

## P E R S P E C T I V E

**The Human Genome And Translational Research: How Much Evidence Is Enough?**

Given the lack of a robust translational infrastructure, conflict between those developing new technologies and those who must use or pay for them seems inevitable.

by **Janet Woodcock**

**ABSTRACT:** Multiple new genomic diagnostic tests are currently under development. Given the lack of an efficient translational infrastructure, it is not clear how, or whether, robust evidence for their clinical value will be generated. [*Health Affairs* 27, no. 6 (2008): 1616–1618; 10.1377/hlthaff.27.6.1616]

MUIN KHOURY and colleagues pose some important questions about an anticipated flood of new genomic diagnostic tests.<sup>1</sup> Should these be introduced into clinical practice in the same haphazard manner that has characterized the use of many other medical technologies? Should a consensus group of stakeholders develop standards for introduction and use, or can the market be relied upon to exert correcting influences? Can the need for an adequate evidence base coexist with adequate incentives for innovation?

These questions reflect the translational dilemma in the United States and other developed countries. Fueled by decades of investment in basic research, the biomedical sciences are delivering new insights into health and disease. But the existing robust basic science enterprise must hand off its discoveries to a weak and radically underfunded translational science infrastructure, whose ineffectiveness derives, in part, from the often unspoken assumption that translation is the role of the private sector. This problem is not

unique to genomic tests: a plethora of other powerful molecular diagnostics and other innovative technologies are moving toward clinical introduction. Will their clinical value be assessed, and will they be worth their cost to health care? The translational science infrastructure that could effectively and efficiently address these questions does not exist.

The current situation for pharmaceutical development is instructive in this regard. Although the bar for market entry is (relatively speaking) extremely high, it is widely recognized that data important to clinical use, such as long-term outcomes and comparative effectiveness, are not included in the internationally recognized standards for drug approval. Given the lack of a translational infrastructure, trials to develop such data can be prohibitively expensive, whether performed by the public or the private sector. This has led to the ongoing controversy about how, when, and by whom these data will be developed. In contrast, the current reimbursement structure for diagnostic testing does not provide the return on investment that would support even a basic

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evaluation of clinical performance prior to market. This explains the desire of diagnostic-product developers to attain the market based on measures of clinical validity (that is, does the test result in a correct measurement in the target population?) rather than clinical utility (that is, what clinical benefit does the test offer?). Any bar to market entry higher than clinical validity would markedly decrease developers' ability to raise the investments necessary to commercially develop such tests.

There are more than a thousand genetic diagnostic tests marketed in the United States. Almost all of these are marketed as laboratory developed tests (LDTs) that have not gone through the Food and Drug Administration (FDA) review process, a paradigm permitted by the agency since 1976. The vast majority also have not undergone rigorous evaluation of their clinical utility. Nevertheless, this approach to market introduction has arguably been quite successful for this early generation of genetic tests that have been primarily used to assist in diagnosis and genetic counseling for rare heritable disorders. The tests have been used in clinical settings that involve a small community of medical experts, specific provision of counseling about the implications of test results, and minuscule tested populations. In contrast, many of the new genomic tests will be intended for clinicians rather than geneticists (and some may even be marketed directly to consumers) and will be used widely. Because newer genomic tests will have a broad range of indications, it is unlikely that a one-size-fits-all set of standards will be applicable, but it is also unlikely that the LDT paradigm will be universally appropriate.

For example, many future genomic tests will likely be used to contribute diagnostic and prognostic information in people who are already have established disease, by identifying genetically based disease subsets or providing prognostic information derived from gene expression profiles. These uses might be supported by association studies rather than prospective outcome trials. In contrast, when the same tests are used as the basis for important therapeutic decisions such as whether or

not to proceed with adjuvant cancer chemotherapy, a higher evidence bar might be needed.

The strongest case for studying outcomes can be made for the most difficult-to-study indications: disease prediction and population screening. Genetic variants are being identified as risk factors for a wide variety of common disorders, many of which have multiple other known phenotypic and "lifestyle" risk factors. Such variants may contribute only a small amount of additional risk. Yet there is often great enthusiasm for population screening. Use of a consensus process to make recommendations based on public health considerations seems wise and would be useful to inform practice guidelines and reimbursement policies.

