that such additional cost to the system is warranted is necessary. This can be achieved by a significant improvement in outcomes, by a demonstration of overall savings to the system, or ideally by both. For example, HLA-B*5701 testing for abacavir has seen a rapid uptake: the high sensitivity and specificity of the test [13] enabled the use of abacavir in a much larger population owing to the ability of the test to detect patients who are at risk for a severe adverse event: the clinical benefit of the test clearly justified the additional expense of a test and likely also compensated for costs associated with the management of the adverse event, which may occur in patients for which abacavir poses a risk: clinical utility of HLA-B*5701 testing seemed apparent, and cost-effectiveness has been demonstrated [14] and also put in perspective by others later on [15]. In contrast, slow uptake was seen in situations in which the performance of the test was less clear, differences in outcomes harder to detect, and/or the information derived from the test more difficult to translate into precise clinical actions. It is interesting to note that in many of these latter cases, the clinical outcome—that is, the benefit of testing—may not be immediately apparent, but observed only over a period of months or even years (e.g., CYP2C19 testing for clopidogrel [16,17]) as opposed to a benefit that is much more rapidly discernible (e.g., HLA-B*5701 testing for abacavir). This delayed feedback makes it more difficult to design studies demonstrating the clinical utility of such tests not only due to long follow-up periods that may be needed but also due to the larger sample size required to demonstrate the correlation between the intervention (e.g., dose adjustment and change in therapy) and a more distant clinical outcome (e.g., prevention of a secondary event [16]). Consequently, it is also significantly more challenging to demonstrate cost-effectiveness in these situations. It is therefore not surprising that the incentives to develop such tests and to demonstrate their clinical and economic impact are misaligned with the interest in realizing an attractive return on investment because studies needed to demonstrate the clinical and economic impact can take several years and are costly. In many cases, it is difficult or even impossible to turn the development cost of such tests into profits, given the rates at which such tests are usually reimbursed. There are some situations, however, in which at least theoretically this approach appears to be more

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