The field of pharmacogenomics, which delineates the relationship between the genome and drug responses, is rapidly developing. Pharmacogenomic tests, particularly for drug metabolizing enzyme (DME) variants, have already been approved by the FDA based on clinical validity. The agency applies differing evidentiary requirements to diagnostic tests based on indication.

Genetically determined variations in DMEs change the dose of a drug needed to attain a given blood level. Individuals with variants can be exposed to much higher- or lower-than-expected levels when given "average" drug doses, sometimes resulting in toxicity or lack of efficacy, respectively. There is much debate about the level of evidence required to incorporate DME testing into clinical practice. Since less common DME variants, by definition, represent outliers, hypothesis-testing trials based on population-mean results require very large numbers to achieve adequate statistical power (because most enrollees, having "average" enzymes, can't benefit). Although population-based outcome trials are a traditional approach, one might debate the wisdom of using scarce resources to investigate such matters when other essential questions go unanswered. And while outcome trials may provide cost-benefit information, patients with enzymatic variants might well question the ra-

tionale of being subjected to suboptimal dosing based on economic factors. Since the dose-response curves for both toxicity and efficacy are well known for many drugs, and since demonstrating the effect of a DME variant on exposure is straightforward, the FDA has used this “mechanistic” approach to putting genetically directed dosing recommendations on drug labels. It is likely that genetic information on a person’s DME status will become a standard part of the medical history that is routinely taken into account for drug therapy, and that most genetically directed dosing adjustment recommendations will be derived from pharmacokinetic studies.

Pharmacogenomic tests are starting to be used to prevent serious drug side effects. Recently, recommendations for genetic pre-screening for specific HLA alleles were placed on the labels for carbamazepine (HLA-B\*1502, associated with Stevens Johnson syndrome, or SJS) and abacavir (HLA-B5701, associated with serious hypersensitivity reactions).<sup>2</sup> The latter included a 1,650-patient, prospective, randomized controlled trial (RCT); the former were derived from case series showing that a large fraction of carbamazepine-associated SJS in certain Asian populations was in people with the specific alleles. This difference in evidence seems appropriate, given that the abacavir problem affected about 8 percent of patients, while SJS is a rare event.

Use of genetic testing to select therapy is well under development, particularly in cancer, where the tumor’s genomes(s) are of interest. This approach is being evaluated with some currently marketed drugs. Also, attempts to codevelop a genetic test with an investigational drug are ongoing. The level of evidence required to reach the market with a drug-diagnostic combination is now being debated.

The FDA has recently issued a proposal for regulation of in vitro diagnostic indexed multiplexed assays (IVDMIAAs), new types of assays, both genomic and other, that use large numbers of analytes (as opposed to a single gene mutation) and are frequently developed using retrospective association studies. This proposal has created much controversy over

the risk of stifling innovation versus the public health risks of inadequately developed IVDMIAAs.<sup>3</sup>

These examples illuminate the challenges faced in translating scientific knowledge about the human genome into rational medical practice. Given the lack of a robust translational infrastructure, ongoing conflict between those developing new technologies and those who must use or pay for them seems inevitable. Careful thought about the needed evidence for any given technology can help mitigate the problem. It is likely that every diagnostic does not need to be supported by RCTs. In fact, the mechanistic information provided by genomic tests represents a paradigm that has been used in other parts of medicine, such as microbiology, where therapy is adjusted based on microbial resistance and even gene sequence information. On the other hand, developers, who have largely been proceeding along the path used for genetic tests for rare disorders, need to understand that diagnostics intended for large populations, or that have large effects on treatment decisions, need robust evidence of utility. And finally, for such important diagnostics, reimbursement may need to be more proportionate to the developmental efforts required.

#### NOTES

1. M.J. Khoury et al., “The Evidence Dilemma in Genomic Medicine,” *Health Affairs* 27, no. 6 (2008): 1600–1611.
2. Food and Drug Administration, “Information on Abacavir (Marketed as Ziagen) and Abacavir-containing Medications,” 24 July 2008, <http://www.fda.gov/cder/drug/infopage/abacavir> (accessed 20 August 2008); and FDA, “Information on Carbamazepine (Marketed as Carbatrol, Equetro, Tegretol, and Generics),” 31 January 2008, <http://www.fda.gov/cder/drug/infopage/carbamazepine> (accessed 20 August 2008).
3. FDA, “Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays,” 26 July 2007, <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf> (accessed 20 August 2008).